A Practical and Efficient Method for the Synthesis of β-Lactones

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This paper describes a convenient one-step preparation of β-lactones based on the addition of thiol ester enolates to carbonyl compounds. Under the proper conditions the resulting aldolates undergo spontaneous cyclization to produce β-lactones in good to excellent yield. The new β-lactone synthesis provides access to 2-oxetanones with a variety of substituents and substitution patterns. In general, thiol ester enolates combine with carbonyl compounds to form the less sterically crowded β-lactone diastereomers, and in some cases the reaction proceeds with excellent stereoselectivity. In conjunction with the stereospecific decarboxylation of β-lactones, this chemistry also provides a very attractive approach to the synthesis of substituted alkenes.

In this paper we report a convenient synthetic route to β-lactones which should greatly improve access to this important class of heterocycles.[2] Interest in β-lactones has increased dramatically during the past 10 years with the recognition that this heterocyclic system constitutes the key structural feature in a number of biologically interesting natural products.[3] During this period the utility of β-lactones as versatile synthetic intermediates has also grown in importance. Nucleophilic cleavage of the strained 2-oxetanone ring takes place under relatively mild conditions with a variety of organometallic reagents and heteroatom nucleophiles, and these reactions have been exploited in useful new syntheses of propionic acid derivatives,[4] tetrahydrofurans,[5] and α-amino acids.[6] Upon thermolysis, β-lactones undergo stereospecific decarboxylation,[2] and as discussed further below, this process provides the basis for a valuable synthetic approach to alkenes.

The synthesis of β-lactones has received considerable attention[2] since the first representative of this class of heterocycles was prepared by Einhorn in 1883.[7] Classical routes to β-lactones generally involved the cyclization of β-halocarboxylate salts[2] and the related "deaminative cyclization" which occurs upon diazotization of β-amino acids.[8] β-Hydroxy acids undergo a similar cyclization under Mitsunobu conditions,[6,9,10] and the halolactonization of α,β-unsaturated acids[11] is a related process of some interest. Although these classical methods have been successfully employed for the preparation of a variety of β-lactones, it should be noted that their utility is often limited by side reactions including β-elimination (to form α,β-unsaturated acids) and decarboxylative elimination (to generate alkenes).

A few methods permit the direct conversion of ketones and aldehdyes to β-lactones in a single step. For example, certain ketenes participate in Lewis acid catalyzed [2 + 2] cycloadditions with carbonyl compounds,[2,12] and β-lactones also result from addition reactions involving ynolate anions.[13] The most popular method for the transformation of ketones and aldehydes to β-lactones employs a two-stage protocol: condensation of the carbonyl compound with a carboxylic acid dianion,[14] followed by cyclization induced by treatment with benzenesulfonyl chloride in pyridine.[15,16] Although not applicable to the

(1) American Chemical Society Division of Organic Chemistry Graduate Fellow, 1988-1989.

(2) For reviews of the chemistry and synthesis of β-lactones, see: (a) Zaugg, H. E. *Org. React.* **1954**, *8*, 305. (b) Kröper, H. In *Methoden der organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Georg Thieme: Stuttgart, 1963; Vol. 6/2, pp 511-559. (c) Etienne, Y.; Fischer, N. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Ed.; Interscience: New York, 1964; Part 2, Vol. 19, Chapter 6, pp 729-884. (d) Searles, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, Chapter 5.13.

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(4) For recent examples, see: (a) Normant, J. F.; Alexakis, A.; Cahiez, G. *Tetrahedron Lett.* **1980**, *21*, 935. (b) Shinoda, M.; Iseka, K.; Oguri, T.; Hayasi, Y.; Yamada, S.-I.; Shibasaki, M. *Tetrahedron Lett.* **1986**, *27*, 87. (c) Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403 and references cited therein.

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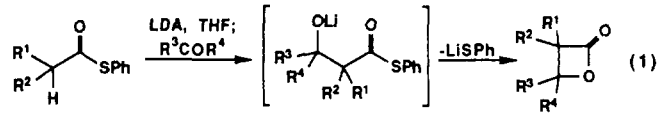
preparation of derivatives that lack α-substituents, this method currently reigns as the most generally useful route to substituted β-lactones.[17]

Results and Discussion

In this paper we describe a very convenient one-step preparation of β-lactones based on the addition of thiol ester enolates to carbonyl compounds. Under the proper conditions the resulting aldolates undergo a spontaneous cyclization to provide β-lactones in good to excellent yield (eq 1).



1 $R^1 = R^2 = H$
2 $R^1 = CH_3$, $R^2 = H$ 5 $R^1 = OMe$, $R^2 = H$
3 $R^1 = i\text{-Pr}$, $R^2 = H$ 6 $R^1 = Et$, $R^2 = H$
4 $R^1 = R^2 = Me$ 7 $R^1 = t\text{-Bu}$, $R^2 = H$

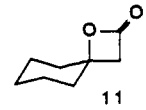
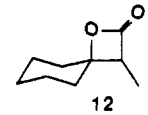
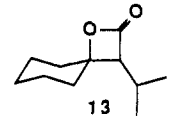
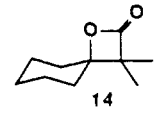
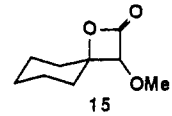
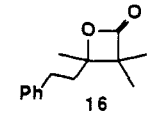
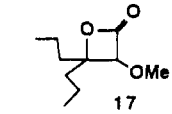
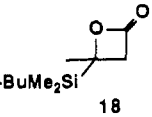
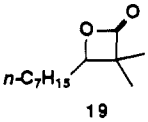
8 9

The thiol esters employed as starting materials for this method are readily available compounds which can either be obtained from commercial sources or prepared in one step from carboxylic acid derivatives.[18] For example, the thiophenol esters **1–7** were conveniently prepared in 80–98% yield via combination of the appropriate commercially available acid chlorides and thiols in the presence of pyridine. Exposure of these thiol esters to 1 equiv of LDA in THF at −78 °C for 30 min furnishes the expected lithium enolates, which smoothly combine with ketones and aldehydes at −78 °C as originally reported by Wemple.[19] Gradual warming (generally to 0 °C) then produces the desired β-lactones.

The facility and generality of this spontaneous lactonization process has not been noted previously. In Wemple's 1975 study the aldol addition reaction was carried out at −78 °C, and low-temperature quenching afforded only the expected β-hydroxy thiol esters. Although similar cyclizations have been detected in thiol ester aldol reactions on two occasions previously, both of these reactions involved unusual, α-functionalized derivatives, and in each case the β-lactone was generated in low yield as a minor byproduct of the aldol reaction.[20,21] Masamune has shown that the cyclization of thiol ester aldol products can be effected as a separate operation by treatment of the β-hydroxy thiol esters at room temperature with excess mercury(II) methanesulfonate and Na_2HPO_4 in acetonitrile.[22]

Both ketones and aldehydes can be employed as carbonyl components in the new β-lactone synthesis. Reactions involving ketones are most conveniently carried out by adding the neat carbonyl compound to the thiol ester enolate solution. Interestingly, under these conditions

Table I. Preparation of β-Lactones via Thiol Esters

entry	carbonyl compound	thiol ester	β-lactone	yield,[a] %
1	cyclohexanone	1	 11	86
2	cyclohexanone	2	 12	92
3	cyclohexanone	3	 13	48, 72[b]
4	cyclohexanone	4	 14	87
5	cyclohexanone	5	 15	78
6	4-phenyl-2-butanone	4	 16	62
7	4-heptanone	5	 17	43
8	$CH_3COSi\text{-}t\text{-}BuMe_2$	1	 18	55
9	*n*-octanal	4	 19	54

[a] Isolated yields of products purified by distillation, recrystallization, or column chromatography on silica gel. [b] Yield obtained by using *S*-2,6-dimethylphenyl 3-methylbutanethioate.

(16) Cyclization of β-hydroxy acids via other mixed anhydride derivatives is generally less efficient. For examples, see: (a) Toivonen, N. J.; Hirsjärvi, P.; Melaja, A.; Kainulainen, A.; Holonen, A.; Pulkkinen, E. *Acta Chem. Scand.* **1949**, *3*, 991. (b) Diassi, P. A.; Dylion, L. M. *J. Am. Chem. Soc.* **1958**, *80*, 3746. (c) Boswell, G. H.; Dauben, W. G.; Ourisson, G.; Rull, T. *Bull. Soc. Chim. Fr.* **1958**, 1598. (d) Sheehan, J. C.; Hasspacher, K.; Yeh, Y. L. *J. Am. Chem. Soc.* **1959**, *81*, 6086. (e) Testa, E.; Fontanella, L.; Mariani, L. *J. Org. Chem.* **1960**, *25*, 1812. (f) Burgstahler, A. W.; Wetmore, D. E. *J. Org. Chem.* **1961**, *26*, 3516. (g) Knunyants, I. L.; Cherburkov, Y. A. *Izv. Akad. Nauk SSSR Otd. Khim. Nauk.* **1961**, 808. (h) Blume, R. C. *Tetrahedron Lett.* **1969**, 1047.

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(20) Dagli, D. J.; Yu, P.-S.; Wemple, J. *J. Org. Chem.* **1975**, *40*, 3173.

