reaction of **22** with 15 equiv of trimethylsilyl cyanide (Aldrich Co.) and 20 equiv of titanium tetrachloride[14] (both freshly distilled) in CH_2Cl_2 at 23 °C for 3.5 h produced a mixture of four diastereomeric isocyanides (70% total yield) which were separated by thin-layer sg chromatography into the following components: diaxial diisocyanide (30%, least polar), diequatorial diisocyanide (15%, most polar), and a mixture of axial–equatorial diisocyanides (55%, intermediate polarity). The two axial–equatorial diisocyanides were separated by HPLC on a Waters Co. 5-μm spherical silica column using 96:4 hexane–*tert*-butyl methyl ether to give 7,20-diisocyanoadociane (**1**) and the less polar 7,20-bis-epi-diisocyanoadociane. Synthetic **1** so obtained was identical with authentic samples[15] by HPLC, sg TLC, 500-MHz ^1H NMR, infrared, and mass spectral comparison. The synthetic material had $[\alpha]^{23}_D$ +23.0° (*c* 0.27, $CHCl_3$) as compared to $[\alpha]^{23}_D$ +47.8° (*c* 0.23, $CHCl_3$) measured for the reference sample of naturally derived 7,20-diisocyanoadociane, a result in accord with the observed ca. 60% enantiomeric excess determined for the Michael product **4**, the first chiral intermediate. Since the absolute configuration of **4** (excess enantiomer) follows from the method of synthesis, the previously unknown absolute configuration of natural 7,20-diisocyanoadociane can now be defined as in **1**.

The simultaneous introduction of the two isocyano groups in this synthesis of **1** has the advantage of shortening the pathway of synthesis and also making available the various diastereomers of **1** as reference compounds. It is possible to adjust the synthetic scheme for separate introduction of the isocyanide groups with control of stereochemistry, such methodology having been developed in these laboratories.[16,17]

Supplementary Material Available: ^1H NMR, IR, UV, and mass spectral data for compounds **1–22** and for the 7,20-diastereomers of **1** (10 pages). Ordering information is given on any current masthead page.

(14) Sasaki, et al. (Sasaki, T.; Nakanishi, A.; Ohno, M. *J. Org. Chem.* **1981**, *46*, 5445) report a similar conversion of adamantyl chloride to the corresponding isocyanide.

(15) We are grateful to Drs. R. J. Wells and M. J. Garson for generously providing reference samples of native 7,20-diisocyanoadociane.

(16) Unpublished work of M. Ishiguro and A. Ghosh.

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Intermediacy of 8-(*R*)-HPETE in the Conversion of Arachidonic Acid to Pre-Clavulone A by *Clavularia viridis*. Implications for the Biosynthesis of Marine Prostanoids

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Among the most surprising developments in the field of organic natural products in recent years was the discovery that a marine organism, the soft coral *Plexaura homomalla*, produces large amounts (ca. 1.8% of dry weight) of prostaglandin A_2 methyl ester acetate (**1**) or the 15-epimer (depending on subspecies).[1] Also unexpected was the finding that the biosynthesis of this substance in coral proceeds by a pathway which differs from that for formation of prostaglandins (PG's) in mammals (endoperoxide pathway).[2] Because of severe practical difficulties associated with biosynthetic research using *Plexaura homomalla*, progress in defining the biosynthetic pathway has been slow.[3] Recently, however, another family of prostanoids, the clavulones (exemplified by clavulone I, **2**), has been identified from the Okinawan soft coral *Clavularia viridis*,[4] which has proved to be much more amenable to biosynthetic studies.[5] It was shown by radiotracer experiments that a homogenate of *C. viridis* is able to convert arachidonic acid to a new eicosanoid, **3** (termed pre-clavulone A), which seems likely to be an intermediate on the pathway to **2**.[5] Because of the structural similarity of **3** and the plant regulator *cis*-jasmonic acid, it was suggested that the biosyntheses of these substances may be closely related and may involve pericyclic ring closure of a 2-oxidopentadienyl cation.[6] Strong evidence for this surmise is reported herein. A logical possibility for the biosynthesis of PGA_2 methyl ester acetate in *P. homomalla* is now apparent.

