Synthesis of β-chloro, β-bromo, and β-iodo α,β-unsaturated ketones

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A new, efficient method for the preparation of β-chloro, β-bromo, and β-iodo α,β-unsaturated ketones is described. The method involves the reaction of β-diketones or α-hydroxymethylenecycloalkanones with triphenylphosphine dihalides in the presence of triethylamine. With the dichloride and dibromide reagents, the reactions are conveniently carried out in benzene at room temperature, while with triphenylphosphine diiodide the reactions are best performed in refluxing acetonitrile (β-diketones) or in acetonitrile–hexamethylphosphoramide (α-hydroxymethylenecycloalkanones). The reaction of triphenylphosphine diiodide – triethylamine with a series of 4-alkyl-1,3-cyclohexanediones provides mainly or exclusively (depending on the size of the alkyl group) 6-alkyl-3-iodo-2-cyclohexen-1-ones, while reaction of this reagent with 2-hydroxymethylenecyclohexanone and 2-hydroxymethylenecyclopentanone affords stereoselectively and regioselectively (*E*)-2-iodomethylenecyclohexanone and (*E*)-2-iodomethylenecyclopentanone, respectively.

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On décrit une nouvelle méthode efficace de préparation des β-chloro, β-bromo et β-iodo cétones α,β-insaturées. La méthode fait intervenir la réaction des β-dicétones ou des α-hydroxyméthylènecycloalcanones avec les dihalogénures de triphénylphosphine en présence de triéthylamine. Les réactions ont lieu dans le benzène à la température ambiante si on utilise les dichlorures ou les dibromures comme réactifs, tandis qu'avec le diiodure de triphénylphosphine, on obtient de meilleures réactions dans l'acétonitrile au reflux (β-dicétones) ou dans un mélange d'acétonitrile–hexaméthylphosphoramide (α-hydroxyméthylènecycloalcanones). La réaction du diiodure de triphénylphosphine dans la triéthylamine avec une série d'alkyl-4 cyclohexanediones-1,3 conduit principalement ou exclusivement (dépendant de la taille du groupe alkyle) aux alkyl-6 iodo-3-cyclohexèn-2 ones-1, tandis que ce même réactif avec l'hydroxyméthylène-2 cyclohexanone et l'hydroxyméthylène-2 cyclopentanone conduit de façon stéréosélective et régiosélective aux iodométhylène-2 cyclohexanone-(*E*) et iodométhylène-2 cyclopentanone-(*E*) respectivement.

[Traduit par le journal]

Introduction

β-Chloro α,β-unsaturated ketones have been known for a long time (1) and, over the years, have served as important and versatile intermediates in organic synthesis.[1] On the other hand, the corresponding bromo compounds, although known, do not appear to have been used a great deal by synthetic organic chemists.[2] Furthermore, prior to the initiation of our work in this area[3] reports in the chemical literature concerning the preparation and use of β-iodo α,β-unsaturated ketones were very rare.[4]

The synthesis of β-chloro α,β-unsaturated ketones from β-diketones has been carried out by treatment of the latter substances with a diversity of reagents: phosphorus trichloride (29–36), phosphorus oxychloride (29, 37), phosgene (38), acetyl chloride (39), oxalyl chloride (40, 9), and triphenylphosphine – carbon tetrachloride (41). Of these, the latter two reagents appear to be the best in terms of convenience and efficiency. Conversion of β-diketones into β-bromo enones has traditionally been accomplished by treatment of the former substrates with phosphorus tribromide (29, 36, 42), although the yield of this process does not appear to be very high. More recently, this type of conversion has been accomplished employing triphenylphosphine – carbon tetrabromide (41). To our knowledge, the direct conversion of β-diketones into β-iodo α,β-unsaturated ketones had not been accomplished prior to our work (19). We report herein the details of our study concerning the transformation of β-diketones and β-hydroxymethylenecycloalkanones into the corresponding β-chloro, β-bromo, and/or β-iodo α,β-unsaturated ketones. Subsequent publications will deal with the use of these versatile substances in organic synthesis.[5]

[1]For some recent examples, see refs. 2–17, inclusive. This list of citations is not meant to be exhaustive, but is provided to give the reader some appreciation for the synthetic utility of β-chloro enones.

[2]For examples, see refs. 11, 13, and 18.

[3]For a preliminary communication regarding part of the work reported herein, see ref. 19.

[4]See, for example, refs. 20 and 21. For some reports concerning the use of β-iodo enones which appeared subsequent to our preliminary communication (19), see refs. 10 and 22–28, inclusive.

Results and discussion

(a) *Conversion of symmetrical β-diketones into β-halo α,β-unsaturated ketones*

When 1,3-cyclohexanedione (**1**) and triethylam-

[5]For some preliminary reports, see refs. 43–49, inclusive.

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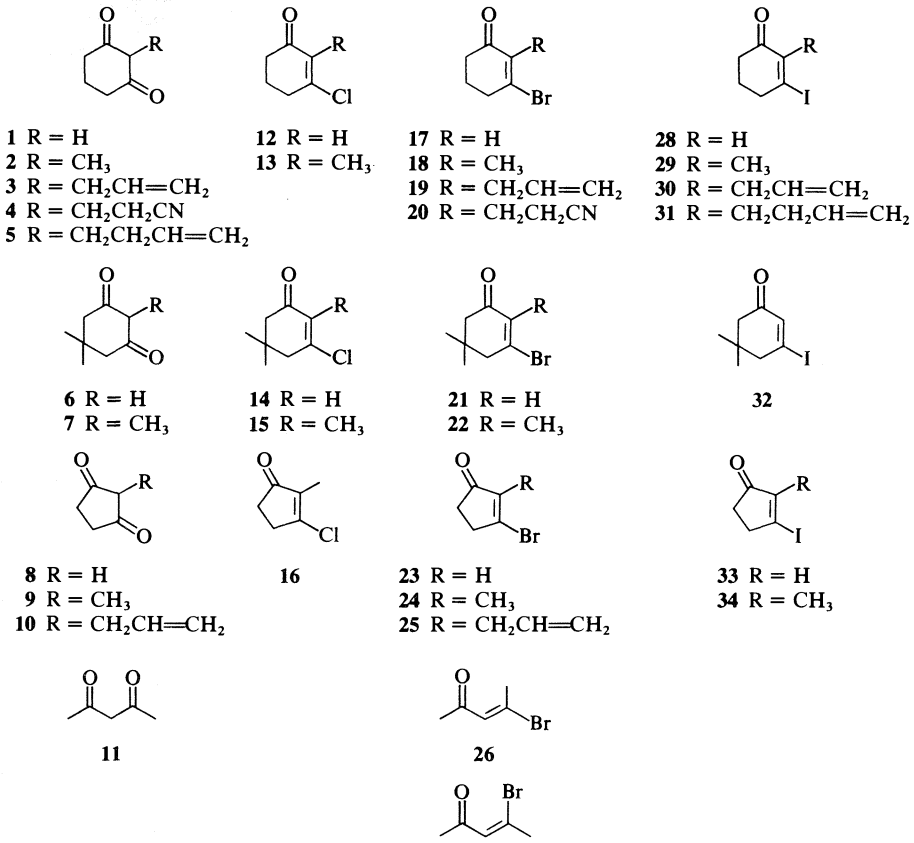
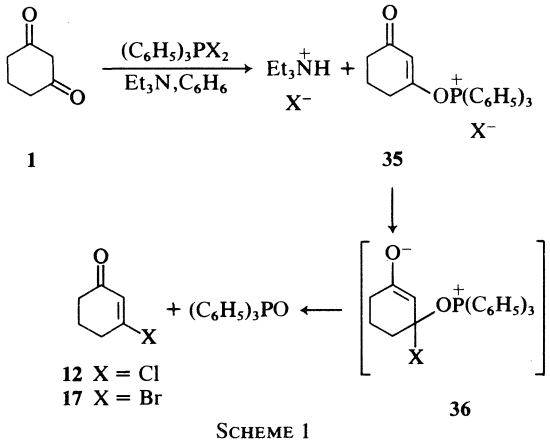


CHART 1

ine were added to a suspension of freshly prepared triphenylphosphine dichloride in benzene and the resulting mixture was stirred at room temperature for 1 h, 3-chloro-2-cyclohexen-1-one (**12**) was produced in 91% yield (see Chart 1). In similar fashion, reaction of **1** with triphenylphosphine dibromide in the presence of triethylamine provided (97%) 3-bromo-2-cyclohexen-1-one (**17**). It seems highly likely that these conversions proceed by way of the phosphonium salt **35**,[6] formed by reaction of the diketone with triphenylphosphine dihalide (see Scheme 1). Conjugate addition of halide ion to **35**, followed by elimination of triphenylphosphine oxide from the resulting intermediate **36** would afford the observed products **12** and **17**.

Reaction of triphenylphosphine dichloride and/or the corresponding dibromide reagent with the symmetrical β-diketones **2–4** and **6–11**, inclusive, gave results comparable to those obtained with 1,3-cyclohexanedione (**1**), and these are summarized in Table 1. Although these results are quite straightforward and require little additional comment, the following points should be noted. It was found to be important to prepare the triphenylphosphine dihalides from freshly recrystallized triphenylphosphine



SCHEME 1

[6]This type of intermediate has been proposed previously in connection with the reaction of 2-bromodimedone with triphenylphosphine (51).

