mixture was stirred at reflux for 16 h. The mixture was poured into 50 g of ice and 10 mL of concentrated HCl and heated on a steam bath for 2 h, during which time a red precipitate formed. The aqueous suspension was extracted with two 40-mL portions of methylene chloride and the combined organic solution was washed with H_2O and dried over Na_2SO_4. Concentration and preparative TLC (Kieselgel 60, eluted with chloroform, two developments) afforded 5 mg of the trihydroxyquinone **27** as a bright red solid, mp 188–192 °C dec: IR ($CHCl_3$) 1608 cm^{-1}; NMR ($CDCl_3$) δ 13.59 (s, 1 H), 12.73 (s, 1 H), 12.20 (s, 1 H), 7.98–6.71 (m, 3 H), 3.00–1.58 (m, 7 H), 2.28 (s, 3 H); UV–vis ($CHCl_3$) nm (log ϵ), 255 (4.76), 448 (4.24), 536 (4.09).

Similarly 3.5 mg of 7,9-dideoxydaunomycinone[21] was treated with 70 mg of aluminum chloride. Following workup and chromatography, 2 mg of **27** was obtained. This material was identical in all respects with that obtained from the demethylation of **23b** described above.

7,9-Dideoxydaunomycinone (3). Quinone **23b** (28 mg) was combined with 78 mg of silver(II) oxide in 15 mL of acetone and 3 mL of 40% nitric acid was added. The mixture became homogeneous after 10 min and was poured into 40 mL of methylene chloride. This solution was washed with 40-mL portions of 2% aqueous sodium hydrosulfite and H_2O and dried over Na_2SO_4. Concentration and preparative TLC (eluted with chloroform, four developments) gave 21 mg (90%) of 7,9-dideoxydaunomycinone (**3**) as a bright red solid, mp 236–241 °C (lit. 244–245 °C,[21b] 243–245 °C[3a]). This material was identical with an authentic sample[21] by ^1H NMR, IR, UV, and TLC in three different solvent systems.

Acknowledgments. We are grateful to Professors Pierre Vogel, Ross Kelly, Andrew Kende, and Francis Johnson for discussions during the course of this work. We would like to express our thanks to the National Cancer Institute, Department of Health, Education, and Welfare (Grant No. CA16524), and the American Cancer Society (Grant No. IN45P to Brown University) for financial support. K.A.P. gratefully acknowledges additional support in the form of an Alfred P. Sloan Foundation Fellowship. K.A.P. and J.K. are especially grateful to Tahir Iqbal and Daniel Dyckman who helped to prepare starting materials for this synthesis.

Sesquiterpene Lactones. Total Synthesis of (±)-Eriolanin and (±)-Eriolangin

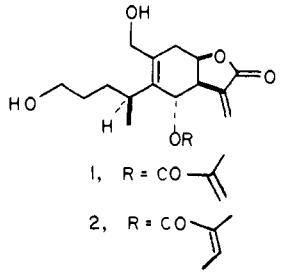
Paul A. Grieco,*[1] Tomei Oguri, and S. Gilman

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received March 28, 1980*

Abstract: The total synthesis of (±)-eriolanin (**1**) and (±)-eriolangin (**2**), highly oxygenated 1,10-*seco*-eudesmanolides isolated from the chloroform extracts of *Eriophyllum lanatum* Forbes (Compositae), is described. The preparation of both **1** and **2** is accomplished in 22 steps, starting from 4α,5α-methanodecalol **8**.

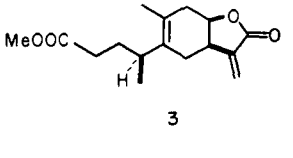
The sesquiterpene lactones (±)-eriolanin (**1**) and (±)-eriolangin (**2**) are novel antileukemic 1,10-*seco*-eudesmanolides containing three consecutive chiral centers on a cyclohexene ring in addition to a chiral center located on an acyclic side chain. Isolated from the chloroform extracts of *Eriophyllum lanatum* Forbes (Compositae) by Kupchan and co-workers,[2] both eriolanin and eriolangin possess significant activity in vivo against P-388 leukemia in mice and in vitro against cell cultures derived from human carcinoma of the nasopharynx (KB). The in vivo tumor-inhibitory activity associated with both **1** and **2** can be attributed to the presence within each molecule of two α,β-unsaturated carbonyl functions.[3]

A rare class of compounds comprised of only three members, the first 1,10-*seco*-eudesmanolide, ivangulin (**3**), was isolated by Herz and co-workers in 1967 from *Iva angustifolia* Natl. (section Linearbractea) found in Texas and Oklahoma.[4] The recently reported total synthesis of ivagulin[5] confirmed the gross structural assignment put forth by Herz nearly 12 years ago and established the configuration at C(4).



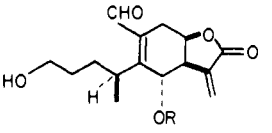
1, R = CO

2, R = CO



3

Structure elucidation of the more highly oxygenated members, eriolanin and eriolangin, required, in addition to a combination of NMR, IR, and mass spectral techniques, an X-ray analysis of a mixed crystal of dehydroeriolanin (**4**) and dehydroeriolangin (**5**).[1,6]



4, R = CO

5, R = CO

With no degradative studies to fall back upon, we embarked on the synthesis of eriolanin and eriolangin, realizing that success could only be claimed after we had reached the ultimate targets. Of critical importance to success was the introduction of the C(4) methyl group with the proper stereochemical relationship to the oxygenated α-methylene-γ-butyrolactone functionality. We detail below an account of the total synthesis of eriolanin and eriolangin.[7]

(1) Address correspondence to this author at the Department of Chemistry, Indiana University, Bloomington, Ind. 47405.

(2) S. M. Kupchan, R. L. Baxter, C.-K. Chiang, C. J. Gilmore, and R. F. Bryan, *J. Chem. Soc., Chem. Commun.*, 842 (1973).

(3) T. A. Geissman and M. A. Irwin, *Pure Appl. Chem.*, **21**, 167 (1970); S. M. Kupchan, *ibid.*, **21**, 227 (1970); S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); A. Rosowsky, N. Papathanasopaulos, H. Lazarus, G. E. Foley, and E. J. Modest, *ibid.*, **17**, 672 (1974); G. A. Howie, I. K. Stamos, and J. M. Cassady, *ibid.*, **19**, 309 (1976); P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *ibid.*, **20**, 71 (1977).

(4) W. Herz, Y. Sumi, V. Sudarsanam, and D. Raulais, *J. Org. Chem.*, **32**, 3658 (1967).

(5) P. A. Grieco, T. Oguri, C.-L. J. Wang, and E. Williams, *J. Org. Chem.*, **42**, 4113 (1977).

(6) R. F. Bryan and C. J. Gilmore, *Acta Crystallogr., Sect. B*, **31**, 2213 (1975).

