JOC*Note*

Highly Efficient 1,4-Addition of 1,3-Diesters to Conjugated Enones by In/TMSCl

Phil Ho Lee,* Dong Seomoon, Kooyeon Lee, and Yunkiu Heo

Department of Chemistry, Kangwon National University, Chunchon 200-701, Republic of Korea

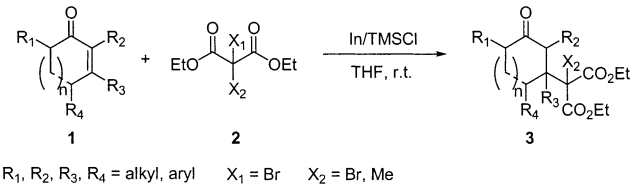
phlee@kangwon.ac.kr

Received October 24, 2002

Abstract: Organoindium reagents derived from indium and diethyl bromomalonates were added to a wide range of conjugated enones in a 1,4-fashion in the presence of TMSCl under mild conditions, and corresponding oxo-1,3-diesters were obtained in good to excellent yields.

The Michael reaction is one of the most efficient methods for C−C bond formation and has wide applications in organic synthesis.[1] It is usually carried out with a base as the reagent. However, it suffers from some side reactions such as autocondensations, bis-additions, rearrangements, polymerizations, and 1,2-additions in the presence of strong bases. In recent years, various reagents (LiI, DBN under high pressure, alumina, $BiCl_3$, and CdI_2) were proposed to overcome these problems.[2] But the high tendency of methyl vinyl ketone to polymerize is a serious limitation of these reagents.[3] Also, β-disubstituted α,β-enones do not undergo smooth reactions because of steric hindrance. Our interests in extending the scope of the Michael addition reaction[4] as well as our interests in applying indium metal to modern organic synthesis[5] have led us to investigate indium-promoted Michael addition reactions. Generally, organoindium reagents reacted with α,β-unsaturated aldehydes to afford 1,2-addition products in good yields.[6] A unique example of α,β-unsaturated ketones, the reaction of 4-phenyl-3-buten-2-one with organoindium reagents, produced regioselective 1,2-addition product.[6a,b] However, little has been reported on the Michael addition reaction to α,β-unsaturated ketones using allylindium reagents. Recently, it was reported that indium-mediated addition of allyl bromide to 1,1-dicyano-2-arylethenes gave good yields to Michael addition products in aqueous media.[7] Tetraorganoindium ate complexes reacted with α,β-unsaturated ketones in a 1,4-addition fashion.[8] The reaction of allylic indium sesquihalides with α,β-unsaturated carbonyl compounds, in which two electron-withdrawing groups were attached to alkenes, proceeded in a 1,2-addition mode. On the other hand, a 1,4-addition reaction took place with 1,1-dicyano-2-arylethenes which was extremely electron deficient olefins.[9] We had reported on the regioselectivity in the reactions of α,β−enones with allylindiums.[10] Despite the latest development, there is still a strong need for *a highly efficient and mild method for 1,4-addition of 1,3-diesters to conjugated enones*. To continue our studies on the development of efficient indium-mediated reactions,[5] described herein are our attempts to achieve this goal with an In and TMSCl system as shown in Scheme 1.

SCHEME 1



1 **2** **3**

R_1, R_2, R_3, R_4 = alkyl, aryl X_1 = Br X_2 = Br, Me

In a test reaction of 2-cyclohexen-1-one (**1j**) with diethyl bromomalonate (**2a**), we found that transformation could be efficiently effected by using indium in the presence of certain additives (Table 1). A survey of various additives revealed that the highest reactivity was achieved with TMSCl. The use of indium trichloride or indium without TMSCl did not produce 1,4-addition product (entries 1

* To whom correspondence should be addressed. Tel: +82 (0)33 250 8493. Fax: +82 (0)33 253 7582.

