CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200500574

Heteroatom-Guided Torquoselective Olefination of α-Oxy and α-Amino Ketones via Ynolates

Mitsuru Shindo,*[a] Takashi Yoshikawa,[b] Yasuaki Itou,[c] Seiji Mori,[c] Takeshi Nishii,[d] and Kozo Shishido[b]

Abstract: Ynolates were found to react with α-alkoxy-, α-siloxy-, and α-aryloxyketones at room temperature to afford tetrasubstituted olefins with high *Z* selectivity. Since the geometrical selectivity was determined in the ring opening of the β-lactone enolate intermediates, the torquoselectivity was controlled by the ethereal oxygen atoms. From experimental and theoretical studies, the high *Z* selectivity is induced by orbital and steric interactions rather than by chelation. In a similar manner, α-dialkylamino ketones provided olefins with excellent *Z* selectivity. These products can be easily converted into multisubstituted butenolides and γ-butyrolactams in good yield.

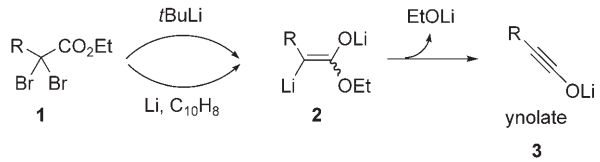
Keywords: density functional calculations · ketones · olefination · torquoselectivity · ynolates

Introduction

The synthesis of alkenes by the olefination of carbonyl compounds has received considerable attention due to the efficiency and convenience of this methodology.[1] In addition to methods based on phosphorus ylides, such as the Wittig[2] and the Horner–Wadsworth–Emmons reactions,[3] other related processes involving sulfur[4] and silicon[5] ylides have been used in synthetic organic chemistry. Furthermore, *gem*-bimetallic reagents (or metal carbenoids) have been reported for the olefination of carbonyl compounds.[6]

Although the phosphorus ylide methods are generally effective in providing di- and trisubstituted olefins from aldehydes and some ketones, the low reactivity and stereoselectivity of these reagents make them less desirable in the olefination of ketones to furnish tetrasubstituted olefins.[7] The other olefination processes, even if they are reactive enough towards hindered ketones, have not been successfully used in the stereoselective synthesis of tetrasubstituted olefins, which serve as important synthetic intermediates for syntheses of complex molecules[8] and useful units in medicinal chemistry[9] and material science.[10] Considering how difficult it is to achieve high efficiency in the olefination of ketones with conventional reagents, development of a novel reaction with a new mechanism would be extremely useful.[11]

We have developed a novel methodology for the generation of ynolate anions **3** by cleavage of ester dianions **2** derived from α,α-dibromo esters **1**[12] (Scheme 1).[13] Since ynolate anions are ketene anion equivalents, they are expected to act as multifunctional reactive species.[14]



Scheme 1. Synthesis of ynolates.

[a] Prof. Dr. M. Shindo
Institute for Materials Chemistry and Engineering, Kyushu University
6-1, Kasugakoen, Kasuga, Fukuoka 816-8580 (Japan)
Fax: (+81) 92-583-7875
E-mail: shindo@cm.kyushu-u.ac.jp

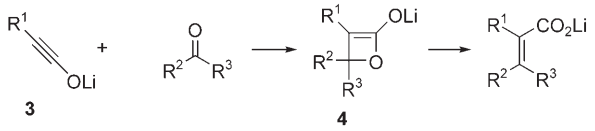
[b] T. Yoshikawa, Prof. Dr. K. Shishido
Institute of Health Biosciences
The University of Tokushima Graduate School
Sho-machi 1, Tokushima 770-8505 (Japan)

[c] Y. Itou, Prof. Dr. S. Mori
Faculty of Science, Ibaraki University
Mito, Ibaraki 310-8512 (Japan)

[d] T. Nishii
Faculty of Pharmaceutical Sciences, Tokushima Bunri University
180 Yamashiro-cho, Tokushima 770-8514 (Japan)

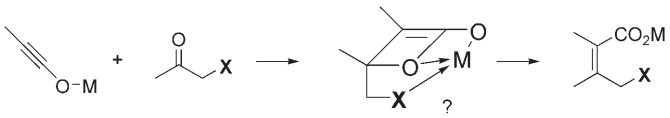
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author: Experimental procedures, spectral data of the starting ketones and the products, and Cartesian coordinates of the optimized TSs (PDF).

We have reported an olefination of aldehydes and ketones using the ynolate anions **3**,[15] via ring opening of the β-lactone enolates (oxetenoxide ions) derived from the cycloaddition of ketones and aldehydes with ynolates, with good to moderate *E*/*Z* selectivity (Scheme 2).[16] When aryl alkyl ketones were used as substrates, the *E*/*Z* selectivity was in the range of 4–8. Furthermore, we found a stereoelectronic effect on the *E*/*Z* selectivity, whereby ketones having an electron-donating group at the *para* position of the aryl substituent exhibited much better *E* selectivity.[17] The *E*/*Z* selectivity is determined in the ring opening of the β-lactone enolate intermediates, and stereocontrol would be governed by torquoselectivity, in which the electron-donating substituent preferentially rotates outward, and the electron-withdrawing substituent inward.[18] The opposite explanation involving geminal bond participations has also been reported.[19] In our case, successful olefinations were limited to electron-rich aryl alkyl ketones. Recently, we achieved high *Z* selectivity in the olefination of acylsilanes to give vinylsilanes (silyl alkenes).[20] In this case, the silyl group efficiently acts as an "electron-accepting" group due to its Si–C σ* orbitals.[21] In spite of these successful results, the development of general methods, in which the stereochemistry is predictable, for the efficient olefination of ketones still remains a challenge.



Scheme 2. Olefination of ketones via ynolates.

As described above, ynolates are potential olefination reagents toward ketones. If this method were to show generally high *E*/*Z* selectivity, it would become an alternative to the ylide and carbenoid methods. To achieve high efficiency, we therefore looked for other efficient, strong stereocontrolling factors for olefination. In the olefination of aldehydes, because it is easy to discriminate between the H and R groups (RC(=O)H), many successful results have been reported. Ketones RC(=O)R′, however, have similar substituents R and R′; thus, olefination reagents cannot easily distinguish between them. We anticipated that highly general and stereo-predictable olefination could be achieved by using a ketone bearing a strongly directing group. The directing group should be a versatile functional group, widely used and readily available, which can be easily converted to other functional groups. Based on mechanistic considerations, and the fact that the *E*/*Z* selectivity is controlled in the thermal ring opening of the β-lactone enolate intermediate, we envisioned an intermediate having a coordination site which would chelate to the lithium cation, as in **5**, and thereby determine the direction of ring opening (Scheme 3). Here we describe a highly *Z*-selective olefination of α-oxy and α-amino-substituted ketones via ynolates to provide tetrasubstituted alkenes, and mechanistic investigations supported by theoretical calculations, which led to an unexpected conclusion.

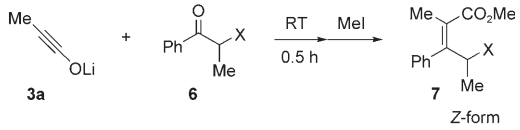


Scheme 3. Initial working hypothesis of stereoselective olefination.

Results

Olefination of α-siloxy- and α-alkoxyketones: Based on this concept, we selected α-alkoxyketones as the substrates, expecting chelation of the ethereal oxygen atom to the lithium cation. Olefinations of α-hydroxy or α-siloxyketones giving tetrasubstituted olefins by the Horner–Emmons reaction[22] or via ynamines[23] have been reported, for some of which good selectivity was achieved, but they are less efficient or lack generality.[24] We first treated α-methoxypropiophenone (**6a**) with lithium ynolate **3a** at room temperature for 30 min to obtain the desired olefin **7a** in good yield with excellent *Z* selectivity after methyl esterification (Table 1, entry 1). The α-methoxymethoxy and α-(*p*-methoxybenzyloxy)propiophenones (**6b**, **6c**) also gave the desired olefins (**7b, 7c**) with high *Z*-selectivities (Table 1, entries 2 and 3), as did the α-siloxypropiophenones (**6d**, **6e**, **6f**), although one would expect the siloxy oxygen atom to be less Lewis basic (Table 1, entries 4–7).[25] Interestingly, even if the lithi-

Table 1. Olefination of α-alkoxy and α-siloxy propiophenones via lithium ynolates.[a]



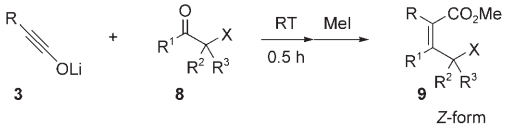
Entry	6	X	7	Ratio [*Z*:*E*][b]	Yield [%]
1	**6a**	OCH_3	**7a**	>99:1	81
2	**6b**	OCH_2OCH_3	**7b**	98:2	50
3	**6c**	$OCH_2C_6H_4OCH_3$-*p*	**7c**	>99:1	76
4	**6d**	OTES	**7d**	99:1	71
5	**6e**	OTBS	**7e**	98:2	85
6	**6e**	OTBS[c]	**7e**	>99:1	40[d]
7	**6f**	OTIPS	**7f**	98:2	85
8	**6g**	OPh	**7g**	98:2	68
9	**6h**	$OC_6H_4OCH_3$-*p*	**7h**	98:2	70
10	**6i**	$OC_6H_4NO_2$-*p*	**7i**	–	0
11[e]	**6j**	CH_3	**7j**	75:25[f]	86
12[e]	**6k**	H	**7k**	86:14[f]	89