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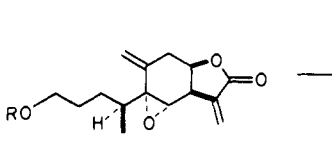
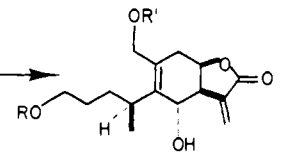
At the outset we made the assumption that the olefinic epoxide **6** would provide, via an S_N2' reaction, direct access to intermediate **7**, a logical precursor to both eriolanin and eriolangin. We were, of course, aware of the potential for aromatization during any attempted treatment of **6** with acid. Furthermore, it was possible that the delicate nature of the transformation **6** → **7** would necessitate either protection of the α-methylene lactone function or require postponement of the α-methylenation sequence until the very last stage of the synthesis. Our strategy toward the synthesis of an intermediate like **6** thus centered around the tricyclic dione **12**. Baeyer–Villiger oxidation of **12** with simultaneous epoxidation



6



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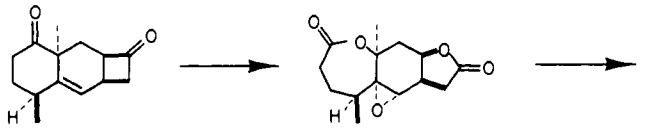
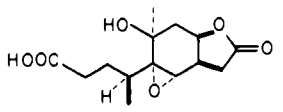


12 13

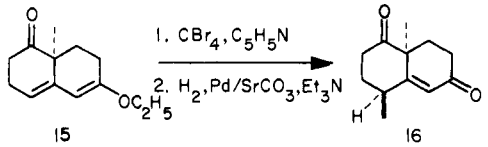


14

of the Δ^5 olefin would give way, after selective hydrolysis of the seven-membered ring lactone (**13** → **14**), to the complete carbon framework of the *seco*-eudesmanolides possessing the critical center of chirality at C(4), minus only the α-methylene unit of the γ-lactone system. It was the intention to call upon our prior work in the vernolepin area for introduction of the α-methylene unit.[8]

Results

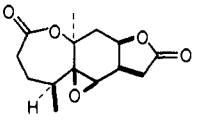
1. Synthesis of Tricyclic Enedione 12. The key intermediate **12**, mp 111–112 °C, was prepared in 43% overall yield by an eight-step sequence from the known 4α,5α-methanodecalol **8**[5] (Scheme I), obtained by cyclopropanation of the corresponding octalol. Exposure of ketal **8** to 70% perchloric acid in methylene chloride resulted in simultaneous cleavage of the cyclopropane ring and equilibration of the methyl group to the more stable equatorial position in 86% yield. NMR (CCl_4) analysis of enone **9** revealed the olefinic proton at C(5) as a doublet centered at δ 5.68 with a coupling constant of J = 1.8 Hz which is in complete agreement with the predicted J value of 1.6–1.8 Hz.[9] The infrared spectrum also confirmed the presence of the enone system as evidenced by bands at 1670 and 1615 cm^{-1}. In an alternate sequence of reactions, enone **9** was prepared by sodium borohydride reduction (EtOH, 0 °C, 86% yield) of enedione **16** which was synthesized by the procedure of Reusch and Telschow in two steps from dienol ether **15**[10] in ~15% overall yield. After completion of our work, a synthesis of enone **9** was reported from the laboratory of Professor Yoshikoshi.[11]



15 16

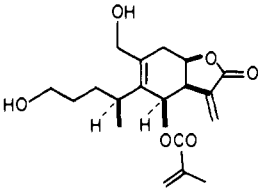
With the structure of **9** assured, we set out to complete the elaboration of compound **8** into tricyclic enedione **12** (Scheme I). Introduction to the 1,3-conjugated diene system was performed on the tosylhydrazone of enone **9** employing a modification of the original procedure by Shapiro and Dauben.[12] Use of excess lithium diisopropyl amide in tetrahydrofuran gave in 90% yield the conjugated diene 10, mp 61–62 °C, which was silylated in near quantitative yield. As a result of the C(10) α-oriented methyl group, in situ cycloaddition of dichloroketene[13] generated from dichloroacetyl chloride and triethylamine in hexane took place predominently from the β face of the diene system providing, after dechlorination and cleavage of the silyl ether, cyclobutanone derivative **11** (62%): IR (CCl_4) 3640, 3460, 1780 cm^{-1}. As much as 10% α adduct could be detected on one occasion. Oxidation of **11** with pyridinium chlorochromate[14] gave in 75% yield crystalline diketone **12**: IR (CCl_4) 1783, 1714 cm^{-1}.

2. Preparation of Hydroxycarboxylic Acid 14. With the tricyclic olefinic diketone **12** in hand, the direct one-step conversion of **12** into **13** was visualized via simultaneous Baeyer–Villiger oxidation of the cyclobutanone and cyclohexanone residues and epoxidation of the Δ^5 carbon–carbon double bond. Bislactone epoxide **13** with all chircal centers established permits, as briefly outlines above, access to eriolanin and eriolangin via carboxylic acid **14**. We were well aware of the possibility that oxidation of **12** might lead to the isomeric bislactone epoxide **17**.



17

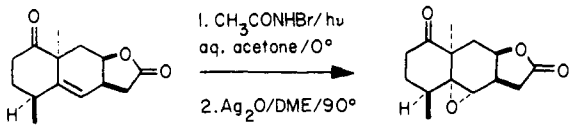
Toward this end, **12** was treated with 4.0 equiv of *m*-chloroperbenzoic acid in methylene chloride containing 4.1 equiv of sodium bicarbonate. Workup gave rise to a single crystalline product, mp 168–169 °C, in 80% yield. With no trace of an isomeric epoxide formed, we were not in a position to unambiguously assign a structure to the epoxidation product. Extensive experimentation culminated in a total synthesis of *epi*-eriolanin (**18**), whose structure was determined by single-crystal X-ray analysis.[15]



18

Disappointed to find that peracid treatment of **12** provided exclusively the wrong epoxide, we set out to prepare the α-oriented epoxide. The obvious solution to overcome the problem would be to proceed via the corresponding bromohydrin which upon treatment with base ought to provide the desired epoxide. Indeed, this old concept gave way to the required epoxide **13** via a four-step sequence of reactions. Treatment of **12** with *tert*-butyl hydroperoxide in tetrahydrofuran containing 10% aqueous sodium hydroxide at 0 °C for 30 min afforded a single crystalline lactone **19**, mp 121–122 °C. The above conditions are extremely mild and useful for differentiating between two keto functions within the same molecule provided that one of the ketones is highly strained. Submission of olefin **19** to bromohydrin formation

(7) For a preliminary account of this work, see P. A. Grieco, T. Oguri, S. Gilman, and G. T. DeTitta, *J. Am. Chem. Soc.*, **100**, 1616 (1978).
(8) P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **99**, 5773 (1977).
(9) D. J. Collins, J. J. Hobbs, and S. Steinhell, *Aust. J. Chem.*, **16**, 1030 (1963).
(10) J. E. Telschow and W. Reusch, *J. Org. Chem.*, **40**, 862 (1975).
(11) M. Kato, H. Kurihara, H. Kosugi, M. Watanabe, S. Asuka, and A. Yoshikoshi, *J. Chem. Soc., Perkin Trans. 1*, 2433 (1977).
(12) For a review of the Shapiro olefin-forming reaction, see R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(13) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87**, 5257 (1965); L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); A. Hassner and V. R. Fletcher, *ibid.*, 5053 (1970); P. A. Grieco and K. Hiroi, *ibid.*, 3467 (1974).
(14) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(15) S. Fortier, G. T. DeTitta, and P. A. Grieco, *Acta Crystallogr., Sect. B*, **35**, 1903 (1979).

