Convenient Preparation of Bis-Enones and Bis-Enoates from Cycloalkenes

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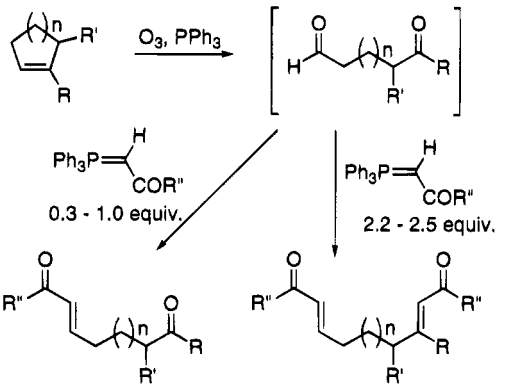
Introduction

Bis-enones and bis-enoates have proven to be valuable intermediates in a variety of methods for the synthesis of carbocyclic ring systems. Most notable among these methods are tandem Michael addition reactions in which enoxy silanes,[1] Grignard reagents with catalytic copper iodide,[2] or lithium silyl amides[3] add in a conjugate fashion to one enone moiety followed by cyclization of the kinetic enolate onto the second enone moiety. β,β-Coupling of bis-enones has also been observed in radical cyclization processes.[4]

Several methods of preparation have been reported for this class of compounds. Bis-acyl chlorides have been converted to bis-enoates by a double bromination/esterification/dehydrobromination sequence.[5] This method suffers from low yields and from difficulties in the separation of olefin isomers. Dialdehydes have been converted to bis-enones by a double Wittig olefination procedure.[1,4a,6] This method suffers primarily from the lack of stability of the requisite aldehydes which must either be freshly prepared and purified or be freshly distilled from commercially-available aqueous solutions. One report of the *in situ* ozonolysis/bis-Wittig olefination of cycloalkenes has appeared,[6a] but poor yields (23–27% for bis-enones, 30–42% for bis-enoates) of isomeric mixtures of the desired bis-enones were obtained. No traditional reducing agent (such as dimethyl sulfide or triphenylphosphine) was used in the decomposition of the ozonide in this report. In the preparation of unsymmetrical bis-enones, the Schreiber ozonolysis procedure for cycloalkenes[7] followed by sequential Wittig olefinations is satisfactory in most cases. However, yields were considerably lower in the cyclopentene series in the preparation of terminally-differentiated oxidation products.

Given our interest in the development of transition metal-mediated routes for the functionalization of bis-enones,[8] we reinvestigated the *in-situ* ozonolysis/Wittig olefination of cycloalkenes in an effort to develop high-yielding and convenient routes to both symmetrical and unsymmetrical bis-enones. The results of this study, which led to practical methods for the preparation of multigram quantities of these valuable intermediates, are described.

Scheme 1



Results and Discussion

Symmetrical Bis-Enones and Bis-Enoates. Treatment of the cycloalkene in dichloromethane at −78 °C with ozone was followed by decomposition of the ozonide with triphenylphosphine in the presence of 2.2 equiv of a stabilized Wittig reagent. After stirring at 25 °C overnight, followed by concentration and chromatographic isolation, 55–83% isolated yields of single isomers of the desired bis-enones or bis-enoates of the trans/trans configuration were obtained (Scheme 1, Table 1). In most cases, no trace of the trans/cis or cis/cis isomers could be detected in the crude reaction mixtures. The procedure worked well with five-, six-, and seven-membered cycloalkenes and with ester- and ketone-stabilized phosphorus ylides (Table 1). A disubstituted phosphorane afforded the corresponding bis-enone with trisubstituted alkenes as a single isomer in good yield after chromatographic isolation (entry 4, Table 1).

Unsymmetrical Bis-Enones and Bis-Enoates. Several precursors to unsymmetrical bis-enones were efficiently prepared by related protocols (Scheme 1, Table 2). Cyclopentenol-derived substrates were converted to both mono- and bis-enones in good yield. Substrate **7** was converted to bis-enone **8** in 65% yield upon ozonolysis and treatment with 2.5 equiv of a Wittig reagent (entry 1, Table 2). The same reaction conducted with 1.05 equiv of the Wittig reagent afforded mono-enone **9** in 51% yield along with 17% yield of bis-enone **8** (entry 2, Table 2). Compound **9** could be converted to a variety of differentially-substituted bis-enones. The keto aldehyde derived from 1-methylcyclopentene was efficiently converted *in situ* to the mono-enone **10** with 1.1 equiv of a stabilized Wittig reagent in 88% yield (entry 3, Table 2). Differentially-substituted bis-enones are available from mono-enones of this type upon treatment with more reactive olefination reagents.

