Pergamon

Tetrahedron 54 (1998) 2411–2422

TETRAHEDRON

Novel Synthesis of Ynolates via the Cleavage of Ester Dianions: α-Bromo and α,α-Dibromo Esters as Precursors

Mitsuru Shindo,* Yusuke Sato, Kozo Shishido

Institute for Medicinal Resources, University of Tokushima

Sho-machi 1, Tokushima 770, Japan

Received 25 November 1997; accepted 24 December 1997

Abstract: Ynolates have been synthesized via the thermally-induced cleavage of ester dianions. The key intermediates, ester dianions, were generated from α-bromocarboxylic acid ester enolates via lithium halogen exchange. α,α-Dibromocarboxylic acid ester also gives lithium amide free ynolates by addition of *tert*-BuLi. The reactions of ynolates, generated by this novel and convenient method, with aldehydes to give β-lactons are discussed.

INTRODUCTION

Over the years there have been a large number of reports on carbanion chemistry.[1] Enolates are the most important carbanions and are well-established and widely used. Ynolates having a triple bond in place of a double bond in enolates are a similar kind of carbanion and their chemistry should be no less interesting than that of enolates. Heretofore, several reports on the ynolate chemistry have been published. In 1975 Schöllkopf and Hoppe succeeded in the generation for the first time of lithium phenylethynolates via extrusion of benzonitrile from 5-lithio-3,4-diphenylisoxazole.[2] Since then, ynolates have been generated by Rathke via deprotonation of silylketenes,[3] by Kowalski via rearrangement of α-ketodianions,[4] by Stang via treatment of alkynyl tosylates with methyllithium,[5] by Julia via oxidation of lithium acetylides,[6] and by Murai via the reaction of lithiosilyldiazomethane with carbon monoxide.[7] It has been reported that ynolates react with aldehydes and ketones to afford β-lactones, with imines to afford β-lactams,[8] with a reductant to afford aldehyde enolates,[9] with epoxides to afford γ-lactones.[7] However, ynolates have received little attention from a synthetic point of view, since these methods for generation of ynolates have some limitations (e.g., limited substrates, multiple operations, accompanied side products, etc.) and have not been established well as general methodology. Therefore, the reactivity of ynolates has not been thoroughly examined. In view of the extremely useful properties of ynolates, development of a more conventional synthetic approach to these species is highly desirable.

lithium ynolate lithiated ketenes

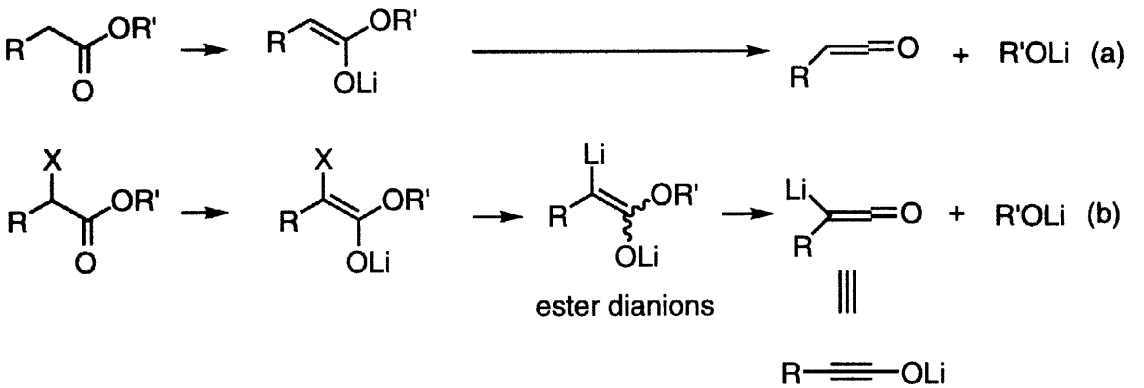
Recently, we reported a new and convenient method for the generation of lithium ynolates via the cleavage of ester dianions prepared from readily available α-bromoesters.[10] Herein we describe the experimental details and an improved and more convenient preparation of lithium ynolates using α,α-dibromoesters as a precursor, along with some results of reactions of ynolates with aldehydes.

0040-4020/98/$19.00
PII: S0040-4020(98)00006-4

RESULTS AND DISCUSSION

The Concept of Ynolate Synthesis

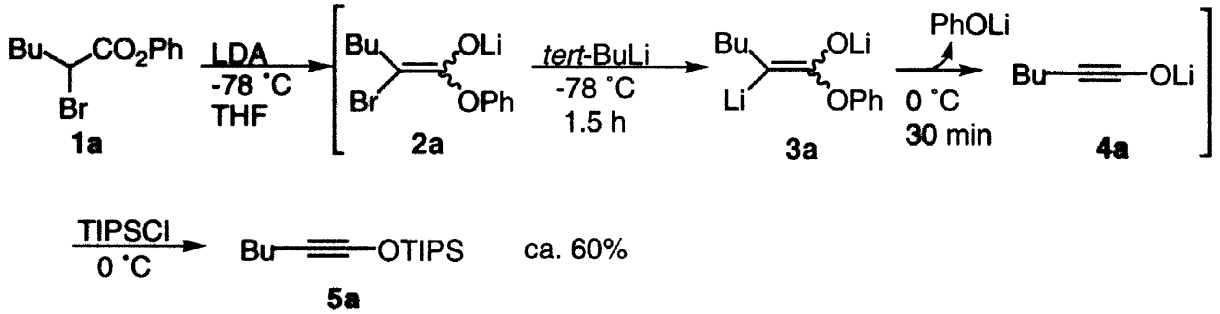
Lithium ynolates are equivalent with lithiated ketenes. Thus, lithium ynolates would be formed via lithiation of ketenes at the vinyl position. Ketenes are unstable and sensitive toward a nucleophile, so that the direct lithiation of ketenes would not be practical. Lithiation of the precursors of ketenes, followed by transformation into lithiated ketenes (ynolates), should be employed. The thermally-induced cleavage of lithium ester enolates has been reported to provide the corresponding ketenes and lithium alkoxides (Scheme 1a).[11] On the basis of these facts, if ester dianions, where ester enolates are lithiated at the vinylic position, can be generated they would provide lithiated ketenes (ynolates) via the thermally induced cleavage (Scheme 1b). Also, alkoxy vinyllithiums, which can be considered to constitute the ester dianions, have been known to be transformed into acetylene via β-elimination.[12] Therefore, the ester dianions, which have not been reported so far to the best of our knowledge, would be the key intermediates in the course of this process. They would be generated via lithium-halogen exchange from the easily available α-bromocarboxylic acid ester enolates and alkyllithium.