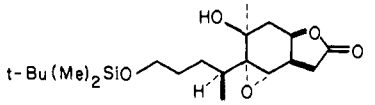


19 20

followed by treatment with silver oxide yielded (74% overall) a single crystalline epoxide (**20**), mp 173–174 °C. Baeyer-Villiger oxidation of **20** employing 3.0 equiv of *m*-chloroperbenzoic acid and 3.0 equiv of sodium bicarbonate at room temperature gave rise after 144 h to a 36% yield of desired bislactone epoxide **13**, mp 177–178 °C. While it was gratifying to have prepared the desired epoxide for the first time, we were most disappointed by the low yield. After extensive experimentation, a substantial improvement in the yield of **13** was realized. Treatment of ketone **20** with 3.0 equiv of *m*-chloroperbenzoic acid in refluxing methylene chloride containing 1.6 equiv of lithium carbonate and the radical inhibitor 4,4′-thiobis(2-*tert*-butyl-6-methylphenol)[16] provided a 64% isolated yield of crystalline **13** along with 22% recovered starting material.

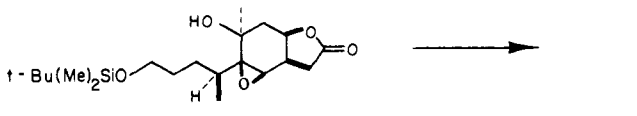
Generation of hydroxycarboxylic acid **14** from the tricyclic compound **13** required selective hydrolysis of the seven-membered ring lactone in the presence of the γ-butyrolactone and the C(5)–C(6) α-oriented epoxide. The transformation **13** → **14** could be effected under acidic or basic conditions. It was found that exposure of **13** to Dowex 50W-X8 (H^+) in aqueous acetone for 48 h provided an excellent yield of hydroxy acid **14**. Success is in part due to the fact that the hydroxy acid derived from the γ-butyrolactone tends to remain in its closed form during the course of the reaction. The lack of any complications due to the presence of the epoxide function attests to the mildness of the above procedure using a resin acid. In contrast, use of mineral acids resulted in extensive decomposition. Whereas initial attempts employing base to effect the selective hydrolysis of the seven-membered lactone **13** into hydroxycarboxylic acid **14** were unsuccessful, success was achieved by converting **13** into the corresponding dicarboxylic acid followed by refluxing briefly in benzene to effect selective closure of the γ-lactone ring. Under these conditions a near-quantitative yield of crystalline **14** could be realized.

3. Eriolanin and Eriolangin. The ready availability of hydroxycarboxylic acid **14** possessing the proper configuration at C(4), C(6), C(7), and C(8) set the stage for completion of the total synthesis of eriolanin and eriolangin. Prior to further elaboration of the six-membered ring, the carboxyl group of **14** was reduced at low temperature with diborane in tetrahydrofuran followed by protection of the resultant primary alcohol as its *tert*-butyldimethylsilyl ether. This two-step procedure resulted in isolation of **21**, mp 47–48 °C, in 76% yield.



21

As a result of our unpublished synthetic efforts in the *epi*-eriolanin series, we found that treatment of tertiary alcohol **22** with



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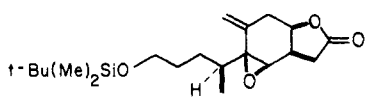
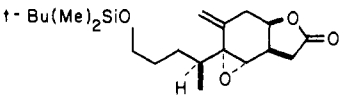
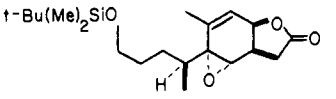


23

a mixture of thionyl chloride, 1,5-diazabicyclo[5.4.0]undec-5-ene, and pyridine in benzene (0 °C, 10 min) resulted in isolation of the exocyclic olefin **23** in 86% yield after chromatography on SilicAR CC-7. Thus, treatment of the desired tertiary carbinol **21** with thionyl chloride in benzene containing pyridine at room temperature for 25 min produced a 46% yield of the sensitive exocyclic olefinic epoxide **24** and a 40% yield of the endocyclic



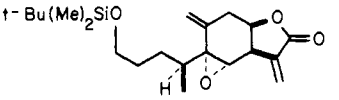
24



25

isomer **25**. Unlike our experience in the *epi*-eriolanin series, we were unable to block the formation of the unwanted endocyclic isomer.

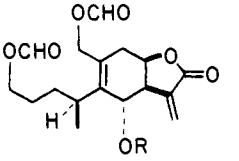
Prior to unravelling the olefinic epoxide moiety present in **24**, we proceeded to subject γ-lactone **24** to α-methylenation. Using the procedure which we introduced a few years ago, lactone **24** was subjected to hydroxymethylation, mesylation, and β elimination in 53% overall yield.[17] That **26**, mp 61.5–62.5 °C, pos-



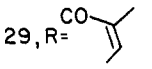
26

sessed the desired α-methylene-γ-butyrolactone ring was clearly evident from examination of spectra data.

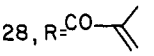
After considerable experimentation, it was found that the crucial S_N2' opening of epoxide **26** could be effected by Dowex 50W-X8 (H^+) suspended in chloroform containing formic acid, giving rise to product **27**, mp 51–52 °C, in 67% isolated yield. We were



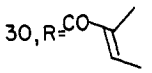
27, R = H



29, R =



28, R =



30, R =

somewhat surprised to find that, during the course of the reaction, the *tert*-butyldimethylsilyl ester cleaved leaving a primary alcohol which was converted into a formate ester. Fortunately, the highly hindered C(6) hydroxyl was left untouched which set the stage for completion of the total synthesis.

Accordingly, alcohol **27** was treated at 25 °C for 30 min with the anhydride[18] of methacrylic acid in tetrahydrofuran containing triethylamine and a catalytic amount of 4-dimethylaminopyridine.[19] Chromatography of the crude reaction product on SilicAR CC-7 furnished methacrylate **28** [mp 90–91 °C; IR ($CHCl_3$) 1778, 1730, 1720, 1640 cm^{-1}] in 93% yield as a crystalline substance. Attempted cleavage of the formate esters employing anhydrous potassium carbonate in methanol under a variety of reaction temperatures resulted in hydrolysis of the formate esters and 1,4 addition of methanol to the α-methylene

(16) Y. Kishi, M. Aratani, H. Tanino, T. Fukuyama, T. Goto, S. Inoue, S. Sugiura, and H. Kakoi, *J. Chem. Soc., Chem. Commun.*, 64 (1972).

(17) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972).

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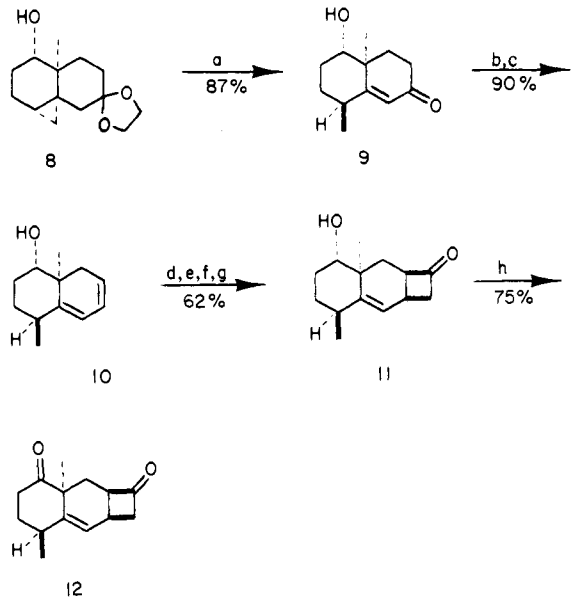
(19) G. Höfle, W. Steglich, and H. Vorbrüggen, *Angew. Chem., Int. Ed. Engl.*, **17**, 569 (1978).

