Unusual Facial Selectivity in the Cycloaddition of Singlet Oxygen to a Simple Cyclic Diene[1]

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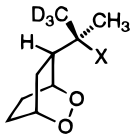
Syntheses of 5-isopropyl-1,3-cyclohexadiene and *syn*-5-isopropyl-2,3-dioxabicyclo[2.2.2]octane, by routes that would allow completely diastereoselective introduction of deuterium labels, are described. The reaction of the isopropyl cyclohexadiene with singlet oxygen is shown to give an endoperoxide that is derived by preferential attack on the more sterically hindered face of the diene. A possible mechanistic explanation of this result is that the attack from the less hindered face leads to "ene" reaction rather than endoperoxide formation. However, this mechanism would require that the "ene" reaction and cycloaddition proceed via a common intermediate—presumably a perepoxide.

Introduction

As part of an ongoing project designed to investigate the role of intramolecular dynamics in the thermal transformations of reactive intermediates,[2] we sought to prepare the deuterium-labeled derivatives of *syn*-5-isopropyl-2,3-dioxabicyclo[2.2.2]octane, **1h** and **1d**, with defined relative stereochemistry at the four stereogenic centers.



1h: X = H
1d: X = D

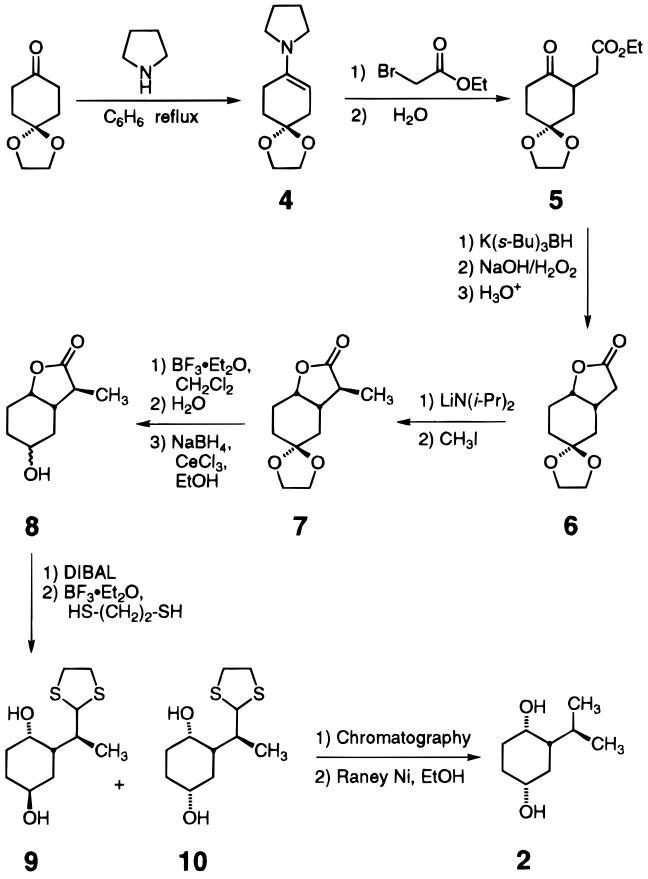
It seemed clear from the outset that the normally most efficient means of constructing the 2,3-dioxabicyclo[2.2.2]-octane skeleton—cycloaddition of O_2 ($^1\Delta_g$) to a 1,3-cyclohexadiene, followed by diimide reduction—would be unlikely to be fruitful in the present case, because attack of the singlet oxygen on the diene would be expected to occur preferentially from the less-hindered face, giving an adduct in which the labeled isopropyl substituent would be *anti* to the peroxide bridge.

In this paper we report a synthetic scheme that allows introduction of the isotopic labels with the desired stereochemistry and reveals that the preferred mode of cycloaddition in fact is *not* the one expected from the above analysis. Mechanistic implications of this observation are discussed.

Results

Our expectation of an unfavorable stereochemistry in the cycloaddition of singlet oxygen to 5-isopropyl-1,3-cyclohexadiene led us first to investigate preparation of **1** by oxidative coupling of *cis,cis*-2-isopropylcyclohexane-1,4-diol, **2**. Compound **2** was prepared by a sequence (Scheme 1) that would allow introduction of the isotopic labels with defined stereochemistry. Thus, introduction

Scheme 1



of the CD_3 could be accomplished by use of CD_3I in place of CH_3I in the alkylation step, and introduction of the tertiary deuterium of **1d** could be accomplished by base-catalyzed H/D exchange on the lactone **6**.

Unfortunately, none of the techniques investigated for the oxidative closure of **2** to **1** was successful. We chose, therefore, to investigate the $^1O_2$ + 5-isopropyl-1,3-cyclohexadiene reaction in the hope that even a small amount of cycloaddition from the more hindered face of the diene would provide enough of the desired endoperoxide to conduct the subsequent investigations.