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and to carefully dry and distil the benzene and triethylamine used in the reactions. If these precautions were not taken, the product yields decreased significantly. However, when the reactions were carried out under the conditions prescribed in the Experimental, the yields were uniformly excellent. From the results summarized in Table 1, it is clear that this method for the conversion of β-diketones into β-chloro α,β-unsaturated ketones compares very favorably with the most recently reported methods (9, 41). Furthermore, for the preparation of β-bromo enones, our method appears to be superior to that involving the reaction of β-diketones with phosphorus tribromide (29, 36, 42) and affords yields marginally higher than those obtained from the triphenylphosphine – carbon tetrabromide method (41).

The reactions summarized in Entries 1–14 of Table 1 involved cyclic β-diketones as the starting materials and, therefore, there were no ambiguities with respect to the stereochemistry of the products. However, in the one acyclic case which was investigated, it was found that the reaction of 2,4-pentanedione (**11**) with triphenylphosphine dibromide in 5:1 acetonitrile–benzene was not totally stereoselective, since a mixture of the two geometrically isomeric β-bromo enones **26** and **27** (ratio ~87:13, respectively) was produced (88% yield). A pure sample of each of the two isomers could be obtained by preparative gas–liquid chromatography (glc) and the stereochemistry of these substances was shown to be as indicated on the basis of the ^{1}H nmr spectra. Thus the major isomer, which exhibited the signal due to the vinyl methyl group at lower field (δ 2.75), was assigned structure **26**, while structure **27** could be assigned to the minor product, which showed the corresponding resonance at higher field (δ 2.45). Similarly, the olefinic protons of the two isomers exhibited the expected relative chemical shifts (**26**: δ 6.73, proton *cis* to bromine; **27**: δ 6.55, proton *trans* to bromine). It is interesting to note that the reaction of 2,4-pentanedione (**11**) with oxalyl chloride affords (50% yield) a 1:1 mixture of (*E*)- and (*Z*)-4-chloro-3-penten-2-one (40, 9), while treatment of **11** with triphenylphosphine – carbon tetrachloride has been reported (41) to yield (81%) only the (*E*) isomer.

TABLE 1. Conversion of symmetrical β-diketones into β-chloro and β-bromo α,β-unsaturated ketones[a]

Entry	β-Diketone	Reagent[b]	Reaction time (h)	Product (yield, %)[c]
1	**1**	A	1	**12** (91)
2	**1**	B	3	**17** (97)
3	**2**	A	4	**13** (97)
4	**2**	B	4	**18** (96)
5	**3**	B	3	**19** (96)
6	**4**	B	17	**20** (82)
7	**6**	A	1	**14** (94)
8	**6**	B	3	**21** (93)
9	**7**	A	7	**15** (90)
10	**7**	B	4	**22** (91)
11	**8**	B	4	**23** (80)
12	**9**	A	4	**16** (92)
13	**9**	B	4	**24** (93)
14	**10**	B	4	**25** (86)
15	**11**	B	19[d]	**26** + **27**[e] (88)

[a] All reactions were carried out at room temperature. The reaction solvent was benzene except when otherwise noted.
[b] Reagent A: triphenylphosphine dichloride. Reagent B: triphenylphosphine dibromide.
[c] Yield of distilled product(s).
[d] The solvent in this case was 5:1 acetonitrile–benzene.
[e] The ratio of **26**/**27** was approximately 87:13, respectively. Also present in the product was a minor (~5%), unidentified compound.

The infrared and ^{1}H nmr spectral data derived from the β-chloro (**12–16**) and β-bromo (**17–27**) α,β-unsaturated ketones, along with appropriate references or elemental analysis data, are summarized in Table 2.

Reaction of 1,3-cyclohexanedione (**1**) with triphenylphosphine diiodide in benzene via a procedure similar to that used in the case of the dichloride or dibromide reagents (*vide supra*) failed to produce 3-iodo-2-cyclohexen-1-one (**28**) (see Chart 1). When the progress of the reaction was monitored by thin-layer chromatography (tlc) it was found that although the starting material **1** disappeared slowly, only a trace of compound **28** had formed even after a period of 20 h. Apparently, under these conditions, the dione **1** reacted with the diiodide reagent to produce the phosphonium salt **35** (X = I, see Scheme 1), but the latter species did not undergo the conjugate addition–elimination sequence (**35** (X = I) → **36** (X = I) → **28**). Some support for this conclusion was forthcoming when it was found that evaporation of the solvent, followed by heating of the residual material to 145–165°C under reduced pressure with direct distillation of product, gave the iodo enone **28** in 46% yield. In similar fashion, this procedure (Procedure A) could be used to convert other β-diketones into the corresponding β-iodo enones (see Table 3, Entries 1, 4, 9, 12). However, it is clear from the data given in Table 3 that this mode of operation did not provide high yields of the desired products.

In efforts to improve this situation, the use of a more polar reaction medium was investigated. Indeed, it was found that reaction of various β-diketones with triphenylphosphine diiodide – triethylamine in dry acetonitrile at room temperature (Procedure B) produced *directly* improved yields of the corresponding β-iodo enones (Table 3, Entries 2, 5, 7, 10). However, even when this polar solvent was used, the reactions at room temperature were slow and, typically, reaction times of ~4 days were required for complete conversion of the

TABLE 2. Spectral data for β-chloro and β-bromo α,β-unsaturated ketones

Compound[a]	Infrared (cm^{-1})[b]	^1H Nuclear magnetic resonance (δ)	Reference or analysis
12	1680, 1608	1.80–2.90 (complex m, 6H), 6.22 (t, 1H, J = 1.5 Hz)	[c]
13	1675, 1626	1.86–2.94 (complex m, 6H), 1.90 (t, 3H, J = 2 Hz)	[d]
14	1678, 1610	1.10 (s, 6H), 2.26 (s, 2H), 2.55 (d, 2H, J = 2 Hz), 6.22 (t, 1H, J = 2 Hz)	[e]
15	1675, 1630	1.08 (s, 6H), 1.93 (t, 3H, J = 2 Hz), 2.32 (s, 2H), 2.62 (q, 2H, J = 2 Hz)	[f]
16	1712, 1640	1.78 (t, 3H, J = 2 Hz), 2.40–2.67 (m, 2H), 2.67–2.98 (m, 2H)	[g]
17	1682, 1605	1.80–2.60 (m, 4H), 2.70–3.00 (m, 2H), 6.50 (t, 1H, J = 2 Hz)	[h]
18	1676, 1620	1.86–2.26 (m, 2H), 1.94 (t, 3H, J = 2 Hz), 2.30–2.63 (m, 2H), 2.73–3.10 (m, 2H)	*Anal.* calcd. for C_7H_9BrO: C 44.41, H 4.79; found: C 44.33, H 4.90
19	3115, 1675 1637, 1613	1.80–2.26 (m, 2H), 2.33–2.63 (m, 2H), 2.77–3.06 (m, 2H), 3.10–3.37 (m, 2H), 4.83–5.30 (m, 2H), 5.46–6.14 (m, 1H)	*Anal.* calcd. for $C_9H_{11}BrO$: C 50.20, H 5.15; found: C 50.33, H 5.19
20	2260, 1675 1615	1.93–2.43 (m, 2H), 2.47–3.27 (m, 8H)	*Anal.* calcd. for $C_9H_{10}BrNO$: C 47.39, H 4.42, N 6.14; found: C 47.70, H 4.44, N 6.10
21	1680, 1608	1.10 (s, 6H), 2.28 (s, 2H), 2.72 (d, 2H, J = 1.5 Hz), 6.49 (t, 1H, J = 1.5 Hz)	[i]
22	1675, 1625	1.08 (s, 6H), 1.96 (t, 3H, J = 2 Hz), 2.32 (s, 2H), 2.80 (q, 2H, J = 2 Hz)	*Anal.* calcd. for $C_9H_{13}BrO$: C 49.78, H 6.03; found: C 49.65, H 5.98
23	1705, 1580	2.43–2.70 (m, 2H), 2.97–3.18 (m, 2H), 6.44 (t, 1H, J = 1.5 Hz)	*Anal.* calcd. for C_5H_5BrO: C 37.30, H 3.13; found: C 37.15, H 3.29
24	1705, 1636	1.77 (t, 3H, J = 2 Hz), 2.42–2.66 (m, 2H), 2.76–3.14 (m, 2H)	*Anal.* calcd. for C_6H_7BrO: C 41.18, H 4.03; found: C 41.38, H 4.15
25	1704, 1626	2.47–2.64 (m, 2H), 2.84–3.14 (m, 4H), 4.93–5.22 (m, 2H), 5.58–6.04 (m, 1H)	*Anal.* calcd. for C_8H_9BrO: C 47.79, H 4.51; found: C 47.66, H 4.56
26	1693, 1603	2.20 (s, 3H), 2.75 (d, 3H, J = 2 Hz), 6.73 (broad s, 1H)	*Anal.* calcd. for C_5H_7BrO: C 36.83, H 4.25; found: C 36.80, H 4.22
27	1695, 1610	2.33 (s, 3H), 2.45 (d, 3H, J = 1.5 Hz), 6.55 (broad s, 1H)	*Anal.* calcd. for C_5H_7BrO: C 36.83, H 4.26; found: C 36.61, H 4.15

[a] All compounds (except **18**, which exhibited mp 21.5–23.5°C) were liquids at room temperature, and were purified by bulb-to-bulb distillation under reduced pressure (water aspirator or vacuum pump).
[b] All infrared spectra were taken on liquid films.
[c] References 9, 30, 32, 50.
[d] References 9, 35.
[e] References 9, 29, 31.
[f] References 9, 33.
[g] Reference 9.
[h] References 30, 50.
[i] Reference 51.