(1) (a) Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1. (c) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley-Interscience: New York, 1980. (d) Taylor, R. J. K. *Synthesis* **1985,** 364. (e) Lipshutz, B. H. *Synthesis* **1987**, 325. (f) Oare. A.; Heathcock, C. H. *Topics in Stereochemistry*; Interscience: New York, 1989; Vol. 19, p 227. (g) Duval, D.; Geribaldi, S. *The Chemistry of Enones Part 1*; Interscience: New York, 1989; p 355. (h) Hulce, M. *Org. React.* **1990**, *38*, 225. (i) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992. (j) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (k) Taylor, R. J. K. *Organocopper Reagents*; Oxford University Press: Oxford, 1994.

(2) (a) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem.* **1980**, *45*, 1246. (b) Ranu, B. C.; Bhar, S. *Tetrahedron* **1992**, *48*, 1327. (c) Antonioletti, R.; Bonadies, F.; Monteagudo, E. S.; Scettri, A. *Tetrahedron Lett.* **1991**, *32*, 5373. (d) Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1997**, *38*, 1449. (e) Dauben, W. G.; Gerdes, J. M. *Tetrahedron Lett.* **1983**, *24*, 3841.

(3) Huffman, J. W.; Potnis, S. M.; Satish, A. V. *J. Org. Chem.* **1985**, 50, 4266.

(4) (a) Lee, P. H.; Shim, S. C.; Kim, S. *Bull. Korean Chem. Soc.* **1986**, *7*, 425. (b) Kim, S.; Lee, P. H.; *Tetrahedron Lett.* **1988**, *29*, 5413. (c) Kim, S.; Lee, P. H.; Kim, S. S. *Bull. Korean Chem. Soc.* **1989**, *10*, 218. (d) Kim, S.; Lee, P. H. *Bull. Korean Chem. Soc.* **1992**, *13*, 580. (e) Lee, P. H.; Cho, M.; Han, I.-S.; Kim, S. *Tetrahedron Lett.* **1999**, *40*, 6975. (f) Lee, P. H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* **1999**, *40*, 7109.

(5) (a) Lee, P. H.; Bang, K.; Lee, K.; Lee, C.-H.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7521. (b) Lee, P. H.; Lee, K.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, 66, 8646. (c) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205. (d) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (e) Lee, P. H.; Lee, K.; Chang, S. *Synth. Commun.* **2001**, *31*, 3189. (f) Lee, P. H.; Bang, K.; Lee, K.; Sung, S.-Y.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781. (g) Lee, P. H.; Bang, K.; Ahn, H.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1385. (h) Lee, P. H.; Seomoon, S.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1380. (i) Bang, K.; Lee, K.; Park, Y. K.; Lee, P. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1272. (j) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (k) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901. (l) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (m) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463.

(6) (a) Araki, S.; Ito, Hirokazu.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1833. (b) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (c) Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, 453.

(7) Wang, L.; Sun, X.; Zhang, Y. *Synth. Commun.* **1998**, *28*, 3263.

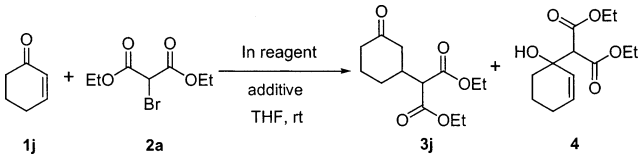
(8) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *Chem. Commun.* **1991**, 824.

(9) Araki, S.; Horie, T.; Kato, M.; Hirashita, T.; Yamamura, H.; Kawai, M. *Tetrahedron Lett.* **1999**, *40*, 2331.

(10) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37.