In the event that the $^1O_2$ cycloaddition afforded enough of the *syn* stereoisomer to make this route to **1** viable, it would be necessary to prepare 5-isopropyl-1,3-cyclohexadiene (**3**) in a manner that permitted stereoselective introduction of the isotopic labels. A synthesis that

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(1) Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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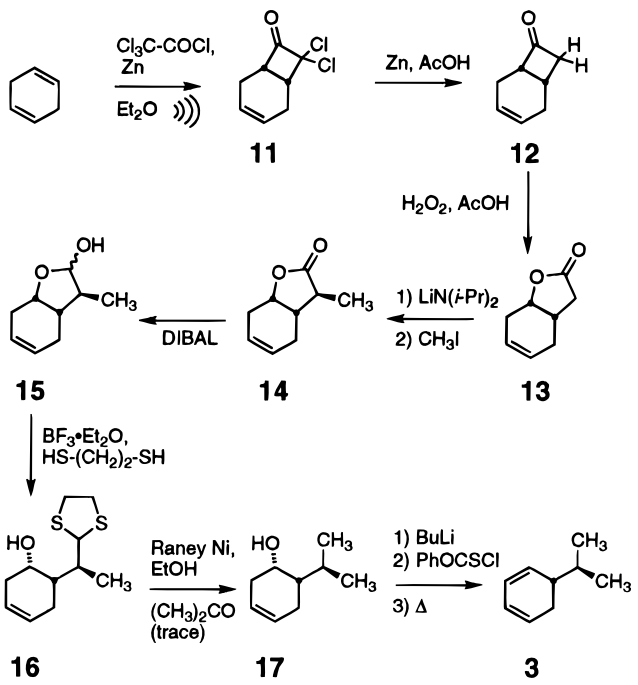
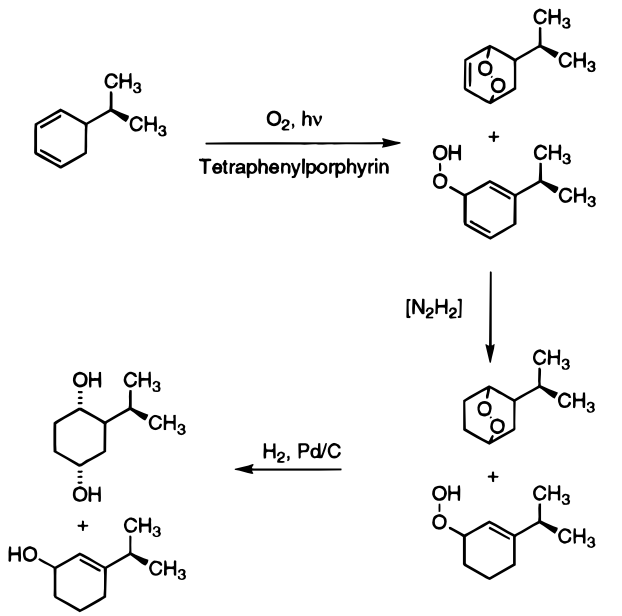
Scheme 2



Scheme 3



accomplished this goal is shown in Scheme 2. As before, the CD_3 could be introduced stereoselectively by use of CD_3I in place of CH_3I in the alkylation, and the tertiary deuterium could be introduced by H/D exchange on the lactone prior to alkylation (or by use of AcOD in the reduction of the dichloroketene cycloadduct).

Tetraphenylporphyrin-photosensitized addition of oxygen to diene **3**, followed by immediate reduction of the double bond with diimide (Scheme 3), yielded a mixture of 5-isopropyl-2,3-dioxabicyclo[2.2.2]octane and 3-hydroperoxy-1-isopropylcyclohexene in a combined isolated yield of approximately 60% and a ratio of approximately 3:2, respectively. Exact yields of these peroxides are difficult to determine because they suffer decomposition during purification.

NMR analysis of the crude reaction mixture suggested that the endoperoxide was a single stereoisomer, although it was not clear which one, or even that the two stereoisomers would be easily distinguishable by this technique. Further evidence for there being only a single stereoisomer of the endoperoxide was obtained by direct reduction of the crude reaction mixture with H_2 and a Pd catalyst, followed by GC-MS analysis. Unambiguous stereochemical assignment could be made by comparison of the diol from H_2/Pd treatment of the endoperoxide with diol **2**. The compounds were identical, as judged by ^1H and ^{13}C NMR and IR spectroscopy.

Discussion

The identity of the diol prepared by reductive cleavage of the 5-isopropyl-2,3-dioxabicyclo[2.2.2]octane, and compound **2** prepared by independent synthesis, implies that the endoperoxide had the desired *syn* stereochemistry, and that it was therefore formed by approach of the singlet oxygen to the *more* hindered face of the diene. Inspection of neither physical nor computational (molecular mechanics) models of the diene reveals any way in which the *syn* approach could be sterically preferred, and so the observation of this as the favored mode of cycloaddition presumably carries mechanistic information.

It is known that polar substituents can influence the facial selectivity of singlet-oxygen 4 + 2 cycloadditions,[3] but, to our knowledge, there is no evidence showing that a simple alkyl substituent has a significant effect of this kind.

One possible explanation is that approach of the oxygen from the *anti* face leads not to cycloaddition but rather to "ene" reaction—yielding the observed hydroperoxide after diimide reduction of the disubstituted double bond. Approach from the *syn* face could not give this product, although an "ene" product derived by hydrogen abstraction from the secondary carbon could have been formed in principle. No such product was detected.

This explanation for the preferred mode of cycloaddition carries with it further implications that become apparent when one takes into account the large amount of work showing that the "ene" reaction of singlet oxygen involves rate-limiting formation of a perepoxide intermediate.[4] Since the hydrogen abstraction is not rate-determining, the presence or absence of a *syn* tertiary hydrogen would have no influence on the ratio of stereoisomeric 4 + 2 cycloadducts, if these adducts were formed in a single-step Diels–Alder reaction. However, if the 4 + 2 adducts and "ene" products came from perepoxides as common intermediates (Scheme 4), then the observed facial selectivity for the cycloaddition might well be the expected outcome. Such an explanation would require that tertiary C–H abstraction by the perepoxide have a smaller activation free energy than would rearrangement to the endoperoxide. There is no easy way to assess whether this is reasonable.

