Synthesis of 2,2-Disubstituted Oxetanes from Ketones with *S*-Methyl-*S*-(sodiomethyl)-*N*-(4-tolylsulfonyl)sulfoximine

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Abstract: A convenient and facile one-step synthesis of 2,2-disubstituted oxetanes from ketones utilizing *S*-methyl-*S*-(sodiomethyl)-*N*-(4-tolylsulfonyl)sulfoximine in dimethyl sulfoxide is presented. The stereochemistry and chemical reactivity of some 2,2-disubstituted oxetanes are discussed. A synthesis of isomarrubiin (**34**) is also described.

Recently, we reported several attempts to convert unreactive cyclopentanone **1a** into (±)-bazzanene (**1c**, Scheme I).[1-3] One plan for the preparation of alkene **1c** involved the conversion of ketone **1a** into epoxide **1b** with an appropriate nucleophilic methylene transfer reagent. Deoxygenation[4] of this resultant epoxide **1b** then would afford (±)-bazzanene (**1c**). The nucleophilic methylene transfer reagent chosen was *S*-methyl-*S*-(sodiomethyl-*N*-(4-tolylsulfonyl)sulfoximine (**2**)[5,6] which was reported by Johnson and co-workers[6b] to convert ketones into epoxides. According to their general reaction method, 1.1 equiv of anion **2** are generated by 1.1 equiv each of sodium hydride and the parent sulfoximine[5,6] in dimethyl sulfoxide followed by the addition of a ketone (1 equiv) and stirring overnight at room temperature (20–25 °C). Under these conditions ketones are smoothly converted into epoxides in good yields.

Since our supply of synthetic **1a** was limited, we opted to use estrone 3-methyl ether as a model cyclopentanone for carrying out this methylene transfer reaction for practice. In an effort for optimized yields, this latter ketone (Scheme I) was added to 3 equiv of reagent **2** in Me_2SO and allowed to stir at 45 ± 2 °C for 20 h. After workup and examination of the infrared (IR) and nuclear magnetic resonance (NMR) spectral data of the product, it was obvious that no carbonyl group or epoxide protons were present. However, the NMR spectrum of the product revealed overlapping triplets at δ 4.28 (CH_2O), and the mass spectrum exhibited a parent ion at m^+/z 312 which is 28 mass units greater than the starting ketone. These data, together with the combustion analysis, confirmed the fact that the product (isolated in 96% yield) was a 64:36 ratio of diastereomeric oxetanes **3** and **4**, respectively. Oxetane **3** previously had been prepared from estrone 3-methyl ether by two independent multistep syntheses.[7]

The syntheses and chemistry of oxetanes have been reviewed.[8-12]

Scheme I

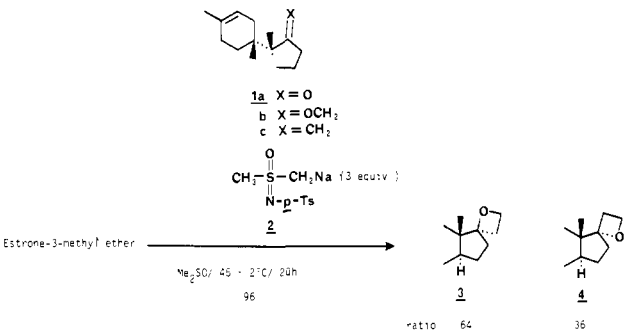
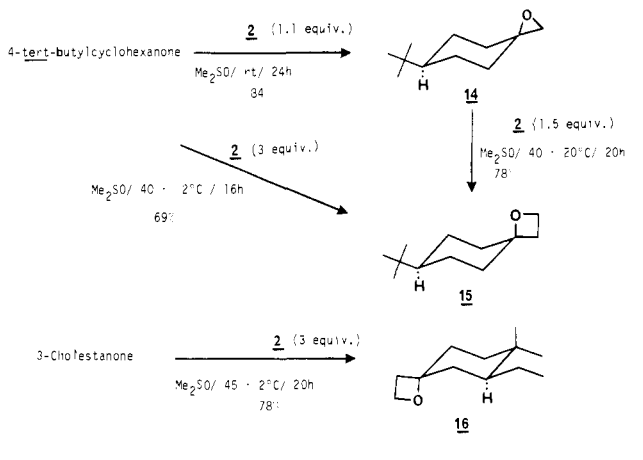


Table I. Yields of Oxetanes from Selected Ketones 5–13

ketone	*t*, °C	isolated yields of oxetanes (%)
5, bicyclo[3.3.1]non-9-one	40 ± 2	68
6, cyclohexanone[a]	40 ± 2	47
7, cycloheptanone	45 ± 2	63
8, cyclooctanone	45 ± 2	59
9, cyclononanone	45 ± 2	65
10, cyclodecanone	45 ± 2	61
11, cyclopentadecanone	45 ± 2	72
12, 2-undecanone	45 ± 2	49
13, 2-tridecanone	45 ± 2	51

[a] Reference 10 d,e.

Scheme II. Stereochemistry of Epoxides and Oxetanes in Unhindered Cyclohexanones



The synthesis of 2,2-disubstituted oxetanes from aliphatic ketones normally requires a multistep sequence of reactions employing

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(5) Dimethyl *N*-(4-tolylsulfonyl)sulfoximine is commerically available from Columbia Organic Chemicals, Inc., Columbia, SC 29209 (Catalog No. D-7082).

(6) For the preparation of dimethyl *N*-(4-tolylsulfonyl)sulfoximine, see: (a) Carr, D.; Seden, T. P.; Turner, R. W. *Tetrahedron Lett.* **1969**, 477–478. (b) Johnson, C. R.; Kirchhoff, R. A.; Reischer, R. J.; Katekar, G. F. *J. Am. Chem. Soc.* **1973**, *95*, 4287–4291. (c) Johnson, C. R.; Kirchhoff, R. A. *J. Org. Chem.* **1979**, *44*, 2280.