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TABLE 3. Reaction of symmetrical β-diketones with triphenylphosphine diiodide. Preparation of β-iodo α,β-unsaturated ketones

Entry	β-Diketone	Procedure[a]	Reaction time (h)	Product (yield %)[b]
1	**1**	A	20	**28** (46)
2	**1**	B	96	**28** (72)
3	**1**	C	9	**28** (87)
4	**2**	A	24	**29** (60)
5	**2**	B	96	**29** (73)
6	**2**	C	9	**29** (73)
7	**3**	B	96	**30** (80)
8	**5**	C	9	**31** (86)
9	**6**	A	24	**32** (62)
10	**6**	B	96	**32** (83)
11	**8**	C	3	**33** (85)
12	**9**	A	24	**34** (71)
13	**9**	C	3	**34** (92)

[a] For details regarding the procedures A, B, and C, see text and the Experimental.
[b] Yield of distilled product.

starting materials into the desired products. Eventually, it was found that the product yields could be improved still further and that the reaction times could be reduced to a matter of hours by carrying out the reactions at elevated temperatures (refluxing acetonitrile, Procedure C). Under these conditions, it was possible to obtain consistently good to excellent yields of the β-iodo enones (Table 3, Entries 3, 6, 8, 11, 13) and this procedure, with few exceptions (*vide infra*), is the preferred one.

The infrared and ^{1}H nmr spectral data derived from the β-iodo α,β-unsaturated ketones, along with elemental analysis data, are summarized in Table 4.

(b) Conversion of unsymmetrical 1,3-cyclohexanediones into β-iodo α,β-unsaturated ketones

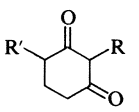
The reaction of triphenylphosphine diiodide with the unsymmetrically substituted 1,3-cyclohexanediones **37–44** (see Chart 2) was also investigated. This study was carried out in order to determine the regioselectivity of the transformations and to produce substances, more highly substituted than compounds **28–31**, which might be of use as intermediates in organic synthesis.

The substrates **37–44** necessary for this investigation were prepared in a straightforward manner (see Scheme 2). The kinetically formed (lithium diisopropylamide (LDA), tetrahydrofuran (THF), −78°C) enolate anions of the isobutyl enol ethers **63** and **64** were alkylated (52) with methyl iodide, allyl bromide and isopropyl iodide. Although alkylation (tetrahydrofuran solution) of the enolate anions with the former two alkylating agents proceeded in excellent yields (**65**: 95%, **66**: 93%, **69**: 94%, **70**: 95%), similar reactions involving isopropyl iodide gave, not unexpectedly (52), poor yields of the desired products **68** (16%) and **72** (13%), even when hexamethylphosphoramide (HMPA) was used as a cosolvent. Nevertheless, quantities of **68** and **72** sufficient to carry out the present study could be obtained quite readily by this rather simple procedure.

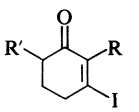
Hydrogenation of the allyl derivatives **66** and **70** in the presence of the homogeneous catalyst tris-(triphenylphosphine)chlororhodium (53) afforded excellent yields of the corresponding *n*-propyl compounds **67** and **71**, respectively.

Careful hydrolysis (54) of the enol ethers **65–72** with 1 *N* hydrochloric acid in acetone provided very good yields of the required 1,3-cyclohexanediones **37–44**, respectively. It is pertinent to point out that this hydrolysis should be done in the absence of oxygen and that the products should be purified carefully and stored under a dry, inert atmosphere. It is well known (55) that 1,3-diones of this type are quite prone to autoxidation, particularly when they are moist.

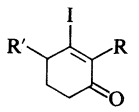
Treatment of 4-methyl-1,3-cyclohexanedione (**37**) with triphenylphosphine diiodide in refluxing acetonitrile in the presence of triethylamine provided, in 92% yield, a product which on the basis of glc and tlc appeared to consist of two components in a ratio of about 70:30. Separation of these components was achieved by preparative tlc. The major



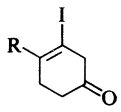
37 R = H, R′ = CH_3
38 R = H, R′ = $CH_2CH{=}CH_2$
39 R = H, R′ = $CH_2CH_2CH_3$
40 R = H, R′ = $CH(CH_3)_2$
41 R = R′ = CH_3
42 R = CH_3, R′ = $CH_2CH{=}CH_2$
43 R = CH_3, R′ = $CH_2CH_2CH_3$
44 R = CH_3, R′ = $CH(CH_3)_2$



45 R = H, R′ = CH_3
46 R = H, R′ = $CH_2CH{=}CH_2$
47 R = H, R′ = $CH_2CH_2CH_3$
48 R = H, R′ = $CH(CH_3)_2$
49 R = R′ = CH_3
50 R = CH_3, R′ = $CH_2CH{=}CH_2$
51 R = CH_3, R′ = $CH_2CH_2CH_3$
52 R = CH_3, R′ = $CH(CH_3)_2$



53 R = H, R′ = CH_3
54 R = H, R′ = $CH_2CH{=}CH_2$
55 R = H, R′ = $CH_2CH_2CH_3$
56 R = H, R′ = $CH(CH_3)_2$
57 R = R′ = CH_3
58 R = CH_3, R′ = $CH_2CH{=}CH_2$
59 R = CH_3, R′ = $CH_2CH_2CH_3$
60 R = CH_3, R′ = $CH(CH_3)_2$



61 R = CH_3
62 R = $CH_2CH{=}CH_2$

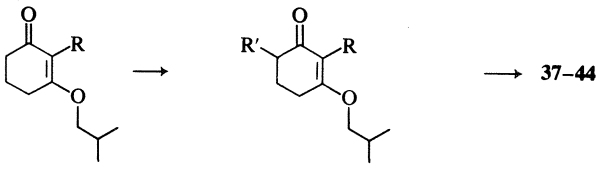
CHART 2

TABLE 4. Infrared, ^{1}H nmr, and elemental analysis data for β-iodo α,β-unsaturated ketones derived from symmetrical β-diketones

Compound	Infrared (cm^{-1})[a]	^{1}H Nuclear magnetic resonance (δ)	Analysis or exact mass determination
28[b]	1675, 1595	1.73–2.60 (m, 4H), 2.77–3.10 (m, 2H), 6.80 (t, 1H, J = 2 Hz)	*Anal.* calcd. for C_6H_7IO: C 32.45, H 3.17; found: C 32.66, H 3.25
29[c]	1670, 1605	1.67–2.20 (m, 2H), 2.03 (t, 3H, J = 2 Hz), 2.30–2.64 (m, 2H), 2.80–3.20 (m, 2H)	*Anal.* calcd. for C_7H_9IO: C 36.04, H 3.87; found: C 36.23, H 4.00
30	3115, 1680, 1635, 1600	1.83–2.23 (m, 2H), 2.34–2.66 (m, 2H), 2.94–3.40 (m, 4H), 4.90–5.34 (m, 2H), 5.46–6.15 (m, 1H)	*Anal.* calcd. for $C_9H_{11}IO$: C 41.24, H 4.23; found: C 41.54, H 4.23
31	1680, 1601	1.66–2.75 (m, 8H), 2.83–3.17 (t, 2H, J = 6 Hz), 4.63–5.20 (m, 2H), 5.46–6.17 (m, 1H)	*Exact Mass* calcd. for $C_{10}H_{13}OI$: 276.0015; found: 276.0019
32	1684, 1596	1.08 (s, 6H), 2.27 (s, 2H), 2.80 (d, 2H, J = 2 Hz), 6.81 (t, 1H, J = 2 Hz)	*Anal.* calcd. for $C_8H_{11}IO$: C 38.42, H 4.43; found: C 38.74, H 4.46
33[d]	1710, 1570	2.34–2.56 (m, 2H), 2.90–3.16 (m, 2H), 6.64 (t, 1H, J = 2 Hz)	*Anal.* calcd. for C_5H_5IO: C 28.88, H 2.42; found: C 28.98, H 2.40
34[e]	1701, 1620	1.83 (t, 3H, J = 2 Hz), 2.40–2.68 (m, 2H), 2.80–3.16 (m, 2H)	*Anal.* calcd. for C_6H_7IO: C 32.42, H 3.15; found: C 32.36, H 3.30

[a] Infrared spectra of compounds which were liquids at room temperature were taken on liquid films, while those of crystalline compounds were recorded on chloroform solutions.
[b] Melting point ~15–16°C.
[c] Melting point 57–59°C.
[d] Melting point 67–68°C.
[e] Melting point 52–53°C.

product provided spectral data consistent with that expected for 3-iodo-6-methyl-2-cyclohexen-1-one (**45**), while the minor component was shown on the basis of the infrared and ^{1}H nmr spectra to consist of a mixture of the isomeric iodo ketones **53** and **61** (ratio ≈8:3, respectively). Apparently, under the reaction conditions, the α,β-unsaturated ketone **53** was partially isomerized to the corresponding β,γ-unsaturated isomer **61**. Since we were unable to effect separation of compounds **53** and **61**, these substances were not individually characterized.



