[2 + 2] Cycloaddition of cyclic vinyl phosphonates with ketenes †

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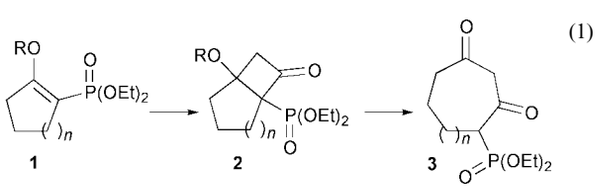
Highly substituted cyclic β-alkoxyvinyl phosphonates underwent thermal [2+2] cycloaddition with activated ketenes to afford bicyclic phosphonates. Fragmentation of the central polarized bond of this bicyclic system occurred readily upon treatment with zinc in acetic acid, to give rise to ring expanded products. This method provides access to cycloheptane-1,3-diones substituted at the 4-position with a phosphonate group.

Introduction

Ring expansion reactions are commonly utilized to prepare medium and large membered rings from smaller ring precursors.[1–3] Highly functionalized medium sized rings are found in a number of natural products, yet are typically difficult to prepare due to the unique structural characteristics which make the use of standard ring forming reactions impossible for their construction.[4] Through ring expansion a smaller and more readily accessible ring can easily be functionalized and enlarged to yield a larger ring with functional groups at remote positions. Most ring enlargements occur *via* fragmentation of the interannular bond or the zero bridge of bicyclic compounds. Grob[5] or Wharton[6] type fragmentations of γ-hydroxy halides or tosylates are typically utilized to afford ring enlarged products. Strained rings can also undergo ring opening, in particular when vicinally substituted with electron donor and electron acceptor groups, which polarize the common bond. Donor–acceptor-substituted cyclopropanes have been studied extensively in ring opening reactions;[7] however, use in ring expansion of [*n*.1.0] systems has been limited.

Interest in our labs has been on the use of phosphonates in ring expansion reactions. Although carbonyl,[8,9] cyano,[10] sulfonyl[11,12] and nitro[13] groups have been studied extensively as electron acceptors in ring opening reactions, phosphonates have not been studied in this regard. We have reported, however, that phosphonates are capable of inducing fragmentation reactions in a tandem Michael–aldol-fragmentation reaction of β-keto phosphonates.[14,15] As part of ongoing studies in our laboratories, we have been interested in the use of phosphonates in fragmentation reactions. We envisioned that bicyclic systems such as **2** might undergo fragmentation to afford [*n*+2] ring enlarged products [eqn. (1)]. In turn these systems might be prepared *via*



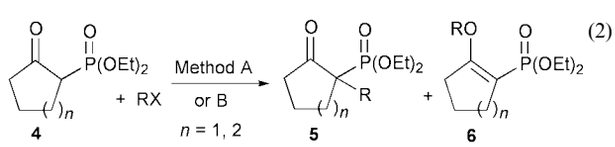
(1)

[2+2] cycloaddition of cyclic β-alkoxy vinyl phosphonate **1** with ketenes. Cycloaddition of alkenes and ketenes[16] is a common route to prepare cyclobutane rings.[17–20] Most cycloaddition reactions reported are with activated, electron rich, mono and disubstituted alkenes.[21,22] To our knowledge, donor–acceptor-substituted alkenes, such as **1**, have not been studied in thermal [2+2] cycloaddition reactions. Powerful electron withdrawing groups may in fact inhibit the cycloaddition reaction of these tetrasubstituted donor–acceptor-substituted alkenes, since it is known that electron poor alkenes like acrylonitrile do not undergo reaction with ketenes.[18] However, we have found that the phosphonate group, although capable of inducing fragmentation reactions, is not so powerful an electron acceptor as to inhibit the cycloaddition of **1** with ketenes.

Herein, we report the regioselective [2+2] cycloaddition reaction of cyclic vinyl phosphonates **1** with ketenes, followed by the subsequent fragmentation of **2** to afford ring enlarged products **3**. We envisioned that ring enlarged compounds bearing a phosphonate functional group, could undergo an intramolecular Horner–Wadsworth–Emmons (HWE) reaction to form bicyclic compounds containing a bridgehead alkene. This reaction could be utilized as a template to synthesize natural products containing this carbon framework.

Results and discussion

The cyclic vinyl phosphonates **6**, utilized in the cycloaddition studies with ketenes, were prepared from cyclic β-keto phosphonates, **4**. Recent methods developed by Wiemer and co-workers, involving the reaction of cyclic ketones with electrophilic phosphorus reagents, allow easy access to five and six membered ring β-keto phosphonates in approximately 70% yield.[23] The cyclic β-keto phosphonates **4** were subsequently converted to cyclic β-alkoxy vinylphosphonates **6**, *via* either phase transfer catalyzed (PTC) alkylation[24] or the polar aprotic method of alkylation of cyclic β-keto phosphonates [eqn. (2)].



(2)

Method A: EtX; NaOH, nBu_4NHSO_4
Method B: ROTs; KH, DMSO

Under the PTC method (Method A), cyclic β-keto phosphonates were combined with ethyl halides in the presence of NaOH and nBu_4NHSO_4, to afford mixtures of C- and O-alkylated products **5** and **6**, respectively. This method tended to give more C-alkylated product **5** than the desired O-alkylated product **6** (Table 1).