Scheme 1

Ynolates from α-Bromoesters (Method A)

At first we chose a phenyl ester of α-bromocaproic acid (**1a**) as the starting material, expecting the phenoxide to be a relatively good leaving group among the alkoxides. Based on the concept described above, **1a** was treated with LDA in THF at -78 °C to form the corresponding enolate (**2a**), followed by addition of *tert*-BuLi (3.2 eq.). After the mixture was stirred at -78 °C for 1.5~3 h to undergo lithium-halogen exchange, that is, dianion (**3a**) formation along with decomposition of *tert*-BuBr and regeneration of LDA, and then at 0 °C for 30 min to eliminate lithium phenoxide, it was treated with excess amount of triisopropylsilyl chloride (TIPSCl) to trap ynolate. Usual workup, followed by bulb-to-bulb distillation, afforded TIPS ynol ether (**5a**),[13] in ca. 60% yield together with a minor amount of by-products. Although **5a** could not be further purified because of its sensitivity towards silica gel, this successful result encouraged us.



Scheme 2

Aldehydes have been known to react with ynolates at -78 °C, followed by protonation, to give β-lactones.[2,4a] In order to trap ynolates efficiently as stable products which can be easily purified for subsequent studies, we selected benzaldehyde as a reactive electrophile for ynolates to examine the generality of this new synthetic approach. Excess benzaldehyde (4 eq.) was added to the ynolate solution at -78 °C to trap ynolates completely. As shown in Table 1, phenyl esters (**1a** and **1d**) were transformed into 3,3,4-trisubstituted β-lactones (**6**, **7**) in good yields (entry 1, 4). A phenylthio ester (**1b**) also gave **6** in good yield (entry 2). It is noteworthy that not only phenyl and phenylthio esters but also ethyl esters gave **6** and **7** in good yields (entry 3, 5), although ethoxide is poorer leaving group than phenoxide and thiophenoxide. Therefore an ethoxide proved to be good enough as a leaving group in this reaction. The ynolate possessing a secondary alkyl substituent was also generated efficiently and gave **8** in 85% yield (entry 6). Phenyl α-bromophenylacetate (**1g**), however, did not give β-lactone (**9**) and a complex mixture (entry 7) was obtained, since carbenes might be formed via α-elimination at the benzylic position.

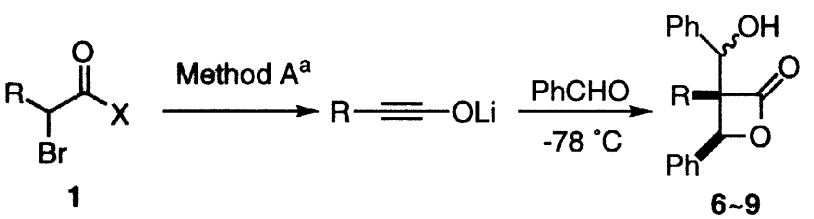


Table 1. Trapping of Ynolates with Benzaldehyde to Form β-Lactones.

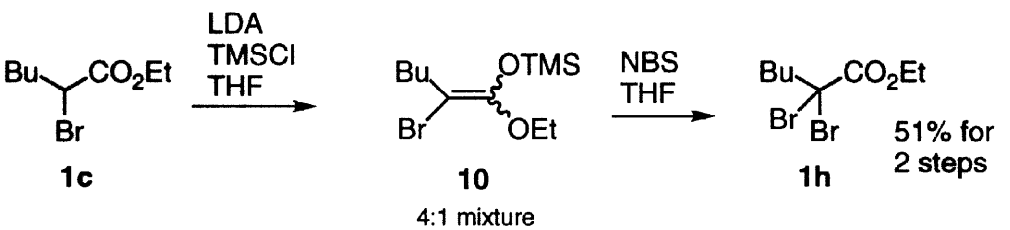
Entry	1			β-Lactone	
		R	X		yield (%)
1	**1a**	Bu	OPh	**6**	69[b]
2	**1b**	Bu	SPh	**6**	74[b]
3	**1c**	Bu	OEt	**6**	88[b]
4	**1d**	Me	OPh	**7**	81[b]
5	**1e**	Me	OEt	**7**	69[b]
6	**1f**	cyclohexyl	OEt	**8**	85[c]
7	**1g**	Ph	OPh	**9**	0

a) Method A: LDA (1 eq); *tert*-BuLi (3 eq) -78° for 1.5~3 h then 0°. See experimental section. b) Mixture of diastereomers (~1 : 1). c) Mixture of diastereomers (**8a**:**8b**:**8c** = 1 : 1 : 0.5).

Ynolates from α,α-Dibromoesters (Method B): An Improved Method

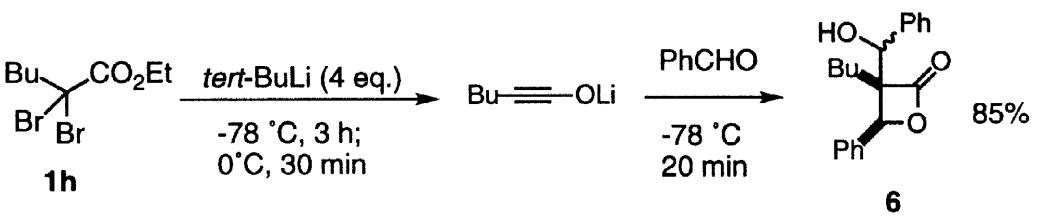
In the original Method A, the ynolate solution contains LDA, which may induce side reactions, e.g., enolization of carbonyl groups in the electrophiles. The presence of other lithium species results not always in such unfavorable effects because they could change the aggregation states and, in some cases, increase the reactivity of ynolates.[14] However, in order to evaluate the reactivity of ynolates in the absence of lithium amides and to avoid side reactions, a more simple reaction system is desirable. This problem could be solved by using a precursor that can be transformed into a lithium bromoenolate without a lithium amide. Trimethylsilyl ketene acetals (e.g., **10**) might serve as the precursors for this purpose, but they are too unstable to be purified; not only silica gel column chromatography but also distillation causes decomposition. In contrast, α,α-dibromo esters were expected to be alternative stable precursors of lithium bromoenolates.

