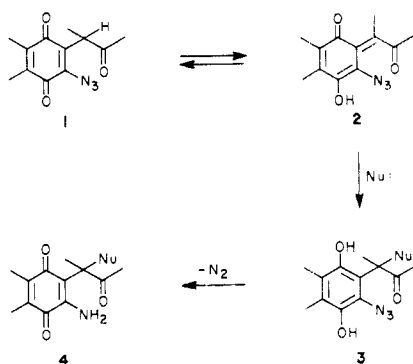
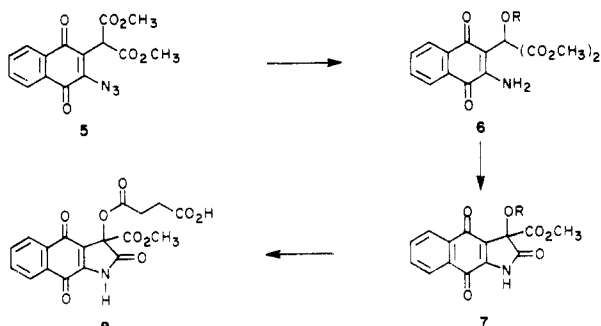


Scheme I

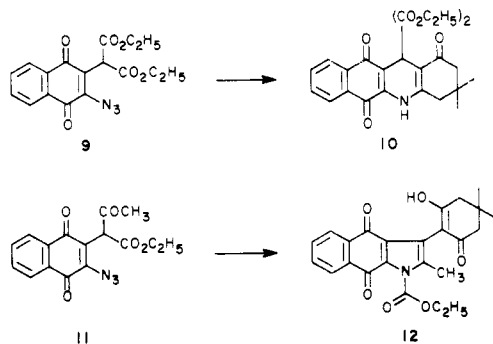


Scheme II



- R
- H
  - CH<sub>3</sub>
  - COCH<sub>3</sub>

Scheme III

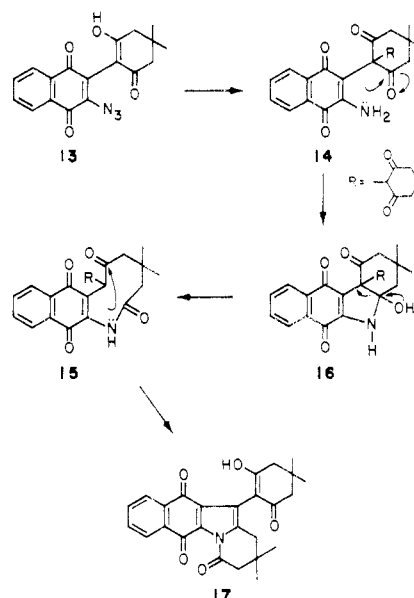


(s, 3 H), 2.46 (d,  $J = 16.0$  Hz, 1 H), 2.68 (d,  $J = 16.0$  Hz, 1 H), 2.75 (s, 2 H), 4.11 (q,  $J = 7.0$  Hz, 2 H), 7.61-7.64 (m, 2 H), 8.06-8.10 (m, 2 H), 10.93 (s, 1 H); MS (CI, M + 1), 422.

The last and most unusual transformation described here was observed when the azidoquinone **13** was treated with dimedone and NaH in THF.<sup>3</sup> In this case, the tetracyclic indoloquinone **17** was realized in 63% yield (Scheme IV): mp 241-242 °C dec; IR (Nujol, cm<sup>-1</sup>) 3432 (w), 1777 (s), 1666 (s), 1696 (s); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.18 (s, 3 H), 1.27 (s, 6 H), 1.43 (s, 3 H), 2.35 (dd,  $J = 13.5$  Hz, 2 H), 2.47-2.72 (m, 6 H), 7.63-7.67 (m, 2 H), 8.05-8.10 (m, 2 H); MS (CI, M + 1), 432. Anal. Found: C, 72.20; H, 5.77.