A more efficient method for formation of the O-alkylated vinyl phosphonates was found to be the polar aprotic method, where O-alkylation was favored by use of the hard alkyl sulfonate

† Spectral data for compounds **6a**, **6b**, **8a**–**c**, **9c**, **9d**, **10**, **11**, **12b**, **13**, **14a** and **14b** are available as supplementary data available from BLDSC (SUPPL. NO. 57704, p. 25) or the RSC Library. See instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).

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Table 1 Synthesis of 1-alkoxy-2(diethoxyphosphoryl)cyclopentene (**6**)

Method	*n*	RX	Yield **5**	Yield **6**
A	1	EtBr	43	32
	1	EtI	60	20
	2	EtI	39	29
B	1	MeOTs	26	54
	1	EtOTs	10	54
	2	MeOTs	4	62

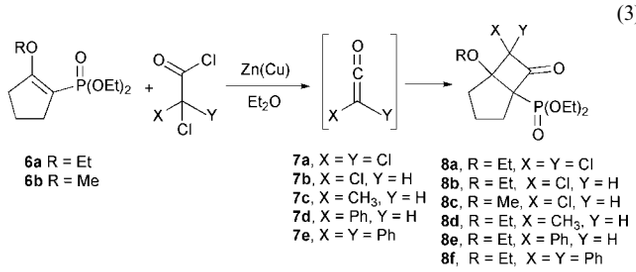
Table 2 [2+2] Cycloadditions of 1-Alkoxy-2-(Diethoxyphosphoryl)-cyclopentene (**6a**, **6b**) with Ketenes

R	Ketene	Product (Yield)
Et	**7a**	**8a** + **8b** (41)
Et	**7b**	**8b** (51)
Me	**7b**	**8c** (47)
Et	**7c**	**8d** (0)
Et	**7d**	**8e** (0)
Et	**7e**	**8f** (0)

reagent in a polar aprotic solvent (Method B). Thus, cyclic β-keto phosphonate **4** was combined with KH and alkyl tosylate in the presence of DMSO. This procedure afforded predominately O-alkylated products **6**, which were easily separated from C-alkylated products *via* chromatography. Attempts to form the siloxy substituted vinyl ether by reaction of cyclic β-keto phosphonates with a variety of bases (NaH, KH, nBuLi, or LDA), followed by addition of chloro trimethylsilane, resulted only in recovery of unreacted starting material. The steric bulk of the large trimethyl silyl group adjacent to the phosphonate group most likely prevented O-silylation.

Thermal [2+2] cycloadditions were carried out in diethyl ether at room temperature using ketenes **7**, generated from the corresponding acid chloride in the presence of activated zinc [eqn. (3)]. Moderate yields of cycloadduct **8** were obtained *via*

(3)



6a R = Et
6b R = Me

7a, X = Y = Cl
7b, X = Cl, Y = H
7c, X = CH_3, Y = H
7d, X = Ph, Y = H
7e, X = Y = Ph

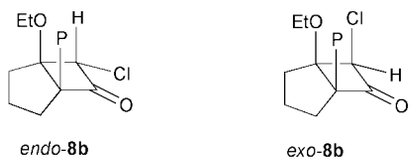
8a, R = Et, X = Y = Cl
8b, R = Et, X = Cl, Y = H
8c, R = Me, X = Cl, Y = H
8d, R = Et, X = CH_3, Y = H
8e, R = Et, X = Ph, Y = H
8f, R = Et, X = Y = Ph

this procedure when reactive chloro ketenes were utilized (Table 2). Only one regioisomer was obtained in all cases. Interestingly, when dichloroketene **7a** was generated and reacted with vinyl phosphonate, two products were isolated, the dichloro bicyclic compound **8a** and the monochloro bicyclic compound **8b**. It was found that the ratio of these products was dependent on the addition rate of acid chloride to the reaction mixture. For example, when the acid chloride was added slowly to the reaction mixture, more of the dichloro product **8a** was isolated (1.4:1 ratio of **8a**:**8b**). Since excess activated zinc was utilized, the zinc caused reduction of a chlorine. Reaction with monochloro ketene **7b** afforded product **8b** as expected in good yields. Less reactive alkyl and aryl ketenes **7c–e** did not result in any cycloaddition products.

The monochloro product **8b** was identified by the ^{1}H NMR signal at 5.32 ppm, characteristic of a methine proton flanked by a halogen and an adjacent carbonyl group. Additionally, all cycloadducts were easily identified by the strong carbonyl absorption in the IR at approximately 1800 cm^{-1}, indicative of a cyclobutanone carbonyl stretch. The ^{1}H and ^{13}C NMR spectra of **8b** attained *via* cycloaddition with chloroketene **7b**, were identical to the NMR spectra of the byproduct isolated upon reaction of dichloroketene **7a**.

Cycloaddition *via* generation of ketenes under basic conditions, using Et_3N in ether, did not afford cycloadducts. This is not surprising since tetrasubstituted alkenes are known to undergo cycloaddition only when using the zinc method for preparation of the ketenes.[25] Although it has been reported that improved yields were observed when the cycloaddition of dichloroketene with unreactive alkenes was conducted in the presence of phosphorus oxychloride,[26] in our hands no additional benefit resulted upon utilization of this procedure.

Cycloaddition of the monosubstituted ketene **7b** occurred to afford a single regioisomer of **8b** and **8c**. Analysis by ^{1}H NMR of **8b** and **8c** showed signals at 5.3 ppm for the methine proton as a doublet (J = 6.9 Hz) for both compounds **8b** and **8c**.



