Revisiting [3 + 3] Route to 1,3-Cyclohexanedione Frameworks: Hidden Aspect of Thermodynamically Controlled Enolates

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We have revisited the traditional consecutive Michael−Claisen [3 + 3] process (MC-[3 + 3]) promising the synthesis of a cyclohexane-1,3-dione derivatives from nonactivated simple ketones and enoates and evaluated its potential in modern organic synthesis. Twenty to thirty examples were demonstrated to be effective. The reactions exhibited remarkable regioselectivity with the Michael addition proceeding through nucleophilic attack by the more hindered site of the ketones without exception. The subsequent Claisen condensation resulted in the formation of carbon−carbon bonds between less hindered site of the ketones and acyl carbon of the enoates. The MC-[3 + 3] process described is useful for the synthesis of Taxol A-ring synthons in multigram quantities and for the synthesis of other six-membered carbocyclic compounds. A number of control experiments have been conducted to provide strong support for the mechanism of this MC-[3 + 3].

Introduction

About 60 years ago, Hurd and Kelso reported that they obtained 1-undecene-3,5-dione (**1**) as a product of Claisen reaction[1] between ethyl acrylate and 2-octanone in the presence of sodium ethoxide: the elemental analysis was the only proof of the product structure. Seventeen years later, Miller and Benneville[2] correctly revised Hurd and Kelso's product to be 4-pentyl-1,3-cyclohexanedione (**2**) (Scheme 1)

They also proposed the mechanism that Michael addition reaction of an enolate generated from the ketone under thermodynamically controlled conditions toward the α,*β*-unsaturated ester took place in the first place followed by intramolecular Claisen condensation to give a 1,3-cyclohexanedione framework of **2** (Michael−Claisen [3 + 3] reaction = MC-[3 + 3]). Although Michael addition reactions of 1,3-dicarbonyl compounds toward α,*β*-unsaturated ketones were also well-known to be followed by intramolecular Claisen cyclizations,[3] the combination of Michael addition and Claisen condensation using *nonactivated simple ketones and* α,*β-unsaturated esters* as starting materials would provide an extremely simple [3 + 3] route to 1,3-cyclohexanedione frameworks.[4,5] However, little effort has been made in this context[6] since the first report of Hurd and Kelso.[1] Such a situation has given us strong incentive to further examine the potential of this MC-[3 + 3] route to the 1,3-cyclohexanedione framework. In this paper, we will describe the generality of the MC-[3 + 3] in the synthesis of wide variety of cyclohexane-1,3-dione derivatives from *nonactivated simple ketones and* α,*β-unsaturated esters* and discuss the mechanistic insight gained through our control experiments.

(1) Hurd, C. D.; Kelso, C. D. *J. Am. Chem. Soc.* **1940**, *62*, 2184−2187.

(2) Miller, J. J.; Benneville, P. L. *J. Org. Chem.* **1957**, *22*, 1268−1269.

(3) See, for instance: (a) Hauser, C. R.; Swamer, F. W.; Adams, J. T. *Org. React.* **1954**, *8*, 59−195. For Michael addition, see: (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapter 1.1. For Claisen condensation, see: (c) Davis, B. R.; Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 3.6.

(4) It is well-known that 2-methyl-1,3-cyclohexanedione is a key starting compound for the synthesis of Wieland−Mischer ketone; see: (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615−1621. (b) Buchschcher, P.; Fürst, A.; Gutzwiller, J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, pp 368−372.

(5) For total synthesis utilizing 1,3-cyclohexanedione derivatives, see: (a) Stork, G.; Kretchmer, R. H.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1968**, *90*, 1647−1648. (b) Canonica, L.; Rindone, B.; Santaniello, E.; Scolastico, C. *Tetrahedron* **1972**, *28*, 4395−4404. (c) Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782−790. (d) Jung, M. E.; McCombs, C. A.; Takeda, T.; Pan, Y.-G. *J. Am. Chem. Soc.* **1981**, *103*, 6677−6685. (e) Magnus, P.; Gopalan, A. *J. Org. Chem.* **1984**, *49*, 2317−2321. (f) Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Krafft, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 1597−1600. (g) Kraus, G. A.; Johnston, B. E.; Applegate, J. M. *J. Org. Chem.* **1991**, *56*, 5688−5691. (h) Myers, A. G.; Fraley, M. E.; Tom, M. J.; Cohen, S. B.; Modar, D. J. *Chem. Biol.* **1995**, *2*, 33−43. (i) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980−12981. (j) Hara, R.; Furukawa, T.; Kashima, H.; Kusama, H.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1999**, *121*, 3072−3082. (k) Dudley, G. B.; Takai, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *2*, 3407−3410.

(6) This work is not concerned with MC-[3 + 3] using activated ketones such as 1,3-dicarbonyl compounds, for which a large number of papers have been published (see ref 3). As far as nonactivated simple ketones and enoates are concerned, only one additional report is available to the best of our knowledge; see: (a) Miller, M. L.; Ray, P. S. *Synth. Commun.* **1997**, *27*, 3991−3996 in which MC-[3 + 3] employing 3-pentanone and methyl acrylate (dropwise addition of a mixture of the ketone and the enoate to NaOMe/xylene at 35 °C and heating at 120 °C to remove the methanol) was described. For other closely related work Zimmerman reported the synthesis of 4,4-diphenylcyclohexane-1,3-dione through MC-[3 + 3] between moderately activated 1,1-diphenylacetone and ethyl acrylate (*t*-BuOK/ether, 18 h at room temperature) without discussion about regiochemical issue of the reaction: (b) Zimmerman, H. E.; Pasteris, R. J. *J. Org. Chem.* **1980**, *45*, 4876−4891.

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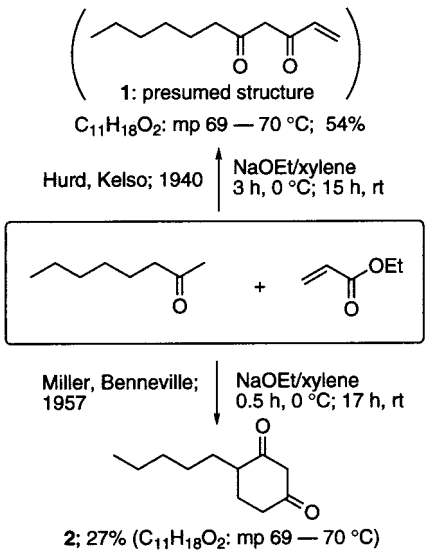
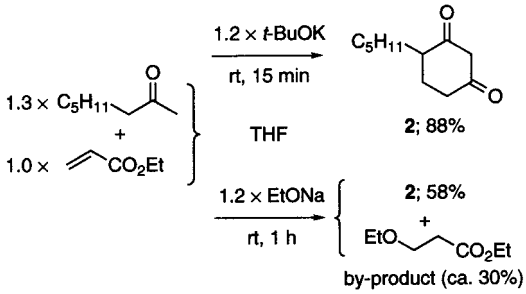
Scheme 1



Scheme 2



Results and Discussion

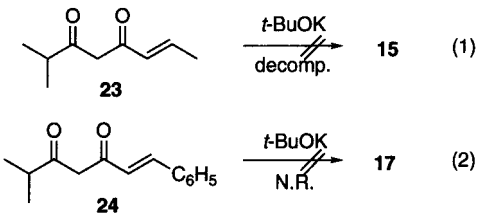
A. Reexamination of the Original MC-[3 + 3]. Initially, the original MC-[3 + 3] between 2-octanone and ethyl acrylate was carefully reexamined. In our hands, the original conditions employing sodium ethoxide resulted in a 58% yield of **2** and a considerable amount of ethyl 3-ethoxypropanoate (30%) (Scheme 2). We found that the combination of commercially available potassium *tert*-butoxide (*t*-BuOK) as a base and THF as a solvent can effect the expected MC-[3 + 3] to efficiently furnish **2** in high yield (88%).