63 R = H
64 R = CH_3

65 R = H, R′ = CH_3
66 R = H, R′ = $CH_2CH{=}CH_2$
67 R = H, R′ = $CH_2CH_2CH_3$
68 R = H, R′ = $CH(CH_3)_2$
69 R = R′ = CH_3
70 R = CH_3, R′ = $CH_2CH{=}CH_2$
71 R = CH_3, R′ = $CH_2CH_2CH_3$
72 R = CH_3, R′ = $CH(CH_3)_2$

SCHEME 2

Reaction of triphenylphosphine diiodide with the unsymmetrical 1,3-cyclohexanediones **38–44** (see Chart 2) under conditions identical with those used for the dione **37** produced results which are summarized in Table 5. It can be seen that all of the transformations were quite efficient and, in terms of the regioselectivity of the reactions, the trends are not unexpected. For example, if one considers the series of 4-alkyl-1,3-cyclohexanediones **37–40**, it can be seen that as the alkyl group adjacent to the C-3 carbonyl function becomes larger, the regioselectivity of the reaction increases. That is, in the case of 4-methyl-1,3-cyclohexanedione (**37**), the iodine atom becomes attached to carbon atoms 1 and 3 in a ratio of ≈70:30 (Table 5, Entry 1) while in the case of the corresponding isopropyl substrate **40**, the reaction is nearly totally regioselective (Table 5, Entry 4). When the C-4 substituent is intermediate in size (allyl, *n*-propyl), the regioselectivity is between these two extremes (Table 5, Entries 2 and 3). A very similar trend is observed with the 4-alkyl-2-methyl-1,3-cyclohexanediones **41–44** (Table 5, Entries 5–8).

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TABLE 5. Reaction of unsymmetrical 1,3-cyclohexanediones with triphenylphosphine diiodide[a]

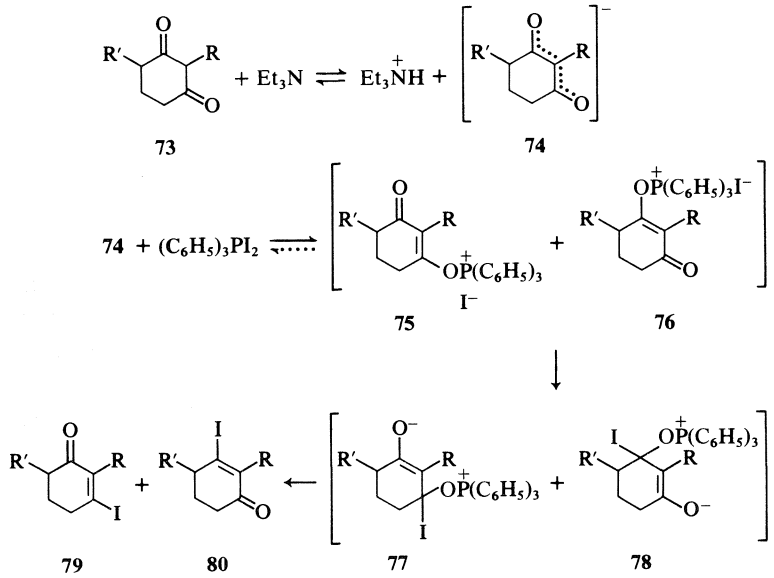
Entry	β-Diketone	Products (yield, %)[b]	Ratio[c]
1	**37**	**45**, **53**, **61** (92)	70:22:8[d]
2	**38**	**46**, **54**, **62** (76)	83:14:3[d]
3	**39**	**47**, **55** (88)	89:11
4	**40**	**48**, **56** (85)	>99:<1
5	**41**	**49**, **57** (91)	83:17
6	**42**	**50**, **58** (71)	88:12
7	**43**	**51**, **59** (78)	87:13
8	**44**	**52**, **60** (90)	>98:<2

[a] All reactions were carried out in refluxing acetonitrile.
[b] Yield of distilled products.
[c] Ratios were determined by a combination of glc and ^{1}H nmr spectroscopy.
[d] Although it was possible to separate (preparative tlc) compounds **45** and **46** from the mixtures of **53** + **61** and **54** + **62**, respectively, we were not able to effect separation of the latter two pairs of products. The ratios **53**/**61** and **54**/**62** were determined by ^{1}H nmr spectroscopy and, in each case, the two compounds were characterized as a mixture (see Table 6).

The observed regioselectivity in these reactions is presumably due to steric factors. Thus, reaction of triphenylphosphine diiodide with the enolate anion **74** of the generalized 1,3-dione **73** would be expected to take place preferentially at the less hindered oxygen atom to provide mainly the phosphonium salt **75**, with species **76** being the minor intermediate (see Scheme 3). On this basis, the ratio of the final products **79** and **80** would be a reflection of the relative proportions of the intermediate phosphonium salts **75** and **76**. As R′ becomes larger, the ratio **75**:**76** should increase, thus accounting for the observed trends.

An alternative rationale is also possible. On the basis of our earlier observations, it appears that the conversion of the phosphonium salts **75** and **76** into the iodo enones **79** and **80** is the rate-determining step in the overall transformation **73** → **79** + **80**. Therefore, if under the reaction conditions the reaction **74** → **75** + **76** were to be readily reversible and a relatively fast equilibrium between **75** and **76** (via **74**) would thus be established, the ratio **79**/**80** would depend upon the relative rates of conversion of **75** and **76** (via **77** and **78**) into the final products. Clearly, attack of iodide ion on the less hindered β carbon of the enone system of **75** would be a more facile process than the corresponding reaction with intermediate **76**. Furthermore, as R′ became larger, this rate difference would be enhanced. In any case, whatever the actual course of events, the observed regioselectivities, especially in those cases where one of the carbonyl groups is quite hindered, should prove to be useful from a synthetic point of view.

The infrared and ^{1}H nmr spectral data for the iodo enones listed in Table 5 are summarized in Table 6. The structural assignments for each of the isomeric pairs of compounds were based mainly on the ^{1}H nmr spectra and, therefore, it is appropriate to discuss briefly how these conclusions were drawn. Firstly, we have observed that in the ^{1}H nmr spectra of all of the substituted 3-iodo-2-cyclohexen-1-ones which we have prepared, the proton or protons at C-4 resonate at lower field (in the region δ 2.75–3.15) than the other ring protons and, in nearly all of the cases, this signal can be identified quite readily. Thus, for example, in the ^{1}H nmr spectrum of the β-iodo enone **47**, the C-4 methylene protons give rise to a *two-proton* multiplet at δ 2.78–2.98, while the C-4 proton of the isomeric compound **55** produces a *one-proton*



SCHEME 3

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TABLE 6. Infrared, ^{1}H nmr, and high resolution mass spectrometric data for β-iodo α,β-unsaturated ketones derived from unsymmetrical 1,3-cyclohexanediones

Compound(s)[a]	Infrared (cm^{-1})[b]	^{1}H Nuclear magnetic resonance (δ)	Exact mass determination[c]
45	1680, 1600	1.12 (d, 3H, J = 6.5 Hz), 1.60–2.14 (m, 3H), 2.16–2.54 (m, 1H), 2.76–3.04 (m, 2H), 6.70 (t, 1H, J = 2 Hz)	*Exact Mass* calcd. for C_7H_9OI: 235.9698; found: 235.9721
53 + **61**[d]	1730, 1680 1595	1.30 (d, J = 7.0 Hz, secondary methyl of **53**), 1.70–2.50 (diffuse m), 2.54 (broad s, vinyl methyl of **61**), 2.64–3.00 (m), 3.38 (unresolved m, $w_{1/2} \approx 6$ Hz, C-2 methylene of **61**), 6.72 (d, J = 2 Hz, vinyl proton of **53**)	*Exact Mass* calcd. for C_7H_9OI: 235.9698; found: 235.9711
46	1670, 1600	1.62–2.72 (diffuse m, 5H), 2.78–3.00 (m, 2H), 4.88–5.16 (m, 2H), 5.48–5.94 (m, 1H), 6.70 (t, 1H, J = 2 Hz)	*Exact Mass* calcd. for $C_9H_{11}OI$: 261.9855; found: 261.9869
54 + **62**[d]	1720, 1670 1595	1.72–2.94 (diffuse m), 3.09 (broad d, $CH_2CH{=}CH_2$ of **62**), 3.46 (broad s, C-2 methylene of **62**), 5.02–5.32 (m), 5.58–6.04 (m), 6.84 (d, J = 1 Hz, ring vinyl proton of **54**)	*Exact Mass* calcd. for $C_9H_{11}OI$: 261.9855; found: 261.9842
47	1670, 1595	0.90 (t, 3H, J = 6 Hz), 1.16–1.58 (m, 4H), 1.60–2.40 (m, 3H), 2.78–2.98 (m, 2H), 6.68 (t, 1H, J = 2 Hz)	*Exact Mass* calcd. for $C_9H_{13}OI$: 264.0011; found: 264.0022
55	1670, 1590	1.00 (t, 3H, J = 6 Hz), 1.20–2.55 (diffuse m, 7H), 2.60–2.88 (m, 1H) 6.79 (d, 1H, J = 1.5 Hz)	*Exact Mass* calcd. for $C_9H_{13}OI$: 264.0011; found: 264.0013
48	1670, 1595	0.84, 0.91 (d, d, 6H, J = 7 Hz), 1.70–2.48 (m, 4H), 2.76–2.98 (m, 2H), 6.67 (t, 1H, J = 2 Hz)	*Exact Mass* calcd. for $C_9H_{13}OI$: 264.0011; found: 264.0005
49	1670, 1610	1.11 (d, 3H, J = 6 Hz), 1.60–2.10 (m, 2H), 1.99 (t, 3H, J = 2 Hz), 2.22–2.56 (m, 1H), 2.90–3.14 (m, 2H)	*Exact Mass* calcd. for $C_8H_{11}OI$: 249.9855; found: 249.9856
57	1680, 1600	1.36 (d, 3H, J = 7 Hz), 1.62–2.76 (diffuse m, 4H), 2.03 (d, 3H, J = 1.5 Hz), 2.80–3.12 (m, 1H)	*Exact Mass* calcd. for $C_8H_{11}OI$: 249.9855; found: 249.9858
50	1670, 1600	1.52–2.72 (diffuse m, 5H), 2.01 (t, 3H, J = 2 Hz), 2.88–3.12 (m, 2H), 4.86–5.14 (m, 2H), 5.49–5.92 (m, 1H)	*Exact Mass* calcd. for $C_{10}H_{13}OI$: 276.0011; found: 276.0013
58	1670, 1600	1.74–3.02 (diffuse m, 7H), 2.01 (d, 3H, J = 1.5 Hz), 4.96–5.22 (m, 2H), 5.52–5.96 (m, 1H)	*Exact Mass* calcd. for $C_{10}H_{13}OI$: 276.0011; found: 276.0024
51	1670, 1600	0.91 (t, 3H, J = 6 Hz), 1.14–2.14 (diffuse m, 7H), 2.00 (t, 3H, J = 2 Hz), 2.16–2.46 (m, 1H), 2.88–3.12 (m, 2H)	*Exact Mass* calcd. for $C_{10}H_{15}OI$: 278.0167; found: 278.0167
59	1670, 1600	0.98 (t, 3H, J = 6.5 Hz), 1.20–2.60 (diffuse m, 8H), 2.03 (d, 3H, J = 1.5 Hz), 2.70–2.98 (m, 1H)	*Exact Mass* calcd. for $C_{10}H_{15}OI$: 278.0167; found: 278.0168
52	1675, 1610	0.84, 0.91 (d, d, 6H, J = 6.5 Hz), 1.62–2.48 (m, 4H), 1.99 (t, 3H, J = 2 Hz), 2.84–3.10 (m, 2H)	*Exact Mass* calcd. for $C_{10}H_{15}OI$: 278.0167; found: 278.0163