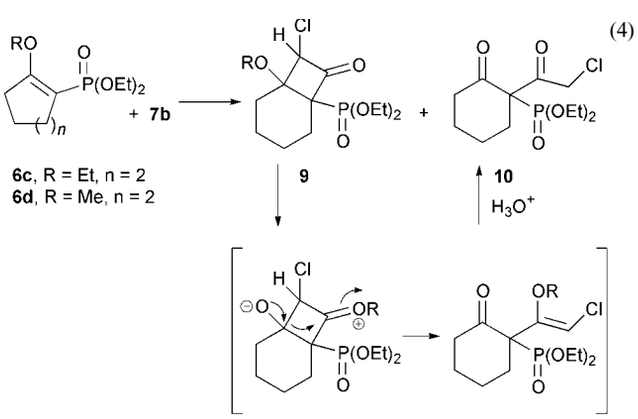
endo-**8b** *exo*-**8b**

P = P(O)(OEt)$_2$

This points to the formation of the *endo* isomer, since the *cis* relationship of the methine proton and the phosphorus would be expected to give strong four-bond P–H coupling as observed. Previous reports have shown that unsymmetrical ketenes undergo cycloaddition stereospecifically to give exclusive formation of the endo isomer.[17]

The vinyl phosphonates **6c** and **6d**, derived from cyclohexanone, proved to be less reactive than the cyclopentanone counterpart [eqn. (4)]. Cycloaddition under the same condi-

(4)



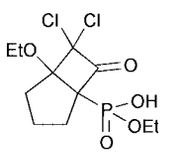
tions with chloroketene **7b** resulted in formation of a mixture of cycloadduct **9**, ring opened product **10**, and keto phosphonate **4** (n = 2), along with approximately 60% of unreacted starting material **6**. Reaction of **6c** with the more reactive dichloroketene **7a** did not yield substantially more cycloadducts.

Ring opened products like **10** have been observed in the cycloaddition of six membered ring silyl enol ethers with dichloroketene.[21] The suggested pathway for formation of these products involves migration of the R group of **9** from the alkoxy oxygen to the carbonyl oxygen. Close proximity of the alkoxy and carbonyl groups allows for this migration to occur readily. Subsequent ring opening of the four membered ring affords a vinyl ether which could be hydrolyzed upon workup to generate **10**.

These results show for the first time that donor–acceptor-substituted alkenes are capable of undergoing cycloaddition with ketenes. In the case of the β-ethoxy vinylphosphonate, the strong donating ability of the ethoxy group outweighs any electron disadvantage provided from the electron-withdrawing phosphonate group. A more powerful electron-withdrawing

group of a donor–acceptor-substituted alkene may inhibit the cycloaddition reaction. This was proven when our attempts at reaction of β-ethoxyvinylphosphonium salts with ketenes did not result in any cycloaddition products. Since the triphenylphosphonium salt is a more powerful electron-withdrawing group, and is also more sterically hindered than the phosphonate group, no cycloadduct was formed.

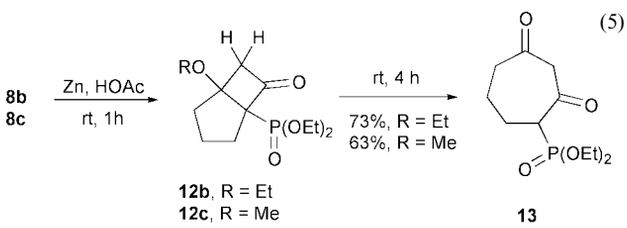
The conditions for dechlorination and fragmentation of the cycloadducts **8**, to afford ring enlarged products, were also examined. Cleavage of the ether group in these bicyclic adducts would afford a bicyclic system containing an electron donating hydroxy group and an electron withdrawing phosphonate group. Fragmentation should readily provide ring expansion by two carbons. Attempted cleavage of the ethyl ether group by use of chlorotrimethylsilane and NaI afforded only starting materials. Alternate attempts to cleave the ethoxy group prior to dechlorination, using tetrachlorosilane and NaI,[27] resulted in cleavage of one of the phosphonate esters to afford monophosphonic acid **11**. Steric congestion around the ethyl ether makes



11

this site less accessible, and thus attack occurred predominately at the phosphonate ester linkage.

Since ether cleavage was not successful, dechlorination of the cycloadducts was attempted in order to decrease the steric hindrance around the ether site. However, dechlorination of **8b** and **8c** by reaction with tributyltin hydride in the presence of 2,2-azobisisobutyronitrile (AIBN) resulted in a small amount of dechlorinated product along with a mixture of unidentifiable materials. However, upon use of zinc in acetic acid, both dechlorination and ether cleavage occurred to yield ring expanded product **13** in good yields [eqn. (5)]. If the reaction



(5)

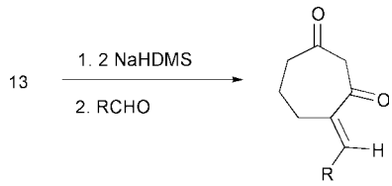
12b, R = Et
12c, R = Me

13

was allowed to stir for short periods of time, dechlorinated cycloadduct **12** was isolated. By allowing the mixture to stir for 5 hours, ether cleavage occurred, and subsequent fragmentation resulted to give cycloheptanone **13**. It is interesting to note that even while heating to 80 °C in acetic acid, none of the monophosphonic acid product **11** was observed.