Ethyl α,α-dibromocaproate was synthesized as shown in Scheme 3. The α-bromoester was converted into the trimethylsilyl ketene acetal (**10**) with LDA and TMSCl. Then **10**, without purification, was treated by NBS to afford the dibromoester (**1h**). This is stable enough towards silica gel and distillation, and can be stored in a refrigerator over months.



Scheme 3

The dibromo ester was treated with *tert*-BuLi (4 eq.) and was kept at -78 °C for 3 h and at 0 °C for 30 min. Then addition of benzaldehyde at -78 °C afforded the β-lactone (**6**) in 85% yield (Scheme 4). The efficiency of generation of the ynolate by this method is substantially as good as that by Method A . The extremely simple procedure for the formation of ynolates free from lithium amide was thus established.



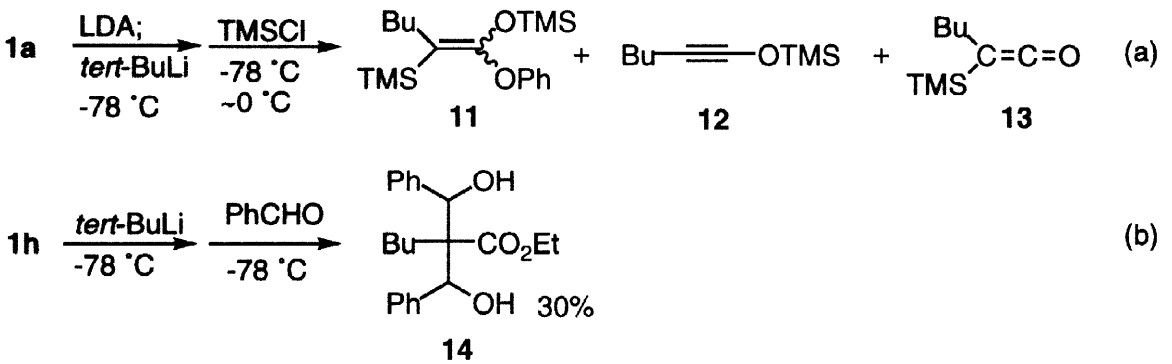
Scheme 4

Ester Dianions

The novel ester dianions (**3**) would be the key intermediates in the course of these processes. In order to prove this mechanism of the ynolate formation other than lithiation of ketenes, we attempted to trap **3a** with TMSCl at -78 °C without warming to 0 °C using Method A (Scheme 5a). But this reaction resulted in an inseparable complex mixture because of its high sensitivity towards silica gel. Although ^{1}H- and ^{13}C-NMR spectra of the crude mixture were too complicated to determine the structures, the presence of keteneacetal (**11**)

can be presumed by EIMS data (m/z 336 (M^+)), which suggests the generation of a dianion. The IR spectrum showed absorption bands for TMS ynol ether (**12**) (2279 cm^{-1})[5,13] and TMS substituted ketene (**13**) (2087 cm^{-1}),[5,13] indicating the presence of the ynolate.

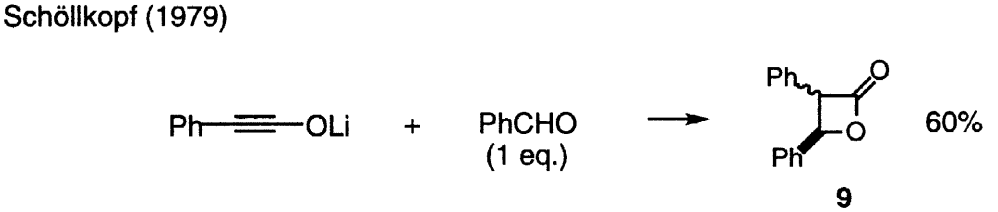
We also tried to trap the dianion (**3c**) with benzaldehyde using Method B (Scheme 5b). Quenching the solution at -78 °C afforded a double aldol adduct (**14**) as a single isomer in 30% yield, but no β-lactones could be detected. The existence of **14** also indicates the generation of the ester dianion. The possibility of the cleavage of β-lactone by lithium ethoxide to give **14** can be ruled out, because **14** could not be observed under the usual conditions of β-lactone formation via ynolates. A ynolate was also generated even at -78 °C in the former reaction, but not in the latter. Presumably, phenoxide would be eliminated even at -78 °C from the dianion. LDA might also affect this transformation. In both reactions, it is clear that warming to 0 °C is important for elimination of alkoxides to give ynolates and, in some cases, for completion of the Li/Br exchange. Another effect of warming to 0 °C is the decomposition of excess *tert*-BuLi, if any.



Scheme 5

Reaction of Ynolates with Aldehydes

Schöllkopf[2] has reported that the ynolate bearing a phenyl substituent reacts with benzaldehyde to give 3,4-disubstituted β-lactone (**9**) (Scheme 6). To clarify the reactivity of an *alkyl*-substituted ynolate towards aldehydes, we examined the reactions with various aldehydes.



Scheme 6

As described above, ynolates reacted with excess benzaldehyde to give 3,3,4-trisubstituted β-lactones (**A**) in good yields. Even if less than one equivalent of benzaldehyde was added (entry 1 in Table 2), 3,4-disubstituted β-lactones (**B**) were not observed at all. This would be due to the higher reactivity of β-lactone enolates than that of ynolates. The steric repulsion between the enolates and the aldehydes would be much smaller than that in the case of phenyl substituted ynolates. It might be also due to the stabilization of carbanion by the phenyl group.

We examined other aldehydes for testing the reactivity of ynolates derived from **1h** (Table 2). Propionaldehyde (R: Et) and isobutyraldehyde (R: iPr) afforded the corresponding β-lactones **A**. No β-lactone **B** was observed even with use of one equivalent of the aldehydes (entry 4, 7). When excess aldehydes were used, 1,3-dioxan-4-one derivatives (**C**) including three equivalents of aldehyde units were also obtained (entry 6, 9).[15] The best yields of **A** were obtained by using 1.6 equivalents of the aldehydes (entry 5, 8).

