α-Peroxylactones via Dehydrative Cyclization of α-Hydroperoxy Acids[1]

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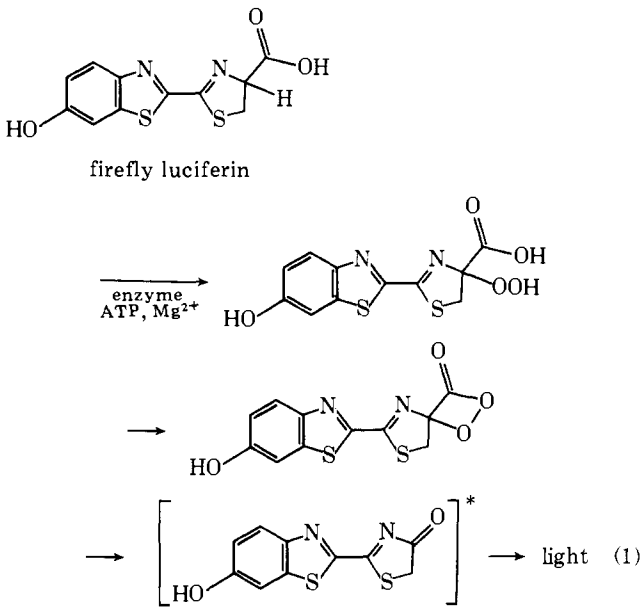
Abstract: The thermally labile di-*tert*-butyl-, *tert*-butyl-, and dimethyl-α-peroxylactones **1a**, **1b**, and **1c** were readily prepared in 35, 50, and 68% yields, respectively, by dicyclohexylcarbodiimide cyclization of the respective α-hydroperoxy acid **2a**, **2b**, and **2c** in methylene chloride at subambient temperatures. These volatile α-peroxylactones were isolated and purified by low-temperature flash distillation and exhibit a characteristic carbonyl frequency at 1860 ± 10 cm^{-1}. The α-hydroperoxy acids were prepared by distinct synthetic routes, e.g., the di-*tert*-butyl derivative **2a** was obtained by perhydrolysis of its α-lactone **6a**, the *tert*-butyl derivative **2b** by silatropic rearrangement of its ketene bis(trimethylsilyl)acetal **7b** and subsequent disilylation of the α-silylperoxy ester product **8b** by methanol, and the dimethyl derivative **2c** by direct oxygenation of the corresponding lithium α-lithio enolate **9c**.

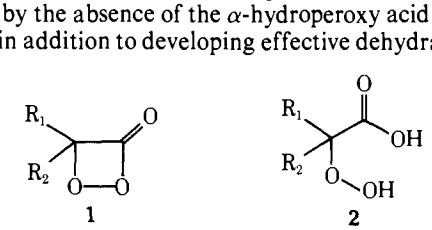
The phenomenon of bioluminescence has only recently been defined at the chemical level.[3] As the mechanism for the firefly luciferin bioluminescence illustrates (eq 1),[4] the corresponding α-peroxylactone, presumably formed by dehydrative cyclization of the corresponding α-hydroperoxy acid, serves as chemienergizer of electronically excited oxyluciferin by decarboxylation.



firefly luciferin

electronically excited oxyluciferin

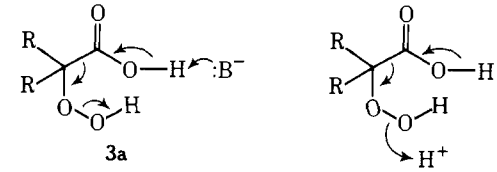
Although the chemistry of 1,2-dioxetanes is quite well elucidated,[5] no literature information on the preparation, isolation, and characterization of α-peroxylactones (1,2-dioxetan-3-ones) **1** was available. Besides the expected thermal, hydrolytic, nucleophilic, and electrophilic lability of these "high energy" molecules, the synthetic problem was further compounded by the absence of the α-hydroperoxy acid precursors **2**. Thus, in addition to developing effective dehydrative cyclization methods of converting α-hydroperoxy acids into α-peroxylactones, we were obliged to devise convenient preparations for the sensitive α-hydroperoxy acids. We now report on the preparation of α-hydroperoxy acids **2** and their cyclization into the corresponding α-peroxylactones **1**. The systems described here are the *tert*-butyl, di-*tert*-butyl, and dimethyl derivatives.



1 2

Results and Discussion

Preparation of α-Hydroperoxy Acids 2. The major difficulty with the α-hydroperoxy acids **2** is their propensity toward base- and acid-catalyzed Grob fragmentations[6] via the respective transition states **3a** and **3b**. It was clear, therefore, that essentially neutral conditions would be required for the preparation of **2**. In fact, early attempts in basic and acidic media led always to decomposition and it was not surprising that prior to our work[7] no authentic examples of these sensitive compounds were reported. Our synthetic strategies circumventing this problem are summarized in Scheme I, using the di-*tert*-butyl (**2a**), *tert*-butyl (**2b**), and dimethyl (**2c**) derivatives as model systems. Each case represents a novel and distinct approach, originating from the respective carboxylic acid **4** precursors.