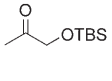
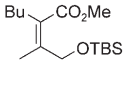
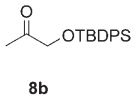
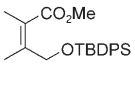
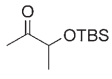
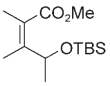
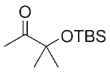
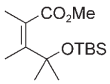
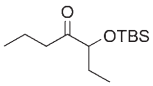
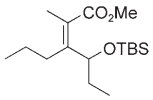
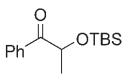
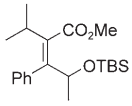
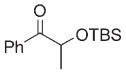
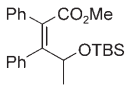
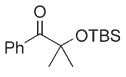
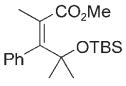
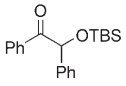
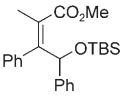
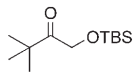
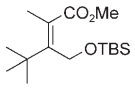
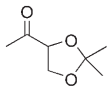
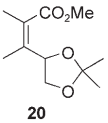
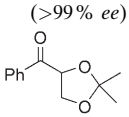
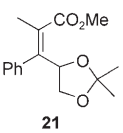
[a] TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl. [b] The stereochemistry was determined by NOE experiments. See Supporting Information. [c] [12]crown-4 (20 equiv) was added to the lithium ynolate solution. [d] The reaction time was 48 h. [e] From ref. [15b]. [f] *E*:*Z* ratio.

um cation was trapped by crown ether, the high selectivity still remained, albeit with moderate yield (Table 1, entry 6). Furthermore, the α-phenoxy and α-(*p*-methoxy)phenoxy groups, the ethereal oxygen atoms of which are much less Lewis basic, afforded excellent *Z* selectivity (Table 1, entries 8 and 9). α-(*p*-Nitrophenoxy)propiophenone (**6i**) did not provide the desired product, and a complex mixture was obtained. By contrast, the reactions of propiophenone (**6k**) and isopropyl phenyl ketone (**6j**) gave olefins with poorer selectivity (Table 1, entries 11 and 12). The dramatic difference in selectivity can be explained by an α-oxygen effect, although it is uncertain if this is the chelation effect shown in Scheme 3.

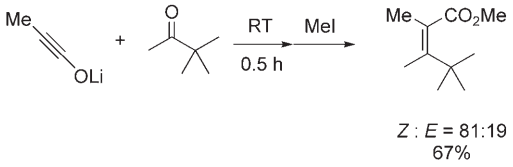
To examine the generality of this process, various kinds of α-siloxy- and α-alkoxyketones (**8**) were subjected to the reaction. As shown in Table 2, most of the acyclic α-oxyalkyl alkyl and α-oxyalkyl aryl ketones afforded olefins with high *Z* selectivity (Table 2, entries 1–12). Even sterically hindered ketones bearing α-quaternary carbon centers can afford the desired olefins in good yield with high *Z* selectivity (Table 2, entries 4, 8, and 10). The optically pure chiral ketones **8i** and **8j**, prepared from D-mannitol, furnished the *Z*-olefins without loss of optical purity (Table 2, entries 11 and 12). It is noteworthy that the reaction of *tert*-butyl *tert*-butyldimethylsiloxymethyl ketone (**8h**) afforded only the *Z*-olefin in which the *tert*-butyl group rotated outward in the ring opening of the β-lactone enolate (Table 2, entry 10), while olefination with pinacolone showed the opposite selectivity (Scheme 4), that is, the *tert*-butyl group preferentially rotated inward. This remarkable contrast sug-

Table 2. *Z*-Selective olefination of α-siloxy and α-alkoxy acyclic ketones via ynolates.[a]



Entry	**3** (R)	Ketone	Major product	Yield [%]	*Z*/*E*
1	Bu	 **8a**	 **10**	59	>99:1
2	Me	 **8b**	 **11**	66	>99:1
3	Me	 **8c**	 **12**	>99	95:5
4	Me	 **8d**	 **13**	98	94:6
5	Me	 **8e**	 **14**	60	92:8
6	*i*Pr	 **6e**	 **15**	76	98:2
7	Ph	 **6e**	 **16**	75	>99:1
8	Me	 **8f**	 **17**	91	>99:1
9	Me	 **8g**	 **18**	93	>99:1
10	Me	 **8h**	 **19**	94	>99:1
11	Me	 **8i** (>99% *ee*)	 **20**	26 (>99% *ee*)	>99:1
12	Me	 **8j** (>99% *ee*)	 **21**	66 (>99% *ee*)	>99:1

[a] TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



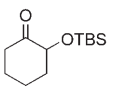
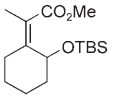
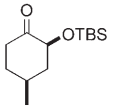
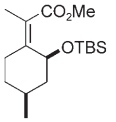
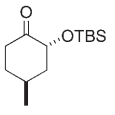
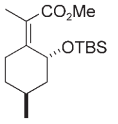
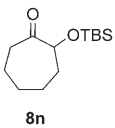
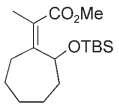
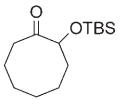
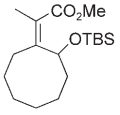
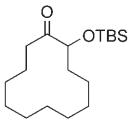
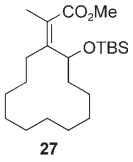
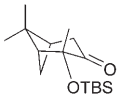
Scheme 4. Olefination of pinacolone.

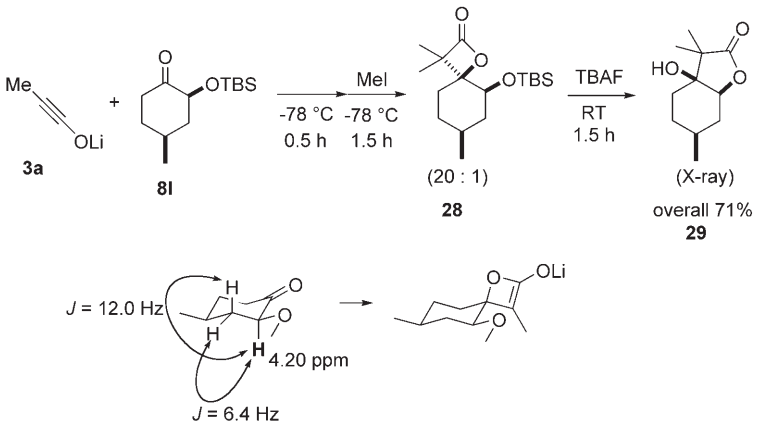
gested that the presence of an α-oxy group is critical for stereocontrol.

Next, α-oxy cyclic ketones were examined (Table 3). Although 2-(*tert*-butyldimethylsiloxy)cyclopentanone did not give the desired olefin but rather a complex mixture, 2-siloxycyclohexanone **8k** afforded the desired *Z* olefin with moderate selectivity (Table 3, entry 1). To investigate the conformational effect of the α-siloxy group, *cis*- and *trans*-4-methyl-2-(*tert*-butyldimethylsiloxy)cyclohexanone (**8l**, **8m**) were subjected to olefination. As shown in entries 2 and 3 in Table 3, *syn* form **8l** gave no selectivity, while *anti* form **8m** showed high *Z* selectivity, albeit in modest yield. This remarkable contrast suggested that the conformation of the siloxy group, which affects the O−C$^{\alpha}$−C=O dihedral angle of the substrate, is related to the torquoselectivity. The chemical shifts and coupling constants in the ^{1}H NMR spectra indicated equatorial orientation of the siloxy group in the *syn* form **8l** (Scheme 5) and axial orientation in the *anti* form **8m** (Scheme 6).

These results suggest that the conformationally fixed equatorial position of the α-siloxy group is not suitable for stereocontrol in ring opening of the β-lactone enolate intermediates, whereas the axial position is. For mechanistic considerations, we tried to determine the stereochemistry of the corresponding β-lactone intermediate to see whether the ynolate attacked the α-siloxycyclohexanones axially or equatorially. Ynolate **3a** reacted with *cis*-2-siloxy-4-methylcyclohexanone (**8l**) at −78 °C, followed by treatment with iodomethane, to give β-lactone **28** with 20:1 diastereoselectivity. The resulting compound was deprotected with TBAF to afford γ-lactone **29** by translactonization in good yield.[26] The X-ray crystal structure analysis of **29** disclosed the *trans*-fused bicyclic structure (Figure 1), which indicates equatorial attack of ynolate **3a** on **8l** (Scheme 5).

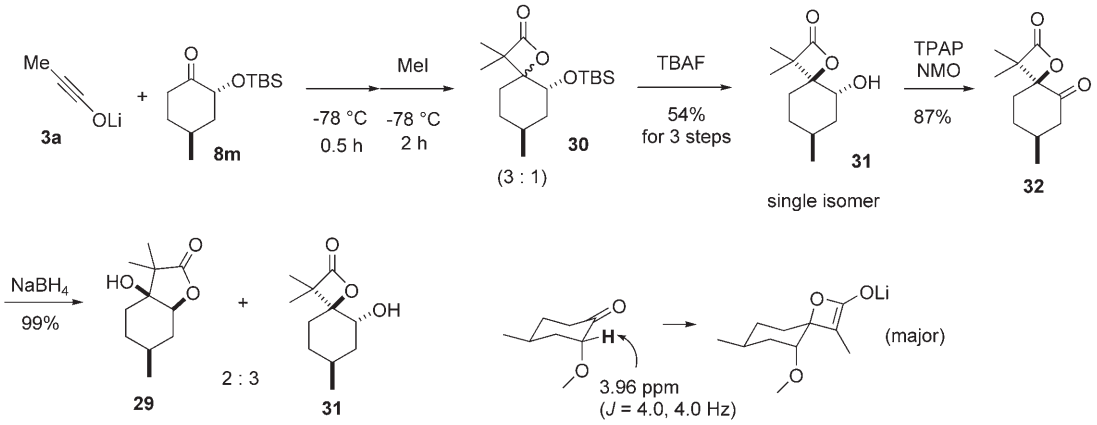
Table 3. *Z*-Selective olefination of α-siloxy cyclic ketones via ynolates.