A mechanistic rationale for the formation of **17** involves the conversion of **13** to **14** which is in analogy to the aminoquinone formation outlined in Scheme I. Subsequent

Scheme IV



transformation of **14** to **17** is an example of "crisscross annelation".<sup>4</sup>

Finally, it is noted that the generalized reaction in Scheme I provides a facile entry to a variety of quinones that meet those structural requirements outlined for bio-reductive alkylating agents.<sup>5</sup> For example, succinylation of **7a** gives **8**, a water-soluble (Na salt) quinone which undergoes an immediate conversion to the desuccinylated quinone upon treatment with sodium dithionite. This transformation most likely involves a quinonemethide intermediate which proceeds to the product upon proton transfer. The biological properties of **8** and related compounds is currently under investigation.

**Acknowledgment.** We thank the National Science Foundation (CHE 80-25567) and the National Institutes of Health (CA 11890) for financial support of this project.

**Supplementary Material Available:** Spectral data for **5-12** and **17** are available (2 pages). Ordering information is given on any current masthead page.

- (4) Oda, K.; Ohmuma, T.; Ban, Y. *J. Org. Chem.* 1984, 49, 953.  
 (5) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* 1981, 1, 249.

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### Limatulone, a Potent Defensive Metabolite of the Intertidal Limpet *Collisella limatula*

**Summary:** The intertidal limpet *Collisella limatula* contains limatulone (**1**), a triterpene consisting of two identical C<sub>15</sub> units, which inhibits fish and crab predation. Limatulone (**1**) is readily oxidized to a monohydroperoxide **2**.

**Sir:** Limpets are marine molluscs that are common to the intertidal zone. Their shells provide physical protection against the harsh environmental conditions that they experience. Among the five most abundant species of limpets along the coast of southern California, *Collisella limatula* is unique in having a chemical defense mechanism that

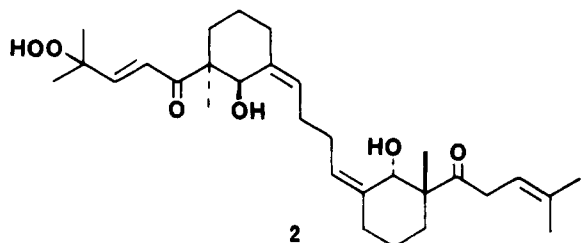
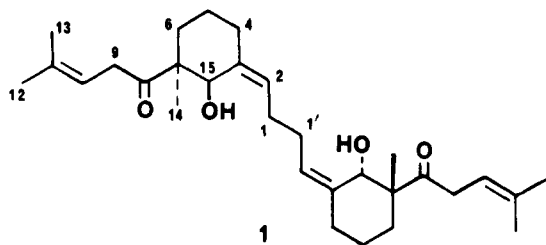
(3) The azidoquinone **13** is very unstable and could not be isolated in pure form. It was thus used directly without attempted purification.

**Table I.** 360-MHz  $^1\text{H}$  NMR Data ( $\text{C}_6\text{D}_6$ ) for Limatulone (1)<sup>a</sup>

H at C	1
1,1'	1.63 (1 H, m)
	2.06 (1 H, m)
2,2'	5.25 (1 H, t, $J = 7$ Hz)
4,4' <sub>ax</sub>	2.54 (1 H, td, $J = 13, 4$ Hz)
4,4' <sub>eq</sub>	1.83 (1 H, brd, $J = 13$ Hz)
5,5' <sub>ax</sub>	1.35 (1 H, m)
5,5' <sub>eq</sub>	1.50 (1 H, m)
6,6' <sub>ax</sub>	2.19 (1 H, td, $J = 13, 4$ Hz)
6,6' <sub>eq</sub>	1.45 (1 H, br d, $J = 13$ Hz)
9,9'	3.18 (2 H, br d, $J = 6.5$ Hz)
10,10'	5.59 (1 H, br t, $J = 6.5$ Hz)
12,12'	1.67 (3 H, br s)
13,13'	1.58 (3 H, br s)
14,14'	0.88 (3 H, s)
15,15'	4.70 (1 H, br s)

<sup>a</sup>Reported as chemical shift (integral, multiplicity, coupling constants)

protects the foot tissue of overturned specimens from predation by fishes and crabs.<sup>1</sup> Hexane and ether extracts of freeze-dried *C. limatula* contain limatulone (1), a very potent feeding inhibitor.