[a] All compounds were liquids at room temperature and all exhibited one peak on glc analysis and one spot by tlc analysis.
[b] All infrared spectra were taken on liquid films.
[c] Satisfactory C, H elemental analyses were obtained on the following representative, randomly chosen compounds: **46**, **49**, **50**, **55**, **57**, **58**.
[d] We were unable to effect separation of **53** and **61** or of **54** and **62**. On the basis of careful integration of the areas under the ^{1}H nmr signals due to the C-2 vinyl protons of **53** (δ 6.72) and **54** (δ 6.84) vs. the C-2 methylene protons of **61** (δ 3.38) and **62** (δ 3.46), the ratios of the two pairs of compounds were estimated to be as follows: **53/61** ≈ 8:3; **54/62** ≈ 4:1.

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multiplet at δ 2.60–2.88. Similar comparisons can be made for the other pairs of isomeric β-iodo enones. Secondly, the C-2 olefinic protons of the β-iodo enones **45–48** and **53–55** exhibit allylic coupling to the C-4 protons, while homoallylic coupling can be observed between the C-2 vinyl methyl protons and the C-4 protons of the iodo enones **49–52** and **57–59**. Thus, for example, in the ^{1}H nmr spectra of the isomeric compounds **47** and **55**, the C-2 olefinic protons give rise to a *triplet* (δ 6.68, $J \approx 2$ Hz) and a *doublet* (δ 6.79, $J \approx 1.5$ Hz), clearly showing that C-4 of these two substances contains two protons and one proton, respectively. Similarly, the C-2 vinyl methyl groups of the isomeric β-iodo enones **51** and **59** produce a *triplet* (δ 2.00, $J \approx 2$ Hz) and a *doublet* (δ 2.03, $J \approx 1.5$ Hz), respectively. Analogous observations could be made for the other iodo enones.

(c) Conversion of 2-hydroxymethylenecycloalkanones into 2-iodomethylenecycloalkanones

Attempts to convert 2-hydroxymethylenecyclohexanone (**81**) into 2-iodomethylenecyclohexanone by reaction of the former substance with triphenylphosphine diiodide – triethylamine under conditions previously used for 1,3-diones proved to be unsuccessful. For example, the reaction in acetonitrile at room temperature was prohibitively slow, while in refluxing acetonitrile a good deal of intractable material was formed and the yield of identifiable product was very low. Eventually it was found that the desired conversion could be carried out successfully and reproducibly by carrying out the reaction at room temperature in a mixture of acetonitrile and HMPA. Under these conditions, **81** was transformed into (*E*)-2-iodomethylenecyclohexanone (**82**) in 94% yield (see Chart 3). In similar fashion, (*E*)-2-iodomethylenecyclopentanone (**84**) could be derived in 73% yield from the corresponding hydroxymethylene compound **83**. In each case, the conversion was highly regioselective and stereoselective, since we were unable to detect the presence of isomeric products.

The assignments made regarding the stereochemistry of compounds **82** and **84** require brief comment. It seems clear that these assignments could have been made very readily if the geometric isomers of **82** and **84** had also been formed in the reactions. That is to say, the ^{1}H nmr signals of the olefinic protons of the geometric isomers of **82** and **84** would have been expected to appear at higher field than the corresponding signals of **82** and **84** themselves. For example, the protons adjacent to the chlorine atoms of the β-chloro enones **85** and **86**

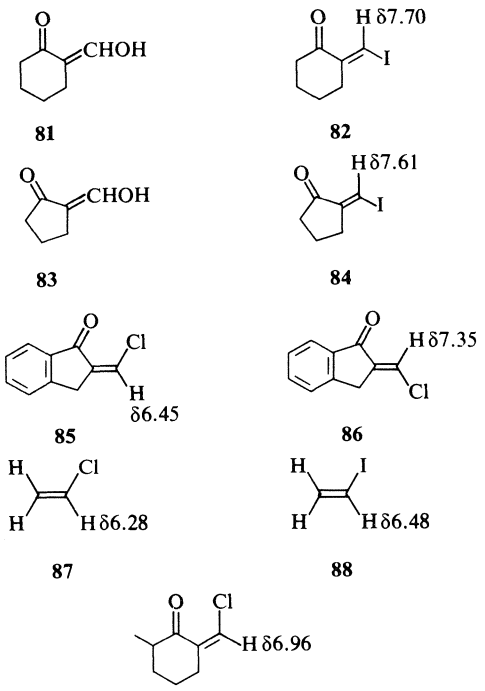

CHART 3

resonate at δ 6.45 and 7.35, respectively (9). However, since the reactions leading to the iodomethylene compounds **82** and **84** were totally stereoselective, only one of the two possible isomers was available in each case, and, therefore, direct comparisons were not possible.

The stereochemical assignments are based on the following arguments. The C-1 protons of vinyl chloride (**87**) and vinyl iodide (**88**) resonate at δ 6.28 and 6.48 respectively (Chart 3). Thus, changing the halogen from Cl to I results in a downfield shift of 0.2 ppm. On this basis, it can be argued that the olefinic protons of the *iodo* compounds corresponding to **85** and **86** (I in place of Cl in each case) should give rise to signals at about δ 6.65 and 7.55, respectively. The latter value is quite close to that of the chemical shift observed for the olefinic proton of the iodomethylenecyclopentanone derived from the reaction discussed above. Therefore, it seems reasonable to conclude that this product has the same relative stereochemistry (i.e. **84**) as that of compound **86**.

A similar argument can be used in the case of the iodomethylenecyclohexanone **82**. Clark and Heathcock (9) have reported that the ^{1}H nmr spectrum of (*Z*)-2-chloromethylene-6-methylcyclohexanone (**89**) exhibits the olefinic proton at δ 6.96. The difference (0.74 ppm) between this chemical shift and that of the olefinic proton of **82** (δ 7.70) would

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appear to be too large for the compounds to possess the same relative stereochemistry. In any case, the olefinic protons of compounds **82** and **84** show very similar chemical shifts and it is therefore highly likely that they have the same configuration.

Finally, a few comments should be made regarding the stability of 2-halomethylenecycloalkanones. It has been stated that 2-chloromethylenecyclohexanone (configuration not specified) "decomposes rapidly at room temperature and even at −20°C under nitrogen is converted into a purple oil in a matter of hours" (56).[7] Indeed, we have found that attempted preparation of 2-chloromethylenecyclohexanone by reaction of **81** with triphenylphosphine dichloride – triethylamine provides a poor yield of a very unstable product. A similar observation was made in the reaction of **81** with triphenylphosphine dibromide – triethylamine. On the other hand, the iodomethylenecycloalkanones **82** and **84**, although certainly less stable than the endocyclic β-iodo enones, can be prepared readily and can be stored in a freezer under an atmosphere of argon for a few months without substantial decomposition. If they are exposed to the air at ambient temperatures, however, they darken in color and decompose extensively in a day or two. Nevertheless, as synthetically employable intermediates, compounds **82** and **84** are certainly to be preferred to the corresponding chloro or bromo derivatives.

(d) Ultraviolet spectra of β-iodo α,β-unsaturated ketones

The well-established Woodward–Fieser rules (57–59) have been employed very successfully in correlating electronic transitions with structural patterns in conjugated chromophores. For example, on the basis of the substitution pattern on the enone system of α,β-unsaturated ketones, it is possible to predict quite accurately the position of the longest wavelength $\pi \rightarrow \pi^*$ absorption band of these compounds (57–59). Since cyclic β-iodo α,β-unsaturated compounds were essentially unknown prior to execution of the work reported herein, nothing was known concerning the effect of a β-iodo substituent on the position of the $\pi \rightarrow \pi^*$ absorption maxima of enones. Therefore, the ultraviolet spectra of methanol solutions of the β-iodo enones prepared in this study were measured, with the hope of establishing the extent of the bathochromic shift caused by a β-iodo group. The results are summarized in Table 7.

