Synthesis of Allenes via Thermal Cycloreversion of α-Alkylidene-β-lactones

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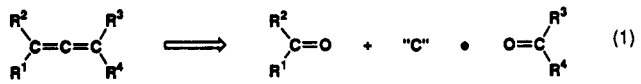
This paper describes the application of the solution-phase [2 + 2] cycloreversion of α-alkylidene-β-lactones as a practical method for the generation of substituted allenes. Upon heating in dimethylformamide solution at 110–125 °C, these unsaturated β-lactone derivatives undergo decarboxylation to provide allenes in good to excellent yield. α-Alkylidene-β-lactones are conveniently prepared via the phenylselenylation of β-lactone enolates followed by oxidative elimination of the resulting α-phenylseleno derivatives. The β-lactone starting materials are synthesized by the addition of thiol ester enolates to ketones and aldehydes according to our recently reported procedure.

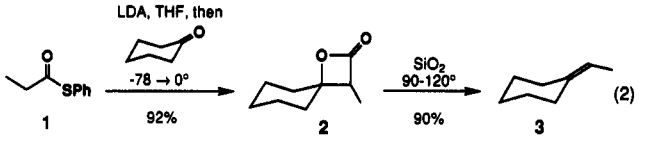
The well-documented utility of allenes as synthetic intermediates has generated considerable interest in the development of improved routes to this important functional group.[1] Recent research in our laboratory has focused on the application of allenes as synthons for the construction of carbocyclic and heterocyclic compounds.[2] In connection with our work in this area, we have undertaken a search for new, highly efficient synthetic approaches to allenes. In this regard, a particularly attractive disconnection is that formulated in eq 1, in which



(1)

a substituted allene is derived from the combination of two carbonyl compounds with a carbon atom or its synthetic equivalent. To our knowledge, no general protocol currently exists for achieving such a *triply-convergent allene synthesis*. The ready availability of a wide range of ketones and aldehydes and the intrinsic efficiency of this highly convergent strategy clearly would make this the method of choice for the preparation of a variety of substituted allenes. We consequently view the development of means for effecting this transformation to be a problem of considerable importance to organic synthesis.

One possible solution to this problem emerged from our recent work in the area of β-lactone chemistry.[3] We have shown that the addition of thiol ester enolates[4] to carbonyl compounds provides the basis for a very convenient one-step synthesis of β-lactones. Under the proper conditions, the intermediate aldolates formed in this reaction undergo spontaneous cyclization to generate β-lactones in good to excellent yield. The transformation outlined in eq 2 is representative.[3] In conjunction with the well-established stereospecific decarboxylation of β-lactones (vide infra), this chemistry also provides an attractive strategy for the stereocontrolled synthesis of substituted alkenes.



(2)

Scheme I outlines one means through which this methodology could serve as the basis for a triply convergent allene synthesis. As a first step, this plan calls for the reaction of a suitably substituted thiol ester **4** with a ketone or aldehyde to generate the β-lactone intermediate **5**. Treatment of **5** (preferably in the same flask) with another equivalent of base and a second carbonyl compound would then furnish **6**, in which Z has been selected to permit spontaneous elimination to form the key α-alkylidene-β-lactone **7**. Upon heating, decarboxylation would then generate the desired substituted allene.

Pivotal to the success of this scheme is the facility of the α-alkylidene-β-lactone cycloreversion step, an unknown transformation when we initiated our investigation.[5] In fact, surprisingly few examples of α-alkylidene-β-lactones have previously been reported in the literature. To our knowledge, the first α-alkylidene-β-lactone to be synthesized was a hydroazulene derivative prepared by Bohlmann and Paul in 1984.[6] Among the few studies in this area published since,[7,8] particularly noteworthy is the work of

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(1) For recent reviews on the synthesis and chemistry of allenes, see: (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley-Interscience: New York, 1984. (b) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (c) *The Chemistry of the Allenes*; Landor, S. R., Ed.; Academic Press: London, 1982; Vols 1-3. (d) *The Chemistry of Ketenes, Allenes, and Related Compounds, Parts 1 and 2*; Patai, S., Ed.; Wiley-Interscience: Chichester, 1980. (e) Brandsma, L.; Verkruijsse, H. D. *Synthesis of Acetylenes, Allenes and Cumulenes*; Elsevier: Amsterdam, 1981. (f) Murray, M. In *Methoden der organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Georg Thieme: Stuttgart, 1977; Vol. V/2a, pp 963-1076.

(2) (a) Danheiser, R. L.; Stoner, E. J.; Koyama, H.; Yamashita, D. S.; Klade, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 4407 and references cited therein. (b) Danheiser, R. L.; Mori, I.; Romines, K. R.; Setoi, H. Submitted for publication.

(3) (a) Danheiser, R. L.; Nowick, J. S. *J. Org. Chem.* **1991**, *56*, 1176. (b) Danheiser, R. L.; Nowick, J. S.; Lee, J. H.; Miller, R. F. Submitted for publication.

(4) Wemple, J. *Tetrahedron Lett.* **1975**, 3255.

(5) A few examples of the conversion of β-alkylidene-β-lactones (ketene dimers) to allenes have been reported: (a) Fitzpatrick, J. T. *J. Am. Chem. Soc.* **1947**, *69*, 2236. (b) Martin, J. C. U.S. Patent 3 131 234, 1964; *Chem. Abstr.* **1964**, *61*, 2969f. (c) Strating, J.; Alberts, A. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1970**, 818. (d) Moore, H. W.; Duncan, W. G. *J. Org. Chem.* **1973**, *38*, 156. (e) Baba, A.; Kitano, S.; Ohshiro, Y. Agawa, T. *Synthesis* **1975**, 537. (f) Berkowitz, W. F.; Ozorio, A. A. *J. Org. Chem.* **1975**, *40*, 527.