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(9) (a) Coyle, J. D.; Carless, H. A. *J. Chem. Soc. Rev.* **1972**, *1*, 465–480. (b) Arnold, D. R. *Adv. Photochem.* **1968**, *6*, 301–423. (c) Muller, L. L.; Hamer, J. "1,2-cycloaddition Reactions"; Interscience: New York, 1967; pp 111–139. (d) Büchi, G.; Kofron, J. T.; Koller, E.; Rosenthal, D. *J. Am. Chem. Soc.* **1956**, *78*, 876–877.

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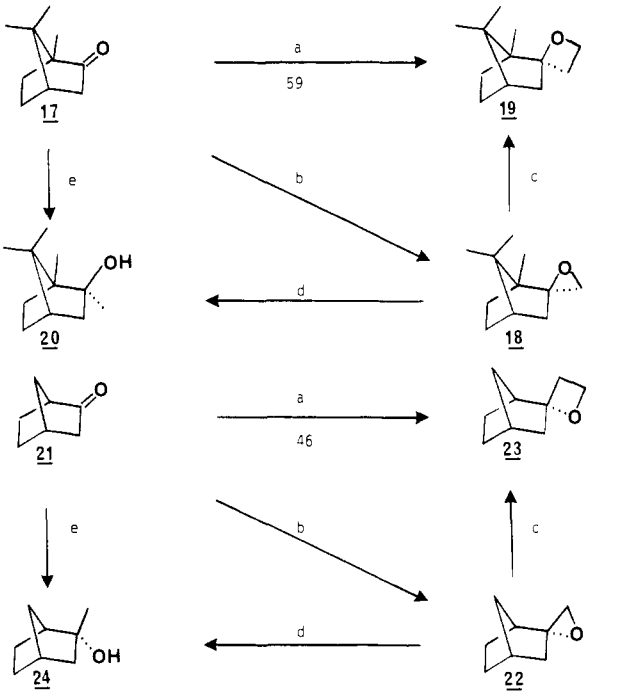
either a Reformatsky ($Zn/BrCH_2CO_2Et$) or Rathke reaction ($LiCH_2CO_2$-*t*-Bu) followed by reduction ($LiAlH_4$), selective esterification (*p*-TsCl or MsCl, pyridine), and base-induced ring closure (NaH or KO-*t*-Bu).[7,10] Heretofore no simple, straightforward single-step synthesis of 2,2-disubstituted oxetanes had been devised or published.[13] Our modification of the conditions of Johnson and co-workers for the utilization of reagent **2** serendipitously has afforded a convenient and facile one-step synthesis of 2,2-disubstituted oxetanes from ketones.

Repetition of these experimental conditions with ketones **5–13** affords the respective oxetane products in 47–72% isolated yields (Table I). Temperature control is not critical in the oxetane-forming process. A temperature of at least 40–45 °C is necessary for good yields. The synthesis of oxetanes has been performed at temperatures as high as 60 °C with no observed formation of homoallylic alcohol as noted in our original support.[13] The crude product obtained after workup can be purified smoothly and quickly by medium-pressure liquid chromatography (MPLC).[14] Standard gravity column chromatography is not recommended for this separation since prolonged contact of these oxetanes with silica gel will lead to significant formation of homoallylic alcohol products. The thermal stability of various 2,2-disubstituted oxetanes was studied also. Solutions of oxetanes from ketones **5** and **12** and oextanes **15** and **19** in Me_2SO were heated at 100 °C under nitrogen for 11 h. In each case the starting oxetane was recovered unaltered. Spectral data on these recovered oxetanes showed no alkene or alcohol products were formed under these conditions.

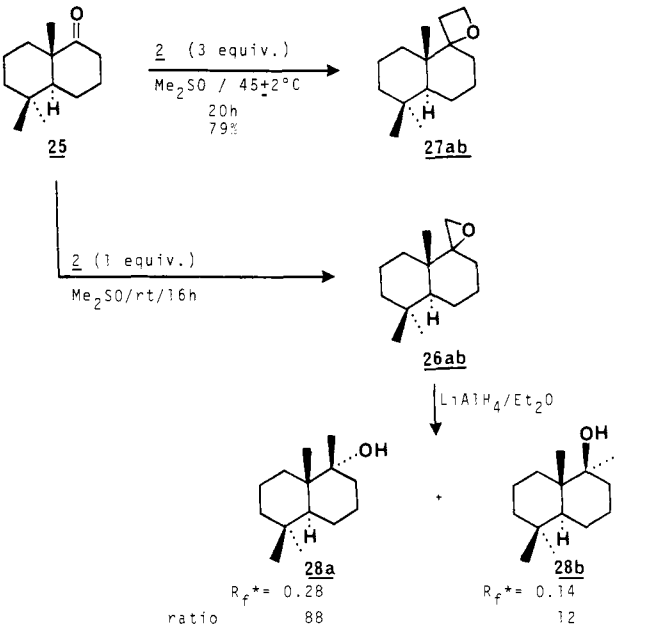
Unhindered cyclohexanones, such as 4-*tert*-butylcyclohexanone and 3-cholestanone (Scheme II), under our conditions afford single oxetanes **15** and **16** in 69% and 78% yields, respectively. The stereochemistry of these oxetanes correlates with observations of Johnson and co-workers in the respective epoxides.[6b,15] In fact, treatment of epoxide **14** (prepared via conditions of Johnson and co-workers)[6b] with 1.5 equiv of reagent **2** in Me_2SO at 40 ± 2 °C for 20 h affords oxetane **15** in 78% yield, thus confirming the intermediacy of epoxides in the formation of oxetanes. The axial C–O bond stereochemistry of epoxides formed in the case of unhindered cyclohexanones from nucleophilic methylene transfer reagents such as **2** or dimethylsulfoxonium methylide[16,17] is accounted for by the fact that the initial attack of the bulky oxosulfonium ylide at the carbonyl carbon atom is reversible.[18,19] Thus, equilibration at this stage of the reaction assures the formation of the less hindered, thermodynamically more stable, axially C–O bonded epoxide in unhindered cyclohexanones. Subsequent nucleophilic attack of excess reagent **2** upon epoxides

Scheme III. Stereochemistry of Epoxides and Oxetanes in Bicyclic Ketones



(a) 2 (3 equiv), Me_2SO, 40–45 °C, 16 h. (b) 2 (1 equiv), Me_2SO, room temperature 16 h. (c) 2 (1.5 equiv), Me_2SO, 40 ± 2 °C, 24 h. (d) $LiAlH_4$, Et_2O, 0–5 °C, 2 h. (e) CH_3MgBr or CH_3MgI, Et_2O, 5 °C, to room temperature.