Scheme I. Synthesis of Tricyclic Diketone **12**[a]



[a] (a) 70% $HClO_4$, CH_2Cl_2, 0 °C; (b) $TsNHNH_2$, $BF_3 \cdot Et_2O$, C_6H_6; (c) LDA (6.0 equiv), THF, −78 °C; (d) *t*-Bu(Me)$_2$SiCl, DMF, imidazole; (e) $Cl_2CHCOCl$, Et_3N, hexane; (f) Zn, HOAc; (g) 10% HCl, THF; (h) $C_5H_5NHCrO_3Cl$, CH_2Cl_2.

lactone. We could detect no products resulting from 1,4 addition of methanol to the methacrylate system. Successful cleavage of the formate esters without complications due to the reactive Michael acceptors in the molecule was achieved with Dowex 1-X8 (OH^- form) suspended in methanol (0 °C, 1 h). Under these conditions we were able to realize, after purification on SilicAR CC-7, a 96% yield of crystalline racemic eriolanin, mp 114.5–115.5 °C. Identity of the synthetic material with an authentic sample provided by Professor A. T. Sneden was established by NMR (250 MHz), IR, and TLC behavior.

To complete the total synthesis of *dl*-eriolangin, intermediate **27** was treated with angelic anhydride,[20] triethylamine, and 4-dimethylaminopyridine[19] in tetrahydrofuran affording a 1:1 mixture of angelate ester **29** and tiglate ester **30** which were separated by preparative thin-layer chromatography. Once again hydrolysis of the formate esters proceeded smoothly (81%) when Dowex 1-X8 (OH^- form) in methanol (0 °C) was employed in place of potassium carbonate. Racemic eriolangin, mp 90–91 °C, thus obtained was identical in all respects (NMR, IR, TLC) with an authentic sample of natural eriolangin.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low resolution mass spectra were recorded on an LKB-9000 spectrometer. High resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide, and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use. Dowex 50W-X8 (H^+) was activated by passing 200 mL of distilled water through a 5-g column of acidic ion-exchange resin until the eluant was neutral. The water and organic impurities were removed from the resin by eluting with 200 mL of reagent grade acetone. The activated resin was dried at 0.5 mm Hg for 3 h. Dowex 1-X8 (OH^- form) was prepared by washing a 5-g column of Dowex 1-X8 (Cl^- form) with 150 mL of distilled water, 90 mL of 10% aqueous sodium hydroxide solution, 200 mL of distilled water, and 200 mL of reagent grade acetone. The resin was dried at 0.5 mmHg for 3 h.

4,4a,5,6,7,8-Hexahydro-5β-hydroxy-4aβ,8α-dimethylnaphthalen-2-(3*H*)-one (9). To a solution of 6.0 g (25 mmol) of cyclopropyl ketal **8**[5] in 600 mL of methylene chloride cooled to 0 °C was added, dropwise over 10 min, 18 mL (180 mmol) of 70% perchloric acid. The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 3.5 h. A color change from clear to deep red was noted. Excess perchloric acid was separated from the reaction mixture followed by evaporation of methylene chloride. The residue was taken up in 300 mL of ethyl acetate and was washed with 50 mL of 10% aqueous sodium thiosulfate, 50 mL of water, 50 mL of a saturated solution of sodium bicarbonate, and 50 mL of brine. The aqueous layers were reextracted with 100 mL of ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The oil (5.0 g) was chromatographed on 50 g of silica gel. Elution with hexanes–ethyl acetate (4:1, 1:1) afforded 3.5 g (73%) of enone **9** as a colorless liquid: bp 148–149 °C (0.5 mmHg); R_f 0.33 (1:1 ether–benzene); IR (CCl_4) 3640, 3450, 3025, 2975, 2945, 2875, 1670, 1618, 1465, 1420, 1380, 1375, 1352, 1338, 1305, 1280, 1245, 1220, 1145, 1090, 1060, 1042, 1025, 1010, 960, 940, 920, 890, 850 cm^{-1}; NMR (CCl_4) δ 5.70 (d, 1 H, J = 1.8 Hz), 3.4 (m, 1 H), 2.8 (brs, 1 H), 2.45–1.67 (m, 10 H), 1.20 (s, 3 H), 1.07 (d, 3 H, J = 6.5 Hz); high-resolution mass spectrum m/e calcd 194.13068, found 194.12882. Anal. ($C_{12}H_{18}O_2$) C, H.

(1α,4β,8aα)-1,2,3,4,8,8a-Hexahydro-4,8a-dimethyl-1-naphthalenol (10). To a suspension of 2.9 g (15 mmol) of octalone **9** and 3.1 g (16.5 mmol) of *p*-toluenesulfonyl hydrazide in 60 mL of anhydrous benzene (dried over sodium) was added dropwise 1.5 mL of boron trifluoride etherate at room temperature. The mixture gradually became homogeneous. After 1.5 h the solvent was removed in vacuo and trace amounts of water were azeotropically distilled with 160 mL of benezene on a rotary evaporator. This process was repeated three times. The resulting tosylhydrazone (5.4 g, 15 mmol, dried at 0.5 mmHg for 1 h) was dissolved in 60 mL of anhydrous tetrahydrofuran, cooled to −78 °C, and treated dropwise with a precooled (−78 °C) solution of lithium diisopropylamide [prepared from 12.6 mL (90 mmol) of diisopropylamine and 56 mL of 1.6 M *n*-butyllithium (in hexane) in 125 mL of dry tetrahydrofuran at −78 °C]. The mixture was stirred at −78 °C for 30 min, gradually warmed to 0 °C over a 1-h period, and stirred at 0 °C for an additional hour, followed by warming to room temperature. After 16 h the reaction mixture was quenched at −10 °C with 10 mL of water. After the tetrahydrofuran was removed under reduced pressure, the crude product was taken up in 200 mL of ethyl acetate and washed with 50 mL portions of a saturated solution of sodium bicarbonate followed by brine. The extract was dried over anhydrous magnesium sulfate, filtered, and condensed. The residue (3.2 g) was purified on 10 g of silica gel. Elution with hexanes–ether (4:1) gave 2.4 g (90%) of diene alcohol **10** as a white crystalline solid: IR (CCl_4) 3640, 3450, 3050, 2975, 2940, 2925, 2875, 2830, 1645, 1590, 1460, 1450, 1400, 1380, 1325, 1262, 1200, 1160, 1050, 1025, 1010, 1005, 980, 965, 935, 925, 880, 860, 840, 705, 695 cm^{-1}; NMR (CCl_4) δ 5.67 (m, 3 H), 3.6 (m, 1 H), 2.55–1.33 (m, 8 H), 1.02 (d, 3 H, J = 6 Hz), 0.92 (s, 3 H). Recrystallization from hexanes provided analytically pure material, mp 61–62 °C. Anal. ($C_{12}H_{18}O$) C, H.

