DOI: 10.1002/ejoc.200800558

The Preparation of α-Alkylidene-γ-Butyrolactones Using a Telescoped Intramolecular Michael/Olefination (TIMO) Sequence: Synthesis of (+)-Paeonilactone B

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Keywords: Tandem reactions / Phosphonates / Michael addition / Horner–Wadsworth–Emmons / Lactones

A novel telescoped intramolecular Michael addition/proton transfer/HWE olefination sequence has been developed to provide rapid access to α-alkylidene-γ-butyrolactones. This methodology has been applied to prepare a range of tetrahydrobenzofuran-2,5-diones, and related systems, and also utilised in an extremely short synthesis of the natural product (+)-paeonilactone B in enantiomerically pure form. In addition, preliminary experiments are described that illustrate a palladium-catalysed variant proceeding by way of a π-allyl intermediate.
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Introduction

The α-alkylidene-γ-butyrolactone motif is found in many synthetically challenging and biologically interesting natural products whose diverse properties include herbicidal activity, transcription-factor inhibition and anticancer activity, amongst others.[1] Representative examples are illustrated in Figure 1, ranging from the relatively simple paeonilactone B (**1**)[2] to more complex examples such as the zinaflavins [e.g., zinaflavin F, (**2**)],[3a] the helenalins (e.g., **3**[3b]) and montahibisciolide (**4**).[3c]

There are a range of published procedures for the preparation of α-alkylidene-γ-butyrolactones, commonly involving lactone construction and subsequent HWE-type methylenation or hydroxymethylation/dehydration, but the majority of the routes are lengthy and low yielding.[1–4] As part of our growing interest in telescoped processes,[5] we devised a streamlined, one-pot approach to α-alkylidene-γ-butyrolactones, as outlined in Scheme 1.

It was envisaged that deprotonation of diethyl phosphonoacetate **5** would trigger intramolecular Michael addition[6–8] to give enolate **6**. We anticipated that subsequent proton transfer (anion exchange) would generate the more stable phosphonate anion **7**, and then addition of an aldehyde should initiate an intermolecular Horner–Wadsworth–Emmons (HWE) olefination[9] to generate cyclic or bicyclic dicarbonyl compounds **8** (Scheme 1). Such a conjunctive sequence[10] introduces the annelated lactone portion as two fragments; the three carbon α-methylene lactone portion (R = H) would be introduced as 2 C (from the phosphonoacetate) + 1 C (from formaldehyde) units, for example. In addition, we anticipated that the sequence would be stereoselective in the formation of a *syn*-fused tetrahydrobenzofuran-2,5-dione (i.e., in the formation of bicycle **8**, $n = 1$).

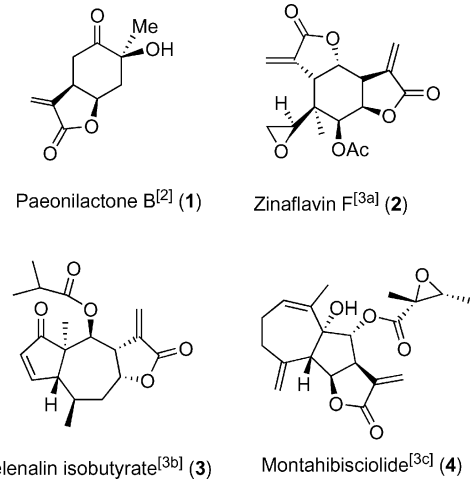

Figure 1. Representative α-alkylidene-γ-butyrolactone natural products.

The success of this approach has been reported in a preliminary communication.[11] Herein, we give a full account of the development and optimisation of this telescoped intramolecular Michael/olefination (TIMO) sequence and discuss investigations to establish its scope, limitations and applications. In addition, a novel variant involving a palladium π-allyl trapping–HWE olefination sequence is discussed. Finally, the application of the TIMO sequence to prepare (+)-paeonilactone B 1 is described.

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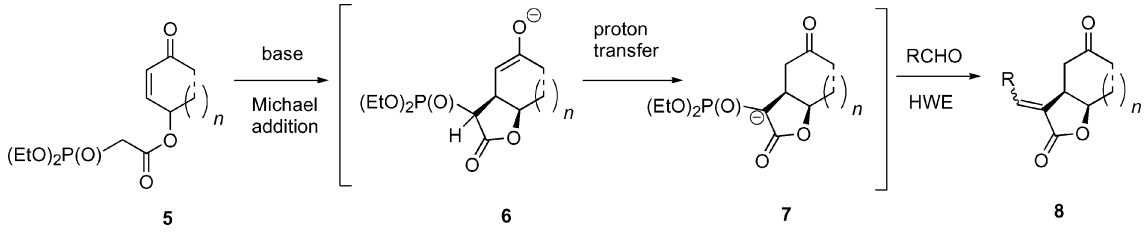


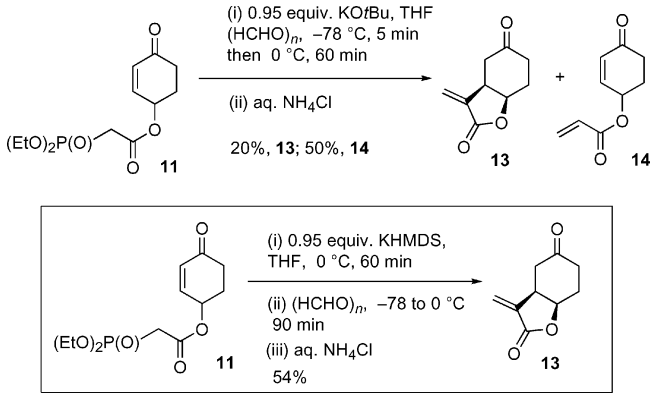
Scheme 1.

Proof of Principle Studies and Optimisation

In order to assess the viability of the TIMO approach, keto–phosphonate **11** was prepared by coupling of readily available 4-hydroxy-2-cyclohexenone (**9**)[12] with commercially available diethyl phosphonoacetic acid (**10**) using propanephosphonic acid anhydride (T3P®)[13] as shown in Scheme 2.

When keto phosphonate **11** was treated with KO*t*Bu in THF, the expected Michael adduct **12** was obtained in 50% yield (Scheme 2). This moderate yield was attributed to purification difficulties; the reaction appeared to go to completion by TLC analysis but the highly polar phosphonyl lactone proved to be very difficult to isolate. Consequently, optimisation, in terms of reaction conditions, was unrewarding [although these studies did identify KHMDS and potassium 3,7-dimethyl-3-octylate (KDMO) as further suitable bases for this transformation]. With phosphonate **12** in hand, the key HWE reaction was explored: treatment of phosphonate **12** with KO*t*Bu in THF, then paraformaldehyde, gave α-methylene-γ-butyrolactone product **13** in good yield (Scheme 2). It was soon established that **13** was highly base sensitive; indeed, **13** was not observed when the HWE reaction was performed with 1.2 equiv. of base, and exposure of **13** to 0.1 equiv. of KO*t*Bu in THF caused rapid degradation. Consequently, the use of a substoichiometric quantity of base (0.95 equiv.) was adopted and this procedure gave product **13** in 83% yield.

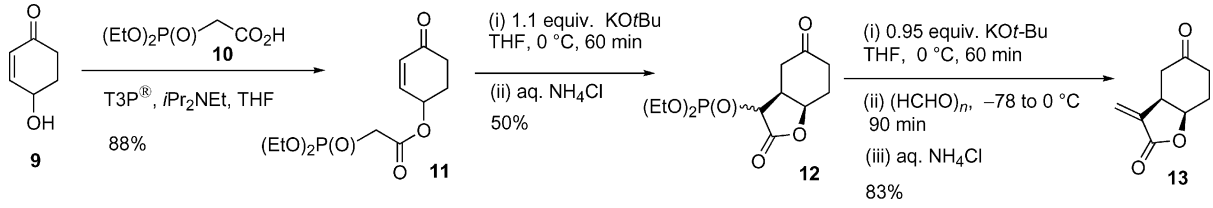
Next, one-pot versions were explored (Scheme 3). We first treated keto–phosphonate **11** with KO*t*Bu in THF in the presence of paraformaldehyde. This procedure successfully produced α-methylene lactone product **13** but only in 20% yield, with the major product being acrylate **14** (50%) resulting from HWE olefination occurring on noncyclised phosphonate **11**.



Scheme 3.

Gratifyingly, an efficient transformation was achieved by performing a sequential, one-pot process (Scheme 3). Thus, treatment of keto–phosphonate **11** with KHMDS (0.95 equiv.) in THF and then, after 60 min, cooling to –78 °C and addition of paraformaldehyde, produced the expected α-methylene lactone **13** directly in 54% overall yield.

Encouraged by this validation of the TIMO strategy, we sought to optimise this lead result through variation in base, solvent, temperature and formaldehyde source (Table 1). It transpired that the choice of base was fundamental to the success of the reaction sequence. Potassium [and to a lesser extent, sodium (Entry 5)] alkoxides efficiently promoted the required reaction (Entries 3 and 6), whereas LiO*t*Bu and $Ba(OH)_2$ were ineffective. The strong phosphazene base, *tert*-butyliminotris(dimethylamino)-phosphorane (P1-*t*Bu), was only moderately effective (Entry 7) and organic bases such as MTBD and DBU were unsuccessful. Notably, the HWE reaction is at its most efficient with user-friendly paraformaldehyde (Entry 3),



Scheme 2.

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Table 1. Optimisation of the TIMO conversion of **11** into **13**.[a]

Entry	Solvent	Base	Formaldehyde source[b]	Michael[c] T [°C] / t [h]	HWE[d] T [°C] / t [h]	Yield [%]
1	THF	KHMDS	A	0 / 1	–78 to r.t. / 15	54
2	THF	KO*t*Bu	A	–78 - 0 / 4	–78 to 0 / 1.5	72
3	**THF**	**KO*t*Bu**	**A**	**0 / 1**	**–78 to 0 / 1.5**	**77**
4	THF	KO*t*Bu	A	0 / 1	–78 to r.t. / 1.5	65
5	THF	$NaOtC_5H_{11}$	A	0 / 1	–78 to r.t. / 15	11
6	THF	KDMO	A	0 / 1	–78 to r.t. / 15	47
7	THF	P1-*t*Bu	A	0 / 24	–78 to r.t. / 15	39
8	Et_2O	KO*t*Bu	A	0 / 1	–78 to 0 / 1.5	40
9	MeCN	KO*t*Bu	A	0 / 1	–78 to 0 / 1.5	63
10	CH_2Cl_2	KO*t*Bu	A	0 / 1	–78 to 0 / 1.5	46
11	THF	KO*t*Bu	B	0 / 1	–78 to 0 / 1.5	55
12	THF	KO*t*Bu	C	0 / 1	–78 to 0 / 1.5	45
13	THF	KO*t*Bu	D	0 / 1	–78 to r.t. / 1.5	–

[a] All reactions were conducted at 0.05 M. [b] A = paraformaldehyde dried with P_2O_5, B = thermally cracked paraformaldehyde, C = ethereal solution of monomeric formaldehyde,[14] D = formaldehyde generated in situ from reaction of *N*-(hydroxymethyl)phthalimide and LDA.[15] [c] Completion of Michael reaction was confirmed by TLC analysis prior to formaldehyde addition. [d] Formaldehyde source was added at –78 °C and after 15 min the reaction was warmed to 0 °C. If no reaction was observed by TLC analysis after 1 h, the reaction was warmed to r.t.

whereas more elaborate and less convenient methods[14,15] of formaldehyde generation were less successful (Entries 11–13). Consequently, it was possible to obtain **13** in 77% yield by exposure of keto–phosphonate **11** to KO*t*Bu in THF, followed by addition of paraformaldehyde (Entry 3).

This result emphasises the advantages of a one-pot process, not only is a complicated workup and purification process avoided, the overall yield is improved (77%, compared with 43% over two steps). Lactone **13** is novel although the corresponding *anti*-isomer is known.[16] To be certain of the *syn*-arrangement of **13**, an X-ray crystal structure was obtained (Figure 2).[17]

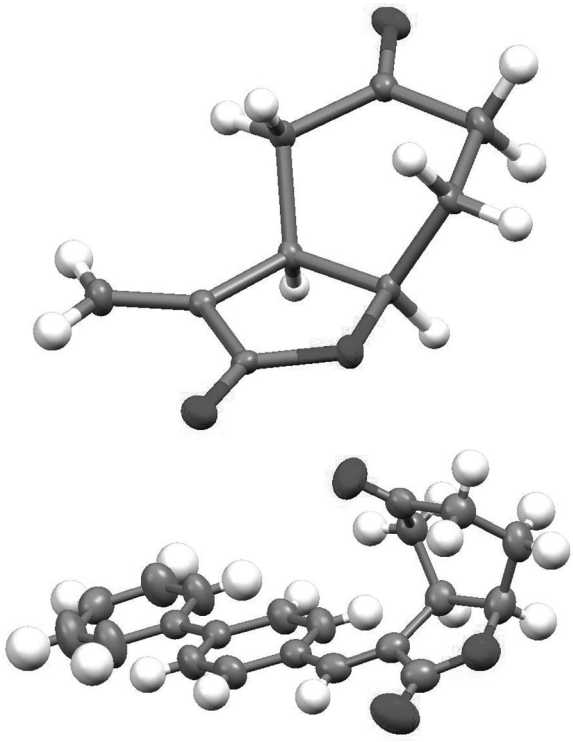

Figure 2. X-ray crystal structure of lactones **13** (top) and **20** (bottom), depicted using Mercury 1.4.

Variation of the Aldehyde Trapping Partner

Following the TIMO optimisation studies, we investigated the scope of the procedure, initially in terms of the aldehyde-trapping component (Table 2). Thus, the use of aliphatic aldehydes such as acetaldehyde and hexanal as HWE partners under the optimised conditions gave lactones **15** and **16**, respectively, in moderate yields as 1:1 mixture of *E*/*Z*-isomers (Table 2, Entries 1 and 2). The HWE process does not appear to be compatible with sterically demanding aldehydes as pivaldehyde was unreactive under these conditions.