10.1021/jo026600t CCC: $25.00
Published on Web 02/14/2003

TABLE 1. Examination of Optimum Condition



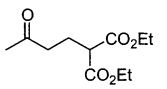
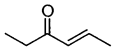
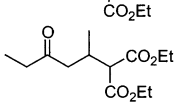
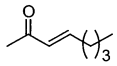
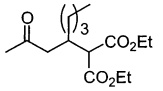
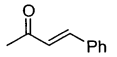
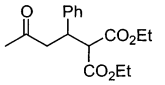
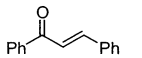
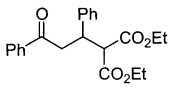
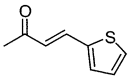
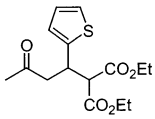
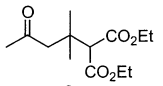
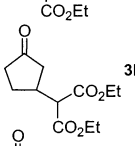
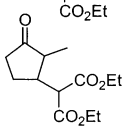
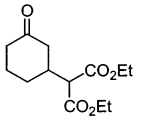
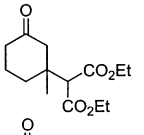
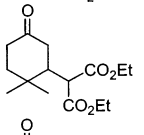
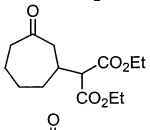
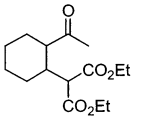
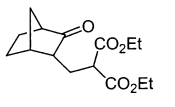
entry	equiv of TMSCl	In reagent	isolated yield[a] (%)
1		$InCl_3$	0
2	5.0	$InCl_3$	0
3		In	0
4	1.0	In[b]	0
5	1.0	In	6[c,d]
6	1.0	In	22[c]
7	5.0	In[b]	0
8	5.0	In[e]	36
9	5.0	In	80[d]
10	5.0	In	92
11	5.0	In	0[f]

[a] Reaction performed in the presence of TMSCl, 1 equiv of In, and 1.5 equiv of diethyl bromomalonate in THF at room temperature for 30 min. [b] 0.1 equiv of In was used. [c] Yield of 1,2-addition product. [d] 1.0 equiv of diethyl bromomalonate was used. [e] 0.5 equiv of In was used. [f] CH_2Cl_2 was used as a solvent.

and 3). The use of indium trichloride did not provide the desired compound **3j** in the presence of TMSCl as an additive (entry 2). Although the use of 1.0 equiv of TMSCl produced 1,2-addition product in low yield (entries 5 and 6), we could obtain the desired product **3j** in 92% yield with 1 equiv of indium and 5 equiv of TMSCl within 30 min at room temperature (entry 10). Test reactions with a catalytic amount of indium did not proceed despite the use of TMSCl (entries 7 and 8). THF was the solvent chosen from several reaction media screened.

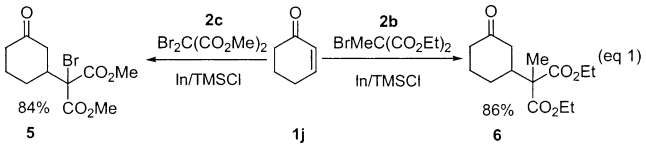
To demonstrate the efficiency and scope of the present method, we applied the optimum conditions to a variety of α,β−enones. The results are summarized in Table 2. As shown in Table 2, this new recipe for 1,4-addition reaction of diethyl bromomalonate to conjugated enones could be applied to a broad range of substrates. For example, methyl vinyl ketone reacted with organoindium derived from indium and diethyl bromomalonate in the presence of TMSCl to give the 1,4-addition product **3a** in 80% yield (entry 1). In addition to methyl vinyl ketone, several other β-substituted acyclic enones also served as good Michael acceptors (entries 2−7). It should be noted that mesityl oxide, in which a β-dimethyl group was attached, was treated with indium reagent to produce **3g** in 88% yield under mild conditions (25 °C, 30 min) despite steric hindrance (entry 7). We next explored the possibility of cyclic α,β-enones. Several cyclic α,β-enones underwent a novel Michael addition with the same efficiency. 2-Cyclopenten-1-one reacted with organoindium to give 1,4-addition product in 92% yield (entry 8). Treatment of 2-methyl-2-cyclopenten-1-one with organoindium gave **3i** in 93% yield (entry 9). In the case of 3-methyl-2-cyclohexen-1-one and 4,4-dimethyl-2-cyclohexen-1-one having steric hindrance, the desired products **3k** and **3l** were produced in 89% and 86% yields, respectively, under optimum conditions (entries 11 and 12). 2-Cyclohepten-1-one was treated with organoindium to give **3m** in 82% yield (entry 13). 1-Acetylcyclohexene, in which planarity was weak, reacted with organoindium to afford 1,4-addition product **3n** (entry 14). It may be worth noting that the reaction of 3-methylene-2-norbornanone with indium reagent gave the corresponding compound **3o** in an excellent yield (entry 15.)