(2aα,4β,7α,7aα,8aα)-2a,4,5,6,7,7a,8,8a-Octahydro-7-hydroxy-4,7a-dimethylcyclobuta[*b*]naphthalen-1(2*H*)-one (11). A solution of 13.2 g (74 mmol) of diene alcohol **10** in 52 mL of distilled dimethylformamide was treated with 10 g (148 mmol) of imidazole and 22.5 g (148 mmol) of *tert*-butyldimethylchlorosilane at 25 °C. After 24 h, the reaction mixture was taken up in 1 L of hexanes, washed with 100 mL portions of water and brine, respectively, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 25 g of colorless oil. Chromatography on 250 g of Florisil (elution with hexanes) provided 19 g (98%) of pure silyl ether as a liquid [R_f 0.81 (hexanes); IR (CCl_4) 3050, 2960, 2940, 2900, 2860, 1470, 1460, 1390, 1370, 1320, 1255, 1100, 1075, 1005, 940, 890, 875, 840 cm^{-1}; NMR (CCl_4) δ 5.57 (m, 3 H), 3.35 (m, 1 H), 2.33–1.33 (m, 7 H), 1.07–0.67 (m, 21 H)] which was used directly in the next reaction.

To a solution of 6.4 g (22.7 mmol) of the above conjugated diene in 140 mL of hexanes was added simultaneously over 1 h via two syringe pumps 5.9 mL (61.3 mmol) of dichloroacetyl chloride in 140 mL of hexanes and 8.9 mL (61.3 mmol) of triethylamine in 140 mL of hexanes. After 2.5 h, 100 mL of anhydrous ether was added to the reaction. The white precipitate formed was removed by filtration and the solvent was reduced in vacuo. The crude dichlorocyclobutanone [8.9 g; dried on a vacuum pump at 0.5 mmHg for 1 h; IR (CCl_4) 1810 cm^{-1}] was dissolved

(20) L. B. Bos and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **82**, 168 (1963).

in 175 mL of glacial acetic acid and treated at 0 °C with 14.8 g (227 mg-atoms) of zinc dust. Cautiously, the reaction mixture was warmed to 60–65 °C. After 4.5 h, the zinc salts were filtered and washed with glacial acetic acid, methanol, and anhydrous ether. The solvent was concentrated on a rotary evaporator and the residue was dissolved in 30 mL of benzene–methanol (1:1) and evaporated to dryness to remove traces of moisture. This process was repeated three times. The resulting keto silyl ether (8 g) was treated with 122 mL of 10% aqueous hydrochloric acid and 175 mL of tetrahydrofuran at room temperature. After 12 h the tetrahydrofuran and water was removed in vacuo. The crude keto alcohol was dissolved in 1 L of benzene–ether (1:1) and washed with 70 mL portions of water, a saturated solution of sodium bicarbonate, and brine. After reextraction of the aqueous layers with 100 mL of benzene–ether (1:1), the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and condensed. Chromatography of the oily residue (4.6 g) on 60 g of silica gel using hexanes–ether (1:1) yielded 3.1 g (62%) of pure **11** as an oil: R_f 0.29 (3:1 hexanes–ethyl acetate); IR (CCl_4) 3640, 3400, 3025, 2975, 2875, 1780, 1465, 1445, 1395, 1380, 1220, 1065, 1045, 1030 cm^{-1}; NMR (CCl_4) δ 5.32 (brs, 1 H), 3.47–2.73 (m, 6 H), 1.98–1.42 (m, 7 H), 1.05 (d, 3 H), 0.95 (s, 1 H); high resolution mass spectrum (calcd for $C_{14}H_{20}O_2$) *m/e* 220.14633, found 220.14821.

(2aα,4β,7aα,8aα)-2a,5,6,7a,8,8a-Hexahydro-4,7a-dimethylcyclobuta[*b*]naphthalene-1,7(2*H*,4*H*)-dione (12). A solution of keto alcohol **11** (2.7 g, 12.3 mmol) dissolved in 18 mL of dry methylene chloride was added at room temperature to a suspension of 4.5 g (21.1 mmol) of pyridinium chlorochromate in 36 mL of dry methylene chloride. After 2 h the reaction mixture was carefully quenched at 0 °C with 4 mL of anhydrous ether and filtered through Celite. The Celite pad was washed thoroughly with 150 mL of ether. The filtrate was concentrated in vacuo, redissolved in 100 mL of ether, and once again passed through the Celite pad. The solvent was condensed under reduced pressure and the residue (2.5 g) was purified on 60 g of Florisil. Elution with hexanes–ether (2:1, 1:1) gave 2.0 g (75%) of diketone **12** as a white crystalline material: IR (CCl_4) 3025, 2975, 2930, 2870, 1783, 1714, 1460, 1370, 1320, 1220 cm^{-1}; NMR (CCl_4) δ 5.58 (brs, 1 H), 3.4–1.4 (m, 11 H), 1.17 (d, 3 H, J = 6.5 Hz), 1.15 (s, 3 H). Recrystallization from ether–hexanes provided analytically pure material, mp 112–113 °C. Anal. ($C_{14}H_{18}O_2$) C, H.

(1a*S,2aα,6aβ,7aβ,10aβ,10bβ)-Hexahydro-2,6a-dimethyl-6a*H*-furo[3,2-*h*]oxireno[*f*][1]benzoxepin-5,9(2*H*,10*H*)-dione (17).** To a suspension of 2.1 g (9.5 mmol) of diketone **12** in 200 mL of methylene chloride containing 3.3 g (39 mmol) of sodium bicarbonate cooled to −10 °C was added 7.8 g (38 mmol) of *m*-chloroperoxybenzoic acid. The reaction mixture was slowly warmed to 0 °C. After 24 h at 25 °C the reaction was quenched with 6 g of solid sodium bisulfite and the solvent was removed in vacuo. The residue was taken up in ethyl acetate and washed with three 50-mL portions of 10% aqueous potassium carbonate and a 20-mL portion of brine solution. The aqueous layers were reextracted with 100 mL of ethyl acetate and the combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Evaporation of the solvent left 2.7 g of crude product which was chromatographed on 50 g of silica gel. Elution with ether followed by ethyl acetate afforded 2 g (80%) of pure dilactone epoxide **17** as a crystalline material: IR (CCl_4) 3040, 2980, 2940, 1782, 1725, 1460, 1418, 1385, 1350, 1320, 1285, 1180, 1160, 1090, 1030, 985, 910 cm^{-1}; NMR ($CDCl_3$) δ 4.65 (m, 1 H), 3.4 (d, 1 H, J = 2.2 Hz), 3.00–2.07 (m, 10 H), 1.63 (s, 3 H), 0.87 (d, 3 H, J = 6 Hz). Recrystallization from chloroform–ether provided analytically pure material, mp 166–168 °C. Anal. ($C_{14}H_{18}O_5$) C, H.

(3aα,5β,8aα,9aα)-3a,6,7,8a,9,9a-Hexahydro-5,8a-dimethylnaphtho[2,3-*b*]furan-2,8(3*H*,5*H*)-dione (19). A solution of 940 mg (4.3 mmol) of diketone **12** dissolved in 35 mL of dry tetrahydrofuran cooled to 0 °C was treated with 1.31 mL (9.5 mmol) of *tert*-butyl hydroperoxide followed by the addition of 2.1 mL (5.2 mmol) of 10% aqueous sodium hydroxide solution. After 30 min at 0 °C, the reaction mixture was neutralized with 1.0 g of Dowex 50W-X8 (H^+), filtered, and concentrated in vacuo. The crude product (860 mg) was dried at 0.5 mmHg for 2 h (until contant weight) and purified on 50 g of silica gel. Elution with ether–methylene chloride (1:20) gave 800 mg (80%) of γ-lactone **19** as a white, needle-like substance: IR ($CHCl_3$) 3025, 2955, 2925, 2870, 1770, 1700, 1450, 1420, 1372, 1330, 1320, 1240, 1171, 1150, 1130, 1010, 940, 909 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 5.39 (dd, 1 H, J = 1.95, 4.43 Hz, C(6) olefinic proton), 4.77 (ddd, 1 H, J = 4.78, 7.61, 11.86 Hz, C(8) H), 1.35 (s, 3 H), 1.15 (d, 3 H, J = 6.55 Hz). Recrystallization from ethyl acetate–hexanes provided analytically pure material, mp 121–122 °C. Anal. ($C_{14}H_{18}O_3$) C, H.