(6) Bohlmann, F.; Paul, A. H. K. *Tetrahedron Lett.* **1984**, *25*, 1697.

(7) (a) Adam, W.; Hasemann, L.; Prechtl, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1536. (b) Adam, W.; Albert, R.; Grau, N. D.; Hasemann, L.; Nestler, B.; Peters, E.-M.; Peters, K.; Prechtl, F.; von Schnering, H. G. *J. Org. Chem.* **1991**, *56*, 5778. (c) Adam, W.; Albert, R.; Hasemann, L.; Nava Salgado, V. O.; Nestler, B.; Peters, E.-M.; Peters, K.; Prechtl, F.; von Schnering, H. G. *J. Org. Chem.* **1991**, *56*, 5782.

(8) (a) Matsuda, I.; Ogiso, A.; Sato, S. *J. Am. Chem. Soc.* **1990**, *112*, 6120. (b) Campi, E. M.; Dyall, K.; Fallon, G.; Jackson, W. R.; Permutter, P.; Smallridge, A. J. *Synthesis* **1990**, 855. (c) Ben Cheikh, A.; Pommelet, J.-C.; Chuche, J. *J. Chem. Soc., Chem. Commun.* **1990**, 615.

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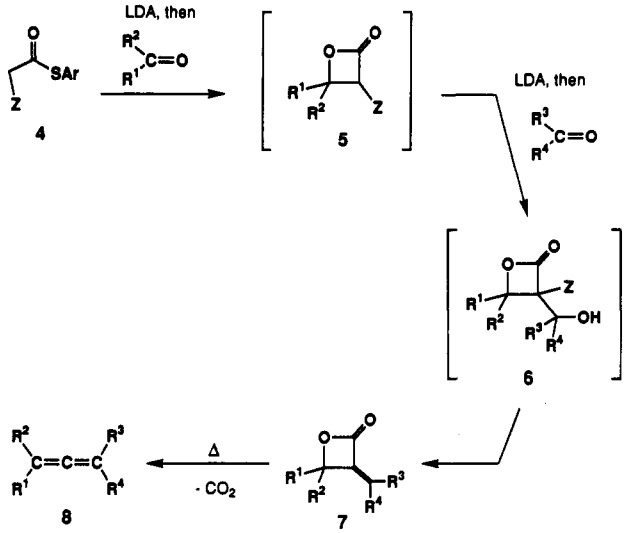
Scheme I



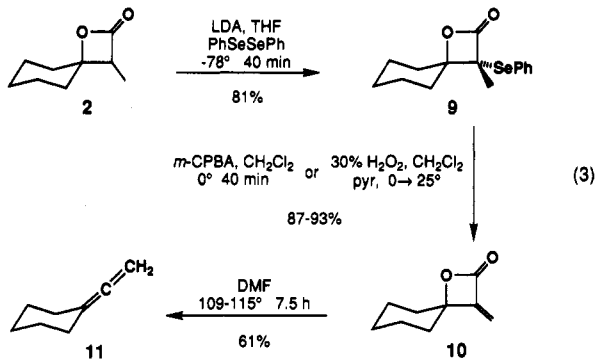
Adam and co-workers, who have prepared several α-*methylene*-β-lactones via a route involving (a) photooxygenation of an acrylic acid derivative, (b) acid-catalyzed cyclization, and (c) Ph_3P-promoted deoxygenation of the resulting α-methylene-β-peroxylactone.[7]

The thermal cycloreversion of β-lactones[9] has proven to be a useful method for producing substituted alkenes. The objective of the study reported herein was to determine whether this process could be extended to the formation of allenes and thus serve as the basis for the strategy outlined in Scheme I. During the course of our investigation Adam and co-workers reported the small-scale flash vacuum pyrolysis of two α-methylene-β-lactone derivatives.[7c] In this article we now describe studies that establish the generality of the *solution-phase* [2 + 2] cycloreversion of α-alkylidene-β-lactones as a practical method for the generation of substituted allenes.

Results and Discussion

As discussed above, the thiol ester chemistry developed in our laboratory provides convenient access to a variety of substituted β-lactones. For our cycloreversion study, we therefore sought an expeditious method for the conversion of lactones such as **2** to the corresponding α-alkylidene derivatives. Prominent among strategies for the introduction of α,β-unsaturation in carbonyl compounds is the methodology introduced by Sharpless[10] and by Reich[11] which employs the phenylselenenylation of enolates in conjunction with the oxidative elimination of the resulting α-phenylseleno derivatives.[12] The mild reaction conditions associated with this chemistry makes it particularly well-suited for application to substrates that incorporate delicate functionality such as β-lactones.

As outlined in eq 3, the conversion of β-lactone **2** to the α-methylene derivative **10** proceeded smoothly under conditions similar to those reported by Grieco and Miyashita for related transformations in the γ-lactone series.[13] However, in contrast to their observations, we found that phenylselenylation of β-lactones proceeds best when the reaction temperature is not allowed to exceed −78 °C and when HMPA is *not* employed as a cosolvent. These modifications proved necessary to suppress side reactions involving cleavage of the β-lactone ring by the LiSePh byproduct of the reaction. Phenylselenenyl halides were found to be less effective than diphenyl diselenide for this selenenylation.



(3)

Oxidation of the α-phenylseleno lactone **9** and in situ syn elimination of the resultant selenoxide was accomplished in 93% yield by reaction with *m*-CPBA in methylene chloride at 0 °C. Alternatively, the same transformation could be achieved in 87% yield using 30% hydrogen peroxide in the presence of pyridine. The α-methylene-β-lactone **10** proved to be surprisingly stable and could be purified by column chromatography on silica gel without difficulty.

