perature. The solvent was removed in vacuo and the crude product was purified by preparative TLC with chloroform as the eluent (three developments) to yield 11 (13 mg, 69%) as an oil: R_f 0.25 (chloroform): FTIR ($CHCl_3$) 3416, 1759, 1725, 1683 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.20 Hz, 3 H, CH_2CH_3), 1.43 (s, 3 H, C(5)CH_3), 3.16–3.24 (m, 2 H, CH_2CH_3), 3.83 (s, 3 H, C(3)-OCH_3), 4.13 (s, 3 H, C(4)OCH_3), 4.16–4.21 (m, 2 H, C(5)CH_2O), 4.74–4.85 (m, 1 H, NH); ^{13}C NMR ($CDCl_3$) 15.08 (CH_2CH_3), 19.58 (C(5)CH_3), 35.90 (CH_2CH_3), 59.39 (OCH_3), 60.42 (OCH_3), 65.15 (C(5)CH_2O), 79.34 (C(5)), 122.22 (C(3)), 155.30 (C(4)), 159.71 (OC(O)NH), 168.18 (C(2)) ppm; MS, m/e (relative intensity) 259 (34), 158 (100), 143 (32), 115 (7), 83 (15), 72 (21), 69 (13); M_r 259.104 93 (calcd for $C_{11}H_{17}NO_6$, 259.105 59). Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.60; N, 5.40. Found: C, 51.09; H, 6.55; N, 5.51.

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Regioselective Oxidation of 3-Alkylfurans to 3-Alkyl-4-hydroxybutenolides

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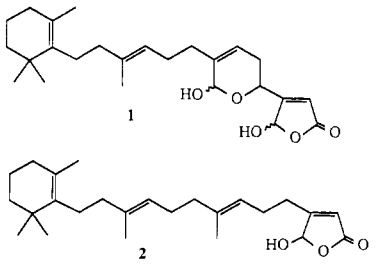
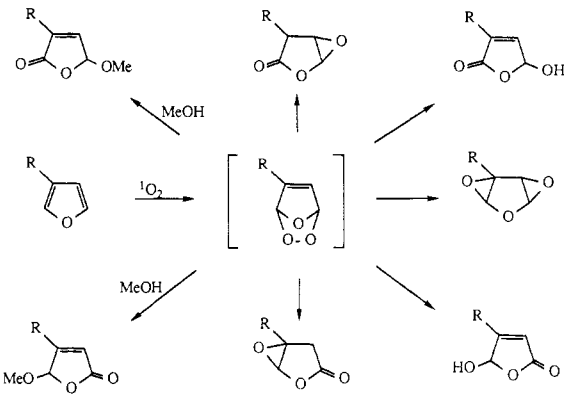
3-Alkyl-4-hydroxybutenolides are synthesized in good to high yields by the oxidation of 3-alkylfurans with singlet oxygen, generated from molecular oxygen with a polymer-bound rose bengal catalyst in dichloromethane solution at −78 °C, in the presence of a hindered base such as 2,2,6,6-tetramethylpiperidine or, preferably, diisopropylethylamine.

The antiinflammatory properties of manoalide (**1**)[1] and luffariellolide (**2**),[2] which are respectively irreversible and reversible inhibitors of the enzyme phospholipase A_2, have caused these and related compounds to become desirable synthetic targets. The common feature of these antiinflammatory agents is the terminal 3-alkyl-4-hydroxybutenolide moiety, which has also been found occasionally in other marine natural products.[3] In contrast with the relatively rare occurrence of the 3-alkyl-4-hydroxybutenolides, their presumed biosynthetic precursors, the 3-alkylfurans, are commonly found as major metabolites of marine sponges.[4] We therefore sought a general method for the regiospecific oxidation of 3-alkylfurans, such as ambliol A (**3**), to obtain the corresponding 3-alkyl-4-hydroxybutenolides (e.g., **6**) for screening as antiinflammatory agents.