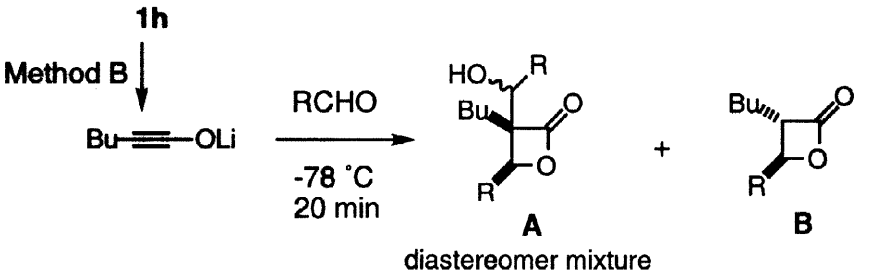
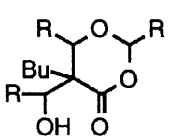


Table 2. Reaction of Ynolate with Aldehydes

Entry	Aldehyde R	Aldehyde eq.	β-Lactones A (%)[a]		β-Lactones B (%)
1	Ph	0.8	**6**	40 (>99)	0
2	Ph	1.0	**6**	36 (71)	0
3	Ph	4.0	**6**	85	0
4	Et	1.0	**15**	25 (50)	0
5	Et	1.6	**15**	52 (66)	0
6	Et	4.0	**15**	35[d]	0
7	iPr	1.0	**16**	30 (61)	0
8	iPr	1.6	**16**	57 (71)	0
9	iPr	4.0	**16**	32[d]	0
10	tBu	1.0	**17a**	0	**17b** 74[b,c]
11	tBu	4.0	**17a**	20[b]	**17b** 30[b,c]

a) Yields are based on **1c**. Numbers in parentheses represent the yields based on aldehydes. b) The yields were estimated by ^{1}H-NMR spectra because the products were fairly unstable. c) *trans* : *cis* = 4:1. d) Dioxanone derivatives (**C**) were also obtained in 35% for entry 6, in 14% for entry 9.

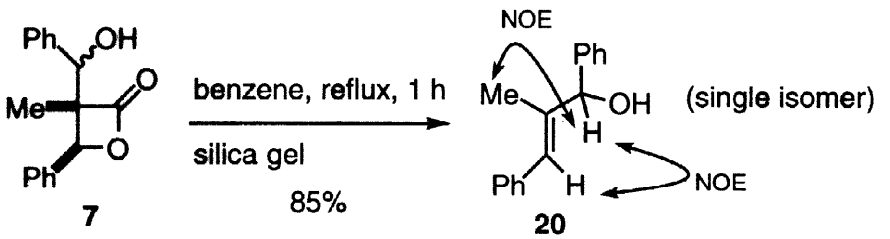


C

On the other hand, we succeeded in getting 3,4-disubstituted β-lactones (**B**) via the reaction of the ynolate with one equivalent of pivalaldehyde (entry 10). By using four equivalents of the aldehyde, **17b** was obtained along with **17a** (entry 11). Steric hindrance between aldehydes and β-lactone enolates would be critical for efficient

suppression of the second addition of the aldehyde.

The β-lactones (**6, 7, 15, 16**) showed two diastereomers (1 : 1) on ^{1}H- and ^{13}C-NMR. In order to confirm the stereochemistry, NOE experiments on **7** were carried out, but useful information relative to the stereochemistry could not be obtained. Then **7** was converted to an alkene via thermal decarboxylation, which is known to proceed via a stereospecific *cis*-elimination.[16] The alkene (**20**) produced was a single isomer, the configuration of which was elucidated to be *E*-form by NOE experiment (Scheme 7). From this result, the relative configuration of **7** was confirmed as shown in Scheme 7. This configuration is consistent with Mulzer's results of aldol additions of β-lactone enolates.[17] The second aldehydes would attack the α-face of the lactones to avoid the steric interaction with the substituents at C-4. On the basis of this result, we assigned the other β-lactones (**6**, **15**, **16**) as having the same relative configuration.



Scheme 7

The relative configuration of **17a** (Table 2, entry 11) was the same as that of the others in terms of the β-lactone ring, determined by NOE experiments. Unexpectedly, the relative configuration of the major isomer of **17b** (Table 2, entry 10, 11) was *trans*, judging from Mulzer's observation as regards the coupling constants ($J_{3,4}$(trans) = 4.5 Hz and $J_{3,4}$(cis) = 6.5 Hz).[18] This means that protonation was performed on the β-face of β-lactone enolate (*cis* to *tert*-butyl). It would be rationalized by assuming that, in the case of protonation, the critical interaction is the severe eclipsing interaction between the *tert*-butyl and *n*-butyl groups in the transition state. This would also explain the poor selectivity of **8**.[19]

In conclusion, we have developed a novel and convenient method for lithium ynolate synthesis via the cleavage of ester dianions from readily available α-bromo and α,α-dibromoesters. We anticipate that this strategy will find considerable use as a method for ynolate synthesis. Investigation on ynolate chemistry and its synthetic application is in progress.

Acknowledgments.

This work was supported by Grants-in-Aid for Scientific Research on Priority Areas (No. 283, "Innovative Synthetic Reactions") from the Ministry of Education, Science, Sports and Culture, Government of Japan.

EXPERIMENTAL

Materials. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Diisopropylamine and trimethylsilyl chloride were distilled from calcium hydride. *N*-Bromosuccinimide was recrystallized from water. All liquid aldehydes were distilled. Butyllithium and *tert*-butyllithium, purchased from Kanto Chemical

Co., Inc., were titrated with diphenylacetic acid. Ethyl 2-bromopropionate was purchased from Katayama Chemical Industries Co., Ltd. and distilled. Phenyl 2-bromopropionate, phenyl 2-bromocaproate,[20] ethyl 2-bromocaproate,[21] and ethyl 2-bromocyclohexaneacetate[22] were prepared according to the references.