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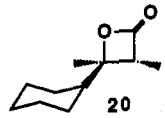
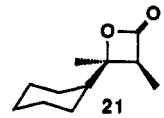
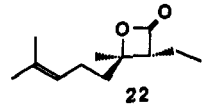
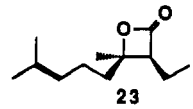
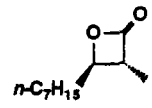
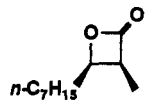
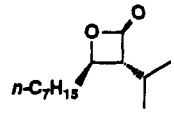
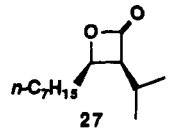
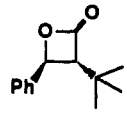
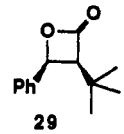
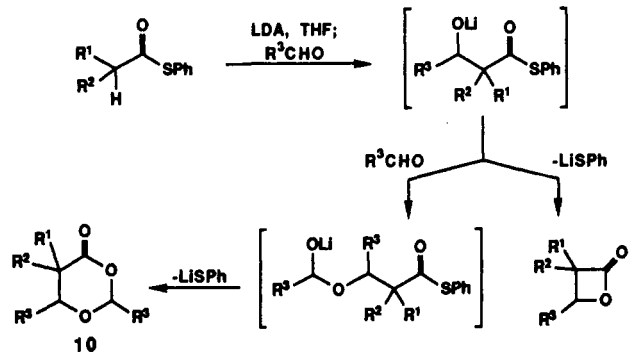
Table II. Stereochemical Course of the β-Lactone Synthesis

entry	carbonyl compd	thiol ester	β-lactone		ratio[a]	yield,[b] %
1	acetylcyclohexane	2	 20	 21	29:1 (180:1)[c]	75
2	6-methyl-5-hepten-2-one	6	 22	 23	1.8:1	84
3	*n*-octanal	2	 24	 25	2.5:1	42
4	*n*-octanal	3	 26	 27	1:3 (5:1)[d]	66
5	benzaldehyde	7	 28	 29	34:1	85

[a] Isomer ratios were determined by ^{1}H NMR analysis of reaction products prior to purification. [b] Isolated yields of products purified by distillation, recrystallization, or column chromatography on silica gel. [c] Ratio of isomers after low-temperature (−78 °C, 3×) recrystallization from pentane. [d] Ratio obtained using the 2,6-dimethylphenyl thiol ester.

Scheme I



10

aliphatic aldehydes react to form substantial quantities of 2:1 adducts of type **10**. As outlined in Scheme I, these byproducts appear to be generated via the interception of the aldolate intermediate by unreacted aldehyde. Fortunately, the formation of this side product can be suppressed simply by adding the aldehyde component slowly as a precooled (−78 °C) solution to the reaction mixture.

As detailed in the Experimental Section, the isolation and purification of the β-lactone products generally is straightforward. Solids (and liquids with melting points near room temperature) are conveniently purified by low-temperature recrystallization from pentane, and other β-lactones can be distilled using a Kugelrohr oven provided that the temperature is kept below 100 °C to minimize thermal decarboxylation. β-Lactones derived from the reactions of aliphatic ketones and aldehydes can also be purified without significant decomposition by column chromatography on silica gel. Note, however, that lactones with cation-stabilizing substituents (e.g. aryl groups) at the C-4 (β) position may decompose unless the chromatographic purification is carried out at −20 °C.[23]

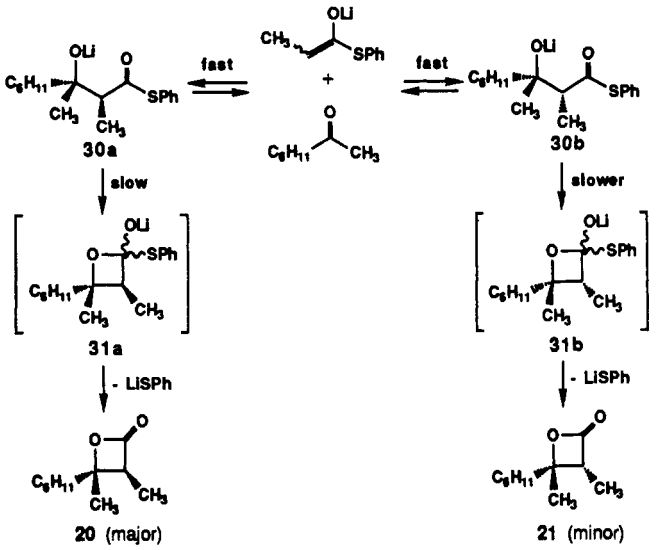
Scope and Limitations of the Method. As delineated in Table I, the new β-lactone synthesis provides access to 2-oxetanones with a variety of substituents and substitution patterns. Thiol ester derivatives of acetic, propionic, and isobutyric acid all participate smoothly in the reaction, producing β-lactones with zero, one, or two substituents at the α-position of the new ring. Thiol esters bearing α-methoxy groups (and presumably other heteroatom substituents) can be used to prepare α-heterosubstituted lactones. To promote facile cyclization of the intermediate aldolates, *thiophenol* ester derivatives are best employed in all of these reactions. No cyclization was observed to take place upon warming the adduct obtained from the reaction of *S*-ethyl ethanethioate (CH_3COSEt) with cyclohexanone.

β-Branching in the thiol ester component appears to have a detrimental effect on the yield of reactions involving ketone (but not aldehyde) substrates. For example, condensation of cyclohexanone with the thiophenol ester derivative of isovaleric acid gave the desired β-lactone **13** in only 48% yield (Table I, entry 3). However, we have found that the yield in this case can be increased considerably by employing the 2,6-dimethylbenzenethiol ester derivative for the reaction, and this stratagem may prove effective in improving the efficiency of other reactions involving sterically encumbered reactants (vide infra).

A variety of ketones, aldehydes, and acylsilanes function as suitable substrates for the β-lactone synthesis, although a few limitations of the method have been noted. α,β-Unsaturated ketones such as methyl vinyl ketone and cyclohexenone fail to yield β-lactones, and spectroscopic analysis of the crude reaction products implicates enone polymerization and conjugate addition processes as competing reaction pathways. Attempts to generate β-lactones with severe steric crowding have also met with limited success. For example, condensation of the isobutyrate ester **4** with cyclododecanone produced the desired β-lactone in less than 10% yield; substantial quantities of both ketone and thiol ester starting materials were recovered from this and similar reactions. Further studies are planned to determine whether the outcome of these problematic re-

(23) See refs 15e, 15f, and the following: Adam, W.; Fick, H.-H. *J. Org. Chem.* **1979**, *44*, 356.

Scheme II



actions can be improved by the use of hindered thiol esters or via other modifications in the experimental procedure.

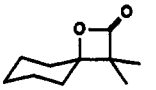
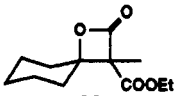
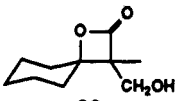
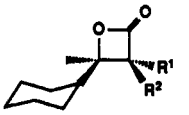
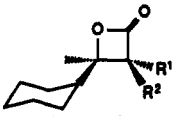
Stereochemical Course of the β-Lactone Synthesis. The data presented in Table II provides useful insight concerning the stereochemical course of the β-lactone synthesis.[24] Not surprisingly, thiol ester enolates combine with ketones to predominantly form the less sterically crowded β-lactone diastereomers, in some cases with excellent stereoselectivity. However, the stereochemical outcome of reactions involving aldehydes have proven to be more complicated. Although most of the aldehyde condensations we have studied have led to the formation of trans-disubstituted lactones, in one anomalous case (Table II, entry 4) the cis isomer was isolated as the major product. Interestingly, this stereoselectivity was reversed when the corresponding 2,6-dimethylphenylthiol ester was used in place of the usual thiophenol derivative. Also noteworthy is the observation that the "normal" trans-substituted lactone is produced when octanal reacts with thiophenol ester derivatives of unbranched carboxylic acids such as propionate (entry 3) and *n*-butyrate (6:1 ratio in a preliminary experiment).

The stereochemical results summarized above are difficult to explain simply on the basis of the kinetic selectivity expected for the initial aldol addition step. Particularly anomalous is the preferential formation of the cis-substituted lactone **27** and the surprisingly high selectivity observed in the reaction of acetylcyclohexane (Table II, entry 1). Scheme II outlines a mechanism which accounts for the stereochemical outcome of the latter reaction. We propose that rapid and *reversible* aldol condensation generates both **30a** and **30b**, and the high anti selectivity observed in this case is then a consequence of the more rapid subsequent cyclization of the anti aldolate to form a less sterically congested tetrahedral intermediate (**31a**).