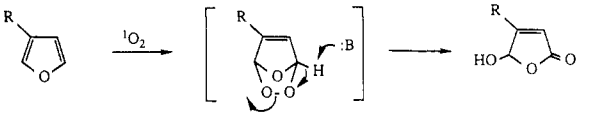


It was known that 3-alkylfurans that were substituted at the 1-position by trimethylsilyl, formyl, or carboxylic acid groups could be oxidized by singlet oxygen to obtain the corresponding 3-alkyl-4-hydroxybutenolides.[5,6] We therefore attempted to prepare a 1-(trimethylsilyl)furan from the sponge metabolite ambliol A (**3**)[7] by treatment with *n*-butyllithium at −78 °C followed by quenching of the lithium derivative with trimethylsilyl chloride but could at best obtain only a 3:1 mixture of the trimethylsilyl derivatives **4** and **5**. As expected, oxidation of the mixture of trimethylsilyl derivatives **4** and **5** with singlet oxygen gave a 3:1 mixture of the 3-alkyl-4-hydroxybutenolide **6** and the 2-alkyl-4-hydroxybutenolide **7**. Other reagents, such as *m*-chloroperbenzoic acid and pyridinium chlorochromate, that had been reported to oxidize furans to the corresponding hydroxybutenolides did not react cleanly with ambliol A(**3**).

Scheme I. Typical Products of $^1O_2$ Oxidation of 3-Alkylfurans



Scheme II. Oxidation of 3-Alkylfurans by $^1O_2$ in the Presence of a Hindered Base



(1) Lombardo, D.; Dennis, E. A. *J. Biol. Chem.* **1984**, *260*, 7234. Glaser, K. B.; Jacobs, R. S. *Biochem. Pharmacol.* **1986**, *35*, 449. Glaser, K. B.; Jacobs, R. S. *Biochem. Pharmacol.* **1987**, *36*, 2079.

(2) Albizati, K. F.; Holman, T.; Faulkner, D. J.; Glaser, K. B.; Jacobs, R. S. *Experientia* **1987**, *43*, 949.

(3) Yunker, M. B.; Scheuer, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 307. Sullivan, B.; Faulkner, D. J. *Tetrahedron Lett.* **1982**, *23*, 907.

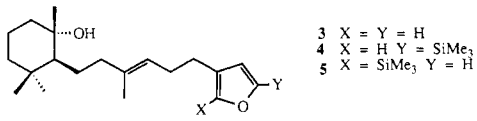
(4) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 551; **1986**, *3*, 1.

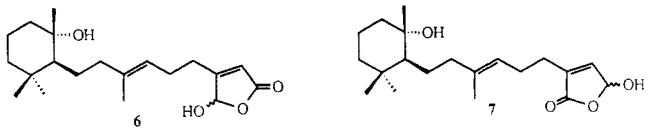
(5) For a recent review, see: Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469.

(6) Tanis, S. P.; Head, D. B. *Tetrahedron Lett.* **1984**, *25*, 4451.

(7) Walker, R. P.; Faulkner, D. J. *J. Org. Chem.* **1981**, *46*, 1098.

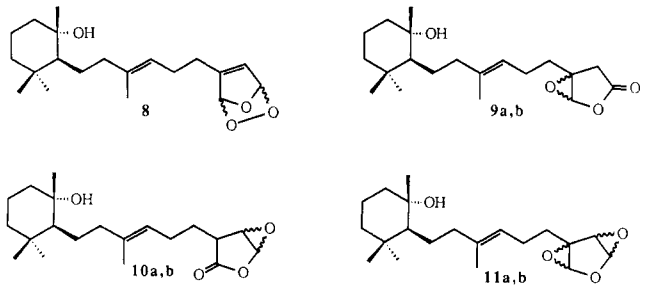
0022-3263/88/1953-2773$01.50/0





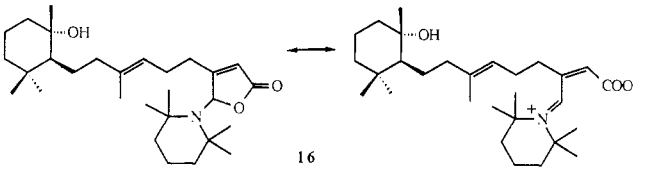
The reaction of singlet oxygen with furans was known to produce many products including 1,3-diepoxides, epoxy lactones, hydroxybutenolides, and, when appropriate, solvent addition products (Scheme I).[5] Most of these products are formed by thermal decomposition of the unstable endoperoxides, exemplified by the endoperoxide mixture **8** from ambliol A (**3**), that result from [4 + 2] addition of singlet oxygen to a 3-alkylfuran. The formation of a 3-alkyl-4-hydroxybutenolide requires the regiospecific removal of the hydrogen at C-1 on the endoperoxide: we reasoned that this could be accomplished by treatment of the endoperoxide with a hindered base at low temperature in order to favor base-catalyzed decomposition rather than thermal decomposition (Scheme II).

