Preparation of γ,δ-Unsaturated β-Ketophosphonates from Tertiary α-Allenic Alcohols. The Synthesis of (±)-(*E*)-α-Atlantone

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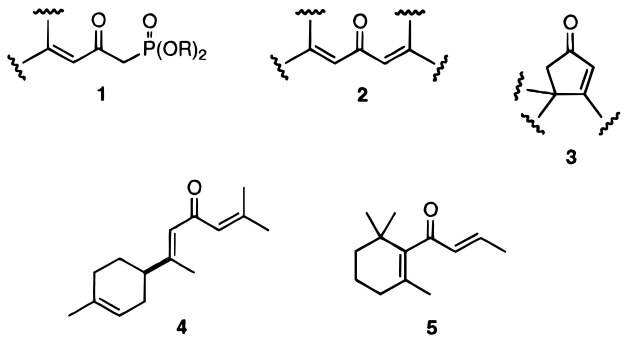
Introduction

β-Ketophosphonates have been shown to be valuable synthetic intermediates for the preparation of α,β-unsaturated carbonyl compounds via the Horner−Wadsworth−Emmons ("HWE") reaction.[1] Such a reaction of γ,δ-unsaturated β-ketophosphonates **1** (or 2-oxo-3-alkenylphosphonates) with carbonyl compounds provides access to α,α′-divinyl ketones (or α,α′-dienones) **2**.[2] A Nazarov cyclization[3] converts these cross-conjugated ketones[4] into the useful and widely encountered 2-cyclopentenone unit **3**.[5] The α,α′-divinyl ketone moiety is also present in a number of terpenoid natural products.[6] α-Atlantone (**4**)[6e,f] and β-damascone (**5**)[6d] are two such examples.



It is possible for γ,δ-unsaturated β-ketophosphonates to be involved in other chemical tranformations, since one can view them as phosphorus-stabilized enones. In a series of very interesting reports, Wada and Kanemasa described their use as heterodienes in an inverse electron-demand Diels−Alder reaction with vinyl ethers, giving rise to 2-alkoxy-6-(phosphinylmethyl)-3,4-dihydro-2*H*-pyran derivatives.[7] They have also shown that these alkenylphosphonates can serve as Michael acceptors in reactions with carbonyl-stabilized carbanions (i.e. derived from β-keto esters, β-diketones or α-sulfonyl ketones) producing 2-cyclohexen-1-ones.[8] Silyl enol ethers also act as Michael donors with this type of phosphonate, to afford either 2-cyclohexen-1-ones[8,9] or 2-phosphinyl-2-cyclohexen-1-ones,[8] depending upon whether basic or acidic conditions, respectively, are used. Simple modifications, like reduction of the olefin moiety,[10] reductive amination of the carbonyl group,[11] functionalization at the α-carbon,[2a,c] or condensation with epoxides (to give α′-cyclopropylenones)[12] can also be performed on γ,δ-unsaturated β-ketophosphonates.

A number of methods currently exist for the preparation of 2-oxo-3-alkenylphosphonates.[13] Aside from a few exceptions,[13f−h,j] these reactions are the same as those that are employed for the preparation of saturated β-ketophosphonates and are based on the acylation of alkylphosphonate anions with α,β-unsaturated carboxylic acid derivatives (i.e. acid chlorides and esters).[13a−d] Surprisingly, as far as we are aware, there are no reports on the preparation of γ,δ-unsaturated β-ketophosphonates by the commonly used Arbuzov reaction[14] between a trialkyl phosphite and an α-haloenone. In spite of its

(1) For reviews on the Horner−Wadsworth−Emmons reaction, including syntheses and applications of β-ketophosphonates, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73. (c) Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

(2) (a) Minami, T.; Nakayama, M.; Fujimoto, K.; Matsuo, S. *J. Chem. Soc., Chem. Commun.* **1992**, 190. (b) Motoyoshiya, J.; Yazaki, T.; Hayashi, S. *J. Org. Chem.* **1991**, *56*, 735. (c) Mikolajczyk, M.; Zurawinski, R. *Synlett* **1991**, 575. (d) Kodama, M.; Shiobara, Y.; Sumitomo, H.; Mitani, K.; Ueno, K. *Chem. Pharm. Bull.* **1987**, *35*, 4039. (e) Sakai, T.; Amano, E.; Miyata, K.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1945. (f) Motoyoshiya, J.; Miyajima, M.; Hirakawa, K.; Kakurai, T. *J. Org. Chem.* **1985**, *50*, 1326.

