Alkylation of enolate anions with dimethyl 3-bromo-2-ethoxypropenylphosphonate. A convergent cyclopentenone annulation method

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A new, convergent synthesis of 2-cyclopenten-1-ones is reported. Treatment of dimethyl 2-oxopropylphosphonate (**21**) with excess triethyl orthoformate in the presence of ferric chloride hexahydrate provides the enol ether **22**, which upon allylic bromination with *N*-bromosuccinimide yields the allylic bromide **19**. Alkylation of the ketones **24–28** with **19**, followed by mild acid hydrolysis of the resultant products **29–33**, affords the diketo phosphonates **34–38**. When the latter substances are treated with sodium hydride in dimethoxyethane, the corresponding 2-cyclopenten-1-ones **40–44** are formed in good yields.

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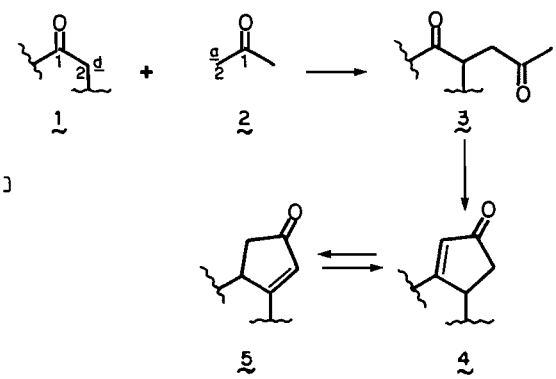
On rapporte une nouvelle synthèse convergente des cyclopentène-2 ones-1. L'oxo-2 propylphosphonate de diméthyle (**21**) réagit avec un excès d'orthoformiate de triéthyle en présence du chlorure ferrique hexahydraté en donnant l'éther énolique **22** qui par bromation allylique avec la NBS conduit au bromure **19**. L'alkylation des cétones **24–28** avec le composé **19** suivie d'une hydrolyse acide douce des produits obtenues (**29–33**) conduit aux dicétophosphonates **34–38**. Ces derniers composés réagissent avec l'hydrure de sodium dans le diméthoxyéthane en donnant les cyclopentène-2 ones-1 correspondantes (**40–44**) avec de bons rendements.

[Traduit par le journal]

Introduction

Functionalized cyclopentane rings are very commonly found in structurally novel, physiologically active, and/or commercially important natural products. Consequently, it is not surprising to find that, particularly in recent times, a great deal of effort has gone into developing new, efficient methods for synthesizing five-membered ring systems.

The overall annulation scheme represented in general terms by eq. [1] constitutes an important, much employed method for preparing substituted 2-cyclopenten-1-ones. In this process, the (theoretical) combination of a d^2 synthon **1** (normal reactivity) (1) with an a^2 synthon **2** (reactivity umpolung) (1) results in the formation of a 1,4-diketone system **3**. Subjection of the latter substance to base-promoted intramolecular aldol condensation, followed by dehydration, would provide the desired enone **4**.



[1]

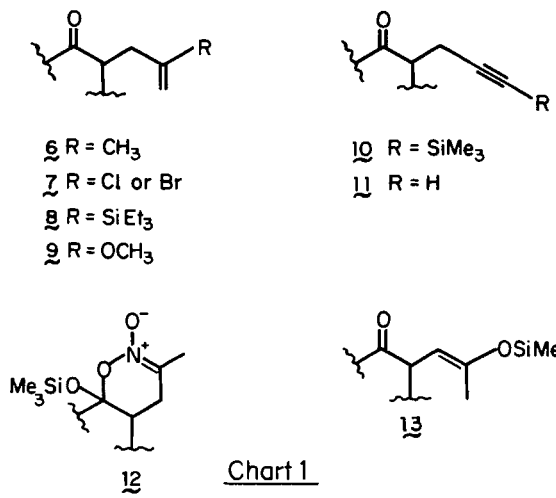


Chart 1

Various species (e.g. enolate anions, enol ethers) corresponding to the d^2 synthon **1** are prepared very readily from the corresponding ketone. However, there has been an ongoing search for efficient and generally applicable synthetic equivalents to the a^2 synthon **2**, and, thus far, a number of reagents have been employed successfully. For example, alkylation of enolate anions with 3-halo-2-methylpropenes (2–4) 2,3-dihalopropenes (5, 6), 3-iodo-2-(triethylsilyl)propene (7), 3-bromo-2-methoxypropene (8), 3-bromo-1-(trimethylsilyl)-propyne (9–11), or 3-bromopropyne (12) provides the corresponding substances of general structure **6–11**, respectively (see Chart 1). On the other hand, reaction of trimethylsilyl enol ethers with 2-nitropropene in the presence of stannic chloride or

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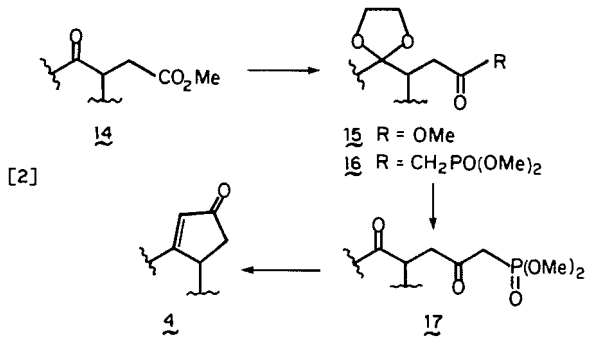
titanium tetrachloride (13) or with diazoacetone in the presence of cupric acetylacetonate (14) yields compounds of general structures **12** or **13**, respectively.