Aromatic aldehydes were next studied as HWE coupling partners (Entries 3–6). In all of these cases KHMDS was found to be the base of choice (KO*t*Bu gave lower yields, possibly due to competing Cannizzaro reactions[18]) and heating was found to be necessary to ensure that the HWE process reached completion. With benzaldehyde (Entry 3), an unoptimised 31% yield of adduct **17** was obtained. Electron-deficient aldehydes (e.g., trifluoromethylbenzaldehyde) were investigated next and, surprisingly, were not successful partners in the TIMO sequence (again, possibly due to Cannizzaro processes). However, electron-rich aldehydes proved more successful (Table 2, Entries 4–6). In the three examples explored, reasonable, unoptimised yields of expected adducts **18**, **19** and **20** were obtained, exclusively as the *E*-isomers. Biphenyl adduct **20** gave crystals suitable for X-ray analysis[19] and this confirmed the *syn*-ring junction and the *E*-configuration of the alkene (Figure 2).

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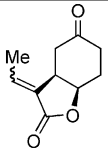
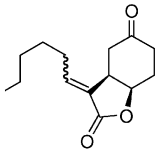
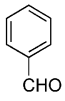
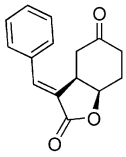
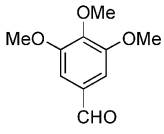
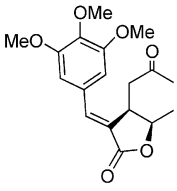
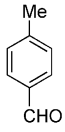
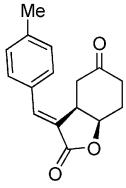
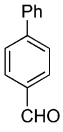
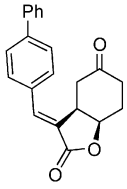
Table 2. Scope of the TIMO reaction – aldehyde coupling partners.[a]

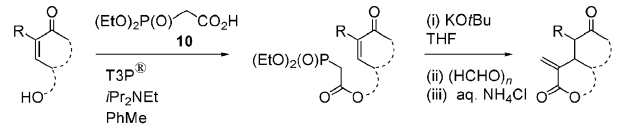
Entry	Aldehyde	Product	HWE Conditions	Yield [%]
1	MeCHO	 **15**	[b]	60[d]
2	$Me(CH_2)_4CHO$	 **16**	[b]	35[d]
3[e,g]		 **17**	[c]	31[f]
4[e,g]		 **18**	[c]	60[f]
5[e]		 **19**	[c]	48[f]
6[e]		 **20**	[c]	55[f]

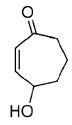
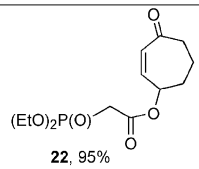
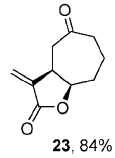
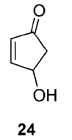
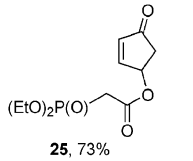
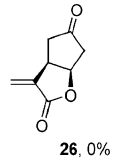
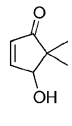
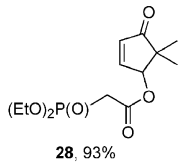
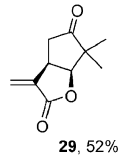
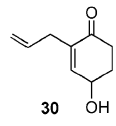
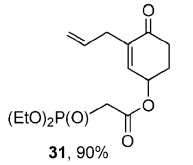
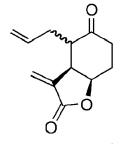
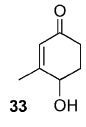
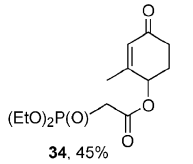
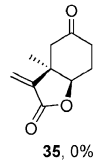
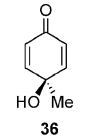
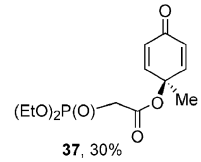
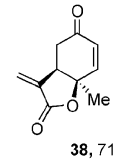
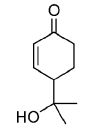
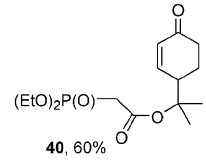
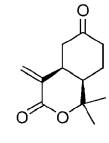
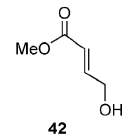
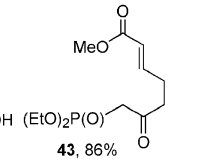
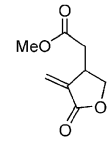
[a] Unless stated, the fist step (Michael addition) was performed with 0.95 equiv. of KO*t*Bu for 1 h at 0 °C. [b] –78 to 0 °C, 1 h. [c] –78 to 0 °C, 15 h, then reflux. [d] 1:1 *E*/*Z* mixture. [e] KHMDS (0.95 equiv.) was used in place of KO*t*Bu. [f] >95:<5 *E*/*Z*. [g] Use of KO*t*Bu gave considerably lower yields (**17**, 22%; **18**, 23%).

Variation of the γ-Hydroxy Enone Substrate

Studies were also carried out to evaluate the scope of the γ-hydroxy enone substrate (Table 3). As can be seen, the ring size was investigated first. Thus (Entry 1), hydroxycycloheptenone **21** was efficiently converted into keto–phos-

Table 3. Scope of the TIMO reaction – hydroxy-enone components.[a]



Entry	Substrate	Phosphonate	HWE conditions	Product
1[b]	 **21**	 **22**, 95%	[d]	 **23**, 84%
2	 **24**	 **25**, 73%	[e]	 **26**, 0%
3[b]	 **27**	 **28**, 93%	[d]	 **29**, 52%
4	 **30**	 **31**, 90%	[e]	 **32**, 84%[f]
5	 **33**	 **34**, 45%	n/a	 **35**, 0%
6	 **36**	 **37**, 30%	[e]	 **38**, 71%
7[c]	 **39**	 **40**, 60%	[e]	 **41**, 75%
8	 **42**	 **43**, 86%	[d]	 **44**, 73%

[a] Unless stated, Michael addition was performed with 0.95 equiv. of KO*t*Bu for 1 h at 0 °C. [b] Michael addition performed overnight at r.t. [c] Michael addition performed at 70 °C, 5 h. [d] –78 °C, 2 h then r.t. [e] –78 to 0 °C, 1 to 1.5 h. [f] 3:1 *anti*/*syn* diastereomers.

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phonate **22** which, in turn, underwent the TIMO sequence in excellent yield, producing the cycloheptanone-annelated product **23**; once again, the telescoped process was far more efficient than the corresponding two-step sequence (84% vs. 22%). The *syn*-ring junction assignment was based on coupling constant analysis (J = 7.9 Hz; for related systems[20] the *syn*-ring junction isomer exhibited J = 8.6 Hz, the *anti* J = 10.7 Hz).

Moving on to the corresponding cyclopentene analogue **24** gave a less successful outcome (Entry 2). Adduct **25** was prepared without problem but unfortunately the TIMO sequence did not produce the expected α-methylene lactone **26**. It appeared that the attempted Michael addition step failed, possibly due to β-elimination of the acyl substituent (this is known to be facile for related 3-acyloxycyclopentenones under basic conditions[21]). Support for this hypothesis was obtained when the corresponding TIMO sequence on 5,5-dimethyl analogue **27** was investigated (Entry 3). This proceeded as expected with keto–phosphonate **28** giving γ-butyrolactone **29** in 52% unoptimised yield.

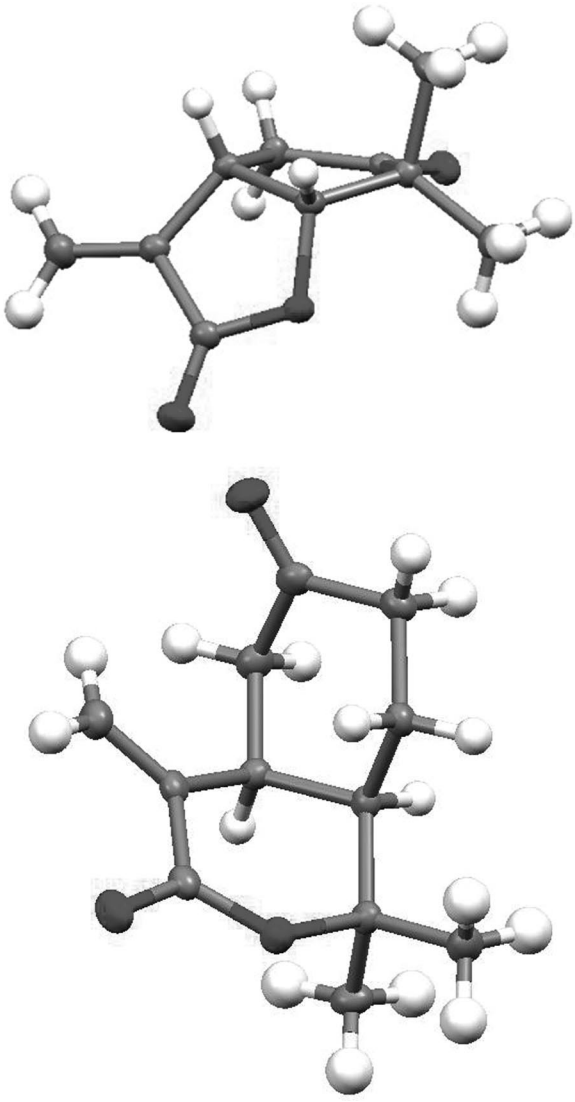

Figure 3. X-ray crystal structure of γ-butyrolactones **29** (top) and **41** (bottom), depicted using Mercury 1.4.

Substitution at the ring positions was studied next (Entries 4–6). In terms of substituent compatibility at the alkene moiety, the TIMO reaction of α-allylated enone **30** was explored and under standard conditions, phosphonate **31** gave the expected bicycloadduct **32** in good yield as a 3:1 diastereomeric mixture (Entry 4). However, the corresponding β-methylated enone **34** failed to undergo the intramolecular Michael reaction even under forcing conditions (Entry 5). In view of the literature examples concerning problematic Michael additions to β-methylcyclohexenone,[22] this is unsurprising. As shown in Entry 6, substitution is possible at the hydroxy centre, however. Thus, tertiary alcohol **36** was converted into phosphonate **37** and the TIMO sequence proceeded successfully giving the highly functionalised bicyclic adduct **38**.

Next, variation in the lactone size was explored (Entry 7). Hence it was shown that alcohol **39** was readily converted into adduct **40** and this, in turn, underwent the TIMO process giving the six-membered bicyclic lactone **41** in 75% yield, again exclusively as the *syn*-diastereoisomer. In this case, the Michael addition was comparatively slow and more forcing conditions were required. Finally, in this section, an acyclic example was investigated (Entry 8). Acyclic allylic alcohol **42** was converted into keto–phosphonate **43** and this underwent the TIMO sequence to produce monosubstituted α-methylene lactone **44** in good yield.

Compounds **29**[23] and **41**[24] were crystalline and their structures were also confirmed by X-ray crystallography (Figure 3).

Palladium-Catalysed π-Allyl Variant

With the TIMO sequence established, we briefly sought to demonstrate the wider applicability of this telescoped chemistry, i.e., by trapping the keto–phosphonate anion using alternative intramolecular electrophiles, followed by HWE elaboration.[25] Given the ready availability of the cyclisation precursors, we decided to study the process illustrated in Scheme 4 involving the intermediacy of a π-allyl palladium complex **46** generated from the corresponding allylic acetate **45**; ring closure to **47** and subsequent HWE olefination should give rise to α-methylene-γ-butyrolactones **48**.

Initial investigation (Scheme 5) focused on acetate **49**, readily derived as a 1:1 mixture from the previously prepared keto–phosphonate **11** by Luche reduction and acetylation. Treatment of **49** with KO*t*Bu and 5 mol-% $Pd(PPh_3)_4$ at reflux in THF, followed by cooling to room temperature and addition of paraformaldehyde, gave the desired α-methylene-γ-butyrolactone **51** in just 13% yield as a 3:1 mixture of diastereoisomers. Both *syn*-[26] and *anti*-[27] **51** have been described in the literature and comparison of the high-field proton NMR spectroscopic data of the mixture with those published indicated that *syn*-**51** predominated. The low

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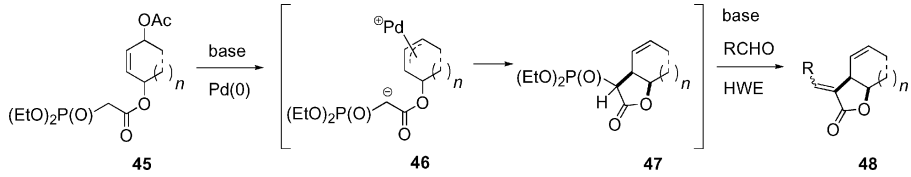
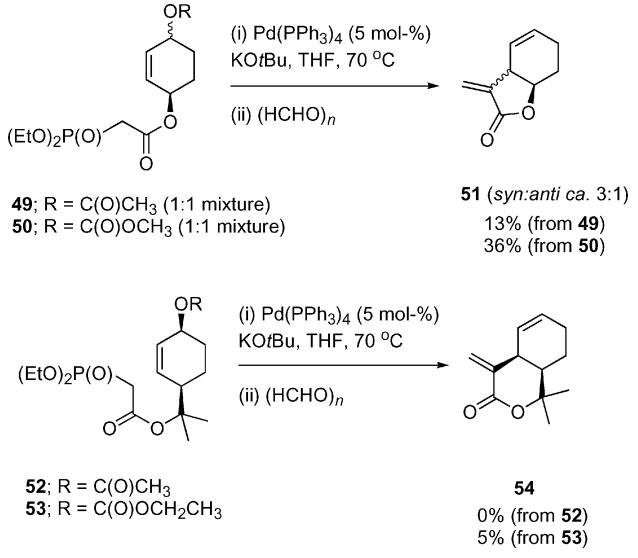


Scheme 4.

yielding nature of the reaction of **49** was attributed to the similar leaving group abilities of the two allylic substituents, i.e., the acetate *and* the phosphonoacetate groups, thereby allowing palladium-catalysed π-allyl formation at either end of the molecule (byproduct analysis substantiated this suggestion). In view of this hypothesis, we went on to prepare the corresponding allylic carbonate **50** (Scheme 5) in order to increase the scope for catalyst discrimination between the allylic substituents. Gratifyingly, treatment of **50** under the conditions employed previously gave the mixture of methylene lactones **51** in a greatly improved (if still modest) 36% yield. With this promising result in hand, we undertook a thorough study of base, catalyst and temperature effects upon this one-pot process.[28] Frustratingly, further optimisation was not achieved. However, this preliminary study does indicate the potential of the palladium procedure for the preparation of *anti*-fused lactones.