Exploratory experiments conducted in acetonitrile and toluene indicated that the desired [2 + 2] cycloreversion proceeds at a satisfactory rate in the temperature range 100–150 °C. Although the addition of silica gel[3,14] was found to have an accelerating effect on the decarboxylation, additional byproducts were observed to form under these conditions. Dimethylformamide proved to be the solvent of choice for the conversion of **10** to **11**; DMF has the advantage that, in contrast to other solvents, it can be conveniently separated from the volatile allene through a simple pentane–water extraction (see the Experimental Section).

The synthesis and decarboxylation of α-methylene-β-lactone **17** was accomplished in good yield employing similar conditions (Scheme II). We have previously reported[3a] that the reaction of phenyl propanethioate with acetylcyclohexane proceeds with high stereoselectivity to afford the trans-substituted β-lactone **13** in 75% yield.[15] Phenylselenylation of **13** provided a 3:1 mixture of **15a** and **15b** (66% yield), which was converted to the α-

(9) For reviews of the chemistry 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, Chapter 6, pp 729–884. (d) Searles, S. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 7, Chapter 5.13.

(10) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.

(11) Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813.

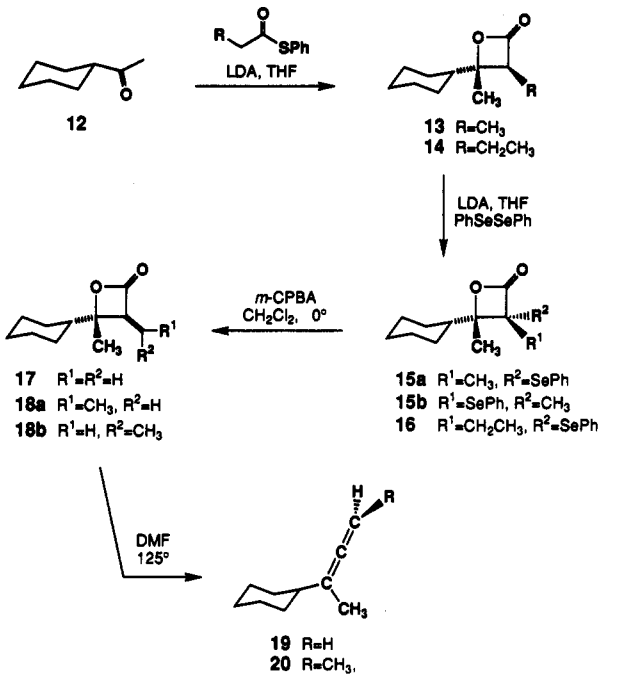
(12) Reviews: (a) Sharpless, K. B.; Gordon, K. M.; Lauer, R. F.; Patrick, D. W.; Singer, S. P.; Young, M. W. *Chem. Scr.* **1975**, *8A*, 9. (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049. (c) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1984; Chapter 4. (d) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986. (e) Back, T. G. In *Organoselenium Chemistry*; Liotta, D., Ed.; Wiley Interscience: New York, 1987; Chapter 1. (f) Astles, P. C.; Mortlock, S. V.; Thomas, E. J. In *Comprehensive Organic Synthesis*; Winterfeldt, E., Ed.; Pergamon Press: Oxford, 1991; Vol. 6, pp 1026–1031.

(13) Grieco, P. A.; Miyashita, M. *J. Org. Chem.* **1974**, *39*, 120.

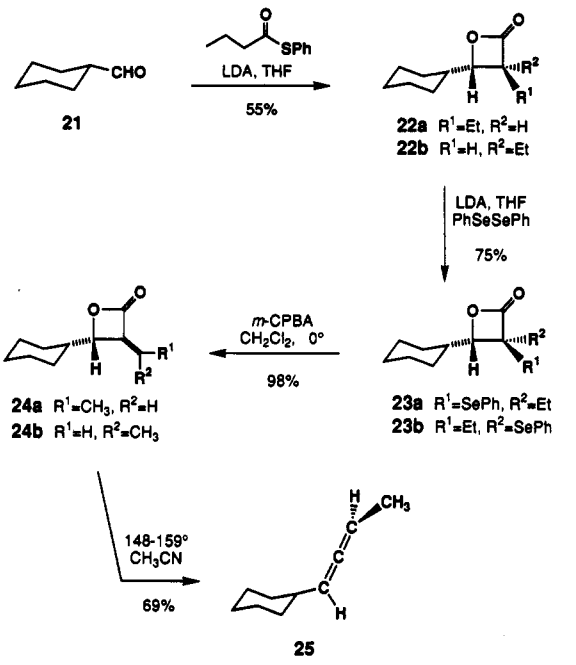
(14) Adam, W.; Encarnacion, L. A. A. *Synthesis* **1979**, 388.

(15) The crude product consists of a 29:1 mixture of diastereomers; the pure trans isomer (**13**) is obtained by recrystallization.

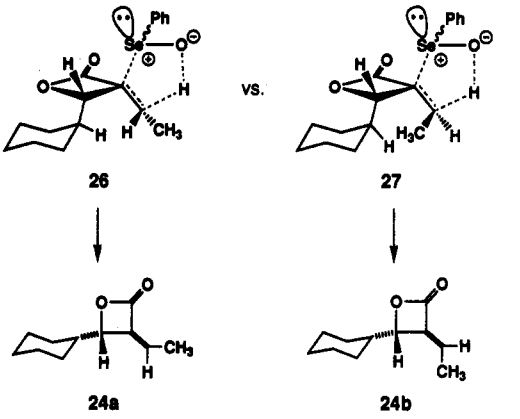
Scheme II



Scheme III



Scheme IV



methylene-β-lactone **17** in quantitative yield using either the *m*-CPBA or hydrogen peroxide protocol. [2 + 2] Cycloreversion in this case occurred at 125–133 °C in DMF to produce 1-cyclohexyl-1-methylallene (**19**)[16] in 84% yield.