In the absence of a base, the reaction of ambliol A (**3**) with singlet oxygen, generated by photolysis of oxygen in the presence of polystyrene-bound rose bengal catalyst, at −78 °C in dichloromethane solution, followed by warming of the reaction mixture to room temperature, gave a mixture of four epoxy lactones **9a,b** and **10a,b** and two *cis*-diepoxides **11a,b**. Although the four epoxy lactones **9a**, **9b**, **10a**, and **10b** and the two *cis*-diepoxides **11a** and **11b** could be separated by LC on Partisil, it was not possible to relate the stereochemistry about the furan ring to that of the remote chiral centers. The structures of compounds **9–11** were elucidated by analysis of spectral data. Upon standing, treatment with acid, or chromatography on silica gel, the epoxy lactones **9a,b** and **10a,b** were converted into the 3-alkyl- and 2-alkyl-4-hydroxybutenolides **6** and **7**, respectively. In a similar manner, the reaction of a dichloromethane solution of ambliofuran (**12**)[7] with singlet oxygen at −78 °C followed by warming to room temperature gave a mixture of the *cis*-diepoxide **13** and two epoxy lactones **14** and **15**.

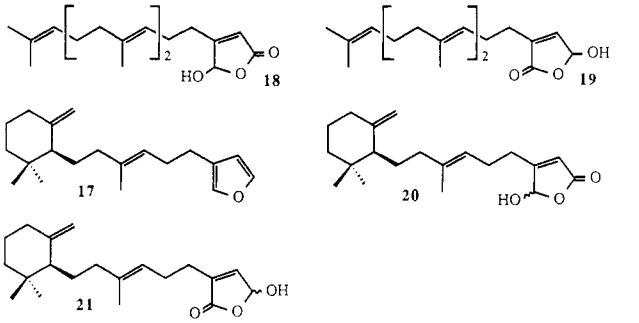


Two strategies for the base-catalyzed decomposition of the intermediate endoperoxides were investigated. In the first procedure, the endoperoxides were prepared as before at −78 °C in dichloromethane solution and 2,2,6,6-tetramethylpiperidine was added to the cold solution. In the second procedure, the substrates were reacted with singlet oxygen at −78 °C in dichloromethane containing diisopropylethylamine. Both procedures gave good to high yields of the required 3-alkyl-4-hydroxybutenolides with little or no contamination by the regioiosmeric 2-alkyl-4-hydroxybutenolides.

In a typical reaction sequence, ambliol A (**3**) was sequentially treated with singlet oxygen in dichloromethane solution at −78 °C followed by 1.5 equiv of 2,2,6,6-tetramethylpiperidine to obtain a single addition product **16** that could be hydrolyzed with dilute hydrochloric acid to obtain the required γ-hydroxybutenolide **6** in 62% overall yield. The precise structure of the intermediate **16** was difficult to define. The infrared spectrum provided evi-



dence for both carboxylic acid [3500–2300 (br), 1672 cm^{-1}] and γ-lactone [1755 cm^{-1}] functionalities while the ^1H and ^{13}C NMR spectra both contained a single set of very broad signals [δ 8.13 (br s, 1 H), 6.29 (br s, 1 H); δ 171.2, 159.3 (br), 137.7 (br), 127.5 (br)] that were consistent with an equilibrium mixture of the γ-amino lactone and the Schiff base. Similar oxidations of ambliofuran (**12**) and 5,18-dehydroambliol A (**17**)[7] gave good yields of the required 3-alkyl-4-hydroxybutenolides **18** and **20**, but they were contaminated with up to 10% of the corresponding 2-alkyl-4-hydroxybutenolides **19** and **21**.