Scheme IV[a]



[a] See Table II for results of Europium NMR shift analysis.

Table II. Europium NMR Shift Analysis

	d, Å[b]	slope[c]	*d*, Å[b]	slope[c]
C_9-Me	2.4	15.1	2.4	15.3
C_{10}-Me	3.9	6.29	2.5	10.6
C_4ax-Me	4.9	1.77	4.5	2.65
C_4eq-Me	4.9	2.59	6.3	2.50

[a] Asterisk indicates chromatography was done on Silica Gel 60 with 15% Et_2O/85% petroleum ether. [b] Measured distance from the indicated methyl group to the OH group by using Dreiding stereomodels. [c] These slopes are calculated by plotting $\Delta\delta$Me vs. Δ[Eu(DPM)$_3$]/[ROH].

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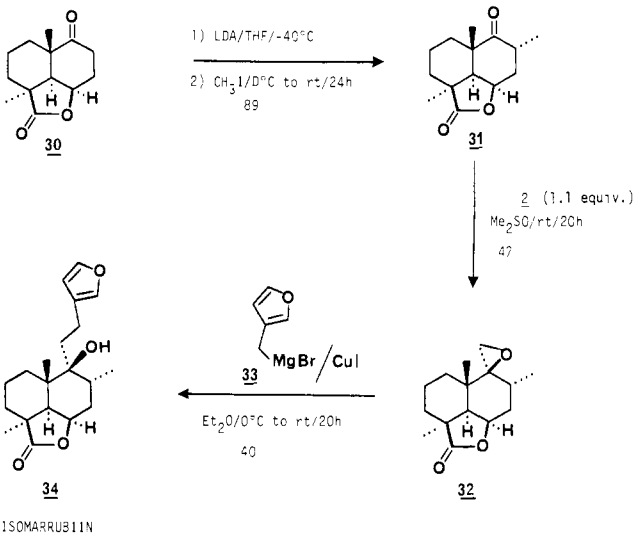
Scheme V

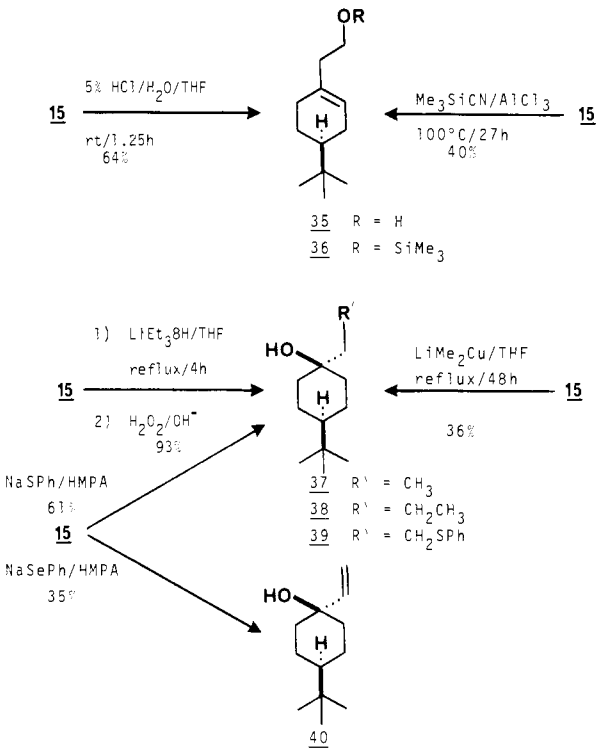


such as **14** at 40–60 °C followed by ring closure will then afford axial C–O bonded oxetanes of the type **15**.

The stereochemistry of epoxide and oxetane formation with reagent **2** was studied in bicyclic ketones camphor (**17**) and bicyclo[2.2.1]heptan-2-one (**21**, Scheme III). Treatment of either **17** or **21** with 3 equiv each of reagent **2** in Me_2SO at 40–45 °C for 16 h affords single oxetanes **19** and **23**, in 59% and 46% yields, respectively. In each case the thermodynamically more stable oxetane was formed exclusively. The stereochemistry of each oxetane **19** and **23** was ascertained by determining the stereochemistry of each intermediate epoxide. Treatment of each ketone **17** and **21** with 1 equiv each of reagent **2** at room temperature for 16 h produces single epoxides **18** and **22** in high yield. The NMR spectral data of **22** correlates with that reported by Bly and co-workers.[20] Each epoxide **18** and **22** upon reaction with 1.5 equiv each of reagent **2** at 40 ± 2 °C for 24 h gives the respective oxetanes **19** and **23** in high yields. In order to confirm the stereochemistry of epoxides **18** and **22**, we reduced each with lithium aluminum hydride to the respective alcohols **20**[21] and **24**.[22] These alcohols were compared to the respective samples prepared by the addition of methylmagnesium bromide or iodide to each ketone **17** and **21**.[23]

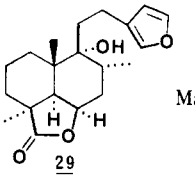
Application of our conditions for reagent **2** to ketone **25** affords oxetanes **27a** and **27b** in 79% yield as an 88:12 ratio of diastereomers, respectively (Scheme IV). On the basis of previously reported data in a similar ring system, it seemed appropriate to assign the stereochemistry of the major isomer **27a** as having an axially C–O bonded oxetane.[24] In order to prove this hypothesis, we allowed ketone **25** to react with reagent **2** under the conditions of Johnson and co-workers to give epoxides **26a** and **26b** as an 88:12 ratio of diastereomers, respectively, in high yield. Reduction of this mixture of epoxides with lithium aluminum hydride in ether

Scheme VI. Selected Reactions of Oxetane 15



then produces an easily separable mixture of axial alcohol **28a** and equatorial alcohol **28b** in a ratio of 88:12, respectively. Treatment of ketone **25** with methyllithium/lithium dimethylcopper complex in ether at −78 °C affords alcohols **28a** and **28b** as a 38:62 ratio of diastereomers, respectively.[25] These two diastereomeric alcohols are easily distinguished by an europium-induced NMR shift analysis experiment (see Table II).[26] In this experiment the NMR absorption of the C-10 methyl group of alcohol **28a** migrates only 0.59 times as fast as the corresponding absorption in alcohol **28b**. This confirms the fact that the C-10 methyl group in **28a** is further away (3.9 Å) from the axial hydroxyl group than the C-10 methyl group in **28b** is from the equatorial hydroxyl group (2.5 Å, Scheme IV).