TABLE 2. Reactions of α,β-Enones with Organoindium in the Presence of TMSCl

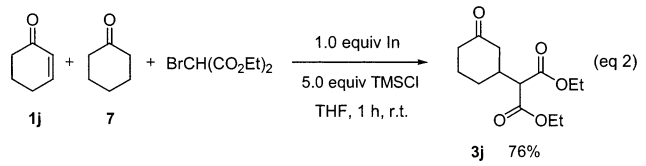
entry	α,β−enone	product		isolated yield(%)
1			**3a**	80
2			**3b**	92
3			**3c**	90
4			**3d**	85
5			**3e**	97
6			**3f**	87
7			**3g**	88
8			**3h**	92
9			**3i**	93 (1:10)[a]
10			**3j**	92
11			**3k**	89
12			**3l**	86
13			**3m**	82
14			**3n**	86 (1:2.5)[a]
15			**3o**	90

[a] Diastereomeric ratio.

With these results in hand, we carried out the reaction of 2-cyclohexen-1-one (**1j**) with organoindium derived from indium and dimethyl dibromomalonate (**2c**) in the presence of TMSCl, which resulted in the desired product **5** in 84% yield (eq 1). Treatment of **1j** with indium and diethyl 2-bromo-2-methylmalonate (**2b**) afforded **6** in 86% yield. In the case of diethyl chloromalonate and ethyl 2-chloroacetoacetate, 1,4-addition products were not produced under the present conditions.



To investigate the chemoselectivity of α,β-enone and ketone, the mixture of 2-cyclohexen-1-one and cyclohexanone was treated with an organoindium compound. This treatment produced a chemoselective Michael addition compound **3j** in 76% yield and recovered cyclohexanone in 95% yield (eq 2).



2-Cyclohexen-1-one did not react with carbanion derived from diethyl malonate and sodium hydride in the presence of TMSCl. Also, the reaction of organoindium reagent derived from indium and diethyl bromomalonate with 2-cyclohexen-1-one in the presence of TMSCl as an additive and TEMPO as a radical scavenger did not produce the desired product. With these results in hand, although the mechanism of the present reaction is not clear, we assume that this reaction proceeds not through carbanion but radical species. These and other plausible mechanistic pathways are under investigation.

In conclusion, we have demonstrated that a novel indium-mediated strategy can be achieved for a 1,4-addition of diethyl bromomalonates to conjugated enones in the presence of TMSCl as an additive under mild conditions. The process is simple to conduct and provides a diverse range of ethyl 2-ethoxycarbonyl-5-oxoalkanoates in good to excellent yields. This protocol is an appealing alternative to the existing two-step Michael reaction route that requires generation of anion of diethyl malonate.

Experimental Section

Reactions were carried out in oven-dried glassware under nitrogen atmosphere. All commercial reagents were used without purification, and all solvents were reaction grade. THF was freshly distilled from sodium/benzophenone under nitrogen. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using Merck silica gel 60 F_{254} precoated glass plates, which were visualized with UV light and then developed using either iodine or a solution of anisaldehyde. Flash column chromatography was carried out using Fluka silica gel 60 (0.040−0.063 mm, 230−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX FT (400 MHz) spectrometer. Deuterated chloroform was used as the solvent, and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.24 for ^{1}H and δ 77.0 for ^{13}C). High-resolution mass spectra were recorded on a VG Autospec Ulpima. Infrared spectra were recorded on a JASCO FT/IR-460 plus FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk.