The use of diisopropylethylamine in place of 2,2,6,6-tetramethylpiperidine significantly improved both the regioselectivity and yield of the oxidation reaction. Oxidation of a solution of ambliol A (**3**) in dichloromethane containing diisopropylethylamine with singlet oxygen at −78 °C gave an 80% yield of the required 3-alkyl-4-hydroxybutenolide **6**. By use of the same method, ambliofuran (**12**) and 6,18-dehydroambliol A (**17**) were oxidized to the corresponding 3-alkyl-4-hydroxybutenolides **18** and **20** in 73% and 74% yields, respectively, with no trace of the regioisomeric γ-hydroxybutenolides **19** and **21**. Further examples of the regiospecific oxidation of furans are given in Table I. Even suvanine (**22**),[8] which is a relatively unstable furan, was oxidized to the corresponding γ-hydroxybutenolides **23a,b** in 86% overall yield and the 50% yield of furodysinin lactone **25** obtained from furodysinin (**24**) represents a great improvement over previous procedures.[9] With the exception of the oxidations of ambliol A (**3**) and suvanine (**27**), Table I reports the results of a single experiment for each entry, and no effort has been made to confirm or maximize the yields reported. The products were characterized primarily by ^1H NMR spectroscopy and were immediately submitted for antiinflammatory testing.[12] The results of the antiinflammatory

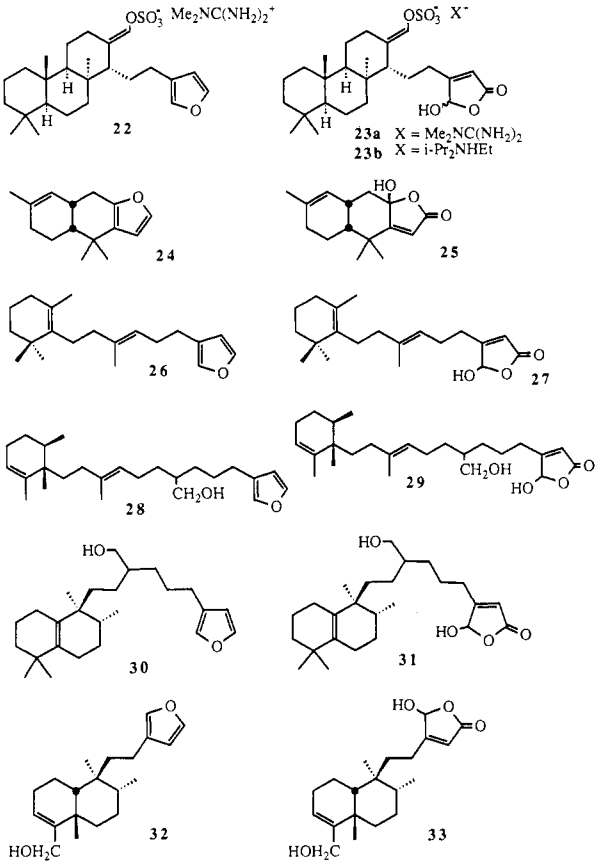
(8) Manes, L. V.; Naylor, S.; Crews, P.; Bakus, G. *J. Org. Chem.* **1985**, *50*, 284. The revised structure is described in: Manes, L. V.; Crews, P.; Kernan, M. R.; Faulkner, D. J.; Fronczek, F. R.; Gandour, R. D. *J. Org. Chem.* **1988**, *53*, 570.

(9) Grode, S. H.; Cardellina, J. H., II *J. Nat. Prod.* **1984**, *47*, 76.

(10) Kernan, M. R. Ph.D. Thesis, University of California, San Diego, 1988. Kernan, M. R.; Faulkner, D. J., manuscript in preparation.