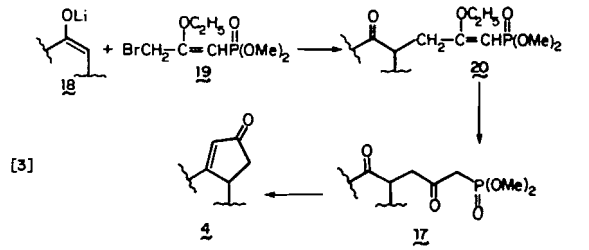
A diversity of reagents and experimental conditions are involved in converting the appendages in **6–13** into the required acetonyl side chain (cf. **3**): **6**, cleavage of the carbon–carbon double bond by ozonolysis (2, 3) or osmium tetroxide – sodium periodate (2, 4); **7**, hydrolysis of the vinyl halide function with concentrated sulfuric acid (5, 6); **8**, epoxidation with peracid, followed by acid hydrolysis of the resultant epoxy silane (7); **9**, hydrolysis of the enol ether function with aqueous oxalic acid (8); **10** and **11**, hydration of the carbon–carbon triple bond with aqueous acid in the presence of mercuric salts (10–12); **12**, hydrolysis with water – stannic chloride (or titanium tetrachloride) in refluxing dichloromethane (13); **13**, hydrolysis of the trimethylsilyl enol ether with water (14).

In general, the methods for converting **1** into **4**, as summarized above, suffer mainly from two difficulties. Firstly, the conditions required to introduce or unmask the various synthetic equivalents to the a^2 synthon **2** often have (or would have) deleterious effects on other functional groups which might be present in the ketonic (or enol ether) substrate. For example, carbon–carbon double or triple bonds and/or acid-sensitive groups[1] would certainly be susceptible to chemical reaction when subjected to many of the reagents and/or conditions summarized above. Secondly, the intramolecular aldol condensation process (**3** → **4**) can be accompanied by an undesirable base-catalyzed isomerization of the initially formed product (**4** ⇆ **5**, see eq. [1]).[2]

A method which circumvents very efficiently the second difficulty mentioned above has been reported by Heathcock and co-workers (16) and is summarized in eq. [2]. Conversion of the keto ester **14** (obtained by alkylation of the requisite ketone with methyl haloacetate) into the corresponding ketal **15**, followed by treatment of the latter substance with 2 equivalents of lithium dimethoxyphosphinylmethide ($LiCH_2PO(OMe)_2$) affords the keto phosphonate **16**. Acid-catalyzed hydrolysis of **16** gives the diketo phosphonate **17**. Treatment of **17** with base (e.g. sodium hydride) effects an intramolecular Horner–Emmons reaction, providing the annulation product **4** in good yield. Importantly, the last step produces in addition to the desired product only the weak base sodium dimethylphosphate, which is incapable of causing isomerization of the initially formed cyclopentenone **4**.



The Heathcock methodology, however, does not eliminate the first drawback mentioned previously. Clearly, the steps involving introduction and removal of the ketal protecting group (formation of **15** and **17**) could readily affect other acid-sensitive groups which might be present in the ketonic substrate. We describe herein an efficient, convergent method for effecting the conversion of **1** into **4** via a route which removes this limitation as well.[3] Essentially, the overall process, summarized in general terms in eq. [3], involves the following steps: (a) treatment of an enolate anion **18** with dimethyl 3-bromo-2-ethoxypropenylphosphonate (**19**) (cf. ref. 18) to provide the alkylation product **20**, (b) hydrolysis of **20** to give the required diketo phosphonate **17**, and (c) intramolecular Horner–Emmons reaction (**17** → **4**).



Results and discussion

(a) *Preparation of dimethyl 3-bromo-2-ethoxypropenylphosphonate* (19)

The required alkylating agent **19** was prepared efficiently as follows (see Chart 2). Treatment of dimethyl 2-oxopropylphosphonate (**21**) with excess triethyl orthoformate in the presence of a catalytic

[1]For an example of hydration of the triple bond of the propargyl group (cf. **11**) with retention of a ketal moiety, see ref. 12.

[2]Recently, an intramolecular, base-promoted aldol condensation of the type **3** → **4** was achieved without causing subsequent isomerization of the initially formed product (15). See also ref. 3.

[3]For a preliminary report regarding this work, see ref. 17.