Typical Experimental Procedure. Indium (114.8 mg, 1.0 mmol), diethyl bromomalonate (359.0 mg, 1.5 mmol) ,and TMSCl (543.2 mg, 5.0 mmol) in THF (1 mL) were slowly added to 2-cyclohexen-1-one (96.1 mg, 1.0 mmol) in THF (1 mL) at room temperature under a nitrogen atmosphere. After 30 min, the reaction mixture was quenched with $NaHCO_3$ (satd aq). The aqueous layer was extracted with diethyl ether (3 × 20 mL), and the combined organics were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with silica gel column chromatography (EtOAc/hexane = 1:10) to give diethyl 2-(3′-oxocyclohexyl)malonate (235.7 mg, 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24−4.18 (m, 4H), 3.30 (d, J = 7.9 Hz, 1H), 2.56−2.50 (m, 1H), 2.47−2.39 (m, 2H), 2.31−2.21 (m, 2H), 2.11−2.05 (m, 1H), 1.96 (d, J = 13.14 Hz, 1H), 1.72−1.66 (m, 1H), 1.56−1.50 (m, 1H), 1.30−1.26 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.66, 167.89, 167.80, 77.23, 61.56, 56.92, 45.12, 41.04, 38.03, 28.80, 24.56, 14.10; IR (film) 1748, 1729, 1715, 1267, 1173, 1158 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_5M^+$ 256.1311, found 256.1303.

Ethyl 2-ethoxycarbonyl-5-oxohexanoate (3a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23−4.16 (m, 4H), 3.39 (t, J = 7.32 Hz, 1H), 2.55 (t, J = 7.28 Hz, 2H), 2.18−2.13 (m, 5H), 1.26 (t, J = 7.15 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.60, 169.52, 61.83, 51.06, 40.85, 30.32, 22.82, 14.44; IR (film) 1746, 1728, 1267, 1157 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{18}O_5M^+$ 230.1154, found 230.1153.

Ethyl 2-ethoxycarbonyl-3-methyl-5-oxoheptanoate (3b): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.13 Hz, 4H), 3.37 (d, J = 6.69 Hz, 1H), 2.81−2.76 (m, 1H), 2.66 (dd, J = 4.72, 16.97 Hz, 1H), 2.45−2.37 (m, 3H), 1.27 (t, J = 7.11 Hz, 6H), 1.11−1.02 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.97, 168.66, 168.62, 61.27, 56.27, 46.30, 36.33, 28.98, 17.76, 14.10, 7.75; IR (film) 1746, 1727, 1277, 1253 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_5M^+$ 258.1467, found 258.1440.

Ethyl 3-*n*-butyl-2-ethoxycarbonyl-5-oxohexanoate (3c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21−4.15 (m, 4H), 3.53 (d, J = 5.52 Hz, 1H), 2.74 (dd, J = 5.20, 17.21 Hz, 1H), 2.69−2.66 (m, 1H), 2.51 (dd, J = 6.55, 17.22 Hz, 1H), 2.14 (s, 3H), 1.38−1.24 (m, 14H), 0.87 (t, J = 6.73 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.57, 169.02, 168.75, 77.23, 61.30, 61.19, 54.04, 45.32, 33.55, 32.18, 31.72, 30.30, 26.62, 22.50, 14.10, 14.00; IR (film) 1745, 1726, 1270, 1261, 1158 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{28}O_5M^+$ 300.1937, found 300.1938.