(3) For reviews, see: (a) Denmark, S. E. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 751−784. (b) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429. For some recent examples and applications, see: (c) Kang, K.-T.; Kim, S. S.; Lee, J. C.; U, J. S. *Tetrahedron Lett.* **1992**, *33*, 3495. (d) Frank-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1992**, *33*, 3879. (e) Paquette, L. A.; Kang, H.-J. *J. Am. Chem. Soc.* **1991**, *113*, 2610. (f) Andrews, J. F. P.; Regan, A. C. *Tetrahedron Lett.* **1991**, *32*, 7731. (g) Yamazaki, S.; Mizuno, W.; Yamabe, S. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1555. (h) See also refs 2a,b.

(4) For some selected examples of other reactions of cross-conjugated ketones, see: (a) Krein, E. B.; Aizenshtat, Z. *J. Org. Chem.* **1993**, *58*, 6103. (b) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Testa, M. G.; Purrello, G. *Heterocycles* **1993**, *36*, 223. (c) Nakamura, E.; Kubota, K.; Isaka, M. *J. Org. Chem.* **1992**, *57*, 5809. (d) Hitchcock, S. A.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4843. (e) Grigg, R.; Kennewell, P.; Savic, V.; Sridharan, V. *Tetrahedron* **1992**, *48*, 10423. (f) Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1992**, 2479. (g) Diaz, E.; Barrios, H.; Toscano, R. A.; Yuste, F.; Reynolds, W. F.; Aguilera, J. L.; Caballero, E. *J. Heterocycl. Chem.* **1992**, *29*, 1325. (h) Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2109. (i) Richter, F.; Otto, H.-H. *Liebigs Ann. Chem.* **1990**, 7. (j) Richter, F.; Otto, H.-H. *Tetrahedron Lett.* **1985**, *26*, 4351. (k) Britten-Kelly, M.; Willis, B. J. *Synthesis* **1980**, 27.

(5) (a) Tolstikov, G. A.; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Ya. L.; Spirikhin, L. V. *Synthesis* **1989**, 625. (b) Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. (c) Ramaiah, M. *Synthesis* **1984**, 529. (d) Ellison, R. A. *Synthesis* **1973**, 397. (e) See also refs 3a, Section 6.3.8, and 3b, Section 8.

(6) (a) Matthes, H. W. D.; Luu, B.; Ourrisson, G. *Phytochemistry* **1980**, *19*, 2643. (b) Kalsi, P. S.; Chhabra, B. R.; Singh, O. S. *Experientia* **1979**, *35*, 481. (c) Kalsi, P. S.; Singh, O. S.; Chhabra, B. R. *Phytochemistry* **1978**, *17*, 576. (d) Snowden, R. L.; Linder, S. M.; Muller, B. L.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1987**, *70*, 1858 and refs cited therein. (e) Pfau, von A. S.; Plattner, P. *Helv. Chim. Acta* **1934**, *17*, 129. (f) Pande, B. S.; Krishnappa, S.; Bisarya, S. C.; Dev, S. *Tetrahedron* **1971**, *27*, 841. (g) de Villiers, D. J. J.; Garbers, C. F.; Laurie, R. N. *Phytochemisry* **1971**, *10*, 1359. (h) Jung, J. H.; Chang, C.-J.; Smith, D. L.; McLaughlin, J. L.; Pummangura, S.; Chaichantipyuth, C.; Patarapanich, C. *J. Nat. Prod.* **1991**, *54*, 500.

(7) (a) Wada, E.; Kanemasa, S.; Tsuge, O. *Chem. Lett.* **1989**, 675. (b) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1198. (c) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 860.

(8) Wada, E.; Funakoshi, J.; Kanemasa, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2456.

(9) Kuo, F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 1745.

(10) Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843.

(11) Varlet, J. M.; Collignon, N.; Savignac, P. *Tetrahedron* **1981**, *37*, 3713.

(12) Jacks, T. E.; Nibbe, H.; Wiemer, D. F. *J. Org. Chem.* **1993**, *58*, 4584.

(13) For reactions of alkylphosphonate anions with α,β-unsaturated carboxylic acid chlorides and/or esters, see: (a) Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc.* **1984**, *106*, 3875. (b) Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649. (c) Aboujaoude, E. E.; Collignon, N.; Teulade, M.-P.; Savignac, P. *Phosphorus Sulfur* **1985**, *25*, 57. (d) See also refs 2b−d,f. For other methods of preparation, see: (e) Koh, Y. J.; Oh, D. Y. *Tetrahedron Lett.* **1993**, *34*, 2147. (f) Tsuge, O.; Kanemasa, S.; Suga, H.; Nakagawa, N. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2463. (g) Peiffer, G.; Courbis, P. *Can. J. Chem.* **1974**, *52*, 2894. (h) See also refs 2e, 7c, and 8. For examples with γ,δ-unsaturation within a carbocycle, see: (i) An, Y.-Z.; An, J. G.; Wiemer, D. F. *J. Org. Chem.* **1994**, *59*, 8197 and refs cited therein. (j) Castagnino, E.; D'Auria, M.; De Mico, A.; D'Onofrio, F.; Piancatelli, G. *J. Chem. Soc., Chem. Commun.* **1987**, 907. (k) See also ref 12 and refs cited therein.