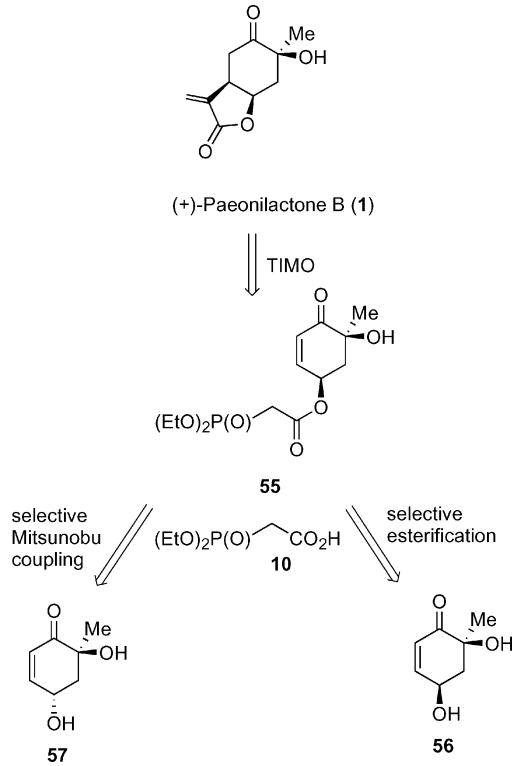
Scheme 5.

In order to completely remove the possibility of competitive π-allyl formation, we prepared cyclisation precursors **52** and **53**. Unfortunately, treatment of acetate **52** with KO*t*Bu and 5 mol-% $Pd(PPh_3)_4$, followed by addition of paraformaldehyde failed to promote the desired transformation with no lactone **54** being observed (recovered starting material and the corresponding alcohol were obtained). With carbonate **53**, however, a very low yield (5%) of desired cyclohexene adduct **54** was obtained. We are unable to satisfactorily explain these disappointing results, which are particularly galling given the success of related cyclisations described in the literature.[29]

Use of the TIMO Sequence to Prepare (+)-Paeonilactone B 1

Following the model studies described, our attention turned to a natural product target with which to validate the utility of the TIMO sequence. Paeony root has a long history of use in Chinese and Japanese medicine for pain relief and, in 1985, paeonilactones A, B and C were isolated from the root of *Paeonia Albiflora* Pallas.[2] (+)-Paeonilactone B (**1**)[2] was chosen for our study as it has been prepared in racemic[30] and optically pure[31] form but the lengthy routes attest to the problems associated with the preparation of such a densely functionalised molecule.

Retrosynthetic analysis (Scheme 6) indicated that the ideal TIMO precursor for paeonilactone B would be keto–phosphonate **55**, with alcohol **56** as the starting material.



Scheme 6.

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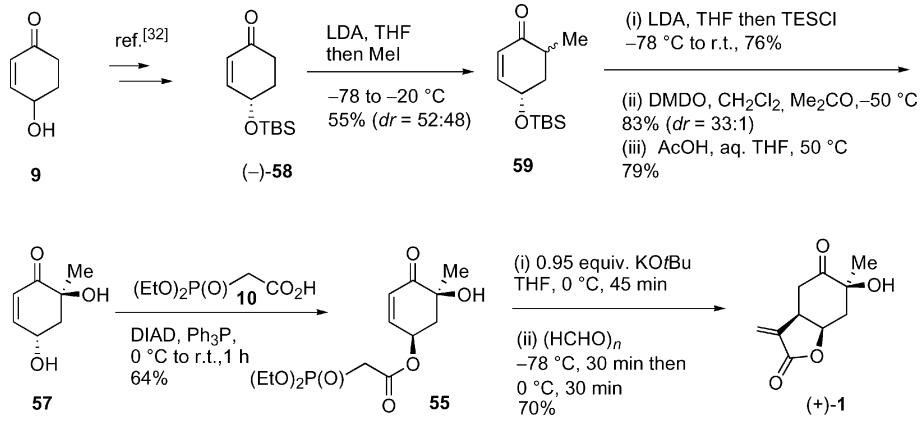

Scheme 7.

However, given that the stereoisomeric alcohol **57** is more accessible (see later), an alternative approach would involve the Mitsunobu coupling of alcohol **57** and diethyl phosphonoacetic acid **10** with consequent inversion of stereochemistry (Scheme 6).

Following the analysis above, diol **57** was obtained in enantiomerically pure form using the route shown in Scheme 7. The Novozyme 435 procedure described by Roberts et al.[32] was employed to convert racemic alcohol **9** into (–)-**58**. Kinetic enolate generation followed by methylation gave **59** as a mixture of diastereomers (the 55% yield reflecting the ease with which aromatisation occurs in these systems). Silyl enol ether formation followed by a modified substrate-controlled, diastereoselective Rubottom epoxidation (DMDO)[33] and deprotection gave required *anti*-diol **57** in an efficient three-step process. NOE experiments on *anti*-diol **57** (and its *syn*-isomer **56**) were employed to confirm the relative stereochemistry of the diol substituents and thus confirm the highly stereoselective (*dr* = 33:1) nature of the sequence; it is noteworthy that the use of DMDO is crucial to obtain high diastereoselectivity in the enol ether epoxidation process (*m*-CPBA gave a 3:1 ratio at best).

With *anti*-diol **57** in hand, we were in a position to explore the endgame. Mitsunobu coupling of alcohol **57** and diethyl phosphonoacetic acid (**10**), in the presence of triphenylphosphane/DIAD, proceeded as predicted with consequent inversion of stereochemistry to give coupled product **55** in a respectable yield (notably, in the presence of the unprotected tertiary alcohol). This appears to be the first example of the use of diethyl phosphonoacetic acid (**10**) in a Mitsunobu coupling reaction. Keto–phosphonate **55** was then subjected to the TIMO cascade using KO*t*Bu in THF at 0 °C, then cooled to –78 °C and treated with paraformaldehyde. We were delighted to observe that this procedure delivered (+)-paeonilactone B (**1**) in 70% yield. Authenticity was confirmed spectroscopically, by HRMS and by comparison of m.p. (86–87 °C, ref.[2] 88–89 °C) and $[\alpha]_D$ = [+23.8 (*c* = 1.04, MeOH), ref.[2] +23.2]. The value of the telescoped intramolecular Michael addition/proton transfer/HWE olefination sequence can be gauged by the brevity of this route to (+)-paeonilactone B (**1**) [6 steps, 13% overall yield from the known[32] and readily accessible, enantiopure starting material (–)-**58**].

In summary, a novel telescoped intramolecular Michael addition/proton transfer/HWE olefination (TIMO) sequence has been developed to provide rapid access to α-alkylidene-γ-butyrolactones commencing from γ-hydroxy-α,β-unsaturated ketones. This methodology has been applied to prepare a range of model tetrahydrobenzofuran-2,5-diones, as well as examples of the corresponding cyclohepta- and cyclopenta-annelated systems and a monocyclic example, in addition, preliminary experiments have been described which illustrate a palladium-catalysed variant proceeding by way of a π-allyl intermediate. Finally, validation of the TIMO methodology was achieved when it was employed as the cornerstone of an extremely short synthesis of the natural product, (+)-paeonilactone B (**1**), in enantiomerically pure form. We are currently exploring further variants of the basic TIMO methodology[25] and investigating its utility for the preparation of more complex natural product targets.

Experimental Section

General Experimental: ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with a JEOL EXC400 spectrometer operating at 400, 100 and 162 MHz, respectively. All spectroscopic data was acquired at 295 K. Chemical shifts are quoted in parts per million (ppm) using the residual solvent peak as an internal standard [^{1}H NMR 7.26 ppm for $CHCl_3$ and ^{13}C NMR 77.0 ppm for $CDCl_3$, ^{1}H NMR 4.84 (s), 3.31 (quintuplet) and ^{13}C NMR 49.05 (septuplet) for D_3COD]. Coupling constants (*J*) are reported in Hz. Multiplicity abbreviations used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br. (broad). Signal assignments were accomplished by analysis of COSY, NOESY, HSQC and HMBC experiments where necessary. Infrared spectra were recorded with a ThermoNicolet IR100 spectrometer using NaCl plates. Low- and high-resolution mass spectra were obtained for all novel compounds. Electrospray ionization (ESI) and chemical ionization (CI, using ammonia gas) were measured with a Micromass Autospec spectrometer. Melting points were determined using a Gallenkamp apparatus and are uncorrected. Thin-layer chromatography (TLC)

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was performed using Merk silica gel $60F_{254}$ pre-coated aluminum-backed plates. The compounds were visualized using UV light (254 nm) and $KMnO_4$ or anisaldehyde. Flash chromatography was performed at medium pressure using slurry packed Fluka silica gel 35–70 μm, 60 Å with the eluant specified. Petroleum ether is the fraction with b.p. 40–60 °C. Tetrahydrofuran was distilled from sodium–benzophenone ketyl immediately before use. Anhydrous toluene and dichloromethane were obtained from an MBraun SPS solvent purification system. Water refers to deionised water. Except where specified, all reagents were purchased from commercial sources and were used without further purification. Paraformaldehyde was dried with P_2O_5 in a vacuum dessicator. *N*,*N*-Diisopropylethylamine was distilled from calcium hydride and stored over potassium hydroxide. The following cyclisation precursors were prepared following the published procedures (or closely related procedures) as follows: **9**,[12] **21**,[34] **24**,[35] **30**,[36] **33**,[37] **36**,[38] **39**[39] and **42**.[40]

General Procedure 1: Preparation of Phosphonoacetate Esters

4-Oxocyclohex-2-enyl Diethoxyphosphorylacetate (11): T3P® in toluene (50% w/w, 15.91 g, 25.00 mmol) was added slowly to a stirred solution of 4-hydroxy-2-cyclohexenone (**9**;[12] 2.16 g, 19.23 mmol), diethylphosphonoacetic acid (**10**; 3.24 mL, 20.19 mmol) and *N*,*N*-diisopropylethylamine (8.71 mL, 49.99 mmol) in toluene (100 mL). The resulting solution was stirred for 2 d at room temperature then diluted with water (100 mL) and extracted with EtOAc (2 × 100 mL). The combined organics were washed with 10% aqueous HCl (50 mL), saturated aqueous $NaHCO_3$ (50 mL), saturated brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The resulting crude residue was purified by passing through a pad of SiO_2, eluting with EtOAc, to afford **11** (4.89 g, 88%) as a yellow oil. R_f = 0.22 (EtOAc). IR (neat): $\tilde{\nu}$ = 2983, 2936, 2910, 1736, 1686, 1445, 1388, 1371, 1318, 1267, 1207, 1164, 1114, 1050, 1025, 971, 913, 875, 863, 837, 786 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.84 (ddd, J = 10.2, 2.8, 1.4 Hz, 1 H, 2-H), 6.10 (ddd, J = 10.3, 1.8, 0.8 Hz, 1 H, 3-H), 5.61 (ddt, J = 6.8, 2.8, 2.0 Hz, 1 H, 1-H), 4.17 (qd, J = 8.1, J_{HP} = 6.7 Hz, 4 H, OCH_2), 3.00 (d, J_{HP} = 21.6 Hz, 2 H, PCH_2), 2.51 (dt, J = 17.0, 5.0 Hz, 1 H, 5-H), 2.48–2.33 (m, 2 H, 5- and 6-H), 2.17–2.08 (m, 1 H, 6-H), 1.34 (td, J = 7.1, J_{HP} = 0.4 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.2, 165.7 (d, J_{CP} = 6.3 Hz), 147.1, 131.4, 68.7, 62.7 (d, J_{CP} = 6.4 Hz), 34.5, 34.2 (d, J_{CP} = 133.5 Hz), 28.2, 16.0 (d, J_{CP} = 6.2 Hz) ppm. $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$): δ = 19.7 ppm. MS (CI, NH_3): m/z (%) = 291 (11) $[M + H]^+$, 308 (56) $[M + NH_4]^+$. HRMS (EI): calcd. for $C_{12}H_{23}NO_6P$ $[M + NH_4]^+$ 308.1263; found 308.1266 (δ =1.0 ppm error).

Diethyl 2,5-Dioxooctahydrobenzofuran-3-yl-phosphonate (12): Potassium *tert*-butoxide (3.88 M solution in THF, 130 μL, 0.55 mmol) was added dropwise to a stirred solution of **11** (168 mg, 0.58 mmol) in THF (10 mL) at 0 °C under argon. The resulting solution was stirred for 1 h at 0 °C then quenched with aqueous saturated NH_4Cl (1.5 mL), dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by passing through a pad of SiO_2, eluting with EtOAc/MeOH, 9:1, to afford **12** (84 mg, 50%) as a yellow oil. R_f = 0.33 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2982, 2931, 1770, 1718, 1249, 1163, 1021, 973 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.00 (ddd, J = 9.9, 7.5, 4.9 Hz, 1 H, 7a-H), 4.22–4.09 (m, 4 H, OCH_2), 3.29 (dddd, J_{HP} = 22.9 Hz, J = 14.3, 7.7, 4.3 Hz, 1 H, 3a-H), 2.78 (dd, J_{HP} = 24.7 Hz, J = 4.3 Hz, 1 H, 3-H), 2.56 (dd, J = 15.8, 6.6 Hz, 1 H, 4-H), 2.43–2.34 (m, 2 H, 6-H), 2.28 (t, J = 5.9 Hz, 1 H, 4-H), 2.24–2.19 (m, 2 H, 7-H), 1.30 (td, J = 7.1 Hz, J_{HP} = 1.5 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 170.4 (d, J_{CP} = 3.6 Hz), 76.0 (d, J_{CP} = 3.9 Hz), 63.9 (d, J_{CP} = 6.8 Hz), 63.0 (d, J_{CP} = 6.8 Hz), 46.7 (d, J_{CP} = 138.6 Hz), 41.7 (d, J_{CP} = 9.6 Hz), 36.0 (d, J_{CP} = 2.2 Hz), 33.9, 25.8, 16.2 (d, J_{CP} = 4.4 Hz), 16.1 (d, J_{CP} = 4.4 Hz) ppm. $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$): δ = 19.6 ppm. MS (ESI): m/z (%) = 291 (100) $[M + H]^+$, 313 (28) $[M + Na]^+$. HRMS (EI): calcd. for $C_{12}H_{20}O_6P$ $[M + H]^+$ 291.0992; found 291.0998 (δ =2.1 ppm error).