Incubation of arachidonic acid (2–3 mM) with an acetone powder[7] from *C. viridis* (7 mg/mL) for 1 h at 24 °C in 100 mM Tris buffer at pH 8.0 provided a more polar compound determined to be 8(*R*)-hydroperoxy-5,11,14(*Z*),9(*E*)-eicosatetraenoic acid (8(*R*)-HPETE),[8] in yields as high at 19% (remainder mainly arachidonic acid). Identification was made by comparison with authentic samples of (±)-8-HPETE[9] and, following reduction, of (±)-8-HETE (HPLC, IR, ^1H NMR, MS), and determination of absolute configuration.[10]

Neither arachidonic acid nor 8-HPETE was converted by acetone powder[7] or homogenate preparations[5,11] from *C. viridis*

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(3) These difficulties include, in addition to the obvious geographical problems, the extreme instabilty of enzyme preparations from *P. homomalla* and the self degradation of this coral even at −78 °C.

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(7) The coral was collected off Ishigaki Island and kept at −78 °C until use. An acetone powder was prepared by homogenizing ca. 5 g of frozen coral in 250 mL of acetone at −20 °C. The milky suspension was decanted from residual skeletal matter and filtered with suction. The resulting off-white powder was washed with acetone and ether, then air dried, and used immediately. A sample of the acetone powder which was stored overnight at −20 °C was completely inactive.

(8) Recently it has been reported that arachidonic acid is converted to 8(*R*)-HPETE in the gorgonian coral *Pseudoplexaura porosa*: Bundy, G. L.; Nidy, E. G.; Epps, D. E.; Mizsak, S. A.; Wnuk, R. J., *J. Biol. Chem.* **1986**, *261*, 747.

(9) Porter, N. A.; Logan, J.; Kontoyiannidou, V. *J. Org. Chem.* **1979**, *44*, 3177.

(10) The absolute configuration of 8-HPETE was determined by correlation with (*S*)-malic acid by the following sequence: (1) conversion to 8-HPETE methyl ester (CH_2N_2 in ether); (2) reduction (trimethyl phosphite in benzene at 25 °C for 10 min); (3) esterification with (−)-menthyl chloroformate in pyridine–methylene chloride containing 4-(dimethylamino)pyridine; (4) ozonolysis (O_3, CH_2Cl_2, −78 °C, 5 min) followed by oxidative treatment with peroxyacetic acid for 18 h at 20 °C; (5) esterification (CH_2N_2 in ether). The resulting *O*-menthyl carbonate derivative of methyl malate was compared by gas chromatography[8] with authentic standards prepared from (*S*)-malic acid and racemic malic acid. The coral-derived compound coeluted with the slower *R* standard indicating that the 8-HPETE from coral possesses the *R* configuration.

(11) A homogenate of *C. viridis* was prepared by blending ca. 5 g of frozen coral in 75 mL of 100 mM Tris buffer, pH 8.0, in a Waring blender for 1 min. at ca. 5 °C. The tan supernatant was used directly.