These stereochemical results on ketone **25** led us to propose a synthetic plan for the construction of (±)-marrubiin (**29**, Scheme V). Marrubiin (**29**) is a diterpene lactone isolated from *Marrubium vulgare*, white horehound.[27,28] Our plan involves the stereoselective preparation of either an axially C–O bonded epoxide or oxetane followed by ring opening with either the Grignard reagent derived from 3-bromomethylfuran or 3-bromofuran, respectively, to form (±)-marrubiin (**29**). We envisioned the formation of either an axially C–O bonded epoxide or oxetane from ketone **31** with reagent **2** to occur under either the conditions of Johnson and co-workers[6b] or ours, respectively. From a Dreiding stereomodel of ketone **31** it did not appear as if the equatorial methyl group as C-8 would cause any significant stereochemical problem. This hypothesis was supported by the fact that Ballantine



Marrubiin

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and Sykes reported identical ratios for the formation of axially:equatorially bonded epoxides (97:3, respectively) in both 3-cholestanone and 2-α-methyl-3-cholestanone when dimethylsulfoxonium methylide was used as the methylene-transfer reagent.[17a]

Our synthesis commences with ketone **30** (Scheme V) which we utilized in a previously reported synthesis of the antibiotic (±)-LL-Z1271α.[29] Alkylation of ketone **30** using 1.2 equiv of lithium diisopropylamide in tetrahydrofuran at −40 °C followed by the addition of methyl iodide at 0 °C produces ketone **31** in 89% yield. Treatment of ketone **31** with 1 equiv of reagent **2** at room temperature for 20 h gives epoxide **32** as a single diastereomer in 47% unoptimized yield. The stereochemistry of this epoxide was uncertain at this stage of the synthesis. However, when epoxide **32** was allowed to react with Grignard reagent **33**, drived from 3-bromomethylfuran, in ether in the presence of copper(I) iodide,[30] (±)-isomarrubiin (**34**) was formed in 40% unoptimized yield. Apparently the equatorial methyl group at C-8 in ketone **31** has a profound effect on the stereochemical outcome for the methylene-transfer reaction of reagent **2** on ketone **31** (Scheme V) relative to our model ketone **25** (Scheme IV).

Since stereochemically homogeneous, axially C–O bonded oxetanes can be prepared from unhindered cyclohexanones (Scheme II) with ease, we elected to study the chemistry of these oxetanes (Scheme VI). Oxetane **15**, upon treatment with 5% aqueous hydrochloric acid in tetrahydrofuran for 1.25 h at room temperature, affords homoallylic alcohol **35** in 64% yield as the only isomer observed and isolated.[10e] Heating oxetane **15** with trimethylsilyl cyanide at 100 °C for 27 h in the presence of anhydrous aluminum chloride produces trimethylsilyl ether **36** in 40% yield.[31]

Reduction of oxetane **15** with lithium triethylborohydride[32] in tetrahydrofuran at reflux for 4 h, followed by workup with basic hydrogen peroxide produces alcohol **37** in 93% yield as a single isomer.[23,33] A similar reduction of oxetane **15** with lithium aluminum hydride in tetrahydrofuran at reflux for 64 h gives alcohol **37** in only 54% yield.[33,34] A reported addition of ethylmagnesium bromide to 4-*tert*-butylcyclohexanone gives a 2.4:1 ratio of diastereomers with alcohol **37** being the major product.[23,33]

When oxetane **15** allowed to react with excess lithium dimethyl copper in tetrahydrofuran[35] from 0 °C to reflux for 48 h, alchol **38** is formed in 36% yield as a single isomer.[36] A reported addition of *n*-propylmagnesium bromide to 4-*tert*-butylcyclohexanone produces a 2.1:1 ratio of diastereomers with alcohol **38** being the major product.[23,36]

Nucleophilic opening of oxetane **15** with sodium thiophenoxide[37] in hexamethylphosphoric triamide at 150 °C for 44 h gives hydroxyl sulfide **39** in 61% yield as a single isomer. However, treatment of oxetane **15** with sodium selenophenoxide in hexamethylphosphoric triamide at 150 °C for 44 h affords vinyl alchol **40** in 35% yield as a single isomer. A reported addition of vinylmagnesium bromide to 4-*tert*-butylcyclohexanone produces a 3:2 ratio of diastereomers with alcohol **40** being the minor product.[23,38]

Finally, oxetane **15** was treated with several other nucleophilic reagents [KCN/THF/18-crown-6/reflux;[39] KCN/Me_2SO/100 °C;[39,40] KCN/HMPA/18-crown-6/150 °C;[41] $PhSCH_2Li$/THF/HMPA/100 °C/44 h;[42] 1,3-dithiane/*n*-BuLi/THF/room temperature;[43] $LiCH_2CO_2$-*t*-Bu/THF/room temperature;[44] $NaCH(CO_2Me)_2$/THF/HMPA/reflux] and these attempted reactions gave only starting oxetane **15**, unaltered.

In summary, reagent **2** when used under the conditions of Johnson and co-workers[6b,18] acts as an exceedingly useful methylene (+CH_2:−) synthon with ketones; however, this same reagent **2** when utilized with ketones under our conditions is a convenient ethylene (+CH_2CH_2:−) synthon. In the case of cyclohexanones these reactions are highly stereoselective. In all cases observed the thermodynamically more stable products are formed predominantly. Unfortunately, the reduced reactivity of 2,2-disubstituted oxetanes toward nucleophilic reagents relative to 2,2-disubstituted oxiranes limits the usefulness of the former in organic synthesis.