It could be that the formation of a perepoxide intermediate is the first step in all of the common reaction modes of $^1O_2$ with dienes, i.e. "ene" reaction,[3] 2 + 2

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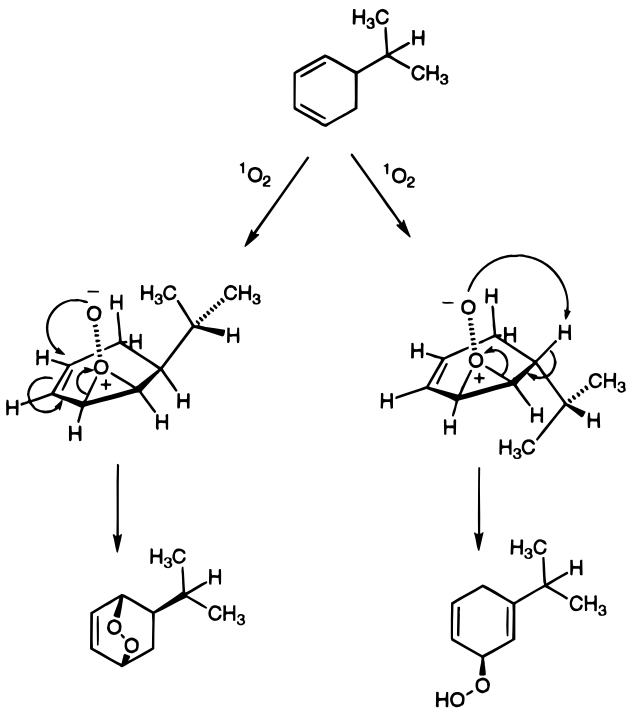
Scheme 4



cycloaddition,[5] and 4 + 2 cycloaddition. The involvement of a perepoxide in the 4 + 2 reaction was apparently first proposed by Dewar and Thiel[6] on the basis of MINDO/3 calculations. Experimentally, Paquette and co-workers[7] have shown that the facial selectivity for 4 + 2 reactions of $^1O_2$ with some tricyclic cyclopentadiene derivatives is unlike that seen for all other 4 + 2 cycloadditions examined, indicating that the mechanism might be different from that of most Diels−Alder reactions. And most recently, De Lucchi et al. have shown that cycloaddition of $^1O_2$ to 3,3′,4,4′-tetrahydro-1,1′-binaphthalene occurs with a preference for antarafacial addition, which could also be consistent with the intermediacy of a perepoxide.[8]

If the 4 + 2 cycloaddition of $^1O_2$ to dienes generally occurs via a perepoxide, the regio- and stereochemistry of the reaction might be quite different from that of the Diels−Alder addition. Such information would be important in the design of syntheses involving the $^1O_2$ reaction.

Experimental Section

General. Reagents were purchased from Aldrich and used without purification unless specified otherwise. Reaction solvents were purified according to standard procedures. All reactions were carried out under dry nitrogen in oven-dried glassware. Chromatographic solvents were used without purification. Thin layer chromotography was carried out on glass plates coated with 0.25 mm of silica gel 60 F_{254}. Visualization was achieved with anisaldehyde stain (prepared from a mixture of 9 mL of anisaldehyde, 340 mL of EtOH, 12.5 mL of sulfuric acid, and 4 mL of glacial acetic acid), and peroxides were visualized with thiocyanate stain (prepared from a mixture of 0.87 g of ferrous ammonium sulfate, 0.65 g of ammonium thiocyanate, 12.5 mL of H_2O, and 0.23 g of sulfuric acid). Column chromatography was gravity fed and carried out with silica gel 60 (0.04−0.063 mm, 230−240 mesh). ^1H NMR spectra were recorded at 200 or 400 MHz and ^{13}C NMR spectra were recorded at 100 MHz. Melting points were uncorrected.

Preparation of Enamine 4. A 250 mL round-bottom flask equipped with a Dean−Stark trap and reflux condenser was charged with 1,4-cyclohexanedione mono-ethylene ketal (5.2 g, 33.3 mmol) and pyrolidine (2.4 mL, 33.3 mmol) in anhydrous benzene (200 mL). The solution was refluxed for 8 h, until no more H_2O was collected in the Dean−Stark trap. The Dean−Stark trap was removed and replaced with a distillation head, and the benzene was removed by distillation. The product was distilled (0.2 torr, 105 °C) to give the known[9] enamine **4** (4.78 g, 23.0 mmol, 69%) as a yellow viscous oil, which was used immediately to avoid decomposition: ^1H NMR (200 MHz, $CDCl_3$) δ 1.82 (m, 4 H, 2.00−2.51 (m, 6 H), 3.02 (m, 4 H), 4.01 (br s, 4 H), 4.10 (m, 1 H).

Preparation of Ketone 5 from Enamine 4. A 250 mL round-bottom flask was equipped with a reflux condenser and charged with anhydrous benzene (150 mL) and freshly distilled enamine **4** (4.78 g, 0.023 mol). Ethyl bromoacetate (3.03 mL, 0.072 mol) was added via syringe. The solution was refluxed for 12 h, and the reflux condenser was replaced with a distillation head. The benzene was removed by distillation almost to dryness to give the enamine salt as a solid. H_2O (150 mL) was added, and the solution was stirred at room temperature for 24 h. The aqueous solution was extracted with diethyl ether (4 × 100 mL), and the combined organic extracts were washed with H_2O (2 × 100 mL) and saturated aqueous NaCl (2 × 100 mL). After being dried over $MgSO_4$, the ether was removed on a rotary evaporator to give the crude ketone **5** (3.05 g, 18.3 mmol, 55%) as a light-brown solid which was used without further purification: mp 49−52 °C; IR (neat) 1716, 1733 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 1.75 (m, 1 H), 1.90−2.20 (m, 3 H), 2.40 (m, 1 H), 2.60-2.80 (m, 2 H), 3.15 (m, 1 H), 4.01 (br s, 4 H), 4.10 (q, J = 7.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$): δ 14.36, 34.05, 34.16, 34.76, 38.02, 38.56, 43.27, 60.69, 64.82, 107.28, 172.23, 209.76.

