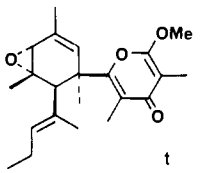
Communications to the Editor

Crispatone, a Metabolite of the Opisthobranch Mollusc *Tridachia crispata*

Sir:

We have recently described the isolation of tridachione (**1**), a propionate-derived metabolite from *Tridachiella diomedea*, a mollusc found in shallow waters of the eastern tropical Pacific.[1] *T. diomedea* belongs to a small group of sacoglossans which contain functional chloroplasts derived from siphonous marine algae.[2] The Caribbean sacoglossan *Tridachia crispata* (Mörch) also contains functional chloroplasts and is found in similar habitats.[3] In this communication, we report the structural elucidation of crispatone (**2**), a major secondary metabolite of *T. crispata*.



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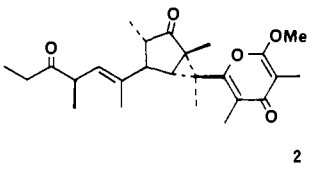

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The ether-soluble fraction of acetone extracts of homogenized *T. crispata* was chromatographed on silica gel to obtain two metabolites, the more polar of which, crispatone (**2**), crystallized from hexane, mp 164.5-166.5 °C (~0.12 mg/animal). Crispatone (**2**), $C_{25}H_{34}O_5$, gave the following spectral data: $[\alpha]_D$ −84.7° (*c* 0.03, $CHCl_3$); IR 1725, 1710, 1660, 1590 cm^{-1}; UV 250 nm (ϵ 6200); ^1H NMR ($CDCl_3$) δ 1.05 (t, 3 H), 1.05 (d, 3 H), 1.18 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 1.24 (s, 3 H), 1.70 (s, 1 H), 1.82 (s, 3 H), 1.83 (s, 3 H), 1.95 (s, 3 H), 2.45 (m, 4 H), 3.48 (m, 1 H), 3.96 (s, 3 H), 5.38 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 216.0 (s), 211.0 (s), 181.1 (s), 162.2 (s), 157.5 (s), 137.0 (s), 126.2 (d), 121.0 (s), 100.0 (s), 55.0 (q), 51.0 (d), 48.8 (d), 45.7 (d), 42.2 (s), 37.4 (d), 33.5 (t), 31.9 (s), 16.6 (q), 15.9 (q), 13.3 (2 q), 11.0 (q), 10.5 (q), 7.8 (q), 6.6 (q). From these data, together with proton decoupling experiments, we could establish the presence of the γ-pyrone ring and the 1,3-dimethyl-1-hexen-4-one side chain. We could deduce that the remaining six nonmethyl carbons were contained in a bicyclic ring system but the lack of coupling in the ^1H NMR spectrum made it impossible to assign a structure on spectral data alone.

The structure of crispatone (**2**) was determined from single-crystal X-ray diffraction data. Crystals of crispatone belonged to the orthorhombic crystal class with a = 8.225 (7), b = 13.518 (13), and c = 22.017 (24) Å. Systematic extinctions, the presence of chirality and an observed and calculated (Z = 4) density of 1.12 g/cm^{-3} indicated space group $P2_12_12_1$ with one molecule of composition $C_{25}H_{34}O_5$ in the asymmetric unit. A total of 1911 unique diffraction maxima were measured on a fully automated four-circle diffractometer using graphite monochromated Cu K_α X-rays (1.54178 Å) and a variable rate ω-scan technique. After correction for Lorentz, polarization, and background effects, 1133 (59%) reflections were judged observed ($F_o^2 \geq 3\sigma(F_o^2)$) and were used in all subsequent calculations. The scattering fell off rapidly at high angles. A preliminary phasing model was arrived at uneventfully using a multiple solution, weighted tangent formula approach.[4] Nonhydrogen atoms were refined anisotropically and hydrogen atoms, located on difference electron density syntheses, were refined isotropically.[5] The standard crystallographic residual is presently 0.074 for the observed reflections.