Finally, ring expanded product **13** was subjected to a base induced HWE reaction. It has been reported that acyclic γ-phosphorylated ethyl acetoacetate, when reacted with two equivalents of base followed by an aldehyde or a ketone, reacted exclusively at the phosphorus terminus to afford moderate to good yields of HWE products.[28–30] Several conditions were explored in the reaction of **13** to afford HWE products. Use of KHMDS in 18-crown-6 afforded none of the desired products. However, when two equivalents of NaHMDS were combined with **13** in THF, followed by addition of an aldehyde, alkene **14** was obtained [eqn. (6)].

In both cases, only the *E*-isomer was isolated. The stereochemistry was evident by the downfield chemical shift of the vinyl proton of **14**. For example, in the spectrum of **14a**, where *R* = Ph, the vinyl signal occurred at 7.73 ppm, and the C-5 protons occurred as a doublet of doublets at 2.97 ppm, being



(6)

14a, R = Ph
14b, R = Pr

in the deshielded region of the phenyl ring. After heating the *E*-isomer, a mixture of *E*- and *Z*-isomers was obtained. The vinyl signal of the *Z*-isomer occurred at 7.55 ppm and the C-5 protons at 2.4 ppm.

In conclusion, we have shown that tetrasubstituted donor–acceptor-substituted alkenes are capable of undergoing [2+2] cycloaddition reactions with reactive chloroketenes, but not with less reactive alkyl or aryl ketenes. These bicyclic adducts undergo facile ring opening in the presence of zinc and acetic acid without affecting the phosphonate group. Thus, this procedure affords access to seven membered rings containing a phosphonate substituent. These rings were shown to undergo a HWE reaction with aldehydes to provide an external alkene. Similar systems, with an appended aldehyde-containing side chain, should be capable of undergoing intramolecular HWE to provide ring expanded bicyclic systems containing bridgehead alkenes.

Experimental

For reactions requiring anhydrous conditions, THF and diethyl ether were distilled from sodium–benzophenone ketyl in a recycling still. Diisopropylamine and triethylamine were distilled from calcium hydride and stored over molecular sieves. Acid chlorides were distilled from anhydrous K_2CO_3 and used immediately. All reactions were carried out under a positive pressure of nitrogen or argon. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 75.61 MHz in $CDCl_3$ using TMS as an internal standard. IR spectra were obtained from neat films and recorded on a Perkin-Elmer Series 1600 FT IR. Column chromatography was performed on E. M. Science silica gel 60 (230–400 mesh). Analyses by gas chromatography were performed on a Shimadzu GC-14A using a methyl 5% silicone glass capillary column (0.32 mm × 15 m). Elemental analyses were conducted at Atlantic Microlabs, Norcross, GA. HRMS analyses were conducted at UCR Mass Spec Facility, Riverside, CA.

1-Ethoxy-2-(diethoxyphosphoryl)cyclopentene (6a)

Method A. Following the general procedure noted in reference 24, 2-(diethoxyphosphoryl)cyclopentanone (9.92 g, 45 mmol) was combined with Bu_4NHSO_4 (15.3 g, 45 mmol), 2 M NaOH (45 mL, 90 mmol) and EtI (8.23 mL, 103.5 mmol) to afford **6a** (2.26 g, 20.5%).

Method B. Cyclic β-keto phosphonate **4** (*n* = 1), (0.526 g, 2.39 mmol) was added to a slurry of KH (0.105 g, 2.63 mmol) in DMSO. After stirring at room temperature for one hour, ethyl toluene-*p*-sulfonate (0.526 g, 2.63 mmol) was added to the reaction mixture. The mixture was stirred at room temperature for 40 h, then the reaction was quenched with ice-cold water. The product was extracted into 20 mL of CH_2Cl_2, and the organic layer was washed with water, dried over $MgSO_4$ and solvent evaporated to form a yellow oil. The product was purified by column chromatography (EtOAc) to afford **5a** (0.061 g, 10.3%) and **6a** (0.321 g, 54.2%). IR (film) 2980, 2904, 2867, 1627, 1444, 1391, 1341, 1237, 1133, 1032, 959 cm^{-1}. ^{1}H NMR δ 4.15–4.0 (m, 6 H), 2.58 (m, 4 H), 1.93 (quintet, *J* = 7.5 Hz, 2 H), 1.33 (t, *J* = 7 Hz, 6 H), 1.30 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR δ 169.6

(d, J_{CP} = 6.8 Hz), 98.4 (d, J_{CP} = 195.8), 65.9, 61.2, 61.1, 31.5 (d, J_{CP} = 16.6 Hz), 30.9 (d, J_{CP} = 11.3 Hz), 21.0 (d, J_{CP} = 13.6 Hz), 16.4, 16.3, 15.4. MS *m*/*z* (relative intensity): 248 (M^+, 5), 233 (13), 219 (24), 191 (12), 163 (68), 145 (15), 111 (32), 83 (70), 81 (67), 65 (40), 29 (base peak), 127 (67).