(11) McCrindle, R.; Nakamura, E.; Anderson, A. B. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1590.

assays will be reported in detail elsewhere.[13]



Experimental Section

Preparation and Oxidation of Trimethylsilyl Derivatives of Ambliol A (3). A solution of *n*-butyllithium (106 μL of 1.55 M solution, 0.165 mmol) was added to a cold (−78 °C) solution of ambliol A (**3**, 20 mg, 0.066 mmol) in anhydrous tetrahydrofuran (10 mL) under an atmosphere of dry nitrogen. The reaction mixture was stirred for 1 h at −78 °C after which trimethylsilyl chloride (20.9 μL, 0.165 mmol) was added and stirring at −78 °C was continued for 3 h. Excess *n*-butyllithium was destroyed by careful addition of 2-propanol (1 mL), and the product was partitioned between ether (50 mL) and water (3 × 50 mL). The product was separated by LC on Partisil with hexane as eluant to obtain ambliol A (**3**, 3.0 mg, 15% yield) and a 3:1 mixture (determined by ^{1}H NMR) of 15-(trimethylsilyl)ambliol A (**4**) and 16-(trimethylsilyl)ambliol A (**5**) (19.5 mg, 80% yield).

15-(Trimethylsilyl)ambliol A (4): ^{1}H NMR ($CDCl_3$) δ 7.41 (s, 1 H), 6.51 (s, 1 H), 5.11 (t, 1 H, J = 7 Hz), 1.67 (br s, 3 H), 1.17 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H), 0.24 (s, 9 H).

16-(Trimethylsilyl)ambliol A (5): ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1 H), 6.29 (s, 1 H), 5.11 (t, 1 H, J = 7 Hz), 1.67 (br s, 3 H), 1.17 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H), 0.29 (s, 9 H).

The 3:1 mixtures of silyl derivatives **4** and **5** (2.0 mg) was dissolved in dichloromethane (5 mL) containing polystyrene-bound rose bengal catalyst (1 mg). The stirred solution was irradiated with a 200-W tungsten lamp at 0 °C under an atmosphere of oxygen. After 2 h, the reaction mixture was filtered to remove the catalyst and the solvent was evaporated to obtain a 3:1 mixture of γ-hydroxybutenolides **6** and **7** (2.1 mg, 99% yield), as judged by the ^{1}H NMR spectrum (for data, see below).

Oxidation of Ambliol A (3) Using Singlet Oxygen (a) in Dichloromethane Solution. A solution of ambliol A (**3**, 49.7 mg, 0.15 mmol) in dichloromethane (10 mL) containing polystyrene-bound rose bengal catalyst (1 mg) was stirred at −78 °C under an atmosphere of oxygen and irradiated with a 200-W tungsten incandescent lamp. Aliquots of the reaction mixture were periodically analyzed by TLC until the reaction appeared complete (5 h). The reaction mixture was allowed to warm to 20 °C and filtered through a pad of cotton, and the solvent was evaporated under a vacuum. The products were purified by LC on Partisil with 1:1 ethyl acetate–hexane as eluant to obtain four epoxy lactones **9a** (2.9 mg, 5.2% yield), **9b** (8.1 mg, 14.7% yield), **10a** (2.0 mg, 3.6% yield), and **10b** (1.9 mg, 3.5% yield) and two diepoxides **11a** (1.8 mg, 3.3% yield) and **11b** (1.3 mg, 2.7% yield). On standing at room temperature, the epoxy lactones **9a** or **9b** and **10a** or **10b** rearranged to the γ-hydroxybutenolides **6** and **7**, respectively.

Table I. Oxidation of Furans with Singlet Oxygen in the Presence of Diisopropylethylamine

starting material (wt, mg)	volume: solvent	volume: *i*-Pr_2NEt	product (wt, mg)	% yield
3[7] (20)	5 mL	100 μL	**6** (17.5)	80
12[7] (10)	5 mL	100 μL	**18** (8.5)	73
17[7] (5)	5 mL	100 μL	**20** (4.1)	74
22[7] (28.5)	10 mL	100 μL	**23a** (20.0), **23b** (7.2)	65, 21
24[9] (4.0)	2 mL	10 μL	**25** (2.1)	50
26[7] (5.0)	10 mL	20 μL	**27** (4.7)	85
28[10] (2.0)	2 mL	20 μL	**29** (1.9)	86
30[10] (5.0)	2 mL	20 μL	**31** (4.2)	75
32[11] (5.0)	2 mL	20 μL	**33** (4.3)	78