General Procedure 2: Preparation of α-Methylene-γ-butyrolactones by TIMO

***syn*-3-Methylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (13):** Potassium *tert*-butoxide (3.88 M solution in THF, 206 μL, 0.798 mmol) was added dropwise to a stirred solution of **11** (244 mg, 0.841 mmol) in THF (10 mL) at 0 °C under argon. The resulting solution was stirred for 1 h at 0 °C then cooled to –78 °C. Paraformaldehyde (252 mg, 8.41 mmol) was added and the reaction was stirred for 15 min then warmed to 0 °C and stirred for 2 h. The reaction was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography, eluting with petrol/EtOAc, 2:3, to afford **13** (108 mg, 77%) as a white solid. M.p. 107.5–108.5 °C. R_f = 0.50 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2969, 2947, 2908, 1761, 1710, 1660, 1475, 1423, 1266, 1142, 1009, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, J = 2.9 Hz, 1 H, =CH), 5.62 (d, J = 2.7 Hz, 1 H, =CH), 5.00 (ddd, J = 8.6, 4.2, 1.6 Hz, 1 H, 7a-H), 3.59 (ddddd, J = 11.9, 8.6, 6.3, 2.9, 2.7 Hz, 1 H, 3a-H), 2.70 (dd, J = 16.4, 6.3 Hz, 1 H, 4-H), 2.57 (dd, J = 16.4, 5.0 Hz, 1 H, 4-H), 2.33–2.16 (m, 4 H, 6- and 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 169.8, 137.6, 124.4, 74.4, 41.1, 35.5, 33.2, 25.9 ppm. MS (ESI): m/z (%) = 167 (100) $[M + H]^+$, 184 (12) $[M + NH_4]^+$, 189 (58) $[M + Na]^+$. HRMS: calcd. for $C_9H_{11}O_3$ $[M + H]^+$ 167.0703; found 167.0706 (δ =1.8 ppm error).

(3*E*)- and (3*Z*)-*syn*-3-Ethylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (15): Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 34 μL, 0.13 mmol), **11** (40 mg, 0.14 mmol) and freshly distilled acetaldehyde (12.0 μL, 0.21 mmol) (the aldehyde was added by syringe pump over 3 h in order to minimise self-condensation and the reaction was then stirred at room temperature overnight) in THF (2.8 mL) gave **15** (14 mg, 60%, 1:1 *E*/*Z*) as a colourless oil. R_f = 0.50 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2958, 1746, 1729, 1713, 1674, 1443, 1357, 1216, 1141, 1028, 1009, 940 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 [qd, J = 7.3, 2.4 Hz, 1 H, =CH(*Z*)], 6.16 [qd, J = 7.3, 2.4 Hz, 1 H, =CH(*E*)], 4.94–4.87 [m, 2 H, 7a-H(*E*+*Z*)], 3.63–3.56 [m, 1 H, 3a-H(*Z*)], 3.55–3.48 [m, 1 H, 3a-H(*E*)], 2.67 [ddd, J = 15.8, 6.7, 2.9 Hz, 2 H, 4-H(*E*+*Z*)], 2.53–2.47 [m, 1 H, 4-H(*E*)], 2.43–2.35 [m, 1 H, 4-H(*Z*)], 2.33–2.21 [m, 2 H, 6-H(*E*+*Z*)], 2.20–2.16 [m, 2 H, 7-H(*E*+*Z*)], 1.89 [dd, J = 7.3, 1.6 Hz, 6 H, CH_3(*E*+*Z*)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 209.5, 170.3, 169.7, 141.8, 138.9, 130.2, 128.2, 74.1, 73.7, 41.8, 40.4, 36.9, 34.8, 33.34, 33.33, 26.1, 25.6, 14.8, 13.8 ppm. MS (CI, NH_3): m/z (%) = 180 (100) $[M + H]^+$. HRMS: calcd. for $C_{10}H_{16}NO_3$ $[M + NH_4]^+$ 198.1129; found 198.1130 (δ =0.8 ppm error).

(3*E*)- and (3*Z*)-*syn*-3-Hexylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (16): Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 126 μL, 0.49 mmol), **11** (141 mg, 0.48 mmol) and freshly distilled hexanal (300 μL, 2.43 mmol) in THF (6.7 mL) gave **16** (36 mg, 35%, 1:1 *E*/*Z*) as a colourless oil. R_f = 0.63 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2957, 2929, 2859, 1752, 1720, 1671, 1371, 1344, 1233, 1187, 1138, 1026, 915, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.79 [td, J = 7.4, 2.4 Hz, 1 H, hexyl 1-H(*Z*)], 6.16 [td, J = 7.8, 2.4 Hz, 1 H, hexyl 1-H(*E*)], 4.95–4.85 [m, 4 H, 7a-H(*E*+*Z*)], 3.58–3.49 [m, 2 H, 3a-

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H(*E*+*Z*)], 2.70 [dddd, *J* = 15.6, 7.5, 4.0, 2.1 Hz, 2 H, 4-H(*E*+*Z*)], 2.63 [ddd, *J* = 15.6, 7.6, 6.1 Hz, 2 H, 4-H(*E*+*Z*)], 2.54–2.37 [m, 4 H, 6-H(*E*+*Z*)], 2.35–2.12 [m, 8 H, hexyl 2-H and 7-H(*E*+*Z*)], 1.48–1.23 [m, 12 H, hexyl 3-, 4- and 5-H(*E*+*Z*)], 0.89–0.83 [m, 6 H, hexyl 6-H(*E*+*Z*)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9, 208.8, 170.1, 169.1, 147.0, 143.9, 128.6, 126.9, 74.1, 73.7, 42.0, 41.0, 37.1, 35.2, 33.6, 33.5, 31.4, 31.3, 29.5, 28.5, 28.0, 27.4, 26.4, 25.9, 22.4, 22.3, 13.9, 13.8 ppm. MS (ESI): *m*/*z* (%) = 237 (97) $[M + H]^+$, 254 (100) $[M + NH_4]^+$. HRMS: calcd. for $C_{14}H_{21}O_3$ $[M + H]^+$ 237.1488; found 237.1485 (δ =1.0 ppm error).

General Procedure 3: Preparation of Substituted α-Arylidene-γ-butyrolactones

(3*E*)-*syn*-3-Benzylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (17): KHMDS (0.5 M solution in toluene, 0.66 mL, 0.327 mmol) was added dropwise to a stirred solution of **11** (100 mg, 0.344 mmol) in THF (7 mL) at –78 °C under argon. After 10 min the reaction was warmed to 0 °C and stirred for 1 h. A solution of benzaldehyde (175 μL, 1.72 mmol) in THF (1 mL) was added and the reaction was warmed to room temperature overnight then heated to reflux for 1 h. The mixture was concentrated in vacuo, diluted with water (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash chromatography, eluting with petrol/EtOAc, 1:1, to afford **17** (26 mg, 31%), as a pale yellow solid. M.p. 130.5–131 °C. R_f = 0.5 (EtOAc). IR (neat): $\tilde{\nu}$ = 2960, 1739, 1710, 1650, 1239, 1188, 1030 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 2.5 Hz, 1 H, =CH), 7.47–7.40 (m, 5 H, Ar-H), 5.01–4.95 (m, 1 H, 7a-H), 4.06 (ddd, *J* = 15.0, 7.0, 2.5 Hz, 1 H, 3a-H), 2.72 (dd, *J* = 16.0, 7.0 Hz, 1 H, 4-H), 2.50 (dd, *J* = 16.0, 7.0 Hz, 1 H, 4-H), 2.48–2.41 (m, 1 H, 6-H), 2.36–2.27 (m, 3 H, 6- and 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 171.1, 138.8, 133.1, 130.4, 129.9, 129.1, 127.5, 74.1, 38.8, 36.3, 33.4, 25.9 ppm. MS (CI): *m*/*z* (%) = 260 (100) $[M + NH_4]^+$, 243 (95) $[M + H]^+$. HRMS: calcd. for $C_{15}H_{18}NO_3$ $[M + NH_4]^+$ 260.1287; found 260.1288 (δ =0.4 ppm error).

(3*E*)-*syn*-3-(3,4,5-Trimethoxybenzylidene)tetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (18): Following general procedure 3, KHMDS (0.5 M solution in toluene, 0.38 mL, 0.19 mmol) and **11** (50 mg, 0.17 mmol) in THF (2.4 mL) and 3,4,5-trimethoxybenzaldehyde (169 mg, 0.86 mmol) in THF (1 mL) gave **18** (34 mg, 60%) as a yellow oil. R_f = 0.51 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 3057, 2962, 2940, 2841, 1747, 1714, 1652, 1580, 1505, 1419, 1334, 1242, 1130, 737 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 2.4 Hz, 1 H, =CH), 6.66 (s, 2 H, Ar-H), 5.48 (ddd, *J* = 9.6, 7.4, 2.4 Hz, 1 H, 7a-H), 4.01 (dtd, *J* = 14.8, 6.80, 2.4 Hz, 1 H, 3a-H), 3.88 (s, 3 H, OMe), 3.85 (s, 6 H, OMe), 2.74 (dd, *J* = 15.8, 6.8 Hz, 1 H, 4-H), 2.59 (dd, *J* = 15.8, 6.8 Hz, 1 H, 4-H), 2.49–2.41 (m, 1 H, 6-H), 2.35–2.29 (m, 3 H, 6- and 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 171.6, 153.8, 140.4, 139.2, 128.7, 126.4, 107.7, 74.2, 60.9, 56.1, 38.6, 36.1, 33.0, 25.5 ppm. MS (ESI): *m*/*z* (%) = 333 (100) $[M + H]^+$, 355 (17) $[M + Na]^+$. HRMS: calcd. for $C_{18}H_{21}O_6$ $[M + H]^+$ 333.1333; found 333.1335 (δ =0.7 ppm error).

(3*E*)-*syn*-3-(4-Methylbenzylidene)tetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (19): Following general procedure 3, KHMDS (0.5 M solution in toluene, 0.38 mL, 0.19 mmol) and **11** (50 mg, 0.17 mmol) in THF (2.4 mL) and 4-methylbenzaldehyde (103 mg, 0.86 mmol) in THF (1 mL) gave **19** (21 mg, 48%) as a white solid. M.p. 123.5–124.5 °C. R_f = 0.24 (petrol/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 2921, 1746, 1716, 1648, 1607, 1346, 1236, 1178 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 2.0 Hz, 1 H, =CH), 7.34 (d, *J* = 8.0 Hz, 2 H, Ar 2- and 6-H), 7.22 (d, *J* = 8.0 Hz, 2 H, Ar 3- and 5-H), 4.98 (ddd, *J* = 7.5, 5.0, 5.0 Hz, 1 H, 7a-H), 4.05 (ddd, *J* = 14.5, 7.5, 2.0 Hz, 1 H, 3a-H), 2.73 (dd, *J* = 16.0, 7.0 Hz, 1 H, 4-H), 2.52 (dd, *J* = 16.0, 7.5 Hz, 1 H, 4-H), 2.50–2.43 (m, 1 H, 6-H), 2.39 (s, 3 H, CH_3), 2.37–2.27 (m, 3 H, 6- and 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.8, 171.3, 141.0, 138.8, 130.3, 130.1, 129.9, 126.2, 76.7, 38.7, 36.3, 33.4, 25.9, 21.5 ppm. MS (CI): *m*/*z* (%) = 274 (100) $[M + NH_4]^+$, 257 (15) $[M + H]^+$. HRMS: calcd. for $C_{16}H_{20}NO_3$ $[M + NH_4]^+$ 274.1443; found 274.1440 (δ =1.2 ppm error).

(3*E*)-*syn*-3-(Biphenyl-4-yl-methylidene)tetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (20): Following general procedure 3, KHMDS (0.5 M solution in toluene, 0.38 mL, 0.19 mmol) and **11** (50 mg, 0.17 mmol) in THF (2.4 mL) and 4-phenylbenzaldehyde (170 mg, 0.86 mmol) in THF (1 mL) gave **20** (30 mg, 55%) as a white solid. M.p. 146–148 °C. R_f = 0.37 (petrol/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 3030, 2957, 2920, 2851, 1743, 1715, 1602, 1485, 1448, 1410, 1344, 1312, 1237, 1180, 1028, 940, 914, 840, 768, 727 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2 H, Ar 3- and 5-H), 7.60–7.64 (m, 3 H, =CH and Ar 8- and 12-H), 7.53 (d, *J* = 8.2 Hz, 2 H, Ar 2- and 6-H), 7.47 (t, *J* = 7.0 Hz, 2 H, Ar 9- and 11-H), 7.40 (t, *J* = 7.0 Hz, 1 H, Ar 10-H), 4.94–4.99 (m, 1 H, 7a-H), 4.11 (dddd, *J* = 7.4, 7.3, 7.0, 2.4 Hz, 1 H, 3a-H), 2.79 (dd, *J* = 15.9, 6.7 Hz, 1 H, 4-H), 2.58 (dd, *J* = 15.9, 7.0 Hz, 1 H, 4-H), 2.46–2.54 (m, 1 H, 7-H), 2.32–2.40 (m, 3 H, 6- and 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.5, 171.2, 143.0, 139.6, 138.2, 131.9, 130.5, 128.9, 128.0, 127.6, 127.2, 127.0, 74.3, 38.7, 36.3, 33.4, 25.8 ppm. MS (CI): *m*/*z* (%) = 336 (45) $[M + NH_4]^+$, 319 (100) $[M + H]^+$. HRMS (CI): calcd. for $C_{10}H_{13}O_4$ $[M + NH_4]^+$ 336.1600, found 336.1605 (δ =1.6 ppm error).

4-Oxocyclohept-2-enyl 2-(Diethoxyphosphoryl)acetate (22): Following general procedure 1, T3P® in toluene (50% w/w, 1.97 g, 3.09 mmol), 4-hydroxycyclohept-2-enone (**21**;[34] 300 mg, 2.38 mmol), diethylphosphonoacetic acid (**10**; 0.40 mL, 2.50 mmol) and *N*,*N*-diisopropylethylamine (1.08 mL, 6.19 mmol) in toluene (7 mL) gave **22** (690 mg, 95%) as a yellow oil. R_f = 0.38 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2984, 2938, 1735, 1672, 1395, 1266, 1112, 1023, 973 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (ddd, *J* = 12.6, 3.3, 1.2 Hz, 1 H, 2-H), 6.04 (ddd, *J* = 12.6, 2.1, 0.6 Hz, 1 H, 3-H), 5.64 (ddt, *J* = 6.8, 3.3, 2.1 Hz, 1 H, 1-H), 4.18 (dq, J_{HP} = 8.3 Hz, *J* = 7.1 Hz, 4 H, OCH_2), 3.00 (d, J_{HP} = 21.7 Hz, 2 H, PCH_2), 2.69–2.56 (m, 2 H, 5-H), 2.25–2.18 (m, 1 H, 6-H), 1.97–1.84 (m, 3 H, 6- and 7-H), 1.34 (dt, *J* = 7.1 Hz, J_{HP} = 0.3 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3, 165.0 (d, J_{CP} = 6.5 Hz), 143.5, 131.7, 73.2, 62.8 (d, J_{CP} = 6.1 Hz), 42.8, 34.4, (d, J_{CP} = 133.3 Hz), 31.5, 18.0, 16.4 (d, J_{CP} = 6.2 Hz) ppm. ^{31}P{^{1}H}NMR (162 MHz, $CDCl_3$): δ = 19.9 ppm. MS (ESI): *m*/*z* (%) = 305 (100) $[M + H]^+$, 327 (31) $[M + Na]^+$. HRMS: calcd. for $C_{13}H_{22}O_6P$ $[M + H]^+$ 305.1155; found 305.1149 (δ =2.1 ppm error).