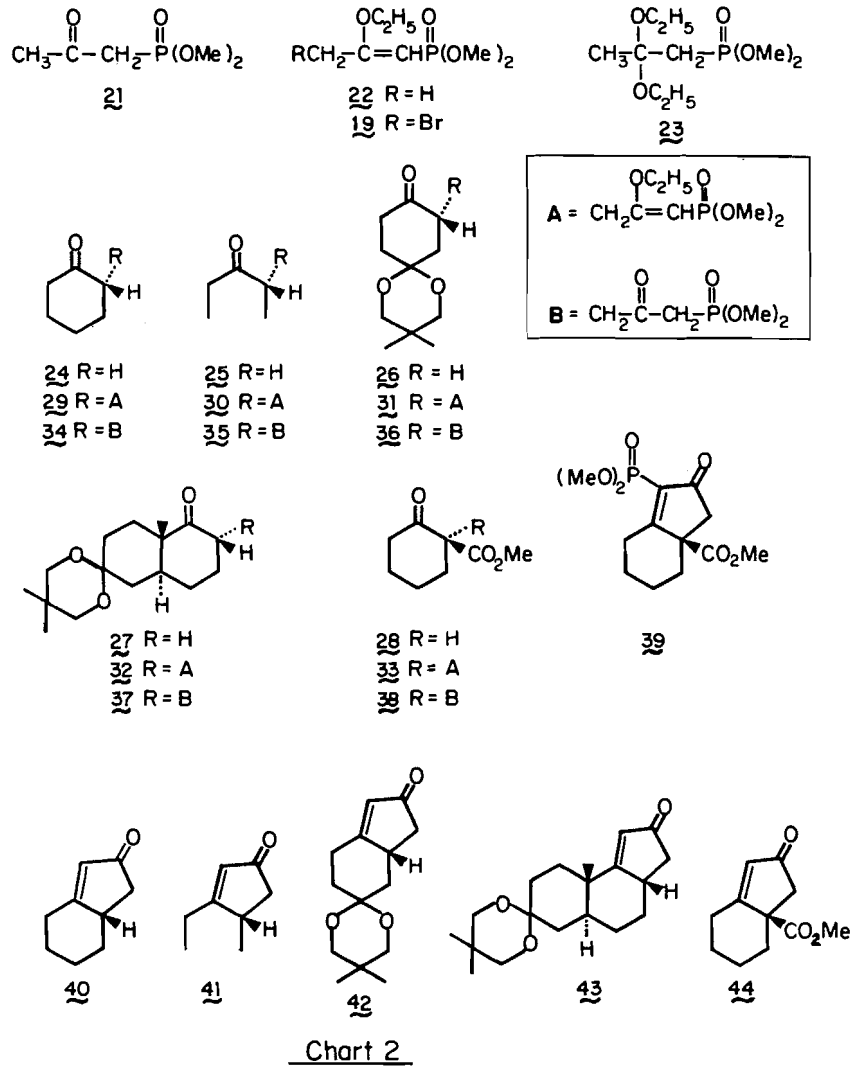


Chart 2

amount of ferric chloride hexahydrate (19) afforded mainly the desired enol ether **22**. In most of the attempts to carry out this transformation, the latter substance was accompanied by small amounts of starting material **21** and variable amounts of a second component which appeared to be dimethyl 2,2-diethoxypropylphosphonate (**23**). Therefore, in each of these cases, a dichloromethane solution of the crude product was treated with an appropriate amount of sodium hydride, which converted **23** into the desired **22** and transformed **21** into the corresponding insoluble (20) sodium salt. Filtration of the resultant mixture, followed by isolation and purification of the product, provided the enol ether **22** in 94% yield.

Allylic bromination of **22** with *N*-bromosuccinimide (21; see also ref. 18) in carbon tetrachloride afforded, after purification of the crude product by column chromatography, dimethyl 3-bromo-2-ethoxypropenylphosphonate (**19**) (76% yield). Although the ^{1}H nmr spectra of compounds **22** and **19** indicated that each of these compounds consisted very largely of one isomer, their configuration is not known. However, this point is irrelevant to the synthetic work reported herein, and therefore did not receive further attention.

(b) *Alkylation of the ketones* ***24–27*** *and the keto ester* **28** *with the bromide* **19**

The allylic bromide **19** proved to be an excellent alkylating agent. Thus, when the enolate anion of cyclohexanone was allowed to react with **19** in tetrahydrofuran (THF) (−78°C, 30 min; 0°C, 30 min; room temperature, 30 min), the alkylation product **29** was formed in quantitative yield (see Chart 2). In identical fashion, 3-pentanone (**25**)

could be converted quantitatively into the alkylated material **30**. On the other hand, application of this procedure to the keto ketal **26** (22)[4] gave the desired product **31** in mediocre yield (~40%). However, a notable improvement could be realized when 1 equivalent of hexamethylphosphoramide (HMPA) was added to the reaction mixture prior to addition of the alkylating agent **19**. This minor modification led to the formation of **31** in 78% yield. In similar fashion, alkylation (**19**, THF, 1 equivalent of HMPA) of the lithium enolates of the keto ketal **27**[5] and the keto ester **28** afforded good yields of compounds **32** and **33**, respectively. In the case of the transformation of **28** into **33**, a longer reaction time (room temperature, 6 h) was required for completion of the reaction.

It is clear from the experiments summarized above that the bromo compound **19** alkylates enolate anions very efficiently. In this sense, **19** compares favorably with the alkylating reagents involved in the formation of compounds of general structure **6–11** (*vide supra*).