(b) Treatment with 2,2,6,6-Tetramethylpiperidine. A solution of ambliol A (**3**, 97.1 mg, 0.32 mmol) in dichloromethane (10 mL) was oxidized with singlet oxygen according to method A above, except that, after 4 h, 2,2,6,6-tetramethylpiperidine (150 μL) was added and the mixture was stirred without irradiation for a further 2 h at −78 °C. The reaction mixture was worked up as before to obtain ambliol A (**3**, 17 mg, 17.5% recovery) and an addition product **16** (79.8 mg, 65% yield); oil, IR ($CHCl_3$) 3600–2200 (br), 1755, 1672, 1618, 1560, 1460, 1390 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.13 (br s, 1 H), 6.29 (br s, 1 H), 5.15 (br t, 1 H, J = 10 Hz), 1.63 (br s, 3 H), 1.15 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 159.3 (br), 137.7, 137.6 (br), 127.5 (br), 122.8, 74.2, 56.8 (2 C), 54.3, 43.5, 42.6, 41.6, 36.1, 35.5, 32.8, 28.6 (2 C), 28.4, 25.8, 24.8, 23.4, 21.5, 20.5, 16.9, 16.1; HRMS, m/z 460.3752 (MH^+), $C_{29}H_{50}NO_3$ requires 460.3790.

Hydrochloric acid (1 N, 2 mL) was added to a solution of the addition product **16** (10 mg) in methanol (2 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into water (5 mL), and the aqueous phase was extracted with chloroform (3 × 5 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed, and the residue was purified by LC on Partisil with 1:1 ethyl acetate in hexane as eluant to obtain the γ-hydroxybutenolide (**6**, 6.7 mg, 95% yield, 62% yield from ambliol A).

By use of the same procedure, ambliofuran (**12**, 14 mg) gave two γ-hydroxybutenolides **19** (8.9 mg, 58% yield) and **20** (1.3 mg, 8% yield), and 5,18-dehydroambliol A (**18**, 5.0 mg) gave γ-hydroxybutenolide **20** (4.8 mg, 81% yield) and **22** (0.5 mg, 10% yield).

(c) Treatment with Diisopropylethylamine. A solution of ambliol A (**3**, 20 mg, 0.066 mmol) in dichloromethane (5 mL) containing diisopropylethylamine (100 μL) and polystyrene-bound rose bengal catalyst (1 mg) was irradiated at −78 °C under oxygen. After 2 h the reaction was judged to be complete and was worked up as in method A above to obtain the γ-hydroxybutenolide **6** (17.5 mg, 80% yield). Other examples are given in Table I. The majority of γ-hydroxybutenolides were characterized by ^{1}H NMR spectroscopy only and were immediately used for antiinflammatory assays, the results of which will be reported elsewhere.

15,16-Dihydro-16-hydroxy-15-oxoambliol A (6): IR ($CHCl_3$) 3600–3000 (br), 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.96 (s, 1 H), 5.87 (s, 1 H), 5.18 (br t, 1 H, J = 7 Hz), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 169.3, 138.6, 122.0, 118.0, 99.4, 74.7, 43.3, 42.3, 41.5, 35.6, 32.8, 29.7, 27.7, 23.3, 21.3, 20.4, 16.3; HRMS, m/z 318.2190 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

15,16-Dihydro-15-hydroxy-16-oxoambliol A (7): IR ($CHCl_3$) 3600–3000 (br), 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.83 (s, 1 H), 6.03

(12) We regret that the entire sample of each product was sent for pharmacological screening and that few of the products were properly characterized by elemental analysis or HRMS.

(13) Glaser, K. B.; Jacobs, R. S.; Kernan, M. R.; Faulkner, D. J., manuscript in preparation.