Flash chromatography of the combined hexane and ether extracts of *C. limatula* on silica gel gave a single active fraction<sup>2</sup> that was eluted with ether. Final purification by LC on Partisil using 40% ethyl acetate in hexane gave limatulone (1; 0.19–0.52% dry weight<sup>3</sup>) as a colorless oil. Although limatulone (1) has a molecular formula of  $\text{C}_{30}\text{H}_{46}\text{O}_4$ , the  $^{13}\text{C}$  NMR spectrum<sup>4</sup> contains only 15 signals, indicating that the molecule is comprised of two identical subunits. Each subunit contains a ketone and a secondary hydroxyl group that give rise to IR bands at 1700 and 3500  $\text{cm}^{-1}$ , respectively, and  $^{13}\text{C}$  NMR signals at  $\delta$  215.4 (s) and 70.0 (d), respectively. There are two trisubstituted olefins and therefore one ring in each subunit. Careful analysis of the  $^1\text{H}$  NMR spectrum (Table I) revealed the structure

(1) Details of the ecological study will be presented elsewhere: Pawlik, J. R.; Albizzati, K. F.; Faulkner, D. J., manuscript in preparation.

(2) Bioassays were performed on the intertidal fish *Gibbonsia elegans*.

(3) The yield of limatulone depends on the collecting site.

(4) Limatulone (1):  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  215.4 (s), 137.2 (s), 134.8 (s), 126.5 (d), 116.3 (d), 70.0 (d), 52.3 (s), 36.8 (t), 31.0 (t), 27.6 (t), 26.9 (t), 25.6 (q), 22.2 (t), 18.7 (q), 18.0 (q); HRMS, found  $m/z$  470.3394, calcd for  $\text{C}_{30}\text{H}_{46}\text{O}_4$ , 470.3395.

of limatulone (1). In particular, the coupling constants of the C(4)–C(6) methylene signals required a six-membered ring. On irradiation of the olefinic proton signal at  $\delta$  5.25, the methylene signals at  $\delta$  2.06 and 1.93 appeared as a complex AA'BB' system, indicating that the two subunits were joined at that methylene group. A 2D COSY experiment<sup>5</sup> clearly showed that the olefinic signal at  $\delta$  5.59 was coupled to both vinyl methyl signals and revealed a W coupling between the methyl signal at  $\delta$  0.88 and the axial proton signal at  $\delta$  2.19, indicating that the methyl group at C-7 is axial. Irradiation of the signal at  $\delta$  4.70 caused a NOE enhancement of the signals at  $\delta$  3.18 (4%), 2.06 and 1.93 (9% combined), and 0.88 (5%). These data require an axial alcohol at C-15 and a (2*Z*)-olefinic bond. The latter was confirmed by observing a NOE enhancement of the signal at  $\delta$  1.83 (C-4 equatorial) on irradiation of the olefinic proton signal at  $\delta$  5.25. The proposed structure of limatulone (1) is fully compatible with the  $^{13}\text{C}$  NMR spectrum.