The preparation of **20** illustrates the application of this chemistry to the generation of trisubstituted allenes. Addition of phenyl butanethioate to **12** followed by phenylselenenylation produced **16** as a single diastereomer in 64% overall yield. The stereochemical outcome of this transformation (and that of **13** described above) is consistent with our previous observation[3] that electrophilic attack on enolates derived from *trisubstituted* β-lactones occurs mainly cis to the larger substituent at C-4. Treatment of **16** with *m*-CPBA at 0 °C next furnished an 82:18 mixture of the *Z* and *E* ethylidene lactones **18a** and **18b**, and cycloreversion at 125–129 °C then gave 1-cyclohexyl-1,3-dimethylallene (**20**) in 73% overall yield after distillation.

The transformations outlined in Scheme III demonstrate the utility of our methodology as applied to the synthesis of 1,3-disubstituted allenes. Thus, addition of phenyl butanethioate to **21** proceeded in the expected fashion to generate a 3.4:1 mixture of the trans and cis-substituted β-lactones **22a** and **22b**. Sequential treatment of this mixture with LDA and diphenyl diselenide then produced a mixture of α-phenylseleno lactones in which the major product is the result of selenenylation from the less sterically encumbered face of the β-lactone enolate. The stereochemical outcome of this reaction is consistent with Mulzer's observation of similar trans selectivity in electrophilic additions to 3,4-disubstituted β-lactone enolates.[17]

Exposure of a mixture of **23a** and **23b** to the action of *m*-CPBA at 0 °C for 25 min furnished the α-ethylidene lactones **24a** and **24b** (68:32) in 98% yield. Selenoxide elimination in this case generates exclusively the exocyclic alkene, in contrast to the mixtures of endocyclic and exocyclic isomers obtained from reactions involving other ring sizes.[12,13] Extrapolation of the results of several experiments provided valuable insight into the stereochemical course of the selenoxide elimination step. Interestingly, elimination of the selenoxide derived from the major α-phenylseleno lactone **23a** affords an 86:14 mixture of the *Z* and *E* alkenes (**24a** and **24b**); this preference for *Z* olefin was also observed in the oxidative elimination of **16** discussed earlier. These results are easily explained on the basis of steric interactions present in the transition states for the syn elimination. For example, as outlined in Scheme IV, severe nonbonded repulsion between the cyclohexyl and methyl groups in **27** disfavors this transition state, thus accounting for the stereoselective formation of the *Z* alkene. On the other hand, this steric interaction is not present in the transition state for the selenoxide derived from minor isomer **23b**, and oxidative elimination in this case was found to afford the *Z* and *E* alkenes in a ratio of 34:66.

The optimal conditions for effecting the [2 + 2] cycloreversion of **24a** and **24b** involved heating the mixture in acetonitrile at 148–159 °C. Under these conditions the

(16) Moreau, J.-L.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *108*, 159.

(17) (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.; Jibril, I.; Huttner, G. *Tetrahedron* **1984**, *40*, 2211.

desired allene **25** could be isolated in 69% yield, together with a small amount of unreacted ethylidene lactone. The observation that the recovered starting material consists of a 38:62 mixture of *Z* and *E* olefins suggests that the more sterically congested *E* isomer **24b** undergoes decarboxylation at a slower rate than the *Z* isomer **24a**. This result is consistent with previous observations that steric congestion retards the rate of cycloreversion in 3,4-disubstituted β-lactones.[18]

The results of the study described here establish the utility of the [2 + 2] cycloreversion of α-alkylidene-β-lactones as a practical method for the generation of substituted allenes. Further studies are underway in our laboratory to apply this process in the context of a triply convergent strategy for the synthesis of allenes.

Experimental Section

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon or nitrogen. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi rotary evaporator at ca. 20 mmHg. Column chromatography was performed on Baker silica gel (230–400 mesh).

Materials. Commercial-grade reagents and solvents were used without further purification except as indicated below. CH_2Cl_2, pyridine, acetonitrile, and diisopropylamine were distilled from CaH_2. DMF was distilled after drying over BaO. THF was distilled from sodium benzophenone ketyl or dianion. Acetylcyclohexane and cyclohexanecarboxaldehyde were purified by distillation at reduced pressure before use. Diphenyl diselenide was dried for 15 h at 50 °C (0.05 mmHg) before use.

General Procedure A for the Selenenylation of β-Lactones. 3-Methyl-3-(phenylseleno)-1-oxaspiro[3.5]nonan-2-one (9). A 500-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with diisopropylamine (6.70 mL, 4.84 g, 47.8 mmol) and 250 mL of THF and then cooled in an ice bath while *n*-butyllithium solution (2.51 M in hexanes, 19.1 mL, 47.9 mmol) was added via syringe over 3 min. After ca. 10 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and a solution of β-lactone **2**[3] (7.059 g, 45.8 mmol) in 10 mL of THF was added dropwise via cannula over 12 min. The resulting pale yellow solution was stirred at −78 °C for 40 min, and then a solution of diphenyl diselenide (14.485 g, 46.4 mmol) in 20 mL of THF was added rapidly (ca. 30 s) via cannula. The reaction mixture was stirred at −78 °C for 40 min and then treated with 250 mL of half-saturated NH_4Cl solution. The resulting mixture was allowed to warm to room temperature and partitioned between 200 mL of diethyl ether and 100 mL of water. The aqueous phase was separated and extracted with two 200-mL portions of diethyl ether, and the combined organic phases were extracted with 400 mL of 10% K_2CO_3 solution and 400 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 14.50 g of an orange oil. Column chromatography on silica gel (elution with 1–5% ethyl acetate–hexanes) gave 11.49 g (81%) of the selenide **9** as a yellow solid: mp 71–71.5 °C; IR (CCl_4) 3060, 2940, 2860, 1815, and 1440 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.74 (m, 2 H), 7.34–7.50 (m, 3 H), 1.8–2.4 (m, 4 H), 1.6–1.8 (m, 6 H), and 1.37 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 162.5, 137.5, 129.3, 129.1, 125.6, 85.5, 57.5, 34.2, 32.6, 24.6, 22.9, 22.5, and 17.4. Anal. Calcd for $C_{15}H_{18}O_2Se$: C, 58.25; H, 5.87. Found: C, 58.23; H, 5.82.