(s, 1 H), 5.11 (br t, 1 H, J = 6 Hz), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); HRMS, m/z 318.2199 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

Epoxy lactones 9a and 9b: IR ($CHCl_3$) 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (s, 1 H), 5.11 (br t, 1 H, J = 6 Hz), 2.83 (d, 1 H, J = 19 Hz), 2.70 (d, 1 H, J = 19 Hz), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); HRMS, m/z 318.2197 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

Epoxy lactones 10a and 10b: IR ($CHCl_3$) 1800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.43 (s, 1 H), 5.11 (br t, 1 H, J = 6 Hz), 2.83 (d, 1 H, J = 19 Hz), 2.70 (d, 1 H, J = 19 Hz), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); HRMS, m/z 318.2199 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

Diepoxide 11a: IR; ^1H NMR ($CDCl_3$) δ 5.59 (s, 1 H), 5.18 (br t, 1 H, J = 6 Hz), 3.81 (s, 1 H), 2.95 (m, 1 H), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); HRMS, m/z 318.2197 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

Diepoxide 11b: ^1H NMR ($CDCl_3$) δ 5.59 (d, 1 H, J = 2 Hz), 5.18 (br t, 1 H, J = 6 Hz), 3.81 (d, 1 H, J = 2 Hz), 2.92 (m, 1 H), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H); HRMS, m/z 318.2197 (M − H_2O), $C_{20}H_{30}O_3$ requires 318.2187.

Diepoxide 12: ^1H NMR ($CDCl_3$) δ 5.48 (d, 1 H, J = 1 Hz), 5.33 (s, 1 H), 5.10 (m, 3 H), 3.58 (d, 1 H, J = 1 Hz), 1.65 (br s, 3 H), 1.60 (br s, 9 H).

Epoxy lactone 14: ^1H NMR ($CDCl_3$) δ 5.14 (s, 1 H), 2.80 (d, 1 H, J = 18 Hz), 2.70 (d, 1 H, J = 18 Hz), 5.10 (m 3 H), 1.65 (br s, 3 H), 1.60 (br s, 9 H).

Epoxy lactone 15: ^1H NMR ($CDCl_3$) δ 5.58 (d, 1 H, J = 1 Hz), 5.10 (m, 3 H), 3.79 (t, 1 H, J = 1 Hz), 2.82 (m, 1 H), 1.65 (br s, 3 H), 1.60 (br s, 9 H).

γ-Hydroxybutenolide 18: ^1H NMR ($CDCl_3$) δ 6.00 (br s, 1 H), 5.84 (br s, 1 H), 5.10 (br t, 3 H), 1.68 (br s, 3 H), 1.65 (br s, 3 H), 1.63 (br s, 6 H).

γ-Hydroxybutenolide 19: ^1H NMR ($CDCl_3$) δ 6.80 (br s, 1 H), 6.04 (br s, 1 H), 5.10 (br t, 3 H), 1.68 (br s, 3 H), 1.65 (br s, 3 H), 1.63 (br s, 6 H).

γ-Hydroxybutenolide 20: ^1H NMR ($CDCl_3$) δ 5.98 (br s, 1 H), 5.87 (br s, 1 H), 5.09 (br t, 1 H, J = 7 Hz), 4.76 (s, 1 H), 4.52 (s, 1 H), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H).

γ-Hydroxybutenolide 21: ^1H NMR ($CDCl_3$) δ 6.78 (br s, 1 H), 6.06 (br s, 1 H), 5.09 (br t, 1 H, J = 7 Hz), 4.77 (s, 1 H), 4.52 (s, 1 H), 1.65 (br s, 3 H), 1.16 (s, 3 H), 0.94 (s, 3 H), 0.82 (s, 3 H).

γ-Hydroxybutenolide 23a: ^1H NMR (DMSO-d_6) δ 7.80 (br s, 2 H, D_2O exchangeable), 7.09 (br s, 2 H, D_2O exchangeable), 6.10 (s, 1 H), 5.96 (s, 2 H), 2.91 (s, 6 H), 0.94 (s, 3 H), 0.81 (s, 6 H), 0.76 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.9, 133.8, 125.1, 101.4, 100.9, 58.7, 53.7, 43.5, 43.3 (2 C), 40.1, 39.0, 35.9 (2 C), 33.9, 26.7, 25.4 23.3, 22.3, 19.9, 18.8, 18.6, 18.2, (DMSO-d_6) δ 171.0 (s), 133.5 (d), 118.5 (s), 116.2 (d), 99.0 (d), 56.7 (d), 51.8 (d), 43.0 (d), 41.6 (t), 38.1 (s), 34.2 (t), 33.2 (q), 26.4 (t), 25.9 (q), 25.3 (s), 23.9 (t), 21.7 (q), 21.6 (t), 19.7 (t), 18.8 (q), 18.3 (t), 18.1 (t), 17.7 (q).