General Procedures. ^{1}H NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using Bruker AM400 and JEOL GSX400 spectrometers (400 MHz), unless otherwise noted. ^{13}C NMR were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) using JEOL GSX400 spectrometers (100 MHz). IR spectra were recorded on a HITACHI 215 and Parkin Elmer 1720 FT-IR spectrometers. Mass spectra were obtained on a JEOL LMS-D300. Column chromatography was performed on silica gel, FUJI SILYSIA CHEMICAL BW-127ZH (100-270 mesh). Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60 F_{245}). Melting points were measured with a Büchi 535 melting point apparatus and are uncorrected. All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. Reaction mixtures were stirred magnetically. Solutions of alkyllithium reagents were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa.

1-Triisopropylsilyloxy-1-hexyne (5a). To a solution of diisopropylamine (0.15 mL, 1.05 mmol) in THF (5 mL) was added a butyllithium solution (1.61 M in hexane, 0.65 mL, 1.05 mmol) at -78 °C. After 30 min, a solution of phenyl 2-bromocaproate (271 mg, 1.0 mmol) in 2 mL of THF was added dropwise. After 20 min, a *tert*-butyllithium solution (1.47 M in pentane, 2.18 mL, 3.20 mmol) was added dropwise. The yellow reaction mixture was stirred at -78 °C for 1.5 h and allowed to warm to 0 °C over 30 min. Triisopropylsilyl chloride (0.86 mL, 4.0 mmol) was then added, and the reaction mixture was stirred for 3 h at 0 °C. Saturated $NaHCO_3$ solution (30 mL) was then added and the resulting mixture was extracted with diethyl ether (40 mL). The organic phase was washed with 5% NaOH solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.85 g of a yellow oil. Kugelrohr distillation (1.5 mmHg, 200 °C) gave 150 mg of **5a** as a colorless oil along with some impurities. ^{1}H NMR δ 0.88 (t, J = 7 Hz, 3H), 1.12 (d, J = 7 Hz, 18H), 1.20-1.45 (m, 7H), 2.06 (t, J = 7 Hz, 2H). ^{13}C NMR δ 11.9 (d), 13.6 (q), 16.9 (t), 17.4 (q), 21.9 (t), 30.5 (s), 32.1 (t), 86.8 (s). IR (neat) 2280 cm^{-1}. CIMS (NH_3) m/z: 255 (MH^+).

Addition of Ynolates to Benzaldehyde. General Procedure (Method A). Preparation of (3*RS*,4*SR*)-3-Butyl-3-(α-hydroxybenzyl)-4-phenyl-2-oxetanone (6) (Table 1, entry 1). To a solution of diisopropylamine (0.15 mL, 1.05 mmol) in THF (5 mL) was added a butyllithium solution (1.61 M in hexane, 0.65 mL, 1.05 mmol) at -78 °C. After 30 min, a solution of phenyl 2-bromocaproate (271 mg, 1.0 mmol) in 2 mL of THF was added dropwise. After 20 min, a *tert*-butyllithium solution (1.47 M in pentane, 2.18 mL, 3.20 mmol) was added dropwise. The yellow reaction mixture was stirred at -78 °C for 1.5 h and allowed to warm to 0 °C. After 30 min, the resulting colorless reaction mixture was cooled to -78 °C and then benzaldehyde (424 mg, 4.0 mmol) in THF (0.5 mL) was added dropwise. After 15 min, saturated NH_4Cl solution (20 mL) was added and then the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was chromatographed over silica gel (10% ethyl acetate in hexane) to yield 215 mg (69%) of **6** as a colorless oil. The diastereomeric mixture was separated via column chromatography (CH_2Cl_2) over silica gel. For one isomer: colorless prisms (CH_2Cl_2/hexane), mp. 86.0-87.0 °C. ^{1}H NMR δ 0.61 (t, J = 7 Hz, 3H), 0.89-1.31 (m, 5H), 1.55 (ddd, J = 5, 12, 12 Hz, 1 H), 2.30 (br-s, 1 H), 5.15. (s, 1 H), 5.71 (s, 1 H), 7.25-7.44 (m, 8 H), 7.57 (d, J = 7 Hz, 2 H). ^{13}C NMR δ 13.4 (q), 22.8 (t), 25.5 (t), 28.0 (t), 69.0 (s), 73.0 (d), 76.9 (d), 125.7 (d), 127.3 (d), 128.2 (d), 128.4 (d), 128.7 (d),

135.1 (s), 139.2 (s), 172.1 (s). IR ($CHCl_3$) 1819 cm^{-1}. CIMS (isoBu) m/z: 311 (MH^+), 249. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.19; H, 7.17. For another isomer: colorless prisms (CH_2Cl_2/hexane), mp. 110.5-111.0 °C. ^1H NMR δ 0.73 (t, J = 7 Hz, 3 H), 0.97-1.20 (m, 4 H), 1.43 (m, 2 H) 2.61 (br-s, 1 H), 5.24 (s, 1 H), 6.07 (s, 1 H), 6.83 (m, 2 H), 7.23-7.50 (m, 8 H). ^{13}C NMR δ 13.6 (q), 22.9 (t) 26.3 (t), 28.5 (t), 69.7 (s), 71.3 (d), 75.6 (d), 125.1 (d), 126.6 (d), 127.8 (d), 128.3 (d), 128.7 (d), 135.0 (s), 139.3 (s), 172.9 (s). IR ($CHCl_3$) 1820 cm^{-1}. CIMS (isoBu) m/z: 311 (MH^+), 249. Anal. Calcd for $C_{20}H_{22}O_3(CH_2Cl_2)_{1/2}$: C, 69.78; H, 6.57. Found: C, 70.11; H, 6.64.