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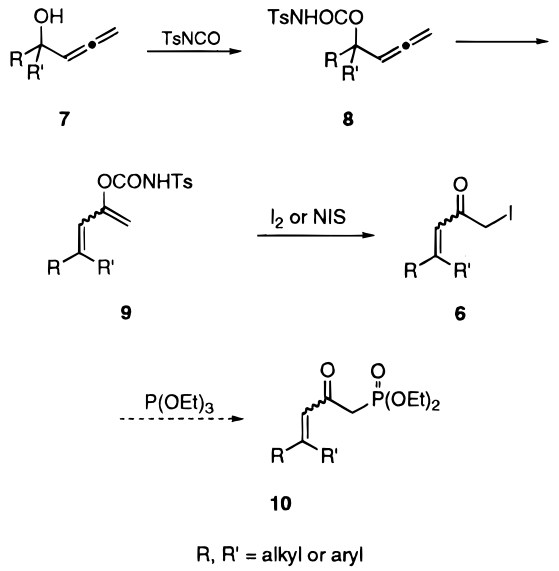
Scheme 1



potential limitations (generally restricted to α-iodoketones, to avoid as much as possible enol phosphate formation from the competing Perkow reaction),[14,15] we decided to investigate the possibility of using the Arbuzov reaction to obtain ketophosphonates of the type **1**.

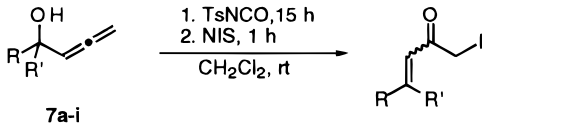
Herein, we describe a new method for the preparation of δ,δ-disubstituted γ,δ-unsaturated β-ketophosphonates from α′-iodoenones, which are obtained from readily available tertiary α-allenic alcohols (Scheme 1).

Results and Discussion

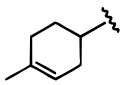
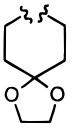
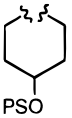
We recently reported that α,β-unsaturated α′-iodoenones of the general structure **6** can be obtained in good yields from tertiary α-allenic alcohols **7**, with moderate to excellent *E*-stereoselectivity when R ≠ R′.[16] The alcohols **7**, upon treatment with *p*-toluenesulfonyl isocyanate, are converted to the carbamate derivatives **8**, which undergo a facile rearrangement reaction to provide 2-*O*-carbamoyl-4,4-disubstituted-1,3-butadienes **9**.[17] Dienes **9** can be isolated in good yields,[17] or directly trapped, *in situ*, with a variety of electrophiles (I_2, NIS, NBS, *N*-(phenylseleno)phthalimide, H^+) in moderate to good yields.[16,18] The idea was therefore to treat the α′-iodoenones **6** with triethyl phosphite, to obtain the desired δ,δ-disubstituted γ,δ-unsaturated β-ketophosphonates **10** as the Arbuzov products (Scheme 1).

We selected the cyclohexanone-derived iodoenone **6b** to determine the optimum conditions required for the conversion to the ketophosphonate **10b**. **6b** was prepared from the tertiary α-allenic alcohol **7b**[19] using NIS, with slight modifications to the previously described experimental conditions.[20] A longer reaction time (15 h, monitored by ^{1}H NMR spectroscopy)[21] was allowed for the rearrangement (**8** to **9** in Scheme 1) to take place before the addition of the electrophile (1.1 equiv), and the aqueous workup was replaced by a dilution with hexane followed by filtration. Under these conditions, **6b** was obtained in a 58% yield from **7b** after chromatography (Table 1, entry 2).