***syn*-3-Methylidenehexahydro-2*H*-cycloheptafuran-2,5(3*H*)-dione (23):** Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 38 μL, 0.147 mmol), **22** (64 mg, 0.211 mmol) and paraformaldehyde (63 mg, 2.10 mmol) in THF gave **23** (32 mg, 84%) as a colourless oil. R_f = 0.52 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2948, 2872, 1758, 1705, 1661, 1272, 1164, 1003, 947 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (d, *J* = 2.7 Hz, 1 H, =CH), 5.70 (d, *J* = 2.4 Hz, 1 H, =CH), 4.71 (ddd, *J* = 9.5, 7.9, 3.8 Hz, 1 H, 8a-H), 3.37 (ddddd, *J* = 11.6, 7.9, 4.5, 2.7, 2.4 Hz, 1 H, 3a-H), 2.82 (dd, *J* = 13.0, 11.6 Hz, 1 H, 4-H), 2.56 (dd, *J* = 13.0, 4.5 Hz, 1 H, 4-H), 2.51 (t, *J* = 7.5 Hz, 2 H, 6-H), 2.21 (dddd, *J* = 16.9, 7.5, 3.8, 2.1 Hz, 1 H, 7-H), 2.08–1.92 (m, 2 H, 7- and 8-H), 1.65–1.54 (m, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 138.1, 123.9, 99.0, 79.8, 44.5, 43.9, 38.6, 29.9, 18.1 ppm.

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MS (ESI): *m/z* (%) = 181 (100) $[M + H]^+$, 203 (9) $[M + Na]^+$. HRMS: calcd. for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0859; found 181.0859 (δ =0.1 ppm error).

4-Oxocyclopent-2-enyl 2-(Diethoxyphosphoryl)acetate (25): Following general procedure 1, T3P® in toluene (50% w/w, 4.34 g, 13.64 mmol), 4-hydroxycyclopent-2-enone (**24**;[35] 1.03 g, 10.49 mmol), diethylphosphonoacetic acid (**10**; 1.77 mL, 11.02 mmol) and *N*,*N*-diisopropylethylamine (4.75 mL, 27.29 mmol) in THF (20 mL) gave **25** (2.11 g, 73%) as a yellow oil. R_f = 0.19 (EtOAc). IR (neat): $\tilde{\nu}$ = 2985, 1723, 1401, 1268, 1112, 1024, 972, 791 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.56 (ddd, *J* = 5.7, 2.4, 1.5 Hz, 1 H, 2-H), 6.35–6.33 (m, 1 H, 3-H), 5.89 (ddd, *J* = 8.5, 3.7, 2.2 Hz, 1 H, 1-H), 4.19–4.10 (m, 4 H, OCH_2), 3.00 (dd, J_{HP} = 21.7 Hz, *J* = 1.5 Hz, 2 H, PCH_2), 2.82 (ddd, *J* = 18.8, 6.4, 1.7 Hz, 1 H, 5-H), 2.34 (ddd, *J* = 18.8, 3.9, 2.2 Hz, 1 H, 5-H), 1.34 (ttd, *J* = 7.1, 2.1 Hz, J_{HP} = 0.5 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.4, 165.4 (d, J_{CP} = 6.4 Hz), 158.2, 137.3, 72.9, 62.81 (d, J_{CP} = 3.9 Hz), 62.79 (d, J_{CP} = 3.9 Hz), 40.7, 34.2 (d, J_{CP} = 133.6 Hz), 16.3 (d, J_{CP} = 6.2 Hz) ppm. $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$): δ = 19.4 ppm. MS (ESI): *m/z* (%) = 277 (100) $[M + H]^+$, 299 (15) $[M + Na]^+$. HRMS: calcd. for $C_{11}H_{18}O_6P$ $[M + H]^+$ 277.0836; found 277.0839 (δ =1.4 ppm error).

4-Hydroxy-5,5-dimethylcyclopent-2-enone (27): A solution of 3-hydroxy-3-methyl-2-ethylfuran[41] (800 mg, 6.34 mmol) in deionised water (675 mL) was stirred vigorously and sparged with argon for 1 h before being heated to reflux for 48 h. After cooling to r.t., the water was removed in vacuo and azeotroped with diethyl ether (2 × 50 mL) to afford **27**[42] (430 mg, 54%) as a viscous colourless oil. R_f = 0.41 (Et_2O). IR (Neat): $\tilde{\nu}$ = 3415, 2973, 2932, 2872, 1697, 1465, 1338, 1132, 1099, 1050, 1008, 861 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (dd, *J* = 5.9, 2.3 Hz, 1 H, 3-H), 6.09 (dd, *J* = 5.9, 1.5 Hz, 1 H, 2-H), 4.47 (ddd, *J* = 7.7, 2.3, 1.5 Hz, 1 H, 4-H), 1.76 (d, *J* = 7.7 Hz, 1 H, OH), 1.05 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.7, 161.6, 132.1, 79.4, 48.3, 22.5, 20.1 ppm. MS (CI, NH_3): *m/z* (%) = 127 (50) $[M + H]^+$, 144 (100) $[M + NH_4]^+$. HRMS: calcd. for $C_7H_{14}NO_2$ $[M + NH_4]^+$ 144.1020, found 144.1025 (δ =3.3 ppm error).

5,5-Dimethyl-4-oxocyclopent-2-enyl 2-(Diethoxyphosphoryl)acetate (28): Following general procedure 1, T3P® in toluene (50% w/w, 2.61 g, 4.10 mmol), 4-hydroxy-5,5-dimethyl-2-cyclopentenone (**27**;[41] 400 mg, 3.15 mmol), diethylphosphonoacetic acid (**10**; 0.53 mL, 3.31 mmol) and *N*,*N*-diisopropylethylamine (1.43 mL, 8.20 mmol) in toluene (8 mL) gave **28** (900 mg, 93%) as a yellow oil. R_f = 0.51 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2980, 2934, 2874, 1720, 1466, 1388, 1333, 1267, 1114, 1086, 1024, 824 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.44 (dd, *J* = 5.9, 2.3 Hz, 1 H, 2-H), 6.04 (dd, *J* = 5.9, 1.4 Hz, 1 H, 3-H), 5.62 (dd, *J* = 2.3, 1.4 Hz, 1 H, 1-H), 4.18 (qd, *J* = 7.1 Hz, J_{HP} = 2.7 Hz, 4 H, OCH_2), 3.03 (d, J_{HP} = 21.7 Hz, 2 H, PCH_2), 1.34 (td, *J* = 7.1 Hz, J_{HP} = 0.5 Hz, 6 H, CH_2CH_3), 1.22 (s, 3 H, 5-CH_3), 1.05 (s, 3 H, 5-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.2, 165.5 (d, J_{CP} = 6.2 Hz), 156.3, 134.5, 81.5, 62.82 (d, J_{CP} = 6.1 Hz), 62.80 (d, J_{CP} = 6.1 Hz), 47.1, 34.1 (d, J_{CP} = 134.4 Hz), 23.2, 20.0, 16.4 (d, J_{CP} = 6.2 Hz) ppm. $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$): δ = 19.6 ppm. MS (ESI): *m/z* (%) = 305 (100) $[M + H]^+$, 322 (11) $[M + NH_4]^+$. HRMS: calcd. for $C_{13}H_{22}O_6P$ $[M + NH_4]^+$ 305.1149; found 305.1150 (δ =0.5 ppm error).

***syn*-6,6-Dimethyl-3-methylidenetetrahydro-2*H*-cyclopentafuran-2,5(3*H*)-dione (29):** Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 25 μL, 0.097 mmol), **28** (31 mg, 0.10 mmol) and paraformaldehyde (30 mg, 1.02 mmol) in THF (2.5 mL) gave **29** (9 mg, 52%) as a white solid. M.p. 86.0–87.0 °C. R_f = 0.56 (EtOAc/MeOH, 9:1). IR (neat): $\tilde{\nu}$ = 2960, 2871, 1762, 1741, 1662, 1274, 1117, 994 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.31 (d, *J* = 1.9 Hz, 1 H, =CH), 5.75 (d, *J* = 1.7 Hz, 1 H, =CH), 4.63 (d, *J* = 6.3 Hz, 1 H, 6a-H), 3.71 (ddddd, *J* = 10.9, 6.3, 6.0, 1.9, 1.7 Hz, 1 H, 3a-H), 3.00 (dd, *J* = 19.6, 10.9 Hz, 1 H, 4-H), 2.21 (dd, *J* = 19.6, 6.0 Hz, 1 H, 4-H), 1.18 (s, 3 H, 5-CH_3), 1.11 (s, 3 H, 5-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 217.6, 169.9, 139.7, 123.6, 86.8, 49.6, 41.1, 36.2, 22.8, 17.3 ppm. MS (ESI): *m/z* (%) = 181 (100) $[M + H]^+$. HRMS: calcd. for $C_{10}H_{13}O_3$ $[M + H]^+$ 181.0859; found 181.0861 (δ =1.2 ppm error).

3-Allyl-4-oxocyclohex-2-enyl 2-(Diethoxyphosphoryl)acetate (31): Following general procedure 1, T3P® in toluene (50% w/w, 148 mg, 0.23 mmol), 2-allyl-4-hydroxycyclohex-2-enone (**30**;[36] 28 mg, 0.18 mmol), diethylphosphonoacetic acid (**10**; 30 μL, 0.19 mmol), *N*,*N*-diisopropylethylamine (81 μL, 0.47 mmol) in toluene (6 mL) gave **31** (54 mg, 90%) as a colourless oil. R_f = 0.33 (EtOAc). IR (neat): $\tilde{\nu}$ = 2982, 2933, 1739, 1681, 1444, 1370, 1266, 1167, 1114, 1025, 972 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 (dd, *J* = 2.9, 1.4 Hz, 1 H, 2-H), 5.56 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H, allyl 2-H), 5.61–5.56 (m, 1 H, 1-H), 5.06–5.01 (m, 2 H, allyl 3-H), 4.14 (qd, *J* = 7.1 Hz, J_{HP} = 0.6 Hz, 4 H, OCH_2), 2.98 (d, J_{HP} = 21.6 Hz, 2 H, PCH_2), 2.92 (ddd, *J* = 6.8, 1.3, 1.3 Hz, 1 H, allyl 1-H), 2.62 (ddd, *J* = 16.9, 5.8, 5.0 Hz, 1 H, 5-H), 2.40 (ddd, *J* = 16.3, 11.4, 4.8 Hz, 1 H, 5-H), 2.35–2.27 (m, 1 H, 6-H), 2.06 (dddd, *J* = 19.8, 11.3, 8.4, 4.5 Hz, 1 H, 6-H), 1.30 (t, *J* = 7.1 Hz, 6 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 165.7 (d, J_{CP} = 6.3 Hz), 142.0, 140.4, 134.7, 117.6, 69.3, 62.6 (d, J_{CP} = 5.4 Hz), 34.7, 34.6 (d, J_{CP} = 133.6 Hz), 32.7, 28.3, 16.0 (d, J_{CP} = 6.2 Hz) ppm. $^{31}P\{^1H\}$NMR (162 MHz, $CDCl_3$): δ = 19.8 ppm. MS (ESI): *m/z* (%) = 353 (100) $[M + H]^+$. HRMS: (ESI) calcd. for $C_{15}H_{23}NaO_6P$ $[M + H]^+$ 353.1124; found 353.1131 (δ =1.9 ppm error).

***anti*- and *syn*-4-Allyl-3-methylidenetetrahydrobenzofuran-2,5(3*H*,4*H*)-dione (32):** Following general procedure 2 (but with heating overnight at reflux), potassium *tert*-butoxide (3.88 M solution in THF, 31 μL, 0.121 mmol), **31** (42 mg, 0.13 mmol) and paraformaldehyde (38 mg, 1.27 mmol) in THF (2.5 mL) gave *anti*-**32** (16 mg, 64%) as a colourless oil. R_f = 0.74 (EtOAc). IR (neat): $\tilde{\nu}$ = 2919, 2851, 1761, 1714, 1642, 1436, 1409, 1344, 1264, 1141 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.35 (d, *J* = 2.4 Hz, 1 H, =CH), 5.77 (dddd, *J* = 13.9, 10.3, 7.1, 6.8 Hz, 1 H, allyl 2-H), 5.69 (d, *J* = 2.1 Hz, 1 H, =CH), 5.13–5.08 (m, 2 H, allyl 3-H), 4.80 (dt, *J* = 7.5, 5.5 Hz, 1 H, 7a-H), 3.27 (dddd, *J* = 8.0, 7.5, 2.4, 2.1 Hz, 1 H, 3a-H), 2.57–2.51 (m, 1 H, 4-H), 2.50–2.34 (m, 3 H, allyl 1-H and 6-H), 2.32–2.25 [m, 3 H, H_2C (allyl 1-H and 7-H)] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 170.0, 138.3, 134.8, 124.0, 118.6, 74.6, 49.2, 41.4, 34.1, 31.8, 26.5 ppm. MS (ESI): *m/z* (%) = 207 (100, 229 ($[M + Na]^+$, 83) $[M + H]^+$). HRMS: calcd. for $C_{10}H_{13}O_3$ $[M + H]^+$ 207.1016; found 207.1016 (δ =0.1 ppm error). Also isolated was *syn*-**32** (5 mg, 20%) as a colourless oil. R_f = 0.65 (EtOAc). IR (neat): $\tilde{\nu}$ = 2919, 2851, 1761, 1714, 1642, 1436, 1409, 1344, 1264, 1141 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.37 (d, *J* = 2.8 Hz, 1 H, =CH), 5.81 (dddd, *J* = 17.1, 10.2, 8.4, 5.5 Hz, 1 H, allyl 2-H), 5.75 (d, *J* = 2.4 Hz, 1 H, =CH), 5.19–5.07 (m, 3 H, allyl 3-H and 7a-H), 3.74 (dddd, *J* = 9.0, 5.4, 2.8, 2.4 Hz, 1 H, 3a-H), 2.84 (ddd, *J* = 8.0, 6.4, 6.3 Hz, 1 H, 6-H), 2.74–2.66 (m, 1 H, 4-H), 2.42–2.16 (m, 3 H, allyl 1-H and 6-H), 2.32–2.25 (m, 2 H, 7-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.4, 169.9, 135.4, 134.4, 126.4, 118.0, 75.2, 48.7, 39.3, 32.9, 28.9, 25.3 ppm. MS (ESI): *m/z* (%) = 207 (100) $[M + H]^+$, 229 (83) $[M + Na]^+$. HRMS: calcd. for $C_{10}H_{13}O_3$ $[M + H]^+$ 207.1016; found 207.1016 (δ =0.1 ppm error).