(c) *Hydrolysis of compounds **29–33**. Formation of the diketo phosphonates **34–38***

The crucial step in each of the annulation sequences described herein involved hydrolysis of the enol ether functional group in the side chain of each of the compounds **29–33**. Although this transformation was expected to be straightforward in the case of the alkylation products **29**, **30**, and **33**, the keto ketals **31** and **32** were particularly important examples of the present methodology, since, in each case, the enol ether group would have to be hydrolyzed under conditions which would not affect the ketal function.

When an acetone solution of **29** containing 1 *N* hydrochloric acid was allowed to stir at room temperature for 30 min, the desired diketo phosphonate **34** was obtained in quantitative yield. An identical procedure also effected smooth conversion of **30** into **35**.

An unexpected difficulty arose in connection with attempted hydrolysis of the alkylation product **33**. Thus, subjection of the latter substance to conditions very similar to those employed for **29** and **30** gave, in addition to some of the expected product **38**, a compound which exhibited *m/e* 330 (M^+) in the mass spectrum. Although the latter material was not fully characterized, the mass spectral data along with a fairly intense infrared absorption at 1605 cm^{-1} (carbon–carbon double bond stretching vibration) suggested that this substance possessed structure **39**. Apparently, under the reaction conditions, some of the initially formed diketo phosphonate had undergone intramolecular aldol condensation. After some experimentation, it was found that this difficulty could be largely avoided quite simply by carrying out the hydrolysis of **33** with more dilute acid (0.5 *N* hydrochloric acid, acetone, room temperature, 35 min). Although the infrared spectrum of the crude product indicated that these conditions still produced small amounts of the enone **39**, the material thus obtained was sufficiently pure to be used directly for the next step.

With respect to the hydrolysis of the keto ketals **31** and **32**, it was eventually found that conditions similar to those employed for compound **33** (0.5 *N* hydrochloric acid, acetone, room temperature) were quite satisfactory. Under these conditions, the enol ether moiety was, in each case, hydrolyzed smoothly, while the ketal function remained essentially unaffected. In the case of compound **31**, reaction times of up to 2 h left the ketal group intact. Using this procedure, the hydrolysis products **36** and **37** were obtained in high yield (92%, 96%, respectively).

(d) *Intramolecular Horner–Emmons reaction of the diketo phosphonates **34–38***

Cyclization of the diketo phosphonates **34–38** was accomplished by treatment of each of these substances with sodium hydride in dimethoxyethane (DME) (16, 24). In general, the reactions were quite efficient, the yields of the products **40** (8), **41** (25), and **42–44** being 74, 82, 72, 86, and 70% (based on **33**), respectively. Importantly, in accord with previous observations (16), the products **41–43** were very clean and, in each of these cases, there was no indication of isomerization to the corresponding isomeric cyclopentenone.

Conclusion

The convergent annulation sequence described in this paper would appear to constitute a general, efficient method for the construction of functionalized 2-cyclopenten-1-one systems. It is appropriate to note that, very recently, this method has been employed successfully in an elegant well-designed synthesis of (±)-quadrone, a structurally novel sesquiterpenoid which exhibits antitumor properties (26).

Finally, two additional pertinent items should be mentioned. Firstly, after appearance of our prelim-

[4]We are grateful to Mr. M. Burmeister for supplying a sample of this compound.

[5]This substance was prepared in a straightforward, unambiguous fashion from the Wieland–Miescher ketone (23). Details will be reported elsewhere.

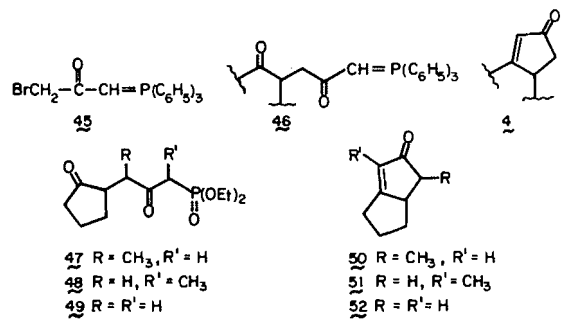


Chart 3

inary report, Altenbach described (27) the alkylation of enolate anions with (bromoacetylmethylene)triphenylphosphorane (**45**) (see Chart 3). Subsequent intramolecular Wittig reaction of the resultant diketo phosphoranes **46** (not isolated) provided the corresponding cyclopentenones **4**. Although, in principle, the Altenbach methodology is very similar to that described in this paper, the reported yields of the annulation products were low (14–39%). Secondly, Pattenden and co-workers have reported (28) very recently that although treatment of the diketo phosphonates **47** and **48** (Chart 3) with sodium hydride in DME at 60°C provided good yields of the bicyclic enones **50** and **51**, respectively, attempted conversion of **49** into **52**[6] under similar conditions failed. Instead, a "tarry mass" was produced. Attempts to transform **49** into **52** using alternative reaction conditions were also unsuccessful.