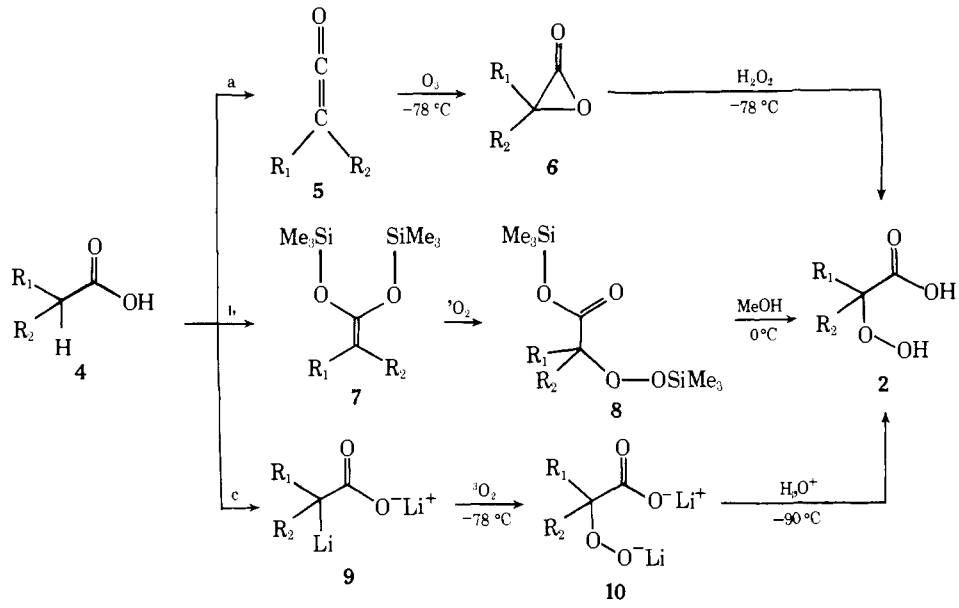


3a 3b

The first synthetic approach entailed the use of α-lactones **6** which are known to add protic nucleophiles forming α-substituted acids.[8] Consequently, we expected that hydrogen peroxide should add to α-lactone **6** to afford α-hydroperoxy acids **2** (Scheme I, path a). Usually α-lactones polymerize extremely readily and can only be handled in matrix isolated form at 77 K.[9] On the other hand, the stable bis(trifluoromethyl)acetolactone reacts with protic nucleophiles by addition at the carbonyl group,[10] rendering our synthetic approach useless. However, the di-*tert*-butylacetolactone (**6a**), which was prepared by Wheland and Bartlett[11] via ozonolysis of di-*tert*-butylketene (**5a**), afforded the desired α-hydroperoxy acid **2a** in high yield and high purity. Besides the appropriate IR and NMR data and 100% iodometric titer, the catalytic reduction to the corresponding α-hydroxy acid (100% acidimetric titer) established the assigned structure beyond any reasonable doubt.

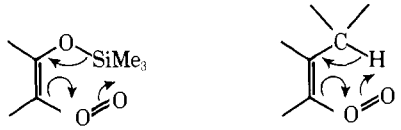
The second synthetic approach made use of the oxygenophilic nature of the trimethylsilyl group. For example, α-trimethylsilyl ketones are converted into trimethylsilyl enol ethers on heating[12] and on singlet oxygenation the latter are trans-

Scheme I



a, $R_1 = R_2 = t$-Bu
b, $R_1 = H$; $R_2 = t$-Bu
c, $R_1 = R_2 = Me$

formed into α-trimethylsilylperoxy ketones.[13] Consequently, such a silatropic shift via transition state **11a**, which is analogous to the prototropic shift of the classical ene reaction[14] via transition state **11b**, would lead to the trimethylsilylperoxy



11a **11b**

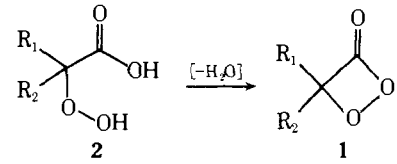
ester **8** on singlet oxygenation of the ketene bis(trimethylsilyl)acetal **7** (Scheme I, path b). The ketene acetals **7** are readily available by trimethylsilylation of the corresponding lithium α-lithiocarboxylates,[9] which in turn are prepared by lithiation of the corresponding carboxylic acids[4] with lithium diisopropylamide (LDA).[15]

We chose the *tert*-butylketene bis(trimethylsilyl)acetal (**7b**) as model substrate to suppress the prototropic shift of the ene reaction[14] since no allylic hydrogens are present. As anticipated, a quantitative yield of the silylperoxy ester **8b** was obtained on singlet oxygenation of ketene acetal **7b**. Not only did we accomplish our goal of introducing a peroxy substituent adjacent to a carboxylate functionality; but in its trimethylsilylated form the α-peroxy acid derivative **8b** can be purified by distillation without risking the menacing Grob fragmentation. Still more important, the α-hydroperoxy acid **2b** can be released quantitatively from its silylated derivative **8b** by disilylation with methanol at subambient temperature. For ketene acetals with nonallylic hydrogens this α-hydroperoxy acid synthesis works well; however, the ene reaction competes seriously when allylic hydrogens are present in the substrate.[16]