1-Methoxy-2-(diethoxyphosphoryl)cyclopentene (6b)

Following Method B keto phosphonate, **4**, (0.55 g, 2.5 mmol), KH (0.11 g, 2.75 mmol) and 10 mL DMSO were combined, followed by addition of methyl toluene-*p*-sulfonate (0.51 g, 2.75 mmol). Purification by column chromatography afforded **5b** (0.154 g, 26%) and **6b** (0.319 g, 54%). IR: (film): 2980, 2919, 2896, 2855, 1629, 1459, 1345, 1236, 1135, 1049, 1029, 958 cm^{-1}. ^1H NMR δ 4.08 (m, 4H), 3.79 (s, 3H), 2.65 (m, 2H), 2.55 (m, 2H), 1.95 (quintet, J = 7.5 Hz, 2H), 1.32 (t, J = 7.1 Hz, 6H). ^{13}C NMR δ 170.6 (d, J_{CP} = 9.1 Hz), 97.4 (d, J_{CP} = 196.9 Hz), 61.2, 61.1, 57.6, 31.2 (d, J_{CP} = 9.1 Hz), 31.1 (d, J_{CP} = 3.8 Hz), 20.8 (d, J_{CP} = 15.9 Hz), 16.4, 16.3. Anal. Calcd. for $C_{10}H_{19}PO_4$: C, 51.27; H, 81.8. Found: C, 51.16; H, 8.11%.

1-Methoxy-2-(diethoxyphosphoryl)cyclohexene (6d)

Following Method B, cyclic β-keto phosphonate, **4** (n = 2), (0.404 g, 1.73 mmol) was combined with KH (76.2 mg, 1.9 mmol) and methyl toluene-*p*-sulfonate (0.355 g, 1.9 mmol) to give **5d** (14 mg, 4%), and **6d** (266 mg, 62%). NMR data were identical to previously reported compounds (reference 23).

General procedure for cycloaddition with ketenes

Activation of zinc. This procedure is a slight modification of the procedure reported by Krepski and Hassner.[21] A suspension of zinc (5.0 g) in 30 mL of H_2O was degassed by bubbling N_2 through it for 15 min. Then $CuSO_4 \cdot 5H_2O$ (0.35 g) was added at once. The black suspension was stirred under N_2 for 45 min. The Zn–Cu couple was transferred to a sintered glass funnel and washed successively with H_2O and acetone. The Zn–Cu couple was then transferred to a round-bottomed flask and dried in a vacuum oven at 100 °C for 24 h.

Ketene generation and cycloaddition. A three-necked flask equipped with two addition funnels, a magnetic stirrer and N_2 inlet was flame dried while being purged with N_2. When cool, the flask was charged with activated zinc (0.25 g) and 5 mL of anhydrous ether. The mixture was stirred under N_2 while a solution of trichloroacetyl chloride (0.094 mL, 0.846 mmol) in 10 mL anhydrous ether and a solution of vinyl phosphonate **6a** (0.07 g, 0.282 mmol) were added dropwise over 5 h. The reaction was allowed to stir at room temperature for 3 more days. The reaction mixture was then filtered to remove unreacted zinc, and the zinc was washed with ether. A saturated solution of $NaHCO_3$ was added to the reaction mixture to precipitate $ZnCl_2$. The solid residue was filtered and the ether extracts were washed again with $NaHCO_3$. The organic phase was then dried over K_2CO_3, filtered and concentrated to give a brownish oil. The crude product was purified by column chromatography on silica gel (1 : 1 EtOAc–CH_2Cl_2) to afford 7,7-dichloro-1-ethoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]heptan-6-one **8a** (24 mg, 24%), 7-chloro-1-ethoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]-heptan-6-one **8b** (16 mg, 17%) and recovered 2-(diethoxyphosphoryl)cyclopentanone **4** (19 mg , 31%).

7,7-Dichloro-1-ethoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]-heptan-6-one (8a). IR (film): 2979, 2930, 1799, 1600, 1445, 1392, 1261, 1154, 1052, 1024, 970 cm^{-1}. ^1H NMR δ 4.3 (m, 2 H), 4.15 (m, 2H), 3.78 (m, 1H), 3.62 (m, 1H), 2.72 (dd, J = 13.1, 6.2 Hz, 1H), 2.45–2.18 (m, 3H), 2.05 (m, 1H), 1.68 (m, 1H), 1.34 (t, J = 6.8 Hz, 6H), 1.32 (t, J = 6.8 Hz, 3H). ^{13}C NMR δ 194.2 (d, J_{CP} = 7.6 Hz), 92.9 (d, J_{CP} = 3 Hz), 91.1 (d, J_{CP} = 6.8 Hz), 75.2 (d, J_{CP} = 141.1 Hz), 63.6 (d, J_{CP} = 6 Hz), 63.1, 62.4 (d, J_{CP} = 6.8 Hz), 35.2 (d, J_{CP} = 3.8 Hz), 34.9 (d, J_{CP} = 1.5 Hz), 25.5 (d, J_{CP} = 15 Hz), 16.5 (d, J_{CP} = 6.8 Hz), 16.4, 15.0. MS *m*/*z* (relative intensity) 358 (M^+, 2), 322 (30), 295 (9), 259 (9), 220 (16), 176 (17), 137 (18), 109 (30), 81 (44), 65 (35), 29 (100), 27 (40). Anal. calcd. for $C_{13}H_{21}Cl_2PO_5$: C, 43.47; H, 5.89; Cl, 19.74. Found: C, 43.59; H, 5.96; Cl, 19.66%.