Entry	**3** (R)	Ketone	Major product	Yield [%]	*Z*:*E*
1	Me	 **8k**	 **22**	60	83:17
2	Me	 **8l**	 **23**	40	50:50
3	Me	 **8m**	 **24**	33	94:6
4	Me	 **8n**	 **25**	83	>99:1
5	Me	 **8o**	 **26**	90	97:3
6	Me	 **8p**	 **27**	70	86:14
7	Me	 **8q**	none	0	–



Scheme 5. Equatorial attack of the ynolate on **8l**. TBS = *tert*-butyldimethylsilyl, TBAF = tetrabutylammonium fluoride.

Similarly, *trans*-2-siloxy-4-methylcyclohexanone (**8m**) was treated with ynolate **3a** at −78 °C, followed by methylation, to afford a 3:1 diastereomeric mixture of β-lactone **30**. Only the major isomer could be desilylated with one equivalent of TBAF to afford hydroxy β-lactone **31** as a single isomer, which could not be converted into the γ-lactone, due to the axial orientation of the hydroxy group. Thus, this hydroxyl



Scheme 6. Equatorial attack on **8m** preferred to axial attack. TPAP = tetrapropylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide.

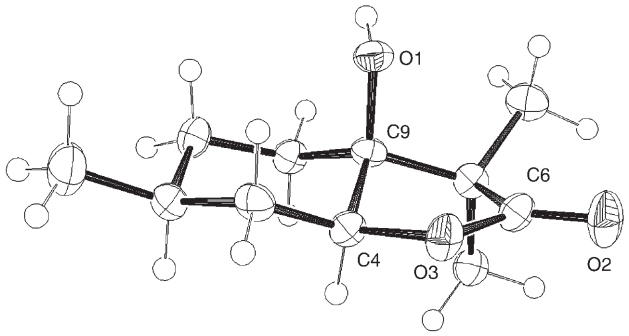


Figure 1. X-ray crystal structure of **29**. ORTEP plot with 50% probability thermal ellipsoids.

group was oxidized with TPAP, and the resulting ketone **32** was reduced by $NaBH_4$ to provide γ-lactone **29** along with the β-lactone **31** (Scheme 6). Judging from the chemical shifts and the coupling constants in the ^{1}H NMR spectrum of **8m**, the siloxy group in **8m** is in the axial position. From this result, it was found that the equatorial attack of the ynolate **3a** on the *trans*-2-siloxy-4-methylcyclohexanone **8m** was predominant.

Seven-, eight-, and twelve-membered cyclic ketones bearing α-*tert*-butyldimethylsiloxy substituents afforded the desired olefins with good to excellent *Z* selectivity (Table 3, entries 4–6). The extremely hindered and conformationally fixed ketone did not react with the ynolate (Table 3, entry 7).

From these results, it was found that acyclic siloxyketones generally provide the desired olefins in good yields with high *Z* selectivity, and in the olefination of cyclic siloxyketones, the conformational flexibility, or certain conformations, might be required to achieve high selectivity and good yields.

Synthesis of butenolides: The (*Z*)-γ-siloxy-α,β-unsaturated esters **9** were treated with acid to provide the butenolides **33** (Table 4), which are frequently found in natural products.[27] Except for the volatile butenolides **34**–**36** (Table 4, entries 1–3), the desired butenolides were obtained in good to excellent yields (Table 4, entries 4–9).

This two-step conversion to the butenolides can be carried out in one pot. Thus, after completion of the olefination, 3% HCl/EtOH was added to the resulting reaction mixture, which was then concentrated in vacuo (conditions A), or heated under reflux (conditions B) to produce the butenolides **33** in good yield (Table 5). Therefore, this is an efficient method for the construction of synthetically important butenolides starting from α-siloxyketones.

Olefination of α-amino ketones: Following the above concept, we examined the olefination of α-aminoketones (Table 6). The reaction of ynolate **3a** with the *N*-methylbenzylaminoketone **46** proceeded smoothly to give a γ-amino unsaturated carboxylate. Since isolation of the resulting amino acid could be potentially difficult, it was treated in situ with thionyl chloride (Method A) to provide *N*-methyl-1,5-dihydropyrrol-2-one (γ-lactam **54**) in 49% yield (Table 6, entry 1). The intermediate acyl chloride probably was immediately trapped by the amino group intramolecularly to generate the lactam by releasing benzyl chloride. Attempted isolation of the amino esters by addition of MeOSOCl, prepared by mixing thionyl chloride and methanol (Method B), resulted in formation of the same γ-lactam **54** quantitatively (Table 6, entry 2). No (*E*)-γ-amino esters could be detected; therefore, we presumed the *Z* selectivity to be extremely high. In the cyclization to the lactams, the leaving groups on nitrogen should be activated by alkyl groups such as benzyl and allyl, since ketone **47** having a dimethylamino group did not furnish the lactam (Table 6, entry 3). In the case of *N*,*N*-dibenzylamine (Table 6, entries 4 and 5), method A provided the lactam **55** in better yield (Table 6, entry 4). The appropriate cyclization conditions seem to be dependent on the substrate. If the *N*-R^1 group were easily removable, this process would be synthetically useful. We therefore tried to use carbamoyl (Boc and Cbz) and *p*-methoxyphenyl groups as R^1, but instead of the desired lactams, only complex mixtures were generated (Table 6, entries 6–8). Reaction of the unprotected compound (R^1 = H) was likewise unsuccessful (Table 6, entry 9). Finally, the *N*,*N*-diallylamine **53** provided the desired γ-lactam **60** in good yield (Table 6, entry 10),

Table 4. Conversion to butenolides.

9 33

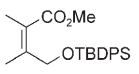
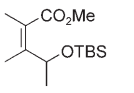
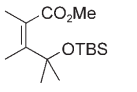
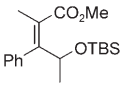
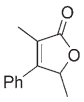
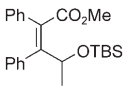
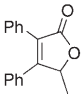
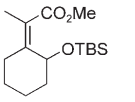
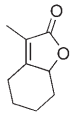
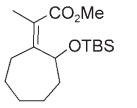
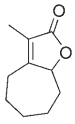
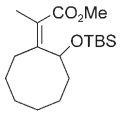
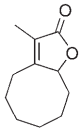
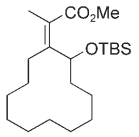
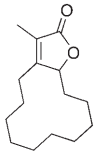
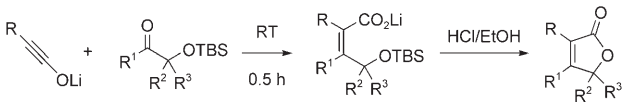
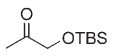
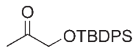
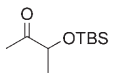
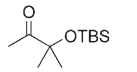
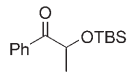
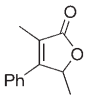
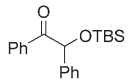
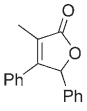
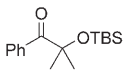
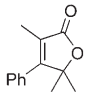
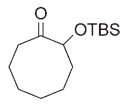
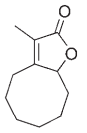
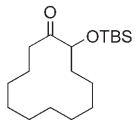
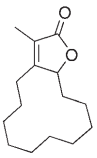
Entry	γ-Siloxyacrylate	Butenolide	Yield [%]
1	 **11**	 **34**	24
2	 **12**	 **35**	68
3	 **13**	 **36**	65
4	 **7e**	 **37**	>99
5	 **16**	 **38**	>99
6	 **22**	 **39**	84
7	 **25**	 **40**	83
8	 **26**	 **41**	>99
9	 **27**	 **42**	65

Table 5. One-pot synthesis of butenolides.



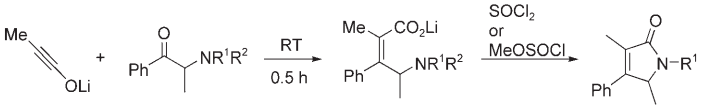
Entry	R	Ketone	Conditions[a]	Butenolide	Yield [%]
1	Bu	 **8a**	B	 **43**	62
2	Me	 **8b**	B	 **34**	14
3	Me	 **8c**	A	 **35**	43
4	Me	 **8d**	A	 **36**	96
5	Me	 **6e**	A	 **37**	75
6	Me	 **8g**	B	 **44**	98
7	Me	 **8f**	A	 **45**	86
8	Me	 **8o**	A	 **41**	80
9	Me	 **8p**	A	 **42**	68

[a] Conditions A: After addition of 3% HCl/EtOH to the carboxylate, the reaction mixture was concentrated in vacuo. Conditions B: After addition of 3% HCl/EtOH to the carboxylate, the reaction mixture was refluxed for 3 h.

and the *N*-allyl group was efficiently removed by treatment with Pd/C in the presence of $BF_3{\cdot}OEt_2$ (Scheme 7).[28]

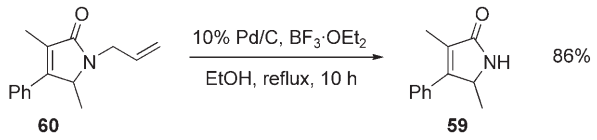
Based on these results, olefination reactions using with several combinations of ynolates and α-aminoketones were examined (Table 7). The less substituted α-aminoacetophenone **61** and the sterically hindered α-aminopinacolone **62** gave γ-lactams **64** and **65**, respectively (Table 7, entries 1 and 2). The phenyl-, isopropyl-, and butyl-substituted ynolates also furnished the desired lactams in good yield (Table 7, entries 3–5). The dialkyl α-amino ketone **63** gave

Table 6. Olefination of α-aminopropiophenone derivatives providing γ-butyrolactams.