In the third approach, exemplified by the preparation of α-hydroperoxyisobutyric acid (**2c**), we returned to our initially abortive attempts[7a] of directly oxygenating α-lithiocarboxylates **9** (Scheme I, path c). In fact, we could show that after removal of the diisopropylamine by low-pressure evaporation of the α-lithiocarboxylate **9c** solution (prepared from the corresponding carboxylic acid **4c** and LDA) to dryness, inverse addition of the redissolved α-lithiocarboxylate **9c** in THF at ca. −90 °C to an O_2-saturated THF solution, protonation of **10** at ca. −90 °C, and aqueous workup below 5 °C afforded the desired α-hydroperoxy acid **2c** in good yield and with high purity.[17] The most critical side reactions are reduction to the corresponding α-hydroxy acids by attack of the enolate **9** on the peroxide bond and Grob fragmentation in aqueous media. Similar results were obtained by Konen and co-workers.[18] Recently[19] we have been able to extend this synthesis even to aromatic α-hydroperoxy acids by using *n*-BuLi as the lithiation agent instead of LDA, thereby avoiding the troublesome diisopropylamine.

The three synthetic methods presented here (Scheme I), i.e., perhydrolysis of α-lactone **6**, singlet oxygenation of ketene bis(trimethylsilyl)acetals **7**, and direct oxygenation of α-lithiocarboxylates **9**, provide ample opportunity for preparing a wide range of diverse α-hydroperoxy acids **2**. However, it must be stressed that these substances are difficult to handle because of their hygroscopic nature and their propensity for thermal and base- and acid-catalyzed decomposition.

Preparation of α-Peroxylactones 1. The dehydrative cyclization of the α-hydroperoxy acids **2** into the α-peroxylactones **1** (eq 2) was expected to be difficult in view of the obvious low

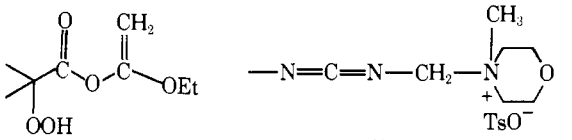


2 **1** (2)

a, $R_1 = R_2 = t$-Bu
b, $R_1 = H$; $R_2 = t$-Bu
c, $R_1 = R_2 = Me$

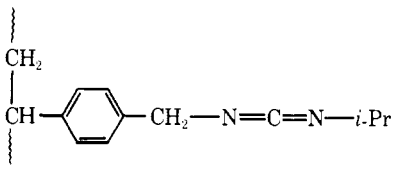
thermal stability of the strained four-membered ring peroxide. Furthermore, control experiments revealed that the α-peroxylactones, as well as the α-hydroperoxy acids, are easily decomposed by nucleophiles, electrophiles, acids, bases, protic solvents, and transition metal ion impurities. Consequently, we required a dehydrative cyclant that works efficiently and rapidly at low temperatures (preferably −78 °C), that is

nonnucleophilic, nonelectrophilic, nonbasic, nonacidic, nonprotic, nonparamagnetic, and, most important of all, that can be readily removed from the reaction mixture in its hydrated form. It is, therefore, not surprising that established dehydration catalysts for β-lactonization, β-lactamization, or peptide synthesis, such as benzenesulfonyl chloride in pyridine,[15] trifluoroacetic anhydride,[20a] Woodward K reagent,[20b] diimidazole ketone,[20c] ketenimines,[20d] ethoxyacetylene,[20e] *N*-alkyl carbodiimidinium salts,[20f] hexafluoroacetone,[20g] diethylphosphoryl cyanide,[20h] *N*-phosponium salts of pyridine,[20i] and ionic resin carbodiimide[20j] have all failed[21] for not complying to one or more of the above conditions. For example, one cyclant for which we had great hopes was ethoxyacetylene. It meets all the above prerequisites except that in the adduct **12** ethyl acetate is not a good enough leaving group to be displaced by the α-hydroperoxide group without base catalysis



12

13a



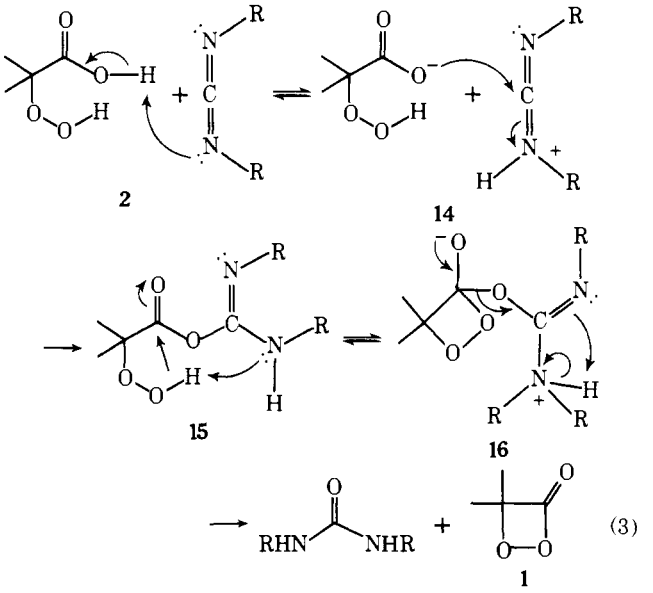
13b

at −40 °C. Increasing the temperature or using a base catalyst destroys the α-peroxylactone.