(1a*S,2aα,5aβ,6aβ,9aβ,9bα)-Hexahydro-2,5a-dimethyl-2*H*-oxireno[4,4a]naphtho[2,3-*b*]furan-5,8(5a*H*,9*H*)-dione (20).** A solution of 1.9 g (13.8 mmol) of *N*-bromoacetamide (recrystallized from benzene prior to use, mp 118–119 °C) in 7 mL of reagent grade acetone and 2.3 mL of distilled water at 0 °C was irradiated with a sun lamp for 30 min. The reaction mixture changed from clear to yellow. Olefin **19** (1.4 g, 6 mmol) was dissolved in 40 mL of reagent grade acetone and added to the reaction mixture. After 30 min the reaction was quenched at 0 °C with ~30 mL of 10% aqueous sodium thiosulfate solution to decompose the excess *N*-bromoacetamide (checked by using postassium–iodide starch paper). The solvent was removed under reduced pressure and the crude product was dissolved in 150 mL of ethyl acetate and washed with 30 mL of a saturated solution of sodium bicarbonate. The organic layer was azeotropically distilled to dryness with benzene and the resultant bromohydrin (2.0 g) was dissolved in 100 mL of dimethoxyethane and treated with 10 g (43 mmol) of silver oxide. The reaction was gently refluxed (90–95 °C) for 1 h and then filtered through a pad of Celite. The black precipitate was washed thoroughly with dimethoxyethane and the filtrate was concentrated in vacuo. The residue (1.2 g) was chromatographed on 20 g of silica gel. Elution with ether–methylene chloride (1:1) afforded 1.0 g (65%) of γ-lactone epoxide **20** as a light yellow solid: IR ($CHCl_3$) 3025, 2975, 2925, 2880, 1770, 1708, 1458, 1420, 1375, 1305, 1270, 1170, 1100, 1080, 1062, 1022, 990, 920, 905, 891 cm^{-1}; NMR ($CDCl_3$) δ 4.43 (m, 1 H), 2.0–3.1 (m, 11 H), 1.28 (s, 3 H), 0.88 (d, 3 H, J = 7 Hz). Recrystallization from ethyl acetate–hexanes provided analytically pure material, mp 171–172 °C. Anal. ($C_{14}H_{18}O_4$) C, H.

[1a(*R),2α,6aβ,7aβ,10aβ,10bα]-Hexahydro-2,6a-dimethyl-6a*H*-furo[3,2-*h*]oxireno[*f*][1]benzoxepin-5,9(2*H*,10*H*)-dione (13).** To a solution of 1.63 g (6.51 mmol) of ketone **20** dissolved in 170 mL of dry methylene chloride was added 3.97 g (19.6 mmol) of *m*-chloroperbenzoic acid, 746 mg (10.1 mmol) of lithium carbonate, and 70 mg (0.2 mmol) of 4,4′-thiobis(2-*tert*-butyl-6-methylphenol). The reaction mixture was gently refluxed for 7 days with daily additions of 15 mg to the radical inhibitor. The reaction was diluted with 80 mL of methylene chloride and washed with 30 mL of 10% aqueous sodium thiosulfate and 30 mL of 10% aqueous potassium carbonate. The organic extract was condensed to 10 mL and purified on 200 g of silica gel. Elution with methylene chloride–ether (20:6, 6:1, 1:1) afforded 360 mg (22%) of recovered starting material. Continued elution with ethyl acetate–ether (1:4) gave 1.10 g (64%) of bislactone **13** as a crystalline compound (81% based on recovered starting material): IR ($CHCl_3$) 3000, 2960, 2945, 2925, 2900, 1775, 1720, 1450, 1420, 1410, 1375, 1365, 1350, 1330, 1320, 1310, 1285, 1275, 1255, 1185, 1170, 1150, 1121, 1105, 1085, 1045, 1015, 995, 976, 968, 960, 950, 915, 890, 880, 860, 850, 840 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 4.65 (dt, 1 H, J = 10.1, 5.14 Hz), 3.34 (m, 1 H), 3.23 (d, 1 H, J = 2.6 Hz), 2.7–2.9 (m, 3 H), 2.6 (m, 1 H), 2.4 (dd, 1 H, J = 19.2, 9.00 Hz), 2.14 (dd, 2 H, J = 3.0, 5.4 Hz), 2.08 (m, 1 H), 1.60 (s, 3 H), 1.44 (m, 1 H), 0.85 (d, 3 H, J = 7 Hz). Recrystallization from ethyl acetate–hexanes provided analytically pure material, mp 177–178 °C. Anal. ($C_{14}H_{18}O_5$) C, H.

[1aα(*R),2α,3aβ,6aβ,6bα]-Hexahydro-2-hydroxy-γ,2-dimethyl-5-oxooxireno[*e*]benzofuran-1a(2*H*)-butanoic Acid (14).** A solution of 483 mg (1.81 mmol) of bislactone epoxide **13** in 20 mL of tetrahydrofuran–water (2:1) was treated with 1.0 mL of a 10% aqueous sodium hydroxide solution. After 1 h 0.5 g of Dowex 50W-X8 (H^+) was added to neutralize the reaction mixture. Filtration through a pad of Celite followed by removal of the solvent in vacuo provided a colorless oil which was dissolved in 50 mL of benzene and refluxed for 30 min. After cooling, the solvent was removed under reduced pressure and the product was crystallized from acetone–hexanes providing 522 mg (100%) of hydroxycarboxylic acid **14**: mp 134–136 °C; IR ($CHCl_3$) 3600–2400, 1775, 1710 cm^{-1}. Anal. ($C_{14}H_{20}O_6$) C, H.

[1aα(*R),2α,3aβ,6aβ,6bα]-1a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methylbutyl]hexahydro-2-hydroxy-2-methyloxireno[*e*]benzofuran-5(2*H*)-one (21).** To a solution of 650 mg (2.3 mmol) of hydroxy acid **14** dissolved in 8.5 mL of dry tetrahydrofuran cooled to −20 °C was added dropwise 3.04 mL (3.1 mmol) of 1.2 M diborane in tetrahydrofuran. The reaction was stirred at −20 °C for 3 h, −10 °C for 3 h, 0 °C for 3 h, and 25 °C for 4.5 h. The reaction was quenched at 0 °C by the addition of 3 mL of water and diluted with 100 mL of ethyl acetate. The organic layer was washed with a saturated solution of sodium bicarbonate and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent left 581 mg (94%) of a diol which was used directly in the next reaction.