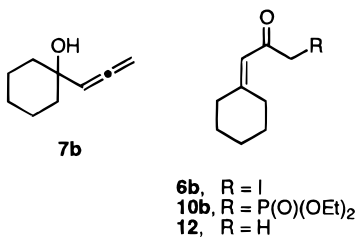
Table 1. Preparation of α,β-Unsaturated α′-Iodoenones 6a−i from Tertiary α-Allenic Alcohols 7a−i



7a-i 6a-i

alcohol[a]	R	R'	*E*:*Z* ratio[b]	product (yield, %)[c]
7a[d]		Me	7 : 1	**6a** (61)
7b			–	**6b** (58)
7c	Me	Me	–	**6c** (54)
7d	*tert*-butyl	Me	>50 : 1[e]	**6d** (66)
7e	*n*-nonyl	Me	1.8 : 1	**6e** (67)
7f	*p*-tolyl	Me	>50 : 1[e]	**6f** (36)
7g			1.6 : 1[f]	**6g** (29)
7h[g]			–	**6h** (48)
7i[h,i]	 TIPSO		–	**6i** (48)

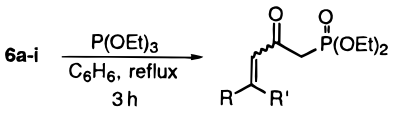
[a] Prepared according to ref 19. [b] Determined from the integration of the vinyl proton in the NMR spectrum of the crude α′-iodoenones (for olefin geometry assignments, see ref 16); *E*- and *Z*-isomers are separable by column chromatography. [c] Isolated, combined yield of *E*- and *Z*-isomers. [d] Mixture of diastereomers. [e] Minor isomer not detectable in ^{1}H NMR spectrum of the crude products. [f] *E*- and *Z*-isomers not separable. [g] **7h** reacted with TsNCO for 7 days. [h] Single unidentified diastereomer. [i] **7i** reacted with TsNCO for 20 h in refluxing $CHCl_3$.



Because of the potential instability of the α′-iodoenones **6** at high temperature, we wanted to avoid typical Arbuzov reaction conditions (no solvent, ~150 °C).[22] When **6b** was exposed to 1 equiv of triethyl phosphite in

(14) For a review, see: Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415.
(15) Lichtenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607.
(16) Friesen, R. W.; Phipps, L. G. *Synlett* **1991**, 420.
(17) Friesen, R. W.; Kolaczewska, A. E.; Khazanovich, N. *Tetrahedron Lett.* **1992**, *33*, 6715.
(18) Kolaczewska, A. E. Reactions of Secondary and Tertiary α-Allenic Alcohol Carbamates; M. Sc. Thesis, University of Toronto, 1991.
(19) The tertiary α-allenic alcohols **7a**−**i** were prepared from the lithium acetylide of THP protected propargyl alcohol and the appropriate ketones, according to a literature procedure: Cowie, J. S.; Landor, P. D.; Landor, S. R. *J. Chem. Soc., Perkin Trans. 1* **1973**, 720.
(20) According to ref 18: Alcohol in CH_2Cl_2 (0.08 M); TsNCO (1.1 equiv) added at rt; after 10 min, electrophile (2 equiv) added; aqueous workup ($Na_2S_2O_3$) after 1 h; column chromatography.
(21) For experimental details and interpretation of a similar experiment, see ref 17.

Table 2. Preparation of γ,δ-Unsaturated β-Ketophosphonates 10a−i from α,β-Unsaturated α′-Iodoenones 6a−i



10a-i

α′-iodoenone **6a−i**[a]	product	yield, %[b]
(*E*)-**6a**	(*E*)-**10a**	94
(*Z*)-**6a**	(*E*)/(*Z*)-**10a**[c]	74
6b	10b	89
6c	10c	87
6d	10d	93
(*E*)-**6e**	(*E*)-**10e**	91
(*Z*)-**6e**	(*Z*)-**10e**	88
6f	10f	94
6g[d]	10g	84
6h	10h	86
6i	10i	88

[a] Refer to Table 1 for the nature of R and R′. [b] After purification (column chromatography followed by heating at 90 °C under high vacuum for 30 min). [c] *E*/*Z* ratio = 1:11. [d] 1.6:1 *E*/*Z* mixture; the same ratio was observed for the ketophosphonate **10g**.

THF and at room temperature,[23] a 50% conversion was observed after 1.5 h. Reflux temperature and the addition of an additional 0.5 equiv of $P(OEt)_3$ was necessary to complete the reaction, affording the corresponding ketophosphonate **10b** in 85% yield after purification. To our surprise, the crude mixture was completely free of the Perkow rearrangement product (enol phosphate), but nevertheless, two other compounds were also present. The first (~10%), identified as the dehalogenated byproduct **12**,[24] is easily removed from **10b** by column chromatography. The other byproduct is a phosphorus-containing impurity which is not related to the phosphonate **10b**.[25] It can be efficiently removed by heating (90 °C) the sample under high vacuum for 30 min. Repetition of the same reaction using 1.5 equiv of phosphite and refluxing the solvent from the beginning of the reaction produced exactly the same result. Substituting benzene, a less polar solvent of the same boiling range, for THF seemed to decrease the formation of the enone **12**. We also found that 1.4 equiv of triethyl phosphite is the minimum amount that one has to use to insure complete conversion of the iodide to the phosphonate, potentially due to partial consumption of the reagent in the formation of the phosphorus-containing impurity mentioned earlier. Under these optimal conditions (1.4 equiv of $P(OEt)_3$, PhH, reflux, 3 h), the yield for the conversion of **6b** to **10b** is 89% (Table 2, entry 3).