One class of dehydration catalysts that has worked reasonably well is the carbodiimide grouping. Thus, at −78 °C in CH_2Cl_2 a maximum yield of ca. 70% of dimethyl-α-peroxylactone (**1c**) was obtained within 5 min by monitoring the rate of appearance of the characteristic 1870-cm^{-1} carbonyl frequency by infrared. The carbodiimide of choice is the dicyclohexyl derivative (DCC) in view of its ready availability, relatively low volatility, insoluble urea product, and fast action. Dimethyl- and diphenylcarbodiimides worked less satisfactorily. Neither could satisfactory results be obtained with the commercially available ionic carbodiimide **13a**,[20j] which could have facilitated greatly the isolation and purification problem in view of the insolubility of its urea product. Along the same lines, encouraging cyclization results were achieved with the polymer-supported carbodiimide **13b**, but this work is in progress and shall be reported separately.[21]

Why does DCC work well as a dehydrative cyclant of α-hydroperoxy acids? The first step in the carbodiimide-catalyzed dehydration[22,23] must be protonation of the carbodiimide by the α-hydroperoxy acid **2**, leading to a carbodiimidinium carboxylate ion pair **14**, which collapses to the adduct **15** by combining (eq 3) with the more nucleophilic carboxylate rather than hydroperoxide site. Urea is an excellent leaving group and cyclization occurs via internal nucleophilic attack by the hydroperoxide group, possibly assisted by deprotonation by the imino nitrogen, leading to the dipolar ion **16**. Precipitation of the urea takes place almost instantaneously when the solution is warmed to ca. −40 °C; presumably there is a small activation barrier for converting adduct **15** to the α-peroxylactone **1** and urea.

Consequently, the success of the cyclization is a delicate timing of nucleophilic activation by proton transfers and this property is inherent with the carbodiimide grouping. In this connection it is of interest to mention that the novel catalyst[20f] *N*-methyl-di-*tert*-butylcarbodiimidinium tetrafluoroborate

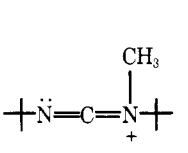


2 **14** **15** **16**

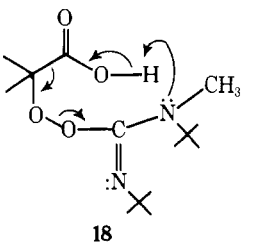
(3)

1

(**17**) caused complete decarboxylation of the α-hydroperoxy acid **2a**. Presumably attack occurred at the more nucleophilic



17



18

hydroperoxide site rather than at the desired carboxylic acid site, setting the system up for Grob fragmentation via transition state **18**.

The most difficult task has been the isolation and purification of the α-peroxylactones in view of their low thermal life. Thus, although in reasonably pure form their half-lives of decomposition are ca. 15–30 min at ~25 °C, as crude reaction mixtures they decarboxylate completely within a few minutes even at ~0 °C. It is, therefore, extremely crucial to isolate and purify the product without delay. Since the three derivatives **1a–c** reported here are all sufficiently volatile, the most convenient workup procedure consisted of first removing all involatile products by flash distilling the reaction mixture at below −40 °C (0.1 mm), collecting solvent, α-peroxylactone, and its decarboxylation product as distillate. For this purpose it was convenient to use small reaction volumes (less than 3 mL) and a large vessel (250-mL volume) with fast magnetic stirring during the flash distillation to provide a large surface area for fast evaporation. Prolongation of this process beyond 30 min would result in low yields of impure α-peroxylactone. Subsequent slow fractionation of the distillate at below −40 °C (0.1 mm) to remove solvent and decarboxylation products gave essentially pure α-peroxylactone as solid residue. This solid material, essentially free of decarboxylation product but with entrapped solvent, as confirmed by IR analysis of the redissolved α-peroxylactone residue in CCl_4, could not be further purified by low-temperature crystallization, sublimation, or chromatography. Even at −78 °C silica gel and other adsorbents induce decarboxylation effectively. In view of these difficulties and the explosive nature of the residue, even at subambient temperatures, no risks were taken in further purification.

Clearly, it would be advantageous to prepare higher molecular weight derivatives with high propensity to crystallize; however, this would encumber the low-temperature flash

distillation in the initial separation of the α-peroxylactone from its reaction medium. An advantageous technique for purification is low-temperature chromatography; but we have as yet not found an adsorbent on which the α-peroxylactone survives. Ideally we would like to employ solid-phase synthesis on polymer-supported carbodiimides; but initial experiments indicate that more reactive solid-phase reagents must be developed to perform the dehydrative cyclization at dry ice temperatures. We are presently engaged in this possibility.