Preparation of Lactone 6. A dry 200 mL round-bottom flask was charged with anhydrous THF (150 mL) and was purged with dry N_2. Ketone **5** (3.0 g, 12.39 mmol) was added, and the solution was cooled to −78 °C using a dry-ice/acetone bath. K-Selectride (1 M in THF) (12.4 mL , 12.4 mmol) was added via syringe. The reaction was stirred at −78 °C for 2 h. The reaction was quenched by the addition of 3 M aqueous NaOH (3 mL), followed by warming to room temperature. A 20 mL amount of 30% aqueous H_2O_2 was added carefully, dropwise. Following the initial exothermic reaction, the solution was stirred for an additional 30 min. Aqueous HCl (5%) (3 mL) was added via syringe, and the solution stirred for 15 min, followed by transfer to a separatory funnel. The aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed successively with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (3 × 50 mL), and saturated aqueous NaCl (2 × 50 mL). The ether was removed on a rotary evaporator to give the crude lactone as a clear yellow oily solid. Purification by chromatography utilizing 10% CH_3CN in CH_2Cl_2 as the eluent gave the lactone **6** (0.87 g, 4.33 mmol, 35%) as a white crystalline solid. Typical yields ranged from 20−40%: mp 55−59 °C; IR (neat) 1774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.50−2.39 (m, 7 H), 2.73 (m, 2 H), 4.01 (br s, 4 H), 4.50 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.83, 28.83, 35.21, 35.70, 37.84, 64.82, 64.82, 78.14, 107.80, 177.33.

Preparation of Methylated Lactone 7. A 100 mL round-bottom flask was equipped with a stir bar and a pressure equalizing funnel and charged with anhydrous THF (50 mL). Approximately 10 mg 1,10-phenanthrolein was added, and the solution was blanketed with argon. Diisopropylamine (0.80 mL, 6.0 mmol) was added via syringe. The solution was cooled

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to 0 °C, and *n*-BuLi (1.6 M in THF) was added dropwise via syringe until the red color of the LDA/1,10-phenanthrolein charge transfer complex persisted. Additional *n*-BuLi (3.60 mL, 6.0 mmol) was then introduced via syringe. After stirring for 30 min at 0 °C, the solution was cooled to −78 °C in a dry ice−acetone slush bath. A solution of lactone **6** (0.87 g, 5.40 mmol) in THF (10 mL) was added dropwise from the addition funnel over a period of 10 min and at a rate which maintained the reaction flask temperature at −78 °C. The solution was stirred an additional 30 min at −78 °C, and methyl iodide (0.4 mL, 6.47 mmol) was added via syringe. The solution was allowed to warm to room temperature over a period of 2 h, and then the reaction was quenched by the addition of H_2O (3 mL). The reaction mixture was transferred to a separatory funnel containing an equivalent volume of saturated aqueous NaCl. The mixture was extracted with three 50 mL portions of ether, and the combined extracts were washed successively with H_2O (5 × 50 mL), 10% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and saturated aqueous NaCl (50 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure, and the crude product was purified by chromatography utilizing 10% acetonitrile in CH_2Cl_2 as the eluent. Pure methylated lactone **7** (0.63 g, 2.97 mmol, 55%) was obtained as a semisolid: IR (neat) 1773 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (d, J = 7.2 Hz, 3 H), 1.50−2.02 (m, 6 H), 2.34 (q, J = 6.7 Hz, 1 H), 2.71 (q, J = 7.3 Hz, 1 H), 3.90 (br s, 4 H), 4.52 (q, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.92, 25.81, 28.54, 35.61, 36.08, 37.90, 64,33, 66.35, 78.20, 108.16, 176.97.

Preparation of Alcohols 8 from Lactone 7. Into a 50 mL round-bottom flask was placed methylated lactone **7** (0.60 g, 2.82 mmol) in 25 mL of CH_2Cl_2 at room temperature. BF_3·-OEt_2 (3.47 mL, 28.2 mol) was added via syringe and the solution stirred for 12 h at room temperature. When the reaction was complete by TLC (10% CH_3CN in CH_2Cl_2), it was quenched by the addition of H_2O (5 mL) and transferred to a separatory funnel containing an equal volume of saturated aqueous NaCl. The solution was extracted with three 10 mL portions of CH_2Cl_2. The combined extracts were washed successively with H_2O (2 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and saturated aqueous NaCl (10 mL). After drying over $MgSO_4$, the solvent was removed on a rotary evaporator and the product was purified by column chromatography utilizing a gradient of 2% to 10% CH_3CN in CH_2Cl_2 to give the ketone (0.39 g, 2.26 mmol, 80%) as a white crystaline solid: mp 43−45 °C; IR (neat) 1712, 1762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (d, J = 7.2 Hz, 3 H), 2.10−2.70 m, 8 H), 4.91 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ15.04, 26.74, 34.78, 40.74, 40.96, 41.14, 74.67, 178.23, 208.66.