In order to probe the scope of this reaction, a variety of α′-iodoenones **6** were prepared. The results obtained for the conversion of the alcohols **7a−i** to α,β-unsaturated α′-iodoketones **6a−i** are presented in Table 1. For most of the examples, moderate to good yields were obtained. α′-Iodoketones which contain extended conjugation (i.e. **6f** and **6g**) were found to be less stable, accounting for the lower yields observed in these cases. In all examples for which geometric isomers were expected (i.e. **6a,d−g**), moderate to excellent *E*-stereoselectivity was obtained.[26] The rearrangement of the tosyl carbamate derivative of the alcohols **7h** and **7i** to their respective enol carbamate intermediate was somewhat slower than for the previous examples. Maximum conversion of **7h** to **6h** was achieved when the reaction mixture was left for 7 days at room temperature before NIS was added. The best yield of **6i** was obtained when the alcohol **7i** was reacted with TsNCO for 20 h in refluxing $CHCl_3$ prior to the addition of the electrophile.

The 4,4-disubstituted 1-iodo-3-buten-2-ones **6a−i** were converted to the corresponding ketophosphonates **10a−i** using the general procedure described above (1.4 equiv of $P(OEt)_3$, PhH, reflux, 3 h). The results are summarized in Table 2. In addition to the results presented in Table 2, several entries deserve further comment. For the iodoenone **6a**, both *E*- and *Z*-isomers were reacted separately. Under the reaction conditions, the minor isomer (*Z*)-**6a** underwent partial isomerization (*E*/*Z* = 1:21) to the *E*-isomer. In the purification step where the phosphorus-containing impurity was removed (90 °C, high vacuum, 30 min), further isomerization occurred (*E*/*Z* = 1:11). For all the other examples involving a pure single geometric isomer (i.e. (*E*)-**6a**, **6d**, (*E*)-**6e**, (*Z*)-**6e**, and **6f**), no such isomerization has been observed, and the yields are excellent. No enol phosphate side products from the Perkow reaction were detected, but small amounts (3−10%) of dehalogenated starting material have usually been observed. Furthermore, the last three examples in Table 2 demonstrate that the method is compatible with functional groups such as double bonds, ketals, and silyl ethers, respectively.

Synthesis of (±)-(*E*)-α-Atlantone. (+)-(*R*)-α-Atlantone (**4**) is a major component of the essential oil from *Cedrus deodora*.[6e,f] When isolated, it exists as a 6:1 *E*/*Z* mixture of isomers.[6f] Several syntheses, both racemic and nonracemic, of this sequiterpene, have been published.[2f,27] We have prepared racemic (*E*)-α-atlantone ((±)-(*E*)-**4**) using the γ,δ-unsaturated β-ketophosphonate (*E*)-**10a** described above. According to Motoyoshiya and co-workers,[2f] (±)-(*E*)-α-atlantone can be prepared by the condensation of the ketophosphonate **10c** (obviously obtained, in their case, by a different method) with (±)-4-acetyl-1-methylcyclohexene (**13**). Employing the conditions that they described (NaH in DME at 70 °C for 3 h), we observed a very low yield (20%) in the "HWE" reaction of (*E*)-**10a** and acetone. The product, (±)-(*E*)-**4**, was also contaminated with the corresponding *Z*-isomer. Under optimized conditions, (*E*)-**10a** was condensed with acetone (excess) using sodium bis(trimethylsilyl)amide as a base (THF, 48 h, rt), in the dark,[28] to afford the desired trienone (±)-(*E*)-**4** in high yield, without any trace of the

(22) The Arbuzov (phosphonate):Perkow (enol phosphate) ratio is greater at high temperature.[15]

(23) Takahashi, H.; Fujiwara, K.; Otha, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1498.

(24) For examples on the dehalogenation of α-haloketones under various conditions, see the following papers and refs cited therein: (a) Kamiya, N.; Tanmatu, H.; Ishii, Y. *Chem. Lett.* **1992**, 293. (b) Perez, D.; Greenspoon, N.; Keinan, E. *J. Org. Chem.* **1987**, *52*, 5570.