The low thermal life of the α-peroxylactones not only complicates their isolation but also their identification. Elemental analysis is completely out of question; however, the quantitative iodometric titer with potassium iodide is a definitive criterion for the peroxide structure. The carbonyl band at ca. 1860 ± 10 cm^{-1} (in CCl_4) is conclusive evidence favoring the α-peroxylactone grouping, especially since α-lactones[9] absorb at 1900 cm^{-1} and β-lactones[15] at 1830 cm^{-1}. All three α-peroxylactones **1a–c** show the characteristic *gem*-dimethyl doublet at 1380 and 1365 cm^{-1}. Only the *tert*-butyl system **1b** possesses a 1,2-dioxetane-type ring proton which occurs as a singlet at δ 5.48 ppm, while the singlet of the *tert*-butyl group resonates at δ 1.10 ppm with respect to Me_4Si in CCl_4. For comparison, 1,2-dioxetane ring protons resonate at δ 4.9–5.2 ppm, which are displaced to δ 5.6–6.8 ppm on alkoxy substitution[25] and to δ 5.6–5.9 ppm on aryl and olefinic substitution. Attempts to obtain a mass spectrum failed since only fragmentation patterns of the decarboxylation product could be observed even using a subambient inlet probe. The only decomposition products are carbon dioxide and the corresponding carbonyl compound.

The most conclusive and convincing evidence favoring the 1,2-dioxetane structure is the fact that all three derivatives chemiluminesce on thermal decarboxylation. The weak direct chemiluminescence can be markedly enhanced by rubrene, 9,10-dibromoanthracene, 9,10-diphenylanthracene, and other fluorescers.[27] Presently, mechanistic work is in progress to assess the efficiency and selectivity of excited state production in the thermal decarboxylation of the α-peroxylactones. The major handicaps have been reliable and accurate counting techniques for excited states.

Surprising was the fact that the three α-peroxylactones **1a–c** exhibited essentially identical thermal stability, as judged by their rates of decarboxylation ($t_{1/2}$ ~15–30 min at ca. 25 °C). The di-*tert*-butyl system **1a** was especially prepared in the hope of increasing its thermal life due to the buttressing effect of the two *tert*-butyl substituents at the α position. It was envisaged that the bulky *tert*-butyl groups would tend to relieve ring compression by widening the external substituent angle at the expense of closing the internal ring angle and thereby comforting the strained peroxide bond in this four-membered ring. However, it appears that as a countertrend the geminal *tert*-butyl groups promote puckering of the four-membered ring and the α-peroxylactone is further along its decomposition coordinate.[3] Thus steric stabilization, which was successfully demonstrated in the di-*tert*-butylacetolactone,[11] is of little utility in increasing the stability of α-peroxylactones. A more promising concept may be electronic stabilization, as illustrated in bis(trifluoromethyl)acetolactone.[17] Although the synthetic challenge is formidable, we are exploring this approach. Preliminary results are encouraging since singlet oxygenation of bis(trifluoromethyl)ketene affords the desired α-peroxylactone, albeit in low yield, whose chemiluminescence is long lived.[21]

Experimental Section

Boiling points and melting points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord 237B and NMR spectra on a Varian T-60. Commercial reagents and solvents were purified to match reported physical and spectral data. Known compounds used in this research were prepared and purified according to literature procedures and will not be reproduced here.

Preparation of α-Peroxylactones. General Cyclization Procedures. A 250-mL, three-necked round-bottom flask with magnetic spin bar was connected by way of two U-tube vacuum traps in series, each provided with one rubber septum entry, to a high-capacity (400 L/min) vacuum pump. While under a nitrogen atmosphere, the reaction flask and vacuum traps were rigorously flame dried. By means of a syringe, the reaction flask was charged with the α-hydroperoxy acid dissolved in minimum methylene chloride. The reaction flask was cooled to dry ice temperature and while stirring magnetically, a solution of dicyclohexylcarbodiimide (DCC) in a minimum of methylene chloride was added slowly by means of a syringe. The reaction mixture was then allowed to stir at dry ice temperature and was periodically monitored by infrared until maximum formation of α-peroxylactone was reached as evidenced by its characteristic carbonyl frequency at 1870 cm^{-1}.

The α-peroxylactone was then flash distilled into the first U-tube trap by applying full vacuum (ca. 10^{-3} mmHg). In this critical operation the U-tube trap was cooled at liquid nitrogen temperature and the reaction flask at ca. −40 °C to avoid thermal decomposition of the α-peroxylactone. The reaction mixture was stirred magnetically to help control the bumping and mechanical carryover of solid particles was prevented by a glass wool plug inserted in the connection between the reaction flask and the first U-tube trap. On evaporation to dryness, the residual white solid was resuspended in a minimum of solvent and again flash distilled as described above. This process was repeated until the reaction flask showed negligible amounts of α-peroxylactone by infrared.

Final isolation of the α-peroxylactone was accomplished by pumping off the solvent and carbonyl decomposition products into the second U-tube trap, using high vacuum and low temperature. Essentially pure α-peroxylactone was left behind in the cooled first U-tube trap as a white powder, contaminated by traces of solvent. Attempts to remove the residual traces of solvent by prolonging the above fractionation processes resulted in loss of α-peroxylactone by evaporation and decomposition.

In view of the explosion hazard of the solid peroxidic residue after solvent evaporation, the product was dissolved in the desired solvent and transferred to a storage vial by means of a syringe. The α-peroxylactone concentration was established by iodometric tritation and the purity by infrared spectra. The α-peroxylactone solution was stored in the freezer (ca. −20 °C) without appreciable decomposition for several weeks. The details of the preparation for the specific systems are described below.