(3*RS*,4*SR*)-3-(α-Hydroxybenzyl)-3-methyl-4-phenyl-2-oxetanone (7). For one isomer: colorless prisms (CH_2Cl_2/hexane), mp. 121 °C. ^1H NMR δ 0.85 (s, 3 H), 2.40 (br-s, 1 H), 5.01 (s, 1 H), 5.79 (s, 1 H), 7.17-7.53 (m, 10 H). ^{13}C NMR δ 13.7 (q), 65.5 (s), 75.7 (d), 77.6 (d), 125.3 (d), 127.3 (d), 128.3 (d), 128.6 (d), 128.7 (d), 128.8 (d), 135.0 (s), 139.0 (s). 172.8 (s). IR ($CHCl_3$) 1821 cm^{-1}. CIMS (isoBu) m/z: 269 (MH^+), 224. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 75.71; H, 6.06. For another isomer: colorless prisms (CH_2Cl_2/hexane), mp. 135.0-135.5 °C. ^1H NMR δ 0.80 (s, 3 H), 2.52 (br-s, 1 H), 5.06 (s, 1 H), 6.08 (s, 1 H), 6.95 (m, 2 H), 7.25 (m, 3 H), 7.46 (m, 5 H). ^{13}C NMR δ 14.3 (q), 65.9 (s), 74.2 (d), 76.3 (d), 125.2 (d), 126.8 (d), 128.0 (d), 128.4 (d), 128.7 (d), 128.9 (d), 135.0 (s), 139.0 (s), 173.5 (s). IR ($CHCl_3$) 1822 cm^{-1}. CIMS (isoBu) m/z: 269 (MH^+), 224. Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.09; H, 6.01. Found: C, 76.06; H, 6.09.

(3*RS*,4*SR*)-3-Cyclohexyl-3-(α-hydroxybenzyl)-4-phenyl-2-oxetanone (8). For one isomer: colorless prisms (CH_2Cl_2/hexane), mp. 179 °C. ^1H NMR δ 0.69-1.73 (m, 11 H), 2.45 (br-s, 1 H), 5.32 (s, 1 H), 6.02 (s, 1H), 7.08 (d, J = 7 Hz, 2 H), 7.25-7.55 (m, 8 H). ^{13}C NMR δ 26.0 (t), 26.46 (t), 26.52 (t), 27.5 (t), 28.6 (t), 37.9 (d), 71.1 (d), 73.1 (s), 76.3 (d), 125.7 (d), 127.1 (d), 128.1 (d), 128.3 (d), 128.8 (d), 128.9 (d), 135.3 (s), 140.5 (s), 172.5 (s). IR ($CHCl_3$) 1816 cm^{-1}. CIMS (isoBu) m/z: 337 (MH^+), 319. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.38; H, 7.25. For the other isomers (1:1 ratio after recrystallization): colorless prisms (CH_2Cl_2/hexane), mp. 150 °C (dec). ^1H NMR δ 0.60-1.80 (m, 10.5 H), 2.16 (br-s, 0.5 H), 4.57 (d J = 3 Hz, 0.5 H), 5.21 (s, 0.5 H), 5.58 (s, 0.5 H), 5.87 (s, 0.5 H), 7.25-7.57 (m, 10 H). ^{13}C NMR δ 25.75 (t), 25.79 (t), 26.02 (t), 26.08 (t), 26.4 (t), 26.6 (t), 27.7 (t), 28.0 (t), 28.3 (t), 28.7 (t), 38.3 (d), 38.5 (d), 71.7 (s), 72.4 (d), 72.6 (d), 75.4 (d), 75.6 (d), 76.6 (d), 125.6 (d), 126.5 (d), 127.5 (d), 127.98 (d), 128.07 (d), 128.14 (d), 128.3 (d), 128.5 (d), 128.60 (d), 128.64 (d), 128.7 (d), 135.1 (s), 135.4 (s), 139.3 (s), 140.1 (s), 170.5 (s), 170.9 (s). IR ($CHCl_3$) 1817 cm^{-1}. CIMS (isoBu) m/z: 319 (M-OH), 275. Anal. Calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.61; H, 7.29.

Ethyl 2,2-dibromocaproate (1h). To a solution of diisopropylamine (7.54 mL, 53.8 mmol) in THF (80 mL) was added a butyllithium solution (1.42 M in hexane, 34.7 mL, 49.3 mmol) at -78 °C. After 15 min, a solution of ethyl 2-bromocaproate (10 g, 44.8 mmol) in 70 mL of THF was added dropwise. After 30 min, trimethylsilyl chloride (11.4 mL, 89.6 mmol) was added dropwise. After 20 min triethylamine (13 mL) was added and then the mixture was poured into saturated $NaHCO_3$ solution (500 mL) and was extracted with hexane (3 x 200 mL). The organic phase was washed with saturated $NaHCO_3$ solution (30 mL) and saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated to afford a crude mixture of trimethylsilylketene acetal (**10**).

The acetal mixture was taken up in a solution of THF (80 mL), and treated with *N*-bromosuccinimide (7.98 g, 44.8 mmol) at 0 °C. After 30 min at 0 °C, the reaction mixture was poured into saturated $NaHCO_3$ solution (300 mL) and was extracted with hexane (3 x 200 mL). The combined organic phase was washed with water (2

x 100 mL) and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (elution with hexane) provided 7.00 g (52%) of **1h** as a colorless oil, which was further purified by distillation (bp. 79-82 °C, 0.7 mmHg). ^{1}H NMR δ 0.96 (t, J = 7 Hz, 3 H), 1.36 (t, J = 7 Hz, 3 H), 1.42 (m, 2 H), 1.60 (m, 2 H), 2.56 (m, 2 H), 4.33 (q, J = 7 Hz, 2 H). ^{13}C NMR δ 13.77 (q), 13.84 (q), 22.0 (d), 29.7 (d), 46.9 (d), 60.8 (s), 63.7 (t), 166.3 (s). IR ($CHCl_3$) 1736 cm^{-1}. EIMS m/z: 300 (M^+), 302 (M+2). Anal. Calcd for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67. Found: C, 31.69; H, 4.57.

Trapping of dianion (Scheme 5a). To a solution of diisopropylamine (0.15 mL, 1.05 mmol) in THF (5 mL) was added a butyllithium solution (1.66 M in hexane, 0.63 mL, 1.05 mmol) at -78 °C. After 15 min, a solution of phenyl 2-bromocaproate (271 mg, 1.0 mmol) in 1 mL of THF was added dropwise. After 20 min, a *tert*-butyllithium solution (1.47 M in pentane, 2.18 mL, 3.20 mmol) was added dropwise. The yellow reaction mixture was stirred at -78 °C for 1.5 h, and then trimethylsilyl chloride (1.3 mL, 10 mmol) was added. The mixture was allowed to warm to room temperature over 1.5 h. After addition of triethylamine (1 mL), the reaction mixture was poured into saturated $NaHCO_3$ (30 mL) and was extracted with diethyl ether (40 mL). The organic phase was washed with saturated $NaHCO_3$ (30 mL) and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.41 g of a colorless oil. Kugelrohr distillation (1.5 mmHg, 150-200 °C) of 0.35 g of the crude mixture gave 190 mg of a colorless oil.