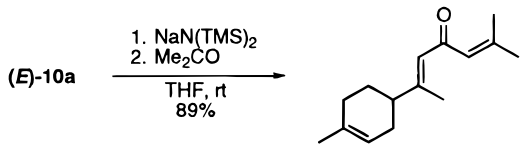
(25) This impurity appears to be the same regardless of the substrate. Its ^{1}H NMR spectrum exhibits only two signals that overlap with the ethoxy groups of the phosphonate moiety of **10**.

(26) For a rationalization on the stereochemical outcome of the reaction, see ref 17.

(27) (a) Isager, P.; Thomsen, I.; Torsell, K. B. G. *Acta Chem. Scand.* **1990**, *44*, 806. (b) Andrianome, M.; Häberle, K.; Delmond, B. *Tetrahedron* **1989**, *45*, 1079. (c) El-Jazouli, M.; Lage, N.; Masson, S.; Thuillier, A. *Bull. Soc Chim. Fr.* **1988**, 883. (d) Andrianome, M.; Delmond, B. *J. Org. Chem.* **1988**, *53*, 542 and refs cited therein. (e) Adams, D. R.; Bhatnagar, S. P.; Cookson, R. C.; Tuddenham, R. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1741.

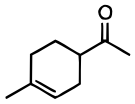
(28) The reaction was performed in the dark as a precaution; according to ref 6f, (*E*)-α-atlantone is known to partially photoisomerize to its *Z*-isomer when irradiated with a quartz Hg vapor lamp (44% yield of a 1:1.3 *E*/*Z* mixture after 1.5 h). When the reaction illustrated in Scheme 2 was conducted under exposure to ambient light, (±)-α-atlantone was obtained as a column chromatography-separable 7:1 *E*/*Z* mixture.

Scheme 2



(±)-(*E*)-**4**

cis-isomer (Scheme 2). Interestingly, these conditions were unsuccessful for the condensation of the ketophosphonate **10c** with **13**. Maximum conversion to (±)-(*E*)-**4** (26% after chromatography) was achieved when the reaction mixture was refluxed for 24 h. A small amount of the corresponding *Z*-isomer was also observed.



13

Conclusion

We have demonstrated a new preparation of δ,δ-disubstituted γ,δ-unsaturated β-ketophosphonates **10**, involving the Arbuzov reaction of 4,4-disubstituted 1-iodo-3-buten-2-ones **6**. These α′-iodoenones were obtained in moderate to good yields, as well as moderate to excellent stereoselectivity, via the rearrangement of carbamates of readily available tertiary α-allenic alcohols **7**. The Arbuzov reaction of the α′-iodoenones **6** with triethyl phosphite is, to the best of our knowledge, the first such example to be reported. Excellent yields were obtained for this reaction and, in examples involving *E*-phosphonates, no isomerization was observed. Furthermore, protecting groups such as olefins, ketals, and silyl ethers were shown to be stable to the reaction conditions. The synthetic utility of the ketophosphonates **10** was demonstrated by a new synthesis of the terpenoid (±)-(*E*)-α-atlantone ((±)-(*E*)-**4**).

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 or 400 MHz in $CDCl_3$, using TMS as internal standard. Broad band proton-decoupled ^{13}C NMR spectra were recorded at 75.5 or 100.6 MHz in $CDCl_3$, also using $CDCl_3$ as internal standard. IR spectra were recorded on neat samples. Anhydrous THF, Et_2O and CH_2Cl_2 were purchased in Sure/Seal bottles from Aldrich. Benzene (BDH, AnalaR) was used as such. All reactions were carried out under an inert atmosphere of argon. Flash chromatography was performed using 230−400 mesh silica gel and compound detection from analytical TLC plates was performed using an acidic ethanolic *p*-anisaldehyde solution and/or UV light. All the compounds prepared were stored in a −78 °C freezer (especially important for α′-iodoenones). CI and FAB high resolution mass spectra were run in NH_3 and glycerol, respectively, at The Biomedical Mass Spectrometry Unit, McGill University, Montréal, Québec, Canada. Elemental analyses were performed by Oneida Research Services, Inc., Whitesboro, NY.

All the ketones used in the preparation of tertiary α-allenic alcohols **7** were commercially available except for **7i** for which the appropriate ketone was easily obtained, in three steps, from commercially available 1,4-cyclohexanedione monoethylene ketal. All the other reagents mentioned below were also commercially available.