Di-*tert*-butyl-1,2-dioxetanone (1a) was prepared according to the above procedure by adding to a solution of 102 mg (0.5 mmol) of 2-*tert*-butyl-3,3-dimethyl-2-hydroperoxybutyric acid (**2a**) in 0.7 mL of CH_2Cl_2 a solution of 103 mg (0.5 mmol) of DCC in 0.7 mL of CH_2Cl_2 at −40 °C while stirring magnetically. After 20 min at −15 °C the product was flash distilled. Removal of the solvent and the di-*tert*-butyl ketone (decomposition product) at −50 °C (0.25 mm) gave a white solid, mp 5 °C,[28] whose infrared showed a single carbonyl band at 1855 cm^{-1}, 35% yield and better than 90% pure by iodometry.

***tert*-Butyl-1,2-dioxetanone (1b)** was prepared according to the above procedure by adding to a solution of 74 mg (0.5 mmol) of 3,3-dimethyl-2-hydroperoxybutyric acid (**2b**) in 0.7 mL of CH_2Cl_2 a solution of 103 mg (0.5 mmol) of DCC in 0.7 mL of CH_2Cl_2 at −40 °C while stirring magnetically. After ca. 20 min at −40 °C the product was flash distilled. Removal of the solvent and pivalaldehyde (decomposition product) at −40 °C (0.1 mm) afforded a white solid, mp 2 °C,[28] whose infrared showed a single carbonyl band at 1870 cm^{-1} and a *gem*-dimethyl doublet at 1380 and 1365 cm^{-1}, 50% yield and better than 90% pure by iodometry. The NMR (CCl_4, Me_4Si) shows singlets at δ 5.48 ppm for ring proton and δ 1.10 ppm for *tert*-butyl in ratio 1:9.

Dimethyl-1,2-dioxetanone (1c) was prepared according to the above procedure by adding to a solution of 300 mg (2.5 mmol) of 2-hydroperoxy-2-methylpropionic acid (**2c**) in 1.0 mL of CH_2Cl_2 a solution of 515 mg (2.5 mmol) of DCC in 1.0 mL of CH_2Cl_2 at −78 °C, while stirring magnetically. After ca. 5 min at −78 °C, the product was flash distilled. Removal of the solvent and acetone (decomposition product) at −40 °C (0.01 mm) left behind a white solid, mp 10 °C,[28] whose infrared showed a single carbonyl band at 1874 cm^{-1}, 68% yield and better than 90% pure by iodometry.

Preparation of α-Hydroperoxy Acids. 2-*tert*-Butyl-3,3-dimethyl-2-hydroperoxybutyric Acid (2a). A test tube (13 × 150 mm) with side arm and ₹ 14/20 joint, equipped with gas inlet tube with sintered-glass disk, was charged with 100 mg (0.64 mmol) of di-*tert*-butylketene in 5 mL of dry pentane and cooled to −78 °C by means of dry ice. Dry ozone was bubbled through the cooled solution until persistence of the blue ozone color. The reaction mixture was efficiently purged with dry nitrogen gas to remove excess ozone, keeping the reaction mixture at −78 °C. The colorless, cold α-lactone solution[11] was then transferred quickly by means of a stainless steel capillary (12G) siphon, cooled at −78 °C, to a solution of 1.2 mL of 98% H_2O_2 in 10 mL of dry ether cooled at −78 °C. The reaction mixture was allowed to warm up slowly to room temperature, the solvent rotoevaporated (0 °C, 10 mm), and the solid residue extracted with 3 × 5 mL of pentane. Low-temperature recrystallization from pentane gave 98 mg (75% yield) of crystalline α-hydroperoxy acid **2a**, mp 82–83 °C dec, 100% pure by iodometry. The spectral data follow: IR (CCl_4) 3500–2600 (-OOH, $-CO_2H$), 1690 (C=O), and 1385 and 1370 cm^{-1} (*tert*-butyl); NMR (60 MHz, CCl_4) δ (Me_4Si) 1.25 (18 H, s, *tert*-butyl) and 12.00 (2 H, s, -OOH and $-CO_2H$, broad).

Additional evidence for the α-hydroperoxy acid structure rests on catalytic reduction to the corresponding α-hydroxy acid, mp 90–91 °C, 99.5% pure by acidimetry. The spectral data follow: IR (CCl_4), 3500–2600 (-OH, $-CO_2H$), 1700 (C=O), and 1380 and 1365 cm^{-1} (*tert*-butyl); NMR (60 MHz, CCl_4) δ (Me_4Si) 1.13 (18 H, s, *tert*-butyl) and 10.80 (2 H, s, -OH and $-CO_2H$, broad).

Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.79; H, 10.71; O, 25.50. Found: C, 63.92; H, 10.48.