Experimental Section

General Procedure. Melting points were determined on a Büchi melting point apparatus. "Bulb-to-bulb" distillation refers to horizontal short-path distillation, where the crude material was heated in either an Aldrich Kugelrohr or a Büchi glass tube oven. Combustion analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Silica gel 60, 70–230 mesh (E. Merck No. 7734), available from Brinkmann Instruments, was used for gravity column chromatography. Medium-pressure liquid chromatography (MPLC)[14] was performed on a chromatograph equipped with a Fluid Metering lab pump Model RPSYX, a pulse dampener (Fluid Metering), and Altex repackable columns packed with silica gel 60, 230–400 mesh (E. Merck No. 9385) available from Brinkmann Instruments. Infrared spectra were recorded on a Perkin-Elmer Model 237B Spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian Associates Model T-60 (60-MHz ^1H NMR) or on a Varian Model FT-80 (80-MHz ^1H and ^{13}C NMR). High- amd low-resolution mass spectra were recorded on a Dupont Flash CEC 21-110B and a Hewlett-Packard Model 5933A spectrometer, respectively, at 70 eV by Dr. T. Marriot at the Rice University High Resolution Mass Spectrometry Laboratory. For all reactions performed under an atmosphere of dry nitrogen or dry argon, the equipment was dried in an oven at 120 °C for at least 4 h and then allowed to cool in a desiccator. All liquid transfers were made with nitrogen-flushed syringes. *S,S*-Dimethyl-*N*-(4-tolylsulfonyl)sulfoximine (mp 167–169 °C), available from Columbia Organics, Columbia, SC 29209, was either recrystallized from acetone/ethanol, or used as received. Sodium hydride was obtained from Aldrich Chemical Co., and used as received in a suspension of mineral oil (61.1%). The need for scrupulously dried dimethyl sulfoxide cannot be overemphasized. Commercially available material (Eastman) was refluxed over calcium hydride (under N_2 atmosphere) for 6 h and then vacuum distilled onto fresh calcium hydride. This latter process was repeated twice, with the last vacuum distillation of dimethyl sulfoxide onto 4-Å molecular sieves (previously dried in a vacuum oven for 3 days). Petroleum ether is Baker Analyzed Reagent, bp 30–60 °C. Ether and tetrahydrofuran, when used as reaction solvents, were distilled from lithium aluminum hydride just prior to use.

Precautions. All reactions should be carried out by using proper technique and in a well-ventilated chemical hood. All reagents should be handled with due respect, but the following properties should be especially noted: dimethyl sulfoxide is readily absorbed through the skin; hexamethylphosphoric triamide is a carcinogen. These solvents should always be handled with good quality rubber gloves.

***cis*-7-*tert*-Butyl-1-oxaspiro[3.5]nonane (15).** *S,S*-dimethyl-*N*-(4-tolylsulfonyl)sulfoximine (2.53 g, 10.2 mmol, 3.3 equiv) was added through a solid addition funnel (under N_2 flow) into a 3-necked 25-mL rounded-bottomed flask equipped with a nitrogen inlet containing sodium hydride (61.1% in mineral oil, 365 mg, 9.30 mmol, 3.0 equiv) and a

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stirring bar (9.5 mm, egg shaped). Triple-distilled Me_2SO (10 mL) was syringed into the flask to give a yellow frothing mixture. After a few minutes a dull green color developed which then disappeared. After 10 h of vigorous stirring at 35 °C, the mixture was clear indicating complete formation of the anion. A solution of 4-*tert*-butylcyclohexanone (477 mg, 3.1 mmol) in triple-distilled Me_2SO (4 mL) was added and the reaction was heated to 47 °C for 18 h. (Temperatures as high as 60 °C and times as long as 30 h can be used.)

The reaction mixture was cooled, diluted with saturated NaCl (100 mL), extracted with ether (4 × 50 mL); the combined ether extracts were washed with saturated NaCl solution (50 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo (no heat applied) to a volume of a few milliliters. Petroleum ether (20 mL) was added to precipitate the soluble salts, and the mixture was filtered through a short column of silica gel 60 (230–400 mesh, elution with petroleum ether). The eluate was reconcentrated to a volume of 3 mL and injected directly into the liquid chromatograph (MPLC).[14] The material was purified with a 15 × 250 mm silica gel 60 column (18 g), using a 10–90 ratio of ether/petroleum ether as the eluting solvent, at a pressure of 13 psi (90 kPa), collecting 5-mL fractions. Removal of the solvent from the appropriately combined fraction gave 360 mg (65%) of oxetane **15**: bp 40 °C (0.6 mmHg) (0.08 kPa); IR ($CHCl_3$) 2930 (CH, aliphatic, 1475, 1440, 1365, 1240, 985, 955, 925, 910, 895 cm^{-1}; NMR ($CDCl_3$) δ 4.42 (t, 2, J = 8 Hz, CH_2O), 2.27 (t, 2, J = 8 Hz, CH_2CH_2O), 2.0–1.0 (m, 9, ring protons), 0.85 (s, 9, *t*-Bu).

Anal. ($C_{12}H_{22}O$) C, H.