Synthetic Elaboration of β-Lactone Products. The ready availability of thiol esters and the simplicity and convenience of the reaction conditions described above should make this new procedure the method of choice for the preparation of a variety of β-lactones. In conjunction with the stereospecific decarboxylation of β-lactones, this chemistry also provides a very attractive approach to the synthesis of substituted alkenes. The utility of this olefination strategy is further enhanced by the ability of our β-lactone products to undergo subsequent synthetic elaboration via the corresponding enolates. Mulzer has previously demonstrated that β-lactone enolates are relatively stable species that combine in good yield with a variety of standard electrophiles.[25,26] Table III illustrates

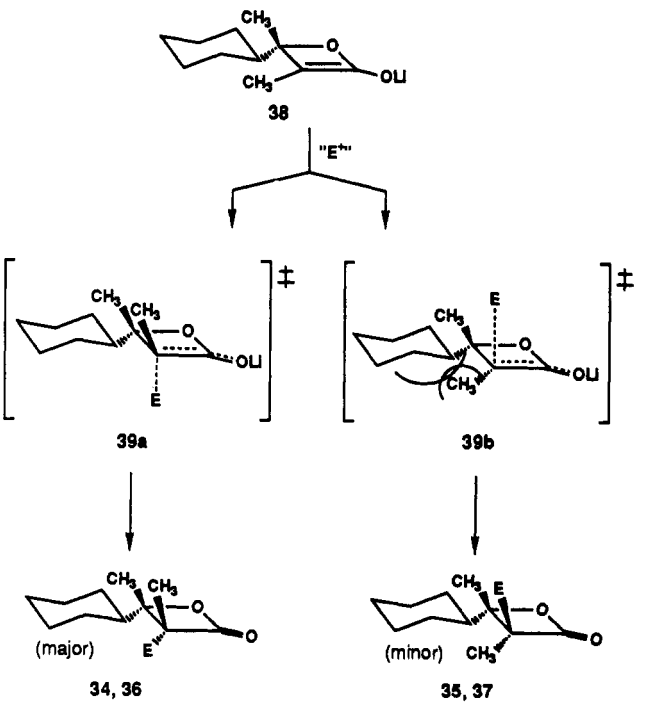
(24) The stereochemistry of β-lactones derived from aldehydes (Table II, entries 3–5) was determined by analysis of ^{1}H NMR coupling constants.[25] In other cases stereochemistry was assigned on the basis of NOE experiments (see the Experimental Section for details).

Table III. Reaction of β-Lactone Enolates with Electrophiles

entry	β-lactone	electrophile	product	ratio[a]	yield,[b] %
1	12	CH_3I	 14		82
2	12	$ClCO_2Et$	 32		87
3	12	HCHO	 33		64
4	20	$ClCO_2Et$	 34 R^1=Me, R^2=CO_2Et 35 R^1=CO_2Et, R^2=Me	1.5:1	82
5	20	$PhCH_2Br$	 36 R^1=Me, R^2=CH_2Ph 37 R^1=CH_2Ph, R^2=Me	4:1	67

[a] Isomer ratios were determined by ^{1}H NMR analysis of reaction products prior to purification. [b] Isolated yields of products purified by distillation, recrystallization, or column chromatography on silica gel.

Scheme III

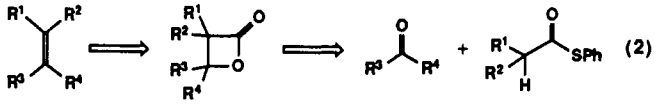


the application of this chemistry to the synthetic elaboration of our β-lactone products. Note that this approach can thus provide access to functionalized and tetrasubstituted β-lactones that would be difficult to generate directly (in one step) by our method.

As indicated in entries 4 and 5 (Table III), reactions of the enolate derived from the trisubstituted β-lactone **20** lead to diastereomeric mixtures in which the major products result from attack of the electrophile cis to the bulky cyclohexyl group. These results stand in contrast to Mulzer's observation of high trans selectivity in substitution reactions involving enolate derivatives of 3,4-disubstituted β-lactones.[25,26] As outlined in Scheme III, the predominant formation of the cis products **34** and **36** can be rationalized by assuming that the most severe steric interaction in the transition state of these reactions is the destabilizing eclipsing interaction involving the cyclohexyl and C-2 methyl groups.

Synthesis of Substituted Alkenes. Since the 19th century it has been known that upon heating β-lactones undergo facile [2 + 2] cycloreversion to generate alkenes and carbon dioxide.[2] This stereospecific process[27] generally takes place at temperatures between 80 and 160 °C, with the rate of reaction highly dependent on the nature of substituents present at the C-4 (β) position of the lactone ring. Electron-donor groups have been shown to greatly facilitate the decarboxylation, while electron-withdrawing substituents have a retarding effect on the rate of cycloreversion.[28] The reaction often proceeds in near quantitative yield, and in recent years has been applied to the synthesis of a variety of types of substituted and functionalized alkenes.[29]

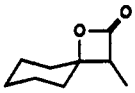
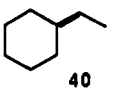
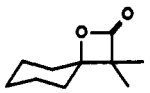
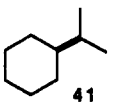
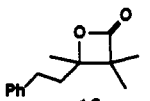
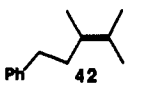
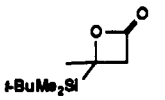
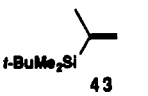
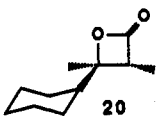
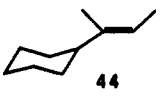
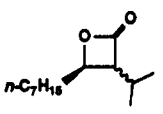
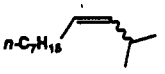
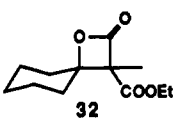
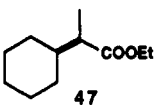
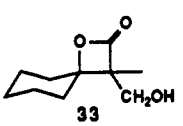
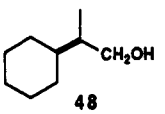
We anticipate that the improved route to β-lactones reported in this paper will increase the attractiveness of this general strategy for the synthesis of alkenes. As formulated in eq 2, this two-step method employs readily available starting materials, involves mild reaction conditions, and is simple and convenient to carry out. In addition, as illustrated in Table IV, the conversion of β-lactones to olefins is generally an extremely efficient process.



(2)

Two experimental protocols were employed to effect these transformations. Alkenes with boiling points of ca. 250 °C or greater were prepared by heating a benzene or cyclohexane solution of the requisite β-lactone at reflux in the presence of an equal weight of chromatographic silica gel[30] (entries 3, 7, and 8). Alkenes boiling at 200 °C or lower were best generated by Kugelrohr distillation at 80–110 °C from a mixture of the lactone and 10 wt % of silica gel[31] at reduced pressure (entries 1, 2, 4, and 5). In these reactions the distillation was performed at a pressure such that the alkene product distilled as it was generated, leaving the less volatile β-lactone behind in the distillation flask. In one case the procedures outlined proved unsatisfactory. Decarboxylation of the mixture of **26** and **27** proceeded in poor yield and at only a slightly enhanced rate in the presence of silica gel. This reaction was therefore best carried out by pyrolyzing the lactone mixture at 175 °C in a Kugelrohr oven at atmosphere pressure; the desired alkenes were obtained stereospecifically in 75% yield in this manner.

Table IV. Conversion of β-Lactones to Alkenes

entry	β-lactone	alkene	yield,[a] %
1	 **12**	 **40**	90
2	 **14**	 **41**	88
3	 **16**	 **42**	95
4	 **18**	 **43**	93
5	 **20**	 **44**	95
6	 **26, 27** (1:3)	 1:3 **45**(trans), **46**(cis)	75 (88)[b]
7	 **32**	 **47**	97
8	 **33**	 **48**	77

[a] Isolated yields of purified products. [b] Yield corrected for unreacted β-lactone.

(25) Mulzer has shown that in a large number of 3,4-disubstituted β-lactones $J_{3,4}$ (cis) = 6.5 Hz and $J_{3,4}$ (trans) = 4.5 ● 0.5 Hz; see: Mulzer, J.; Kerkmann, T. *J. Am. Chem. Soc.* **1980**, *102*, 3620.

(26) (a) Mulzer, J.; Chucholowski, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 777. (b) Mulzer, J.; Chucholowski, A.; Lammer, O.; Jibril, I.; Huttner, G. *J. Chem. Soc., Chem. Commun.* **1983**, 869. (c) Mulzer, J.; de Lasalle, P.; Chucholowski, A.; Blaschek, U.; Brüntrup, G. *Tetrahedron* **1984**, *40*, 2211.

(27) (a) Noyce, D. S.; Banitt, E. H. *J. Org. Chem.* **1966**, *31*, 4043. (b) Sultanbawa, M. U. S. *Tetrahedron Lett.* **1968**, 4569. (c) Mageswaran, S.; Sultanbawa, M. U. S. *J. Chem. Soc., Perkin Trans. 1* **1976**, 884. (d) Mulzer, J.; Pointner, A.; Chucholowski, A.; Bruntrup, G. *J. Chem. Soc., Chem. Commun.* **1979**, 52.