3,3-Dimethyl-2-hydroperoxybutyric Acid (2b). A 50-mL round-bottom flask with magnetic spin bar was charged with 15.6 g (53.4 mmol) of trimethylsilyl 3,3-dimethyl-2-trimethylsilylperoxybutyrate and 30 mL of ice-cold, dry methanol and stirred at 0–5 °C for 4 h. After rotoevaporation (10 °C, 0.07 mm) of the solvent, the residual solid was recrystallized from an ether–hexane mixture affording white plates, mp 69–70 °C, in 87% yield, 99.5% pure by iodometry. The spectral data follow: IR (CCl_4) 3500–2600 (-OOH, $-CO_2H$), 1715 (C=O), and 1380 and 1365 cm^{-1} (*tert*-butyl); NMR (60 MHz, CCl_4) δ (Me_4Si) 1.05 (9 H, s, *tert*-butyl), 4.30 (1 H, s, methinyl), and 9.52 (2 H, s, $-CO_2H$ and -OOH).

As additional chemical structure proof, a sample of 22.2 mg (0.15 mmol) of the α-hydroperoxy acid in 1.5 mL of methanol was catalytically reduced over PtO_2 affording the expected α-hydroxy acid, mp 85–87 °C (lit.[29] mp 87–88 °C), in 84% yield after solvent rotoevaporation (ca. 30 °C, 20 mm) and recrystallization from ether–pentane.

Trimethylsilyl 3,3-Dimethyl-2-trimethylsilylperoxybutyrate (8b). A 150 × 20 mm Pyrex test tube was capped with a rubber septum, which supported a sintered glass (medium porosity) inlet tube and a hypodermic needle (22G) as gas vent. The beam of a DVY-650 W Sylvania tungsten–halogen lamp, air cooled by an air gun, was focused with a parabolic mirror through an ultraviolet glass filter (Corning No. 3-75) and infrared liquid filter (0.2 M $CuCl_2$ and 0.5 M $CaCl_2$) onto the photooxygenation vessel. While a gentle stream of dry oxygen gas was passed through a solution of 8.0 g (31.0 mmol) of *tert*-butylketene bis(trimethylsilyl)acetal and 1.0 mg of tetraphenylporphyrin (sensitizer) in 40 mL of dry CCl_4, the reaction mixture was irradiated as described above. The progress of the photooxygenation was monitored by IR, following the disappearance of the olefinic ketene acetal band at 1660 cm^{-1} and the appearance of the trimethylsilyl ester doublet at 1715 and 1730 cm^{-1}. After completion of the reaction (ca. 5 h), the solvent was rotoevaporated (ca. 25 °C, 10 mm) and the residue rectified by fractional distillation, bp 50 °C (0.1 mm), affording 8.0 g (90% yield) of product, 98% pure by iodometry.[31] The spectral data follow: IR (CCl_4) 2960 (aliphatic CH), 1715 and 1730 doublet (C=O), 1380 and 1365 (*tert*-butyl), and 1090 cm^{-1} (Si-O); NMR (60 MHz, CCl_4) δ (Me_4Si) 0.30 (9 H, s, $-OOSi(CH_3)_3$), 0.20 (9 H, s, $-CO_2Si(CH_3)_3$), 0.98 (9 H, s, *tert*-butyl), and 3.97 (1 H, s, methinyl).

***tert*-Butylketene bis(trimethylsilyl)acetal** was prepared in 72% yield according to the method of Ainsworth and Kwo,[30] bp 42–43 °C (0.4 mm) (lit.[30] bp 42 °C (0.5 mm)). A 500-mL, three-necked, round-bottom flask, equipped with a N_2 gas inlet and outlet (the latter connected to a gas bubbler), a serum cap, a magnetic spin bar, and a low-temperature thermometer, was flame dried under N_2 atmosphere. A solution of 20.0 g (0.2 mol) of diisopropylamine in 150 mL of dry THF was added by means of a syringe, maintaining the reaction temperature at 0 °C. After stirring for 20 min at 0 °C, the mixture was cooled to −78 °C and 11.6 g of 3,3-dimethylbutyric acid was added dropwise. The mixture was stirred at −78 °C for 40 min and by means of a syringe 50 mL (0.5 mol) of chlorotrimethylsilane, previously well purged with dry N_2 to displace adventitious HCl, was added slowly. After warmup to room temperature (ca. 30 °C) and stirring for an additional 30 min, the LiCl precipitate was removed by filtration through a sintered glass funnel under N_2. The THF was rotoevaporated (ca. 30 °C, 15 mm), 20 mL of dry ether was added, the heterogeneous mixture filtered again, and the filter cake washed with 2 × 3 mL of ether. The ether was rotoevaporated (ca. 30 °C, 25 mm) and the residue fractionally distilled at reduced pressure. The spectral data follow: IR (CCl_4) 2960 (aliphatic C-H), 1660 (C=C), 1380 and 1365 (*tert*-butyl), and 1025 and 1065 cm^{-1} (Si-O); NMR (60 MHz, CCl_4) δ (Me_4Si) 0.2 (18 H, s, $-Si(CH_3)_3$), 1.03 (9 H, s, *tert*-butyl), and 3.55 (1 H, s, vinylic CH).