2-Methyl-4-oxocyclohex-2-enyl (Diethoxyphosphoryl)acetate (34): Following general procedure 1, T3P® in toluene (50% w/w, 177 mg,

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0.278 mmol), 2-methyl-4-oxocyclohex-2-en-1-ol (**33**;[37] 27 mg, 0.214 mmol), diethylphosphonoacetic acid (**10**; 46 mg, 0.235 mmol), *N*,*N*-diisopropylethylamine (97 μL, 0.556 mmol) in THF (2.0 mL) gave **34** (29 mg, 45%) as a colourless oil. R_f = 0.17 (petrol/EtOAc, 1:4). IR (neat): $\tilde{\nu}$ = 2984, 2920, 1737, 1674, 1433, 1385, 1262, 1204, 1163, 1114, 1023, 972 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (br. s, 1 H, 3-H), 5.57 (dd, J = 7.3, 4.9 Hz, 1 H, 1-H), 4.16 (qd, J = 7.0 Hz, J_{HP} = 0.5 Hz, 2 H, OCH_2), 4.14 (qd, J = 7.0 Hz, J_{HP} = 0.5 Hz, 2 H, OCH_2), 3.00 (d, J_{HP} = 21.7 Hz, 2 H, PCH_2), 2.56 (ddd, J = 16.8, 7.3, 4.9 Hz, 1 H, 5-H), 2.38 (ddd, J = 16.8, 9.5, 4.9 Hz, 1 H, 5-H), 2.27 (dddd, J = 14.3, 7.3, 4.9, 4.9 Hz, 1 H, 6-H), 2.11 (dddd, J = 14.3, 9.5, 7.3, 4.9 Hz, 1 H, 6-H), 1.97 (s, 3 H, 2-CH_3), 1.34 (t, J = 7.0 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.7, 165.3 (d, J_{CP} = 6.1 Hz), 157.4, 129.0, 70.9, 62.8 (d, J_{CP} = 6.1 Hz), 62.7 (d, J_{CP} = 6.1 Hz), 34.4 (d, J_{CP} = 132.0 Hz), 34.0, 28.1, 20.6, 16.3, 16.2 ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 19.8 ppm. MS (ESI): *m*/*z* (%) = 327 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{21}NaO_6P$ [M + Na]$^+$ 327.0968; found 327.0969 (δ =0.2 ppm error).

1-Methyl-4-oxocyclohexa-2,5-dienyl (Diethoxyphosphoryl)acetate (37): Following general procedure 1, T3P® in toluene (50% w/w, 770 mg, 0.121 mmol), 4-hydroxy-4-methylcyclohexa-2,5-dienone (**36**;[38] 100 mg, 0.806 mmol), diethylphosphonoacetic acid (**10**; 205 mg, 1.05 mmol), *N*,*N*-diisopropylethylamine (420 μL, 2.42 mmol) in THF (8.0 mL) gave **37** (96 mg, 30%) as a cream solid. M.p. 82–84 °C. R_f = 0.36 (CH_2Cl_2/Me_2CO, 4:1). IR (CH_2Cl_2): $\tilde{\nu}$ = 2985, 2933, 1743, 1668, 1629, 1445, 1393, 1266, 1176, 1096, 1046, 1023, 971, 859, 796 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 [2- and 6-H, J = 10.0 Hz, 2 H, br. d (AA′*BB*′)], 6.20 [br. d (*AA*′BB′), J = 10.0 Hz, 2 H, 3- and 5-H], 4.13 (q, J = 7.0 Hz, 2 H, OCH_2), 4.11 (q, J = 7.0 Hz, 2 H, OCH_2), 2.91 (d, J_{HP} = 21.7 Hz, 2 H, PCH_2), 1.54 (s, 3 H, 1-CH_3), 1.31 (t, J = 7.0 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.3, 164.6 (d, J_{CP} = 6.1 Hz), 148.7, 128.5, 75.2, 62.6 (d, J_{CP} = 6.1 Hz), 34.6 (d, J_{CP} = 132.0 Hz), 25.8, 16.0, 15.9 ppm. ^{31}P{^{1}H} NMR (162 MHz, $CDCl_3$): δ = 19.7 ppm. MS (ESI): *m*/*z* (%) = 325 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{13}H_{19}NaO_6P$ [M + Na]$^+$ 325.0811; found 325.0809 (δ =0.9 ppm error).

(3a*R,7a*R**)-7a-Methyl-3-methylidene-3a,7a-dihydro-3*H*,4*H*-benzofuran-2,5-dione (38):** Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 54 μL, 0.210 mmol), **37** (67 mg, 0.221 mmol) and paraformaldehyde (69 mg, 2.21 mmol) in THF (6 mL) gave **38** (28 mg, 71%) as a colourless solid. M.p. 148–150 °C (dec.). R_f = 0.41 (petrol/EtOAc, 1:1). IR (CH_2Cl_2): $\tilde{\nu}$ = 2982, 2904, 1759, 1679, 1423, 1393, 1352, 1306, 1254, 1238, 1164, 1117, 1071, 1036, 1001, 944, 914, 870, 804, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.59 (dd, J = 10.4, 1.8 Hz, 1 H, 7-H), 6.30 (d, J = 3.4 Hz, 1 H, =CH), 5.98 (d, J = 10.4 Hz, 1 H, 6-H), 5.58 (d, J = 2.8 Hz, 1 H, =CH), 3.32–3.38 (m, 1 H, 3a-H), 2.83–2.86 (m, 2 H, 4-H), 1.74 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 168.6, 147.0, 137.7, 129.1, 122.7, 80.0, 44.8, 35.7, 23.5 ppm. MS (CI): *m*/*z* (%) = 196 (100) [M + NH_4]$^+$. HRMS (CI): calcd. for $C_{10}H_{14}NO_3$ [M + NH_4]$^+$ 196.0974; found 196.0977 (δ =1.6 ppm error).

2-(4-Oxocyclohex-2-en-1-yl)propan-2-yl (Diethoxyphosphoryl)acetate (40): Following general procedure 1, T3P® in toluene (50% w/w, 3.38 g, 5.30 mmol), **39**[39] (628 mg, 4.08 mmol), diethylphosphonoacetic acid (**10**; 839 mg, 4.28 mmol), *N*,*N*-diisopropylethylamine (1.4 mL, 8.16 mmol) in THF (30 mL) gave **40** (816 mg, 60%) as a colourless oil. R_f = 0.30 (EtOAc). IR (neat): $\tilde{\nu}$ = 2983, 1730, 1680, 1391, 1276, 1114, 1025 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (dd, J = 10.5, 2.0 Hz, 1 H, 2-H), 6.08 (ddd, J = 10.5, 2.5, 0.5 Hz, 1 H, 3-H), 4.16 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2), 3.18 (dddd, J = 11.5, 4.5, 2.5, 2.5 Hz, 1 H, 1-H), 2.92 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 2.54 (dt, J = 16.5, 3.0 Hz, 1 H, 5-H), 2.38 (ddd, J = 16.5, 14.5, 5.0 Hz, 5-H), 2.17–2.09 (m, 1 H, 6-H), 1.83–1.70 (m, 1 H, 6-H), 1.55 (s, 3 H, Me), 1.46 (s, 3 H, Me), 1.34 (t, J = 7.0 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.2, 164.8 (d, J_{CP} = 6.0 Hz), 150.1, 130.4, 85.2, 62.5 (d, J_{CP} = 6.0 Hz), 45.0, 37.3, 35.6 (d, J_{CP} = 134.0 Hz), 24.3, 23.7, 22.9, 16.3 (d, J_{CP} = 7.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 355 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{15}H_{25}NaO_6P$ [M + Na]$^+$ 355.1281; found 355.1275 (δ =1.6 ppm error).

***syn*-1,1-Dimethyl-4-methylidenetetrahydro-1*H*-isochromene-3,6(4*H*,5*H*)-dione (41):** Potassium *tert*-butoxide (3.88 M solution in THF, 42 μL, 0.163 mmol) was added dropwise to a stirred solution of **40** (57 mg, 0.172 mmol) in THF (3.5 mL) under argon. The resulting solution was heated to reflux for 5 h then cooled to –78 °C. Paraformaldehyde (252 mg, 8.41 mmol) was added and the reaction was stirred for 15 min, then warmed to 0 °C and stirred for 1 h. The reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography, eluting with petrol/EtOAc, 3:7, to afford **41** (27 mg, 75%) as a white solid. M.p. 126–127 °C. R_f = 0.60 (EtOAc). IR (neat): $\tilde{\nu}$ = 2956, 1710, 1624, 1295, 1124, 964 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (d, J = 2.5 Hz, 1 H, =CH), 5.74 (d, J = 2.5 Hz, 1 H, =CH), 3.59–3.53 (m, 1 H, 4a-H), 2.82 (dt, J = 15.0, 2.5 Hz, 1 H, 5-H), 2.64 (ddd, J = 15.0, 5.5, 0.5 Hz, 1 H, 5-H), 2.46–2.38 (m, 1 H, 7-H), 2.38–2.28 (m, 1 H, 7-H), 2.20–2.11 (m, 2 H, 8- and 8a-H), 1.75–1.66 (m, 1 H, 8-H), 1.56 (s, 3 H, Me), 1.44 (s, 3 H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.1, 162.1, 133.7, 130.5, 81.5, 42.7, 41.6, 39.7, 36.0, 28.8, 27.0, 22.6 ppm. MS (ESI): *m*/*z* (%) = 231 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{16}NaO_3$ [M + Na]$^+$ 231.0922; found 231.0933 (δ =0.4 ppm error).

Methyl (2*E*)-4-{[(Diethoxyphosphoryl)acetyl]oxy}but-2-enoate (43): Following general procedure 1, T3P® in toluene (50% w/w, 4.31 g, 6.77 mmol), **42**[40] (604 mg, 5.21 mmol), diethylphosphonoacetic acid (**10**; 1.07 g, 5.47 mmol), *N*,*N*-diisopropylethylamine (1.8 mL, 10.4 mmol) in THF (40 mL) gave **43** (1.31 g, 86%) as a colourless oil. R_f = 0.40 (EtOAc). IR (neat): $\tilde{\nu}$ = 2986, 1734, 1726, 1438, 1268, 1024 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (dt, J = 15.5, 4.5 Hz, 1 H, 3-H), 6.12 (dt, J = 15.5, 2.0 Hz, 1 H, 2-H), 4.81 (dd, J = 4.5, 2.0 Hz, 2 H, 4-H), 4.18 (dq, J = 7.5, 7.0 Hz, 4 H, CH_2CH_3), 3.74 (s, 3 H, MeO), 3.02 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 1.34 (t, J = 7.0 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 165.1 (d, J_{CP} = 6.0 Hz), 140.7, 122.0, 63.4, 62.8 (d, J_{CP} = 6.0 Hz), 51.7, 34.2 (d, J_{CP} = 134.0 Hz), 16.3 (d, J_{CP} = 6.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 317 (100) [M + Na]$^+$. HRMS (ESI): calcd. for $C_{11}H_{19}NaO_7P$ [M + Na]$^+$ 317.0761; found 317.0755 (δ =1.7 ppm error).

Methyl (4-Methylidene-5-oxotetrahydrofuran-3-yl)acetate (44): Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 83 μL, 0.323 mmol), **43** (100 mg, 0.340 mmol) and paraformaldehyde (102 mg, 3.40 mmol) in THF (7 mL) gave **44** (42 mg, 73%) as a colourless oil. R_f = 0.80 (EtOAc). IR (neat): $\tilde{\nu}$ = 2917, 1766, 1731, 1436, 1174, 1117 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (d, J = 2.5 Hz, 1 H, =CH), 5.65 (d, J = 2.5 Hz, 1 H, =CH), 4.61 (t, J = 9.0 Hz, 1 H, CH_2CO), 4.04 (dd, J = 9.0, 6.0 Hz, 1 H, CH_2CO), 3.70 (s, 3 H, OMe), 3.54–3.43 (m, 1 H, 3-H), 2.74 (dd, J = 17.0, 5.5 Hz, 1 H, 2-H), 2.56 (dd, J = 17.0, 9.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 169.9, 136.9, 122.8, 70.8, 52.0, 37.9, 34.9 ppm. MS (ESI): *m*/*z* (%) = 171

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(100) $[M + H]^+$. HRMS (ESI): calcd. for $C_8H_{11}O_4$ $[M + H]^+$ 171.0652; found 171.0653 (δ =0.3 ppm error).