B. Generality of the MC-[3 + 3]: Synthesis of Various Cyclohexane-1,3-diones. To assess the generality of MC-[3 + 3] for the synthesis of various cyclohexane-1,3-diones, we applied the conditions (*t*-BuOK/THF) to various simple ketone[7] and enoate combinations, and the results are summarized in Table 1. Although reactivities or product yields depended on the structures of substrates and/or enoates, the expected MC-[3 + 3] was effected for every case examined (21 entries). The best choice of enoate alkyl group was a *tert*-butyl group, the typical cases of which are shown in Table 1, entries 6 and 7 or 12 and 13. Interestingly, Michael addition proceeded through nucleophilic attack by more hindered site of the ketones without exception, which, in turn, means that Claisen condensation resulted in the formation of carbon−carbon bond between less hindered site of the ketones and acyl carbon of the enoates (Table 1, entries 1−5 and 12−21). Therefore, no regioisomers were isolated at all.

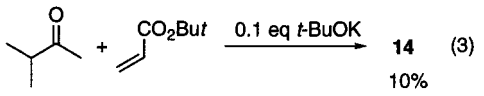
The proportions of homo coupling products under the standard conditions were 2% at most as far as ethyl methyl ketone, diethyl ketone, and isopropyl methyl ketone were concerned: also we observed that acetone was a special ketone to result in violent reaction giving a complex dark mixture under the standard conditions. As already mentioned above *t*-BuOK is the key to the successful MC-[3 + 3] (see the EtONa example in Scheme 2). The nature of the countercation, however, seems unimportant in terms of reactivity or regioselectivity: as far as three cations (*t*-BuO^-M^+; M = Li, Na, and K) were concerned, no difference was observed in every respect.[8]

C. Mechanism of the MC-[3 + 3] in THF: (1) Proposal. The plausible mechanism of MC-[3 + 3] is illustrated in Scheme 3. The reaction reproduces *t*-BuOK after the Michael addition, which plays the role of second-stage deprotonation for Claisen cyclization, and an enoate-based alkoxide was eventually produced. This base was, however, destined to deprotonate from the final products 1,3-diones. Therefore, the equimolar amount of the base was strictly required for the completion of the MC-[3 + 3].

(2) Control Experiments to Support the Mechanism. When enediones such as **23** or **24** were treated with *t*-BuOK, no intramolecular Michael adduct such as **15** or **17** was furnished at all as shown in eqs 1 and 2. Therefore, there seems no chance of initial Claisen reaction followed by intramolecular Michael addition.



The use of 10 mol % of *t*-BuOK for the reaction of isopropyl methyl ketone with *tert*-butyl acrylate resulted in the formation of **14** in 10% yield (eq 3). This result clearly indicated that the regenerated *t*-BuOK was trapped by highly acidic cyclohexane-1,3-dione derivatives to give $\mathbf{E}_5$ (Scheme 3) as a final product before quenching.



Kuwajima reported in 1976 that the kinetic generation of enolate from methyl ketones became feasible when a solution of the ketones in THF was treated with sterically hindered bases even in the presence of aldehydes.[9] Indeed, when isopropyl methyl ketone was treated with *t*-BuOK in the presence of methyl benzoate, kinetically controlled Claisen condensation took place to give a 1,3-

(7) These ketones were prepared by alkylation of ethyl methyl ketone with requisite alkyl halides in the presence of *t*-BuOK. The regioselective alkylation of simple ketones using alkoxide bases are under active investigation in this laboratory.

(8) The regioselectivity for aldol reaction of 2-methylcyclohexanone enolate depended on the nature of countercations such as K^+ or Li^+; see: Duhamel, P.; Cahard, D.; Quesnel Y.; Poirier J.-M. *J. Org. Chem.* **1996**, *61*, 2232−2235.

(9) Kuwajima, I.; Sato, T.; Arai, M.; Minami, N. *Tetrahedron Lett.* **1976**, 1817−1820.

Table 1. Results of MC-[3 + 3] between Simple Ketones and Enoates Leading to Cyclohexane-1,3-diones Promoted by *t*-BuOK in THF[a]

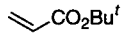
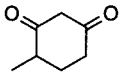
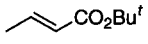
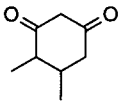
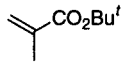
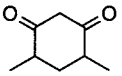
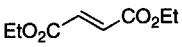
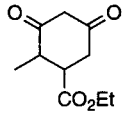
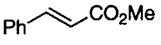
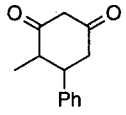
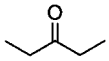
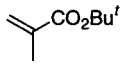
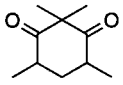
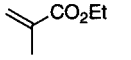
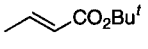
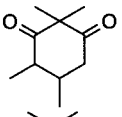
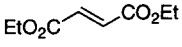
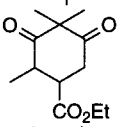
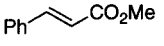
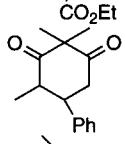
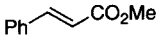
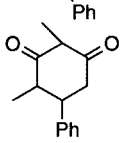
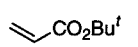
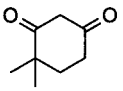
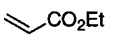
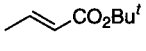
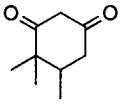
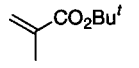
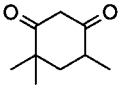
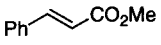
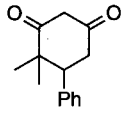
Entry	Ketone	Enoate	Temp/Time: °C/h[b]	E[c]	Product[d]		Yield/%
1			25/0.5	aq HCl		**4**	88
2			25/0.5	aq HCl		**5**	85
3			25/0.5	aq HCl		**6**[e]	81
4			25/0.5	aq HCl		**7**	58
5			40/12	aq HCl		**8**	78
6			25/0.5	CH_3I		**9**	98
7			25/0.5	CH_3I		**9**	56
8			25/0.5	CH_3I		**10**[f]	70
9			45/3	CH_3I		**11**[g]	23
10			25/7	CH_3I		**12**[h]	44
11			25/4	aq HCl		**13**	34
12			25/0.5	aq HCl		**14**	99
13			25/0.5	aq HCl		**14**	85
14			40/24	aq HCl		**15**	50
15			25/0.5	aq HCl		**16**	97
16			25/4	aq HCl		**17**	68

Table 1. (Continued)

Entry	Ketone	Enoate	Temp/Time: °C/h[b]	E[c]	Product[d]		Yield/%
17		EtO_2C CO_2Et	25/2	aq HCl	CO_2Et	**18**	42
18		CO_2Et	25/12	aq HCl		**19**	12
19[i]	OPMB	CO_2Et	40/24	aq HCl	PMBO	**20**	64
20		Ph CO_2Me	40/17	aq HCl	PMBO Ph	**21**	59
21[i]	Ph	CO_2Bu^t	25/12	aq HCl	Ph	**22**	63

[a] Standard conditions:

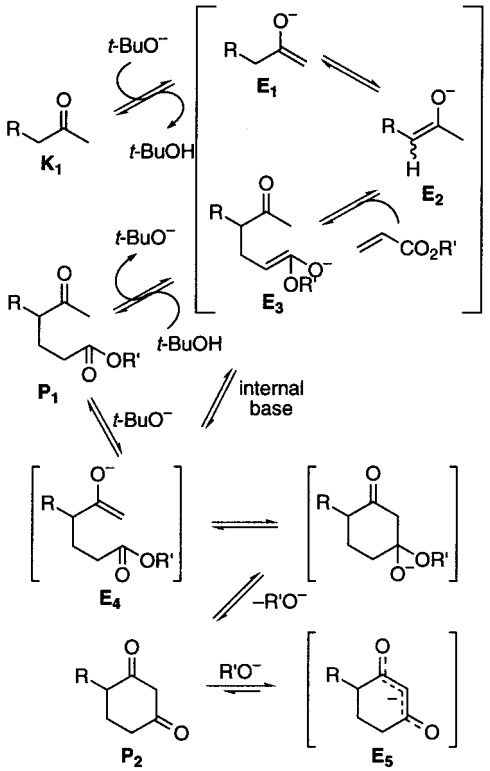
ketone 1.2 eq + enoate 1.0 eq + *t*-BuOK 1.2 eq → step1 → step 2 (E) → workup ⟹ SiO_2 column chromat.