A 50 mL round-bottom flask equipped with a magnetic stirer was charged with MeOH (50 mL), $CeCl_3$·$7H_2O$ (0.10 g, 0.37 mmol), and ketone prepared as above (0.31 g, 1.83 mmol). The stirred solution was cooled to 0 °C, and $NaBH_4$ (0.35 g, 9.1 mmol) was added in portions over a 5 min period. The suspension was stirred for 30 min upon completion of the addition, and excess reducing agent was destroyed by pouring the suspension into a mixture of ice and 10% HCl. After stirring to dissolve completely, the solution was transferred to a separatory funnel containing an equal volume of saturated aqueous NaCl and was extracted with three 50 mL portions of ether. The combined extracts were washed successively with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL) and were dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude products were purified by chromatography utilizing 50% ethyl acetate in hexanes as the eluent. This gave the alcohols **8** (0.25 g, 1.46 mmol, 80%) (approximately a 1:1 mixture of epimers by ^1H NMR) which were not separated: IR (neat) 1767, 3200 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (2d, J = 7.2 Hz, 3 H total), 1.50−2.05 (m, 4 H), 2.11 (m, 2 H), 2.45 (m, 1 H), 2.60 (m, 1 H), 3.81,3.94 (m, m, 1 H), 4.52 (m, 1 H).

Preparation of Thioketals 9 and 10. A 100 mL round-bottom flask equipped with a magnetic stirer was charged with with alcohols **8** (181 mg, 1.1 mmol) in THF and cooled to −78 °C. Di-isobutylaluminum hydride (DIBAL) (2.1 mL of 1.0 M in THF, 2.2 mmol) was added via syringe over a period of 5 min. The solution was stirred for 1 h at −78 °C and then allowed to warm to 0 °C and quenched by addition of methanol, dropwise, over a period of 10 min until no further reaction occurred (about 0.5 mL). The reaction was warmed to room temperature, excess MeOH was added, and the reaction was stirred until precipitation of white borane salts was completed. The solution was filtered through a pad of Celite to remove the borane salts and washed with hot MeOH (50 mL) and diethyl ether (50 mL). The solvent was removed on a rotary evaporator to provide the crude reduction product. Purification was achieved by elution down a silica gel column with a gradient of 10% to 50% of CH_3CN in CH_2Cl_2. This provided the lactol (0.14 g, 0.83 mmol, 75%) as a mixture of epimers: IR (neat) 3200−3300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.03−1.12 (m, 3 H), 1.50−2.30 (m, 8 H), 3.45−3.95 (m, 1 H), 4.01−4.32 (m, 1 H), 5.02,5.60 (m, m, 1 H).

Into a 10 mL round-bottom flask was placed the lactol (0.030 g, 0.174 mmol), 1,2-ethanedithiol (0.032 mL, 0.34 mmol), and CH_2Cl_2 (5 mL) under a N_2 blanket. BF_3·OEt_2 (0.022 mL, 0.174 mmol) was added via syringe. The reaction was stirred at room temperature for 2 h, followed by the addition of H_2O (3 mL). The solution was transferred to a separatory funnel containing an equal volume of saturated aqueous NaCl. The solution was extracted with three 20 mL portions of CH_2Cl_2. The combined organic extracts were washed successively with H_2O (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous NaCl (20 mL). After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. This gave the product as a mixture of stereoisomeric thioketals **9** and **10**. The mixture was separated by column chromatography utilizing a solvent gradient of 1% to 20% CH_3CN in CH_2Cl_2. Purification gave the first thioketal (0.015 g, 0.061 mmol, 35%) as a viscous oil (R_f = 0.5, 10% CH_3CN in CH_2Cl_2). Further elution afforded the second thioketal (0.014 g, 0.061, 35%) as a white semisolid (R_f = 0.4, 10% CH_3CN in CH_2Cl_2). The stereochemistry of the *cis* and *trans* diols was determined by mass spectroscopy, and the first product was determined to be the *cis* isomer **10** and the second product the *trans* isomer **9**.

10: IR ($CDCl_3$) 3300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.10 (d, J = 7.0 Hz, 3 H), 1.47−2.01 (m, 7 H), 3.20 (m, 4 H), 4.15 (br s, 2 H), 5.02 (d, J = 3.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 12.93, 26.90, 28.69, 31.88, 39.58, 40.01, 40.86, 41.19, 5.03, 66.99, 67.84.

9: IR ($CDCl_3$) 3300 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (d, J = 7.0, 3 H), 1.10−2.10 (m, H), 3.22 (m, 4 H), 3.61 (br s, 1 H), 4.09 (br s, 1 H), 4.91 (d, J = 4.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 13.30, 29.76, 32.75, 34.25, 39.59, 39.96, 41.28, 46.46, 58.39, 66.87, 71.36.

Preparation of *cis,cis*-2-Isopropylcyclohexane-1,4-diol (2). A 50 mL round-bottom flask was equipped with a reflux condenser and was charged with the thioketal **10** (10 mg, 0.040 mmol) in 20 mL of anhydrous ethanol. Raney nickel in EtOH was added in small portions over a period of 4 h while the reaction was monitored by TLC, utilizing 25% EtOAc in hexanes as the eluent and visualizing with anisaldehyde stain. When none of the dithiane remained, the suspension was filtered through a bed of Celite and washed with acetone. The solvent was removed on a rotary evaporator to give the *cis,-cis*-2-isopropylcyclohexane-1,4-diol (**2**) (6.5 mg, 0.039 mmol, 98%) as a white solid: mp 102−103 °C; IR (neat) 3300 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6) δ 1.89 (d, J = 7.0 Hz, 3 H), 1.91 (d, J = 7.0 Hz, 3 H), 1.20−2.03 m, 8 H), 3.51 (br s, 2 H); ^{13}C NMR (acetone-d_6) δ 21.198, 21.273, 29.322, 34.685, 48.264, 65.408, 70.984 (2 resonances obscured by the solvent). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 67.95; H, 11.41.