Ethyl 2-ethoxycarbonyl-5-oxo-3-phenylhexanoate (3d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.18 (m, 5H), 4.19 (q, J = 7.13 Hz, 2H), 4.00−3.92 (m, 3H), 3.69 (d, J = 9.88 Hz, 1H), 2.98−2.91 (m, 2H), 2.02 (s, 3H), 1.25 (t, J = 7.15 Hz, 3H), 1.01 (t, J = 7.11 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 206.09, 168.22, 167.65, 140.41, 128.48, 128.15, 127.22, 61.65, 61.33, 57.44, 47.44, 40.49, 30.31, 14.03, 13.76; IR (film) 2940, 1748, 1730, 1263, 1155 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{22}O_5M^+$ 306.1467, found 306.1464.

Ethyl 4-benzoyl-2-ethoxycarbonyl-3-phenylbutanoate (3e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 7.43 Hz, 2H), 7.53 (t, J = 7.37 Hz, 1H), 7.42 (t, J = 7.63 Hz, 2H), 7.27−7.15 (m, 5H), 4.24−4.15 (m, 3H), 3.95 (q, J = 7.12 Hz, 2H), 3.82 (d, J = 9.75 Hz, 1H), 3.57−3.42 (m, 2H), 1.24 (t, J = 7.15 Hz, 3H), 1.01 (t, J = 7.14 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 197.55, 168.36, 167.74, 140.45, 136.80, 133.03, 128.54, 128.39, 128.24, 128.09, 127.13, 77.23, 61.66, 61.35, 57.59, 42.63, 40.80, 14.02, 13.76; IR (film) 1748, 1731, 1687, 1264, 1156 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{24}O_5M^+$ 368.0405, found 368.1624.

Ethyl 2-ethoxycarbonyl-5-oxo-3-(2′-thienyl)hexanoate (3f): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 4.82 Hz, 1H), 6.89−6.87 (m, 2H), 4.26 (q, J = 7.38 Hz, 1H), 4.22−4.16 (m, 2H), 4.05 (q, J = 7.12 Hz, 2H), 3.74 (d, J = 8.59 Hz, 1H), 3.00 (d, J = 6.84 Hz, 2H), 2.09 (s, 3H), 1.25 (t, J = 7.14 Hz, 3H), 1.12 (t, J = 7.09 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 205.74, 167.91, 167.57, 143.55, 126.60, 125.77, 124.22, 61.69, 61.55, 57.76, 47.96,

35.67, 30.32, 14.01, 13.86; IR (film) 1747, 1730, 1238, 1155 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_5M^+$ 312.1031, found 312.1043.

Ethyl 2-ethoxycarbonyl-3,3-dimethyl-5-oxohexanoate (3g): ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, J = 7.14 Hz, 4H), 3.84 (s, 1H), 2.75 (s, 2H), 2.11 (s, 3H), 1.26 (t, J = 7.11 Hz, 6H), 1.21 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.96, 168.55, 77.24, 60.95, 58.19, 51.79, 35.26, 31.86, 25.67, 14.10; IR (film) 1747, 1725, 1268, 1155 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{22}O_5M^+$ 258.1467, found 258.1468.

Diethyl 2-(3′-oxocyclopentyl)malonate (3h): ^1H NMR (400 MHz, $CDCl_3$) δ 4.26−4.18 (m, 4H), 3.34 (d, J = 9.41 Hz, 1H), 2.89−2.83 (m, 1H), 2.52 (dd, J = 18.45, 18.42 Hz, 1H), 2.38−2.16 (m, 3H), 2.03 (dd, J = 18.51, 18.45 Hz, 1H), 1.72−1.64 (m, 1H), 1.28 (q, J = 6.89 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 217.18, 168.16, 168.07, 77.23, 61.64, 61.62, 56.55, 42.93, 38.22, 36.33, 27.51, 14.11, 14.09; IR (film) 1741, 1264, 1155 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{18}O_5M^+$ 242.1154, found 242.1152.