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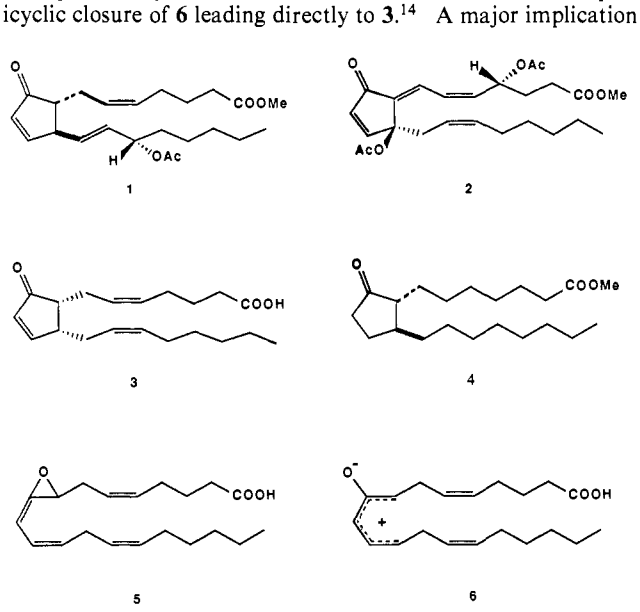
to any of the clavulones. However, when ^{3}H-8(*R*)-HPETE[12] (19 μM) was incubated with a coral homogenate[11] a product was obtained in up to 13% radiochemical yield after diazomethane esterification and HPLC[13] separation. Although the product coeluted with 8-HPETE methyl ester by HPLC,[13] it was clearly different since it did not undergo reduction or change upon exposure to trimethyl phosphite. The structure of this compound was established as **3** by HPLC comparison with authentic biosynthetic pre-clavulone A[5] and, after epimerization (1,8-diazabicyclo[5.4.0]undec-7-ene, THF), with synthetic 8-*epi*-pre-clavulone A.[5] Additionally, catalytic hydrogenation of the methylated coral product followed by epimerization provided 9-oxoprostanoic acid (**4**) indistinguishable from material prepared by the catalytic hydrogenation (Pd-C catalyst) of prostaglandin A_2 methyl ester acetate (**1**).

The data outlined herein establish the intermediacy of 8-(*R*)-HPETE in the biosynthesis of preclavulone A (**3**) from arachidonic acid. During the biosynthesis of **3**, oxygen must migrate from C(8) to C(9) in a situation paralleling that which occurs in the biosynthesis of *cis*-jasmonic acid.[6] It seems likely that the conversion of 8(*R*)-HPETE to **3** occurs via allene oxide **5** and oxidopentadienyl cation **6** intermediates,[6] with antarafacial pericyclic closure of **6** leading directly to **3**.[14] A major implication



of these results is that the biosynthesis of prostaglandin methyl ester acetate (**1**) in *Plexaura homomalla* may proceed in an analogous manner: arachidonic acid → 8,15-bis-HPETE → allene oxide → oxidopentadienyl cation → PGA_2. Experiments to test this proposal for the biosynthesis of PG's by *P. homomalla* are in progress. Further, it remains to continue the study of clavulone biosynthesis using fresh (rather than frozen) coral in order to obtain more information regarding the last stages of biosynthesis.[15]

(12) ^{3}H-8(*R*)-HPETE was prepared by incubation of commercial [5,6,8,9,11,12,14,15-$^3H_8$]arachidonic acid (specific activity 83.6 Ci/mmol, 20 μCi) and unlabeled arachidonic acid (1 mg) with 50 mg of *C. viridis* acetone powder in 2.0 mL of 100 mM Tris buffer pH 8.0 for 1 h. The product was purified by thin-layer chromatography (ether/hexane/acetic acid, 50:50:1) at 0 °C and used immediately (the tritiated 8-HPETE was much less stable than the unlabeled 8-HPETE). This provided 8-HPETE with a specific activity of 6.08 Ci/mol. Reduction of this material with $(MeO)_3P$ followed by HPLC analysis (radioactivity detection) established that this 8-HPETE preparation was uncontaminated by pre-clavulone A.

(13) A retention time of 8.5 min was found by using a Zorbaz Sil 4.6 mm × 25 cm column (Du Pont), hexane-THF (15:1), flow rate 2.0 mL/min.