Entry	Amino ketone			Conditions[a]	γ-Lactam	
		R^1	R^2			Yield [%]
1	**46**	Me	benzyl	A	**54**	49
2	**46**	Me	benzyl	B	**54**	>99
3	**47**	Me	Me	B	**54**	complex mixture
4	**48**	benzyl	benzyl	A	**55**	68
5	**48**	benzyl	benzyl	B	**55**	36
6	**49**	Boc	benzyl	B	**56**	complex mixture
7	**50**	Cbz	benzyl	B	**57**	complex mixture
8	**51**	*p*-methoxyphenyl	benzyl	B	**58**	complex mixture
9	**52**	H	benzyl	B	**59**	complex mixture
10	**53**	allyl	allyl	A	**60**	87
11	**53**	allyl	allyl	B	**60**	53

[a] Method A: A THF solution of $SOCl_2$ (3 equiv) was added at −10 °C and the solution was stirred at room temperature for 12–17 h. Method B: A THF solution of MeOSOCl, prepared from $SOCl_2$ and MeOH, was added at −10 °C and the solution was stirred at room temperature for 12–17 h.



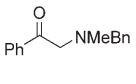
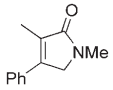
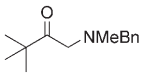
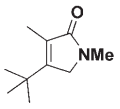
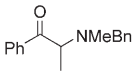
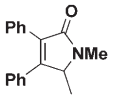
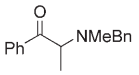
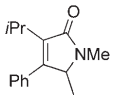
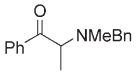
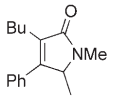
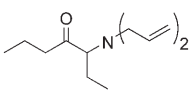
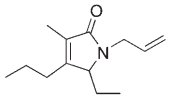
Scheme 7. Removal of the *N*-allyl moiety.

69 under conditions B in good yield. Moreover, the *E* isomers could not be detected in any of these cases.

Chelation or not?: The *E*/*Z* stereochemistry of the olefination products is determined in the thermally conrotatory ring opening of the β-lactone enolate. Since this ring opening would be an irreversible, exothermic reaction, the relative thermodynamic stability of the products might contribute very little to the selectivity, compared with the relative energy of the transition states of the ring-opening process, which must therefore be responsible for the *E*/*Z* selectivity.

Originally, we proposed chelation control as a working hypothesis, in which the ethereal oxygen atom chelates the lithium cation to produce the *Z* olefin (Scheme 3). However, the following experimental observations are not consistent with the chelation mechanism:

Table 7. Olefination of α-aminoketones affording γ-butyrolactams.

Entry	Ynolate (R)	Aminoketones	Conditions[a]	Product	Yield [%]
1	Me	 **61**	A	 **64**	52
2	Me	 **62**	A	 **65**	53
3	Ph	 **46**	A	 **66**	90
4	*i*Pr	 **46**	A	 **67**	60
5	Bu	 **46**	A	 **68**	79
6	Me	 **63**	B	 **69**	73

[a] Conditions A: MeOSOCl (ca. 3 equiv) in methanol was added a room temperature. Conditions B: $SOCl_2$ (ca. 3 equiv) was added at −10 °C.

1) The sterically hindered siloxy and phenoxyl groups, the ethereal oxygen atoms of which are supposed to be much poorer Lewis bases,[25] are also effective for the induction of high *Z* selectivity (Table 1, entries 5 and 7; Table 2, entry 2).
2) Even when olefination of **6e** was carried out in the presence of an excess of [12]crown-4, the selectivity still remained high (*Z*:*E* >99:1) (Table 1, entry 6). This suggests that the metal cation is not always required for stereoselection, and indeed in this case, chelation is not a stereocontrolling factor.
3) In the olefination of 2-siloxycyclohexanones, an axially oriented siloxy group induced high *Z* selectivity (Table 3, entry 3), while an equatorial group afforded no selectivity (Table 3, entry 2). Ynolates predominantly undergo equatorial attack in both cases to furnish β-lactone enolates, as

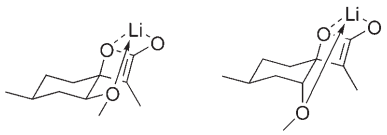


Figure 2. Hypothetical chelation of the lithium cation by equatorial (left) and axial (right) ethereal oxygen atom.

shown in Schemes 5 and 6. If the torquoselectivity is controlled by chelation, the equatorial siloxy group should have been more potent than the axial siloxy group (Figure 2), although organolithium compounds form complex aggregation networks in solution.[29] The experimental results, however, would indicate the opposite trend, as described above.

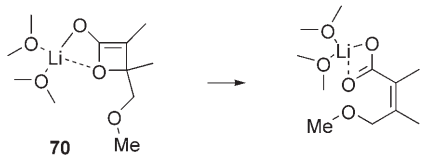
Theoretical studies: The following questions still remain regarding the stereoselectivity: 1) What is the reaction mechanism of the ring opening of the β-lactone enolate? 2) Is the proposed chelation control a genuinely important factor? 3) If not, then what is the role of the α-oxy group in the stereoselectivity? To help us answer these questions, we employed B3LYP hybrid DFT calculations. Natural bond orbital (NBO) theory,[30] which is particularly helpful in determining the stereoelectronic effects of conformations and organic reactions,[31] was used for analyses of the stereoselectivity. The importance of hyperconjugative effects on the stereoselectivities in ring opening of two β-lactone enolates, namely, 4-*tert*-butyl-4-methyloxet-2-enoxide and 4-trimethylsilyl-4-methyloxet-2-enoxide, are already known on the basis of NBO theory.[21]

Computational methods: We employed the B3LYP hybrid functional[32] with the 6-31G(d) basis set[33] for a β-lactone enolate intermediate, namely, lithium 4-methoxymethyl-3,4-dimethyloxet-2-enoxide (**70**), in which the lithium atom is solvated by two Me_2O molecules; the transition states of the ring opening process; and the products.[34,35] Normal coordinate analyses were performed for stationary points. One imaginary frequency was confirmed at each optimized TS structure.

The origin of the stereoelectronic effects of the ring opening of the β-lactone enolate derivative was examined with the aid of NBO analysis.[36] The transition states of the ring opening are reactantlike rather than productlike according the optimal Lewis structure search. Second-order perturbation analysis of bonding NBOs and antibonding NBOs was carried out for these transition states. The second order interaction energy is expressed as Equation (1), where σ/σ^* and F are the filled/vacant NBO and Fock matrices, respectively, ε_σ and ε_σ are the NBO energies of the bonding/lone pair and those of antibonding/Rydberg, respectively, and NBOs are mutually orthogonal.

$$E^{(2)}_{\sigma\sigma^*} = -2\frac{\langle\sigma|F|\sigma^*\rangle^2}{\varepsilon_{\sigma^*}-\varepsilon_\sigma} = -2\frac{F^2_{ij}}{\Delta\varepsilon} \quad (1)$$

Computational reaction pathway: To assess the possibility of chelation by the 4-alkoxymethyl group in the ring-opening reaction, we optimized the transition-state structures in the reaction of **70** (Scheme 8). We found four TSs that lead to *Z*



Scheme 8. Reaction for theoretical calculations.

alkenes (**TSZ1**–**TSZ4**) and three that lead to *E* alkenes (**TSE1**–**TSE3**). The structures are shown in Figure 3, and the relative energies are listed in Table 8. Transition states **TSZ4** and **TSE3** are chelated structures, wherein both the methoxyl and the carboxylate groups are coordinated to the lithium atom, and are much higher in electronic energy, enthalpy, and Gibbs free energy than the other, nonchelated TSs. Hence chelation pathways can be ruled out.[37] The higher energies of **TSZ4** and **TSE3** are due to the deformations of the substrate structure. This is consistent with the high selectivity found experimentally even when a crown ether is added or a lithium ynolate reacts with a bulky siloxy ketone.

Among the TSs investigated, **TSZ1** and **TSE1** were the most stable giving *Z* and *E* alkenes, respectively; **TSZ1** is more stable than **TSE1** by 11.0 kJ mol^{-1} in enthalpy and 13.8 kJ mol^{-1} in Gibbs energy. These results are in good agreement with the high *Z* selectivity obtained experimentally. In **TSZ1**, the methoxyl group at the inwardly rotated 4-methoxymethyl group is nearly perpendicular to the breaking $C^4\cdot\cdot O^1$ bond, and the C^5–H^a bond is antiperiplanar to the breaking $C^4\cdots O^1$ bond (O^1-C^4-C^5-H^a dihedral angle −168.2°; labeling of the C, O, and H atoms is shown in Figure 3). Transition state **TSZ2**, in which the O^6–C^5 bond and the breaking $C^4\cdots O^1$ bond are mutually antiperiplanar, is slightly higher in energy than **TSZ1**. To clarify the hyperconjugative interactions in the transition states which govern the torquoselectivity, an NBO analysis was attempted. As in the transition states described in our previous report,[21] several hyperconjugative interactions were ob-

Table 8. Relative activation energies ($\Delta\Delta E^{\neq}$), activation enthalpies ($\Delta\Delta H^{\neq}$), and Gibbs free energies of activation ($\Delta\Delta G^{\neq}$) at 298.15 K of TSs relative to **TSZ1** in kJ mol^{-1} at the B3LYP/6-31G(d) level. The values in bold are the lowest energies of the **TSE** and **TSZ**.