Revised workup procedure (recommended especially for large-scale syntheses where clogging of the separatory funnel with the voluminous precipitate is a problem): The reaction mixture was cooled and diluted with saturated NaCl (150 mL) and pentane (100 mL). Most of the voluminous precipitate was removed by filtration of the entire mixture through a large wad of glass wool in a funnel. The separated aqueous layer was extracted with pentane (5 × 50 mL); the combined pentane layers were dried (Na_2SO_4), filtered, and concentrated by distilling most of the solvent through a Vigreux column to obtain a solution of the crude product (2 mL), which can be injected directly into the liquid chromatograph.[14]

Methylation of Keto Lactone 30. To a stirred solution of methyllithium (1 mL, 1.3 mmol, 1.3 M in ether) in dry THF (5 mL) as −40 °C was added freshly distilled diisopropylamine (9.13 g, 0.183 mL, 1.3 mmol). After strirring for 0.5 h at −40 °C, keto lactone **30** (0.248 g, 1.11 mmol) in THF was added dropwise over a period of 5 min at 0 °C, and the mixture was stirred for 1 h. The mixture was cooled to −10 °C, methyl iodide (0.426 g, 0.187 mL, 3 mmol) was added, and the reaction mixture was brought to room temperature and stirred for 20 h. The mixture was diluted with cold aqueous HCl (10%, 25 mL), extracted with ether (3 × 25 mL); the combined ethereal extracts were washed with saturated NaCl solution dried ($MgSO_4$), filtered ($MgSO_4$), concentrated in vacuo, and chromatographed (gravity column, silica gel 60, 30 g), to afford 0.235 g (89%) of pure methylated lactone **31**:[28] IR (CCl_4) 2950 (CH), 1770 (lactone CO), 1715 cm^{-1} (ketone CO); NMR ($CDCl_3$) δ 5.02 (m, 1, oxy methine), 2.8–1.9 (m), 1.60 (m), 1.33 (s, 3 CH_3), 1.20 (d, 3, J = 8 Hz, $CHCH_3$), 1.18 (s, 3, CH_3); low-resolution mass spectrum, m/e (rel intensity) 236 (M+, 11), 149 (28), 136 (12), 121 (11), 109 (100), 96 (23), 93 (27), 79 (23), 67 (23), 41 (42).

Anal. ($C_{14}H_{20}O_3$) C,H.

Epoxylactone 32. *S,S*-Dimethyl-*N*-(4-tolylsulfonyl)sulfoximine (0.050 g, 0.20 mmol, 1.0 equiv) was added to a flask containing sodium hydride (61.1% in mineral oil, 0.008 g, 0.20 mmol, 1.0 equiv). Dry Me_2SO (2.5 mL) was syringed into the flask and the reaction was stirred at room temperature for 4 h. A solution of methylated ketolactone **31** (0.046 g, 0.20 mmol) in Me_2SO (1 mL) was added, and the mixture was stirred for 20 h at room temperature. The reaction mixture was diluted with water (15 mL), extracted with ether (3 × 20 mL); the ethereal extracts were wahsed with saturated NaCl solution, dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated to give 0.06 g of the crude product. The material was chromatographed (gravity column, silica gel 60, 10 g, 20/80 ether/petroleum ether eluant) to give 0.023 g (47%) of epoxylactone **32**: IR (CCl_4) 2950 (CH), 1780 (lactone CO), 1245, 860 cm^{-1}; NMR (CCl_4) δ 4.65 (m, 1, oxymethine), 2.53 (s, 2, epoxy CH_2O), 2.4–1.4 (m), 1.25 (s, 3, CH_3), 1.20 (s, 3, CH_3), 0.72 (d, 3, J = 6 Hz, $CHCH_3$); low-resolution mass spectrum, m/e (rel intensity) 250 (M+, 16), 235 (27), 175 (71), 161 (27), 159 (27), 119 (78), 109 (100), 107 (52), 105 (86), 97 (100), 93 (53), 91 (77), 41 (70).

Anal. ($C_{15}H_{22}O_3$) C, H.

Isomarrubiin (34). 3-Bromomethylfuran (0.497 g, 3.1 mmol) was added to a mixture of freshly activated magnesium turnings (0.075 g, 3.1 mmol) in dry ether (8 mL) with stirring under N_2 at 0 °C. After 2 h of stirring, a 1.5-mL aliquot of this Grignard reagent was added to a mixture of epoxylactone **32** (0.015 g, 0.06 mmol) and copper(I) iodide (0.005 mmol, catalyst) in dry ether (5 mL) at 0 °C, and the mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL), extracted with ether (3 × 20 mL); the ethereal extracts were washed with water (50 mL), dried ($MgSO_4$), filtered ($MgSO_4$), and concentrated in vacuo to give 0.055 g of the crude product. The matieral was chromatographed (gravity column, silica gel 60, 10 g, 20/80 ether/petroleum ether eluant) to give 0.0098 g (40%) of pure **34**: IR (CCl_4) 3580 (OH, weak), 2930 (CH, aliphatic), 1775 cm^{-1} (CO); NMR (100-MHz ^1H, $CDCl_3$) δ 7.19 (s, 2, CH=C*H*OC*H*, furan ring), 6.12 (3, 1, J = 1.8 Hz, C*H*=CHOCH, furan ring), 4.66 (t, 1, oxy methine, J = 5.3 Hz), 2.76 (d, 2, J = 2.3 Hz), 2.21 (d, 2, J = 4.6 Hz), 1.91 (s), 1.22 (s), 1.19 (s, 3, CH_3), 1.01 (s, 3, CH_3), 0.78 (d, 3, J = 6.1 Hz, $CHCH_3$).

Anal. ($C_{20}H_{28}O_4$) C,H.

2-(4-*tert*-Butyl-1-cyclohexenyl)ethanol (35). Oxetane **15** (87 mg, 0.48 mml) was dissolved in THF (1 mL) was treated with 5% HCl solution (3 drops). The solution was stirred for 1.25 h, filtered through $MgSO_4$, and concentrated to an oil which was purified by MPLC (elution with 7/93 ether/petroleum ether eluant) to yield 56 mg (64%) of alcohol **35** as an oil which was distilled (bulb-to-bulb): bp 70 °C (0.05 mmHg) (7 Pa); IR ($CHCl_3$) 3500 (br, OH), 2950 (CH, aliphatic), 1475, 1435, 1390, 1365, 1040 cm^{-1}; NMR ($CDCl_3$) δ 5.53 (m, 1, olefinic), 3.65 (t, 2, J = 6.5 Hz, CH_2OH), 2.22 (t, 2, J = 6.5 Hz, CH_2CH_2OH), 2.1–1.0 (m, 7, ring protons), 0.90 (s, 9, *t*-Bu).

Anal. ($C_{12}H_{22}O$) C,H.