Diethyl 2-(2′-methyl-3′-oxocyclopentyl)malonate (3i): ^1H NMR (400 MHz, $CDCl_3$) isomer A δ 4.23 (q, J = 7.13 Hz, 4H), 3.46 (d, J = 7.02 Hz, 1H), 2.43−2.36 (m, 2H), 2.23−2.13 (m, 2H), 2.08−2.03 (m, 1H), 1.77−1.69 (m, 1H), 1.31−1.26 (m, 6H), 1.08 (d, J = 6.99 Hz, 3H), isomer B δ 4.23 (q, J = 7.13 Hz, 4H), 3.37 (d, J = 11.06 Hz, 1H), 2.43−2.36 (m, 2H), 2.23−2.13 (m, 2H), 2.08−2.03 (m, 1H), 1.77−1.69 (m, 1H), 1.31−1.26 (m, 6H), 0.97 (d, J = 7.69 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (isomer A) 218.90, 168.39, 167.97, 61.61, 61.53, 54.73, 47.66, 43.62, 36.78, 24.70, 14.13, 14.07, 13.18, (isomer B) 220.09, 168.39, 167.97, 61.67, 53.33, 44.92, 39.66, 36.90, 24.40, 14.13, 14.07, 13.18, 10.47; IR (film) 1740, 1266, 1152 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_5M^+$ 256.1311, found 256.1335.

Diethyl 2-(1′-methyl-3′-oxocyclohexyl)malonate (3k): ^1H NMR (400 MHz, $CDCl_3$) δ 4.23−4.17 (m, 4H), 3.31 (s, 1H), 2.76 (d, J = 13.76 Hz, 1H), 2.33−2.28 (m, 3H), 1.98−1.92 (m, 2H), 1.86−1.81 (m, 2H), 1.30−1.26 (m, 6H), 1.14 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.70, 167.61, 167.51, 77.22, 61.30, 61.28, 61.65, 50.93, 40.79, 40.54, 33.72, 22.34, 21.39, 14.10; IR (film) 1750, 1726, 1273, 1259, 1154 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_5M^+$ 270.1467, found 270.1462.

Diethyl 2-(2′,2′-dimethyl-5′-oxocyclohexyl)malonate (3l): ^1H NMR (400 MHz, $CDCl_3$) δ 4.22−4.16 (m, 4H), 3.57 (d, J = 4.86 Hz, 1H), 2.65 (t, J = 13.68 Hz, 1H), 2.56−2.51 (m, 1H), 2.46−2.28 (m, 3H), 1.72−1.63 (m, 2H), 1.27 (q, J = 7.44 Hz, 6H), 1.06 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.10, 168.87, 168.63, 77.23, 61.82, 61.44, 52.29, 45.18, 40.43, 40.05, 37.81, 33.21, 28.72, 20.16, 14.00 IR (film) 1748, 1727, 1300, 1260, 1203, 1174 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}O_5M^+$ 284.1624, found 284.1608.

Diethyl 2-(3′-oxocycloheptyl)malonate (3m): ^1H NMR (400 MHz, $CDCl_3$) δ 4.24−4.18 (m, 4H), 3.31 (d, J = 6.74 Hz, 1H), 2.61−2.47 (m, 5H), 1.97−1.87 (m, 3H), 1.57−1.37 (m, 3H), 1.28 (t, J = 7.11 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 212.65, 168.23, 168.15, 77.23, 61.54, 57.50, 47.28, 43.61, 35.66, 34.16, 28.80, 24.46, 14.10; IR (film) 1741, 1268, 1156 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_5M^+$ 270.1467, found 270.1430.