	$\Delta\Delta E^{\neq}$	$\Delta\Delta H^{\neq}$	$\Delta\Delta G^{\neq}$
TSZ1	**0.0**	**0.0**	**0.0**
TSZ2	4.0	4.5	3.0
TSZ3	14.8	14.3	10.9
TSZ4	16.3	16.3	20.2
TSE1	**10.7**	**11.0**	13.8
TSE2	12.1	11.6	**7.4**
TSE3	31.7	32.2	42.6

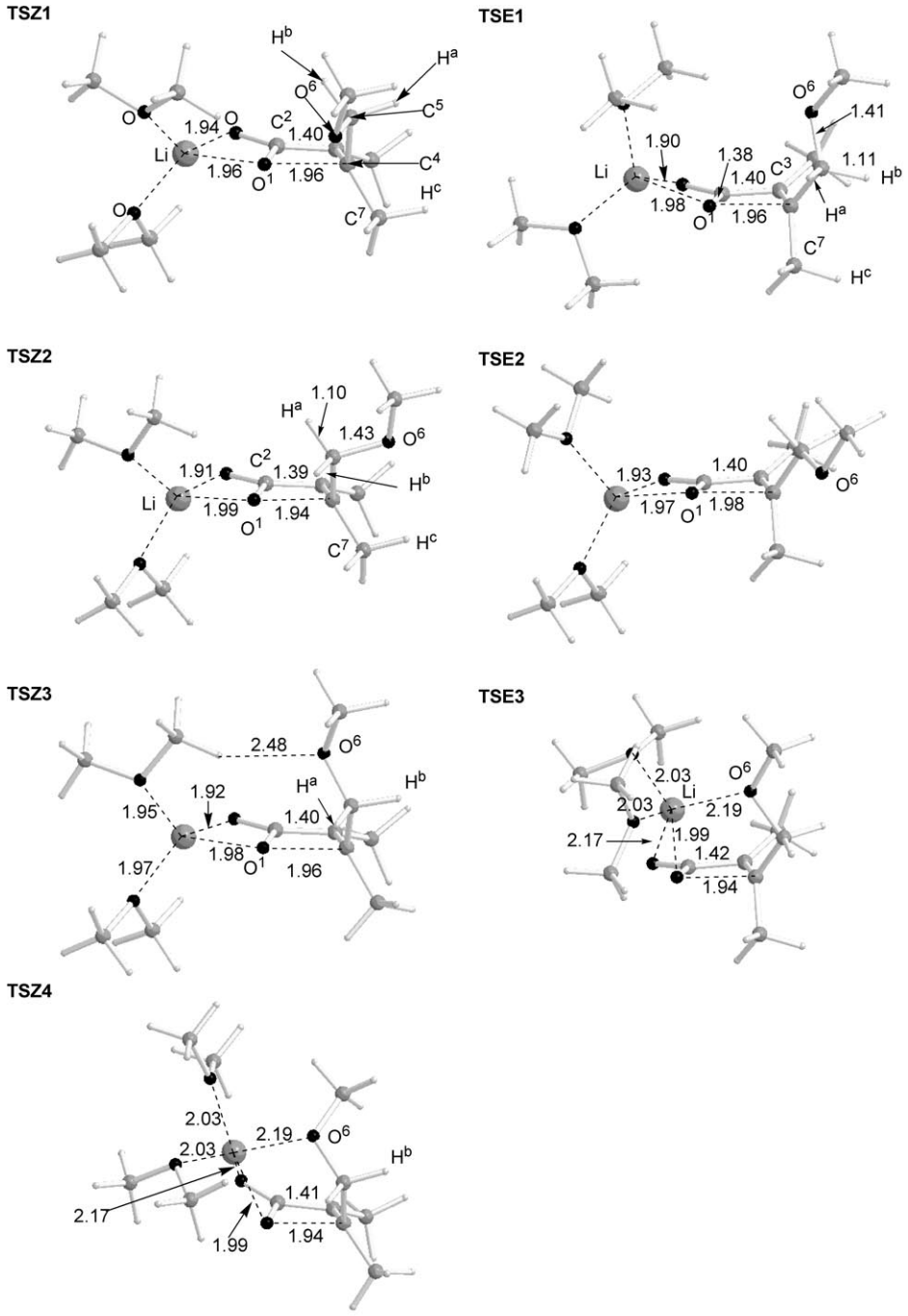


Figure 3. Structures of the transition states of ring opening of $2Me_2O$-solvated lithium 4-methoxymethyl-4-methyloxet-2-enoxide with bond lengths [Å].

served. Although the interactions between $\sigma^*(C^4–O^1)$ and antiperiplanar $\sigma(C^7–H^c$ and $C^5–H^a)$ lead to high stabilization energy in **TSZ1**, **TSZ3**, **TSE1**, and **TSE2**, no definitive differences were observed among them. In **TSZ2**, the interaction of $\sigma(C^4–O^1)$ with antiperiplanar $\sigma^*(C^5–O^6)$ of $-15.8\,kJ\,mol^{-1}$ is one of the most important secondary NBO interactions, and is larger than that of $-3.6\,kJ\,mol^{-1}$ in **TSZ1**. The total steric exchange energy[38] of **TSZ2** is larger than that of **TSZ1** by $16.7\,kJ\,mol^{-1}$. This suggests that the higher energy of **TSZ2** is due to its larger steric repulsion. The larger dipole moment of **TSZ2** (6.33 D) compared with that of **TSZ1** (5.26 D) suggests that the former could be detected in polar media.

Mechanistic considerations: Torquoselectivity in the ring opening of the β-lactone enolates should be considered in elucidating the stereoselectivity. Houk et al. found that torquoselectivity in ring opening of cyclobutenes is subject to stereoelectronic and steric effects. According to their theoretical and experimental studies, the electron-donating substituent preferentially rotates outward, and the electron-withdrawing substituent inward.[18] In their early articles,[39] the stereoelectronic factors of the substituents mainly involved unsaturated groups with π orbitals and halo substituents with lone pairs. The π orbitals and the lone pairs are electron-donating, while the π* orbitals are electron-withdrawing. Recently, Murakami et al.[40] and Houk et al.[41] indicated the significant role of σ* orbitals in the ring-opening transition states of cyclobutenes (Figure 4). They pointed out that, in the transition states of the ring opening of cyclobutenes, trialkylsilyl and fluoromethyl groups with low-lying σ* orbitals prefer inward rotation, because the overlap between the breaking σ orbital and the σ* orbital of the substituents stabilizes the transition states of the inward rotation. Recent NBO studies by Mori and Shindo also support the hypotheses of Houk and Murakami on the basis of the ring opening of the β-lactone enolate, especially the importance of the interaction of the electron-rich oxygen atom with the C–Y bond antiperiplanar to the breaking C···O bond. Inagaki et al. ascribed a different explanation, namely, participation of the geminal C–X bond. However, such C–X bond participation is not important in ring opening of alkylsilyloxetenoxides and dialkyloxetenoxides compared with the X–Y bond participation, es-

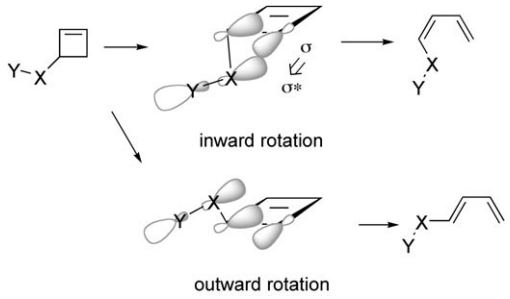


Figure 4. Orbital interaction of the transition states for cyclobutene ring opening, as depicted by Murakami and Houk.

pecially in ring opening of 4-methoxymethyl-4-methyloxet-2-enoxide.

Alabugin and Zeidan published theoretical studies on the hyperconjugative acceptor ability of σ bonds.[42] According to the NBO analysis, σ*(C–OH) and σ*(C–NH_2) are much better acceptors than σ*(C–H) and σ*(C–CH_3). Based on these reports and on our NBO second-order perturbation analyses, we propose the following stereocontrol mechanism of the olefination of α-oxy and α-amino ketones. In the ring opening of β-lactone enolates, the breaking σ(C^4–O^1) orbital of the substituent overlaps with the σ*(C^5–OR) orbitals efficiently to stabilize the inward transition state (Figure 5).

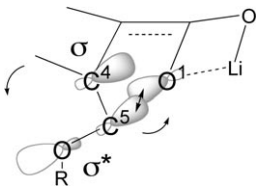


Figure 5. Transition state of inward rotation is stabilized by orbital interaction between σ(C^4–O^1) and σ*(C^5–OR).

The high *Z* selectivity of the ketones, even with less Lewis basic or sterically hindered ethereal α-oxygen atoms, can be explained by this mechanism, and lithium cations are not required for the stereoselectivity. In the conformationally fixed enolates, the σ* orbital of the axially oriented C^5–OR bond can efficiently overlap with that of the breaking C^4–O^1 bond, while the σ* orbital of the equatorially oriented C^5–OR bond can not (Figure 6). This would explain why the former transition states led to good *Z* selectivity and the latter to none. The α-acyloxy ketones, which should have

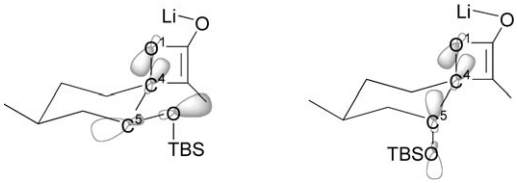


Figure 6. Orbital interactions of the conformationally fixed system.

lower lying σ*(C–O) orbitals, would have been thought to afford better selectivity, but gave instead a complex mixture that included a small amount of the desired products.