THF (10 mL)/ketone (1 gram)

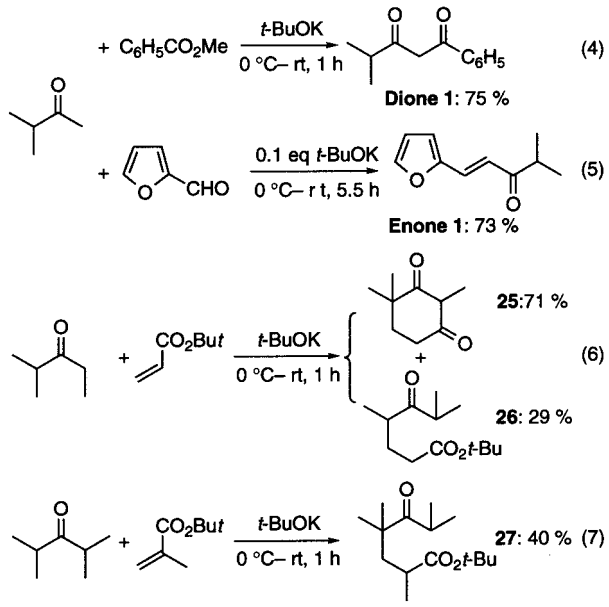
step1: added *t*-BuOK to a solution of ketone + enoate in THF at 0 °C
step 2: E = aq HCl (1.5 eq) or CH_3I (3 eq) 50 °C, 3 h

[b] After the addition of *t*-BuOK. [c] Aqueous HCl as a better proton source than ammonium chloride. [d] Diastereomer ratio were not determined unless otherwise indicated. [e] Cis/trans = 4:1. [f] Cis/trans = 2:3. [g] Trans only. [h] Cis/trans = 2:3. [i] See ref 7.

Scheme 3



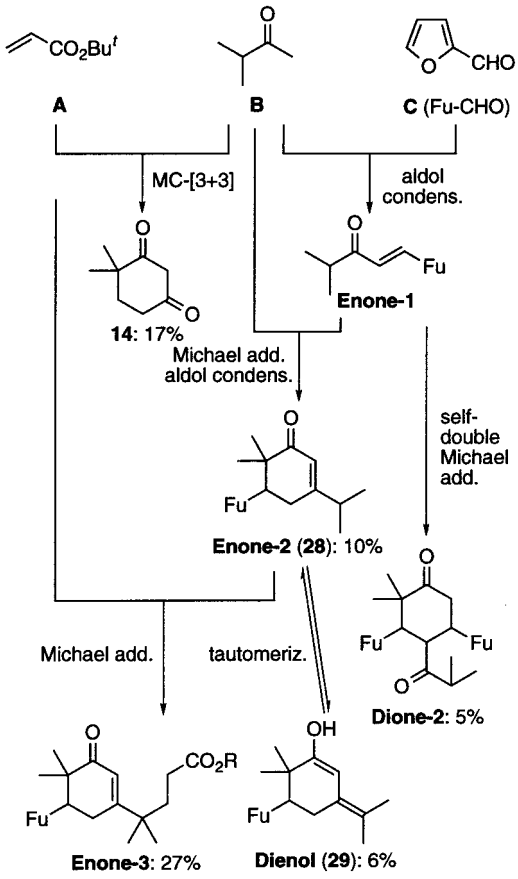
diketone (**dione 1**: 75%) as shown in eq 4. Also treatment of the same simple ketone with catalytic amount of *t*-BuOK (10 mol %) in the presence of an aromatic aldehyde such as furfural furnished aldol condensation product as a result of kinetically generated enolate addition to the aldehyde (eq 5).[10] These two control experiments clearly indicated the presence of kinetically generated enolate of isopropyl methyl ketone (**E_1** in Scheme 3). Nevertheless, no Michael reaction between **E_1** and enoate was detected at all for the present MC-[3 + 3].[11]



As shown in Table 1, the ketone enolates generated from ethyl methyl ketone (entries 1−5), isopropyl methyl

(10) For review of aldol condensation, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.5.

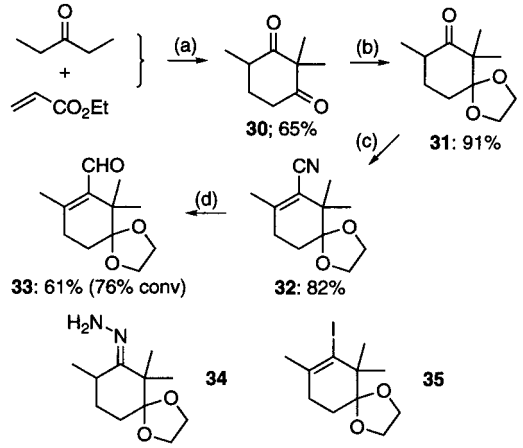
Scheme 4



ketone (entries 12−18), 5-(*p*-methoxybenzyl)oxy-3-methyl-2-pentanone (entries 19 and 20), 4-methyl-1-phenyl-(1*E*)-hexen-5-one (entry 21), and 2-octanone (Scheme 2) exhibited perfect and clear-cut selectivity that the more substituted site plays a role of a Michael donor: the methyl group never did this. However, we found that, for ethyl isopropyl ketone, both sites could serve as the Michael donor to give a mixture of the MC-[3 + 3] product (**25**: 71%) and the regioisomeric Michael product (**26**: 29%) (eq 6). Thus, the ring-closing Claisen reaction suffered from structure limitations: diisopropyl ketone did not afford cyclohexane-1,3-dione derivatives but led only to Michael adduct **27** (40%) under the conditions (eq 7), which was the same trend as the fact that no ring-closing Claisen reaction of **26** took place.

(3) Additional Evidence Supporting the Intrinsic Chemoselectivity of Equilibrating Enolates. When isopropyl methyl ketone (**B**) was treated with *t*-BuOK in THF in the presence of both *tert*-butyl acrylate (**A**) and furfural (**C**: Fu-CHO), five identifiable products [**14**, **28** (**enone-2**), **enone-3**, **dione-2**, and **29** (**dienol**)] were obtained.[12] Aside from **14**, we need a plausible mechanism that can explain the formation of the remaining four products. These results and the mechanism are shown in Scheme 4. Those four products contain an **enone-1**-based segment with them. Interestingly, such a segment

Scheme 5[a]



[a] Key: (a) (1) *t*-BuOK/THF/0.5 h, rt, (2) CH_3I/3 h, 50 °C; (b) $HO(CH_2)_2OH$/THF/TsOH/$HC(OEt)_3$/rt, 12 h; (c) (1) TMSCN/CH_2Cl_2/TMSOTf/rt, 6 h, (2) pyrid/$SOCl_2$/Et_2O/rt, 12 h; (d) DIBAL/CH_2Cl_2/−78 °C, 0.5 h.

was apparently introduced through Michael reaction between the **enone 1** and the *more substituted enolate* generated from **B** followed by intramolecular aldol condensation to give **enone-2** (**28**), which acted as a *more substituted* Michael donor toward **A**, affording **enone-3**. **Dione 2** was apparently provided through self-double Michael addition of **enone-1**. Thus, neither aldol reaction between furfural and *more substituted enolates* nor Michael reaction between **enone-1** or *tert*-butyl acrylate and *less substituted enolates* proceeded at all.

D. Application of the MC-[3 + 3]: (1) A-Ring Segment of Taxol. 2,2,4-Trimethylcyclohexane-1,3-dione (**30**)[6a] is the well-known A-ring segment employed recently in the total synthesis of Taxol by Danishefsky,[13] and his route to **30**[14] was originally reported by Hickmott et al.[15] MC-[3 + 3] between 3-pentanone and ethyl acrylate followed by iodomethane treatment furnished this important intermediate (65% yield) in multigram quantities (Scheme 5). All staff required in this transformation are cheap and safe commercial products, available in bulk quantities, and used as received without any further purification. It also features high yield, operational simplicity, short reaction time, and environmental consciousness in terms of the coproducts of the reaction (*t*-BuOH, EtOH, and KI). When *tert*-butyl acrylate was used in place of ethyl acrylate, the yield of **30** was somewhat improved (71% yield).