γ-Hydroxybutenolide 23b: ^1H NMR (DMSO-d_6) δ 7.80 (br s, 2 H, D_2O exchangeable), 7.09 (br s, 2 H, D_2O exchangeable), 6.10 (s, 1 H), 5.96 (s, 2 H), 4.08 (dd, 1 H, J = 15.8, 10.8 Hz), 3.53 (m, 1 H), 1.21 (d, 6 H, J = 6.5 Hz), 1.17 (d, 6 H, J = 6.5 Hz), 0.94 (s, 3 H), 0.81 (s, 3 H), 0.81 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 171.0 (s), 133.4 (d), 118.3 (s), 116.1 (d), 99.0 (d), 56.7 (d), 53.4 (d), 51.8 (d), 46.3 (d), 42.9 (d), 41.6 (t), 40.8 (s), 40.7 (s), 39.8 (s), 38.3 (s), 38.1 (s), 34.2 (t), 33.2 (q), 33.0 (s), 26.4 (t), 25.9 (q), 23.9 (t), 21.6 (q), 21.6 (t), 19.6 (t), 18.7 (q, 2 C), 18.3 (t), 18.1 (t), 17.7 (q).

γ-Hydroxybutenolide 27: ^1H NMR ($CDCl_3$) δ 6.00 (br s, 1 H), 5.88 (br s, 1 H), 5.09 (br t, H, J = 7 Hz), 1.67 (br s, 3 H), 1.65 (br, s 3 H), 0.99 (s, 6 H).

γ-Hydroxybutenolide 29: ^1H NMR ($CDCl_3$) δ 5.98 (br s, 1 H), 5.87 (br s, 1 H), 5.28 (br s, 1 H), 5.10 (br t, 1 H, J = 7 Hz), 3.55 (br d, J = 5 Hz), 1.65 (br s, 6 H), 0.88 (d, 3 H, J = 7 Hz), 0.87 (s, 3 H).

γ-Hydroxybutenolide 31: IR ($CDCl_3$) 3600–3000 (br), 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.98 (br s, 1 H), 5.87 (br s, 1 H), 3.55 (br d, 2 H, J = 5 Hz), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.82 (d, 3 H, J = 7 Hz), 0.80 (s, 3 H).

γ-Hydroxybutenolide 33: IR ($CDCl_3$) 3600–3000 (br), 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.01 (br s, 2 H), 5.88 (br s, 1 H), 5.65 (br t, 1 H, J = 6 Hz), 4.20 (m, 2 H), 1.15 (s, 3 H), 0.84 (s, 3 H), 0.78 (d, 3 H, J = 7 Hz).

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Registry No. **3**, 72613-30-0; **4**, 114301-61-0; **5**, 114301-62-1; **6**, 114301-63-2; **7**, 114301-64-3; **9** (isomer 1), 114350-11-7; **9** (isomer 2), 114417-86-6; **10**, 114301-66-5; **11**, 114301-67-6; **12**, 76215-29-7; (±)-**13**, 114301-68-7; (±)-**14**, 114301-69-8; **15**, 114301-70-1; **16** (lactone), 114350-44-6; **16** (iminium carboxylate), 114301-65-4; **17**, 76249-87-1; (±)-**18**, 107581-01-1; (±)-**19**, 114301-71-2; **20**, 114301-72-3; **21**, 114301-73-4; **22**, 94203-53-9; **24a**, 114301-75-6; **23b**, 114301-83-6; **24**, 70546-63-3; **25**, 89837-72-9; **26**, 114301-76-7; (±)-**27**, 114301-77-8; **28**, 114301-78-9; **29**, 114301-79-0; **30**, 114301-80-3; **31**, 114301-81-4; **32**, 54165-66-1; **33**, 114301-82-5.