The most interesting observation that one can make regarding the data given in Table 7 is that, whether or not there is an alkyl substituent at C-2, the $\pi \rightarrow \pi^*$ absorption maxima of all of the 3-iodo-2-cyclohexen-1-ones which were measured appear in nearly the same position. Thus, the average of the λ_{max} values of the 3-iodo-2-cyclohexen-1-ones is 258 nm, with a range of 256–261 nm. The analogous values for 3-iodo-2-alkyl-2-cyclohexen-1-ones are 259 nm and 257–260 nm. Furthermore, if one compares these ultraviolet absorption maxima with those of the "parent" enones (2-cyclohexen-1-one, λ_{max} 226 nm; 2-methyl-2-cyclohexen-1-one, λ_{max} 234 nm), then the "increments" for a 3-iodo group should be ~32 nm for those cyclohexenones having a proton at C-2 and ~25 nm for the corresponding substances possessing a C-2 alkyl substituent.

The positions of the ultraviolet $\pi \rightarrow \pi^*$ absorption maxima of 3-iodo-2-cyclopenten-1-one (**33**) (λ_{max} 249 nm) and the 2-methyl analog **34** (λ_{max} 248 nm) are also very similar. Not unexpectedly (2-cyclopenten-1-one, λ_{max} 218 nm; 2-methyl-2-cyclopenten-1-one, λ_{max} 226 nm), these values are about 10 nm lower than those of the cyclohexenone compounds.

TABLE 7. Longest wavelength $\pi \rightarrow \pi^*$ ultraviolet absorption bands of β-iodo α,β-unsaturated ketones (methanol solution)

Compound	λ_{max}, nm (ε)
3-Iodo-2-cyclohexen-1-ones	
28	257 (8 430)
32	256 (8 380)
45	257 (8 700)
46	260 (8 860)
47	259 (8 680)
48	257 (8 150)
55	261 (8 330)
3-Iodo-2-alkyl-2-cyclohexen-1-ones	
29	258 (9 500)
30	259 (9 440)
31	260 (9 200)
49	256 (8 720)
50	258 (8 700)
51	257 (9 840)
52	262 (7 140)
57	260 (9 140)
58	260 (8 300)
59	259 (8 760)
3-Iodo-2-cyclopenten-1-ones	
33	249 (11 350)
34	248 (11 520)

[7]This substance has, however, been employed subsequently as a synthetic intermediate (15). Furthermore, Clark and Heathcock (9) have reported the preparation and characterization of (*Z*)-2-chloromethylene-6-methylcyclohexanone (**89**), although no mention is made regarding the stability (or instability) of this material.

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Experimental

General

Melting points, which were taken on a Fisher–Johns melting point apparatus, and distillation temperatures are uncorrected. Ultraviolet (uv) spectra were recorded on methanol solutions using a Cary 15 spectrophotometer. 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 Varian Associates spectrometers, models T-60 and/or HA-100 or XL-100. Signal positions are given in δ units, with tetramethylsilane as the internal standard. High resolution mass spectrometric measurements were recorded on a Kratos MS-50 mass spectrometer. Gas–liquid chromatography (glc) was carried out with a Hewlett–Packard model 5832 A gas chromatograph (analytical) or with a Varian Aerograph model 90-P instrument (preparative). Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver, B.C.

Triphenylphosphine was recrystallized from ethyl acetate – methanol or from benzene. The solvents and reagents employed were freshly distilled from the following materials: benzene – potassium metal; acetonitrile – phosphorus pentoxide; triethylamine and tetrahydrofuran (THF) – lithium aluminum hydride; hexamethylphosphoramide (HMPA) and diisopropylamine – calcium hydride.

General procedure for the conversion of β-diketones into β-chloro α,β-unsaturated ketones (Table 1, Entries 1, 3, 7, 9, 12)

To an ice-cold, stirred solution of recrystallized triphenylphosphine (576 mg, 2.2 mmol) in 20 mL of dry benzene was added 3.7 mL of a 0.6 *M* solution of chlorine in carbon tetrachloride. After the addition was complete, tlc analysis of the mixture indicated that triphenylphosphine was absent. To the resulting suspension was added successively triethylamine (220 mg, 2.2 mmol) and the appropriate β-diketone (2.0 mmol). Stirring was continued at room temperature for the required length of time. The suspension was filtered through a short column of silica gel and the column was eluted with ether. Removal of the solvent from the combined eluate, followed by bulb-to-bulb distillation of the residual oil under reduced pressure (water aspirator, ~10–11 Torr) provided the β-chloro enone as a colorless oil. The yields of the β-chloro enones which were prepared by this procedure are summarized in Table 1, while the spectral data are given in Table 2.

General procedure for the conversion of β-diketones into β-bromo α,β-unsaturated ketones (Table 1, Entries 2, 4–6, 8, 10, 11, 13, 14)

To an ice-cold, stirred solution of recrystallized triphenylphosphine (576 mg, 2.2 mmol) in 20 mL of dry benzene was added dropwise 2.2 mL of a 1 *M* solution of bromine in benzene. To the resulting suspension was added successively triethylamine (220 mg, 2.2 mmol) and the appropriate β-diketone (2.0 mmol). Stirring was continued at room temperature for the indicated length of time. The reaction mixture was filtered through a short column of silica gel and the column was eluted with ether. Removal of the solvent from the combined eluate, followed by bulb-to-bulb distillation of the residual oil under reduced pressure (water aspirator, ~10–11 Torr or, in the case of product **20**, vacuum pump, 0.45 Torr) provided the β-bromo enone as a colorless oil. The yields of the β-bromo enones which were prepared by this procedure are summarized in Table 1, while the appropriate spectral data are given in Table 2.

*Conversion of 2,4-pentanedione (**11**) into a mixture of (E)- and (Z)-4-bromo-3-penten-2-one (**26**, **27**) (Table 1, Entry 15)*

To a stirred solution of recrystallized triphenylphosphine (5.76 g, 22 mmol) in dry acetonitrile (100 mL) was added successively a solution of bromine (3.52 g, 22 mmol) in 20 mL of dry benzene, triethylamine (2.2 g, 22 mmol), and 2,4-pentanedione (2.0 g, 20 mmol). The resulting mixture was stirred at room temperature for 19 h. The bulk of the solvent was removed by careful distillation (water aspirator). The residual brown material was diluted with ether (50 mL) and the resulting mixture was filtered through a short column of silica gel (~40 g). The column was washed with ether. Removal of the solvent from the combined eluate, followed by distillation (air-bath temperature 50–70°C/~25 Torr) of the residual oil (which contained some solid triphenylphosphine oxide) gave 3.02 g of a clear liquid. Gas–liquid chromatographic analysis of this material indicated that it consisted of a mixture of **26** and **27** (ratio ~87:13, respectively) along with an unidentified minor compound (~5%). A pure sample of each of the geometric isomers **26** and **27** was obtained by preparative glc, and the spectral data are summarized in Table 2.

General procedures for the conversion of symmetrical β-diketones into β-iodo α,β-unsaturated ketones

(a) Benzene as solvent (Procedure A, Table 3, Entries 1, 4, 9, 12)

To a stirred solution of recrystallized triphenylphosphine (576 mg, 2.2 mmol) in 20 mL of dry benzene was added 559 mg (2.2 mmol) of iodine and the mixture was stirred at room temperature for 16 h. To the resulting yellow-brown suspension was added successively dry triethylamine (220 mg, 2.2 mmol) and the appropriate β-diketone (2.0 mmol). The mixture was stirred at room temperature for the indicated period of time, during which a brown oil separated from the benzene solution. Examination of the latter by tlc indicated that it contained, at most, only a trace of the desired product. The entire reaction mixture was concentrated under reduced pressure and the residual material was heated at 145–180°C under reduced pressure (water aspirator, ~10–12 Torr) with direct distillation of the product. The distillate thus obtained was redistilled (bulb-to-bulb) under reduced pressure (water aspirator, 10–12 Torr or vacuum pump, 0.2–1 Torr) to provide the β-iodo enone. The yields of the latter substances which were prepared by this procedure are given in Table 3. Physical and spectral data are summarized in Table 4, while ultraviolet absorption maxima are given in Table 7.

(b) Acetonitrile as solvent (Procedures B and C, Table 3, Entries 2, 3, 5–8, 10, 11, 13)

To a stirred solution of recrystallized triphenylphosphine (576 mg, 2.2 mmol) in 20 mL of dry acetonitrile was added 559 mg (2.2 mmol) of iodine and the mixture was stirred at room temperature for 2 h. To the resulting orange-yellow suspension was added successively triethylamine (220 mg, 2.2 mmol) and the appropriate β-diketone (2.0 mmol). The mixture was either stirred at room temperature for 4 days (Procedure B, Table 3, Entries 2, 5, 7, 10) or was heated at reflux temperature for the indicated length of time (Procedure C, Table 3, Entries 3, 6, 8, 11, 13). The reaction mixture was concentrated under reduced pressure and the residual material was filtered through a short column of silica gel (~5 g). The column was eluted with 100 mL of ether. Removal of the solvent from the combined eluate, followed by bulb-to-bulb distillation of the residual oil under reduced pressure (water aspirator, ~10–12 Torr or vacuum pump, 0.2–1 Torr) gave the β-iodo enone. The yields of the

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latter substances which were prepared by these procedures are given in Table 3, and the physical and spectral properties of the products are summarized in Table 4. Ultraviolet absorption maxima are provided in Table 7.