Experimental

General

Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. Distillation temperatures (also uncorrected) refer to the mean air bath temperature during a short path (bulb-to-bulb) distillation. Infrared (ir) spectra were obtained on liquid films or chloroform solutions, employing Perkin Elmer models 710 or 710B spectrophotometers. Proton magnetic resonance (^{1}H nmr) spectra (deuterochloroform solution) were measured using Bruker WP-80 or WH-400 instruments or Varian Associates T-60, HA-100, and/or XL-100 spectrometers. Signal positions are given in δ units, with tetramethylsilane as the internal standard. Gas–liquid chromatography (glc) was carried out with a Hewlett–Packard model 5832A gas chromatograph. High resolution mass spectrometric measurements were recorded on a Kratos MS-50 mass spectrometer. Microanalyses were carried out by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver, B.C.

The solvents and reagents employed were freshly distilled under an atmosphere of argon as follows: THF and DME from sodium benzophenone ketyl; HMPA from barium oxide; diisopropylamine from calcium hydride; carbon tetrachloride and dichloromethane from phosphorus pentoxide.

Dimethyl 2-ethoxypropenylphosphonate (22)

To dimethyl 2-oxopropylphosphonate (**21**) (5.1 g, 37.8 mmol) was added triethyl orthoformate (9.0 g, 60.8 mmol) and ferric chloride hexahydrate (0.2 g). The mixture was stirred briefly and then allowed to stand at room temperature for 3 days. The volatile byproducts and excess triethyl orthoformate were removed under reduced pressure and the residual material was dissolved in 50 mL of dry dichloromethane. The solution was treated with 0.5 g of sodium hydride (washed free of mineral oil with hexane) and the resultant mixture was stirred for 10 min and then filtered. Removal of the solvent from the filtrate, followed by distillation (air bath temperature 80°C/0.05 Torr) of the residual material gave 6.89 g (94%) of the enol ether **22** as a colorless oil; ir (film): 1605, 1250, 1050, 1025 cm^{-1}; ^{1}H nmr δ: 1.33 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.14 (d, 3H, J_{H-P} = 2 Hz, vinyl methyl), 3.65 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.77 (q, 2H, J = 7 Hz, CH_3CH_2O), 4.35 (d, 1H, J_{H-P} = 7 Hz, vinyl proton). *Anal.* calcd. for $C_7H_{15}O_4P$: C 43.30, H 7.79; found: C 43.13, H 7.70. *Exact mass* calcd.: 194.0707; found: 194.0708.

Dimethyl 3-bromo-2-ethoxypropenylphosphonate (19)

To a solution of the enol ether **22** (3.0 g, 15.5 mmol) in 150 mL of dry carbon tetrachloride was added 3.1 g (17.4 mmol) of *N*-bromosuccinimide. The well-stirred mixture was heated (reflux) while it was being irradiated with a sun lamp (Westinghouse, 275 W, 110–120 V). After 15 min the reaction mixture was cooled and filtered. The filtrate was concentrated under reduced pressure to a volume of approximately 50 mL and then cooled in an ice-bath to precipitate residual succinimide. The mixture was filtered through a small amount of neutral alumina (Act. I). Removal of the solvent from the filtrate gave a yellow oil which was subjected to column chromatography on silica gel (160 g). Elution of the column with ethyl acetate, followed by distillation (air bath temperature 110°C/0.05 Torr) of the crude oil thus obtained gave 3.2 g (76%) of dimethyl 3-bromo-2-ethoxypropenylphosphonate (**19**) as a colorless oil, which exhibited one peak by glc analysis and one spot by tlc analysis; ir (film): 1605, 1250, 1050–1025 (broad) cm^{-1}; ^{1}H nmr δ: 1.39 (t, 3H, J = 7 Hz, CH_3CH_2O), 3.76 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.91 (q, 2H, J = 7 Hz, CH_3CH_2O), 4.42 (s, 2H, CH_2Br), 4.57 (d, 1H, J_{H-P} = 5 Hz, vinyl proton). *Exact Mass* calcd. for $C_7H_{14}{}^{79}BrO_4P$: 271.9813; found: 271.9815.

Alkylation of the ketones 24–27 and the keto ester 28 with the allylic bromide 19

(a) *Preparation of compound 29*

To a cold (−78°C) stirred solution of lithium diisopropylamide (LDA) (1.2 mmol) in dry THF (2 mL) under an atmosphere of argon was added 98 mg (1 mmol) of cyclohexanone. The cooling bath was removed and replaced by an ice-water bath, and the solution was allowed to stir for 1 h. The reaction mixture was recooled to −78°C and 330 mg (1.2 mmol) of the alkylating agent **19** was added. After the reaction mixture had been stirred at −78°C for 30 min, at 0°C for 30 min, and at room temperature for 30 min, the THF was removed under reduced pressure. The residual material was dissolved in dichloromethane and the resultant solution was washed twice with brine and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure (water aspirator, followed by vacuum pump) gave 290 mg (100%) of the alkylated ketone **29** as a colorless oil. Both tlc and glc indicated that this material consisted of one component; ir (film): 1710, 1605, 1250, 1060–1025 (broad) cm^{-1}; ^{1}H nmr δ: 1.26 (t, 3H, J = 7 Hz, CH_3CH_2O), 1.42–3.06 (diffuse,

[6]For a recent successful synthesis of this substance, see ref. 29.

11H), 3.62 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.72 (q, 2H, J = 7 Hz, CH_3CH_2O), 4.36 (d, 1H, J_{H-P} = 7 Hz, vinyl proton). *Exact Mass* calcd. for $C_{13}H_{23}O_5P$: 290.1283; found: 290.1301.