To confirm the structure of **30** and also to prepare a novel A-ring synthon (**33**) for taxane diterpenoids,[16] the following transformations were conducted. After the C(1)-carbonyl group of **30** was protected as an acetal (**31**), the remaining carbonyl group was converted to cyanohydrin (TMSCN/TMSOTf)[17] followed by dehydration ($SOCl_2$) to

(11) The regioselectivity of this class has been fragmentary observed; see: (a) Bruson, H. A.; Riener, T. W. *J. Am. Chem. Soc.* **1942**, *64*, 2850−2858. (b) Barkley, L. B.; Levine, R. *Ibid.* **1950**, *72*, 3966−3701. (c) Ross, N. C.; Levine, R. *J. Org. Chem.* **1964**, *29*, 2341−2346.

(12) Treatment of **enone-2** (**28**) with *t*-BuOK in THF afforded tautomeric **dienol** (**29**), which was so stable that it could be isolated by silica gel column chromatography.

(13) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723−1726.

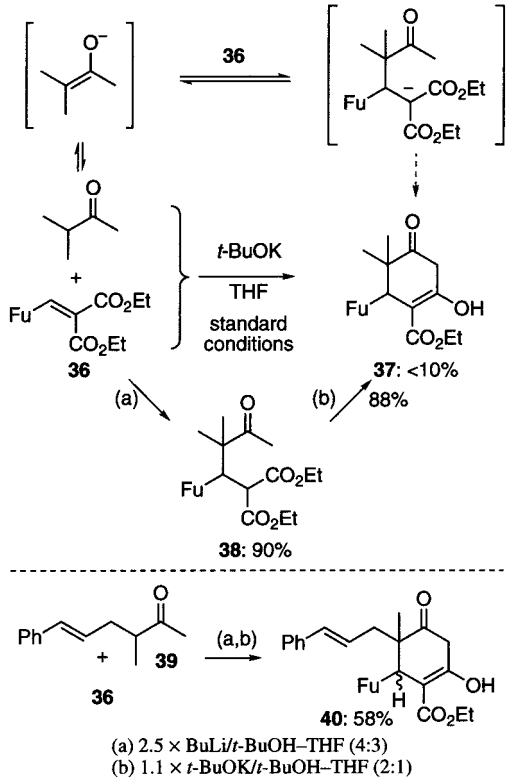
(14) (a) Queneau, Y.; Krol, W. J.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1992**, *57*, 4043−4047. (b) Grandi, M. J. D.; Jung, D. K.; Krol, W. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 4989−4992.

(15) Hargreaves, J. R.; Hickmott, P. W.; Hopkins, B. J. *J. Chem. Soc. C* **1968**, 2599−2603.

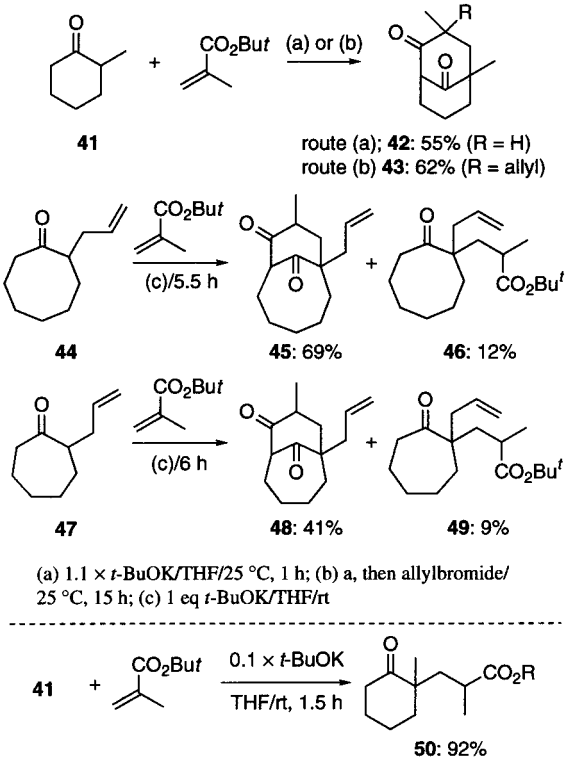
(16) For the synthesis of A-ring synthon of Taxol by means of intramolecular Claisen condensation, see: Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165−3174.

(17) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899−3910.

Scheme 6



Scheme 7



furnish an α,β-unsaturated nitrile (**32**), which was led to enal **33** via DIBALH reduction. The known iodoolefin (**35**) was also prepared via the hydrazone (**34**) by means of the Barton protocol.[18] Spectroscopic data for **33** or **35** involving IR and NMR were fully consistent with the expected structures.

(2) More Complex and Functionalized Cyclohexane-1,3-diones. When isopropyl methyl ketone was reacted with a highly functionalized Michael acceptor such as diethyl furfurylidenemalonate (**36**) under the standard conditions, the desired MC-[3 + 3] product (**37**) was only a minor one (Scheme 6). This is probably because retro-Michael reaction from malonate anion intermediate would be very easy which, in turn, means that the chance of subsequent Claisen cyclization must be scarce. In addition, inevitable moisture involved in the reaction system might serve as a Michael donor to attack **36** leading to furfural and diethyl malonate. Indeed, although **37** was only in <10% yield, unreacted **36** was not recovered at all.

The initial Michael reaction became the acceptable level by employing protic solvent such as dry *t*-BuOH to afford **38** in high yield (90%). In addition, Claisen cyclization of **38** proceeded very efficiently under the protic conditions to afford **37** (88%). It also turned out that such conditions (b in Scheme 6) can be employed to effect the one-pot MC-[3 + 3] between isopropyl methyl ketone and **36** to give **37** in somewhat lower yield (48%). This MC-[3 + 3] under protic conditions was also used for the 4-methyl-1-phenyl-1-hexen-5-one (**39**)[7] and **36** system to afford highly functionalized cyclohexane-1,3-dione derivative **40** (58%).

(3) Bicyclic 1,3-Diones. The present MC-[3 + 3] strategy was applicable to bicyclic systems. For example, the reaction of 2-methylcyclohexanone (**41**) with *tert*-butyl methacrylate led to 1,3-dimethylbicyclo[3.3.1]nonane-4,9-dione (**42**: 55%) under the standard conditions (Scheme 7). Again, Michael addition was effected only between the more substituted enolate and the enoate in marked contrast to eq 6.[19] The final treatment of the reaction with allyl bromide resulted in allylation not at the bridgehead carbon but at the carbon corresponding to the α-carbon of *tert*-butyl methacrylate to furnish **43** (62%). Cyclohexanone itself was not amenable to the MC-[3 + 3]. This was also the case for other cyclic ketones such as cycloheptanone or cyclooctanone, and only α-substituted versions (**44** or **47**) led to the MC-[3 + 3] product **45** (69%) or **48** (41%), respectively. In addition, enoates were requested to bear an α-substituent for the MC-[3 + 3] to be effected under the standard conditions.[20]

Interestingly, the reaction of 2-methylcyclohexanone with *tert*-butyl methacrylate using 10 mol % of *t*-BuOK resulted in only Michael addition to give **50** (92%) in marked contrast to the case of acyclic simple ketone such as isopropyl methyl ketone in which MC-[3 + 3] took place to the extent equal to the amount of the base used (see eq 3). The use of over 10 mol % of the base gave a mixture of **50** and **42**, and the amount of **42** gradually increased with the increase in the amount of the base.

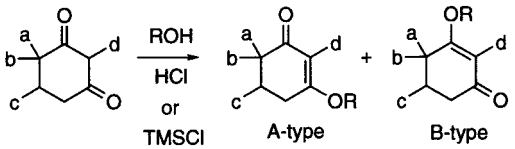
(4) Cyclohexenone Derivatives: Tandem Aldol Condensation, Michael Addition, and Aldol Condensation. We were intrigued with the idea to take advantage of above-mentioned regiochemical features to realize three components coupling process consisted of

(18) Barton, D. H. R.; Bashiardes, G.; Fourrey, J. *Tetrahedron* **1988**, *44*, 147−162.

(19) The reaction between 2-methylcyclohexanone and *tert*-butyl acrylate gave only Michael adducts (61%) as a mixture of regioisomers in a ratio 93:7 (10 mol % of *t*-BuOK in *t*-BuOH); see: House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646−655.