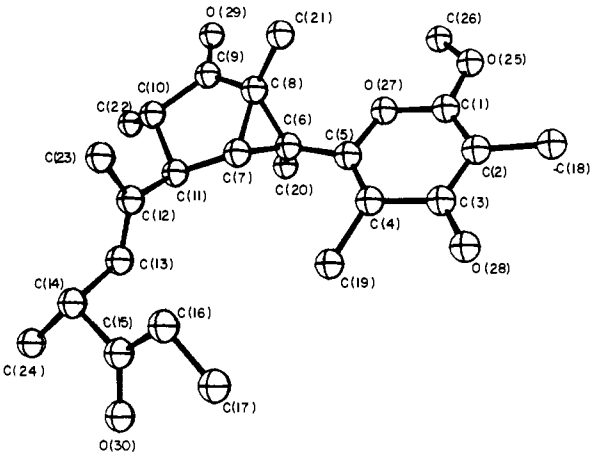

Figure 1. A computer-generated perspective drawing of the X-ray model of crispatone. Hydrogens are omitted for clarity and no absolute configuration is implied.

Figure 1 is a computer-generated drawing of the final X-ray model. The enantiomer depicted is an arbitrary choice since the diffraction experiment did not distinguish enantiomers. The five-membered ring is essentially planar with a mean standard deviation of 0.06 Å. The relative configurations for the asymmetric centers are C(6) (*S**), C(7) (*S**), C(8) (*S**), C(10) (*S**), C(11) (*R**), and C(14) (*R**). Bond distances and angles generally agree well with accepted values and there are no abnormally short intermolecular contacts. Further crystallographic details can be found in the supplementary material.

The carbon skeleton of crispatone (**2**) has not previously been reported. Comparison of the structures of tridachione (**1**) and **2** reveals an additional "propionate" unit in **2** suggesting that both molecules were formed by cyclizations of "polypropionate" molecules of seven and eight units, respectively. The relationship between the ring systems has been established and is discussed elsewhere.[6]

The structural similarities and differences between **1** and **2** do not help to define whether these metabolites are produced by the molluscs, the chloroplasts, or a symbiotic combination of chloroplasts and molluscs. A dietary source[7] of these compounds appears unlikely since the same compounds are found in the animals wherever they have been collected.

Acknowledgments. The molluscs were collected during a cruise on R/V Alpha Helix, supported by the National Science Foundation (OCE 76-80874). This research was supported by a grant from the National Science Foundation (PCM 72-02539). The NMR Facility at the Chemistry Department, University of California—San Diego, was supported by a grant from the National Institutes of Health (RR-00708).

Supplementary Material Available: Fractional coordinates (Table 1), important bond distances (Table 2), important bond angles (Table 3), and observed and calculated structure factors (Table 4) (9 pages). Ordering information is given on any current masthead page.

References and Notes

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(8) Camille and Henry Dreyfus Teacher-Scholar Grant Awardee, 1972-1977 (J.C.).

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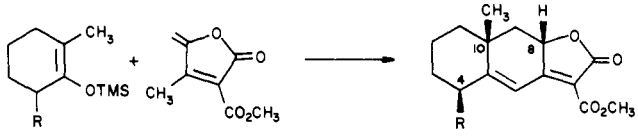
Synthesis of *dl*-7,8-Epialantolactone. A Tandem S_N2' Dehydrobromination–Organocuprate Addition Exemplified

Sir:

The development of methods for total synthesis of the α-methylene-γ-butyrolactones continues to be a vigorous and productive area of research. Recently, we reported an annelation approach to certain eudesmane and elemane sesquiterpenes, in which the 1,6-annelation reagent **2** is used in construction of the linear tricyclic lactone **3a**.[1]

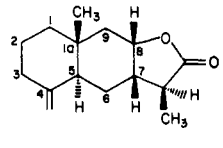


1a, R = H
b, R = CH_3

2

3a, R = H
b, R = CH_3
c, R = Br

The relative stereochemistry at C(8) and C(10) in **3** is identical with that present in dihydrocallitrisin (**4**), a new sesquiterpene lactone isolated from the heartwood of *Callitris columellaris*.[2] This configuration is rare and differs from that found in the more common eudesmane sesquiterpenes such as alantolactone (**5**).[3] Herein, we establish the flexibility of our approach to these sesquiterpenes by reporting the synthesis of *dl*-7,8-epialantolactone (**9**). In a future report, we will present the first total synthesis of *dl*-dihydrocallitrisin (**4**).