Symmetrical cycloalkenes could be conveniently converted in two steps to unsymmetrical bis-enones. Starting with cyclopentene, syringe-drive addition of 0.3 equiv of a Wittig reagent solution to the intermediate glutaraldehyde solution resulted in the direct formation of mono-enone **11** in 62% yield along with 10–15% of bis-enone **3** (entry 4, Table 2). Compound **11** may then easily be

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(2) (a) Saito, S.; Hirohara, Y. Narahara, O. Moriwake T. *J. Am. Chem. Soc.* **1989**, *111*, 4533. (b) Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T.; Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292.

(3) (a) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Chem. Soc. Chem. Commun.* **1989**, 113. (b) Uyehara, T.; Shida, N.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 3139. (c) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049.

(4) (a) Enholm, E. J.; Kinter, K, S. *J. Am. Chem. Soc.* **1991**, *113*, 7784. (b) Taniguchi, Y.; Kusudo, T.; Beppu, F.; Makioka, Y.; Takaki, K.; Fujiwara, Y. *J. Chem. Soc. Jpn.* **1994**, *1*, 62.

(5) Scheffer, J. R.; Wostradowski, R. A. *J. Org. Chem.* **1972**, *37*, 4317.

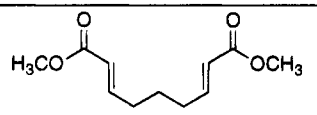
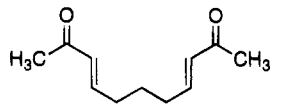
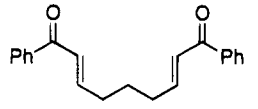
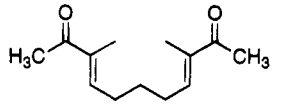
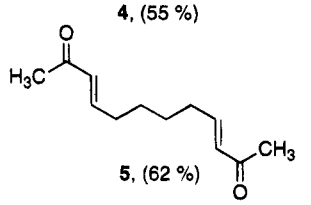
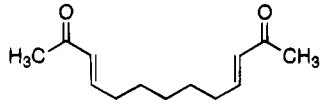
(6) (a) Hon, Y.-S.; Chu, K.-P.; Hong, P.-C.; Lu, L. *Synth. Commun.* **1992**, *22*, 429. (b) House, H. O.; Cronin, T. H. *J. Org. Chem.* **1965**, *30*, 1061.

(7) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867. (b) Claus, R. E.; Schreiber, S. L. *Organic Syntheses*; John Wiley and Sons: New York, 1990; Coll. Vol. VII, p 168.

(8) Montgomery, J.; Savchenko, A. V. Submitted for publication.

0022-3263/95/1960-5699$09.00/0

Table 1. Symmetrical Products

entry	cycloalkene	product (yield)
1		 **1**, (83 %)
2		 **2**, (68 %)
3		 **3**, (72 %)
4		 **4**, (55 %)
5		 **5**, (62 %)
6		 **6**, (57 %)

converted to differentially-substituted bis-enones. We found this procedure to be the most convenient for readily-available, inexpensive cycloalkenes, whereas the Schreiber ozonolysis procedure[7] may be more satisfactory for more valuable cycloalkenes.