(20) It should be noted that no reaction between 2-methylcyclohexanone and *tert*-butyl methacrylate with 10 mol % of the base in protic solvent such as *t*-BuOH took place; see ref 19.

Table 2. Enol Ether from Cyclohexane-1,3-diones[a]



cyclohexane-1,3-dione	enone yield/% (R)	enone A/B
13, a = d = Me; b = H; c = Ph	86 (Me)	**53/54** = 5.6:1
17, a = b = Me; c = Ph; d = H	92 (Me)	**55/56** = 3:1
18, a = b = Me; c = CO_2Et; d = H	82 (Et)	**57/58** = 3.6:1
19, a = b = Me; c = 1-propenyl; d = H	73 (Me)	**59/60** = 2.8:1
22, a = PhCH=$CHCH_2$; b = Me; c = d = H	78 (Me)	**61/62** = 2.4:1

[a] **A** (0.3 equiv), **B** (1 equiv), **C** (0.3 equiv)/*t*-BuOK (0.62 eq) /*t*-BuOH−THF (1:1), 0 °C rt, 12 h: the yields based on **B**.

Scheme 8

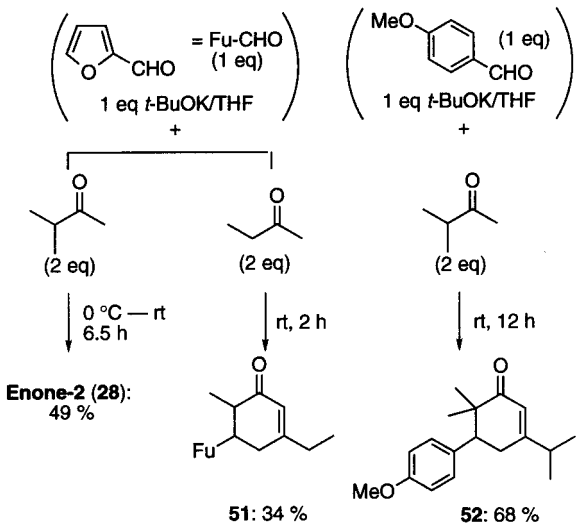
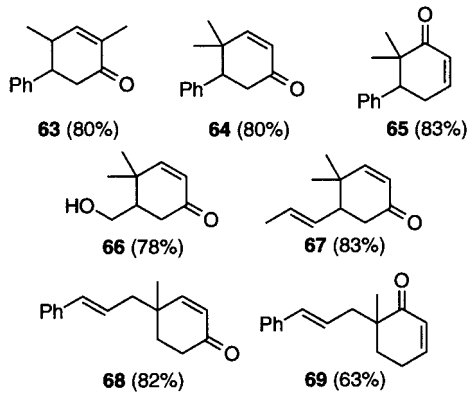


Chart 1



tandem aldol condensation of ketones with aldehydes to give enones, Michael addition of ketone enolates to thus-generated enones furnishing 1,5-diketone frameworks, and final intramolecular aldol condensation of the 1,5-diketones to cyclohexenone derivatives (AMA-[3+1+2]).[21] We have succeeded in realizing the idea by using two parts of a simple ketone, one part of an aromatic aldehyde, and one part of *t*-BuOK which is summarized in Scheme 8. Three of these were uniformly regioselective for carbon−carbon bond formations which occurred three times in this three-component coupling process. Interestingly, the initial one part of the base got involved in generating the enolates three times because it was able to be regenerated. Thus, the AMA-[3 + 1 + 2] process might become a simple, efficient and highly convenient way of synthesizing cyclohexenones bearing aromatic substituent at C(5) such as **enone-2** (**28**), **51**, or **52**.

(5) Convenient Synthesis of Substituted Cyclohexenone Derivatives from Cyclohexane-1,3-diones. The transformation of cyclohexane-1,3-diones to 2-cyclohexen-1-ones is well-known.[22] Thus, we selected several diones such as **13**, **17**−**19**, and **22**, which were converted to enol ethers in a usual way. The observed regioselectivities were summarized in Table 2, which range from 70 to 85% in preference to less hindered carbonyl groups (Table 2, Chart 1).

The kind of alcohol exhibited almost no effect on this regioselection. These enol ethers were readily separated by means of simple silica gel column chromatography. A part of thus-obtained 3-alkoxy-2-cyclohexen-1-ones (**53**, **55**−**57**, **59**, **61**, **62**) led to 2-cyclohexen-1-one derivatives (**63**−**69** in 63−83% yield, Chart 1), respectively, through LAH reduction and acid treatment.

Conclusions

It needs to be economical, safe, environmentally conscious, and resource- and energy-saving for organic synthesis to be practical.[23] As a part of programs to be as close to such ultimate goals as possible, we revisited an already existing but forgotten organic reaction and have succeeded in evaluating its high potential in modern organic synthesis. A system consisting of nonactivated simple ketones, enoates, and *t*-BuOK in THF as a practical method for the synthesis of cyclohexane-1,3-dione derivatives deserves consideration. It requires no skill and no special equipment and leaves behind only environmentally benign coproducts other than the desired products. The clear-cut, fabulous reactivity trend observed for the thermodynamically equilibrating enolates generated from simple aliphatic ketones should be the main thrust of the revisiting chemistry and be taken up as synthetic strategy in myriad aspects.

(21) For review of aldol condensation, see: Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, Chapter 1.5.

(22) (a) Gannon, W. F.; House, H. O. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 294−296 and 539−544. (b) Stork, G.; Danheiser. R. L. *J. Org. Chem.* **1973**, *38*, 1775−1776.

(23) For example, see: Sato, K.; Aoki, M.; Noyori, R. *Science* **1998**, *281*, 1646−1647.

Experimental Section

General Methods. For general remarks, see ref 24.

Materials. Unless otherwise noted, materials were obtained from commercial suppliers, and reagent-grade materials were used without further purification. Toluene, triethylamine (Et_3N), dichloromethane (CH_2Cl_2), acetonitrile, and benzene were freshly distilled from CaH_2 prior to use. Methanol (MeOH) and ethanol (EtOH) were distilled from magnesium turnings under argon. *tert*-Butyl alcohol (*t*-BuOH) was dried over 4 Å molecular sieve prior to use. Tetrahydrofuran (THF) purchased from Kanto Chemical Co., Inc. was dehydrated and stabilizer-free grade and used as received.

4-Pentyl-1,3-cyclohexanedione (2). To a solution of 2-octanone (1.50 g, 11.6 mmol) in THF (10 mL) was added *t*-BuOK (1.24 g, 10.7 mmol) at room temperature, and the mixture was stirred at 0 °C for 5 min. To the mixture was introduced ethyl acrylate (0.92 g, 9.2 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 20 min and the reaction quenched with a saturated aqueous solution of NH_4Cl (5 mL) followed by the addition of anhydrous $MgSO_4$. The organic solutions were concentrated to give an oil, which, on CC (1:1 hexane/AcOEt), afforded dione **2** (1.48 g, 88%) as a colorless solid: mp 62−64 °C; ^{1}H NMR for keto form δ 0.89 (t, 3H, J = 6.6 Hz), 1.22−1.43 (m, 8H) 1.52−1.66 (m, 2H), 1.75−1.92 (m, 2H), 2.16 (dq, 2H, J = 5.1, 14.0 Hz), 2.41−2.51 (m, 1H), 2.59 (dd, 1H, J = 5.5, 11.5 Hz) 2.70 (dt, 1H, J = 4.7, 16.2 Hz) 3.42 (s, 2H); IR (film) 1730, 2980 cm^{-1}; ^{13}C NMR signals for this compound were difficult to assign because of indistinguishable signals due to keto−enol tautomers.