***cis*-1-Ethyl-4-*tert*-butylcyclohexanol (37). Method A.** Freshly distilled THF (5 mL) was added to $LiAlH_4$ (158 mg, 4.16 mmol, 16 Al equiv) in a round-bottomed flask equipped with a stirring bar and nitrogen inlet. A solution of oxetane **15** (48 mg, 0.264 mmol) in THF (5 mL) was added, and the mixture was stirred at room temperature for 2.5 h, at which point no product could be detected by TLC. The mixture was brought to reflux and after 64 h the reaction was judged to be completed by TLC.

The mixture was cooled, treated with H_2O (0.15 mL), 15% aqueous NaOH (0.45) mL), and again H_2O (0.45 mL), filtered through $MgSO_4$, concentrated in vacuo, and purified by MPLC, giving 26 mg (54%) of alcohol **37**. This was distilled (bulb-to-bulb) to give 11 mg of a clear oil: IR ($CHCl_3$) 3600 (sh, OH), 3450 (br), 2950 (CH, aliphatic), 1460, 1360, 1230, 1190, 1110, 1000, 940, 825 cm^{-1} (lit.[32] 2.8, 2.9, 12.1 μm); NMR ($CDCl_3$) δ 1.8–1.0 (m, 13, aliphatic), 0.90 (s, 9, *t*-Bu); NMR ($CDCl_3$ with 50 mol; Eu($C_{11}H_{19}O_2$) δ 2.00 (t, CH_3CH_2), 1.08 (s, *t*-Bu).

Method B. Oxetane **15** (150 mg, 0.82 mmol) was charged into a 25-mL round-bottomed flask equipped with a stirring bar, reflux condenser, and nitrogen inlet. A solution of lithium triethylborohydride (1 M in THF, 10 mL, 10 mmol, 12 equiv) was added slowly via syringe. The reaction mixture was stirred vigorously and brought to reflux for 4 h, at which point the reaction was judged to be completed by TLC. The solution was cooled to 0 °C (ice bath) and an alkaline peroxide solution (30% H_2O_2 and 15% NaOH, 15 mL:15 mL) was added dropwise while the reaction mixture was stirred vigorously. Stirring was continued at 0 °C for 0.5 h and then at room temperature overnight. The solution was poured into water (100 mL) and extracted with ether (4 × 50 mL); the combined ethereal extracts were washed with 10% NaOH solution 50 mL) and saturated NaCl solution (50 mL) dried ($MgSO_4$), filtered ($MgSO_4$), then filtrated through a short column of 230–400 mesh silica gel 60. Elution with 40 mL of ether gives a clear solution which was concentrated in vacuo to give 150 mg (93%) of a clear oil: NMR ($CDCl_3$) identical with spectrum of distilled product prepared by method A. Bulb-to-bulb distillation at 100 °C (0.1–0.5 mmHg) (13–67 Pa) gave 120 mg of a clear oil: the NMR ($CDCl_3$) and IR ($CDCl_3$) spectra were identical with the spectra of product prepared by method A.

***cis*-4-*tert*-Butyl-1-propylcyclohexanol (38).** A slurry of copper(I) iodide (581 mg, 3.05 mmol, 3 equiv) in THF (12 mL) was prepared in a 50-mL 3-necked round-bottomed flask equipped with a reflux condenser and a sampling stopcock. The stirred slurry was brought to 0 °C and was treated with methyllithium (1.1 ± 0.1 M in ether, 5.3 mL, 5.9 mmol) slowly over 2 min. As the first equivalent of MeLi was added, the solution turned from clear to deep yellow, then upon completion of the addition the soln was essentially clear. The resulting solution of lithium dimethylcopper was stirred at 0 °C for 5–10 min, then a solution of oxetane **15** (176 mg, 0.96 mmol) in THF (8 mL) was added via syringe at the rate of 0.5 mL/min. The mixture was allowed to warm to room temperature and then brought to reflux for 48 h.

The reaction mixture was cooled and hydrolyzed by the addition of saturated NH_4Cl solution (50 mL). The mixture was stirred at room temperature 2 h then the ether layer was separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined ether extracts were washed with saturated NaCl solution (50 mL), dried (Na_2SO_4), concentrated to a thick oil containing some crystalline material, and chromatographed (15 × 250 mm column, silica gel 60, 230–400 mesh (18 g),

10/90 ether/petroleum ether eluant, 15 psi, 5-mL fractions), to give 70 mg (36%) of alcohol **38** as a white crystalline solid: mp 73–74 °C (sharp); bp 100 °C (0.05 mmHg) (6.7 Pa); IR ($CHCl_3$) 3610 (m, sh), 3450 (m, br, OH), 2900 (CH, aliphatic), 1464, 1350, 1230, 1174, 1125, 985, 940, 855, 825 cm^{-1} (lit.[35] (3630, 3490, 1364, 958, 940, 885 cm^{-1}); 60-MHz ^1H NMR ($CDCl_3$) δ 2.0–1.0 (m, aliphatic), 0.88 (s, *t*-Bu); 80-MHz ^{13}C NMR ($CDCl_3$) 70.69, 48.11, 46..84, 37.49, 32.43, 27.62, 22.55, 16.44, 14.79.

Anal. ($C_{13}H_{26}O$) C,H.

***cis*-4-*tert*-Butyl-1-ethenylcyclohexanol (40).** Oxetane **15** (107 mg, 0.59 mmol) and sodium selenophenoxide (300 mg, 1.68 mmol, 3 equiv) were charge into a 10-mL round-bottomed flask equipped with an N_2 inlet, septum, and 10-mm stirring bar. Hexamethylphosphoric triamide (2 mL) was added via syringe. The reaction was heated at 150 ± 2 °C with mild stirring for 44 h.