Summary

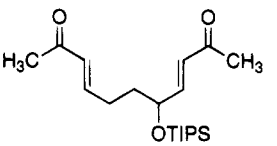
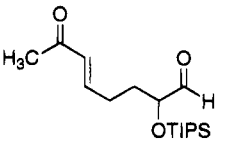
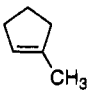
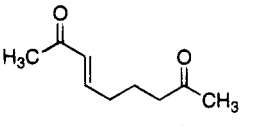
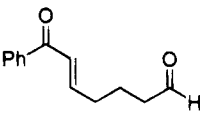
Efficient methods were developed for the synthesis of a variety of bis-enones and bis-enoates from readily-available cycloalkenes. Symmetrical bis-enones and bis-enoates may be obtained from cycloalkenes in a high-yielding one-pot reaction. Analogous unsymmetrical compounds may be obtained from either symmetrical or unsymmetrical cycloalkenes without the use of protecting groups. Whereas this study focused exclusively on the synthesis of bis-enones and bis-enoates, the procedures should be generally applicable in the synthesis of compounds requiring the preparation and differential functionalization of dialdehydes.

Experimental Procedures

Unless otherwise indicated, reagents were commercially available and were used without purification. 1-(Triisopropylsiloxy)-2-cyclopentene (**7**) was prepared from 2-cyclopenten-1-one following standard procedures.[9] Phosphoranes were synthesized from the corresponding α-halo ketones by literature methods.[10] All reactions were conducted in flame-dried glassware under a nitrogen atmosphere.

(9) (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41.

Table 2. Unsymmetrical Products

entry	cycloalkene	product (yield)
1	 **7**	 **8**, (65 %)[a]
2	 **7**	 **9**, (51 %)[b,c]
3		 **10**, (88 %)[b]
4		 **11**, (62 %)[d]

[a] Employing 2.5 equiv of Wittig reagent. [b] Employing 1.05 equiv of Wittig reagent. [c] Compound **8** was also obtained in 17% yield. [d] Employing 0.3 equiv of Wittig reagent; yield is based on the Wittig reagent. Compound **3** was also obtained in 10−15% yield.

General Procedure. A 0.3−0.4 M solution of the cycloalkene (1 equiv) in dry CH_2Cl_2 was cooled to −78 °C, and ozone was bubbled through until a blue color appeared. The excess ozone was removed by a flow of dry N_2, and PPh_3 (1 equiv) followed by the Wittig reagent (2.2−2.4 equiv.) were added as solids. The resulting mixture was allowed to warm to room temperature and was stirred for 16 h. After concentration on a rotary evaporator, the residue was purified by flash chromatography on silica gel to afford the pure bis-enone.

(2*E*,7*E*)-Dimethyl-2,7-nonadienedioate (1). Following the general procedure, cyclopentene (0.64 g, 9.4 mmol), PPh_3 (2.47 g, 9.4 mmol), and methyl(triphenylphosphoranylidene)acetate[10a] (7.60 g, 22.7 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 5.5:1), in order of elution, 0.12 g (6%) of the *E,Z*-isomer of **1** and 1.54 g (77%) of **1** both as colorless oils which were homogeneous by TLC analysis. Spectral data were identical to that previously reported.[6a]

(2*E*,8*E*)-3,8-Undecadiene-2,10-dione (2). Following the general procedure, cyclopentene (1.02 g, 15.0 mmol), PPh_3 (4.19 g, 16.0 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (9.90 g, 31.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 6:4), 1.83 g (68%) of **2** as a colorless oil which was homogeneous by TLC analysis. Spectral data were identical to that previously reported.[1a]

(2*E*,7*E*)-1,9-Diphenyl-2,7-nonadiene-1,9-dione (3). Following the general procedure, cyclopentene (1.02 g, 15.0 mmol), PPh_3 (3.93 g, 15.0 mmol), and 1-phenyl-2-(triphenylphosphoranylidene)ethanone[10b] (12.55 g, 33.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 4:1), 3.30 g (72%) of **3** as a pale yellow oil which was homogeneous by TLC analysis. Spectral data were identical to that previously reported.[6a]

(3*E*,8*E*)-3,9-Dimethyl-3,8-undecadiene-2,10-dione (4). Following the general procedure, cyclopentene (0.68 g, 10.0 mmol),

(10) (a) Lang, R. W.; Hansen, H.-J. *Organic Syntheses;* Wiley: New York, 1990; Coll. Vol. VII, p 232. (b) Ramirez, F.; Dershowitz, S. *J. Org. Chem.* **1957**, *22*, 41. (c) Tatsuta, K.; Amemiya, M.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837.