General Procedure 4: Preparation of Allylic Esters and Carbonates

***syn*- and *anti*-4-(Acetyloxy)cyclohex-2-en-1-yl (Diethoxyphosphoryl)-acetate (49):** Cerium trichloride heptahydrate (0.4 M solution in MeOH, 4.8 mL, 1.91 mmol) was added to a stirred solution of the enone **11** (555 mg, 1.91 mmol) in dichloromethane (15 mL) at –78 °C. After 0.5 h, sodium borohydride (108 mg, 2.87 mmol) was added and the reaction was slowly warmed to room temperature. After 3 h, the reaction was quenched with water (20 mL), the layers were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to give a crude product. Purification by flash chromatography, eluting with MeOH/EtOAc, 5:95, gave an intermediate alcohol. A stirred solution of the alcohol in pyridine (4.5 mL) was treated with acetic anhydride (1.5 mL). After 16 h, the reaction was concentrated in vacuo to give a crude residue. Purification by flash chromatography, eluting with EtOAc, gave **49** (327 mg, 51%; 1:1 *syn*:*anti*) as a colourless oil. R_f = 0.30 (EtOAc/MeOH, 8:2). IR (neat): $\tilde{\nu}$ = 2984, 1731, 1672, 1242, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; apostrophe denotes *syn* isomer): δ = 5.91–5.88 (m, 4 H, 2-, 2′-, 3- and 3′-H), 5.39–5.21 (m, 4 H, 1-, 1′-, 4-, and 4′-H), 4.17 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2), 4.16 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2'), 2.96 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 2.95 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2'), 2.14–2.10 (m, 2 H, 6- and 6′-H), 2.05 (s, 3 H, Me), 2.04 (s, 3 H, Me′), 1.94–1.83 (m, 4 H, 5-, 5′-, 6- and 6′-H), 1.79–1.66 (m, 2 H, 5- and 5′-H), 1.34 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.34 (t, J = 7.0 Hz, 3 H, CH_2CH_3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.63, 170.60, 165.4 (d, J_{CP} = 7.0 Hz), 165.3 (d, J_{CP} = 6.0 Hz), 130.9, 130.7, 129.6, 129.4, 68.7, 68.4, 68.3, 67.30, 67.28, 62.73 (d, J_{CP} = 6.0 Hz), 62.66 (d, J_{CP} = 6.0 Hz), 34.42 (d, J_{CP} = 133.5 Hz), 34.40 (d, J_{CP} = 133.5 Hz), 25.5, 25.4, 24.7, 24.6, 21.24, 21.23, 16.31 (d, J_{CP} = 6.0 Hz), 16.30 (d, J_{CP} = 6.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 357 (100) $[M + Na]^+$. HRMS: calcd. for $C_{14}H_{23}NaO_7P$ $[M + Na]^+$ 357.1074; found 357.1085 (δ =2.6 ppm error).

***syn*- and *anti*-4-[(Methoxycarbonyl)oxy]cyclohex-2-en-1-yl (Diethoxyphosphoryl)acetate (50):** Following general procedure 4, cerium trichloride heptahydrate (0.4 M solution in MeOH, 5.2 mL, 2.07 mmol), enone **11** (600 mg, 2.07 mmol) and sodium borohydride (116 mg, 3.11 mmol) in dichloromethane (20 mL); then methyl chloroformate (1.5 mL) in pyridine (6 mL) gave **50** (326 mg, 45%; 1:1 *syn*:*anti*) as a colourless oil. R_f = 0.30 (EtOAc). IR (neat): $\tilde{\nu}$ = 2983, 1742, 1444, 1263, 1023 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; apostrophe denotes *syn* isomer): δ = 5.98 (d, J = 10.5 Hz, 1 H, 3-H), 5.97 (d, J = 10.5 Hz, 1 H, 3′-H), 5.92 (d, J = 10.5 Hz, 2 H, 2- and 2′-H), 5.39–5.34 (m, 1 H, 4-H), 5.30–5.25 (m, 1 H, 4′-H), 5.20–5.16 (m, 1 H, 1-H), 5.12–5.07 (m, 1 H, 1′-H), 4.16 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2), 4.15 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2'), 3.79 (s, 3 H, OMe), 3.79 (s, 3 H, OMe′), 2.97 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 2.96 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2'), 2.22–2.10 (m, 2 H, 6- and 6′-H), 1.99–1.88 (m, 4 H, 5-, 5′-, 6- and 6′-H), 1.84–1.70 (m, 2 H, 5- and 5′-H), 1.34 (t, J = 7.0 Hz, 12 H, CH_2CH_3 and CH_2CH_3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.32 (d, J_{CP} = 3.0 Hz), 165.30 (d, J_{CP} = 3.0 Hz), 155.29, 155.27, 130.11, 130.10, 130.04, 130.00, 71.0, 70.9, 68.4, 68.3, 62.68 (d, J_{CP} = 6.0 Hz), 62.66 (d, J_{CP} = 6.0 Hz), 54.78, 54.76, 34.42 (d, J_{CP} = 133.0 Hz), 34.40 (d, J_{CP} = 133.0 Hz), 25.3, 25.2, 24.7, 24.5, 16.31 (d, J_{CP} = 6.0 Hz), 16.30 (d, J_{CP} = 6.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 373 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{14}H_{23}NaO_8P$ $[M + Na]^+$ 373.1023; found 373.1025 (δ =0.17 ppm error).

***syn*-[26] and *anti*-3-Methylidene-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (51):**[27] Potassium *tert*-butoxide (3.88 M solution in THF, 59 μL, 0.228 mmol) was added to a stirred solution of **50** (84 mg, 0.240 mmol) and tetrakis(triphenylphosphane)palladium(0) (14 mg, 0.012 mmol) in THF (5 mL) under argon. The resulting solution was heated to reflux for 4 h then cooled to r.t. Paraformaldehyde (72 mg, 2.40 mmol) was added and the reaction was stirred for 18 h. The reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography, eluting with petrol/EtOAc, 1:1, to afford **51** (13 mg, 36%; 3:1 *syn*:*anti*) as a colourless oil. R_f = 0.60 (petrol/EtOAc, 1:1). IR (neat): $\tilde{\nu}$ = 2919, 1761, 1264, 1136 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$; apostrophe denotes *anti*-isomer): δ = 6.27 (d, J = 2.5 Hz, 1 H, $=CH_2'$), 6.22 (d, J = 2.0 Hz, 1 H, $=CH_2$), 6.12–6.05 (m, 1 H, 4′-H), 5.94–5.85 (m, 1 H, 4-H), 5.61 (d, J = 2.5 Hz, 1 H, $=CH_2'$), 5.61 (d, J = 2.5 Hz, 1 H, $=CH_2$), 5.58–5.54 (m, 2 H, 5′-H and 5-H), 4.92–4.87 (m, 1 H, 7a′-H), 4.77 (ddd, J = 6.0, 6.0, 3.0 Hz, 1 H, 7a-H), 3.52 (dddd, J = 8.5, 4.5, 2.0, 2.0 Hz, 1 H, 3a-H), 3.22–3.14 (m, 1 H, 3a′-H), 2.22–2.08 (m, 2 H, 6- and 6′-H), 2.08–1.93 (m, 4 H, 6-, 6′-, 7- and 7′-H), 1.90–1.80 (m, 2 H, 7- and 7′-H) ppm. MS (ESI): *m*/*z* (%) = 151 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_9H_{11}O_2$ $[M + H]^+$ 151.0754; found 151.0754 (δ =0.3 ppm error).

***syn*-2-[4-(Acetyloxy)cyclohex-2-en-1-yl]propan-2-yl (Diethoxyphosphoryl)acetate (52):** Following general procedure 4, cerium trichloride heptahydrate (0.4 M solution in MeOH, 4.0 mL, 1.60 mmol), enone **40** (530 mg, 1.60 mmol) and sodium borohydride (91 mg, 2.40 mmol) in dichloromethane (20 mL); then acetic anhydride (1 mL) in pyridine (3 mL) gave *syn*-**52** (421 mg, 70%) as a colourless oil. R_f = 0.50 (EtOAc). IR (neat): $\tilde{\nu}$ = 2984, 1729, 1371, 1244, 1028 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.77 (dd, J = 10.5, 1.5 Hz, 1 H, 2-H), 5.64 (d, J = 10.5 Hz, 1 H, 3-H), 5.27–5.18 (m, 1 H, 4-H), 4.09 (dq, J = 7.5, 7.0 Hz, 4 H, OCH_2), 2.83 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 2.83–2.77 (m, 1 H, 1-H), 2.12–2.01 (m, 1 H, 5-H), 1.95 (s, 3 H, Ac), 1.82–1.74 (m, 1 H, 5-H), 1.50–1.25 (m, 2 H, 6-H), 1.38 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.28 (t, J = 7.0 Hz, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 164.6 (d, J_{CP} = 7.0 Hz), 130.4, 128.9, 86.0, 69.8, 62.3 (d, J_{CP} = 6.0 Hz), 43.9, 35.3 (d, J_{CP} = 134.0 Hz), 28.0, 23.0, 22.4, 22.1, 21.2, 16.2 (d, J_{CP} = 7.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 399 (70) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{17}H_{29}NaO_7P$ $[M + Na]^+$ 399.1543; found 399.1539 (δ =1.0 ppm error).

***syn*-2-{4-[(Ethoxycarbonyl)oxy]cyclohex-2-en-1-yl}propan-2-yl (Diethoxyphosphoryl)acetate (53):** Following general procedure 4, cerium trichloride heptahydrate (0.4 M solution in MeOH, 0.47 mL, 0.189 mmol), enone **40** (63 mg, 0.189 mmol) and sodium borohydride (11 mg, 0.284 mmol) in dichloromethane (5 mL); then ethyl chloroformate (0.5 mL) in pyridine (1.5 mL) gave *syn*-**53** (63 mg, 82%) as a colourless oil. R_f = 0.50 (EtOAc). IR (neat): $\tilde{\nu}$ = 2983, 1729, 1371, 1262, 1114, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.96–5.90 (m, 1 H, 2-H), 5.88 (dd, J = 10.5, 1.0 Hz, 1 H, 3-H), 4.60–4.55 (m, 1 H, 4-H), 4.15 (dq, J = 7.5, 7.0 Hz, 4 H, $POCH_2$), 4.14 (q, J = 7.0 Hz, 2 H, OCH_2), 2.88 (d, J_{HP} = 21.5 Hz, 2 H, PCH_2), 2.89–2.83 (m, 1 H, 1-H), 2.17–2.10 (m, 1 H, 5-H), 2.00–1.86 (m, 1 H, 5-H), 1.70 (dt, J = 9.0, 3.5 Hz, 2 H, 6-H), 1.48 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.32 (t, J = 7.0 Hz, 9 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (d, J_{CP} = 6.0 Hz), 149.8, 131.1, 128.8, 86.2, 73.4, 62.44 (d, J_{CP} = 6.0 Hz), 62.41, 54.3, 44.1, 35.4 (d, J_{CP} = 133.0 Hz), 31.2, 23.5, 22.6, 18.3, 16.2 (d, J_{CP} = 7.0 Hz) ppm. MS (ESI): *m*/*z* (%) = 429 (40) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{18}H_{31}NaO_8P$ $[M + Na]^+$ 429.1649; found 429.1659 (δ =2.0 ppm error).

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***syn*-1,1-Dimethyl-4-methylidene-1,4,4a,7,8,8a-hexahydro-3*H*-isochromen-3-one (54):** Potassium *tert*-butoxide (3.88 M solution in THF, 36 μL, 0.141 mmol) was added to a stirred solution of **53** (60 mg, 0.148 mmol) and tetrakis(triphenylphosphane)palladium(0) (9 mg, 0.0074 mmol) in THF (3 mL) under argon. The resulting solution was heated to reflux for 16 h then cooled to r.t. Paraformaldehyde (44 mg, 1.48 mmol) was added and the reaction was stirred for 18 h. The reaction was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organics were dried (Na_2SO_4) and concentrated in vacuo. The resulting crude residue was purified by flash column chromatography, eluting with petrol/EtOAc, 7:3, to afford **51** (1.4 mg, 5%) as a colourless oil. R_f = 0.30 (petrol/EtOAc, 7:3). IR (neat): $\tilde{\nu}$ = 2921, 2851, 1734, 1463, 1375, 1260 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, J = 2.5 Hz, 1 H, $=CH_2$), 5.95–5.89 (m, 1 H, 5-H), 5.84–5.78 (m, 1 H, 6-H), 5.71 (dd, J = 2.5, 1.0 Hz, 1 H, $=CH_2$), 3.51–3.44 (m, 1 H, 4a-H), 2.20–2.12 (m, 1 H, 8a-H), 2.11–2.00 (m, 2 H, 7-H), 1.95–1.88 (m, 1 H, 8-H), 1.78 (ddd, J = 12.5, 6.0, 2.5 Hz, 1 H, 8-H), 1.47 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3) ppm. HRMS (ESI): calcd. for $C_{12}H_{17}O_2$ $[M + H]^+$ 193.1223; found 193.1223 (δ =0.2 ppm error).

(4*S*,6*R*)- and (4*S*,6*S*)-4-*tert*-Butyldimethylsilyloxy-6-methylcyclohex-2-en-1-one (59): *n*Butyllithium (2.5 M solution in hexanes, 3.50 mL, 8.75 mmol) was added dropwise to a stirred solution of diisopropylamine (1.33 mL, 9.48 mmol) in THF (40 mL) at 0 °C under argon. After 30 min the reaction was cooled to –78 °C and a solution of (*S*)-(–)-**58** (1.65 g, 7.29 mmol) in THF (15 mL) was added dropwise. The resulting solution was stirred for 30 min at –78 °C, then iodomethane (2.27 mL, 36.5 mmol) was added and after 5 min, the solution was warmed to –20 °C. After 1 h, the reaction was quenched with aqueous 3 M NH_4OH (25 mL) and vigorously stirred. EtOAc (150 mL) and water (50 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were washed with aqueous saturated $CuSO_4$ (100 mL) and saturated brine (150 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash column chromatography, eluting with petrol/EtOAc, 19:1, to give **59** (972 mg, 55%; 52:48 mixture of diastereoisomers) as a pale yellow liquid. R_f = 0.45 (petrol/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 2954, 2930, 2857, 1686, 1471, 1462, 1380, 1254, 1213, 1110, 1048, 1011 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, minor diastereomer is indicated by the use of an apostrophe): δ = 6.77 (ddd, J = 10.1, 2.0, 2.0 Hz, 1 H, 3-H), 6.74 (ddd, J = 10.1, 4.0, 1.0 Hz, 1 H, 3′-H), 5.91 (dd, J = 10.1, 2.0 Hz, 1 H, 2-H), 5.89 (dd, J = 10.1, 1.0 Hz, 1 H, 2′-H), 4.59 (dddd, J = 10.3, 5.1, 2.0, 2.0 Hz, 1 H, 4-H), 4.47 (dddd, J = 5.6, 4.2, 4.0, 1.0 Hz, 1 H, 4′-H), 2.80 (dqd, J = 8.6, 7.2, 4.9 Hz, 1 H, 6′-H), 2.36 (dqd, J = 13.8, 6.7, 4.4 Hz, 1 H, 6-H), 2.20 (dddd, J = 12.5, 5.1, 4.4, 2.0 Hz, 1 H, 5-H), 2.06 (dddd, J = 13.4, 5.6, 4.9, 1.0 Hz, 1 H, 5′-H), 1.94 (ddd, J = 13.4, 8.6, 4.2 Hz, 1 H, 5′-H), 1.76 (ddd, J = 13.8, 12.5, 10.3 Hz, 1 H, 5-H), 1.15 (d, J = 7.2 Hz, 3 H, 6′-CH_3), 1.14 (d, J = 6.7 Hz, 3 H, 6-CH_3), 0.90 (s, 9 H, *t*Bu), 0.88 (s, 9 H, *t*Bu′), 0.11 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 201.8, 154.5, 149.6, 128.7, 128.5, 68.0, 63.8, 41.2, 40.0, 39.2, 37.5, 25.4, 25.4, 17.8, 17.8, 14.9, 14.7, –5.0, –5.1, –5.19, –5.17 ppm. MS (CI, NH_3): m/z (%) = 241 (100) $[M + H]^+$, 183 (35). HRMS (CI): calcd. for $C_{13}H_{25}O_2Si$ $[M + H]^+$ 241.1623; found 241.1627 (δ =1.4 ppm error).