Trapping of dianion (Scheme 5b). Ethyl 2,2-bis(α-hydroxybenzyl)caproate (14). To a solution of **1c** (271 mg, 1.0 mmol) in THF (6 mL) was added a *tert*-butyllithium solution (1.44 M in pentane, 2.78 mL, 4.0 mmol) at -78 °C. The yellow reaction mixture was stirred at -78 °C for 3 h, then benzaldehyde (424 mg, 4.0 mmol) in THF (2.0 mL) was added dropwise. After 20 min, saturated NH_4Cl solution (20 mL) was added and then the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was chromatographed over silica gel (10% ethyl acetate in hexane) to yield 132 mg (37%) of **14** as a colorless oil. ^{1}H NMR δ 0.75 (t, J = 7 Hz, 3 H), 1.05 (tq, J = 7 Hz, 2 H), 1.16 (t J = 7 Hz, 3 H), 1.24 (m, 2 H), 1.39 (tt, J = 7, 7 Hz, 2 H), 3.85 (br, 2 H), 4.18 (q, J = 7 Hz, 2 H), 5.13 (s, 2 H), 7.28-7.34 (m, 10 H). ^{13}C NMR δ: 13.7 (t), 23.6 (t), 26.6 (t), 30.0 (t), 58.4 (s), 60.9 (t), 77.7 (d), 127.6 (d), 127.8 (d), 127.9 (d), 140.3 (s), 175.3 (s). IR ($CHCl_3$) 3477, 1703 cm^{-1}. FABMS (NBA) m/z: 379 (M+Na), 357 (MH^+). FAB HRMS (NBA) Calcd for $C_{22}H_{29}O_4$ (MH^+) 357.2066, Found 357.2061.

Addition of a Ynolate to Aldehydes. General Procedure (Method B). Preparation of (3*RS*,4*SR*)-3-Butyl-3-(α-hydroxybenzyl)-4-phenyl-2-oxetanone (6) (Table 2, entry 3). To a solution of **1h** (302 mg, 1.0 mmol) in THF (6 mL) was added a *tert*-butyllithium solution (1.44 M in pentane, 2.78 mL, 4.0 mmol) at -78 °C. The yellow reaction mixture was stirred at -78 °C for 3 h and allowed to warm to 0 °C. After 30 min, the mixture was cooled to -78 °C and then benzaldehyde (424 mg, 4.0 mmol) in THF (2.0 mL) was added dropwise. After 20 min, saturated NH_4Cl solution (20 mL) was added and then the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was chromatographed over silica gel (10% ethyl acetate in hexane) to yield 265 mg (85%) of **6** as a colorless oil.

(3*RS*, 4*SR*)-3-Butyl-4-ethyl-3-(1-hydroxypropyl)-2-oxetanone (15a). Colorless oil. ^{1}H NMR δ (t, J = 7 Hz, 3 H), 1.01–1.08 (m, 6 H), 1.2-1.9 (m, 10 H), 2.00 (br, 1 H), 3.76 (dd J = 2.7, 10 Hz, 0.5 H), 3.89 (dd, J = 2, 10 Hz, 0.5 H), 4.46 (dd, J = 4, 9 Hz, 0.5 H), 4.60 (dd, J = 5, 9 Hz, 0.5 H). ^{13}C NMR δ

10.1 (q), 10.4 (q), 10.7 (q), 13.77 (q), 13.81 (q), 22.9 (t), 23.3 (t), 24.2 (t), 25.0 (t), 26.0 (t), 26.5 (t), 26.7 (t) 26.8 (t), 65.6 (s), 66.2 (s), 70.5 (d), 72.4 (d), 78.6 (d), 80.2 (d), 173.4 (s), 174.2 (s). IR ($CHCl_3$) 3469, 1814 cm^{-1}. CIMS (isoBu) m/z: 215 (MH^+), 197. HRMS (CI, isoBu) Calcd for $C_{12}H_{23}O_3$ (MH^+) 215.1647, Found 215.1642.

(3*RS*,4*SR*)-3-Butyl-3-(1-hydroxy-2-methylpropyl)-4-methylethyl-2-oxetanone (16a). Colorless oil. ^1H NMR δ 0.90-1.09 (m, 15H), 1.26-2.11 (m, 9 H), 3.61 (d, J = 6 Hz, 0.5 H), 3.90 (d, J = 2 Hz 0.5 H), 4.12 (d, J = 10 Hz, 0.5 H), 4.42 (d, J = 9 Hz, 0.5 H). ^{13}C NMR δ: 13.7 (q), 13.8 (q), 15.6 (q), 17.8 (q), 18.2 (q), 18.9 (q), 19.3 (q), 19.6 (q), 20.8 (q), 21.5 (q), 23.4 (t), 26.4 (t), 26.8 (t), 27.06 (t), 27.09 (t), 28.2 (d), 29.0 (d), 30.6 (d), 64.9 (s), 65.3 (s), 73.2 (d), 76.0 (d), 82.0 (d), 83.5 (d), 173.2 (s), 174.5 (s). IR ($CHCl_3$) 3469, 1816 cm^{-1}. CIMS (isoBu) m/z: 243 (MH^+). HRMS (CI, isoBu) Calcd for $C_{14}H_{27}O_3$ (MH^+) 243.1960, Found 243.1980.

(3*RS*,4*SR*)-3-Butyl-3-(1-hydroxy-2,2-dimethylpropyl)-4-(*tert*-butyl)-2-oxetanone (17a). Colorless oil. ^1H NMR δ: 0.93 (t, J = 7 Hz, 3 H), 1.07 (s, 9 H), 1.08 (s, 3 H), 1.33 (qt, J = 7, 7 Hz, 2 H), 1.53 (m, 1 H), 1.67 (m, 1 H), 1.91 (ddd, J = 4, 13, 13 Hz, 1 H), 2.00 (d, J = 3 Hz, 1 H), 2.05 (ddd, J = 4, 13, 13 Hz, 1 H), 3.58 (d, J = 4 Hz, 1 H), 4.43 (s, 1 H). ^{13}C NMR δ: 13.9 (q), 23.5 (t), 27.02 (q), 27.06 (q), 27.3 (t), 29.8 (t), 33.8 (s), 36.6 (s), 79.3 (d), 84.8 (d), 174.0 (s). IR ($CHCl_3$) 3516, 1784 cm^{-1}. CIMS (isoBu) m/z: 243 (MH^+), 225. HRMS (CI, isoBu) Calcd for $C_{16}H_{31}O_3$ (MH^+) 271.2273, Found 271.2278.

