Biomimetic Synthesis of a Cyclopropane Containing Eicosanoid from the Coral *Plexaura homomalla*. Assignment of Relative Configuration

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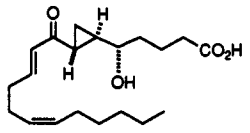
The arachidonic acid (AA) pathway in marine organisms has been found to produce, in addition to metabolites of the prostanoid family,[1] C_{20} cyclopropanes which invariably contain sites of oxygenation adjacent to the three-membered ring.[2] A singular example is **1**, isolated from incubation of AA with an acetone powder of the Caribbean soft coral *Plexaura homomalla* and characterized as the δ-lactone **2**.[3] The latter is clearly related to



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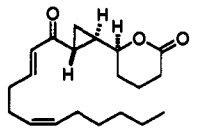

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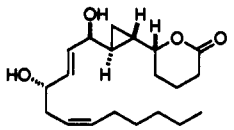

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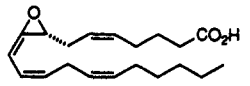

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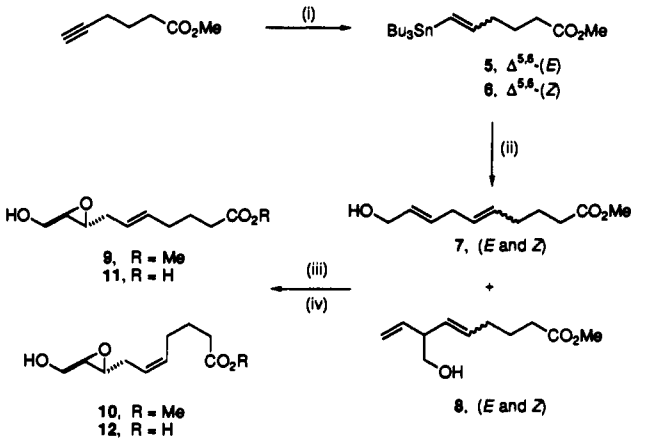
the constanalactones, e.g., **3**, which occur in the red alga *Constantinea simplex*.[4] A unifying biogenetic hypothesis accommodating **1** and the 5,6-trans prostanoids present in *P. homomalla* has been proposed on the basis of the allene oxide **4**.[3,5] This epoxide, presumably formed via an (8*R*)-lipoxygenase pathway, was originally put forward by Corey as a key intermediate in the biosynthesis of preclavulone A from 8-(*R*)-HPETE in *P. homomalla*[6] and has been isolated by Brash from an acetone powder of the coral.[7] The biogenetic pathway from **4** to **1** postulates that epoxide opening triggers carbocyclization to a cyclopropyl carbinyl cation which is followed by trapping of the carbocation by the terminal carboxyl group or water. We describe on the basis of this precept a synthesis of **1** via **2** which features construction of the cyclopropyl lactone moiety and which unambiguously defines its relative configuration as shown.

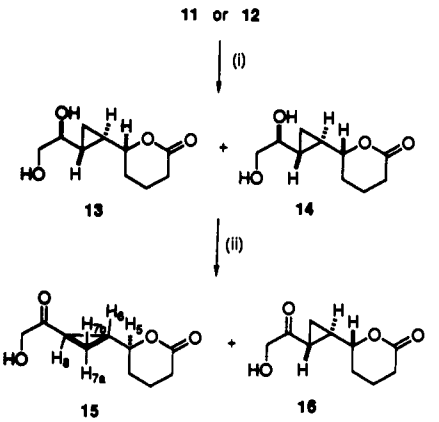
Hydrostannylation of methyl 5-hexynoate gave an inseparable 4:1 mixture of (*E*)- and (*Z*)-vinylstannanes **5** and **6**,[8] respectively. When this mixture was treated with butadiene monoepoxide in the presence of a palladium catalyst,[9] the 1,4- and 1,2-addition products **7** and **8** were obtained in a 4:1 ratio. As expected, only the major isomer **7** underwent Katsuki-Sharpless epoxidation[10] and, with (−)-tartrate as the catalyst, afforded (*E*) and (*Z*) olefins **9** and **10**, respectively. These were readily separated by radial chromatography on silica impregnated with 4% silver nitrate, and the pure geometrical isomers were saponified to give carboxylic acids **11** and **12** (Scheme I).

Scheme I [a]



[a] (i) *n*-Bu_3SnH, AIBN, 65 °C (85%); (ii) butadiene monoepoxide, $PdCl_2(MeCN)_2$, DMF–H_2O (93%); (iii) *t*-BuOOH, $Ti(OiPr)_4$, (−)-diethyl tartrate, CH_2Cl_2 (91%); (iv) LiOH, THF–H_2O, 1.5 h, 0 °C (99%).

Scheme II [a]



[a] (i) $SnCl_4$, $MeNO_2$, 1.5 h, 0 °C (54% from **11**, 44% from **12**); (ii) Br_2, $(n\text{-}Bu_3Sn)_2O$, CH_2Cl_2, 1.5 h (58–64%).

The key cyclization was carried out separately on **11** and **12** with essentially identical results (Scheme II). A solution of stannic chloride in nitromethane[11] yielded a ca. 1.5:1 mixture of cyclopropanes **13** and **14** in each case. These unstable diols were converted by selective oxidation of the secondary alcohol[12] to α-hydroxy ketones **15** and **16**, which were separated by radial chromatography. Careful examination of the ^1H NMR spectrum of the major ketone **15** by means of a phase-sensitive COSY experiment[13] permitted assignment of chemical shifts and coupling constants to the cyclopropane protons, as shown in Table I. This analysis connected each of the geminal protons H_{7a} and H_{7b} to

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(11) These conditions, patterned on van Tamelen's studies of the cyclization of squalene oxide (van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc.* **1972**, *94*, 8225), were notably more successful than many others investigated.