Conclusion

We have developed a highly *Z*-selective olefination of α-oxy and α-amino ketones via ynolate anions under mild conditions. The stereocontrol mechanism can be explained by orbital interactions between the σ orbital of the breaking C–O bond or π orbital of the enolate and the σ* orbital of the C–O or C–N bonds of the substituent in the ring opening of the β-lactone enolate intermediates, and/or the chelation to lithium. This is therefore the first general method for the olefination of ketones, and the stereochemistry can be theoretically predicted. In addition, the products are easily converted to synthetically useful multisubstituted butenolides and γ-lactams. These results demonstrate that ynolates are not only efficient olefination reagents but also can be used as multifunctional carbanions.

Experimental Section

General methods: ^{1}H NMR spectra were measured in $CDCl_3$ solution and referenced to TMS (0.00 ppm) on AL400 (400 MHz) spectrometers, unless otherwise noted. ^{13}C NMR spectra were measured in $CDCl_3$ solution and referenced to $CDCl_3$ (77.0 ppm) on AL400 spectrometers (100 MHz). IR spectra were recorded on a JASCO FT/IR-410 spectrometer. Mass spectra were obtained on a JEOL GX303 and GCMS (JMS-AM SUN 200). Column chromatography was performed on silica gel (Kanto Chemical Co.). Thin-layer chromatography was performed on precoated plates (0.25 mm, silica gel Merck Kieselgel 60 F_{245}). Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. *tert*-Butyllithium was titrated with diphenylacetic acid. All reactions were performed in oven-dried glassware under positive pressure of argon, unless otherwise noted. The stereochemistry was determined by NOE experiments (Supporting Information), unless otherwise noted.

Representative procedure for olefination of α-oxyketones: (*Z*)-methyl 4-methoxy-2-methyl-3-phenyl-2-pentenoate (7a): A solution of *tert*-butyllithium (3.58 mL, 4.8 mmol, 1.34 M in pentane) was added dropwise to a solution of ethyl 2,2-dibromopropionate (312 mg, 1.2 mmol) in THF (6 mL) at −78 °C under argon. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless reaction mixture was warmed to room temperature, and then a solution of 2-methoxy-1-phenylpropan-1-one (**6a**, 164 mg, 1.0 mmol) in THF (2 mL) was added. After 0.5 h, methyl iodide (0.62 mL, 10 mmol) and hexamethylphosphoramide (HMPA) (1.7 mL, 10 mmol) were added. After 18 h, saturated NH_4Cl solution (10 mL) was added and the resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil, which was purified by HPLC to yield 190 mg (81 %) of the ester as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.18$ (d, $J = 6.4$ Hz, 3H), 1.71 (s, 3H), 3.36 (s, 3H), 3.81 (s, 3H), 4.40 (q, $J = 6.4$ Hz, 1H), 7.11 (dd, $J = 1.2$ Hz, 8.0 Hz, 2H), 7.28–7.38 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta =$ 17.7, 19.9, 51.7, 56.7, 77.6, 127.2, 128.0, 128.1, 128.8, 137.3, 145.4, 170.7 ppm; IR (neat): $\tilde{\nu} = 1730\ cm^{-1}$; MS (EI): *m*/*z*: 234 [M^+], 59 (100 %); HRMS (EI) calcd for $C_{14}H_{18}O_3$: 234.1256; found: 234.1248.

3a-Hydroxy-3,3,6-trimethylhexahydrobenzofuran-2-one (29): A solution of *tert*-butyllithium (3.18 mL, 4.8 mmol, 1.51 M in pentane) was added dropwise to a solution of ethyl 2,2-dibromopropionate (312 mg,

1.2 mmol) in THF (6 mL) at −78 °C under argon. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting pale yellow reaction mixture was cooled to −78 °C, and a solution of α-oxyketone **8l** (242 mg, 1.0 mmol) in THF (2 mL) was added. After 0.5 h, methyl iodide (0.31 mL, 5 mmol) was added. After 1.5 h, saturated $NaHCO_3$ solution (10 mL) was added, and the mixture was allowed to warm to room temperature. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and concentrated to give a 20:1 diastereomeric mixture of the β-lactone **28** (346 mg) as a pale yellow oil. Tetrabutylammonium fluoride (TBAF, 1.0 mL, 1.0 mmol, 1.0 M in THF) was added to a solution of the β-lactone **28** (200 mg) in THF (10 mL) at 0 °C, and then the mixture was stirred for 1.5 h at room temperature. Water was added, and the reaction mixture was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated to give a residue, which was purified by column chromatography (silica gel, $CHCl_3$/AcOEt 90/10) to afford γ-lactone **29** (71.4 mg, 71 % in two steps) as a colorless solid. Lactone **29** was recrystallized from ethyl acetate/hexane: m.p. 144–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (d, $J =$ 5.6 Hz, 3H), 1.17 (s, 3H), 1.23 (s, 3H), 1.43 (dt, $J = 4.4$ Hz, 12.8 Hz, 1H), 1.48–1.71 (m, 5H), 1.99–2.04 (m, 1H), 2.17 (s, 1H), 4.20 ppm (dd, $J =$ 4.0 Hz, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.3$ (q), 19.9 (q), 21.8 (q), 27.8 (t), 30.8 (d), 31.5 (t), 47.8 (s), 78.0 (s), 80.8 (d), 181.6 ppm (s); IR ($CHCl_3$): $\tilde{\nu} = 1777$, 3610 cm^{-1}; MS (EI): m/z: 198 [M^+], 70 (100 %); elemental analysis calcd (%) for $C_{11}H_{18}O_3$: C 66.64, H 9.15; found: C 66.39, H 9.13.

CCDC-261697 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

5-Hydroxy-3,3,7-trimethyl-1-oxaspiro[3.5]nonan-2-one (31): A solution of *tert*-butyllithium (3.22 mL, 4.8 mmol, 1.49 M in pentane) was added dropwise to a solution of ethyl 2,2-dibromopropionate (312 mg, 1.2 mmol) in THF (6 mL) under argon at −78 °C. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting pale yellow solution was cooled to −78 °C and then a solution of α-oxyketone **8m** (242 mg, 1.0 mmol) in THF (2 mL) was added. After 0.5 h, methyl iodide (0.31 mL, 5 mmol) was added and the solution was stirred for 1.5 h. Saturated $NaHCO_3$ solution (10 mL) was added, and the mixture was allowed to warm to room temperature. The resulting mixture was extracted with ethyl acetate. The organic phase was washed with water, saturated $NaHCO_3$ solution, and brine, dried over $MgSO_4$, filtered, and concentrated to give a 3:1 diastereomeric mixture of β-lactone **30** as a pale yellow oil. Tetrabutylammonium fluoride (TBAF, 1.0 mL, 1.0 mmol, 1.0 M in THF) was added to a solution of β-lactone **30** in THF (20 mL) at 0 °C, and the mixture was stirred for 1.0 h at room temperature. Water was added and the mixture was extracted with Et_2O, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 70/30) to afford β-lactone **31** (107 mg, 54 % in 2 steps) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.93$ (d, $J = 6.4$ Hz, 3H), 1.19–1.30 (m, 1H), 1.30 (s, 3H), 1.39–1.41 (m, 1H), 1.45 (s, 3H), 1.47–1.51 (m, 1H), 1.61–1.69 (m, 1H), 1.73–1.83 (m, 1H), 1.86–2.01 (m, 2H), 4.13–4.16 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 18.0$ (q), 18.2 (q), 21.7 (q), 24.5 (d), 26.8 (t), 29.6 (t), 38.4 (t), 54.7 (s), 68.7 (d), 83.5 (s), 176.0 ppm (s); IR (neat): $\tilde{\nu} = 1805$, 3492 cm^{-1}; MS (EI): m/z: 198 [M^+], 70 (100 %); HRMS (EI): calcd for $C_{11}H_{18}O_3$: 198.1256; found: 198.1254.

3,3,7-Trimethyl-1-oxaspiro[3,5] nonane-2,5-dione (32): *N*-Methylmorpholine *N*-oxide (NMO, 23.4 mg, 0.2 mmol) and powdered 4 Å molecular sieves (50 mg) were added to a solution of β-lactone **31** (19.8 mg, 0.1 mmol) in dry CH_2Cl_2 (1.0 mL) at room temperature. After 10 min, tetrapropylammonium perruthenate (3.5 mg, 0.01 mmol) was added to the mixture, which was stirred for 1 h at room temperature, then filtered through Celite. The filtrate was washed with saturated Na_2SO_3, saturated $CuSO_4$, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 70/30) to afford ketone **32** (17.1 mg, 87 %) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.05$ (d, $J = 7.6$ Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.74–1.81 (m, 1H), 1.83–1.91 (m, 1H), 2.22–2.42 (m, 4H), 2.50–2.56 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 17.3$ (q), 18.8 (q), 19.9 (q), 28.9 (t), 30.0 (t), 31.4 (d), 48.6 (t), 56.4 (s), 86.7 (s), 172.9 (s), 205.4 ppm (s); IR (neat): $\tilde{\nu} = 1724$, 1828 cm^{-1}; MS (EI): m/z: 196 [M^+], 70 (100 %); HRMS (EI) calcd for $C_{11}H_{16}O_3$: 196.1099; found: 196.1098.

Synthesis of 29 and 31 from 32: $NaBH_4$ (2.2 mg, 0.058 mmol) was added to a solution of β-lactone **32** (11.4 mg) in MeOH (0.5 mL) at 0 °C, and the mixture was stirred for 15 min at 0 °C. The reaction mixture was then concentrated in vacuo. Water was added to the residue, which was extracted with AcOEt, dried over $MgSO_4$, filtered, and concentrated to give a 3:2 mixture of **31** and **29** (11.4 mg, 99 %) as a colorless turbid oil.