For the alcohol **7d** and the α′-iodoenone **6c**, it was not possible to obtain either a satisfactory elemental analysis or a HRMS. Since the α′-iodoenone **6g** and the β-ketophosphonate **10g** are unseparable mixtures of *E*- and *Z*-isomers, their respective NMR data do not appear in this section. Copies of ^{1}H and ^{13}C NMR spectra for all four compounds listed above are included in the supporting information.

Preparation of Tertiary α-Allenic Alcohols 7a−i. The alcohols **7a**−**i** were prepared according to the two-step method of Landor and co-workers.[19] The procedure described below for the preparation of **7a** is typical.

Alcohol 7a. To a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (4.00 g, 28.5 mmol) in THF (60 mL) at −78 °C was added *n*-BuLi (12.0 mL, 30.0 mmol of a 2.5 M solution in hexane) dropwise (20 min). The resulting mixture was stirred for 30 min, and (±)-4-acetyl-1-methylcyclohexene (4.60 mL, 31.4 mmol) was added dropwise (20 min). After 2 h at −78 °C, the mixture was allowed to warm to 0 °C and quenched by the addition of a saturated NH_4Cl solution. The THF layer was concentrated and the residue dissolved in EtOAc. The aqueous layer was extracted with the same solvent, and the combined organic extracts were washed with a 25% NH_4OAc solution (pH 7), water, and brine. Drying ($MgSO_4$) and concentration afforded a light yellow oil that was dissolved in Et_2O (40 mL) and cooled to 0 °C. $LiAlH_4$ (31.4 mL, 31.4 mmol of a 1.0 M solution in THF) was added dropwise (10 min), and the mixture was allowed to warm to rt. After 1.5 h, the reaction was carefully quenched by the successive addition of H_2O (1.2 mL), 15% aqueous NaOH (1.2 mL), and H_2O (3.6 mL). The resulting suspension was filtered through Celite and washed with Et_2O. Drying ($MgSO_4$) and concentration of the filtrate afforded a residue that was purified by column chromatography (EtOAc/hexane 1:9). The alcohol **7a**, a colorless viscous oil (3.41 g, 67%) that solidified in the freezer, displayed the following physical properties: ^{1}H NMR (300 MHz) δ 1.21−1.36 (m, 4H), 1.57−1.69 (m, 5H), 1.74−2.16 (m, 5H), 4.89 (m, 2H), 5.28 (m, 1H), 5.38 (br s, 1H); ^{13}C NMR (100.6 MHz) δ 23.2, 23.7, 23.8, 25.0, 25.3, 26.5, 26.6, 30.6, 30.7, 44.4, 44.6, 73.0, 73.1, 78.0, 78.2, 97.6, 98.4, 120.3, 120.4; IR 3390, 3040, 3010, 1955, 1450, 1435, 1375 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.68; H, 10.10.

Preparation of α′-Iodoenones 6a−i. The procedure described below for the preparation of α′-iodoenone **6a** is typical.

α′-Iodoenones (*E*)/(*Z*)-6a. To a solution of the alcohol **7a** (705 mg, 3.95 mmol) in CH_2Cl_2 (35 mL) at rt was added *p*-toluenesulfonyl isocyanate (692 μL, 4.55 mmol) dropwise. The resulting mixture was stirred overnight at the same temperature, and *N*-iodosuccinimide (979 mg, 4.35 mmol) was added in one portion. After 1 h, the mixture was diluted with hexane (170 mL), stirred for 5 min and filtered through Celite. The cake was washed with hexane and the filtrate concentrated to afford a pale orange residue that was analyzed by ^{1}H NMR spectroscopy for *E*/*Z* ratio determination (see footnote b in Table 1). The crude product was then subjected to column chromatography ($CHCl_3$/hexane 2:3 → 1:1) affording, in the order, the α′-iodoenones (*Z*)-**6a** (71 mg, 6%) and (*E*)-**6a** (507 mg, 42%), both as a pale yellow oil. Mixed fractions (154 mg, 13%) were also collected for a total yield of 61%. The isomers displayed the following physical properties. (*Z*)-**6a:** ^{1}H NMR (400 MHz) δ 1.52−1.70 (m, 5H), 1.86−2.02 (m, 6H), 2.08−2.20 (m, 1H), 3.72 (m, 1H), 3.79 (s, 2H), 5.40 (br s, 1H), 6.17 (s, 1H); ^{13}C NMR (75.5 MHz) δ 8.9, 21.0, 23.4, 27.1, 29.0, 30.1, 36.3, 120.0, 120.3, 133.8, 167.7, 191.8; IR 3010, 1665, 1600, 1435 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{18}IO$ (M + H)$^+$ 305.0402, found 305.0403. (*E*)-**6a:** ^{1}H NMR (300 MHz) δ 1.51−1.70 (m, 4H), 1.76−1.87 (m, 1H), 1.90−2.18 (m, 4H), 2.19 (s, 3H), 2.21−2.35 (m, 1H), 3.80 (s, 2H), 5.41 (br s, 1H), 6.24 (s, 1H); ^{13}C NMR (75.5 MHz) δ 8.7, 17.9, 23.3, 27.1, 29.9, 30.1, 44.4, 118.2, 119.6, 133.8, 167.0, 192.6; IR 3010, 1680, 1610, 1435 cm^{-1}. Anal. Calcd for $C_{12}H_{17}IO$: C, 47.39; H, 5.63. Found: C, 47.14; H, 5.60.