*General procedure for the alkylation of 3-isobutoxy-2-cyclohexen-1-one (**63**) and 3-isobutoxy-2-methyl-2-cyclohexen-1-one (**64**) with methyl iodide and allyl bromide*

To a cold (−78°C) stirred solution of LDA (22 mmol) in dry THF (80 mL) under an atmosphere of dry nitrogen was added 20 mmol of the ketone **63** or **64**. The solution was stirred for 1 h. The alkylating agent (methyl iodide or allyl bromide, 26 mmol) was added, the solution was allowed to warm slowly to room temperature, and stirring was continued for 4 h. Brine (50 mL) was added and the resulting mixture was extracted thoroughly with petroleum ether (bp 30–60°C). The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by bulb-to-bulb distillation of the residual oil under reduced pressure, afforded the desired product.

The following compounds were obtained by means of this procedure.

3-Isobutoxy-6-methyl-2-cyclohexen-1-one (**65**): 95% yield; distillation temperature 80–90°C (air bath)/0.07 Torr; ir (film): 1690, 1610 cm^{-1}; uv (methanol) λ_{max}: 247 nm (ε 17 800); ^1H nmr δ: 0.98 (d, 6H, J = 6 Hz), 1.16 (d, 3H, J = 7 Hz), 1.54–2.58 (diffuse m, 6H), 3.59 (d, 2H, J = 6 Hz), 5.33 (s, 1H). *Anal.* calcd. for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.70, H 9.97.

6-Allyl-3-isobutoxy-2-cyclohexen-1-one (**66**): 93% yield; distillation temperature 95–100°C (air bath)/0.4 Torr; mp 37–38°C (lit. mp (52) 37–38°C); ir ($CHCl_3$): 1660, 1605 cm^{-1}; uv (methanol) λ_{max}: 247 nm (ε 19 600); ^1H nmr δ: 0.98 (d, 6H, J = 6.5 Hz), 1.46–2.78 (diffuse m, 8H), 3.60 (d, 2H, J = 6 Hz), 4.98–5.20 (m, 2H), 5.34 (s, 1H), 5.61–6.05 (m, 1H). *Anal.* calcd. for $C_{13}H_{20}O_2$: C 74.96, H 9.68; found: C 75.05, H 9.54.

3-Isobutoxy-2,6-dimethyl-2-cyclohexen-1-one (**69**): 94% yield; distillation temperature 100–110°C (air bath)/0.2 Torr; ir (film): 1650, 1630 cm^{-1}; uv (methanol) λ_{max}: 265 nm (ε 18 800); ^1H nmr δ: 0.96 (d, 6H, J = 7 Hz), 1.11 (d, 3H, J = 6.5 Hz), 1.48–2.38 (diffuse m, 5H), 1.68 (t, 3H, J = 2 Hz), 2.40–2.64 (m, 1H), 3.71 (d, 2H, J = 7 Hz). *Exact Mass* calcd. for $C_{12}H_{20}O_2$: 196.1463; found: 196.1470.

6-Allyl-3-isobutoxy-2-methyl-2-cyclohexen-1-one (**70**): 95% yield; bp 110°C/0.35 Torr; ir (film): 1640, 1620 cm^{-1}; uv (methanol) λ_{max}: 265 nm (ε 18 600); ^1H nmr δ: 1.00 (d, 6H, J = 6.5 Hz), 1.52–2.40 (diffuse m, 6H), 1.72 (t, 3H, J = 1.5 Hz), 3.77 (d, 2H, J = 6.5 Hz), 4.92–5.18 (m, 2H), 5.60–6.04 (m, 1H). *Exact Mass* calcd. for $C_{14}H_{22}O_2$: 222.1620; found: 222.1606.

*Hydrogenation of compounds **66** and **70**. Preparation of 3-isobutoxy-6-*n*-propyl-2-cyclohexen-1-one (**67**) and 3-isobutoxy-2-methyl-6-*n*-propyl-2-cyclohexen-1-one (**71**)*

To a solution of the ketone **66** or **70** (15 mmol) in 150 mL of dry benzene was added approximately 10% by weight of tris(triphenylphosphine)chlororhodium. The resultant solution was stirred vigorously and subjected to an atmosphere of hydrogen at room temperature for 18 h. The solvent was removed under reduced pressure and the residual material was treated with 150 mL of petroleum ether (bp 30–60°C). The mixture was filtered through Celite. Removal of the solvent from the filtrate, followed by distillation of the residual oil under reduced pressure gave the desired products.

3-Isobutoxy-6-n-propyl-2-cyclohexen-1-one (**67**): 95% yield; distillation temperature 95–105°C (air bath)/0.1 Torr; mp 25–28°C; ir ($CHCl_3$): 1630, 1600 cm^{-1}; uv (methanol) λ_{max}: 247 nm (ε 19 400); ^1H nmr δ: 0.82–1.06 (superimposed d, J = 6.5 Hz, and poorly resolved t, 9H), 1.20–2.30 (diffuse m, 8H), 2.44 (t, 2H, J = 7 Hz), 3.59 (d, 2H, J = 6.5 Hz), 5.30 (s, 1H). *Anal.* calcd. for $C_{13}H_{22}O_2$: C 74.24, H 10.54; found: C 74.47, H 10.40.

3-Isobutoxy-2-methyl-6-n-propyl-2-cyclohexen-1-one (**71**): 94% yield; distillation temperature 100–110°C (air bath)/0.2 Torr; ir (film): 1645, 1625 cm^{-1}; uv (methanol) λ_{max}: 265 nm (ε 17 500); ^1H nmr δ: 0.91 (t, 3H, J = 7 Hz), 0.98 (d, 6H, J = 6 Hz), 1.14–2.24 (diffuse m, 8H), 1.68 (t, 3H, J = 1.5 Hz), 2.40–2.66 (m, 2H), 3.72 (d, 2H, J = 7 Hz). *Exact Mass* calcd. for $C_{14}H_{24}O_2$: 224.1776; found: 224.1786.

*Preparation of 3-isobutoxy-6-isopropyl-2-cyclohexen-1-one (**68**) and 3-isobutoxy-6-isopropyl-2-methyl-2-cyclohexen-1-one (**72**)*

To a cold (−78°C) stirred solution of LDA (55 mmol) in 60 mL of a 5:1 mixture of dry THF and dry HMPA was added 50 mmol of the ketone **63** or **64**, and the solution was stirred for 1 h. A solution of isopropyl iodide (9.35 g, 55 mmol) in 10 mL of dry THF was added, the resultant mixture was allowed to warm to room temperature, and stirring was continued for 16 h. Water (50 mL) was added and the resultant mixture was extracted thoroughly with petroleum ether (bp 30–60°C). The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent produced an oil which was subjected to column chromatography on silica gel (300 g). The eluant was a 7:3 mixture of *n*-hexane – ether. In addition to minor, unidentified products and a major amount of starting material, the following desired products were obtained.

3-Isobutoxy-6-isopropyl-2-cyclohexen-1-one (**68**): 16% yield; distillation temperature 70–90°C (air bath)/0.2 Torr; mp 22.5–24°C; ir (film): 1650, 1605 cm^{-1}; uv (methanol) λ_{max}: 247 nm (ε 12 800); ^1H nmr δ: 0.83 (d, 3H, J = 6.5 Hz), 0.94 (d, 9H, J = 6.5 Hz), 1.60–2.16 (m, 4H), 2.25–2.56 (m, 3H), 3.53 (d, 2H, J = 6.5 Hz), 5.26 (s, 1H). *Exact Mass* calcd. for $C_{13}H_{22}O_2$: 210.1620; found: 210.1618.

3-Isobutoxy-3-isopropyl-2-methyl-2-cyclohexen-1-one (**72**): 13% yield; distillation temperature 85–95°C (air bath)/0.1 Torr; ir (film): 1640, 1620 cm^{-1}; uv (methanol) λ_{max}: 266 (ε 18 300); ^1H nmr δ: 0.84 (d, 3H, J = 5 Hz), 0.97 (d, 9H, J = 6 Hz), 1.58 (t, 3H, J = 1.5 Hz), 1.60–2.78 (diffuse m, 7H), 3.77 (d, 2H, J = 6 Hz). *Exact Mass* calcd. for $C_{14}H_{24}O_2$: 224.1770; found: 224.1780.

*General procedure for the hydrolysis of compounds **65–72**. Preparation of the unsymmetrical 1,3-cyclohexanediones **37–44***

To a solution of the β-isobutoxy α,β-unsaturated ketone (**65–72**) (30 mmol) in acetone (80 mL, spectro-grade, previously purged with a stream of nitrogen for 15 min) was added with vigorous stirring 30 mL of 1 *N* hydrochloric acid (previously purged with nitrogen for 15 min). The resultant solution was stirred under an atmosphere of nitrogen for 6 h. Most of the acetone was removed under reduced pressure, the residual material was diluted with 20 mL of brine, and the resultant mixture was extracted thoroughly with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent, followed by purification of the residual material by distillation under reduced pressure and/or by recrystallization, gave the following desired products.