General Procedure B for the Conversion of α-(Phenylseleno)-β-lactones to α-Alkylidene-β-lactones. 3-Methylene-1-oxaspiro[3.5]nonan-2-one (10). A 1-L, three-necked, round-bottomed flask fitted with two rubber septa and an argon inlet adapter was charged with selenide **9** (19.25 g, 62.2 mmol) and 500 mL of CH_2Cl_2 and then cooled to 0 °C with an ice bath while a solution of *m*-CPBA (32.54 g, 85% pure, 160.3 mmol) in 250 mL of CH_2Cl_2 was added dropwise via cannula over 30 min. The reaction mixture was stirred at 0 °C for 40 min and then partitioned between 200 mL of CH_2Cl_2 and 500 mL of 10% K_2CO_3 solution. The aqueous phase was separated and extracted with 200 mL of CH_2Cl_2, and the combined organic layers were washed with 500 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 20.521 g of a pale yellow oil. Column chromatography on silica gel (elution with 10% ethyl acetate–hexanes) provided 8.82 g (93%) of β-lactone **10**[7b] as a colorless oil: IR (film) 2940, 2860, 1810, 1450, and 1410 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.80 (d, J = 1.4 Hz, 1 H), 5.34 (d, J = 1.4 Hz, 1 H), and 1.5–2.0 (m, 10 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 163.8, 150.2, 113.0, 87.2, 34.5, 24.6, and 23.0; MS *m/e* 137, 124, 108, 93 (100), 81, and 74; HRMS *m/e* calcd for C_8H_{12} ($M^+ - CO_2$) 108.0939, found 108.0938.

General Procedure C for the Conversion of α-(Phenylseleno)-β-lactones to α-Alkylidene-β-lactones. 3-Methylene-1-oxaspiro[3.5]nonan-2-one (10). A 25-mL, three-necked, round-bottomed flask fitted with two rubber septa and an argon inlet adapter was charged with seleno lactone **9** (1.052 g, 3.40 mmol), pyridine (0.54 g, 0.55 mL, 6.8 mmol), and 10 mL of CH_2Cl_2 and then cooled at 0 °C while 30% H_2O_2 (1.54 g, 1.39 mL, 13.6 mmol) was added dropwise via syringe over 1 min. The reaction mixture was stirred at 0 °C for 2 h and then allowed to warm to rt and stirred for an additional hour. The resulting mixture was diluted with 20 mL of CH_2Cl_2 and washed with 10 mL of 10% K_2CO_3 solution. The aqueous layer was extracted with 10 mL of CH_2Cl_2, and the combined organic layers were washed with 10 mL of 10% K_2CO_3 solution, two 10-mL portions of saturated $CuSO_4$ solution, and 10 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 0.539 g of a yellow liquid. Column chromatography on silica gel (elution with 3–5% ethyl acetate–hexanes) provided 0.450 g (87%) of **10** as a colorless oil.

General Procedure D for the Decarboxylation of α-Alkylidene-β-lactones. Ethenylidenecyclohexane (11). A 200-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with a rubber septum and an argon inlet needle was charged with α-methylene-β-lactone **10** (8.82 g, 57.9 mmol) and 90 mL of DMF and then heated at 109–115 °C (bath temperature) for 7.5 h. The reaction mixture was allowed to cool to rt and then was placed in an ice bath and diluted with 50 mL of pentane and 50 mL of water. The aqueous layer was separated and extracted with two 50-mL portions of pentane, and the combined organic layers were extracted with three 50-mL portions of water and 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by careful distillation through a short-path column. Purification by Kugelrohr distillation (oven temperature 144 °C) gave 3.818 g (61%) of allene **11**[19] as a colorless oil: IR (toluene) 2900, 2815, 1950, and 1810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.56–4.59 (m, 2 H), 2.14–2.19 (m, 4 H), and 1.53–1.67 (m, 6 H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.5, 101.1, 72.5, 31.1, 27.2, and 26.1; MS *m/e* 109, 108, 93, 81, 79 (100), 67, 55, 41, and 39; HRMS *m/e* calcd for C_8H_{12} 108.0939, found 108.0938.

***cis*-4-Cyclohexyl-3,4-dimethyl-3-(phenylseleno)-1-oxetan-2-one (15a) and *trans*-4-Cyclohexyl-3,4-dimethyl-3-(phenylseleno)-1-oxetan-2-one (15b).** Reaction of 4-cyclohexyl-3,4-dimethyloxetan-2-one (**13**)[3a] (3.275 g, 18.0 mmol) with lithium diisopropylamide (18.9 mmol) and diphenyl diselenide (5.665 g, 18.1 mmol) in 100 mL of THF was performed according to general procedure A. Workup and purification by column chromatography on silica gel (gradient elution with 1–3% ethyl acetate–hexanes) gave 4.016 g (66%) of **15a** and **15b** (3:1 mixture of isomers as determined by ^1H NMR analysis) as a yellow oil. **15a**: IR (film) 3080, 2930, 2860, 1815, and 1445 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.72–7.76 (m, 2 H), 7.28–7.39 (m, 3 H), 1.71–2.22 (m, 6 H), 1.49 (s, 3 H), 1.44 (s, 3 H), and 0.93–1.39 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8, 137.8, 129.4, 129.0, 125.8, 87.9, 58.1, 45.8, 29.4, 27.1, 26.3, 25.9, 25.7, 18.6, and 17.1. Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57. Found: C, 60.61; H, 6.81. **15b**:

(18) (a) Mulzer, J.; Zippel, M.; Brüntrup, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 465. (b) Imai, T.; Nishida, S. *J. Org. Chem.* **1980**, *45*, 2354.