3,4-Dimethyl-2(5*H*)-furanone (34)[43] (Table 4, entry 1): 6 M HCl solution was added to a solution of methyl ester **11** (30 mg, 0.078 mmol) in EtOH (1 mL), and then the mixture was refluxed for 2.5 h. Water was added to the reaction mixture and it was extracted with CH_2Cl_2. The organic layer was washed with a saturated $NaHCO_3$ solution (pH > 7) and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by column chromatography (silica gel, hexane/AcOEt 80/20), followed by preparative TLC to afford butenolide **34** (2.1 mg, 24 %) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.83$ (s, 3H), 2.02 (s, 3H), 4.62 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.4$ (q), 12.3 (q), 72.5 (t), 123.1 (s), 156.1 (s), 175.2 ppm (s); IR (neat): $\tilde{\nu} = 1748$ cm^{-1}; MS (EI): m/z: 112 [M^+], 55 (100 %); HRMS (EI) calcd for $C_6H_8O_2$: 112.0524; found: 112.0530.

Representative procedure for one-pot synthesis of butenolides (Table 5, conditions B): A solution of *tert*-butyllithium (3.48 mL, 4.8 mmol, 1.38 M in pentane) was added dropwise to a solution of ethyl 2,2-dibromopropionate (312 mg, 1.2 mmol) in THF (6 mL) at −78 °C under argon. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless or pale yellow reaction mixture was warmed to room temperature, and a solution of α-oxyketone **8a** (188 mg, 1.0 mmol) in THF (2 mL) was added. After 0.5 h, 3 % HCl/EtOH was added to the mixture, which was refluxed for 3 h and concentrated in vacuo. The residue was quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 90/10 to 80/20) to afford butenolide **43** (95.0 mg, 62 %) as a yellow oil. 3-Butyl-4-methyl-2(5*H*)-furanone (**43**)[44] (Table 5, entry 1): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.92$ (t, $J = 7.2$ Hz, 3H), 1.32 (sext, $J = 7.2$ Hz, 2H), 1.48 (quint, $J = 7.2$ Hz, 2H), 2.02 (s, 3H), 2.26 (t, $J = 7.6$ Hz, 2H), 4.62 ppm (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 12.2$ (q), 13.7 (q), 22.4 (t), 23.0 (t), 29.9 (t), 72.3 (t), 127.1 (s), 156.4 (s), 174.9 ppm (s); IR (neat): $\tilde{\nu} =$ 1747 cm^{-1}; MS (EI): m/z: 154 [M^+], 112 (100 %).

General procedure for one-pot synthesis of the butenolides (Table 5, conditions A): A solution of *tert*-butyllithium (4.8 equiv) was added dropwise to a solution of ethyl 2,2-dibromopropionate (1.2 equiv) in THF at −78 °C under argon. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless or pale yellow reaction mixture was warmed to room temperature, and a solution of the α-oxyketone (1.0 equiv) in THF was added. After 0.5 h, 3 % HCl/EtOH was added, and the resulting mixture was concentrated in vacuo. The residue was neutralized with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography to afford the butenolide.

General procedure for one-pot synthesis of γ-lactam from α-amino ketone (Table 6, method B): A solution of *tert*-butyllithium (4.8 equiv) was added dropwise to a solution of ethyl 2,2-dibromopropionate (1.2 equiv) in THF at −78 °C under argon. The yellow solution was stirred for 3 h at −78 °C and allowed to warm to 0 °C. After 30 min, the resulting colorless or pale yellow reaction mixture was warmed to room temperature, and a solution of the α-amino ketone (1.0 equiv) in THF was added. After 0.5 h, MeOSOCl (ca. 3 equiv), prepared from MeOH and $SOCl_2$ at −10 °C, was added at room temperature. After 15–20 h, the reaction mixture was concentrated in vacuo, and MeOH was added. The residue was concentrated in vacuo, diluted with Et_2O, acidified with 5 % HCl, and extracted with Et_2O. The water phase was basified with 28 %

aqueous NH_3 and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give a residue, which was purified by column chromatography to afford the lactam.

3,5-dimethyl-4-phenyl-1,5-dihydro-2-pyrrolone (59):[45] $BF_3{\cdot}Et_2O$ (0.063 mL, 0.5 mmol) was added to a solution of *N*-allyl lactam **60** (113 mg, 0.5 mmol) and 10% Pd/C (113 mg) in absolute EtOH (5 mL) at room temperature, and then the mixture was refluxed. After 11 h, the reaction mixture was filtered through Celite and concentrated. The residue was purified by column chromatography (silica gel, hexane/AcOEt 40/60) to afford γ-lactam **59** (80.1 mg, 86%) as a yellow powder: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, J = 6.4 Hz, 3H), 2.02 (d, J = 1.6 Hz, 3H), 4.59 (q, J = 7.2 Hz, 1H), 7.33 (dd, J = 1.2 Hz, 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.46 ppm (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8 (q), 19.0 (q), 54.3 (d), 127.9 (d), 128.4 (d), 128.5 (d), 128.5 (s), 133.0 (s), 155.1 (s), 174.6 ppm (s); IR (neat): $\tilde{\nu}$ = 3232, 1682 cm^{-1}; MS (EI): m/z: 187 $[M]^+$ (100%).

Acknowledgement

This work was supported in part by a Grant-in-Aid for Scientific Research in the Priority Area (A) "Exploitation of Multi-Element Cyclic Molecules" from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and PRESTO, JST. We thank Prof. R. L. Danheiser (MIT) for helpful discussions. The generous allotment of computational time from the Research Center for Computational Science, the National Institutes of Natural Sciences, Japan, is gratefully acknowledged.

[1] S. E. Kelly in *Comprehensive Organic Synthesis, Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 729–817.

[2] For a representative review of Wittig olefination, see: B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.

[3] For a representative review of the Horner–Wadsworth–Emmons reaction, see: W. S. Wadsworth, *Org. React.* **1977**, *25*, 73–253.

[4] For a review, see: P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.

[5] For reviews, see: a) D. J. Ager, *Org. React.* **1990**, *38*, 1; b) A. G. M. Barrett, J. M. Hill, E. M. Wallace, J. A. Flygare, *Synlett* **1991**, 764–770; c) L. F. van Staden, D. Gravestock, D. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195–200.

[6] For selected examples, see: a) F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613; b) N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. For reviews, see c) O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789–2834; d) R. C. Hartley, G. J. McKierman, *J. Chem. Soc. Perkin Trans. 1* **2000**, 2763–2793.

[7] For recent examples of olefination of ketones leading to tetrasubstituted olefins, see: a) S. Sano, K. Yokoyama, R. Teranishi, M. Shiro, Y. Nagao, *Tetrahedron Lett.* **2002**, *43*, 281–284; b) S. Sano, T. Takehisa, S. Ogawa, K. Yokoyama, Y. Nagao, *Chem. Pharm. Bull.* **2002**, *50*, 1300–1302; c) T. Mantani, K. Shiomi, T. Konno, T. Ishihara, H. Yamanaka, *J. Org. Chem.* **2001**, *66*, 3442–3448.

[8] For example, the Sharpless asymmetric epoxidation of trisubstituted allylic alcohols (tetrasubstituted olefins) provides the corresponding epoxides with high enantioselectivity. Since the products have contiguous asymmetric carbon atoms, they would be useful for synthesis of natural products: a) T. J. Erickson, *J. Org. Chem.* **1986**, *51*, 934–935; b) J. A. Marshall, T. M Jenson, *J. Org. Chem.* **1984**, *49*, 1707–1712.

[9] For an example, see: A. S. Levenson, V. C. Jordan, *Eur. J. Cancer* **1999**, *35*, 1628–1639.

[10] For recent examples, see: a) T. Fukaminato, T. Sakaki, T. Kawai, T. Tamai, M. Irie, *J. Am. Chem. Soc.* **2004**, *126*, 14843–14849; b) J. F. Valliant, P. Schaffer, K. A. Stephenson, J. F. Britten, *J. Org. Chem.* **2002**, *67*, 383–387; c) R. Rathore, M. I. Deselnicu, C. L. Burns, *J. Am. Chem. Soc.* **2002**, *124*, 14832–14833; d) N. Harada, A. Saito, N. Koumura, H. Uda, B. de Lange, W. F. Jager, H. Wynberg, B. L. Feringa, *J. Am. Chem. Soc.* **1997**, *119*, 7241–7248.

[11] For recent examples of stereoselective construction of tetrasubstituted olefins via carbometalation of alkynes, see: a) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670–14671; b) C. Zhou, D. E. Emrich, R. C. Larock, *Org. Lett.* **2003**, *5*, 1579–1582; c) N. Zhu, D. G. Hall, *J. Org. Chem.* **2003**, *68*, 6066–6069; d) P. E. Tessier, A. J. Penwell, F. E. S. Souza, A. G. Fallis, *Org. Lett.* **2003**, *5*, 2989–2992; e) L. F. Tietze, K. Kahle, T. Raschke, *Chem. Eur. J.* **2002**, *8*, 401–407; f) J. P. Marino, H. N. Nguyen, *J. Org. Chem.* **2002**, *67*, 6291–6296; g) M. Hojo, Y. Murakami, H. Aihara, R. Sakuragi, Y. Baba, A. Hosomi, *Angew. Chem.* **2001**, *113*, 641–643; *Angew. Chem. Int. Ed.* **2001**, *40*, 621–623. For other approaches, see h) I. Maciagiewicz, P. Dybowski, A. Skowronska, *Tetrahedron* **2003**, *59*, 6057–6066; i) M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, T. Hiyama, *J. Am. Chem. Soc.* **2001**, *123*, 6947–6948; j) H. Kakiya, H. Shinokubo, K. Oshima, *Tetrahedron* **2001**, *57*, 10063–10069; k) M. Ide, M. Nakata, *Synlett Synlett* **2001**, 1511–1515; l) X. Liu, M. Shimizu, T. Hiyama, *Angew. Chem.* **2004**, *116*, 897–900; *Angew. Chem. Int. Ed.* **2004**, *43*, 879–882.