(28) For discussion of the mechanism of this thermal decarboxylation, see: (a) Krabbenhoft, H. O. *J. Org. Chem.* **1978**, *43*, 1305. (b) Imai, T.; Nishida, S. *J. Org. Chem.* **1979**, *44*, 3574. (c) Imai, T.; Nishida, S. *J. Org. Chem.* **1980**, *45*, 2354. (d) Mulzer, J.; Zippel, M. *Tetrahedron Lett.* **1980**, *21*, 751. (e) Mulzer, J.; Zippel, M.; Brüntrop, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 465. (f) Issacs, N. S.; Laila, A. H. *Tetrahedron Lett.* **1983**, *24*, 2897. (g) Minato, T.; Yamabe, S. *J. Org. Chem.* **1983**, *48*, 1479. (h) Moyano, A.; Pericàs, M. A.; Valenti, E. *J. Org. Chem.* **1989**, *54*, 573.

(29) For examples, see refs 15, 23, and the following: (a) Marshall, J. A.; Faubl, H. *J. Am. Chem. Soc.* **1970**, *92*, 948. (b) Ganem, B.; Holbert, G. W.; Weiss, L. B.; Ishizumi, K. *J. Am. Chem. Soc.* **1978**, *100*, 6483. (c) Luengo, J. I.; Koreeda, M. *Tetrahedron Lett.* **1984**, *25*, 4881. (d) Renzoni, G. E.; Yin, T.-K.; Miyake, F.; Borden, W. T. *Tetrahedron* **1986**, *42*, 1581.

(30) The use of silica gel to promote the decarboxylation of β-lactones has previously been reported by Adam.[15f]

(31) Less silica gel is used in this variant to minimize the quantity of water released during distillation. Completely anhydrous silica gel (flame-dried in vacuo) was found to catalyze olefin isomerization in some cases and could not be used for the decarboxylation.

In contrast to the uncatalyzed process, the stereochemical course of the silica gel promoted decarboxylation of β-lactones has not previously been examined. Entry 5 in Table IV demonstrates that under these conditions the cycloreversion is indeed a stereospecific process.

In conclusion, we anticipate that this strategy will find considerable use as a method for the stereoselective synthesis of alkenes. Although this olefination strategy involves one more step than the classic Wittig reaction, in many cases it may prove to be the more practical method. Thiol esters have a number of advantages over phosphonium salts as starting materials (thiophenol is considerably less expensive than triphenylphosphine), and the byproducts in this approach (thiophenol and CO_2) are much easier to separate from reaction products than is triphenylphosphine oxide. With respect to the number of operations, the β-lactone strategy is no more involved than the Wittig approach, since the decarboxylation step can often be accomplished simply by distilling the crude lactone product. Finally, the scope, overall efficiency, and stereoselectivity of the β-lactone route compares favorably to the Wittig, Julia-Lythgoe, and related established strategies for the synthesis of tri- and tetrasubstituted alkenes.

Experimental Section

Materials. Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, pyridine, and diisopropylamine were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl or dianion. Ethyl chloroformate and all liquid ketones and aldehydes were distilled before use; sufficient foreruns were discarded to ensure removal of water azeotropes. Methyl iodide and benzyl bromide were passed through a short plug of flame-dried neutral Al_2O_3 prior to use. Acetylcyclohexane was purified by column chromatography on silica gel after distillation under reduced pressure. Merck or Baker silica gel (230–400 mesh) was used in the decarboxylation of β-lactones. *n*-Butyllithium was titrated with *sec*-butyl alcohol using 1,10-phenanthroline as indicator.[32]

General Procedures. All reactions were performed in flame- or oven-dried glassware under a positive pressure of argon or nitrogen (with the exception of reactions performed under reduced pressure). Reaction mixtures were stirred magnetically unless otherwise indicated. Solutions of alkyllithium reagents were transferred by syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions were concentrated by using a Buchi rotary evaporator at 1–30 mmHg. Column chromatography was performed on Merck or Baker silica gel (230–400 mesh).

General Procedure for the Preparation of Thiol Esters. Preparation of *S*-Phenyl Propanethioate (2). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with 100 mL of methylene chloride, thiophenol (10.2 mL, 100 mmol), and pyridine (8.1 mL, 100 mmol) and then cooled in an ice bath while butanoyl chloride (10.4 mL, 100 mmol) was added by syringe over 5 min. The resulting suspension of white solid was stirred for an additional 5 min at 0 °C and at room temperature for 30 min and then poured into 100 mL of H_2O. The aqueous phase was separated and extracted with 25 mL of methylene chloride, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Short-path distillation (62–70 °C, ca. 0.05 mmHg) afforded 17.5 g (97%) of thiol ester **2** as a colorless oil: IR (film) 3058, 2964, 2930, 2870, and 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (app s, 5 H), 2.63 (t, J = 7.4 Hz, 2 H), 1.73 (m, 2 H), and 0.99 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 134.6, 129.4, 129.3, 128.1, 45.3, 18.8, and 13.2.

Thiol esters **3–7** were prepared by means of this procedure in 80–98% yield. Thiol ester **1** was purchased from Aldrich Chemical Co.

(32) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

General Procedure A for the Preparation of β-Lactones from Thiol Esters and Ketones. Preparation of 3-Methyloxetan-2-one-4-spirocyclohexane (12). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and thermometer was charged with 100 mL of THF and diisopropylamine (3.1 mL, 22 mmol) and then cooled in an ice bath while *n*-butyllithium solution (1.67 M in hexanes, 12.4 mL, 20.7 mmol) was added via syringe over 2 min. (When preparing β-lactones on a 1–5-mmol scale, the reaction was performed at 0.1 M concentration, and the temperature was measured externally.) After 15 min, the ice bath was replaced with a dry ice-acetone bath (–78 °C), and *S*-phenyl propanethioate **2** (3.340 g, 20.1 mmol) was added dropwise via syringe over 2 min. After 30 min, cyclohexanone (2.085 mL, 20.1 mmol) was added dropwise via syringe over 1 min. The reaction mixture was stirred at –78 °C for 30 minutes and then allowed to warm to 0 °C over 1.5 h. Half-saturated NH_4Cl solution (100 mL) was then added, and the resulting mixture was partitioned between 150 mL of water and 150 mL of diethyl ether. The organic phase was extracted with two 250-mL portions of 10% K_2CO_3 solution, 250 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.095 g of a pale yellow oil. Kugelrohr distillation (oven temperature 50 °C, 0.03 mmHg) followed by low-temperature (–78 °C) recrystallization from pentane[33] afforded 2.860 g (92%) of **12** as a low-melting (ca. 25 °C) white solid: IR (film) 2936, 2860, and 1816 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.22 (q, J = 7.7 Hz, 1 H), 1.33–1.95 (m, 10 H), and 1.29 (d, J = 7.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 81.9, 52.3, 37.0, 30.9, 24.6, 22.9, 22.3, and 8.2. Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.20; H, 9.34.

General Procedure B for the Preparation of β-Lactones from Thiol Esters and Aldehydes. Preparation of *trans*- and *cis*-4-Heptyl-3-isopropyloxetan-2-one (26 and 27). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and thermometer was charged with 100 mL of THF and diisopropylamine (3.1 mL, 22 mmol), and then cooled in an ice bath while *n*-butyllithium solution (1.67 M in hexanes, 12.4 mL, 20.7 mmol) was added via syringe over 2 min. (When preparing β-lactones on a 1–5-mmol scale, the reaction was performed at 0.1 M concentration, and the temperature was measured externally). After 15 min, the ice bath was replaced with a dry ice–acetone bath (–78 °C), and *S*-phenyl 3-methylbutanethioate **3** (3.886 g, 20.0 mmol) was added dropwise via syringe over 5 min. After 30 min, a solution of *n*-octanal (2.56 g, 20.0 mmol) in 25 mL of THF was added dropwise over 20 min via a cannula which was cooled at –78 °C by passage through a glass tube filled with dry ice and acetone and capped at the bottom with a rubber septum. The reaction mixture was stirred at –78 °C for 30 min and then allowed to warm to 0 °C over 75 min. Half-saturated NH_4Cl solution (100 mL) was then added, and the resulting mixture was partitioned between 150 mL of water and 150 mL of diethyl ether. The organic phase was extracted with two 250-mL portions of 10% K_2CO_3 solution and 250 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 4.566 g of a pale yellow oil. Kugelrohr distillation (80 °C, ca. 0.001 mmHg), followed by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) gave 2.792 g (66%) of a mixture of **26** and **27** as a very pale yellow oil (1:3 mixture of isomers as determined by ^1H NMR analysis): IR (film) 2958, 2928, 2856, and 1822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for the cis isomer **27** δ 4.54 (ddd, J = 9.4, 6.4, 4.2 Hz, 1 H), 3.30 (dd, J = 11.4, 6.4 Hz, 1 H), 2.12–2.26 (m, 1 H), 1.71–1.79 (m, 2 H), 1.53–1.61 (m, 1 H), 1.23–1.44 (m, 9 H), 1.16 (d, J = 6.6 Hz, 3 H), 0.94 (d, J = 6.5 Hz 3 H), and 0.89 (app t, J = 6.8 Hz, 3 H); for the trans isomer **26** δ 4.27 (ddd, J = 7.4, 5.9, 4.0 Hz, 1 H), 2.97 (dd, J = 8.4, 3.9 Hz, 1 H), 2.00–2.16 (m, 1 H), 1.65–1.91 (m, 2 H), 1.23–1.44 (m, 10 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.6 Hz, 3 H), and 0.89 (app t, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) for the cis isomer **27** (partial data) δ 171.7, 75.8,

(33) In a typical low-temperature recrystallization procedure, an argon filled flask fitted with a rubber septum bearing an argon inlet needle was charged with a solution of the β-lactone in pentane and cooled in a –78 °C bath. After crystallization was complete, the mother liquor was removed using a cannula. The crystals were then washed with additional solvent, the cooling bath removed, and the crystals dried in vacuo.