A mixture of 581 mg (2.2 mmol) of the above diol, 204 mg (3.1 mmol) of imidazole, and 421 mg (2.9 mmol) of *tert*-butyldimethylsilyl chloride in 2.5 mL of dry dimethylformamide was allowed to stir at room temperature for 18 h. The reaction was quenched with anhydrous ether (120 mL) and the organic layer was washed with 10 mL of water. The organic phase was dried over magnesium sulfate, filtered and evaporated in vacuo. Chromatography of the crude product (700 mg) on 30 g of SilicAR CC-7 using hexanes–ether (1:1) provided 635 mg (76%) of silyl ether **21** as a pure white crystalline compound: IR ($CHCl_3$) 3580, 2960, 2940, 2900, 2855, 1780, 1675, 1460, 1415, 1380, 1360, 1350, 1335, 1310, 1260, 1200, 1155, 1090, 1005, 985, 950, 935, 900, 835, 810 cm^{-1}. Recrystal-

lization from hexanes afforded analytically pure material, mp 47–48 °C. Anal. ($C_{20}H_{36}O_5Si$) C, H.

[1aα(S*),3aβ,6aβ,6bα]-1a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methylbutyl]hexahydro-2-methylenoxireno[e]benzofuran-5(2H)-one (24). A solution of 635 mg (1.7 mmol) of hydroxy silyl ether **21** dissolved in 5.3 mL of pyridine and 13 mL of benzene cooled to 0 °C was treated at once with 180 μL (2.5 mmol) of thionyl chloride in 18 mL of benzene. After 25 min at room temperature the reaction was quenched with 200 mL of ether. The organic layer was washed with 25 mL of water and 25 mL of brine, dried over magnesium sulfate, and filtered, and the solvent was removed under reduced pressure. Purification of the crude product (600 mg) on 25 g of SilicAR CC-7 [elution with ether–hexanes (1:4, 1:3, 1:2)] gave 243 mg (40%) of the undesired endocyclic isomer **25** [R_f 0.90 (4:1 ether–hexanes)] and 280 mg (46%) of the desired exocyclic olefin **24** (R_f 0.77): IR (CCl_4) 2955, 2935, 2900, 2860, 1788, 1650, 1475, 1465, 1432, 1395, 1365, 1355, 1340, 1300, 1262, 1222, 1195, 1175, 1104, 1051, 1030, 1011, 970, 918, 843 cm^{-1}; NMR (CCl_4) δ 5.30 (brs, 2 H), 4.50 (m, 1 H), 3.52 (m, 2 H), 0.85 (s, 9 H), 0.86 (d, 3 H, J = 7 Hz), 0.0 (s, 6 H); high resolution mass spectrum (calcd for $C_{20}H_{34}O_4Si$–C_4H_9) m/e 309.15220, found 309.15096.

[1aα(S*),3aβ,6aβ,6bα]-1a-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1-methylbutyl]hexahydro-2,6-bis(methylene)oxireno[e]benzofuran-5(2H)-one (26). To a solution of diisopropylamine (102 μL, 0.72 mmol) in 9.0 mL of dry tetrahydrofuran cooled to −78 °C was added 450 μL (0.72 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After 30 min a solution of 120 mg (0.33 mmol) of lactone **24** in 4.5 mL of dry tetrahydrofuran was added. After 10 min at −78 °C, the reaction was warmed to −25 °C and stirring was continued for an additional 10 min prior to addition of formaldehyde. Formaldehyde, generated from 250 mg of paraformaldehyde at 149–152 °C, was passed into the reaction mixture with the aid of a stream of nitrogen (cooling bath was maintained at −23 °C). After depolymerization was complete (~15 min), the reaction was stirred at −23 °C for 10 min prior to quenching with 200 mg of ammonium chloride and 250 μL of water. After filtration of the reaction mixture through a pad of Celite with the aid of 75 mL of tetrahydrofuran, the solvent was removed in vacuo. The crude product was chromatographed on 30 g of SilicAR CC-7. Elution with ether–hexanes (1:1) afforded 85 mg (60%) of hydroxymethylated lactone as an oil: R_f 0.36 (2:1 ether–hexane); IR (CCl_4) 3650, 3475, 2960, 2930, 2900, 2865, 2850, 1778, 1650, 1460, 1420, 1390, 1361, 1290, 1260, 1190, 1100, 1060, 1040, 1008, 940, 910, 838 cm^{-1}; NMR (CCl_4) δ 5.26 (brs, 2 H), 4.57 (m, 1 H), 3.80 (m, 2 H), 3.52 (m, 2 H), 2.97 (m, 1 H), 2.9–2.0 (m, 6 H), 1.7–1.1 (m, 4 H), 0.87 (brs, 12 H), 0.0 (s, 6 H); high resolution mass spectrum (calcd for $C_{21}H_{36}O_5Si$–C_4H_9) m/e 339.16277, found 339.16405.

A solution of 83 mg (0.21 mmol) of the above hydroxymethylated lactone in 830 μL of dry methylene chloride containing 32 μL (0.42 mmol) of methanesulfonyl chloride and 638 μL (0.84 mmol) of pyridine was stirred at room temperature. After 4.5 h 5.0 mL of benzene was added to the reaction mixture and the solvent was removed in vacuo. The crude mesylate was dissolved in 6.0 mL of benzene and treated with 312 μL (2.1 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 40 min the reaction was diluted with 40 mL of ether, washed with 10 mL of water, and dried over anhydrous magnesium sulfate. Evaporation of the filtrate left 75 mg of crude α-methylene lactone **26** which was chromatographed on 15 g of SilicAR CC-7. Elution with ether–hexanes (1:4, 1:3) gave 61 mg (77%) of pure lactone **26** as fine white needles: mp 61–62 °C; IR (CCl_4) 2950, 2930, 2880, 2855, 1775, 1580, 1550, 1475, 1460, 1400, 1385, 1360, 1344, 1270, 1255, 1220, 1130, 1100, 1040, 1005, 950, 910 cm^{-1}; NMR (CCl_4) δ 6.24 (d, 1 H, J = 2.5 Hz), 5.65 (d, 1 H, J = 2.5 Hz), 5.31 (brs, 1 H), 4.50 (m, 1 H), 3.7–3.3 (m, 3 H), 2.95 (brs, 1 H), 0.85 (brs, 12 H), 0.0 (s, 6 H). An analytical sample was prepared by recrystallization from hexanes, mp 62–63 °C. Anal. ($C_{21}H_{34}O_4Si$) C, H.

[3aα,4α,5(S*),7aα]-6-[(Formyloxy)methyl]-5-[4-(formyloxy)-1-methylbutyl]-3a,4,7,7a-tetrahydro-3-methylene-4-[(2-methyl-1-oxo-2-propenyl)oxy]-2(3H)-benzofuranone (28). To a solution of 20 mg (0.53 mmol) of epoxide **26** in 1.3 mL of chloroform was added 453 μL (106 mmol) of formic acid and 102 mg (5.3 mmol) of Dowex 50W-X8 (H^+). After 3 h the reaction mixture was filtered through a pad of Celite and washed thoroughly with chloroform. The solvent was removed in vacuo and the residue was chromatographed on 7.0 g of SilicAR CC-7. Elution with ether–hexanes (1:1) afforded 12 mg (67%) of diformate alcohol **27** as a solid. Recrystallization from ethyl acetate–hexanes provided pure **27**: mp 51–52 °C; IR ($CHCl_3$) 3025, 2960, 2925, 2850, 1760, 1720, 1460, 1400, 1350, 1320, 1278, 1170, 1150, 1090, 1030, 958 cm^{-1}; NMR ($CDCl_3$) δ 8.08 (brs, 1 H), 8.02 (brs, 1 H), 6.35 (d, 1 H, J = 3.0 Hz), 5.72 (d, 1 H, J = 3 Hz), 5.02 (m, 1 H), 4.69 (AB q, 2 H, J = 12, $\Delta\nu_{AB}$ = 25.3 Hz), 4.23 (m, 1 H), 4.03 (m, 3 H), 1.10 (d, 3 H, J = 7 Hz).