7-Chloro-1-ethoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]-heptan-6-one (8b). Following the general procedure for cycloaddition with ketenes, β-ethoxyvinyl phosphonate **6a** (0.36 g, 1.48 mmol) was combined with chloroacetyl chloride (0.43 mL, 4.43 mmol) and activated zinc (1.3 g) in 90 mL anhydrous ether to yield **8b** (0.24 g, 51%) and 2-(diethoxyphosphoryl)-cyclopentanone (0.08 g, 25%) was recovered. IR (film): 2978, 2933, 2879, 1792, 1445, 1392, 1315, 1257, 1098, 1026, 969 cm^{-1}. ^1H NMR δ 5.32 (d, J = 6.9 Hz, 1H), 4.18 (m, 4H), 3.62 (m, 2H), 2.52 (dd, J = 6.4, 12.5 Hz, 1H), 2.3–1.9 (m, 4H), 1.5 (m, 1H), 1.31 (t, J = 7Hz, 3H), 1.30 (t, J = 7 Hz, 3H), 1.25 (t, J = 7 Hz, 3H). ^{13}C NMR δ 198.5 (d, J_{CP} = 5.7 Hz), 88.8, (d, J_{CP} = 4.5 Hz), 74.8 (d, J_{CP} = 144.4 Hz), 68.4 (d, J_{CP} = 3.8 Hz), 62.8 (d, J_{CP} = 6 Hz), 62.6 (d, J_{CP} = 6 Hz), 62.2, 33.3, 32.5 (d, J_{CP} = 4.5 Hz), 25.2 (d, J_{CP} = 15.1 Hz), 16.5 (d, J_{CP} = 2.3 Hz), 16.4 (d, J_{CP} = 3 Hz), 15.5. MS *m*/*z* (relative intensity) 324 (M^+, 1.3), 288 (9), 261 (14), 231 (7), 205 (7), 186 (8), 163 (10), 109 (12), 81 (20), 29 (100), 27 (41). Anal. Calcd. for $C_{13}H_{22}ClPO_5$: C, 48.08; H, 6.83; Cl, 10.92. Found: C, 47.82; H, 6.79; Cl, 10.69%.

7-Chloro-1-methoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]-heptan-6-one (8c). Following the general procedure for cycloaddition with ketenes, **6b** (260 mg, 1.11 mmol) was combined with chloroacetyl chloride (0.32 mL, 3.33 mmol) and activated zinc (0.9 g) in 70 mL anhydrous ether. Purification by column chromatography gave **8c** (161 mg, 47%) and recovered **4** (51 mg, 21%). ^1H NMR δ 5.31 (d, J = 6.9 Hz, 1 H), 4.17 (m, 4 H), 3.45 (s, 3 H), 2.55 (m, 1 H), 2.3–1.9 (m, 4 H), 1.5 (m, 1 H), 1.34 (t, J = 7.1 Hz, 3 H), 1.33 (t, J = 7.1 Hz, 3 H). ^{13}C NMR δ 198.3 (d, J_{CP} = 6.0 Hz), 89.4 (d, J_{CP} = 4.5 Hz), 74.4 (d, J_{CP} = 144.4 Hz), 67.9 (d, J_{CP} = 3.8 Hz), 62.9 (d, J_{CP} = 3.0 Hz), 54.1, 33.3, 31.9 (d, J_{CP} = 3.8 Hz), 25.1 (d, J_{CP} = 15.1 Hz), 16.5, 16.4. IR (film) 2978, 2936, 2834, 1793, 1445, 1392, 1313, 1256, 1097, 1027, 968 cm^{-1}. Anal. Calcd. for $C_{12}H_{20}ClPO_5$: C, 46.39; H, 6.49; Cl, 11.41. Found: C, 46.10; H, 6.39; Cl, 11.29%.

8-Chloro-1-ethoxy-5-(diethoxyphosphoryl)bicyclo[4.2.0]-octan-7-one (9c). Following the general procedure for cycloaddition with ketenes, β-ethoxyvinyl phosphonate **6c** (0.207 g, 0.79 mmol) was combined with chloroacetyl chloride (0.23 mL, 2.37 mmol) and activated zinc (0.7 g) in 50 mL anhydrous ether. After work-up a brownish oil was obtained. From the GC of the reaction mixture, 64% was unreacted vinylphosphonate **6c**, 15% was cycloadduct **9**, 7% was **10** and 8% was β-keto-phosphonate **4** (n = 2). Purification by column chromatography gave **9c** (16.5 mg, 21%), **10** (7.7 mg, 10.8%), **6c** (0.146 g) and **4** (15.5 mg, 29%). IR (film) 2980, 2938, 2867, 1795, 1445, 1392, 1290, 1244, 1052, 1024, 968 cm^{-1}. ^1H NMR δ 5.92 (d, J = 4.8 Hz, 1H), 4.22 (m, 2H), 4.08 (m, 2H), 3.68 (m, 2H), 2.15 (m, 2H), 1.92 (m, 1H), 1.75–0.9 (m, 5H), 1.33 (t, J_{CP} = 6.9 Hz, 3H), 1.3 (t, J = 6.9 Hz, 3 H), 1.28 (t, J_{CP} = 6.9 Hz, 3H). ^{13}C NMR δ 194.9 (d, J_{CP} = 6.8 Hz), 76.2 (d, J_{CP} = 8.3 Hz), 68.8 (d, J_{CP} = 1.5 Hz), 68.4 (d, J_{CP} = 130.8 Hz), 63.5 (d, J_{CP} = 6.0 Hz), 62.5 (d, J_{CP} = 6.0 Hz), 61.0, 26.6 (d, J_{CP} = 5.3 Hz), 23.8 (d, J_{CP} = 3.0 Hz), 20.2 (d, J_{CP} = 7.6 Hz), 18.4, 16.4 (d, J_{CP} = 6.8 Hz), 16.3, 15.6. Anal. Calcd. for $C_{14}H_{24}ClPO_5$: C, 49.64; H, 7.14; Cl, 10.47. Found: C, 49.92; H, 7.18; Cl, 10.24%.