(b) *Preparation of compound* ***30***

This compound was prepared via a procedure identical with that described above. From 86 mg (1 mmol) of 3-pentanone there was obtained, after distillation (air bath temperature 140°C/0.05 Torr) of the crude product, 278 mg (100%) of the alkylated material **30** as a colorless oil, which exhibited one peak by glc analysis and one spot by tlc analysis; ir (film): 1705, 1605, 1250, 1050–1025 (broad) cm^{-1}; ^1H nmr δ: 1.04 (t, 3H, J = 7 Hz, CH_3CH_2CO), 1.12 (d, 3H, J = 6 Hz, secondary methyl), 1.28 (t, 3H, J = 7 Hz, CH_3CH_2O), 2.50 (q, 2H, J = 7 Hz, CH_3CH_2CO), 2.66–2.98 (diffuse, 3H), 3.66 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.76 (q, 2H, J = 7 Hz, CH_3CH_2O), 4.39 (d, 1H, J_{H-P} = 6 Hz, vinyl proton). *Exact Mass* calcd. for $C_{12}H_{23}O_5P$: 278.1283; found: 278.1277.

(c) *Preparation of compound* ***31***

For the alkylation of the keto ketal **26** (198 mg, 1 mmol) the procedure described above was modified as follows. Just prior to addition of the alkylating agent **19**, HMPA (180 μL, 1 mmol) was added to the reaction mixture (−78°C). After work-up, most of the HMPA was removed from the crude product (air bath temperature ~100°C/0.05 Torr) and the residual oil was subjected to column chromatography on silica gel (10 g). Elution of the column with ethyl acetate gave 304 mg (78%) of the alkylated ketone **31** as a colorless oil which, according to analyses by glc and tlc, consisted of one component; ir (film): 1715, 1610, 1250, 1030 cm^{-1}; ^1H nmr δ: 0.94, 1.01 (s, s, 3H each, tertiary methyls), 1.30 (t, 3H, J = 6 Hz, CH_3CH_2O), ~1.4–3.2 (diffuse, 9H), 3.48 (s, 4H, ketal methylene protons), 3.67 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.78 (q, 2H, J = 6 Hz, CH_3CH_2O), 4.43 (d, 1H, J_{H-P} = 6 Hz, vinyl proton). *Exact Mass* calcd. for $C_{18}H_{31}O_7P$: 390.1808; found: 390.1796.

(d) *Preparation of compound* ***32***

Alkylation of **27** was accomplished via a procedure identical with that described above (preparation of **31**). From 266 mg (1 mmol) of the keto ketal **27**, there was obtained 348 mg (76%) of the alkylated substance **32** as a white solid. Recrystallization (ether–hexane) of a small amount of this material provided an analytical sample, mp 99–100°C; ir ($CHCl_3$): 1705, 1610, 1250, 1060–1020 (broad) cm^{-1}; ^1H nmr δ: 0.93, 1.02, 1.16 (s, s, s, 3H each, tertiary methyls), 1.32 (t, 3H, J = 7 Hz, CH_3CH_2O), ~1.4–3.2 (diffuse, 14H), 3.4–3.6 (m, 4H, ketal methylene protons), 3.72 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$), 3.80 (q, 2H, J = 7 Hz, CH_3CH_2O), 4.44 (d, 1H, J_{H-P} = 6 Hz, vinyl proton). *Exact Mass* calcd. for $C_{23}H_{39}O_7P$: 458.2434; found: 458.2412.

(e) *Preparation of compound* ***33***

Alkylation of 2-carbomethoxycyclohexanone (**28**) (156 mg, 1 mmol) was carried out via a procedure very similar to that employed for the preparation of compounds **31** and **32**. However, 1.5 mmol of each of LDA, the allylic bromide **19** (413 mg), and HMPA (270 μL) were employed instead of the quantities indicated above and the reaction mixture was stirred at room temperature for 6 h instead of for 30 min. Distillation (air bath temperature 180°C/0.05 Torr) of the material obtained from the chromatography column afforded 247 mg (71%) of the alkylated keto ester **33** as a colorless oil. Both glc and tlc indicated that this material consisted of one component; ir (film): 1740, 1710, 1610, 1240, 1060–1020 (broad) cm^{-1}; ^1H nmr δ: 1.28 (t, 3H, J = 7 Hz, CH_3CH_2O), ~1.5–2.5 (diffuse, 8H), 3.11, 3.37 (d of d, d of d, 1H each, J_{H-H} = 16 Hz, J_{H-P} = 2 Hz in each case, allylic methylene protons), 3.56–3.84 (a series of partially overlapped signals consisting of: d, 6H, $PO(OCH_3)_2$; s, 3H, CO_2Me; q, 2H, CH_3CH_2O), 4.40 (d, 1H, J_{H-P} = 5 Hz, vinyl proton). *Exact Mass* calcd. for $C_{15}H_{25}O_7P$: 348.1338; found: 348.1333.