PPh_3 (2.62 g, 10.0 mmol), and 3-(triphenylphosphoranylidene)-2-butanone[10c] (7.70 g, 23.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 3:1) , in order of elution, 0.10 g (5%) of the *E,Z*-isomer of **4** and 1.04 g (50%) of **4** both as slightly-colored oils which were homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (dt, J = 1.6, 7.3 Hz, 2H), 2.29 (s, 6H), 2.27 (m, 4H), 1.75 (s, 6H), 1.65 (quintet, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 199.5, 142.3, 138.1, 28.7, 27.6, 25.4, 11.1; IR (film) 1665, 1639 cm^{-1}; HRMS (EI) m/e calcd for $C_{12}H_{17}O_2$ 193.1229, found 193.1234 (M − CH_3^+).

(3*E*,9*E*)-3,9-Dodecadiene-2,11-dione (5). Following the general procedure, cyclohexene (0.82 g, 10.0 mmol), PPh_3 (2.62 g, 10.0 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (7.64 g, 24.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 3:1), 1.20 g (62%) of **5** as a pale yellow oil which was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dt, J = 15.9, 6.9 Hz, 2H), 6.01 (dt, J = 15.9, 1.5 Hz, 2H), 2.1−2.3 (m, 4H), 2.18 (s, 6H), 1.46 (quintet, J = 3.7 Hz, 4H); ^{13}C NMR (75 MHz) δ 198.5, 147.6, 131.5, 32.1, 27.5, 26.8; IR (film) 1694, 1672, 1624 cm^{-1}; HRMS (EI) m/e calcd for $C_{12}H_{19}O_2$ 195.1385, found 195.1388 ((M + H)$^+$). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.15; H 9.26.

(3*E*,10*E*)-3,10-Tridecadiene-2,12-dione (6). Following the general procedure, cycloheptene (1.01 g, 10.5 mmol), PPh_3 (2.75 g, 10.5 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (8.00 g, 25.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 4:1), 1.25 g (57%) of **6** as a yellow oil which was homogeneous by TLC analysis. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.9, 6.9Hz, 2H), 6.07 (d, J = 15.9 Hz, 2H), 2.1−2.3 (m, 4H), 2.24 (s, 6H), 1.49 (quintet, J = 7.3 Hz, 4H), 1.3−1.4 (m, 2H); ^{13}C NMR (75 MHz) δ 198.6, 148.1, 131.4, 32.2, 28.6, 27.8, 26.8; IR (film) 1695, 1671, 1625 cm^{-1}; HRMS (EI) m/e calcd for $C_{13}H_{21}O_2$ 209.1542, found 209.1541 ((M + H)$^+$). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.79; H 9.69.

(3*E*,8*E*)-5-(Triisopropylsilyloxy)-3,8-undecadiene-2,10-dione (8). The general procedure was followed with following modifications: A solution of 1-(triisopropylsiloxy)-2-cyclopentene (**7**) (0.50 g, 2.1 mmol) in dry 1,2-dichloroethane (10 mL) was treated with ozone at −10 °C. PPh_3 (0.54 g, 2.1 mmol) and 1-(triphenylphosphoranylidene)-2-propanone[10b] (1.74 g, 5.4 mmol) were added, and reaction mixture was stirred for 2 h at 0 °C and then for 7 h at 50 °C. Flash chromatography (hexanes/EtOAc 4:1) afforded, in order of elution, 26 mg (4%) of **9** and 0.48 g (65%) of **8** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (dt, J = 15.9, 6.9 Hz, 1H), 6.71 (dd, J = 15.9, 5.1 Hz, 1H), 6.25 (dd, J = 15.9, 1.0 Hz, 1H), 6.06 (dt, J = 15.9, 1.2 Hz, 1H), 4.55 (q, J = 5.4 Hz, 1H), 2.1−2.5 (m, 2H), 2.27 (s, 3H), 2.23 (s, 3H), 1.7−1.9 (m, 2H), 1.05 (m, 21H); ^{13}C NMR (75 MHz) δ 198.4, 198.2, 148.8, 147.4, 131.4, 129.8, 71.1, 35.6, 27.3,26.9, 26.8, 17.9, 12.2; IR (film) 1697, 1675, 1627 cm^{-1}; HRMS (EI) m/e calcd for $C_{17}H_{29}O_3Si$ 309.1886, found 309.1883 (M − $CH(CH_3)_2^+$).