2-Diethoxyphosphoryl-2-(2-chloroacetyl)cyclohexanone (10). ^1H NMR δ 4.25 (s, 2 H), 4.05 (m, 4 H), 2.3 (m, 4 H), 1.8 (m, 2 H), 1.65 (m, 2 H), 1.35 (t, J = 7.0 Hz, 6 H).

8-Chloro-1-methoxy-5-(diethoxyphosphoryl)bicyclo[4.2.0]-octan-7-one (9d). Following the general procedure for cyclo-

addition with ketenes, **6d** (0.15 g, 0.605 mmol) was combined with chloroacetyl chloride (0.17 mL, 1.81 mmol) and activated zinc (0.5 g) in 35 mL anhydrous ether. After work-up, a brownish oil was obtained. GC of the reaction mixture showed that 49% was unreacted starting material **6d**, 11.1% was cycloadduct **9d**, 8.6% was compound **10** and 17.7% was β-keto phosphonate **4**. Purification by column chromatography gave **9d** (16.8 mg, 16%), **10** (11.2 mg, 11.2%) and recovered **6d** (70 mg) and **4** (16.6 mg, 23.4%). IR (film) 2944, 2896, 2834, 1794, 1450, 1391, 1291, 1244, 1051, 1023, 969 cm^{-1}. ^1H NMR δ 5.89 (d, $J = 4.9$ Hz, 1 H), 4.15 (m, 4 H), 3.45 (s, 3 H), 2,15 (m, 2 H), 1.95 (m, 2 H), 1.75–1.4 (m, 4 H), 1.32 (t, $J = 7.0$ Hz, 3 H), 1.31 (t, $J = 7.0$ Hz, 3 H). ^{13}C NMR δ 194.8 (d, $J_{CP} = 6.9$ Hz), 76.4 (d, $J_{CP} = 6.8$ Hz), 68.4 (d, $J_{CP} = 4.5$ Hz), 68.0 (d, $J_{CP} = 129.8$ Hz), 63.3 (d, $J_{CP} = 6.0$ Hz), 62.5 (d, $J_{CP} = 6.8$ Hz), 52.7, 25.5 (d, $J_{CP} = 4.5$ Hz), 23.7 (d, $J_{CP} = 3.0$ Hz), 20.1 (d, $J_{CP} = 9.1$ Hz), 18.3, 16.4 (d, $J_{CP} = 3.0$ Hz), 16.3 (d, $J_{CP} = 3.8$ Hz). Anal. Calcd. for $C_{13}H_{22}ClPO_5$: C, 48.08; H, 6.83; Cl, 10.92. Found: C, 47.84; H, 6.77; Cl, 10.82%.

General procedure for dechlorination and ring expansion of cycloadduct

4-(Diethoxyphosphoryl)cycloheptane-1,3-dione (13). In a round-bottomed flask, cycloadduct **8b** (0.69 g, 2.16 mmol) was combined with unactivated zinc dust (1.13 g) and 10 mL of acetic acid. The mixture was allowed to stir at room temperature for 5 h. The reaction mixture was filtered to remove the unreacted zinc, and the solids were washed with ethyl acetate. The organic layer was then washed with water and saturated $NaHCO_3$ solution, dried over anhydrous K_2CO_3, filtered and evaporated to afford a yellow oil. Purification by column chromatography (EtOAc) gave ring expansion product **13** (0.41 g, 73%). IR (film) 2984, 2932, 1721, 1701, 1452, 1393, 1250, 1023, 968 cm^{-1}. ^1H NMR δ 4.25–4.1 (m, 5 H), 3.43 (d, $J = 13.5$ Hz, 1 H), 3.15 (m, 1 H), 2.6 (m, 2 H), 2.4–2.15 (m, 3 H), 1.75 (m, 1 H), 1.34 (t, $J = 7.3$ Hz, 3 H), 1.31 (t, $J = 7.3$ Hz, 3 H). ^{13}C NMR δ 202.0, 199.1 (d, $J_{CP} = 6.0$ Hz), 63.1 (d, $J_{CP} = 2.3$ Hz), 63.0 (d, $J_{CP} = 2.3$ Hz), 59.7, 53.5 (d, $J_{CP} = 128.5$ Hz), 43.7, 25.7 (d, $J_{CP} = 4.5$ Hz), 22.8 (d, $J_{CP} = 15.1$ Hz), 16.5, 16.4. Anal. Calcd. for $C_{11}H_{19}O_5P$: C, 50.38; H, 7.30. Found: C, 50.27; H, 7.26%.

1-Ethoxy-5-(diethoxyphosphoryl)bicyclo[3.2.0]heptan-6-one (12b). In the above procedure, when the reaction was quenched after one hour, the dechlorinated product **12b** was obtained. IR (film) 1782 cm^{-1}. ^1H NMR δ 4.2 (m, 4 H), 3.65–3.45 (m, 3 H), 2.91 (dd, $J = 17.8$ Hz, 5.3 Hz, 1 H), 2.25–2.0 (m, 5 H), 1.6 (m, 1 H), 1.31 (t, $J = 7.1$ Hz, 6 H), 1.26 (t, $J = 7.0$ Hz, 3 H).