Preparation of γ,δ-Unsaturated β-Ketophosphonates 10a−i. The procedure described below for the preparation of the ketophosphonate (*E*)-**10a** is representative.

Ketophosphonate (*E*)-10a. To a solution of the α′-iodoenone (*E*)-**6a** (210 mg, 0.690 mmol) in C_6H_6 (2.7 mL) at rt was added triethyl phosphite (166 μL, 0.966 mmol) in one portion. The resulting mixture was stirred at reflux temperature for 3 h, allowed to cool to rt, and applied, as such, on a column of silica for chromatography (acetone/toluene 1:4). To remove a coeluting volatile impurity,[25] the product so obtained was heated at 90 °C under high vacuum (∼2 mmHg) for 30 min, affording the ketophosphonate (*E*)-**10a** as a colorless oil (204 mg, 94%) that displayed the following physical properties: ^{1}H NMR (300 MHz)

δ 1.33 (t, J = 7.1 Hz, 6H), 1.48−1.70 (m, 4H), 1.76−1.86 (m, 1H), 1.90−2.31 (m, 8H), 3.09 (d, J_{HP} = 22.4 Hz, 2H), 4.14 (m, 4H), 5.40 (br s, 1H), 6.25 (s, 1H); ^{13}C NMR (100.6 MHz) δ 16.1 (d, J_{CP} = 6.2), 17.8, 23.1, 27.0, 29.9, 30.0, 43.0, 44.3, 62.1 (d, J_{CP} = 6.4), 119.6, 121.7, 133.6, 165.0, 191.0 (d, J_{CP} = 6.0); IR 1685, 1610, 1440, 1390, 1255, 1030 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{28}O_4P$ $(M + H)^+$ 315.1725, found 315.1726.

(±)-(*E*)-α-Atlantone ((±)-(*E*)-4). To a solution of the ketophosphonate (*E*)-**10a** (200 mg, 0.636 mmol) in THF (2.5 mL) at 0 °C was added sodium bis(trimethylsilyl)amide (649 μL, 0.649 mmol of a 1.0 M solution in THF) dropwise (5 min). The resulting mixture was stirred for 10 min at 0 °C and 20 min at rt before an excess of acetone (2.5 mL, 34.0 mmol) was added. The reaction was left 48 h at the same temperature, in the absence of light and quenched by the addition of a 25% NH_4OAc solution (pH 7). The aqueous layer was extracted with EtOAc (3x), and the combined organics were successively washed with the NH_4OAc solution, water, and brine. Drying ($MgSO_4$) and concentration afforded a residue that was subjected to column chromatography ($CHCl_3$/hexane 1:1). The trienone (±)-(*E*)-**4**, a pale yellow oil (124 mg, 89%), displayed the following physical properties: ^{1}H NMR (400 MHz) δ 1.50−1.61 (m, 1H), 1.66 (br s, 3H), 1.76−1.82 (m, 1H), 1.89 (d, J = 1.1 Hz, 3H), 1.92−2.13 (m, 4H), 2.14−2.24 (m, 7H), 5.41 (br s, 1H), 6.05 (m, 1H), 6.07 (m, 1H); ^{13}C NMR (100.6 MHz) δ 17.4, 20.4, 23.3, 27.3, 27.6, 30.2, 30.3, 44.4, 120.0, 124.2, 126.4, 133.7, 153.9, 161.6, 191.9; IR 3040, 3010, 1670, 1620, 1610, 1440, 1375 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.41; H, 10.23.

Supporting Information Available: Experimental procedures for **7b**−**i**, **6b**−**i**, and **10b**−**i**; copies of ^{1}H NMR spectra for **7b**−**d**, **7g**, **7i**, (*Z*)-**6a**, **6c**,**d**, **6g**,**h**, (*E*)-**10a**, (*Z*)-**10e**, and **10g**−**i**, as well as ^{13}C NMR spectra for **7d**, **6c**, **6g**, and **10g** (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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