Preparation of Dichlorocyclobutanone 11. A 500 mL three-neck round bottom flask equipped with a pressure-equalizing addition funnel was placed under a blanket of N_2 and placed into the middle of an ultrasound bath. A 300 mL amount of anhydrous ether was placed in the flask; Zn powder (6.92 g, 110.0 mmol) and 1,4-cyclohexadiene (10.3 mL, 110.0 mmol) were added, and the ultrasound was started. The water bath was cooled to 15 °C by adding pieces of ice periodically.

A solution of trichloroacetyl chloride (8.96 mL, 110.0 mmol) in 100 mL of anhydrous ether was added over a period of 1.5 h, followed by ultrasound for 1 h, while maintaining the water bath temperature at 15 °C. When the reaction was complete, the solids were removed by vacuum filtration and the ether was washed with H_2O (3 × 100 mL), saturated aqueous $NaHCO_3$ (3 × 100 mL), and saturated aqueous NaCl (200 mL). The ether was dried with $MgSO_4$ and removed using a rotary evaporator. The resulting brown oil was purified by bulb-to-bulb distillation (80 °C, 0.2 torr) to give the known[10] dichlorocyclobutanone **11** as a clear oil (7.8 g, 44.0 mmol, 40%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00−2.68 (m, 4 H), 2.31 (ddd, J = 10.8, 7.8, 2.3 Hz, 1 H), 4.11 (ddd, J = 10.8, 7.2, 2.5 Hz, 1 H), 5.85 (m, 2 H).

Preparation of Cyclobutanone 12. A 250 mL round-bottom flask was charged with Zn (15 g, 0.23 mol) in HOAc (75 mL). The dichloroketone **11** (7.5 g, 0.039 mol) dissolved in 25 mL of HOAc was added, dropwise to the solution, while stirring with a mechanical stirrer. The solution became warm but required no external cooling if the dichloride was added slowly. The reaction was then warmed to 70 °C for 1 h and then allowed to cool to room temperature and stirred for 8 h. The mixture was diluted with diethyl ether (100 mL), and the solids were filtered off, washing with diethyl ether. The solution was transferred to a separatory funnel and washed with H_2O (5 × 50 mL), with saturated aqueous $NaHCO_3$ until no HOAc remained and then with saturated aqueous NaCl (2 × 50 mL). After drying with $MgSO_4$, the solvent was removed using a rotary evporator and the product was purified by bulb-to-bulb distillation under reduced pressure (80 °C, 35 torr) to give the known[10] ketone **12** (4.05 g, 0.19 mol, 84%) as a clear oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.02−2.60 (m, 5 H), 2.81 (m, 1 H), 3.20 (ddd, J = 18.0, 9.0, 4.1 Hz, 1 H), 3.41 (m, 1 H), 5.92 (m, 2 H).

Preparation of Lactone 13. A 250 mL round-bottom flask was equiped with a stir-bar and charged with ketone **12** (4.0 g, 32.8 mmol) in 60 mL of 90% aqueous HOAc. The solution was cooled to 0 °C and 30% H_2O_2 (10.0 g) was added in 40 mL of 90% HOAc. The reaction was stirred at 0 °C for 24 h and then diethyl ether (200 mL) was added and the solution transferred to a separatory funnel. The ether was washed with H_2O (3 × 100 mL) and then with aqueous $NaHCO_3$ until no acid remained. After drying with $MgSO_4$, the ether was removed using a rotary evporator, giving the lactone **13** (3.98 g, 28.9 mmol, 88%) as a clear oil. No further purification was required: IR (neat) 1775 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89−2.82 (m, 7 H), 4. (m, 1 H), 5.85 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.07, 27.30, 32.03, 36.64, 77.72, 123.91, 125.61, 177.08.

Preparation of Methylated Lactone 14. A 200 mL round-bottom flask was charged with THF (50 mL). Approximately 10 mg of 1,10-phenanthrolein was added, and the solution was blanketed with argon. Diisopropylamine (1.40 mL, 9.9 mmol) was added via syringe. The solution was colled to 0 °C, and 1.6 M *n*-BuLi was added dropwise via syringe until the red color of the LDA/1,10-phenanthrolein charge transfer complex persisted. Additional 1.6 M *n*-BuLi (6.24 mL, 9.99 mmol) was then introduced via syringe. After stirring for 30 min at 0 °C, the solution was cooled to −78 °C in a dry ice−acetone slush bath. A solution of lactone **13** (1.06 g, 7.68 mmol) in THF (50 mL) was added dropwise from the addition funnel over a period of 10 min and at a rate which maintained the reaction flask temperature at approximately −78 °C. The solution was stirred an additional 30 min at −78 °C, and methyl iodide (0.53 mL, 9.99 mmol) was added via syringe. The solution was allowed to warm to room temperature over a period of 2 h, and then the reaction was quenched by the addition of H_2O (3 mL). The reaction mixture was transferred to a separatory funnel containing an equivalent volume of saturated aqueous NaCl. The mixture was extracted with three 50 mL portions of ether, and the combined extracts were washed successively with H_2O (5 × 50 mL), 10% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and saturated aqueous NaCl (50 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by chromatography utilizing 10% CH_3CN in CH_2Cl_2 as the eluent. Pure methylated lactone **14** (0.65 g, 4.22 mmol, 55%) was obtained as an oil: IR (neat) 1776 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35 (d, J = 6.4 Hz, 3 H), 2.10−2.72 (m, 6 H), 4.71 (m, 1 H), 5.7 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.60, 25.19, 27.97, 39.34, 39.99, 74.85, 123.76, 124.89.