Control Experiments: Reaction of Isopropyl Methyl Ketone with *tert*-Butyl Acrylate in the Presence of Furfural. To a solution of isopropyl methyl ketone (0.72 mL, 6.7 mmol), *tert*-butyl acrylate (0.3 mL, 2.0 mmol), and furfural (0.17 mL, 2.0 mmol) in THF (5 mL)−*t*-BuOH (5 mL) mixed solvent was slowly added *t*-BuOK (470 mg, 4.2 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h and quenched with a saturated aqueous solution of NH_4Cl (5 mL) followed by the addition of anhydrous $MgSO_4$. The organic solutions were concentrated to give a crude oil, which was purified by CC (10:1−1:1 hexane/AcOEt) to give **enone-2** (**28**) (0.32 mmol, 10%), **dione-2** (0.173 mmol, 5.4%), **dienol** (**29**) (0.21 mmol, 6.2%), **enone-3** (0.91 mmol, 27%), and **14** (1.12 mmol, 17%): the yields were based on the ketone.

Enone-2 (**28**) was identified by comparing its NMR spectra with those of an authentic sample prepared as described below.

5-(2-Furyl)-3-isopropyl-6,6-dimethyl-2-cyclohexen-1-one (Enone-2: 28). To a solution of 3-methyl-2-butanone (2.59 mL, 24.2 mmol) in THF (50 mL) was added *t*-BuOK (1.40 g, 12.5 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 min. To the solution was added furfural (1.00 mL, 12.1 mmol) dropwise at 0 °C, and the mixture was stirred at room temperature for 6.5 h. The reaction was quenched by adding saturated aqueous solution of NH_4Cl and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a crude oil, which was purified by CC (10:1 hexane/AcOEt) to give **28** (1.39 g, 49%) as a colorless oil: ^{1}H NMR δ 1.00 (s, 3H), 1.08 (s, 3H), 1.12 (dd, 6H, J = 1.4, 6.9 Hz), 2.35−2.50 (m, 2H), 2.73 (dq, 1H, J = 2.2, 10.7 Hz), 3.17 (dd, 1H, J = 4.7, 10.4 Hz), 5.87 (t, 1H, J = 1.1 Hz), 6.09 (dd, 1H, J = 0.8, 3.3 Hz), 6.31 (dd, 1H, J = 1.9, 3.3 Hz), 7.32 (dd, 1H, J = 0.8, 1.9 Hz); ^{13}C NMR δ 20.0, 20.5, 20.8, 30.0, 35.4, 44.3, 44.7, 106.9, 110.0, 121.9, 141.1, 155.2, 168.0, 204.2; IR (film) 1670 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.79.

3,5-Di(2-furyl)-4-isobutyryl-2,2-dimethylcyclohexan-1-one (dione-2): ^{1}H NMR δ 0.92 (d, 3H, J = 6.9 Hz), 0.96 (d, 3H, J = 6.9 Hz), 0.91 (s, 3H), 1.13 (s, 3H), 2.72 (dd, 1H, J = 6.0, 14.8 Hz), 2.72−2.82 (m, 1H), 3.06 (dd, 1H, J = 6.0, 14.8 Hz), 3.51 (d, 1H, J = 11.8 Hz), 3.88 (dt, 1H, J = 4.7, 6.0 Hz), 4.00 (dd, 1H, J = 4.7, 11.8 Hz), 5.95 (d, 1H, J = 3.7 Hz), 6.01 (d, 1H, J = 4.3 Hz), 6.22−6.28 (m, 2H), 7.24−7.27 (m, 2H); ^{13}C NMR δ 17.1, 18.4, 22.7, 27.3, 35.4, 40.2, 41.0, 47.8, 49.5, 50.3, 106.3, 108.6, 109.8, 110.3, 141.0, 142.1, 152.0, 155.0; IR (film) 1742 cm^{-1}. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.02; H, 7.49.

5-Furyl-3-isopropylidene-6,6-dimethyl-1-cyclohexen-1-ol (dienol 29): ^{1}H NMR δ 1.06 (s, 3H), 1.14 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 2.54 (dd, 1H, J = 4.7, 18.7 Hz), 2.79 (dd, 1H, J = 10.2, 18.7 Hz), 3.16 (dd, 1H, J = 4.7, 10.2, Hz), 4.00−4.01 (b, 1H), 6.12 (d, 1H, J = 3.1 Hz), 6.33 (dd, 1H, J = 1.9, 3.1 Hz), 6.75 (s, 1H), 7.34 (m, 1H); ^{13}C NMR δ 20.0, 23.1, 27.2, 27.6, 28.1, 43.7, 43.8, 73.0, 107.3, 110.1, 135.2, 140.0, 141.4, 154.5, 199.5; IR (film) 3395 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.42; H, 8.81.

4-(5-Furyl-4,4-dimethyl-3-oxo-1-cyclohexenyl)-4-methylpentanoic Acid (Enone-3). Enone-3 was obtained not as *tert*-butyl ester but as a free carboxylic acid: ^{1}H NMR δ 1.00 (s, 3H), 1.08 (s, 3H), 1.14 (s, 6H), 1.77−1.83 (m, 2H), 2.14−2.19 (m, 2H), 2.54 (dd, 1H,J = 5.0, 18.4 Hz), 2.67 (ddd, 1H, J = 1.7, 9.9, 18.4 Hz), 3.14 (dd, 1H, J = 5.0, 9.9 Hz), 5.93 (d, 1H, J = 1.7 Hz), 6.09 (d, 1H, J = 3.0 Hz), 6.31 (dd, 1H, J = 1.9, 3.0 Hz), 7.31−7.33 (m, 1H); ^{13}C NMR δ 19.9, 23.1, 26.2, 26.3, 28.1, 29.7, 34.9, 39.3, 44.4, 44.5, 107.1, 110.0, 123.5, 141.2, 154.9, 166.8, 178.9, 204.2; IR (film) 3650−2400 (very broad with shoulders at 3450, 3150, and 2700), 1709, 1664 cm^{-1}.

2,2,4-Trimethylcyclohexane-1,3-dione (30). To a solution of 3-pentanone (30.0 g, 348 mmol) in THF (500 mL) was added *t*-BuOK (45.9 g, 409 mmol) at room temperature, and the mixture was stirred at 0 °C for 10 min. To the mixture was added ethyl acrylate (34.1 g, 341 mmol) dropwise at 0 °C, and the reaction was stirred at room temperature for 20 min followed by the addition of iodomethane (142 g, 1.0 mol). The mixture was warmed to 50 °C and stirred for 3 h. The reaction was quenched by the addition of water and extracted with AcOEt. The combined organic layers were dried with Na_2SO_4 and concentrated to give a crude oil, which was purified by CC (5:1 hexane/AcOEt) to afford dione **30** (34.0 g, 65%) as a colorless oil: ^{1}H NMR δ 1.10 (d, 3H, J = 6.6 Hz), 1.18 (s, 3H), 1.32 (s, 3H), 1.42 (dq, 1H, J = 4.9, 13.4 Hz), 2.02−2.12 (m, 1H), 2.57 (ddd, 1H, J = 3.0, 4.9, 15.9 Hz), 2.70−2.88 (m, 2H); ^{13}C NMR δ 14.7, 18.8, 25.9, 26.3, 37.1, 40.6, 61.0, 210.6, 211.3; IR (film) 1730 cm^{-1}.

3,3-(Ethylenedioxy)-2,2,6-trimethyl-1-cyclohexanone (31). To a solution of **30** (1.23 g, 7.97 mmol) in THF (15 mL) were added ethylene glycol (0.67 mL, 12.0 mmol), *p*-toluenesulfonic acid monohydrate (150 mg, 0.80 mmol), and triethyl orthoformate (1.60 mL, 9.56 mmol) at room temperature. The mixture was stirred at room temperature for 8 h. The reaction was quenched by the addition of Et_3N (0.22 mL, 1.59 mmol). The solution was concentrated to afford a crude oil, which was purified by CC (20:1 hexane/AcOEt) to give **31** (1.43 g, 91%) as a colorless oil: ^{1}H NMR δ 0.98 (d, 3H, J = 6.6 Hz), 0.98 (s, 3H), 1.22 (s, 3H), 1.35 (dq, 1H, J = 4.1, 13.2 Hz), 1.71 (ddd, 1H, J = 2.6, 4.3, 13.5 Hz), 1.78−1.87 (m, 1H), 2.03−2.2.15 (m, 1H), 2.55−2.70 (m, 1H), 3.80−4.00 (m, 4H); ^{13}C NMR δ 14.6, 16.4, 24.0, 28.1, 30.0, 39.0, 54.6, 65.2, 65.3, 113.5, 213.5; IR (film) 1709 cm^{-1}; exact mass m/z 198.1243 (calcd for $C_{11}H_{18}O_3$ m/z 198.1255). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.55; H, 9.33.