(19) (a) Bailey, W. J.; Pfeifer, C. R. *J. Org. Chem.* **1955**, *20*, 95. (b) Tsuji, J.; Sugiura, T.; Minami, I. *Synthesis* **1987**, 603.

IR (film) 3060, 2940, 2860, 1815, and 1440 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70–7.74 (m, 2 H), 7.28–7.39 (m, 3 H), 1.48–1.91 (m, 5 H), 1.64 (s, 3 H), 1.57 (s, 3 H), and 0.96–1.26 (m, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.0, 137.5, 129.4, 129.1, 125.9, 88.3, 58.2, 43.9, 28.7, 27.0, 26.3, 26.0, 18.6, and 18.2.

4-Cyclohexyl-4-methyl-3-methylene-1-oxetan-2-one (17). Reaction of the mixture of lactones **15a** and **15b** (1.022 g, 3.03 mmol) with *m*-CPBA (0.569 g, 3.30 mmol) in 50 mL of CH_2Cl_2 was performed according to general procedure B except that the reaction mixture was stirred at 0 °C for 5 h. Workup and column chromatography on silica gel (elution with 5% ethyl acetate–hexanes) afforded 0.546 g (100%) of **17** as a pale yellow oil: IR (film) 2940, 2860, and 1820 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (d, J = 1.9 Hz, 1 H), 5.32 (d, J = 1.9 Hz, 1 H), 1.66–1.85 (m, 6 H), 1.55 (s, 3 H), and 1.02–1.27 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 163.9, 149.3, 113.5, 89.6, 44.9, 27.2, 27.0, 26.0, 25.9, and 20.6. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.99; H, 9.06.

Preparation of 4-Cyclohexyl-4-methyl-3-methylene-1-oxetan-2-one (17) via Procedure C. Reaction of the mixture of lactones **15a** and **15b** (1.501 g, 4.45 mmol) with pyridine (0.72 mL, 0.70 g, 8.90 mmol) and 30% H_2O_2 (1.60 mL, 1.78 g, 15.66 mmol) in 35 mL of CH_2Cl_2 was performed according to general procedure C except that the reaction mixture was stirred at 0 °C for 4 h. Workup and column chromatography (gradient elution with 1–5% ethyl acetate–hexanes) provided 0.795 g (99%) of **17** as a colorless oil.

(1-Methyl-1,2-propadienyl)cyclohexane (19). The [2 + 2] cycloreversion of 4-cyclohexyl-4-methyl-3-methylene-1-oxetan-2-one (**17**) (3.95 g, 21.9 mmol) was performed in 50 mL of DMF according to general procedure D except that the reaction mixture was heated at 125–133 °C for 2 h. Workup and purification by Kugelrohr distillation (oven temperature 140–160 °C, 760 mmHg) furnished 2.520 g (84%) of **19**[16] as a colorless oil: IR (film) 2920, 2840, 1960, 1450, and 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.59 (app quintet, J = 2.8 Hz, 2 H), 1.68 (t, J = 3.1 Hz, 3 H), 1.55–1.84 (m, 6 H), and 1.03–1.37 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.8, 103.5, 74.4, 41.1, 31.8, 26.6, 26.5, and 17.1; MS m/e 98, 83, 79, 70, 67, 55(100), 43, 41, 39; HRMS m/e calcd for $C_{10}H_{17}$ (M^+ + H) 137.1330, found 137.1327.

4-Cyclohexyl-3-ethyl-4-methyl-1-oxetan-2-one (14). A 500-mL, three-necked, round-bottomed flask equipped with two rubber septa and an argon inlet adapter was charged with 200 mL of THF and diisopropylamine (5.0 mL, 3.61 g, 35.7 mmol) and then cooled in an ice bath while an *n*-butyllithium solution (2.51 M in hexanes, 13.5 mL, 33.9 mmol) was added via syringe over 5 min. After 10 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and *S*-phenyl butanethioate (5.940 g, 33.0 mmol) was added via cannula over 5 min. After 30 min, acetylcyclohexane (4.160 g, 33.0 mmol) was added dropwise via cannula over 2 min. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to 0 °C over 2 h. Half-saturated NH_4Cl solution (200 mL) was then added, and the resulting mixture was partitioned between 200 mL of water and 200 mL of diethyl ether. The organic phase was extracted with three 400-mL portions of 10% K_2CO_3 solution and 200 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 8.595 g of a yellow oil which was used directly in the next step without purification. An analytical sample of **14** was obtained by column chromatography on silica gel (gradient elution with 3–5% ethyl acetate–hexanes): IR (film) 2920, 2860, 1810, and 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (t, J = 8.1 Hz, 1 H), 1.55–1.89 (m, 8 H), 1.38 (s, 3 H), 0.96–1.32 (m, 5 H), and 1.05 (t, J = 4.5 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.9, 84.5, 58.1, 47.8, 28.3, 27.1, 26.6, 26.0, 25.7, 18.3, 15.8, and 12.1. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.72; H, 10.47.