Hydrolysis of the enol ether functional group of the alkylation products ***29–33***

(a) *Preparation of compound* **34**

To a stirred solution of compound **29** (290 mg, 1 mmol) in 25 mL of acetone at room temperature was added 0.5 mL of 1 *N* hydrochloric acid. After the resultant mixture had been stirred at room temperature for 30 min, the acid was neutralized by addition of anhydrous potassium carbonate and the acetone was removed under reduced pressure. Dichloromethane was added to the residual material and the organic solution was washed twice with saturated aqueous potassium bicarbonate and then was dried over anhydrous sodium sulfate. Removal of the solvent, followed by distillation (air bath temperature 182°C/0.02 Torr) of the residual oil gave 262 mg (100%) of the diketo phosphonate **34** as a colorless oil, glc and tlc analyses of which indicated that it consisted of one component; ir (film): 1710, 1260, 1030 cm^{-1}; ^1H nmr δ: ~1.1–2.6 (diffuse, 9H), ~2.75–3.2 (diffuse, 2H), 3.16, 3.36 (d, d, 1H each, J = 14 Hz, —$COCH_2PO$—), 3.72 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$). *Exact Mass* calcd. for $C_{11}H_{19}O_5P$: 262.0970; found: 262.0987.

(b) *Preparation of compound* ***35***

Hydrolysis of the enol ether **30** was accomplished by a procedure identical with that described above. The crude product obtained from 278 mg (1 mmol) of **30** was subjected to column chromatography on 8 g of silica gel. Elution of the column with ethyl acetate, followed by removal (reduced pressure) of the solvent from the appropriate fractions, gave 250 mg (100%) of compound **35** as a colorless oil. Analysis of this material by glc and tlc indicated that it consisted of one component; ir (film): 1710, 1270, 1040 cm^{-1}; ^1H nmr δ: 1.07 (t, 3H, J = 8 Hz, CH_3CH_2CO), 1.08 (d, 3H, J = 8 Hz, secondary methyl group), 2.42–2.88 (m, 3H, CH_3CH_2CO and tertiary proton), 2.90–3.40 (m, 4H, CH_2COCH_2PO—), 3.75 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$). *Exact Mass* calcd. for $C_{10}H_{19}O_5P$: 250.0970; found: 250.0965.

(c) *Preparation of compound* ***36***

To a stirred solution of compound **31** (195 mg, 0.5 mmol) in 25 mL of acetone at room temperature was added 0.5 mL of 0.5 *N* hydrochloric acid. After the reaction mixture had been stirred at room temperature for 2 h, it was subjected to a work-up procedure identical with that described above (preparation of compound **34**). The crude product was purified by means of column chromatography on silica gel (8 g). Elution of the column with ethyl acetate, followed by removal (reduced pressure) of the solvent from the appropriate fractions gave 167 mg (92%) of the diketo phosphonate **36** as a colorless oil (one peak by glc analysis and one spot by tlc analysis); ir (film): 1710, 1260, 1025 cm^{-1}; ^1H nmr δ: 0.98, 1.04 (s, s, 3H each, tertiary methyl groups), ~1.35–3.30 (diffuse, 11H), 3.42–3.64 (m, 4H, ketal methylene protons), 3.81 (d, 6H, J_{H-P} = 11 Hz, $PO(OCH_3)_2$). *Exact Mass* calcd. for $C_{16}H_{27}O_7P$: 362.1494; found: 362.1491.

(d) *Preparation of compound* ***37***

This substance was prepared by hydrolysis of compound **32** via a procedure identical with that described above (preparation of **36**), except that the reaction time was 15 min instead of 2 h. From 229 mg (0.5 mmol) of **32** there was obtained 206 mg (96%) of the diketo phosphonate **37** as a colorless oil which could be crystallized from ether–hexane. Recrystallization provided a pure sample, mp 107–109°C; ir ($CHCl_3$): 1705, 1260, 1030 cm^{-1}; ^1H nmr (400 MHz) δ: 0.90, 1.03, 1.17 (s, s, s, 3H each, tertiary methyl groups), 1.32–1.85 (diffuse, 8H), 1.94 (d of t, 1H, J = 2, 13 Hz), 2.08 (m, 1H), 2.32–2.43 (m, 2H), 2.97–3.16 (8-line m,

2H), 3.28–3.65 (m, 6H), 3.80, 3.81 (d, d, 3H each, J_{H-P} = 11 Hz in each case, $PO(OCH_3)_2$). *Exact Mass* calcd. for $C_{21}H_{35}O_7P$: 431.2198; found: 431.2159.

(e) *Preparation of compound 38 (crude)*

To a stirred solution of compound **33** (174 mg, 0.5 mmol) in 15 mL of acetone at room temperature was added 0.5 mL of 0.5 *N* hydrochloric acid. After the resultant mixture had been stirred at room temperature for 35 min, it was subjected to a work-up procedure identical with that described above (preparation of compound **34**). Since the crude product thus obtained contained a small amount of the bicyclic keto ester **39** in addition to the desired product **38**, it was not purified further but was used directly for the next step.