59.6, 29.8, 28.8, 25.4, 24.3, 21.8, 19.9, and 13.7; for the trans isomer **26** δ 171.2, 76.1, 62.9, 34.4, 31.4, 29.0, 28.8, 27.4, 24.9, 22.3, 20.1, 19.5, and 13.7. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.28; H, 11.53.

Oxetan-2-one-4-spirocyclohexane (11).[22] Reaction of *S*-phenyl ethanethioate **1** (0.152 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and cyclohexanone (0.098 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to −6 °C over 1.5 h. Workup afforded 0.131 g of a pale yellow oil, which was purified by Kugelrohr distillation (oven temperature 25–40 °C, ca. 0.001 mmHg) to give 0.120 g (86%) of **11** as a colorless oil. An analytical sample was obtained by low-temperature recrystallization from pentane: IR (film) 2936, 2858, and 1817 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.07 (s, 2 H), 1.66–1.96 (m, 6 H), and 1.47 (br s, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 78.7, 47.1, 35.7, 24.4, and 23.1. Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.70; H, 8.85.

3-Isopropyloxetan-2-one-4-spirocyclohexane (13). Reaction of *S*-phenyl 3-methylbutanethioate **3** (0.194 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and cyclohexanone (0.098 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to 0 °C over 2 h. Workup afforded 0.201 g of a pale yellow oil, which was purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) to give 0.087 g (48%) of **13** as a colorless oil: IR (film) 3026, 2940, 2870, and 1809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75 (d, J = 11.6 Hz, 1 H), 2.08–2.25 (m, 1 H), 1.86–2.02 (m, 2 H), 1.52–1.80 (m, 7 H), 1.18–1.32 (m, 1 H), 1.15 (d, J = 6.5 Hz, 3 H), and 0.94 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 82.4, 65.6, 37.4, 31.0, 24.8, 24.2, 22.4, 21.9, 21.5, and 19.9. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.55; H, 10.10.

3,3-Dimethyloxetan-2-one-4-spirocyclohexane (14). Reaction of *S*-phenyl 2-methylpropanethioate **4** (9.0 g, 50 mmol) with lithium diisopropylamide (52 mmol) and cyclohexanone (4.9 g, 50 mmol) in 100 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to 0 °C over 2 h. Workup afforded 7.82 g of oily white crystals which were purified by washing with 100 mL of ice-cold pentane to give 7.04 g (84%) of **14** as white crystals. The pentane wash was concentrated, and the resulting oily solid washed with an additional 5 mL of pentane to yield an additional 0.23 g (3%) of white crystals: mp 109–111 °C; IR ($CHCl_3$) 3020, 2936, 2864, and 1807 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.90–2.04 (m, 2 H), 1.57–1.67 (m, 7 H), 1.32 (s, 6 H), and 1.22–1.39 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 85.1, 54.2, 32.0, 24.5, 22.4, and 17.8. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.37; H, 9.69.

3-Methoxyoxetan-2-one-4-spirocyclohexane (15). Reaction of *S*-phenyl 2-methoxyethanethioate **5** (0.182 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and cyclohexanone (0.098 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to 0 °C over 105 min. Workup afforded 0.157 g of a pale yellow oil, which was purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) to give 0.134 g (78%) of **15** as a colorless oil: IR (film) 2988, 2936, 2858, and 1826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (s, 1 H), 3.57 (s, 3 H), and 1.38–1.91 (m, 10 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 87.8, 85.0, 59.2, 35.2, 30.1, 24.7, 23.0 and 22.0. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.73; H, 8.50.

4-(2-Phenylethyl)-3,3,4-trimethyloxetan-2-one (16). Reaction of *S*-phenyl 2-methylpropanethioate **4** (0.901 g, 5.00 mmol) with lithium diisopropylamide (5.2 mmol) and 4-phenylbutan-2-one (0.741 g, 5.00 mmol) in 50 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to 14 °C over 2 h. Workup afforded 1.203 g of a pale yellow oil, which was purified by low temperature (−78 °C) recrystallization from pentane, followed by filtration of an ether solution (to remove suspended solids), concentration, recrystallization (−78 °C) twice more from pentane, and washing with pentane (0 °C) to give 0.672 g (62%) of **16** as a white crystalline solid: mp 51.5–55.5 °C; IR ($CHCl_3$) 3084, 3062, 3022, 2986, 2934, 2868, and 1811 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31 (app t, J = 7.1 Hz, 2 H), 7.19–7.24 (m, 3 H), 2.63–2.77 (m, 2 H), 1.99–2.21 (m, 2 H), 1.57 (s, 3 H), and 1.35 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 141.3, 128.7, 128.3, 126.4, 84.9, 54.8, 38.5, 30.4, 20.0, 19.1, and 18.2. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03, H, 8.31. Found: C, 77.23; H, 8.49.

4,4-Dipropyl-3-methoxyoxetan-2-one (17). Reaction of *S*-phenyl 2-methoxyethanethioate **5** (0.182 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and 4-heptanone (0.114 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure A except that the reaction mixture was allowed to warm to 0 °C over 2 h. Workup afforded 0.190 g of a pale yellow oil, which was purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) to give 0.079 g (43%) of **17** as a colorless oil: IR (film 2966, 2940, 2878, 2840, and 1830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.33 (s, 1 H), 3.54 (s, 3 H), 1.60–1.96 (m, 4 H), 1.30–1.50 (m, 4 H), 0.99 (t, J = 7.3 Hz, 3 H), and 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 87.4, 87.3, 59.1, 37.5, 33.0, 17.0, 15.9, 14.0, and 13.8. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.46; H, 10.04.

4-(*tert*-Butyldimethylsilyl)-4-methyloxetan-2-one (18). Reaction of *S*-phenyl ethanethioate **1** (0.761 g, 5.00 mmol) with lithium diisopropylamide (5.20 mmol) and 1-(*tert*-butyldimethylsilyl)-1-ethanone[34] (0.792 g, 5.00 mmol) in 50 mL of THF was performed according to general procedure A to afford 1.015 g of a yellow oil. Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) provided 0.550 g (55%) of **18** as a colorless oil: IR (film) 2962, 2938, 2892, 2864, and 1822 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (d, AB pattern, J = 16.4 Hz, 1 H), 3.06 (d, AB pattern, J = 16.3 Hz, 1 H), 1.66 (s, 3 H), 0.98 (s, 9 H), 0.13 (s, 3 H), and 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 73.6, 47.2, 26.9, 25.0, 16.9, −8.8, and −8.9. Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 60.23; H, 10.10.

3,3-Dimethyl-4-heptyloxetan-2-one (19). Reaction of *S*-phenyl 2-methylpropanethioate **4** (0.180 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and *n*-octanal (0.128 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure B except that the reaction mixture was allowed to warm to −40 °C over 50 min. Workup afforded 0.207 g of a pale yellow oil, which was purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) followed by Kugelrohr distillation (oven temperature 50 °C, ca. 0.001 mmHg) to provide 0.108 g (54%) of **19** as a colorless oil: IR (film) 2924, 2852, and 1819 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23 (dd, J = 8.6, 5.2 Hz, 1 H), 1.61–1.81 (m, 2 H), 1.41–1.54 (m, 1 H), 1.41 (s, 3 H), 1.26–1.40 (m, 9 H), 1.26 (s, 3 H), and 0.89 (app t, J = 5.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 83.5, 53.1, 31.4, 30.2, 29.0, 28.8, 25.3, 22.3, 16.0, and 13.7. Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.95; H, 11.35.

***r*-4-Cyclohexyl-*t*-3,4-dimethyloxetan-2-one (20) and *r*-4-Cyclohexyl-*c*-3,4-dimethyloxetan-2-one (21).** Reaction of *S*-phenyl propanethioate **2** (3.334 g, 20.06 mmol) with lithium diisopropylamide (20.7 mmol) and acetylcyclohexane (2.534 g, 20.08 mmol) was performed according to general procedure A except that the reaction mixture was allowed to warm to 5 °C over 2 h. Workup afforded 3.733 g of a light yellow oil, which was purified by low-temperature (−78 °C) recrystallization three times from pentane to give 2.734 g (75%) of a mixture of **20** and **21** as a light yellow oil (99.6:0.4 mixture of isomers as determined by ^1H NMR analysis): IR (film) 2986, 2930, 2860, and 1818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for isomer **20** δ 3.31 (q, J = 7.7 Hz, 1 H), 1.58–1.89 (m, 6 H), 1.36 (s, 3 H), 1.25 (d, J = 7.7 Hz, 3 H), and 0.93–1.32 (m, 5 H); for isomer **21** (partial data) δ 3.87 (q, J = 7.0 Hz). ^1H NMR NOE experiment: Irradiation of **20** at δ 3.31 (ring CH) produces enhancement at δ 1.8–1.9 (7%, cyclohexyl methine) and 1.6–1.7 (4%, equatorial cyclohexyl H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 84.3, 51.0, 47.9, 27.0, 26.4, 25.9, 25.5, 15.7, and 9.0. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.64; H, 10.06.