5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenecarbonitrile (32). To a solution of **31** (1.07 g, 5.41 mmol) and trimethylsilyl cyanide (2.72 mL, 21.6 mmol) in CH_2Cl_2 (15 mL) was added trimethylsilyl trifluoromethanesulfonate (0.12 mL, 0.54 mmol) at room temperature. The mixture was stirred at room temperature for 6 h, quenched by the addition of water, and extracted with AcOEt−hexane (1:1) mixed solvent. The combined extracts were dried with Na_2SO_4 and concentrated to give an oil, which, on CC, gave a cyanohydrin as a colorless oil (1.03 g, 85%). To a solution of the cyanohydrin (241 mg, 1.07 mmol) and pyridine (0.86 mL, 10.7 mmol) in ether (3 mL) was added thionyl chloride (0.38 mL, 5.35 mol) at room temperature. The mixture was stirred at room temperature for 8 h, quenched by the addition of water, and extracted with AcOEt−hexane (1:1) mixed solvent. The combined extracts were dried with Na_2SO_4 and concentrated to

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give an oil, which was purified by CC (10:1 hexane/AcOEt) to give **32** (215 mg, 97%) as a colorless oil: ^{1}H NMR δ 1.18 (s, 6H), 1.77 (t, 2H, J = 6.6 Hz), 1.90 (t, 3H, J = 0.6 Hz), 2.30 (dt, 2H, J = 0.6, 6.6 Hz), 3.96−3.99 (m, 4H); ^{13}C NMR δ 22.5, 23.0, 26.1, 30.5, 40.7, 64.9, 109.7, 115.9, 116.9, 151.0; IR (film) 2211 cm^{-1}; exact mass m/z 207.1263 (calcd for $C_{12}H_{17}NO_2$ m/z 207.1259). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27. Found: C, 69.67; H, 8.31.

5,5-(Ethylenedioxy)-2,6,6-trimethyl-1-cyclohexenecarbaldehyde (33). To a solution of **32** (1.85 g, 8.94 mmol) in CH_2Cl_2 (20 mL) precooled at −78 °C was added dropwise DIBAL-H (13.4 mL, 1.34 mmol) over 30 min, and the mixture was stirred at 0 °C for an additional 30 min. The reaction was quenched by the addition of water and filtered through a Celite pad, the filter cake being thoroughly rinsed with ethyl acetate. The combined organic solutions were dried with Na_2SO_4 and concentrated to give an oil, which was purified by CC (5:1 hexane/AcOEt) to afford **33** (873 mg, 46%) as a colorless oil and recovered **32** (437 mg, 24%): ^{1}H NMR δ 1.26 (s, 6H), 1.80 (dt, 2H, J = 4.1, 6.8 Hz), 2.00 (s, 3H), 2.40 (t, 2H, J = 6.6 Hz), 3.97−4.00 (m, 4H), 10.08 (s, 1H); ^{13}C NMR δ 18.9, 21.8, 26.2, 33.6, 41.4, 65.7, 111.5, 139.3, 153.9, 192.0; IR (film) 1726 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.39; H, 8.72.

[3,3-(Ethylenedioxy)-2,2,6-trimethylcyclohexylidene]-hydrazine (34) and 4,4-(Ethylenedioxy)-2-iodo-1,3,3-trimethyl-1-cyclohexene (35). These compounds were prepared after the reported procedure by Danishefsky et al. (ref 14b).

Diethyl 2-[1-(2-Furyl)-2,2-dimethyl-3-oxobutyl]malonate (38). To a solution of *t*-BuOH (10 mL) in THF (10 mL) was added butyllithium in hexane (3.75 mL, 5.63 mmol) at 0 °C followed by the addition of isopropyl methyl ketone (0.72 mL, 6.75 mmol). To the mixture was added a solution of diethyl furfurylidenemalonate **36** (536 mg, 2.25 mmol) in THF (2 mL), and stirring was continued at 0 °C for 5 min. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated to afforded a crude oil, which was purified by CC (3:1 hexane/AcOEt) to give **38** (657 mg, 90%) as a colorless oil. ^{1}H NMR δ 1.20 (t, 3H, J = 7.1 Hz), 1.20 (s, 3H), 1.33 (s, 3H), 2.73 (ddd, 1H, J = 1.4, 2.8, 16.2 Hz), 2.81 (dd, 1H, J = 2.8, 5.5, Hz), 2.90 (dd, 1H, J = 5.5, 16.2 Hz), 3.45 (m, 2H), 4.11 (dq, 2H, J = 2.2, 7.1 Hz); ^{13}C NMR δ 13.9, 21.6, 24.3, 39.7, 45.9, 49.2, 53.8, 61.6, 172.8, 202.3, 205.8; IR (film) 2981, 1732 cm^{-1}.

Ethyl [6-(2-Furyl)-2-hydroxy-5,5-dimethyl-4-oxo-1-cyclohexene]carboxylate (37). To a solution of **38** (160 mg, 0.50 mmol) in *t*-BuOH (5 mL) and THF (5 mL) was added *t*-BuOK (160 mg, 1.50 mmol) at 0 °C. The mixture was stirred at room temperature for 1.5 h and quenched with 6 N HCl (0.25 mL) followed by the addition of anhydrous $MgSO_4$. The organic solutions were concentrated to give a crude oil, which was purified by CC (1:1 hexane/AcOEt) to afford **37** (121 mg, 88%) as a colorless oil: ^{1}H NMR δ 0.89 (s, 3H), 1.24 (s, 3H), 1.26 (t, 3H, J = 7.1 Hz), 3.26 and 3.38 (ABq, 2H, J = 22.4 Hz), 4.11−4.28 (m, 2H), 5.95 (d, 1H, J = 3.0 Hz), 6.17 (dd, 1H, J = 1.8, 3.0, Hz), 7.17 (d, 1H, J = 1.8 Hz), 12.25 (s, 1H); ^{13}C NMR δ 14.1, 21.0, 25.7, 40.7, 44.5, 48.0, 60.9, 99.0, 106.6, 109.9, 141.5, 154.4, 168.4, 171.1, 208.4; IR (film) 1724, 1656 cm^{-1}; exact mass, m/z 278.1167 (calcd for $C_{15}H_{18}O_5$ m/z 278.1154). Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.74; H, 6.52. Found: C, 64.61; H, 6.82.

3,5-Dimethylbicyclo[3.3.1]nonane-2,9-dione (42) and *tert*-Butyl 3-(1-Methyl-2-oxocyclohexyl)-2-methylpropanoate (50). To a solution of 2-methylcyclohexanone (1.00 mL, 7.96 mmol) in THF (20 mL) was added *t*-BuOK (921 mg, 8.21 mmol) at room temperature, and the mixture was stirred at 0 °C for 5 min. To the mixture was added *tert*-butyl methacrylate (1.29 mL, 7.96 mmol) dropwise at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl, and the resulting mixture was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a crude oil, which was purified by CC (20:1 hexane/AcOEt) to give **42** (588 mg, 41%) and **50** (506 mg, 25%) as a colorless oil for each. Data for **42**: ^{1}H NMR δ 1.07 (d, 3H, J = 6.3 Hz), 1.17 (s, 3H), 1.37−1.93 (m, 7H), 2.19−2.32 (m, 1H), 2.42−2.51 (m, 1H), 3.00 (t, 1H, J = 3.9 Hz); ^{13}C NMR δ 13.0, 19.3, 24.3, 34.9, 38.3, 44.4, 44.8, 46.6, 60.9, 211.3, 213.3; IR (film) 1705 cm^{-1}; exact mass m/z 180.1144 (calcd for $C_{11}H_{16}O_2$ m/z 180.1150). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.41; H, 8.86. Data for **50**: ^{1}H NMR δ 1.05 (s, 3H), 1.13 (d, 3H, J = 6.6 Hz), 1.40−1.90 (m, 17H), 2.23−2.41 (m, 2H), 2.51−2.63 (m, 1H); ^{13}C NMR δ 20.8, 21.6, 23.0, 27.7, 36.4, 38.4, 39.9, 40.7, 41.0, 48.6, 79.7, 176.4, 215.3; IR (film) 1735, 1710 cm^{-1}.