[12] M. Shindo, Y. Sato, R. Koretsune, T. Yoshikawa, K. Matsumoto, K. Itoh, K. Shishido, *Chem. Pharm. Bull.* **2003**, *51*, 477–478.

[13] a) M. Shindo, *Tetrahedron Lett.* **1997**, *38*, 4433–4436; b) M. Shindo, Y. Sato, K. Shishido, *Tetrahedron* **1998**, *54*, 2411–2422; c) M. Shindo, R. Koretsune, W. Yokota, K. Itoh, K. Shishido, *Tetrahedron Lett.* **2001**, *42*, 8357–8360.

[14] For reviews, see a) M. Shindo, *Synthesis* **2003**, 2275–2288; b) M. Shindo, *J. Syn. Org. Chem. Jpn.* **2000**, *58*, 1155–1166; c) M. Shindo, *Yakugaku Zasshi* **2000**, *120*, 1233–1246; d) M. Shindo, *Chem. Soc. Rev.* **1998**, *27*, 367–374.

[15] a) M. Shindo, Y. Sato, K. Shishido, *Tetrahedron Lett.* **1998**, *39*, 4857–4860; b) M. Shindo, Y. Sato, T. Yoshikawa, R. Koretsune, K. Shishido, *J. Org. Chem.* **2004**, *69*, 3912–3916.

[16] For pioneering work, see: a) C. J. Kowalski, K. W. Fields, *J. Am. Chem. Soc.* **1982**, *104*, 321–323. For Lewis acid mediated olefination with silyl ynol ethers, see: b) C. J. Kowalski, S. Sakdarat, *J. Org. Chem.* **1990**, *55*, 1977–1979.

[17] M. Shindo, Y. Sato, K. Shishido, *J. Org. Chem.* **2000**, *65*, 5443–5445.

[18] a) W. R. Dolbier, Jr., H. Koroniak, D. J. Burton, A. R. Bailey, G. S. Shaw, S. W. Hansen, *J. Am. Chem. Soc.* **1984**, *106*, 1871; b) W. Kirmse, N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1984**, *106*, 7989–7991; c) N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111; d) E. A. Kallel, Y. Wang, D. C. Spellmeyer, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 6759–6763; e) S. Niwayama, E. A. Kallel, C. Sheu, K. N. Houk, *J. Org. Chem.* **1996**, *61*, 2517–2522; f) for a review, see: g) W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471–477.

[19] a) H. Ikeda, T. Kato, S. Inagaki, *Chem. Lett.* **2001**, 270–271; b) M. Yasui, Y. Naruse, S. Inagaki, *J. Org. Chem.* **2004**, *69*. 7246–7249.

[20] M. Shindo, K. Matsumoto, S. Mori, K. Shishido, *J. Am. Chem. Soc.* **2002**, *124*, 6840–6841.

[21] S. Mori, M. Shindo, *Org. Lett.* **2004**, *6*, 3945–3949.

[22] F. Bonadies, A. Cardilli, A. Lattanzi, S. Pesci, A. Scettri, *Tetrahedron Lett.* **1995**, *36*, 2839–2840.

[23] a) S. I. Pennanen, *Tetrahedron Lett.* **1977**, *18*, 2631–2632; b) S. I. Pennanen, *Tetrahedron Lett.* **1980**, *21*, 657–658.

[24] For other olefinations of α-oxy ketones and aldehydes, see: a) M. Koreeda, P. D. Patel, L. Brown, *J. Org. Chem.* **1985**, *50*, 5910–5912; b) P. Garner, S. Ramakanth, *J. Org. Chem.* **1987**, *52*, 2629–2631. c) C. Harcken, S. F. Martin, *Org. Lett.* **2001**, *3*, 3591–3593; d) K. Ukai, D. Arioka, H. Yoshino, H. Fushimi, K. Oshima, K. Utimoto, S. Matsubara, *Synlett* **2001**, 513–514.

[25] In Cram's chelation model, siloxy groups did not give efficient chelation. a) X. Chen, E. R. Hortelano, E. L. Eliel, S. V. Frye, *J. Am. Chem. Soc.* **1992**, *114*, 1778–1784; b) S. Mori, M. Nakamura, E. Nakamura, N. Koga, K. Morokuma, *J. Am. Chem. Soc.* **1995**, *117*, 5055–5065; for a review, see: c) A. Mengel, O. Reiser, *Chem. Rev.* **1999**, *99*, 1191–1223.

[26] For translactonization of siloxy β-lactones to γ-lactones, see: a) R. Zemribo, M. S. Champ, D. Romo, *Synlett* **1996**, 278–280; b) L. Fournier, A. Gaudel-Siri, P. J. Kocienski, J.-M. Pons, *Synlett* **2003**, 107–111.
[27] For a recent review, see: N. B. Carter, A. E. Nadany, J. B. Sweeney, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2324–2342.
[28] S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313–1316.
[29] For a representative review, see: D. Seebach, *Angew. Chem.* **1988**, *100*, 1685; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624–1654.
[30] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926, and references therein.
[31] a) V. Pophristic, L. Goodman, *Nature* **2001**, *411*, 565–568; b) F. Weinhold, *Nature* **2001**, *411*, 539–541; c) F. M. Bickelhaupt, E. Baerends, *Angew. Chem.* **2003**, *115*, 4315–4320; *Angew. Chem. Int. Ed.* **2003**, *42*, 4183–4188; d) F. Weinhold, *Angew. Chem.* **2003**, *115*, 4320–4326; *Angew. Chem. Int. Ed.* **2003**, *42*, 4188–4194; e) Y. Mo, W. Mu, L. Song, M. Ling, Q. Zhang, J. Gao, *Angew. Chem.* **2004**, *116*, 2020–2024; *Angew. Chem. Int. Ed.* **2004**, *43*, 1986–1990; f) Recent experimental results show that the equilibrium conformation of 3-hexyne is *syn*-eclipsed. R. K. Bohn, *Phys. Chem. A J. Phys. Chem. B* **2004**, *108*, 6814–6816.
[32] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[33] W. J. Hehre, L. Radom, P. von R. Schleyer, J. A. Pople, *Ab Initio Molecular Orbital Theory*, John Wiley, New York, **1986**, and references therein.
[34] For previous theoretical studies on ring opening of oxetenes, in addition to ref. [5], see: a) K. van der Meer, J. J. C. Mulder, *Theor. Chim. Acta.* **1975**, *37*, 159–169; b) H. Yu, W-T. Chan, J. D. Goddard, *J. Am. Chem. Soc.* **1990**, *112*, 7529–7537; c) R. P. Hsung, C. A. Zificsak, L.-L. Wei, C. J. Douglas, H. Xiong, J. A. Mulder, *Org. Lett.* **1999**, *1*, 1237–1240; d) M. Oblin, M. Rajzmann, J.-M. Pons, *Tetrahedron* **2001**, *57*, 3099–3104.
[35] Gaussian 98, Revision A.11.3, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
[36] NBO Version 5.0 implemented by E. D. Glendening, A. E. Reed, J. E. Carpenter, F. Weinhold.
[37] If one assumes unsolvated pathways, the chelated TSs are more stable than the nonchelated ones. These results suggest that we must take into account solvent coordination in the current studies.
[38] a) J. K. Badenhoop, F. Weinhold, *J. Chem. Phys.* **1997**, *107*, 5406–5421; b) J. K. Badenhoop, F. Weinhold, *J. Chem. Phys.* **1997**, *107*, 5422–5432; c) J. K. Badenhoop, F. Weinhold, *Int. J. Quantum Chem.* **1999**, *72*, 269–280.
[39] a) S. Niwayama, E. A. Kallel, C. Sheu, K. N. Kouk, *J. Org. Chem.* **1996**, *61*, 2517–2522; b) S. Niwayama, E. A. Kallel, D. C. Spellmeyer, C. Sheu, K. N. Houk, *J. Org. Chem.* **1996**, *61*, 2813–2825, and references therein.
[40] a) M. Murakami, Y. Miyamoto, Y. Ito, *Angew. Chem.* **2001**, *113*, 182–184; *Angew. Chem. Int. Ed.* **2001**, *40*, 189–190; b) M. Murakami, M. Hasegawa, H. Igawa, *J. Org. Chem.* **2004**, *69*, 587–590; c) M. Murakami, M. Hasegawa, *Angew. Chem.* **2004**, *116*, 4982–4984; *Angew. Chem. Int. Ed.* **2004**, *43*, 4874–4876; d) M. Murakami, I. Usui, M. Hasegawa, T. Matsuda, *J. Am. Chem. Soc.* **2005**, *127*, 1366–1367.
[41] P. S. Lee, X. Zhang, K. N. Houk, *J. Am. Chem. Soc.* **2003**, *125*, 5072–5079.
[42] I. V. Alabugin, T. A. Zeidan, *J. Am. Chem. Soc.* **2002**, *124*, 3175–3185.
[43] E. P. Woo, F. C. W. Cheng, *J. Org. Chem.* **1986**, *51*, 3706–3707.
[44] R. L. Edwards, A. J. S. Whalley, *J. Chem. Soc. Perkin Trans. 1* **1979**, 803–806.
[45] B. Kryczka, A. Laurent, B. Marguet, *Tetrahedron* **1978**, *34*, 3291–3298.

Received: May 24, 2005
Published online: September 28, 2005