***t*-3-Ethyl-4-methyl-*r*-4-(4-methylpent-3-enyl)oxetan-2-one (22) and *c*-3-Ethyl-4-methyl-*r*-4-(4-methylpent-3-enyl)oxetan-2-one (23).** Reaction of *S*-phenyl butanethioate **6** (0.180 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and 6-methylhept-5-en-2-one (0.126 g, 1.00 mmol) in 10 mL of THF was performed according to general procedure A except that the

(34) Nowick, J. S.; Danheiser, R. L. *Tetrahedron* **1988**, *44*, 4113.

reaction mixture was allowed to warm to −2 °C over 100 min. Workup afforded 0.206 g of a pale yellow oil, which was purified by column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) followed by rotary evaporation (50 °C, 2 mmHg, to remove unreacted 6-methylhept-5-en-2-one) to give 0.165 g (84%) of a mixture of **22** and **23** as a colorless oil (64:36 mixture of isomers as determined by ^{1}H NMR analysis): IR (film) 2972, 2934, 2890, 1817, and 806 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) for **22** δ 5.09 (app, t, J = 6.7 Hz, 1 H), 3.12 (t, J = 8.4 Hz, 1 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.46 (s, 3 H), and 1.05 (t, J = 7.2 Hz, 3 H); for **23** δ 5.11 (app t, J = 7.5 Hz, 1 H), 3.14 (t, J = 7.9 Hz, 1 H), 1.69 (s, 3 H), 1.62 (s, 3 H), 1.57 (s, 3 H), and 1.06 (t, J = 7.7 Hz, 3 H); for both isomers (**22** and **23**) δ 2.02–2.17 (m, 2 H) and 1.62–1.94 (m, 4 H). ^{1}H NMR NOE experiments: Irradiation of **22** at δ 1.46 (ring CH_3) produces no enhancement at 3.12 (ring CH). Irradiation of **23** at δ 1.57 (ring CH_3) produces enhancement at 3.14 (10%, ring CH); ^{13}C NMR (75 MHz, $CDCl_3$): for **22** δ 171.5, 132.6, 122.6, 82.0, 58.5, 40.8, 25.5, and 22.8; for **23** δ 171.6, 132.5, 122.9, 81.7, 60.7, 34.9, 24.7, and 22.2; unassigned resonances (**22** or **23**) δ 19.2, 18.3, 17.6, 17.5, 12.1, and 12.0. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.65; H, 10.33.

***trans*- and *cis*-4-Heptyl-3-methyloxetan-2-one (24 and 25).** Reaction of *S*-phenyl propanethioate **2** (0.332 g, 2.00 mmol) with lithium diisopropylamide (2.08 mmol) and *n*-octanal (0.256 g, 2.00 mmol) was performed according to general procedure B except that the reaction mixture was allowed to warm to −30 °C over 1.75 h and maintained at −30 °C for 2 h. Workup afforded 0.384 g of a very pale yellow oil. Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) followed by Kugelrohr distillation (oven temperature 90–100 °C, 0.5 mmHg) gave 0.154 g (42%) of a mixture of **24** and **25** as a colorless oil (2.5:1 mixture of isomers as determined by ^{1}H NMR analysis): IR (film) 2928, 2868, and 1825 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) for the trans isomer **24** δ 4.17 (ddd, J = 7.4, 6.5, 3.9 Hz, 1 H), 3.22 (qd, J = 7.7, 4.0 Hz, 1 H), 1.6–1.9 (m, 2 H), 1.23–1.50 (m, 10 H), 1.39 (d, J = 7.6 Hz, 3 H), and 0.89 (app t, J = 6.9 Hz, 3 H); for the cis isomer **25** δ 4.55 (ddd, J = 9.4, 6.2, 4.7 Hz, 1 H), 3.74 (qd, J = 7.6, 6.4 Hz, 1 H), 1.6–1.9 (m, 2 H), 1.23–1.50 (m, 10 H), 1.28 (d, J = 8.0 Hz, 3 H), and 0.89 (app t, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) for the trans isomer **24** δ 171.9, 79.4, 50.5, 34.0, 31.5, 29.0, 28.9, 24.8, 22.4, 13.9, and 12.4. For the cis isomer **25** (partial data) 172.6, 75.6, 47.1, 38.3, 29.8, 29.1, 25.5, 25.3, 23.2, and 7.9. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.73; H, 11.31.

***trans*- and *cis*-3-*tert*-Butyl-4-phenyloxetan-2-one (28 and 29).**[28d] Reaction of *S*-phenyl 3,3-dimethylbutanethioate **7** (4.17 g, 20.0 mmol) with lithium diisopropylamide (20.7 mmol) and benzaldehyde (2.03 mL, 20.0 mmol) was performed according to general procedure B except that the reaction mixture was allowed to warm to 0 °C over 1.5 h. Workup afforded 3.96 g of a pale yellow oil. Kugelrohr distillation (oven temperature 80–90 °C, ca. 0.005 mmHg) gave 3.49 g (85%) of a mixture of **28** and **29** as a colorless oil which solidified upon standing (97:3 mixture of isomers as determined by ^{1}H NMR analysis): mp 22–32 °C; IR (film) 3064, 3016, 2962, 2874, and 1823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) for the trans isomer **28** δ 7.35–7.41 (m, 5 H), 5.31 (d, J = 4.3 Hz, 1 H), 3.36 (d, J = 4.2 Hz, 1 H), and 1.12 (s, 9 H); for the cis isomer **29** (partial data) δ 5.66 (d, J = 7.0 Hz, 1 H), 3.86 (d, J = 6.9 Hz, 1 H), and 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) for the trans isomer **28** δ 170.4, 137.9, 129.0, 125.5, 74.0, 70.7, 31.0, and 26.9. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.48; H, 7.89.

General Procedure C for the Preparation of β-Lactone Enolates and Subsequent Reaction with Electrophiles. Preparation of 3-Carbethoxy-3-methyloxetan-2-one-4-spirocyclohexane (32). A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter, and a rubber septum was charged with 10 mL of THF and diisopropylamine (0.154 mL, 1.10 mmol) and then cooled in an ice bath while *n*-butyllithium solution (1.67 M in hexanes, 0.62 mL, 1.04 mmol) was added rapidly via syringe. After 15 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and a solution of β-lactone **12** (0.154 g, 1.00 mmol) in 0.2 mL of THF was added dropwise by microliter syringe over ca. 30 s (the syringe used for the addition was rinsed with two 0.2-mL portions of THF). After 30 min, ethyl chloroformate (0.115 mL, 1.20 mmol) was added over ca. 15 s, and the reaction mixture was allowed to warm to room temperature over 1 h. Half-saturated NH_4Cl solution (10 mL) was then added, and the resulting mixture was partitioned between 20 mL of H_2O and 20 mL of diethyl ether. The organic phase was extracted with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.229 g of a pale yellow oil. Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) furnished 0.196 g (87%) of **32** as a colorless oil: IR (film) 2980, 2938, 2862, 1836, and 1735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18–4.35 (m, 2 H), 1.83–2.00 (m, 2 H), 1.57–1.68 (m, 7 H), 1.56 (s, 3 H), 1.32 (t, J = 7.1 Hz, 3 H), and 1.22–1.41 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 168.4, 83.9, 65.3, 61.9, 32.7, 31.5, 24.6, 22.2, 14.0, and 13.5. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.83; H, 8.09.

3,3-Dimethyloxetan-2-one-4-spirocyclohexane (14). Reaction of β-lactone **12** (0.077 g, 0.50 mmol) with lithium diisopropylamide (0.52 mmol) and methyl iodide (0.156 mL, 2.50 mmol) in 5 mL of THF followed by warming to 4 °C over 2 h was performed according to general procedure C to yield 0.082 g of white crystals. Washing with two 0.6-mL portions of ice-cold pentane afforded 0.069 g (82%) of **14** as white crystals.

3-(Hydroxymethyl)-3-methyloxetan-2-one-4-spirocyclohexane (33). A 25-mL, two-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and magnetic stirring bar was charged with 10 mL of THF and diisopropylamine (0.154 mL, 1.10 mmol) and then cooled in an ice bath while *n*-butyllithium solution (1.67 M in hexanes, 0.62 mL, 1.04 mmol) was added rapidly via syringe. After 15 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and a solution of β-lactone **12** (0.154 g, 1.00 mmol) in 0.2 mL of THF was added dropwise by microliter syringe over ca. 30 s (the syringe used for the addition was rinsed with two 0.2-mL portions of THF). After 30 min, the rubber septum was replaced with a Schlenk tube containing 0.30 g of paraformaldehyde. The paraformaldehyde was pyrolyzed using a heat gun (ca. 150 °C, 5 min), and the reaction mixture was then allowed to stir at −78 °C for an additional 15 min. Half-saturated NH_4Cl solution (10 mL) was then added, and the resulting mixture was partitioned between 20 mL of H_2O and 20 mL of diethyl ether. The organic phase was extracted with 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.170 g of an oily white solid. Recrystallization from diethyl ether–hexanes provided 0.119 g (64%) of **33** as white crystals: mp 73–75 °C; IR ($CHCl_3$) 3620, 3480, 3020, 2938, 2860, and 1808 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (dd, ABX pattern, J = 11.6 (AB), J = 6.1 Hz, 1 H), 3.85 (dd, ABX pattern, J = 11.4 (AB), J = 5.4 Hz, 1 H), 2.15–2.25 (m, 2 H), 1.89–2.03 (m, 1 H), 1.74–1.86 (m, 1 H), 1.58–1.72 (m, 6 H), 1.36 (s 3 H), and 1.23–1.38 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 85.6, 62.7, 60.0, 33.0, 31.2, 24.8, 22.5, 22.4, and 13.0. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.23; H, 8.51.