***cis*-4-Cyclohexyl-3-ethyl-4-methyl-3-(phenylseleno)-1-oxetan-2-one (16).** Reaction of unpurified β-lactone **14** (6.756 g) with lithium diisopropylamide (36.1 mmol) and diphenyl diselenide (10.828 g, 34.7 mmol) in 190 mL of THF was performed according to general procedure A. Workup and purification by column chromatography on silica gel (gradient elution with 1–5% ethyl acetate–hexanes) provided 5.806 g (64% overall yield based on acetylcyclohexane) of seleno lactone **16**: IR (film) 2900, and 1800 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.76–7.79 (m, 2 H), 7.29–7.42 (m, 3 H), 1.70–2.19 (m, 8 H), 1.07–1.61 (m, 5 H), 1.49 (s, 3 H), and 1.08 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3, 137.5, 129.4, 129.0, 125.4, 88.4, 65.1, 45.4, 29.1, 27.1, 26.2, 25.9, 25.8, 21.5, 16.4, and 9.3. Anal. Calcd for $C_{18}H_{24}O_2Se$: C, 61.53; H, 6.88. Found: C, 61.60; H, 7.00.

(*Z*)-4-Cyclohexyl-3-ethylidene-4-methyl-1-oxetan-2-one (18a) and (*E*)-4-Cyclohexyl-3-ethylidene-4-methyl-1-oxetan-2-one (18b). Reaction of seleno lactone **16** (3.030 g, 8.62 mmol) with *m*-CPBA (4.462 g, 25.9 mmol) in 70 mL of CH_2Cl_2 was performed according to general procedure B to afford 1.867 g of a yellow oil. Column chromatography on silica gel (gradient elution with 1–5% ethyl acetate–hexanes) gave 1.400 g of **18a** and 0.337 g of **18b** as pale yellow oils, used in the next step without further purification. **18a**: IR (film) 2900, 2850, 1795, and 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.86 (q, J = 7.5 Hz, 1 H), 2.07 (d, J = 7.5 Hz, 3 H), 1.56–1.89 (m, 6 H), 1.52 (s, 3 H), and 0.98–1.34 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.4, 141.4, 129.6, 88.3, 45.3, 27.2, 27.1, 26.1, 26.0, 20.8, and 14.7. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.04; H, 9.45. **18b**: IR (film) 2900, 2850, 1790, and 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.35 (q, J = 7.2 Hz, 1 H), 1.55–1.95 (m, 6 H), 1.82 (d, J = 7.2 Hz, 3 H), 1.62 (s, 3 H), and 1.06–1.34 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.5, 142.1, 127.1, 89.4, 44.7, 27.2, 27.0, 25.9, 25.8, 25.7, 21.2, and 14.2. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.98; H, 9.17.

(1-Methyl-1,2-butadienyl)cyclohexane (20). The [2 + 2] cycloreversion of α-ethylidene-β-lactone **18a** (1.135 g, 5.84 mmol) was performed in 10 mL of DMF according to general procedure D except that the reaction mixture was heated at 125–129 °C for 6 h. Workup and purification by Kugelrohr distillation (bath temperature 100 °C, 15 mmHg) gave 0.639 g (73% overall from **16**) of allene **20** as a colorless oil: IR (film) 2977, 2928, 2851, 1964, and 1446 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.92–5.04 (m, 1 H), 1.68–1.82 (m, 6 H), 1.65 (d, J = 2.8 Hz, 3 H), 1.61 (d, J = 6.8 Hz, 3 H), and 1.02–1.32 (m, 5 H), ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 201.5, 103.8, 85.1, 41.7, 32.0, 31.9, 26.5, 26.4, 17.5, and 15.0; MS m/e 135, 107, 93, 91, 81, 79, 77, 67 (100), 55, and 41; HRMS m/e calcd for $C_{11}H_{18}$ 150.1408, found 150.1407.

***trans*- and *cis*-4-Cyclohexyl-3-ethyl-1-oxetan-2-one (22a and 22b).** 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 an *n*-butyllithium solution (2.46 M in hexane, 8.5 mL, 20.9 mmol) was added via syringe over 5 min. After 20 min, the ice bath was replaced with a dry ice–acetone bath (−78 °C), and a solution of *S*-phenyl butanethioate (3.610 g, 20.0 mmol) in 4 mL of THF was added dropwise via cannula over 7 min. After 45 min, a precooled (−78 °C) solution of cyclohexanecarboxaldehyde (2.245 g, 20.0 mmol) in 30 mL of THF was added dropwise over 30 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 −5 °C over 2 h. Half-saturated NH_4Cl solution (100 mL) was then added, and the resulting mixture was partitioned between 100 mL of water and 150 mL of diethyl ether. The organic phase was extracted with two 200-mL portions of 10% Na_2CO_3 solution and 200 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 3.771 g of a yellow oil. Kugelrohr distillation (85–95 °C oven temperature, 0.05–0.1 mmHg) followed by column chromatography on silica gel (elution with 2–5% ethyl acetate–hexanes) furnished 1.999 g (55%) of **22a** and **22b** as a colorless oil (3.4:1 mixture of isomers as determined by ^1H NMR analysis): IR (film) 2940, 2860, 1820, 1450, and 1130 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) for the trans isomer **22a** δ 3.89 (dd, J = 4.0, 8.3 Hz, 1 H), 3.16 (ddd, J = 4.0, 6.6, 8.5 Hz, 1 H), 1.5–2.0 (m, 8 H), 1.0 (t, J = 7.4 Hz, 3 H), and 0.86–1.36 (m, 5 H); for the cis isomer **22b** (partial data) δ 4.13 (dd, J = 6.2, 10.4 Hz, 1 H) and 3.49 (app dt, J = 6.0, 10.8 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) for the trans isomer **22a** δ 171.3, 81.2, 55.5, 41.6, 28.4, 27.1, 25.9, 25.3, 25.0, 21.2, and 11.2; ^{13}C NMR (67.5 MHz, $CDCl_3$) for the cis isomer **22b** (partial data) δ 172.1, 78.9, 53.8, 38.1, 28.9, 28.3, 17.6, and 11.9. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.76; H, 10.04.