(*S*)-(–)-5-*tert*-Butyldimethylsilanyloxy-1-methyl-2-(triethylsilanyloxy)-cyclohexa-1,3-diene (60): *n*Butyllithium (2.5 M solution in hexanes, 1.6 mL, 3.96 mmol) was added dropwise to a stirred solution of diisopropylamine (601 μL, 4.39 mmol) in THF (55 mL) at 0 °C under argon. After 30 min the reaction was cooled to –78 °C and a solution of **59** (794 mg, 3.30 mmol) in THF (5 mL) was added dropwise. The resulting solution was stirred for 1 h at –78 °C, then TESCl (1.39 mL, 8.26 mmol) was added dropwise. After 1 h, the mixture was warmed to room temperature, stirred for 1 h and quenched with aqueous saturated NH_4Cl (30 mL). Pentane (150 mL) was added and the layers were separated. The organic extract was washed with H_2O (100 mL), aqueous saturated $CuSO_4$ (100 mL) and saturated brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography, eluting with pentane/Et_2O, 50:1, to give **60** (890 mg, 76%) as a colourless oil. $[a]_D^{21.5}$ = –141.9 (c = 1.00, $CHCl_3$). R_f = 0.36 (pentane/Et_2O, 50:1). IR (neat): $\tilde{\nu}$ = 3045, 2955, 2929, 2879, 2856, 1665, 1600, 1461, 1398, 1251, 1195, 1122, 1070, 1006, 910, 836, 775, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, J = 10.1 Hz, 1 H, 3-H), 5.63 (dd, J = 10.1, 3.4 Hz, 1 H, 4-H), 4.36–4.42 (m, 1 H, 5-H), 2.19–2.35 (m, 2 H, 6-H), 1.69 (s, 3 H, 1-CH_3), 0.98 (t, J = 7.6 Hz, 9 H, CH_2CH_3), 0.87 (s, 9 H, *t*Bu), 0.67 (q, J = 7.6 Hz, 6 H, $SiCH_2$), 0.06 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 129.2, 126.8, 111.5, 66.2, 38.5, 25.5, 17.8, 15.8, 6.3, 4.9, –5.0, –5.1 ppm. MS (CI, NH_3): m/z (%) = 355 (38) $[M + H]^+$, 354 (30), 297 (18), 223 (100), 132 (15), 115 (15), 104 (17), 75 (26). HRMS (CI): calcd. for $C_{19}H_{39}O_2Si_2$ $[M + H]^+$ 355.2489; found 355.2483 (δ =1.7 ppm error).

(4*S*,6*S*)- and (4*S*,6*R*)-(–)-4-*tert*-Butyldimethylsilanyloxy-6-hydroxy-6-methylcyclohex-2-en-1-one (61): DMDO (0.0556 M solution in Me_2CO, 34 mL, 2.00 mmol; in contrast to the previous work of Adam and coworkers,[33] the DMDO solution was NOT predried with 4 Å mol. sieves) was added over 30 min to a stirred solution of **60** (546 mg, 1.54 mmol) in CH_2Cl_2 (5 mL) at –50 °C. The resulting suspension was stirred for 50 min then carefully concentrated in vacuo. The residue was taken up in CH_2Cl_2 (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography, eluting with petrol/EtOAc, 9:1, to give (4*S*,6*S*)-(–)-**61** (326 mg, 83%). $[a]_D^{21.5}$ –150.8 (c = 1.00, $CHCl_3$). M.p. 42–43.5 °C. R_f = 0.19 (petrol/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 3402, 2930, 2857, 1677, 1465, 1409, 1378, 1251, 1214, 1166, 1106, 1064, 862, 836, 774 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.75 (ddd, J = 10.1, 4.0, 1.0 Hz, 1 H, 3-H), 5.98 (dd, J = 10.1, 1.0 Hz, 1 H, 2-H), 4.59 (dddd, J = 5.1, 4.2, 4.0, 1.0 Hz, 1 H, 4-H), 3.05 (s, 1 H, OH), 2.25 (dd, J = 14.0, 5.1 Hz, 1 H, 5-H), 2.11 (ddd, J = 14.0, 4.2, 1.0 Hz, 1 H, 5-H), 1.46 (s, 3 H, 6-CH_3), 0.90 (s, 9 H, *t*Bu), 0.12 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 150.6, 125.9, 72.5, 64.3, 43.4, 27.0, 25.4, 17.6, –5.2, –5.3 ppm. MS (ESI): m/z (%) = 279 (100) $[M + Na]^+$, 257 (20) $[M + H]^+$. HRMS (ESI): calcd. for $C_{13}H_{24}NaO_3Si$ $[M + Na]^+$ 279.1387; found 279.1397 (δ =3.8 ppm error). Also isolated was (4*S*,6*R*)-**61** (10 mg, 2.5%) as a cream solid. M.p. 52–54 °C. R_f = 0.24 (petrol/EtOAc, 9:1). IR (neat): $\tilde{\nu}$ = 3479, 2954, 2930, 2857, 1688, 1462, 1380, 1257, 1161, 1134, 1078, 864, 838, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.82 (ddd, J = 10.2, 2.0, 2.0 Hz, 1 H, 3-H), 6.00 (dd, J = 10.2, 2.2 Hz, 1 H, 2-H), 4.55 (dddd, J = 9.8, 5.3, 2.2, 2.0 Hz, 1 H, 4-H), 3.66 (s, 1 H, OH), 2.41 (ddd, J = 12.6, 5.3, 2.0 Hz, 1 H, 5-H), 2.06 (dd, J = 12.6, 9.8 Hz, 1 H, 5-H), 1.29 (s, 3 H, 6-CH_3), 0.90 (s, 9 H, *t*Bu), 0.12 (s, 3 H, $SiMe_3$), 0.11 (s, 3 H, $SiMe_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.6, 154.5, 125.3, 73.1, 66.9, 46.4, 25.4, 24.9, 17.7, –5.0, –5.3 ppm. MS (ESI): m/z (%) = 279 (100) $[M + Na]^+$. HRMS (ESI): calcd. for $C_{13}H_{24}NaO_3Si$ $[M + Na]^+$ 279.1387; found 279.1397 (δ =3.7 ppm error).

(4*S*,6*S*)-(–)-4,6-Dihydroxy-6-methylcyclohex-2-en-1-one (57): Glacial acetic acid (18 mL) was added to a stirred solution of (4*S*,6*S*)-

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(–)-**61** (309 mg, 1.21 mmol) in THF/water (1:1, 12 mL). The resulting suspension was stirred vigorously and heated to 50 °C for 13 h. The reaction was cooled to room temperature, diluted with EtOAc (150 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography, eluting with petrol/EtOAc, 1:2, to give (4*S*,6*S*)-(–)-**57** (134 mg, 79%) as a cream solid. $[\alpha]_D^{21.5}$ = –116.8 (*c* = 0.895, MeOH). M.p. 95–97 °C. R_f = 0.26 (petrol/EtOAc, 1:2). IR (neat): $\tilde{\nu}$ = 3365, 2978, 2923, 2853, 1680, 1453, 1375, 1252, 1216, 1159, 1125, 1104, 1037, 947, 864, 824 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (ddd, *J* = 10.1, 1.0, 1.0 Hz, 1 H, 3-H), 6.04 (dd, *J* = 10.1, 1.4 Hz, 1 H, 2-H), 4.73 (br. s, 1 H, 4-H), 2.87 (s, 1 H, 6-OH), 2.39 (dd, *J* = 14.0, 5.0 Hz, 1 H, 5-H), 2.12 (dd, *J* = 14.0, 5.3 Hz, 1 H, 5-H), 1.98 (br. s, 1 H, 4-OH), 1.45 (s, 3 H, CH_3) ppm. ^1H NMR (400 MHz, CD_3OD): δ = 6.95 (ddd, *J* = 10.3, 2.0, 1.8 Hz, 1 H, 3-H), 5.91 (dd, *J* = 10.3, 2.0 Hz, 1 H, 2-H), 4.66 (ddd, *J* = 7.4, 4.8, 2.0 Hz, 1 H, 4-H), 2.39 (ddd, *J* = 13.5, 5.1, 1.7 Hz, 1 H, 5-H), 1.87 (dd, *J* = 13.5, 8.5 Hz, 1 H, 5-H), 1.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 200.8, 155.3, 127.5, 73.0, 65.2, 46.8, 24.8 ppm. MS (CI): *m*/*z* (%) = 160 (100) $[M + NH_4]^+$. HRMS (CI): calcd. for $C_7H_{14}NO_3$ $[M + NH_4]^+$ 160.0972; found 160.0973 (δ =0.7 ppm error).

(1*R*,5*S*)-(+)-5-Hydroxy-5-methyl-4-oxocyclohex-2-enyl Diethoxyphosphorylacetate (55): Triphenylphosphane (251 mg, 0.956 mmol) then DIAD (188 μL, 0.956 mmol) were added to a stirred solution of (4*S*,6*S*)-(–)-**57** (69 mg, 0.478 mmol) and diethyl phosphonoacetic acid (**10**; 141 mg, 0.718 mmol) in THF (12 mL) at 0 °C under argon. After 0.5 h the cool bath was removed and the reaction was stirred for 0.5 h as the reaction warmed to room temperature. The resulting solution was concentrated in vacuo and the crude material was purified by flash chromatography (it is extremely important to remove all traces of Ph_3PO prior to the next reaction), eluting with CH_2Cl_2/EtOAc (1:1)→EtOAc, to give (1*R*,5*S*)-(+)-**55** (99 mg, 64%) as a colourless oil. $[\alpha]_D^{21.5}$ = +134.1 (*c* = 1.10, $CHCl_3$). R_f = 0.21 (EtOAc). IR (neat): $\tilde{\nu}$ = 3443, 2983, 2934, 1739, 1693, 1391, 1371, 1264, 1165, 1108, 1023, 979, 818 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.78 (ddd, *J* = 10.3, 2.0, 2.0 Hz, 1 H, 2-H), 6.09 (dd, *J* = 10.3, 2.3 Hz, 1 H, 3-H), 5.66 (dddd, *J* = 10.1, 5.5, 2.3, 2.0 Hz, 1 H, 1-H), 4.17–4.08 (m, 4 H, OCH_2), 3.77 (br. s, 1 H, OH), 2.98 (d, J_{HP} = 21.7 Hz, 2 H, PCH_2), 2.51 (ddd, *J* = 12.3, 5.5, 2.0 Hz, 1 H, 6-H), 2.10 (dd, *J* = 12.3, 10.1 Hz, 1 H, 6-H), 1.33 (s, 3 H, 6-CH_3), 1.32–1.26 (m, 6 H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.8, 165.5 (d, J_{CP} = 6.5 Hz), 148.2, 127.5, 73.0, 69.0, 62.8 (d, J_{CP} = 6.1 Hz), 62.7 (d, J_{CP} = 6.3 Hz), 41.8, 34.0 (d, J_{CP} = 133.3 Hz), 24.7, 16.0, 15.9 ppm. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ = 19.5 ppm. MS (CI): *m*/*z* (%) = 338 (42) $[M + NH_4]^+$, 321 (100) $[M + H]^+$. HRMS (CI): calcd. for $C_{13}H_{22}O_7P$ $[M + H]^+$ 321.1101; found 321.1103 (δ =0.7 ppm error).

(+)-Paeonilactone (1):[2] Following general procedure 2, potassium *tert*-butoxide (3.88 M solution in THF, 47 μL, 0.184 mmol), (1*R*,5*S*)-(+)-**55** (62 mg, 0.193 mmol) and paraformaldehyde (58 mg, 1.93 mmol) in THF (4.5 mL) gave **1** (26 mg, 70%) as a colourless solid. $[\alpha]_D^{20.5}$ = +23.8 (*c* = 1.04, MeOH) [ref.[2] +23.2]. M.p. 86–87 °C [ref.[2] 88–89 °C]. R_f = 0.42 (EtOAc). IR (neat): $\tilde{\nu}$ = 3442, 2970, 2927, 2849, 1757, 1722, 1660, 1409, 1339, 1271, 1237, 1159, 1101, 1029, 993, 948 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.34 (d, *J* = 3.0 Hz, 1 H, =CH), 5.66 (d, *J* = 2.7 Hz, 1 H, =CH), 4.98 (ddd, *J* = 8.9, 8.2, 5.8 Hz, 1 H, 7a-H), 3.67 (ddddd, *J* = 8.9, 7.6, 4.3, 3.0, 2.7 Hz, 1 H, 3a-H), 3.42 (s, 1 H, OH), 2.94 (dd, *J* = 16.1, 7.6 Hz, 1 H, 4-H), 2.77 (dd, *J* = 16.1, 4.3 Hz, 1 H, 4-H), 2.50 (dd, *J* = 14.0, 5.8 Hz, 1 H, 7-H), 1.96 (dd, *J* = 14.0, 8.9 Hz, 1 H, 7-H), 1.39 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.8, 168.8, 136.4, 123.1, 73.8, 73.1, 41.4, 39.2, 36.7, 24.9 ppm. MS (ESI): *m*/*z* (%) = 214 (11) $[M + NH_4]^+$, 197 (100) $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{13}O_4$ $[M + H]^+$ 197.0808; found 197.0807 (δ = 0.9 ppm error).

CCDC-658935 (for **13**), -659261 (for **20**), -658922 (for **29**), -686541 (for **41**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

We thank Elsevier Science for postdoctoral funding (M.G.E., M.N.K. and M.S.S.) and the Engineering and Physical Sciences Research Council for studentship (R.R.A.K.) and fellowship (A.P.) support. We are also grateful to Dr. T. Dransfield (University of York, mass spectrometry) for technical assistance, Archimica for a gift of T3P®, BASF for a gift of KDMO in heptanes and GlaxoSmithKline for additional support.

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Received: June 10, 2008
Published Online: August 28, 2008

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