***r*-3-Carbethoxy-*c*-4-cyclohexyl-3,4-dimethyloxetan-2-one (34) and *r*-3-Carbethoxy-*t*-4-cyclohexyl-3,4-dimethyloxetan-2-one (35).** Reaction of β-lactone **20** (0.182 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and ethyl chloroformate (0.143 mL, 1.50 mmol) followed by warming to 0 °C over 2 h was performed according to general procedure C to afford 0.282 g of pale yellow oil. Excess β-lactone **20** was removed by Kugelrohr distillation (oven temperature 50 °C, ca. 0.01 mmHg).[35] Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) afforded 0.208 g (82%) of a mixture of **34** and **35** as a colorless oil (1.5:1 mixture of isomers as determined by ^{1}H NMR analysis): IR (film) 2988, 2938, 2872, 1833, and 1737 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) for **34** δ 1.55 (s, 3 H), 1.429 (s, 3 H), and 1.35 (t, J = 7.3 Hz, 3 H); for **35** δ 1.65 (s, 3 H), 1.432 (s, 3 H), and 1.32 (t, J = 7.1 Hz, 3 H); for both isomers (**34** and **35**) δ 4.20–4.36 (m, 2 H), 1.57–1.92 (m, 6 H), and 0.89–1.31 (m, 5 H). ^{1}H NMR NOE experiments: Irradiation of isomer **34** at δ 1.428 (ring CH_3) produces enhancement at 1.55 (2.5%, ring CH_3). Irradiation of isomer **35** at δ 1.432 (ring CH_3) produces no detectable (<0.5%) enhancement at 1.65 (CH_3): ^{13}C NMR (125

(35) Some of the desired product codistilled with the unreacted starting material, resulting in a slight reduction in yield. A slightly higher yield may be obtained by using column chromatography to purify the product.

MHz, $CDCl_3$) for **34** δ 86.8, 65.8, 62.1, and 43.9; for **35** δ 86.1, 66.0, 61.9, and 42.7; for both isomers (**34** and **35**) δ 168.7, 168.64, 168.58, 28.6, 28.0, 26.6, 26.4, 26.22, 26.16, 26.05, 25.95, 25.93, 25.88, 17.3, 16.4, 14.6, 14.3, 14.1, and 14.0. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.18; H, 8.98.

***r*-4-Cyclohexyl-3,4-dimethyl-*c*-3-(phenylmethyl)oxetan-2-one (36) and *r*-4-Cyclohexyl-3,4-dimethyl-*t*-3-(phenylmethyl)oxetan-2-one (37).** Reaction of β-lactone **20** (0.182 g, 1.00 mmol) with lithium diisopropylamide (1.04 mmol) and benzyl bromide (0.178 mL, 1.50 mmol) followed by warming to 0 °C over 2 h was performed according to general procedure C to afford 0.311 g of a mixture of pale yellow oil and solid. Excess benzyl bromide was removed by Kugelrohr distillation (oven temperature 50 °C, ca. 0.01 mmHg). Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) afforded 0.184 g (67%) of a mixture of **36** and **37** as a white solid (4.0:1 mixture of isomers as determined by ^1H NMR analysis): mp 92–102 °C; IR (film) 3028, 2990, 2932, 2858, and 1806 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for **36** δ 3.50 (d, J = 13.8 Hz, 1 H), 2.76 (d, J = 13.8 Hz, 1 H), 2.09 (tt, J = 11.5, 2.8 Hz, 1 H), 1.56–1.64 (m, 1 H), 1.43 (s, 3 H), and 1.16 (s, 3 H); for **37** δ 3.25 (d, J = 14.2 Hz, 1 H), 2.82 (d, J = 14.2 Hz, 1 H), 1.56 (s, 3 H), and 1.24 (s, 3 H); for both isomers (**36** and **37**) δ 7.22–7.34 (m, 5 H), 1.70–1.95 (m, 4 H, **36**; 6 H, **37**), and 0.89–1.41 (m, 5 H). ^1H NMR NOE experiment: Irradiation of δ 3.50 (major isomer PhCH) produces enhancement at 2.09 (15%, cyclohexyl methine), 2.76 (20%, PhCH), and 7.3 (3%, ortho C_6H_5): ^{13}C NMR (75 MHz, $CDCl_3$) for **36** δ 174.9, 136.4, 130.6, 128.3, 127.0, 87.0, 58.4, 43.0, 38.0, 28.9, 26.6, 26.2, 25.9, 25.8, 17.1, and 16.0; for **37** (partial data) δ 175.5, 130.3, 128.4, 87.8, 58.4, 43.4, 37.6, 28.5, 26.1, 17.0, and 15.6. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.26; H, 9.09.

General Procedure D for the Preparation of Alkenes from β-Lactones. Preparation of 2,3-Dimethyl-5-phenyl-2-pentene (42). A 25-mL, one-necked, round-bottomed flask equipped with a cold-finger condenser fitted with an argon inlet adapter was charged with 0.152 g of β-lactone **15**, 5 mL of cyclohexane, and 0.152 g of 230–400-mesh silica gel. The reaction mixture was heated at reflux for 45 min and then allowed to cool to room temperature and filtered. The residue was washed with an additional 5 mL of cyclohexane, and the combined filtrates were concentrated to afford 0.115 g (95%) of **42** as a colorless oil: IR (film) 3086, 3062, 3026, 2988, 2918, and 2856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.29 (m, 2 H), 7.14–7.19 (m, 3 H), 2.64 (app t, J = 8.1 Hz, 2 H), 2.31 (app t, J = 8.1 Hz, 2 H), 1.67 (s, 3 H), 1.64 (s, 3 H), and 1.58 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 128.6, 128.4, 127.1, 125.8, 124.9, 36.6, 34.5, 20.3, 19.7, and 18.2. Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.62; H, 10.61.

General Procedure E for the Preparation of Volatile Alkenes from β-Lactones. Ethylidenecyclohexane (40). A 25-mL, one-necked, round bottomed flask fitted with a Kugelrohr receiver bulb bearing a plug of glass wool in its neck (to exclude silica gel from the distillate) was charged with 0.030 g of 230–400-mesh chromatographic silica gel and 0.300 g of β-lactone **12**. The apparatus was evacuated (48 mmHg), the Kugelrohr bulb was cooled with dry ice, and the round-bottomed flask was warmed to 90 °C over 20 min. This temperature was maintained for 10 min during which time most of the product distilled, and then the temperature was raised to 120 °C over 10 min and maintained at 120 °C for 5 min. The apparatus was then filled with nitrogen and allowed to cool to room temperature, thus furnishing 0.194 g (90%) of **40** as a colorless oil: IR (film) 3042, 2924, 2852, and 805 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.13 (q, J = 6.6 Hz, 1 H), 2.06–2.15 (m, 4 H), 1.56 (d, J = 6.9 Hz, 3 H), and 1.45–1.57 (m, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) 140.1, 115.0, 37.1, 28.6, 28.2, 27.6, 27.0, and 12.5.

Isopropylidenecyclohexane (41). A 50-mL, one-necked, round-bottomed flask fitted with a Kugelrohr receiver bulb was charged with 6.991 g of β-lactone **14** and 0.699 g of 230–400-mesh silica gel. The apparatus was evacuated (61 mmHg), the Kugelrohr bulb was cooled with dry ice, and the round-bottomed flask was warmed to 110 °C over ca. 15 min, whereupon the β-lactone began to melt and product began to distill. The temperature was maintained at 110–120 °C for ca. 20 min during which time most of the product distilled as a colorless oil contaminated with the β-lactone as a white solid. The distillate was returned to the round-bottomed flask by tilting the apparatus, two additional 1-mL portions of material were distilled and returned to the flask in order to rinse the walls of the Kugelrohr bulb, and then the entire sample distilled (110–120 °C, 61 mmHg) to afford 4.625 g (88%) of **41** as a colorless oil: IR (film) 2988, 2962, 2920, and 2850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.13–2.17 (m, 4 H), 1.65 (s, 6 H), and 1.44–1.57 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.2, 120.1, 30.4, 28.0, 27.0, and 19.9.