Preparation of Lactol 15. A 100 mL round-bottom flask equipped with a magnetic stirrer was charged with with methylated lactone **14** (0.68 g, 4.44 mmol) in anhydrous toluene and cooled to −78 °C. DIBAL (8.9 mL 2.0 M in toluene, 8.9 mmol) was added via syringe over a period of 5 min. The solution was stirred for 2 h at −78 °C and then quenched by addition of 1 mL of methanol (added until gas evolution ceased) dropwise over a period of 10 min. The reaction was allowed to warm to room temperature, and excess MeOH (1 mL) was added. The solution was transferred to a separatory funnel with an equal volume of saturated aqueous NaCl. HCl 5% was added to break up the resulting emulsion. The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL), H_2O (50 mL), and saturated aqueous NaCl (100 mL). The solvent was removed on a rotary evaporator to provide the crude reduction product. Purification was achieved by bulb-to-bulb distillation (110 °C, 0.5 torr). This provided the lactol **15** (0.55 g, 3.60 mmol, 81%) as a mixture of epimers: IR (neat) 3200−3300 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97−1.22 (m, 3 H), 1.80−2.51 (m, 5 H), 2.90, 3.41 (br s, br s, 1 H), 4.21, 4.52 (m, m, 1 H), 5.01, 5.30 (m, m, 1 H), 5.70,5.80 (m, m, 1 H).

Preparation of Thioketal 16. Into a 100 mL round-bottom flask was placed lactol **15** (1.98 g, 12.86 mmol), dithiol (2.0 mL, 23.8 mmol), and CH_2Cl_2 (80 mL) under a N_2 blanket. $BF_3{\cdot}OEt_2$ (2.0 mL, 16.2 mmol) was added via syringe. The reaction was stirred at room temperature for 2 h, followed by the addition of H_2O (20 mL). The solution was transferred to a separatory funnel. The layers were separated, and the aqueous solution was extracted with two 50 mL portions of CH_2Cl_2. The organic extracts were combined and washed successively with H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL mL), and saturated aqueous NaCl (50 mL). After drying over $MgSO_4$, the solvent was removed on a rotary evaporator. This gave the crude thioketal **16** (2.68 g, 11.70 mmol, 91%) as an oil which was used without further purification: IR ($CDCl_3$) 3200 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (d, J = 7.0 Hz, 3 H), 1.80−2.52 (m, 6 H), 3.21 (m, 4 H), 4.19 (br s, 1 H), 5.02 (d, J = 7.0 Hz, 1 H), 5.50 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.32, 28.14, 34.23, 38.30, 38.51, 39.87, 41.88, 57.13, 65.33, 122.35, 126.36.

Preparation of 6-Isopropylcyclohex-3-en-1-ol (17). A 250 mL round-bottom flask was equipped with a reflux condenser and was charged with thioketal **16** (1.6 g, 7.77 mmol) in 100 mL anhydrous ethanol. Acetone (0.5 mL) was added, to deactivate the Raney nickel and avoid reduction of the olefin. The solution was heated to reflux, and Raney nickel in EtOH was added in small portions over a period of 12 h while the reaction was monitored closely by TLC (eluting with 25% EtOAc in hexanes and visualizing with anisaldehyde stain). When none of the thioketal remained, the suspension was filtered through a bed of Celite and washed with acetone. The solvent was removed on a rotary evaporator to give the crude product, which was purified by bulb-to-bulb distillation (0.50 g, 3.57 mmol, 46%) to give **17** as a clear oil: IR (neat) 3200−3300 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 6.1 Hz, 3 H), 0.98 (d, J = 6.1 Hz, 3 H), 1.50−2.50 (m, 6 H), 3.70 (m, 1 H), 5.6 (m, 1 H), 5.8 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.68, 20.61, 25.01, 29.47, 34.63, 44.25, 65.43, 122.65, 127.14.

Preparation of 5-Isopropyl-1,3-cyclohexadiene (3). Alcohol **17** (1.2 g, 8.57 mmol) was dissolved in 100 mL of anhydrous ether in a round-bottom flask and cooled to 0 °C under an N_2 blanket. *n*-BuLi (1.6 M in THF) (6.43 mL, 1.03 × 10−2 mol) was added via syringe, and the solution was stirred at 0 °C for 1 h. Phenyl chlorothionoformate (1.31 mL, 9.43 mmol) was added via syringe, and the solution was allowed to warm up to room temperature and then stirred for

(10) Liotta, F. J.; Van Duyne, G.; Carpenter, B. K. *Organometallics* **1987**, *6*, 1010.

12 h. The LiCl salts which had formed were dissolved by the adition of H_2O, the mixture was transferred to a separatory funnel, and the layers were separated. The aqueous layer was extracted with ether (2 × 20 mL), and the organic layers were combined and washed with H_2O (20 mL), saturated aqueous $NaHCO_3$ (2 × 20 mL), and saturated aqueous NaCl (20 mL). After drying with $MgSO_4$, the ether was removed using a rotary evaporator and the product was dried further under reduced pressure, to remove any remaining traces of phenyl chlorothionoformate. The product was purified by column chromotography utilizing 20% EtOAc in hexanes to give the thioester (1.55 g, 5.3 mmol, 62%) as a yellow solid: mp 81-85 °C; IR ($CDCl_3$) 1224 (w) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, J = 6.1 Hz, 3 H), 1.00 (d, J = 6.1 Hz, 3 H), 1.30−1.61 (m, 2 H), 2.00−2.70 (m, 4 H), 5.60 (m, 1 H), 5.80 (m, 2 H), 7.10−7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 20.78, 25.82, 29.51, 30.32, 43.39, 4742, 80.22, 121.79, 126.35, 126.79, 127.09, 129.35, 153.22, 194.51.