A solution of 7.5 mg (0.02 mmol) of the above alcohol (**27**) in 231 μL of dry tetrahydrofuran was treated at 0 °C with 46 μL of the anhydride[18] of methacrylic acid [prepared by treating a solution of 1.7 g (0.2 mol) of methacrylic acid in 40 mL of benzene containing 2.0 g (0.2 mol) of triethylamine and 170 mg of hydroquinone with 7.3 mL (0.1 mol) of thionyl chloride], 42 μL of triethylamine, and a catalytic amount of 4-dimethylaminopyridine (1.2 mg). After 30 min at room temperature, the reaction was quenched by the addition of 2.0 mL of benzene. The crude product, obtained by removal of the solvent in vacuo, was chromatographed on 5 g of SilicAR CC-7. Elution with ether–hexanes (1:1) gave 8.3 mg (93%) of methacrylate **28** as a crystalline compound: IR ($CHCl_3$) 3030, 2960, 2940, 1765, 1725, 1660, 1635, 1460, 1435, 1405, 1380, 1355, 1320, 1295, 1280, 1155, 1030, 1010, 980, 955, 865, 815 cm^{-1}; NMR (250 MHz, CCl_4) δ 7.98 (s, 1 H), 7.90 (s, 1 H), 6.41 (d, 1 H, J = 2.5 Hz), 6.05 (s, 1 H), 6.00 (d, 1 H, J = 2.5 Hz), 5.61 (m, 1 H), 5.33 (d, 1 H, J = 1.8 Hz), 5.01 (ddd, 1 H, J = 2.25, 3.37, 7.70 Hz), 4.76 (AB q, 2 H, J = 12.2, $\Delta\nu_{AB}$ = 81.3 Hz), 4.06 (m, 2 H), 3.56 (m, 1 H), 2.6–2.8 (m, 3 H), 1.94 (s, 3 H), 1.55 (s, 3 H), 1.0–1.5 (m, 4 H), 0.93 (d, 3 H, J = 6.7 Hz). An analytical sample was prepared by recrystallization from ether–hexanes, mp 90–91 °C. Anal. ($C_{21}H_{26}O_8$) C, H.

Eriolanin (1). A solution of 8.5 mg (0.02 mmol) of diformate **28** in 640 μL of absolute methanol containing 4.2 mg of Dowex 1-X8 (OH^-) was allowed to stir at 0 °C. After 1.25 h the reaction mixture was diluted with 5.0 mL of ethyl acetate and filtered through a pad of Celite. After the Celite was washed with 20 mL of ethyl acetate, the combined organic fractions were concentrated in vacuo and the crude product was purified on 5.0 g of SilicAR CC-7. Elution with ether–ethyl acetate (2:1) afforded 7 mg (96%) of racemic eriolanin as colorless prisms: mp 114.5–115.5 °C (ether–hexanes); IR ($CHCl_3$) 3600, 3440, 3000, 2960, 2930, 2860, 1758, 1710, 1660, 1635, 1451, 1430, 1400, 1380, 1350, 1315, 1295, 1275, 1151, 1070, 1028, 1009, 975, 950, 890, 860, 814 cm^{-1}; NMR (250 MHz $CDCl_3$) δ 6.45 (d, 1 H, J = 2.5 Hz), 6.08 (s, 1 H), 6.05 (d, 1 H, J = 3 Hz), 5.61 (brs, 1 H), 5.27 (d, 1 H, J = 2.5 Hz), 5.05 (dt, 1 H, J = 2.5, 8.0 Hz), 4.23 (AB q, 2 H, J = 12, $\Delta\nu_{AB}$ = 21.2 Hz, allylic CH_2OH), 3.4–3.6 (m, 3 H, $-CH_2CH_2OH$, $CHC{=}CH_2$), 2.80 [AM portion of an AMX system, 2H, J = 16, 2.5 (downfield proton), J = 16, 3.0 Hz (upfield protion) $\Delta\nu_{AM}$ = 80.4 Hz], 2.77 (m, 1 H, $-CHCH_3$), 1.93 (s, 3 H), 1.0–1.4 (m, 4 H, $-CH_2CH_2-$), 0.90 (d, 3 H, J = 7 Hz). Anal. ($C_{19}H_{26}O_6$) C, H.

Eriolangin (2). A solution of 15 mg (0.044 mmol) of alcohol **27** in 700 μL of anhydrous tetrahydrofuran containing 36 μL of pyridine and 0.5 mg of 4-dimethylaminopyridine was treated with 80 μL (0.44 mmol) of angelic anhydride.[20] After 43 h at room temperature, the reaction mixture was diluted with 2.0 mL of benzene and the solvent was removed under reduced pressure. The residue was chromatographed on 7.0 g of SilicAR CC-7. Elution with ether–hexanes (1:1) provided 15 mg (81%) of a 1:1 mixture of angelate **29** [R_f 0.27 (1:1 ether–hexanes), two developments] and tiglate **30** (R_f 0.21). Separation of the mixture on preparative TLC plates (Merck, 2 mm) by using ether–hexanes (1:1) afforded 5.0 mg of pure **29** (identical with a sample obtained by formylation of natural eriolangin), 4.5 mg of a mixture of **29** and **30**, and 5.3 mg of pure **30**. Recrystallization of **29** from ether–hexanes provided colorless needles, mp 83–84 °C.

A solution of 5 mg (0.012 mmol) of angelate **29** in 2.0 mL of absolute methanol was treated with 10 mg of Dowex 1-X8 (OH^- form) at 0 °C. After 2 h the reaction mixture was diluted with 4.0 mL of ethyl acetate and filtered through a pad of Celite. The Celite was washed with 15 mL of ethyl acetate and the combined organic fractions were concentrated in vacuo. The crude product (5.0 mg) was purified on 4.0 g of SilicAR CC-7. Elution with ether followed by ethyl acetate provided 3.5 mg (81%) of racemic eriolangin (**2**) which was crystallized from ether–hexanes: mp 90–91 °C; IR ($CHCl_3$) 3600, 3450, 3000, 2960, 2925, 2875, 2850, 1755, 1705, 1655, 1645, 1460, 1440, 1408, 1385, 1355, 1315, 1280, 1260, 1230, 1210, 1150, 1085, 1070, 1040, 1028, 1005, 975, 955, 900, 855, 818 cm^{-1}; NMR (250 MHz) δ 6.41 (d, 1 H, J = 2.5 Hz), 6.11 (q, 1 H, J = 7.5 Hz), 6.06 (d, 1 H, J = 2.5 Hz), 5.33 (brs, 1 H), 5.04 (dt, 1 H, J = 2.5, 8.0 Hz), 4.20 (AB q, 2 H, J = 13.7, $\Delta\nu_{AB}$ = 17.2 Hz), 3.4–3.6 (m, 3 H), 3.0–2.6 (m, 3 H), 2.00 (d, 3 H, J = 7.5 Hz), 1.83 (s, 3 H), 1.0–1.4 (m, 4 H), 0.91 (d, 3 H, J = 7 Hz). Anal. ($C_{20}H_{28}O_6$) C, H.

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