***tert*-Butyldimethyl(1-methylethenyl)silane (43).** An admixture of β-lactone **18** (0.178 g) and silica gel (0.018 g) was warmed and distilled according to general procedure E (25–120 °C, 44 mmHg) to afford 0.130 g (93%) of **43** as a colorless oil: IR (film) 3052, 2958, 2934, 2890, 2858, and 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66–5.69 (m, 1 H), 5.26–5.28 (m, 1 H), 1.87 (app t, J = 1.4 Hz, 3 H), 0.91 (s, 9 H), and 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1 126.8, 26.6, 24.0, 16.6, and –6.6. Anal. Calcd for $C_9H_{20}Si$: C, 69.14; H, 12.89. Found: 69.12; H, 13.02.

***(E)*-2-Cyclohexyl-2-butene (44).** An admixture of β-lactone **20** (0.300 g) and silica gel (0.300 g) was allowed to stand at 25 °C for 16 h and then warmed and distilled according to general procedure E (25–120 °C, 6 mmHg) to afford 0.217 g (95%) of **44** as a colorless oil: IR (film) 2922, 2850, 1664, and 815 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17–5.22 (m, 1 H), 1.57 (s, 3 H), 1.56 (app d, J = 5 Hz, 3 H), 1.49–1.84 (m, 6 H), and 1.10–1.30 (m, 5 H). ^1H NMR NOE experiment: Irradiation at δ 5.20 (vinyl H) produces enhancement at 1.78–1.84 (9%, cyclohexyl methine): ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 116.1, 47.3, 32.0, 26.8, 26.5, 14.0, and 13.3. Anal. Calcd for $C_{10}H_{18}$: C, 86.88; H, 13.12. Found: C, 87.11; H, 12.78.

***(E)*-2-Methyl-3-undecene (45) and *(Z)*-2-Methyl-3-undecene (46).** A 25-mL, one-necked, round-bottomed flask fitted with two Kugelrohr receiver bulbs was charged with 0.195 g of a mixture of β-lactones **26** and **27** and then evacuated (1 mmHg) and filled with argon. This procedure was repeated twice more, and then the round-bottomed flask was heated at 175–180 °C in a Kugelrohr oven for 1 h while the first receiver bulb was cooled with dry ice. Cycloreversion generates the desired alkene product which gradually distills into the first receiver bulb; however, some of the β-lactone starting material is also transferred to the receiver. This receiver bulb was therefore inserted into the oven and heated for 1 h at 175–180 °C while the second receiver bulb was cooled with dry ice. The flask and first bulb were then allowed to cool to room temperature, and then heated again at 80 °C (0.25 mmHg) to distill any remaining material into the second bulb. A total of 0.153 g of colorless oil was collected; ^1H NMR analysis indicated the distillate to be a 1:3 mixture of alkenes **45** and **46** contaminated with 15 mol % of a 2:1 mixture of β-lactones **27** and **26**. Filtration through a plug of silica gel with the aid of 15 mL of pentane followed by concentration afforded 0.115 g (75%) of a 3:1 mixture of pure alkenes **45** and **46** as a colorless oil: IR (film) 2998, 2956, 2922, 2850, 969, and 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) for *Z* isomer **46** δ 5.13–5.28 (m, 2 H), 2.51–2.67 (m, 1 H), 2.03 (app q, J = 6.7 Hz, 2 H), 1.20–1.40 (m, 10 H), 0.94 (d, J = 6.9 Hz, 6 H), and 0.88 (app t, J = 6.8 Hz, 3 H); for *E* isomer **45** δ 5.29–5.42 (m, 2 H), 2.17–2.28 (m, 1 H), 1.96 (app q, J = 5.7 Hz, 2 H), 1.20–1.40 (m, 10 H), 0.96 (d, J = 6.0 Hz, 6 H), and 0.88 (app t, J = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) for *Z* isomer **46** δ 137.5, 127.5, 31.9, 30.0, 29.33, 29.28, 27.3, 26.5, 23.2, 22.7, 14.1; for *E* isomer **45** δ 137.5, 127.3, 32.6, 31.0, 29.7, 29.25, 29.17, 22.7, 14.1. Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.78; H, 14.15.

Ethyl 2-Cyclohexylidenepropanoate (47). A mixture of β-lactone **32** (0.149 g) and silica gel (0.149 g) in 5 mL of cyclohexane was heated at reflux for 4 h according to general procedure D and then filtered with the aid of 10 mL of 10% diethyl ether in hexanes to afford 0.116 g (97%) of **47** as a colorless oil: IR (film) 2988, 2926, 2854, and 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1 Hz, 2 H), 2.42 (br s, 2 H), 2.22 (br s, 2 H), 1.86 (s, 3 H), 1.58 (br s, 6 H), and 1.30 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 147.3, 119.8, 60.1, 32.4, 31.1, 28.1, 27.6, 26.5, 15.1, and 14.3. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.48; H, 9.81.

2-Cyclohexylidene-1-propanol (48). A mixture of β-lactone **33** (0.110 g) and silica gel (0.110 g) in 5 mL of benzene was heated at reflux for 4 h according to general procedure D and then filtered with the aid of 5 mL of methylene chloride to afford 0.079 g of

a colorless oil. Column chromatography on silica gel (gradient elution with ethyl acetate–hexanes) afforded 0.065 g (77%) of **48** as a colorless oil: IR (film) 3320 (br), 2964, 2922, 2858, and 1658 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 2 H), 2.23 (app t, J = 5.1 Hz, 2 H), 2.17 (app t, J = 5.1 Hz, 2 H), 1.76 (s, 3 H), and 1.48–1.65 (m, 7 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 124.3, 63.2, 30.5, 29.9, 28.2, 27.6, 26.6, and 15.9. Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.97; H, 11.78.

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Optically Active Ketones as Chiral Auxiliaries in the [2,3]-Wittig Rearrangement

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The stereochemical aspects of the [2,3]-Wittig rearrangement of optically active tertiary allyl ethers derived from (+)-camphor and (−)-fenchone were investigated. The rearrangement of the (+)-camphor derivative yielded two olefin products in a 70/30 E/Z ratio. The geometry of the trisubstituted olefin produced during the rearrangement was assigned by NOE experiments. The configuration of the newly formed carbinol center of the products was established by kinetic resolution, Mosher's method, and conversion to derivatives of known absolute configuration. The absolute configuration of the carbinol center for the Z isomer was assigned to be S and that of the E isomer to be R. The (−)-fenchone derivative gave only a single Z olefin product, which was assigned the S configuration at the carbinol center.

Introduction

The efficient conservation of chiral elements during sigmatropic rearrangements has made possible the development of many useful methods for asymmetric synthesis.[1] Several variants of the [2,3]-Wittig rearrangement have been found to be particularly useful members of this class of reactions.[2] The use of chiral auxiliaries adjacent to the carbanion center[3] and the rearrangement of optically active secondary allyl ethers[4] are two of the most successful strategies investigated. In the interest of expanding the scope of the [2,3]-Wittig rearrangement, we have undertaken a project to investigate preparation and rearrangement of optically active tertiary bis-allyl ethers.

Our strategy was to prepare these substrates by the addition of organometallic reagents to readily available optically active ketones (Figure 1). The optically active allyl alcohols produced may be converted to bis-allyl ethers under modified Williamson ether synthesis conditions.[5] Treatment of the bis-allyl ethers with an appropriate base would effect the [2,3]-Wittig rearrangement. The terminal olefin of the product serves as a convenient handle for further elaboration of the substrate. Cleavage of the newly formed trisubstituted double bond regenerates the chiral auxiliary and produces a new optically active chiral fragment. (+)-Camphor and (−)-fenchone were the ketones chosen for the initial evaluation of this strategy.

Discussion

The addition of vinyl Grignard reagent to (+)-camphor in the presence of $CeCl_3$ provided the optically active tertiary exo alcohol **2** in high yield (Figure 2).[6] Exclusion addition of the Grignard reagent to the endo face of the bicyclic ketone is due to the steric impairment of approach to the exo face of the carbonyl group by the *gem*-dimethyl group on the methylene bridge of the rigid terpene skeleton. Optically active allyl ether **3** was prepared by using modified Williamson conditions as reported by Marshall.[5] The rearrangement of the bis-allyl ether was attempted under the conditions we had employed previously[4a] (*n*-BuLi, THF, −78 °C to room temperature) for the [2,3]-Wittig rearrangement of optically active secondary allyl ethers. However, only starting material was recovered. After an extensive search for a base that would effect the desired rearrangement, it was found that *t*-BuOK/*t*-BuLi would induce the [2,3]-Wittig rearrangement.[7] When a solution of *t*-BuLi was added slowly to a mixture of *t*-BuOK and **3** in THF at −85 °C followed by warming to 0 °C, two products were produced in a 2.3:1 ratio. Examination of the products by ^1H and ^{13}C NMR indicated that they were the E and Z isomers (**4a** and **5a**) of the allylic alcohol product.

The geometry of the trisubstituted double bond was established by NOE studies on a 500-MHz NMR spectrometer. The proton NMR spectrum of the E isomer (**4a**) contained three signals for the methyl groups on the bicyclic terpene skeleton. Irradiation of the bridgehead methyl signals at δ 0.906 produced a NOE effect on the olefin resonance at δ 5.04. This observation demonstrates that the olefin proton is configurationally close to the

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