The thioester (1.55 g, 5.3 mmol) was heated to 105 °C in a bulb-to-bulb distillation flask. As the ester was pyrolyzed the resulting diene was distilled and trapped in the collection flask at −78 °C in a dry ice/acetone slush bath. The hydrocarbon product was purified by column chromatography utilizing pentane as the eluent, to remove traces of phenol biproduct. The pentane was removed using a rotary evaporator at 0 °C. 5-Isopropyl-1,3-cyclohexadiene (**3**) (0.32 g, 2.65 mmol, 50%) was obtained as a clear oil: IR (neat) 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, J = 6.0 Hz, 3 H), 0.94 (d, J = 6.0 Hz, 3 H), 1.50−2.33 (m, 4 H), 5.65−5.80 (m, 2 H), 5.80−6.01 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 19.67, 25.36, 31.24, 39.30, 123.85, 123.96, 126.31, 129.91.

Singlet Oxygen Addition to 5-Isopropyl-1,3-cyclohexadiene (3). A 100 mL three-neck round-bottom flask was equipped with a thermometer and placed under a N_2 blanket. 5-Isopropyl-1,3-cyclohexadiene (**3**) (320 mg, 2.6 mmol) and approximately 10 mg of tetraphenylporphyrin (TPP) in 50 mL of CH_2Cl_2 were placed in the flask and then cooled to −78 °C. O_2 was bubbled continuously through the solution, and a sunlamp was shone on it for 5 h, while maintaining the temperature constant at −78 °C. A second 250 mL three-neck round-bottom flask was prepared: it was equipped with a stir bar, pressure-equalizing funnel, and placed under a N_2 blanket while being cooled to −78 °C. Into this flask were placed potassium azodicarboxylate (PADC) (2.7 g, 14.6 mmol) in 50 mL of CH_2Cl_2. HOAc (1.59 g, 26.5 mmol) in 50 mL of CH_2Cl_2 was placed in the addition funnel. The diene solution was transferred into the PADC solution via cannula, while the HOAc solution was added dropwise at aproximately the same rate. The additions were made over a period of 30 min, while the temperature was maintained at −78 °C . The PADC solution was then allowed to warm up to room temperature slowly, over 2−3 h, and stirred overnight. The yellow solid was then filtered through a glass fritted filter, washing with CH_2Cl_2. The CH_2Cl_2 was removed at 0 °C using a rotary evaporator. The residue was purified by silica gel chromatography (utilizing CH_2Cl_2 as the eluent and visualizing with thiocyanate stain for peroxides) to give 3-hydroperoxy-1-isopropylcyclohexene (0.10 g, 0.62 mmol, 24%). Further elution afforded 5-isopropyl-2,3-dioxabicyclo[2.2.2]octane (**1**) (0.15 g, 0.94 mmol, 36%) as an oily solid.

5-Isopropyl-2,3-dioxabicyclo[2.2.2]octane (1): ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, J = 8.1 Hz, 3 H), 0.95 (d, J = 8.1 Hz, 3 H), 1.20−1.40 (m, 2 H), 1.50−1.90 (m, 4 H), 2.00−2.40 (m, 2 H), 4.00−4.10 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 20.47(2), 24.53, 30.37, 31.17, 31.78, 42.12, 71.60, 73.54. Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 69.72; H, 10.32.

3-Hydroperoxy-1-isopropylcyclohexene: ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J = 7.2, 3 H), 0.97 (d, J = 7.1, 3 H), 1.50−2.40 (m, 7 H), 4.61 (m, 1 H), 6.62 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.42, 19.81, 20.47, 28.69, 32.49, 40.72, 73.86, 130.19, 132.64. Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 69.85; H, 10.38.

Reduction of 5-Isopropyl-2,3-dioxabicyclo[2.2.2]octane to 2-Isopropyl-1,4-cyclohexanediol with H_2/Pd. A solution of 5-isopropyl-2,3-dioxabicyclo[2.2.2]octane (**1**) (20 mg, 0.13 mmol) in ethanol (10 mL) was placed in a high pressure bottle. Approximately 15 mg of 5% palladium on carbon was added, and the suspension was shaken for 2 h at room temperature under 50 psi of H_2. After removal of the catalyst by filtration through a Celite pad, the solvent was removed on a rotary evaporator to give 2-isopropyl-1,4-cyclohexanediol (15 mg, 0.098 mmol, 75%) as a white solid, exactly identical to diol **2**, prepared as described above: mp 101−104 °C; IR (neat) 3300 cm^{-1}; ^1H NMR (200 MHz, acetone-d_6): δ 1.9 (d, J = 7.0 Hz, 3 H), 1.9 (d, J = 7.0 Hz, 3 H), 1.2−2.0 m, 8 H), 3.5 (br s, 2 H); ^{13}C NMR (acetone-d_6): δ 21.19, 21.27, 32.88, 34.66, 48.26, 65.39, 70.98 (2 resonances obscured by the solvent).

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Supporting Information Available: NMR spectra of new compounds (15 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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