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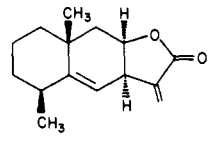

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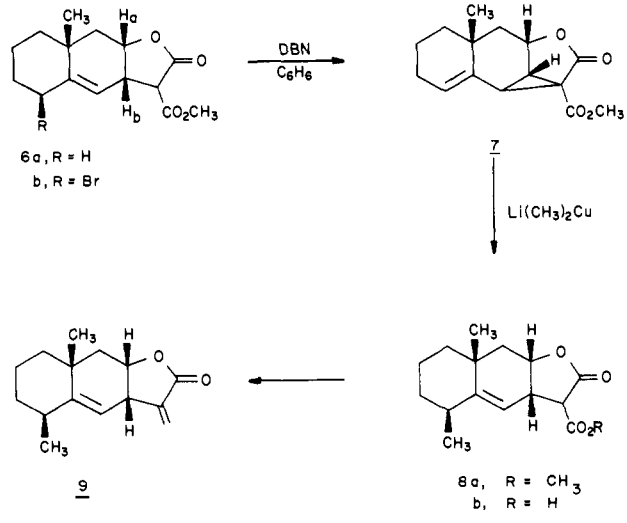
An obvious albeit stereochemically perilous approach to **9** would involve the diene lactone **3b**. To this end, **2** was reacted[1] with silyl enol ether **1b** to give the keto lactone resulting from 1,6 addition to **2**; however, this keto lactone resisted all attempts at cyclization to **3b**. A conceptually superior route to **9** was at hand when we discovered that **3a** undergoes selective bromination at C(4) with *N*-bromosuccimide[4] in refluxing carbon tetrachloride to give bromo diene **3c** (99% yield; mp 118-119 °C dec).[5]

Conjugate reduction of alkylidenemalonic esters has been performed with a variety of metal hydrides.[6] The instability of bromo diene **3c** to base suggested the use of sodium cyanobrohydride in acidic medium and we were delighted to find that bromo diene **3c** reacts with sodium cyanoborohydride in THF-ethanolic hydrogen chloride (3:1) to give allylic bromide **6b** in 97% yield (mp 121-122 °C dec; IR 5.62, 5.75 μ). Diene lactone **3a** also undergoes conjugate reduction to give **6a** (mp 92-94 °C) suggesting that this technique will be generally useful in preparation of cis-fused γ-butyrolactones from fused ring α-carboalkoxy-α,β-butenolides.

That the stereochemistry at the lactone fusion in **6a** and **6b** is as shown rests on ^1H NMR spectral data and inferential crystallographic analysis of **9** (vide infra). Thus, the vicinal coupling constant $J_{a,b}$ for **6a** and **6b** is 7.5 Hz, which strongly suggests the presence of a cis-lactone fusion in these intermediates.[7] Stereochemistry at C(4) follows from comparison of chemical shift data for the C(10) methyl group in **6a** (δ 1.12) and **6b** (1.46); the dramatic downfield shift of the angular methyl resonance in **6b** relative to that in **6a** must be a result of deshielding by the axial bromine atom.

Treatment of **6b** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in benzene solution at room temperature (1 h) results in an internal S_N2'-like displacement of bromide ion from the enolate of **6b** to give vinylcyclopropane **7**[8] in 95% isolated yield (mp 113-114 °C; IR 5.65, 5.79 μ; electron impact mass spectrum, *m/e* 262).



6a, R = H
b, R = Br

7

9

8a, R = CH_3
b, R = H

Activated vinylcyclopropanes undergo homoconjugate and vinylogous homoconjugate addition depending on the nature of the reagent used; with lithium dialkylcuprates, exclusive 1,7 addition has been observed.[9] Addition of lithium dimethylcuprate to vinylcyclopropane **7** (ether solution, −20 to −5 °C, 40 min) gives the desired 1,7-addition product **8a** in 75% yield. Conversion of **8a** to *dl*-7,8-epialantolactone (**9**) is accomplished by hydrolysis to the lactone acid **8b** (aqueous-methanolic sodium hydroxide followed by acidification) and α-methylenation[10] of **8b**: (1) formalin-diethylamine, (2) sodium acetate-acetic acid. The structure of **9** thus obtained (70% yield; mp 109-110 °C; IR 5.69 μ) was firmly established by crystallographic study.

Suitable crystals of **9** were grown from an EtOAc-hexane solution and belonged to the monoclinic crystal class. Accurate cell constants, determined by a least-squares fitting of 15 moderate 2θ values, were a = 10.592 (2), b = 12.650 (2), c =

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