7,7-Dichloro-1-ethoxy-5-(ethoxyhydroxyphosphoryl)bicyclo-[3.2.0]heptan-6-one (11). Cycloadduct **8a** (46 mg, 0.128 mmol) and NaI (28.6 mg, 0.192 mmol) were dissolved in acetonitrile in a vial. Then 1.0 M $SiCl_4$ (0.192 mL, 0.192 mmol) was added to form iodotrichlorosilane. The solution turned yellow and NaCl precipitated immediately. The vial was heated at 55 °C for 16 h. Methanol was then added to the vial and insoluble solids were filtered out. Solvents were evaporated to give a brownish residue. Purification of the crude compound **11** (33.4 mg, 79%) was attempted by column chromatography (silica gel, EtOAc was first applied to remove impurities, then the solvent was changed to 1 : 1 EtOAc–CH_3COOH to pull off the polar compound) but no clean spectrum was obtained. Crude ^1H NMR δ 4.25 (m, 2 H), 3.7 (m, 2 H), 2.75 (m, 1 H), 2.45–2.15 (m, 3 H), 2.05 (m, 1 H), 1.68 (m, 1 H), 1.35 (m, 6 H). IR (film) 3404 (br), 2977, 2930, 1788, 1711, 1572, 1447, 1314, 1217, 1150, 1078 cm^{-1}.

(4*E*)-4-(Benzylidene)cycloheptane-1,3-dione (14a). In a round-bottomed flask, 1.0 M sodium bis(trimethylsilyl) amide (0.76 mL, 0.76 mmol) was added slowly to a solution of ring expansion product **13** (100 mg, 0.38 mmol) in 10 mL THF at 0 °C. The solution was then warmed to room temperature. After stirring for 1.5 h, freshly distilled benzaldehyde (0.039 mL, 0.38 mmol) was added to the dianion and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic layer was then washed with saturated NaCl solution, dried over $MgSO_4$ and the solvent was evaporated to give a yellow oil. By GC, the yield of compound **14a** was 61%. Preparative TLC (CH_2Cl_2 as solvent) was used to purify compound **14a** (20 mg, 24%). IR (film) 3055, 3024, 2931, 2867, 1715, 1682, 1607, 1574, 1493, 1446, 1265, 1200, 1160, 1028, 1012, 916 cm^{-1}. ^1H NMR δ 7.73 (s, 1 H), 7.4 (m, 5 H), 3.82 (s, 2 H), 2.97 (dd, $J = 6.7$, 6.4 Hz, 2 H), 2.69 (t, $J = 7.0$ Hz, 2 H), 2.06 (quintet, $J = 6.7$ Hz, 2 H). ^{13}C NMR δ 203.6, 194.3, 139.0, 135.3, 129.5, 128.9, 128.7, 58.9, 43.5, 26.0, 24.2. HRMS, calcd. for $C_{14}H_{14}O_2$ 214.0994, found 214.0983.

(4*Z*)-4-(Benzylidene)-cycloheptan-1,3-dione (14a). Compound **14a** was partially converted to its *Z*-isomer upon heating or storage at room temperature over a period of time. The ^1H NMR spectrum of a mixture of *E*- and *Z*-isomers was recorded. The NMR peaks of the *Z*-isomer could be assigned as follows. ^1H NMR δ 7.55 (s, 1 H), 7.4 (m, 5 H), 2.55 (m, 2 H), 2.48 (s, 2 H), 2.4 (t, $J = 7.0$ Hz, 2 H), 1.8 (quintet, $J = 6.7$ Hz, 2 H).

(4*E*)-4-(Butylidene)cycloheptane-1,3-dione (14b). In a round-bottomed flask, 1.0 M sodium bis(trimethylsilyl) amide (0.33 mL, 0.33 mmol) was added slowly to a solution of ring expansion product **13** (43.4 mg, 0.165 mmol) in 5 mL THF at 0 °C. The solution was then warmed to room temperature. After stirring for 1.5 h, freshly distilled butyraldehyde (15 μL, 0.165 mmol) was added to the dianion and the reaction mixture was stirred at room temperature for 24 h. Following the general work-up procedure as in formation of **14a**, the yield of **14b** was 41% by GC. The mixture was then purified by preparative TLC (CH_2Cl_2 as solvent) to give pure **14b** (6.0 mg, 20%). IR (film) 2960, 2919, 2861, 1713, 1684, 1618, 1455, 1208, 1138, 908 cm^{-1}. ^1H NMR δ 6.83 (t, $J = 7.7$ Hz, 1 H), 3.70 (s, 2 H), 2.71 (dd, $J = 6.7$, 6.4 Hz, 2 H), 2.62 (t, $J = 7.0$ Hz, 2 H), 2.18 (q, $J = 7.5$ Hz, 2 H), 1.92 (quintet, $J = 6.7$ Hz, 2 H), 1.5 (sextet, $J = 7.4$ Hz, 2 H), 0.95 (t, $J = 7.4$ Hz, 3 H). ^{13}C NMR δ 204.4, 194.0, 142.8, 137.0, 58.7, 43.5, 30.1, 25.2, 24.2, 22.0, 14.0. HRMS, calcd. for $C_{11}H_{16}O_2$ 180.1150, found 180.1155.

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