2-Hydroperoxy-2-methylpropionic acid (2c) was prepared in 68% yield, mp 44–46 °C, with gas evolution at 70 °C (96% pure by iodometric titration) according to the procedure reported by Adam, Cueto, and Ehrig,[17] by direct oxygenation adding to a THF solution saturated with oxygen at ca. −90 °C a THF solution of lithium α-lithioisobutyrate, prepared from 0.05 mol of isobutyric acid and 0.11 mol of lithium diisopropylamide. The oxygenated mixture was acidified at ca. −90 °C by addition of 15% aqueous HCl and worked up by ether extraction below 5 °C. Several recrystallizations from ether–pentane below 5 °C in a glove bag afforded the pure product. It is critical to keep a dry atmosphere and subambient temperature when handling this unstable and hygroscopic hydroperoxide. The NMR (60 MHz, CCl_4) shows δ (Me_4Si) 1.5 (6 H, s, $-CH_3$) and 9.7 (2 H, -OOH and CO_2H) proton resonances and the IR (CCl_4) shows bands at 3500–2600 (-OOH and $-CO_2H$), 1710 (C=O), and 1380 and 1360 cm^{-1} (*gem*-dimethyl).

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(31) Although the titrimetric purity is high (>98%), elemental and mass spectral analyses have been consistently poor for this material. A possible reason for this is the fact that **8b** deteriorates on standing even in the freezer and is thus quite difficult to handle.

Sesquiterpene Lactones: Total Synthesis of (±)-Vernolepin and (±)-Vernomenin[1,2]

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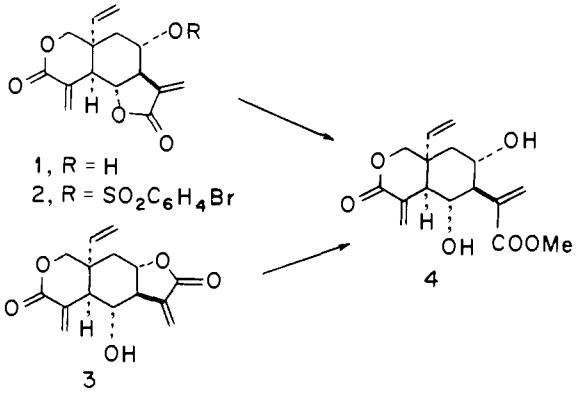
Abstract: Vernolepin (**1**) and vernomenin (**3**), the major constituents of *Vernonia hymenolepis*, have been synthesized in racemic form from *trans*-2,2-ethylenedioxy-10β-methoxymethyl-8-decalone (**20**).

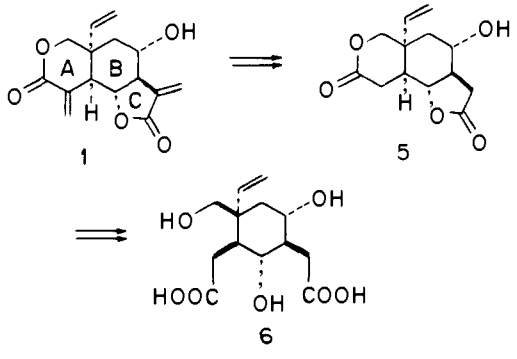
It was during the course of searching for tumor inhibitory compounds from plant sources that Professor S. Morris Kupchan and co-workers obtained an alcoholic extract of *Vernonia hymenolepis*, native to Ethiopia, which exhibited inhibitory activity in vitro. A systematic study aimed at isolation and structure elucidation revealed two novel elemanolide dilactones: vernolepin (**1**), the major active principle, and vernomenin (**3**), a closely related dilactone.



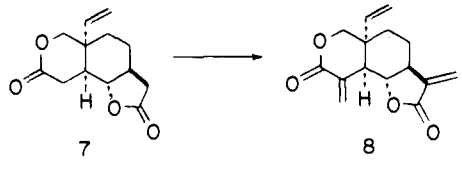
The structure of vernolepin, mp 181–182 °C, was established by x-ray crystallographic examination of the *p*-bromobenzenesulfonate ester **2**.[4] Pure crystalline vernolepin showed significant in vivo inhibitory activity against the Walker intramuscular carcinosarcoma 256 and in vitro cytotoxicity against KB cell culture. Vernomenin was isolated as an amorphous solid whose NMR signals in pyridine-d_5 were similar to those of vernolepin. Treatment of vernomenin with methanolic hydrochloric acid gave the methanol adduct **4**, mp 174–175 °C, which was identical in all respects with a sample of the methanol adduct obtained from vernolepin under identical conditions, thus indicating that both differ only in the attachment of the ring C γ-lactone unit.[5]

Retrosynthetic analysis of the vernolepin molecule (Scheme I) reveals the need for a simultaneous introduction of the two

Scheme I



reactive α-methylene units during the latter stages of the synthesis. It is without question that the α-methylene-γ-butyrolactone and to a lesser extent the α-methylene-δ-valerolactone contribute to vernolepin's biological activity.[6] The extreme ease with which α-methylene lactones react with thiols and other biological nucleophiles is well documented.[7] It is primarily for the reasons set forth above that we initiated some years ago a program designed to explore methods for the construction of both α-methylene-γ- and -δ-lactones,[8] as well as to examine the feasibility of bis-α-methylenation in dilactone systems (cf. **7** → **8**).[9]



As indicated in Scheme I, cleavage of the two lactone units of the tricyclic dilactone **5** generates a cyclohexane derivative