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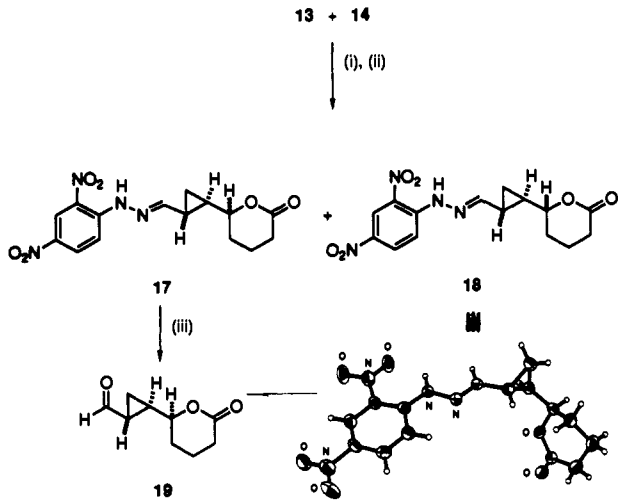
Table I. Chemical Shifts and Coupling Constants of Cyclopropane Protons in **15** and **2**[a]

compd	proton	chemical shift (ppm)	coupling constant (Hz)
15	H_6	1.90	H_6, H_{7a} 4.6; H_6, H_{7b} 8.3
15	H_{7a}	1.11	H_{7a}, H_{7b} 4.3; H_{7a}, H_8 9.2
15	H_{7b}	1.41	H_{7b}, H_8 6.5
15	H_8	2.05	
2	H_6	1.64–1.74	H_6, H_{7a} 6.1
2	H_{7a}	0.91–1.00	H_{7a}, H_{7b} 3.8; H_{7a}, H_8 8.2
2	H_{7b}	1.22–1.31	
2	H_8	2.25–2.33	

[a] Data from ref 3.

Scheme III [a]

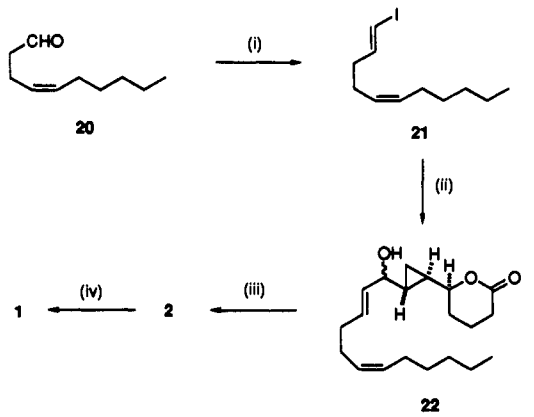


[a] (i) $NaIO_4$, Et_2O–H_2O (91%); (ii) 2,4-dinitrophenylhydrazine, EtOH (92%); (iii) O_3, EtOAc, then Me_2S (61%).

H_6 and H_8, showing that the latter were cis to different geminal protons and thereby specifying a trans orientation of the substituents at the cyclopropane of **15**.[14] The configuration at C_5 could not be determined spectroscopically, and for this purpose each diol, **13** and **14**, was subjected to oxidative cleavage with periodate[15] and the resulting aldehydes were converted to crystalline 2,4-dinitrophenylhydrazones **17** and **18**. The latter upon X-ray analysis was found to possess the relative configuration shown in Scheme III. Thus, both cyclization products **13** and **14** contain a trans cyclopropane and differ only with respect to the stereogenic center at the δ-lactone.

The pure aldehyde **19**, whose spectroscopic properties accorded well with those of **2**,[3] was most conveniently obtained by medium-pressure liquid chromatographic separation of **17** and **18**, followed by ozonolysis of the former. This aldehyde was then advanced toward **2** by coupling with a segment representing the C_{10}–C_{20} portion of the eicosanoid structure (Scheme IV). For this purpose, (*Z*)-dec-4-enal (**20**) was converted to (1*E*,5*Z*)-1-iodoundecene (**21**) by reaction with iodoform in the presence of chromium(II) chloride.[16] Coupling of **19** with **21** was carried out with chromium(II) chloride in the presence of a catalytic amount of nickel(II) chloride[17] and yielded a 1:1 mixture of stereoisomeric alcohols **22**. The mixture was oxidized with the Dess–Martin periodinane[18] to give **2**, which possessed spectral properties identical to those reported by Brash.[3] A final saponification of **2** yielded **1**, which relactonized to **2** in the presence of mineral acid or upon standing in $CDCl_3$. Naturally derived **1**, in contrast to **3**,[4] is reported to be racemic and thus leaves the absolute configuration of other members of this eicosanoid series in doubt. However, further studies to be reported[19] indicate that optically active members of this family are antipodal to **1**.

Scheme IV [a]



[a] (i) CHI_3, $CrCl_2$, THF (95%); (ii) $CrCl_2$, $NiCl_2$ (catalyst), **19**, DMF (61%); (iii) periodinane, CH_2Cl_2 (84%); (iv) LiOH, THF–H_2O (96%).

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Supplementary Material Available: Physical and spectroscopic data for **1**, **2**, **5**–**15**, **17**–**19**, **21**, and **22**; tables of crystal data and details of the structure determination of **18**, including atomic coordinates, thermal parameters, bond lengths, and bond angles (11 pages); listing of observed and calculated structure factors for **18** (16 pages). Ordering information is given on any current masthead page.

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