3-Allyl-3,5-dimethylbicyclo[3.3.1]nonane-2,9-dione (43). To a solution of 2-methylcyclohexanone (1.00 mL, 7.96 mmol) in THF (20 mL) was added *t*-BuOK (983 mg, 8.76 mmol) at room temperature. The mixture was stirred at 0 °C for 5 min. To the mixture was added *tert*-butyl methacrylate (1.29 mL, 7.96 mmol) dropwise at 0 °C, and stirring was continued at room temperature for 1 h followed by the addition of allyl bromide (2.00 mL, 23.9 mmol). The mixture was stirred at room temperature for 15 h followed by the addition of water. The resulting mixture was extracted with AcOEt, and the combined organic layers were dried over $MgSO_4$ and concentrated to afford a crude oil, which was purified by CC (10:1 hexane/AcOEt) to give **43** (1.08 g, 62%) as a colorless oil: ^{1}H NMR δ 1.10 (s, 3H), 1.18 (s, 3H), 1.39−2.10 (m, 9H), 2.43−2.52 (m, 1H), 3.00 (t, 1H, J = 4.0 Hz), 4.95−5.07 (m, 2H), 5.52 (ddt, 1H, J = 7.4, 10.2, 16.8 Hz); ^{13}C NMR δ 19.3, 20.6, 25.0, 36.7, 41.4, 44.0, 45.9, 46.1, 50.1, 59.8, 119.3, 131.7, 213.2, 214.8; IR (film) 1712 cm^{-1}. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.21; H, 9.31.

1-Allyl-9-methylbicyclo[5.3.1]undecane-8,11-dione (45) and *tert*-Butyl 3-(1-Allyl-2-oxocyclooctyl)-2-methylpropanoate (46). To a solution of 2-allylcyclooctanone **44** (548 mg, 3.30 mmol) in THF (15 mL) was added *t*-BuOK (382 mg, 3.40 mmol) at room temperature. The mixture was stirred at 0 °C for 5 min. To the mixture was added *tert*-butyl methacrylate (0.53 mL, 3.30 mmol) dropwise at 0 °C, and the mixture was stirred at room temperature for 5.5 h. The reaction was quenched by adding saturated aqueous solution of NH_4Cl and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a crude oil, which was purified by CC (20:1 hexane/AcOEt) to give **45** (529 mg, 69%) and **46** (123 mg, 12%) as a colorless oil, respectively. Data for **45**: ^{1}H NMR δ 1.14 (d, 3H, J = 6.6 Hz), 1.31−1.75 (m, 9H), 1.87−2.13 (m, 3H), 2.26−2.53 (m, 2H), 2.93−3.07 (m, 1H), 3.19 (t, 1H, J = 8.5 Hz), 5.02−5.14 (m, 2H), 5.66−5.84 (m, 1H); ^{13}C NMR δ 16.0, 22.4, 23.1, 28.6, 31.9, 32.4, 37.6, 38.8, 40.6, 50.3, 62.1, 118.8, 133.8, 210.3, 212.8; IR (film) 1715 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.71; H, 9.57. Data for **46**: ^{1}H NMR δ 1.08 (d, 3H, J = 6.9 Hz), 1.27−1.87 (m, 19H), 2.01−2.22 (m, 4H), 2.27−2.38 (m, 1H), 2.54 (dd, 1H, J = 8.5, 15.1 Hz), 2.72 (dt, 1H, J = 3.3, 11.5 Hz), 5.04 (m, 2H), 5.60−5.74 (m, 1H); ^{13}C NMR δ 20.4, 24.4, 24.8, 26.0, 27.9, 30.4, 31.4, 34.0, 35.6, 37.5, 52.7, 80.3, 118.0, 134.1, 175.8, 219.6; IR (film) 1727, 1697 cm^{-1}.

3-Ethoxy-5-(ethoxycarbonyl)-6,6-dimethyl-2-cyclohexen-1-one (57) and 3-Ethoxy-5-(ethoxycarbonyl)-4,4-dimethyl-2-cyclohexen-1-one (58). To a solution of **18** (294 mg, 1.39 mmol) in EtOH (7 mL) was added chlorotrimethylsilane (0.3 mL, 1.6 equiv) at room temperature. The mixture was stirred at room temperature for 4 h, quenched by the addition of Et_3N (0.35 mL), and concentrated to give a crude residue, which was subjected to CC (10:1 hexane/AcOEt) to afford **57** (213 mg, 64%) and **58** (60 mg, 18%) as a colorless oil for each. Data for **57**: ^{1}H NMR δ 1.10 (s, 3H), 1.18 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.33 (t, 3H, J = 7.1 Hz), 2.42−2.53 (m, 1H), 2.75−2.86 (m, 2H), 3.88 (q, 2H, J = 7.1 Hz), 4.05−4.22 (m, 2H), 5.25 (s, 1H); ^{13}C NMR δ 14.1, 14.2, 20.5, 23.5, 29.1, 42.5, 48.8, 60.6, 64.3, 100.4, 172.1, 173.1, 201.8; IR (film) 1615 cm^{-1}. Data for **58**: ^{1}H NMR δ 1.20 (s, 3H), 1.24 (t, 3H, J = 7.1 Hz), 1.29 (s, 1H), 1.34 (t, 3H, J = 7.1 Hz), 2.48 (dd, 1H, J = 4.7, 17.3 Hz), 2.69 (dd, 1H, J = 11.1, 17.3 Hz), 2.87 (dd, 1H, J = 4.7, 11.1 Hz), 3.82−3.90 (m, 2H), 4.08−4.19 (m, 2H), 5.25 (s, 1H); ^{13}C NMR δ 13.9, 14.1, 21.5, 25.0, 36.3, 38.2, 49.5, 60.7, 74.7, 100.9, 172.0, 181.0, 196.6; IR (film) 1615 cm^{-1}.

4,4-Dimethyl-5-phenyl-2-cyclohexen-1-one (64). To a suspension of $LiAlH_4$ (49.4 mg, 1.3 mmol) in THF (5 mL) was added a solution of **55** (1.00 g) in THF (10 mL) at 0 °C. The mixture was stirred at 0 °C to room temperature for 12 h. The reaction was quenched by the addition of water and filtered through a Celite pad, the pad being rinsed with AcOEt. The combined organic solutions were concentrated to give a crude solid, which was subjected to the next reaction without further purification. This solid was dissolved in MeOH (10 mL), and to this mixture was added *p*-toluenesulfonic acid monohydrate (165 mg, 0.87 mmol) at room temperature. The resulting mixture was stirred at room temperature for 2 h and quenched by the addition of Et_3N (0.15 mL, 1.09 mmol). The resulting mixture was concentrated to give a crude oil, which was purified by CC (15:1 hexane/AcOEt) to afford **64** (0.70 g, 80%) as a colorless oil: ^{1}H NMR δ 0.98 (s, 3H), 1.08 (s, 3H), 2.51 (ddd, 1H, J = 1.1, 3.6, 16.7 Hz), 2.96 (dd, 1H, J = 14.3, 16.7 Hz), 3.20 (dd, 1H, J = 3.6, 14.3 Hz), 5.96 (dd, 1H, J = 1.1, 9.9 Hz), 6.75 (d, 1H, J = 9.9 Hz), 7.16−7.38 (m, 5H); ^{13}C NMR δ 20.8, 28.1, 37.1, 40.0, 50.0, 126.3, 127.0, 128.0, 129.1, 139.9, 160.6, 200.1; IR (film) 2960, 1683 cm^{-1}. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.79; H, 8.21.

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Supporting Information Available: Copies of ^{1}H and/or ^{13}C NMR spectra for compounds **enone-2** (**28**), **dione-2**, **enone-3**, **dienol** (**29**), **32**, **33**, **37**, **40**, **42**, **43**, **52**, **55**, **56**, **64**, and **65** and spectral data for compounds **4**−**12**, **14**−**22**, **40**, **48**, **49**, **51**−**56**, **59**, **60**−**63**, and **65**−**69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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