Solutions of limatulone (1) in organic solvents have a relatively short half-life of  $\sim 4$  days at room temperature. The first and only recognizable product is the hydroperoxide 2, the result of an "ene" reaction of limatulone with one molecule of oxygen. The low-resolution mass spectrum of the hydroperoxide 2 showed the expected molecular ion at  $m/z$  502. The UV absorption at 222 nm ( $\epsilon$  14 000) indicated the presence of an  $\alpha,\beta$ -unsaturated ketone. The  $^1\text{H}$  NMR spectrum<sup>6</sup> not only contained signals at  $\delta$  6.67 (d, 1 H,  $J = 15.5$  Hz) and 6.90 (d, 1 H,  $J = 15.5$  Hz) assigned to the olefinic protons of the  $\alpha,\beta$ -unsaturated ketone in one subunit but also contained a signal at  $\delta$  3.21 (br d, 1 H,  $J = 7$  Hz) due to the C-9 methylene group in the unaltered subunit. In addition to two olefinic methyl signals at  $\delta$  1.60 and 1.78, there are two methyl signals at  $\delta$  1.38 and 1.41 due to methyl groups on a carbon atom bearing oxygen. The presence of a hydroperoxide group was confirmed by its ability to liberate iodine from aqueous sodium iodide solution and by the  $^{13}\text{C}$  NMR signal at  $\delta$  81.9, which is 10 ppm downfield from the value of the corresponding carbon in a model alcohol.<sup>7</sup> The hydroperoxide 2 was synthesized in 39% yield by the reaction of a methanolic solution of limatulone (1) with singlet oxygen that was generated by photolysis of oxygen in the presence of rose bengal.

Limatulone (1) is optically inactive and may either be racemic or have internal symmetry. The biosynthesis of limatulone (1) from squalene probably involves oxidation of both subunits of squalene to keto aldehydes which then undergo aldol condensations.

Limatulone (1) is the most potent fish feeding inhibitor that we have encountered and is about an order of magnitude more effective than polygodial.<sup>8</sup> Food pellets containing limatulone at levels of 0.05% dry weight or more induced regurgitation in the intertidal fish *Gibbonsia elegans*, a known limpet predator.<sup>9</sup> Although it is prob-

(5) Bax, A. "Two-Dimensional Nuclear Magnetic Resonance in Liquids"; Delft University Press: Delft, Holland, 1984.

(6) Monohydroperoxide 2:  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.01 (s, 3 H), 1.05 (s, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.60 (br s, 3 H), 1.78 (br s, 3 H), 3.18 (OH), 3.21 (d, 2 H,  $J = 6.5$  Hz), 4.65 (br, s, 1 H), 4.70 (br s, 1 H), 5.30 (br, t, 2 H,  $J = 7$  Hz), 5.41 (br, t, 1 H,  $J = 7$  Hz), 6.67 (d, 1 H,  $J = 15.5$  Hz), 6.90 (d, 1 H,  $J = 15.5$  Hz), 8.37 (OH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  216.0, 205.4, 149.2, 137.1, 137.0, 135.0, 126.7, 126.6, 123.3, 116.0, 81.9, 70.0, 69.8, 52.3, 51.3, 36.9, 31.0, 29.6, 27.7, 27.4, 27.1, 27.0, 25.7, 24.4, 24.1, 22.2, 22.1, 18.8, 18.5, 18.1.

(7) Banaigs, B.; Francisco, C.; Gonzalez, E.; Codomier, L.; Fenical, W. *Tetrahedron Lett.* 1982, 23, 3271.

(8) Nakanishi, K.; Kubo, I. *Isr. J. Chem.* 1977, 16, 28. Cimino, G.; De Rosa, S.; De Stefano, S.; Sodano, G. *Comp. Biochem. Physiol. B: Comp. Biochem.* 1982, 73B, 471. Okuda, R. K.; Scheuer, P. J.; Hochlowski, J. E.; Walker, R. P.; Faulkner, D. J. *J. Org. Chem.* 1983, 48, 1866.

ably not present in the limpet, the hydroperoxide **2** is also a feeding inhibitor of approximately equal potency.

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(9) Mitchell, D. J. *Am. Midl. Nat.* 1953, 49, 862.

## Additions and Corrections

Vol. 48, 1983

**H. Kwart,\* K. A. Wilk, and D. Chatellier.** Verification and Characterization of the E2C Mechanism. The Weak Base Catalyzed Elimination Reaction of  $\beta$ -Phenylethyl Substrates.

Page 757. An erroneous correction factor was used to derive the  $(k_H/k_D)_{\text{corr}}$  values in Table I (see footnote *b* of table); values of  $(k_H/k_D)$  given in Table I are too high by a factor of 0.143/0.102. Revised values of  $(k_H/k_D)$ ,  $[\Delta E_a]_{\text{H}}^{\text{D}}$  and  $A_H/A_D$  are given in Table IV of the paper by Kwart and Wilk (Kwart, H.; Wilk, K. J. *Org. Chem.* 1985, 50, 817).