(14) Studies of the biomimetic synthesis of the pre-clavulone A system via allene oxide and oxidopentadienyl cation intermediates have shown the feasibility of this chemical route to prostanoids (Ritter, K.; Yus, M.; Nājera, C.; Corey, E. J., unpublished results). See also: Malacria, M.; Roumestant, M. L. *Tetrahedron Lett.* **1977**, *33*, 2813.

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Insertion of Carbon Dioxide into Metal Alkoxide Bonds. Synthesis and Structure of Tungsten Tetracarbonyl Carbonate

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Mechanistic aspects of insertion reactions of carbon dioxide into M-R bonds (R = H, alkyl, or aryl) have received and warranted much attention.[2] Contrastingly, much less effort has been expended on the analogous insertion reactions of CO_2 into M-OR bonds.[3] In a series of studies involving the reactivity of the recently synthesized tungsten pentacarbonyl aryl oxide complexes, $W(CO)_5OR^-$ (R = Ph, $C_6H_4CH_3$-*m*), we have found that reaction with CO_2 occurs quite readily, forming the tungsten pentacarbonyl aryl carbonate species (eq 1). Hydrolysis of these

$$W(CO)_5OR^- + CO_2 \rightarrow W(CO)_5OC(O)OR^- \quad (1)$$

metal aryl carbonates, accompanied by loss of a carbon monoxide ligand, leads to formation of the tungsten tetracarbonyl η^2-carbonate dianion, $W(CO)_4(\eta^2\text{-}CO_3)^{2-}$. The assignment of the structure of this complex has been established by X-ray crystallography.

The complexes $[Et_4N][W(CO)_5OR]$[4] were prepared from the reaction of $W(CO)_5THF$ (obtained by photolysis of $W(CO)_6$ in tetrahydrofuran) with the corresponding salts, $[Et_4N][OR]$.[5] In solution, $W(CO)_5OR^-$ is extremely CO labile, decomposing readily to $W_4(CO)_{12}(\mu_3\text{-}OR)_4^{4-}$ in the absence of a CO atmosphere. These tetrameric species have been independently synthesized from $W(CO)_3(CH_3CN)_3$ and $[Et_4N][OR]$ and were shown via IR and ^{13}C NMR to be structurally analogous to the well-characterized chromium tetramers.[5,6] Isolation of the mononuclear complex was only accomplished by crystallization from carbon monoxide saturated solutions. The $[Et_4N][W(CO)_5OR]$ complexes are yellow-orange air and moisture sensitive solids.

Treatment of bright orange THF or acetone solutions of $[Et_4N][W(CO)_5OR]$ with CO_2 ($P_{CO_2} < 760$ mm) at ambient temperature or lower results in increases in the ν(CO) frequencies.[7] This is due to CO_2 insertion into the W-OR bond, producing $W(CO)_5OC(O)OR^-$, the tungsten pentacarbonyl aryl carbonate. This complex has been characterized by IR spectroscopy and ^{1}H and ^{13}C NMR spectroscopies.[8] The addition of small quantities

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(7) For example, the ν(CO) bands due to $W(CO)_5OPh^-$ (2057 (w), 1903 (s), and 1852 (m)) shift to 2063 (w), 1910 (s), and 1854 (m) cm^{-1}. This reaction provides enhanced yields if performed in the presence of some carbon monoxide (preventing decomposition of the tungsten pentacarbonyl alkoxide to the tetramer, which precipitates from the solution). However, large excesses of CO will cause displacement of the aryl carbonate ligand, alternatively reducing yields.

(8) $[Et_4N][W(CO)_5O_2COPh]$: ^{1}H NMR (CD_3CN) (cation) δ 3.22 (q, CH_2), 1.186 (t, CH_3), (anion) 6.51-7.23 (m, C_6H_5); ^{13}C NMR (CD_3CN) (cation) δ 52.91 (CH_2), 7.55 (CH_3), (anion) δ 159.8 (O_2COPh, identified by using $^{13}CO_2$ in synthesis), 108.8, 116.6, 129.9, 155.9 (C_6H_5).

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