Intramolecular Horner–Emmons reactions of the diketo phosphonates 34–38

(a) *Preparation of compound 40*

To a cold (0°C), stirred suspension of sodium hydride (14 mg, 0.6 mmol) in dry DME (2 mL), under an atmosphere of argon, was added, dropwise, a solution of the diketo phosphonate **34** in 1 mL of dry DME. After the reaction mixture had been stirred at room temperature for 30 min, it was warmed to 65°C and kept at that temperature for 1 h. The cooled mixture was poured into aqueous sodium chloride solution and the resultant mixture was extracted thoroughly with ether. The combined extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent, followed by distillation (air bath temperature 45°C/0.02 Torr) of the residual oil gave 51 mg (74%) of the bicyclic enone **40** (8) as a colorless liquid (one peak by glc analysis); ir (film): 1700, 1620 cm^{-1}; ^1H nmr δ: 1.02–2.92 (diffuse, 11H), 5.88 (s, 1H, olefinic proton). *Exact Mass* calcd. for $C_8H_{12}O$: 136.0888; found: 136.0891.

(b) *Preparation of compound 41*

This substance was prepared via a procedure identical with that described above, except that the reaction mixture was stirred at 65°C for 3 h instead of for 1 h. Distillation (air bath temperature 100°C/15 Torr) of the crude product gave 51 mg (82%) of 3-ethyl-4-methyl-2-cyclopenten-1-one (**41**) (25) as a colorless liquid which exhibited one peak by glc analysis; ir (film): 1700, 1610 cm^{-1}; ^1H nmr δ: 1.20 (t, 3H, J = 7 Hz, CH_3CH_2), 1.21 (d, 3H, J = 7 Hz, secondary methyl group), 1.96–2.96 (diffuse, 5H), 5.94 (narrow m, 1H, olefinic proton). *Exact Mass* calcd. for $C_8H_{12}O$: 124.0888; found: 124.0893.

(c) *Preparation of compound 42*

The procedure employed was identical with that used for the preparation of the cyclopentenone **41**, except that the quantities of reactants used were sodium hydride, 9 mg (0.38 mmol) and diketo phosphonate **36**, 118 mg (0.33 mmol). The crude product was subjected to chromatography on 4 g of silica gel. Elution of the column with ethyl acetate produced a light yellow solid which was distilled (air bath temperature 155–160°C/0.05 Torr) to yield 56 mg (72%) of the bicyclo enone **42**. An analytical sample, obtained by recrystallization of this material from ether–hexane, exhibited mp 73–74°C; ir ($CHCl_3$): 1700, 1620 cm^{-1}; ^1H nmr δ: 1.00, 1.02 (s, s, 3H each, tertiary methyl groups), ~1.2–3.1 (diffuse, 9H), 3.56 (s, 4H, ketal methylene protons), 5.91 (broad s, 1H, olefinic proton). *Exact Mass* calcd. for $C_{14}H_{20}O_3$: 236.1412; found: 236.1422.

(d) *Preparation of compound 43*

This compound was prepared via a procedure identical with that employed for the synthesis of **42**, except that the reaction mixture was maintained at 65°C for 2 h instead of for 3 h. The crude product obtained from 142 mg (0.33 mmol) of the diketo phosphonate **37** was purified by chromatography on 4 g of silica gel. Elution of the column with ethyl acetate – hexane (1:1) gave 86 mg (86%) of the tricyclic enone **43** as a white solid, an analytical sample of which was obtained by recrystallization of this material from ether–hexane, mp 116–117°C; ir ($CHCl_3$): 1680, 1610 cm^{-1}; ^1H nmr (400 MHz) δ: 0.94, 1.00 (s, s, 3H each, ketal methyl groups), 1.13 (s, 3H, angular methyl group), 1.18 (q of d, 1H, J = 5 Hz, 13 Hz), 1.39–1.67 (diffuse, 6H), 1.73 (q of d, 1H, J = 4, 14 Hz), 1.96 (d of d, 1H, J = 2, 18 Hz), 1.99 (d of t, 1H, J = 3, 13 Hz), 2.18 (m, 1H), 2.34 (d of q, 1H, J = 3, 13 Hz), 2.58 (d of d, 1H, J = 7, 18 Hz), 2.98 (m, 1H), 3.42–3.61 (m, 4H, ketal methylene protons), 5.80 (d, 1H, J = 1.5 Hz, olefinic proton). *Exact Mass* calcd. for $C_{19}H_{28}O_3$: 304.2039; found: 304.2029.

(e) *Preparation of compound 44*

The crude diketo phosphonate **38** (*vide supra*) was subjected to cyclization via a procedure identical with that described above (preparation of **40**), except that the reaction mixture was stirred at 65°C for 2 h instead of for 1 h. Distillation (air bath temperature 110°C/0.05 Torr) of the crude product gave 68 mg (70%, based on the enol ether **33**) of the bicyclic keto ester **44** (colorless oil, one peak by glc analysis and one spot by tlc analysis); ir (film): 1730, 1710, 1625 cm^{-1}; ^1H nmr δ: ~1.2–2.9 (diffuse, 8H), 2.26, 2.60 (d, d, 1H each, J = 18 Hz, $—CH_2CO$), 3.66 (s, 3H, CO_2CH_3), 5.93 (d, 1H, J = 2 Hz, olefinic proton). *Exact Mass* calcd. for $C_{11}H_{14}O_3$: 194.0944; found: 194.0944.

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