***trans*-4-Cyclohexyl-3-ethyl-3-(phenylseleno)-1-ox-**

etan-2-one (23a) and *cis*-4-Cyclohexyl-3-ethyl-3-(phenylseleno)-1-oxetan-2-one (23b). Reaction of a mixture of β-lactones **22a** and **22b** (1.805 g, 9.90 mmol) with lithium diisopropylamide (10.33 mmol) and diphenyl diselenide (3.175 g, 10.17 mmol) in 60 mL of THF was performed according to general procedure A. Workup and purification by column chromatography on silica gel (elution with 3% ethyl acetate–hexanes) gave 2.498 g (75%) of a 1.5:1 mixture of **23a** and **23b** as a colorless oil which solidified upon standing. Further chromatographic purification provided a pure sample of the major isomer **23a**: mp 54–57 °C; IR (film): 3050, 2940, 2860, 1820, and 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.66 (m, 2 H), 7.29–7.47 (m, 3 H), 4.04 (d, J = 10.6 Hz, 1 H), 2.21 (dq, J = 7.4, 14.7 Hz, 1 H), 1.93–1.97 (m, 5 H), 1.85 (dq, J = 7.4, 14.7 Hz, 1 H), 1.28 (t, J = 7.4 Hz, 3 H), 1.08–1.49 (m, 4 H), and 0.7–0.97 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 170.9, 137.6, 129.7, 129.4, 125.0, 86.1, 60.8, 38.0, 28.9, 28.0, 26.0, 25.0, 23.3, and 10.4. Anal. Calcd for $C_{17}H_{22}O_2Se$: C, 60.53; H, 6.57. Found: C, 60.65; H, 6.72. For the minor isomer **23b**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.76 (m, 2 H), 7.26–7.43 (m, 3 H), 3.99 (d, J = 10.5 Hz, 1 H), 1.59–2.05 (m, 8 H), 1.1–1.46 (m, 3 H), 1.01 (t, J = 7.3 Hz, 3 H), and 0.83–1.09 (m, 2 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.5, 137.5, 129.3, 129.0, 124.5, 84.2, 61.2, 39.9, 29.2, 28.8, 26.4, 26.0, 24.9, and 9.7.

(*Z*)-4-Cyclohexyl-3-ethylidene-1-oxetan-2-one (24a) and (*E*)-4-Cyclohexyl-3-ethylidene-1-oxetan-2-one (24b). Reaction of the mixture of selenides **23a** and **23b** (2.259 g, 6.70 mmol) with *m*-CPBA (4.351 g, 80% pure, 20.17 mmol) in 160 mL of CH_2Cl_2 was performed according to general procedure B except that the reaction mixture was stirred at 0 °C for 25 min. Workup and purification by column chromatography on silica gel (elution with 1–3% ethyl acetate–hexanes) gave 0.810 g (67%) of **24a** as a pale yellow oil and 0.380 g (31%) of **24b** as a pale red oil. For the *Z* isomer **24a**: IR (film) 2920, 2850, 1810, and 1710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.94 (dq, J = 1.4, 7.2 Hz, 1 H), 4.58 (m, 1 H), 2.07 (dd, J = 1.4, 7.2 Hz, 3 H), 1.60–1.93 (m, 6 H), 0.96–1.36 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.0, 137.0, 131.3, 82.1, 41.0, 27.8, 27.3, 26.0, 25.3, 25.2, and 14.7. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.08; H, 8.94. For the *E* isomer **24b**: IR (film) 2930, 2850, 1810, and 1715 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.43 (dq, J = 1.9, 7.3 Hz, 1 H), 4.84 (m, 1 H), 1.83 (dd, J = 1.1, 7.3 Hz, 3 H), 1.65–1.90 (m, 6 H), and 1.06–1.36 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 164.2, 137.2, 128.8, 83.0, 40.5, 28.5, 26.8, 25.9, 25.8, 25.5, and 14.7. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.01; H, 8.96.

1,2-Butadienylcyclohexane (25). A threaded Pyrex tube (ca. 115-mL capacity) fitted with a rubber septum and an argon inlet needle was charged with a solution of lactones **24a** (0.546 g, 3.03 mmol) and **24b** (0.118 g, 0.65 mmol) in 20 mL of CH_3CN. The solution was degassed by three freeze–thaw cycles and then sealed with a threaded Teflon cap. The reaction mixture was heated at 148–159 °C (bath temperature) for 46 h and then allowed to cool to room temperature. The resulting mixture was partitioned between 50 mL of pentane and 30 mL of water, and the aqueous phase was separated and extracted with 25 mL of pentane. The combined organic phases were extracted with two 20-mL portions of water and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated by short-path distillation to afford a yellow liquid. Column chromatography on silica gel (gradient elution with 0–10% ethyl acetate–pentane) gave 0.123 g (18%) of a 1:1.6 mixture of unreacted lactones **24a** and **24b** and 0.345 g (69%) of the allene **25** as a colorless oil: IR (film) 2930, 2860, 1970, and 1450 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.97–5.17 (m, 2 H), 1.86–2.04 (m, 1 H), 1.53–1.83 (m, 5 H), 1.65 (dd, J = 3.4, 6.4 Hz, 3 H), and 0.96–1.42 (m, 5 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 203.6, 96.4, 86.2, 37.2, 33.1, 26.2, 26.0, and 14.7. Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 87.98; H, 11.62.

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