4-Methyl-1,3-cyclohexanedione (**37**): 96% yield; distillation temperature 85–100°C (air bath)/0.03 Torr; recrystallization from ether – petroleum ether (bp 30–60°C), mp 53–57°C; ir ($CHCl_3$): 3400–2400 (broad), 1700, 1610–1580 (broad) cm^{-1}; ^1H nmr δ: 1.16 (d, 3H, J = 6 Hz), 1.38–2.80 (diffuse m, 5H), 3.38 (s, ~1H, C-2 methylene of keto tautomer), 5.42 (s, ~0.5H, C-2 vinyl proton of enol tautomer). *Anal.* calcd. for $C_7H_{10}O_2$: C 66.75, H 7.99; found: C 66.79, H 7.99.

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4-Allyl-1,3-cyclohexanedione (**38**): 90% yield; distillation temperature 90–100°C (air bath)/0.08 Torr; mp 34–36°C; ir ($CHCl_3$): 3600–2400 (broad), 1720, 1710, 1640–1590 (broad) cm^{-1}; ^1H nmr δ: 1.40–2.80 (diffuse m, 7H), 3.38 (s, ~1H, C-2 methylene of keto tautomer), 4.90–5.20 (m, 2H), 5.42 (s, ~0.5H, C-2 vinyl proton of enol tautomer), 5.52–6.00 (m, 1H). *Exact Mass* calcd. for $C_9H_{12}O_2$: 152.0838; found: 152.0845.

4-n-Propyl-1,3-cyclohexanedione (**39**): 60% yield; distillation temperature 110–125°C (air bath)/0.9 Torr; mp 69–71°C; ir ($CHCl_3$): 3500–2400 (broad), 1730, 1710, 1600 (broad) cm^{-1}; ^1H nmr δ: 0.91 (t, 3H, J = 7 Hz), 1.16–2.72 (diffuse m, 9H), 3.40 (s, ~0.7H, C-2 methylene of keto tautomer), 5.40 (s, ~0.7H, C-2 vinyl proton of enol tautomer). *Exact Mass* calcd. for $C_9H_{14}O_2$: 154.0994; found: 154.1005.

4-Isopropyl-1,3-cyclohexanedione (**40**): 95% yield; distillation temperature 110–130°C (air bath)/0.07 Torr; mp 106–107°C; ir ($CHCl_3$): 1730, 1710, 1615 cm^{-1}; ^1H nmr δ: 0.80–1.14 (series of overlapping d, 6H), 1.58–2.86 (diffuse m, 6H), 3.36 (s, ~1.4H, C-2 methylene of keto tautomer), 5.42 (s, ~0.3H, C-2 vinyl proton of enol tautomer). *Exact Mass* calcd. for $C_9H_{14}O_2$: 154.0994; found: 154.0992.

2,4-Dimethyl-1,3-cyclohexanedione (**41**): 97% yield; distillation temperature 80–95°C (air bath)/ 0.3 Torr; mp 108–110°C; ir ($CHCl_3$): 3650–2450 (broad), 1745, 1705, 1630 cm^{-1}; ^1H nmr δ: 1.10–1.34 (series of d), 1.34–2.94 (diffuse m), 1.72 (s, vinyl methyl of enol tautomer), 3.38–3.68 (m, C-2 protons of diastereomeric keto tautomers). On the basis of the relative integrated areas of the latter two signals, the keto–enol ratio was ~1:1. *Exact Mass* calcd. for $C_8H_{12}O_2$: 140.0838; found: 140.0841.

4-Allyl-2-methyl-1,3-cyclohexanedione (**42**): 88% yield; distillation temperature 110–120°C (air bath)/ 0.3 Torr; mp 51–53°C; ir ($CHCl_3$): 3575, 3500–2600 (broad), 1735. 1705, 1615 (broad) cm^{-1}; ^1H nmr δ: 1.19, 1.21 (d, d, J = 6.5 Hz), 1.32–2.86 (diffuse m), 1.71 (s, vinyl methyl of enol tautomer), 3.50 (q, J = 6.5 Hz, C-2 proton of keto tautomers), 4.90–5.20 (m, 2H), 5.52–6.00 (m, 1H). On the basis of the relative integrated areas of the signals at δ 1.71 and 3.50; the keto–enol ratio was ~1:1. *Exact Mass* calcd. for $C_{10}H_{14}O_2$: 165.9994; found: 166.1007.

2-Methyl-4-n-propyl-1,3-cyclohexanedione (**43**): 95% yield; distillation temperature 100–110°C (air bath)/0.03 Torr; mp 67–69°C, ir ($CHCl_3$): 3650–2500 (broad), 1740, 1705, 1635 cm^{-1}; ^1H nmr δ: 0.82–1.04 (m, 3H), 1.18, 1.20 (d, d, J = 6.5 Hz), 1.24–2.76 (diffuse m), 1.72 (s, vinyl methyl of enol tautomer), 3.36–3.68 (m, C-2 protons of diastereomeric keto tautomers). The relative integrated areas of the latter two signals was ~4:1. *Exact Mass* calcd. for $C_{10}H_{16}O_2$: 168.1150; found: 168.1146.

4-Isopropyl-2-methyl-1,3-cyclohexanedione (**44**): 96% yield; sublimes at 95–100°C (air bath)/0.01 Torr; mp 104–105°C; ir ($CHCl_3$): 3560, 3500–3000 (broad), 1735, 1700, 1625 (broad) cm^{-1}; ^1H nmr δ: 0.80–1.26 (series of d), 1.26–2.90 (diffuse m), 1.70 (s, vinyl methyl of enol tautomer), 3.32–3.62 (m, C-2 protons of diastereomeric keto tautomers). The relative integrated areas of the latter two signals was ~2.5:1. *Exact Mass* calcd. for $C_{10}H_{16}O_2$: 168.1150; found: 168.1151.

General procedure for the conversion of unsymmetrical 1,3-cyclohexanediones into β-iodo α,β-unsaturated ketones (Table 5)

To a stirred suspension of iodine (660 mg, 2.6 mmol) in 15 mL of dry acetonitrile under an atmosphere of nitrogen was added 681 mg (2.6 mmol) of recrystallized triphenylphosphine and the mixture was stirred for 30 min. To the resultant yellow suspension was added successively dry triethylamine (263 mg, 2.6 mmol) and 2.4 mmol of the appropriate 1,3-cyclohexanedione (**37**–**44**). The dark solution was stirred at room temperature for 1 h and then was heated at reflux temperature for 12 h. The solvent was removed under reduced pressure and the residue was extracted (decantation) with 6 × 25 mL of ether. Removal of the ether from the combined extracts produced a mixture of a solid and an orange oil. This material was washed with 3 × 15 mL of 7:1 *n*-pentane–ether and the combined washings were applied to a dry column consisting of a mixture of 20 g of Florisil (100–120 mesh) and 10 g of alumina (neutral, activity I). The column was eluted with 7:1 *n*-pentene–ether and the fractions containing the desired products were combined. Removal of the solvent from the combined eluate, followed by bulb-to-bulb distillation of the residual oil, provided the desired product(s). In each case, the distilled material was subjected to analysis by glc (6 ft × 0.125 in. column containing 5% OV-17 on 100–120 mesh HP Chromosorb W) and, where possible (see footnote *d*, Tables 5 and 6), the products were separated by preparative tlc on silica gel (plates developed with 7:3 *n*-pentane–ether). The results are recorded in Table 5, and appropriate characterization data and ultraviolet absorption maxima for the various products are summarized in Table 6 and Table 7, respectively.

Preparation of (E)-2-iodomethylenecyclopentanone (84) and (E)-2-iodomethylenecyclohexanone (82)

To a stirred solution of recrystallized triphenylphosphine (2.88 g, 11 mmol) in a mixture of dry acetonitrile (50 mL) and dry HMPA (8 mL) was added 2.79 g (11 mmol) of iodine, and the mixture was stirred at room temperature for 20 min. To the resulting yellow suspension was added successively dry triethylamine (1.1 g, 11 mmol) and the α-hydroxymethylenecycloalkanone (**83**, **81**), and stirring was continued for 72 h when the starting material was **83** and for 15 h when the starting material was **81**. Most of the solvent was removed under reduced pressure. The residual material was extracted by stirring and decantation with 5 × 50 mL of pentane. The combined extracts were washed with 3 × 30 mL of water and dried over anhydrous magnesium sulfate. Removal of the solvent, followed by bulb-to-bulb distillation of the residual oil, provided the following products.

(E)-2-Iodomethylenecyclopentanone (**84**): 73% yield; recrystallized from ether, mp 31.5°C; ir ($CHCl_3$): 1720, 1608 cm^{-1}; uv (methanol) λ_{max}: 276 nm (ε 9 200), shoulder at 263 nm; ^1H nmr δ: 1.8–3.0 (diffuse m, 6H), 7.61 (t, 1H, J = 2 Hz). *Exact Mass* calcd. for C_6H_7IO: 221.9543; found: 221.9544.

(E)-2-Iodomethylenecyclohexanone (**82**): 94% yield; distillation temperature 60–70°C (air bath)/ 0.4 Torr; crystallizes in refrigerator, mp ~15°C; ir (film): 1695, 1570 cm^{-1}; uv (methanol) λ_{max}: 265 nm (ε 7 200); ^1H nmr δ: 1.60–2.04 (m, 4H), 2.30–2.66 (m, 4H), 7.70 (t, 1H, J = 2 Hz). *Anal.* calcd. for C_7H_9IO: C 35.62, H 3.84; found: C 35.65, H 3.76.

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