Diethyl 2-(2′-acetylcyclohexyl)malonate (3n): ^1H NMR (400 MHz, $CDCl_3$) δ (isomer A) 4.22−4.12 (m, 4H), 3.74 (d, J = 11.19 Hz, 1H), 2.89−2.86 (m, 1H), 2.34−2.27 (m, 1H), 2.10 (s, 3H), 2.06−2.01 (m, 1H), 1.95−1.83 (m, 2H), 1.76−1.62 (m, 3H), 1.54−1.47 (m, 2H), 1.36−1.17 (m, 6H), (isomer B) 4.22−4.12 (m, 4H), 3.44 (d, J = 4.32 Hz, 1H), 2.61−2.58 (m, 1H), 2.44−2.43 (m, 1H), 2.10 (s, 3H), 2.06−2.01 (m, 1H), 1.95−1.83 (m, 2H), 1.76−1.62 (m, 3H), 1.54−1.47 (m, 2H), 1.36−1.17 (m, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ (isomer A) 210.77, 168.98, 168.96, 77.23, 61.26, 61.23, 54.70, 48.51, 38.97, 29.58, 28.09, 26.23, 25.41, 21.92, 14.17, (isomer B) 211.77, 168.76, 168.63, 77.23, 61.19, 61.05, 53.58, 53.51, 37.80, 30.05, 29.44, 27.55, 25.65, 25.48, 14.10; IR (film) 1747, 1726, 1710, 1265, 1217, 1162 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{24}O_5M^+$ 284.1624, found 284.1628.

Diethyl 2-(2′-oxobicyclo[2.2.1]heptan-3-yl)methylmalonate (3o): ^1H NMR (400 MHz, $CDCl_3$) δ 4.23−4.17 (m, 4H), 3.57 (t, J = 7.64 Hz, 1H), 2.62 (d, J = 7.64 Hz, 1H), 2.59 (s, 1H), 2.27−2.20 (m, 1H), 2.07−2.03 (m, 1H), 1.88−1.81 (m, 2H), 1.68 (d, J = 10.42 Hz, 1H), 1.63−1.57 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 218.53, 169.34, 169.01, 77.22, 61.51, 51.04, 50.47, 50.37, 38.69, 36.96, 25.71, 25.36, 21.21, 14.07; IR (film) 1743, 1269 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_5M^+$ 282.1467, found 282.1465.

Dimethyl 2-bromo-2-(3′-oxocyclohexyl)malonate (5): ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 3.82 (s, 3H), 2.67−2.61 (m, 1H), 2.55−2.51 (m, 1H), 2.42 (t, J = 13.44 Hz, 2H), 2.31−2.23 (m, 1H), 2.14−2.05 (m, 2H), 1.72−1.64 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.09, 166.41, 166.17, 67.71, 54.11, 54.03, 44.44, 43.93, 40.85, 27.54, 23.90; IR (film) 1746, 1715, 1268 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{15}BrO_5M^+$ 306.0103, found 306.0077.

Diethyl 2-methyl-2-(3′-oxocyclohexyl)malonate (6): ^1H NMR (400 MHz, $CDCl_3$) δ 4.27−4.15 (m, 4H), 2.52 (tt, J = 3.32, 12.56 Hz, 1H), 2.43−2.33 (m, 2H), 2.27−2.19 (m, 2H), 2.12−2.06 (m, 1H), 1.91 (d, J = 12.88 Hz, 1H), 1.71−1.60 (m, 1H), 1.41 (s, 3H), 1.26 (t, J = 7.12 Hz, 6H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.33, 171.04, 170.88, 61.47, 61.41, 56.79, 43.39, 42.52, 41.15, 26.66, 24.76, 16.80, 14.05; IR (film) 1729, 1715, 1263, 1118 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_5M^+$ 270.1467, found 270.1464.

Acknowledgment. This work was supported financially by a KOSEF Grant No. R02-2002-000-00046-0 from the Basic Research Program of the Korea Science & Engineering Foundation and the CMDS at KAIST. We thank Keuckchan Bang for the preliminary experiments. The gas chromatograms were provided by GC facility, supported by Research Center for Advanced Mineral Aggregate Composite Products.

Supporting Information Available: Spectral data of all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026600T