(5*E*)-7-Oxo-2-(triisopropylsilyloxy)-5-octenal (9). Following the general procedure, 1-(triisopropylsiloxy)-2-cyclopentene (**7**) (0.50 g, 2.1 mmol), PPh_3 (0.54 g, 2.1 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (0.70 g, 2.2 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 5:1), in order of elution, 0.33 g (51%) of **9** and 0.14 g (17%) of **8** both as pale yellow oils which were homogeneous by TLC analysis. For **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.65 (d, J = 1.8 Hz, 1H), 6.74 (dt, J = 16.0, 6.6 Hz, 1H), 6.06 (d, J = 15.9 Hz, 1H), 4.13 (dt, J = 1.2, 5.7 Hz, 1H), 2.2−2.5 (m, 2H), 2.21 (s, 3H), 1.8−1.9 (m, 2H), 1.05 (m, 21H); ^{13}C NMR (75 MHz) δ 204.5, 198.4, 146.8, 131.8, 76.7, 31.9, 26.9, 26.8, 17.9, 12.1; IR (film) 1734, 1697, 1675, 1625 cm^{-1}; HRMS (EI) m/e calcd for $C_{16}H_{33}O_2Si$ 283.2093, found 283.2088 (M − CHO$^+$).

(3*E*)-3-Nonene-2,8-dione (10). Following the general procedure, 1-methyl-1-cyclopentene (0.82 g, 10.0 mmol), PPh_3 (2.62 g, 10.0 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (3.50 g, 11.0 mmol) were employed to produce, after flash chromatography (hexanes/EtOAc 3:1), in order of elution, 58 mg (3%) of (3*E*,8*E*)-4-methyl-3,8-undecadiene-2,10-dione and 1.37 g (88%) of **10** both as pale yellow oils which were homogeneous by TLC analysis. IR spectral data were previously reported.[11] For **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dt, J = 16.0, 6.8 Hz, 1H), 6.00 (dt, J = 16.0, 1.6 Hz, 1H), 2.41 (t, J = 7.3 Hz, 2H), 2.17 (s, 3H), 2.17 (dq, J = 1.4, 7.8 Hz, 2H), 2.07 (s, 3H), 1.69 (quintet, J = 7.3 Hz, 2H); ^{13}C NMR (75 MHz) δ 207.9, 198.4, 147.1, 131.6, 42.5, 31.5, 29.9, 26.8, 21.8.

(5*E*)-7-Oxo-7-phenyl-5-heptenal (11). Cyclopentene (1.38 g, 20.2 mmol), CH_2Cl_2 (45 mL), PPh_3 (5.30 g, 20.2 mmol), and 1-(triphenylphosphoranylidene)-2-propanone[10b] (2.20 g, 5.8 mmol) were employed. The general procedure was followed with following modifications: After addition of PPh_3, the reaction mixture was stirred for 2 h at room temperature; the Wittig reagent was added dropwise as a solution in 10 mL of CH_2Cl_2 over 0.5 h by syringe drive. Flash chromatography (hexanes/EtOAc 4:1) afforded 0.73 g (62%) of **11** as a pale yellow oil, which was homogeneous by TLC analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (t, J = 1.2 Hz, 1H), 7.90−7.95 (m, 2H), 7.40−7.60 (m, 3H), 7.01 (dt, J = 15.6, 6.6 Hz, 1H), 6.90 (d, J = 15.6 Hz, 1H), 2.51 (dt, J = 0.9, 7.2 Hz, 2H), 2.36 (q, J = 7.2 Hz, 2H), 1.86 (quintet, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz) δ 201.7, 190.5, 148.1, 137.7, 132.8, 128.6, 128.5, 126.5, 43.0, 31.8, 20.4; IR (film) 1723, 1669, 1650, 1620 cm^{-1}; HRMS (EI) m/e calcd for $C_{13}H_{14}O_2$ 202.0994, found 202.0992 (M$^+$).

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of **4**, **5**, **6**, **8**, **9**, and **11** (12 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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(11) Kovalev, B. G.; Altmark, E. M. *Zh. Org. Khim.* **1972**, *8*, 1582.