Vol. 50, 1985

**Richard E. Moore,\* Joseph J. Barchi, Jr., and Giovanni Bartolini.** Use of Borate Complexation in Assigning Relative Stereochemistry of Acyclic Polyhydroxylated Compounds.

Pages 375, 377, 378, and supplementary material. The correct names for compounds **22** and **23** are *meso-glycero-gulo*-heptitol and *D-glycero-D-manno*-heptitol, respectively. We thank Professor S. J. C. Angyal for pointing out these errors.

**Thomas E. Young\* and William Thomas Beidler.** Direct Synthesis of 5-Methyl-3-aryl-1,2,4-oxadiazoles from Aryl Aldehydes, Nitroethane, and Ammonium Acetate.

Page 1182, column 1, line 8. *N'*-Acyl-*N,N*-dimethylamides should read *N'*-acyl-*N,N*-dimethylamidines.

**Mohammad Behforouz,\* Joseph L. Bolan, and Michael S. Flynt.** 2,4-Dinitrophenylhydrazones: A Modified Method for the Preparation of These Derivatives and an Explanation of Previous Conflicting Results.

Page 1187, Table II, entry 2. 2-Butanone should be replaced by 2-pentanone.

Page 1187, Table I, entry 3, last column. 117 should be replaced by 123.

Page 1188. In eq 2 R and H need to be interchanged in all four structures.

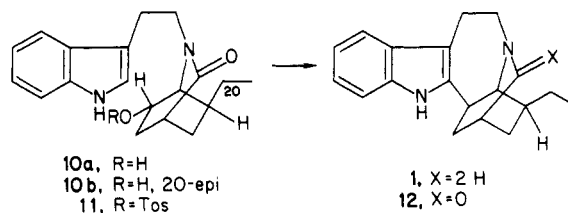
Page 1188, in footnote 23. NMR should be corrected as  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45 (s, 6 H), 1.96 (s, 1 H disappeared with  $\text{D}_2\text{O}$ ),

2.2 (s, 3 H), 2.6 (s, 2 H), 7.8 (d, 1 H,  $J = 10$  Hz), 8.5 (dd, 1 H,  $J = 10$  and 3 Hz), 9 (d, 1 H,  $J = 3$  Hz) and 11.86 (br, 1 H disappeared with  $\text{D}_2\text{O}$ ). Careful NMR studies of the three 2,4-DNPH's described in footnotes 20 and 21 and at the top of page 1189 each showed one additional signal (br, 1 H disappeared with  $\text{D}_2\text{O}$ ) at  $\delta$  10.93, 10.93, and 11.1, respectively.

Page 1189, column 2, line 7 from the bottom. 2-Butanone DNP, 958-60-1, should be replaced by 2-pentanone DNP, 1636-82-4; line 15 from the bottom, 2-butanone, 78-93-3, should be replaced by 2-pentanone, 107-87-9.

**Martin E. Kuehne\* and Paul J. Reider.** A Synthesis of Ibo-gamine.

Page 1465. Structure **10a**, **10b**, **11** and structure **12** have a misplaced carbonyl oxygen. The correct structures are



Page 1466, line 26, should read 3-oxoibogamine not 5-oxoibogamine.

Page 1467, line 30, should read 2-(2-Indol-3-ylethyl)-3-oxo-6-endo-hydroxy-7-ethyl-2-azabicyclo[2.2.2]octanes. Line 53 should read 2-(2-Indol-3-ylethyl)-3-oxo-6-endo-(tosyloxy)-7-exo-ethyl-2-azabicyclo[2.2.2]octane.

**William R. Roush,\* Michael A. Adam, and David J. Harris.** Stereochemistry of Crotylboronate Additions to  $\alpha,\beta$ -Dialkoxy Aldehydes.

Page 2002, column 1, line 1. Structure **5** should be