***trans*-3-Butyl-4-*tert*-butyl-2-oxetanone (17b).** Colorless oil. ^1H NMR δ 0.92 (t, J = 7 Hz, 3 H), 0.99 (s, 7.2 H), 1.05 (s, 1.8 H), 1.30-1.40 (m, 4 H), 1.55-2.00 (m, 2 H), 3.27 (ddd, J = 4, 8, 8 Hz, 0.8 H), 3.61 (ddd, J = 5, 6, 11 Hz, 0.2 H), 3.94 (d, J = 4 Hz, 0.8 H), 4.21 (d, J = 7 Hz, 0.2 H). ^{13}C NMR δ: 13.8 (q), 22.5 (t), 24.4 (q), 28.3 (t), 29.1 (t), 32.8 (s), 51.0 (d), 85.2 (d), 171.7 (s). IR ($CHCl_3$) 1825 cm^{-1}. CIMS (isoBu) m/z: 185 (MH^+). HRMS (CI, isoBu) Calcd for $C_{11}H_{21}O_2$ (MH^+) 185.1542, Found 185.1554.

(*E*)-2-Methyl-1,3-diphenyl-2-propen-1-ol (20).[23] A mixture of β-lactone (**7**) (21 mg) and silica gel (30 mg) suspended in benzene (2 mL) was heated at reflux for 1 h and then allowed to cool to room temperature and filtered. The filtrates were concentrated to afford 14.8 mg (85 %) of **20** as a colorless oil. ^1H NMR δ 1.74 (s, 3 H), 2.15 (br, 1 H), 5.28 (s, 1 H), 6.78 (s, 1 H), 7.24-7.45 (m, 10 H).

References and Notes

1. (a) House, H. O. *Modern Synthetic Reactions,* 2nd ed.; W. A. Benjamin, Inc.: California, 1972; p 492-628. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 99-319.
2. (a) Schöllkopf, U.; Hoppe, I. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 765. (b) Hoppe, I.; Schöllkopf, U. *Liebigs Ann. Chem.* **1979**, 219-226.
3. (a) Woodbury, R. P.; Long, N. R. Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 376. See also; (b) Kita, Y.; Tsuzuki, Y.; Kitagaki, S.; Akai, S. *Chem. Pharm. Bull.*, **1994**, *42*, 233-236. (c) Akai, S.; Kitagaki, S.; Naka, T.; Yamamoto, K.; Tsuzuki, Y.; Matsumoto, K.; Kita, Y. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 1705-1709.
4. (a) Kowalski, C. J.; Fields, K. W. *J. Am. Chem. Soc.* **1982**, *104*, 7321-7323. (b) Kowalski, C. J.; Haque, M. S.; Fields, L. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429-1430. (c) Kowalski, C. J.; Haque, M.

S. *J. Org. Chem.* **1985**, *50*, 5140-5142. (d) Kowalski, C. J.; Lal, G. S. *Tetrahedron Lett.* **1987**, *28*, 2463-2466. (e) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194-7208. (f) Reddy, R. E.; Kowalski, C. J. *Org. Synth.* **1993**, *71*, 146. Satoh and Yamakawa reported a similar method using α-chloro α-sulfinyl ketones: (g) Satoh, T.; Mizu, Y.; Hayashi, Y.; Yamakawa, K. *Tetrahedron Lett.* **1994**, *35* 133-134.

5. Stang, P. J.; Roberts, K. A. *J. Am. Chem. Soc.* **1986**, *108*, 7125-7127.
6. Julia, M.; Saint-Jalmes, V. P.; Verpeaux, J. N. *Synlett* **1993**, 233-234.
7. Kai, H.; Iwamoto, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **1996**, *118*, 7634-7635.
8. Adlington, R. M.; Barrett, A. G. M.; Quayle, P.; Walker, A. *J. Chem. Soc., Chem. Comm.* **1981**, 404-405.
9. (a) Kowalski, C. J.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 1325-1327. (b) Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1986**, *108*, 5356-5357.
10. Shindo, M. *Tetrahedron Lett.* **1997**, *38*, 4433-4436.
11. (a) Sullivan, D. F.; Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 2038-2039. (b) Haner, R.; Laube, T.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 5396-5403. In this article, the authors described that addition of alkyllithium to monosubsituted ketenes generated from ester enolates was unsuccessful because ynolates might be formed. (c) Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276-2277. (d) For zinc enolate: Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956-5964.
12. (a) Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595-1598. (b) Schlosser, M.; Wei, H.-x. *Tetrahedron* **1997**, *53*, 1735-1742.
13. Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127-7128.
14. The aggregation and its effect on reactivity of lithium amides and lithium halides is being examined in detail; see: Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1994** *116*, 9198-9202 and references cited therein.
15. They were found to be single isomers by ^{1}H- and ^{13}C-NMR spectra, but their relative configurations have not been determined.
16. (a) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176-1185. For reviews of the chemistry of β-lactones, see: (b) Pons, J.-M.; Pommier, A. *Synthesis* **1993**, 441-459. (c) *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 6, p 342-350.
17. Mulzer, J.; Chucholowski, A. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 777-778.
18. Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620-3622.
19. The relative configuration of **8a** is the same as that of one of the β-lactone isomers (**6**), but those of **8b** and **8c** were determined by NOE of the corresponding olefin via decarboxylation.
20. Schick, H.; Ludwig, R.; Kleiner, K.; Kunath, A. *Tetrahedron* **1995**, *51*, 2939-2946.
21. Berry, J. P.; Isbell, A. F.; Hunt, G. E. *J. Org. Chem.* **1972**, *37*, 4396-4399.
22. Kawahara, S.; Kawakami, H. *Yakugaku Zasshi* **1961**, *81*, 1057-1062.
23. Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281-5284.