The reaction mixture was cooled, diluted with saturated $NaHCO_3$ solution (50 mL), and extracted with ether (3 × 50 ml); the combined ether extracts were washed with water (3 × 20 mL), dried ($MgSO_4$), filtered ($MgSO_4$), concentrated to an oil, and chromatographed (MPLC, 15 × 250 mm silica gel 60, 230–400 mesh (18 g), 20/80 ether/petroleum ether eluant, 18 psi, 5-mL fractions) giving 37 mg (35%) of alcohol **40**: mp 40–41 °C (lit.[38] mp 43–44 °C); bp 100 °C (0.5 mmHg) (67 Pa); IR ($CHCl_3$) 3600 (sh, OH), 2950 (CH, aliphatic), 2860 (CH), 1480, 1365 cm^{-1}; NMR ($CDCl_3$) δ 5.95 (dd, 1 J = 17, 10 Hz, C*H*=CH_2), 5.18 (dd, 1, J = 17, 2 Hz, CH=CH_2 trans), 4.95 (dd, 1 J = 11, 2 Hz, CH=CH_2 cis), 2.0-1.0 (m, 9, ring protons), 0.88 (s, 9, *t*-Bu).

***cis*-4-*tert*-Butyl-1-(2-phenylthioethyl)cyclohexanol (39).** Oxetane **15** (104 mg, 0.57 mmol) and sodium thiophenoxide (226 mg, 1.71 mmol, 3 equiv) was charged into a 10-mL round-bottomed flask equipped with an N_2, septum, and 10-mm stirring bar. Hexamethylphosphoric triamide (2 mL) was added via syringe. The reaction was heated at 150 ± 2 °C with mild stirring for 44 h.

The reaction mixture was worked up and chromatographed as for **40**, giving 101 mg (61%) of alcohol **39**: mp 52.5–53.0 °C, bp 150 °C (0.02 mmHg) (2.7 Pa), IR ($CHCl_3$) 3600 (sh, OH), 3460, 2940, 1590, 1485, 1440, 1370, 1235, 1090, 1025, 985, 910, 790 cm^{-1}; NMR ($CDCl_3$) δ 7.23 (m, 5, aromatic), 3.02 (t, 2, J = 8 Hz, CH_2O), 1.72 (t, 2, J = 8 Hz, CH_2CH$_2$O), 2.0–1.0 (m, 9, ring protons), 0.87 (s, 9, *t*-Bu); low-resolution mass spectrum, *m/e* (rel intensity) 292 (M^+, 22), 274 (12), 217 (51), 193 (23), 165 (62), 123 (45), 57 (100).

Anal. Calcd for $C_{18}H_{28}OS$: exact mass = 292.1861. Found: *m/e* 292.1863, 1.0-ppm error (by high-resolution mass spectroscopy).

2-(4-*tert*-Butylcyclohexenyl)ethyl Trimethylsilyl Ether (36). Oxetane **15** (182 mg, 1 mmol) and $AlCl_3$ (3 mg, 0.02 mmol) were chared into a 10-mL pear-shaped flask equipped with a sampling cock and stirring bar. The system was flushed with N_2 and then trimethylsilyl cyanide (0.15 mL, 109 mg, 1.1 equiv) was added via syringe. The reaction mixture was stirred and heated at 100 °C for 27 h.

The resultant brown oil was dissolved in a small amount of 10/90 ether/petroleum ether and applied directly onto a gravity column (10 × 250 mm, silica gel 60, 70–230 mesh, 10 g, 10/90 ether/petroleum ether eluant, 5-mL fractions). The combined initial fractions gave 102 mg (40%) of **36**: bp 125 °C (2 mmHg) (0.27 kPa); IR ($CHCl_3$) 2950, 1365, 1250, 1080, 875, 840 cm^{-1}; NMR ($CDCl_3$) δ 5.45 (m, 1, alkene), 3.62 (t, 2, J = 7.5 Hz, CH_2OSiMe_3), 2.17 (t, 2, J = 7.5 Hz, CH_2CH$_2$OSiMe$_3$), 1.92 (m, 4, CH_2CH=CCH_2), 1.5–1.0 (m, 3), 0.88 (s, 9, *t*-Bu), 0.13 (s, 9, $Si(CH_3)_3$); low-resolution mass spectrum, *m/e* (rel intensity) 254 (M^+, 4), 239 (6), 183 (8), 164 (31), 149 (41), 129 (22), 122 (20), 121 (59), 108 (47), 103 (68), 73 (100), 57 (93).

Anal. ($C_{15}H_{30}OSi$) C,H.

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Registry No. 2, 83929-01-5; **3**, 16377-13-2; **4**, 72150-42-6; **5**, 17931-55-4; **6**, 108-94-1; **7**, 502-42-1; **8**, 502-49-8; **10**, 1502-06-3; **11**, 502-72-7; **12**, 112-12-9; **13**, 593-08-8; **14**, 7787-78-2; **15**, 72091-16-8; **17**, 76-22-2; **18**, 83997-36-8; **19**, 72091-15-7; **20**, 2371-42-8; **21**, 497-38-1; **22**, 16282-11-4; **23**, 72150-41-5; **24**, 3212-16-6; **25**, 16776-05-9; **26a**, 83929-07-1; **26b**, 83997-38-0; **27a**, 72091-17-9; **27b**, 83997-37-9; **28a**, 56239-54-4; **28b**, 56239-55-5; (±)-**30**, 55102-06-2; (±)-**31**, 83997-34-6; (±)-**32**, 83929-02-6; (±)-**34**, 83997-35-7; **35**, 54281-02-6; **36**, 83929-04-8; **37**, 17328-78-8; **38**, 27557-56-8; **39**, 83929-03-7; **40**, 7103-35-7; 4-*tert*-butylcyclohexanone, 98-53-3; spiro[bicyclo[3.3.1]nonane-9,2′-oxetane], 72091-18-0; 1-oxaspiro[3.5]nonane, 185-18-2; 1-oxaspiro[3.6]decane, 33941-16-1; 1-oxaspiro[3.7]undecane, 67239-59-2; 1-oxaspiro[3.8]dodecane, 72091-19-1; 1-oxaspiro[3.9]tridecane, 72091-20-4; 1-oxaspiro[3.14]octadecane, 72091-21-5; 2-methyl-2-nonyloxetane, 83929-05-9; 2-methyl-2-undecyloxetane, 83929-06-0; estrone-3-methyl ether, 1624-62-0; 3-cholestanone, 15600-08-5; 3-(bromomethyl)furan, 63184-61-2.

Supplementary Material Available: Listing of elemental analyses and IR and ^1H NMR data for synthesized oxetanes (12 pages). Ordering information is given on any current masthead page.