cyclopentadiene regioisomer, C(H)($CO_2CH_2CH_3$)C(CO_2CH_3)=C(CH_3)C(Ph)=C(Ph), **9**, in 70% isolated yield.[6,11b] The overall transformation represents the metal-mediated cyclization of two different alkynes and a carbene to generate a highly substituted cyclopentadiene product. The further scope as well as the mechanism of this novel cyclopentadiene methodology is currently under exploration.

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Supplementary Material Available: Tables of atomic coordinates, complete bond lengths and angles, and anisotropic thermal parameters for $C_{27}H_{25}O_4Co$, and characterization of all new compounds (6 pages); tables of observed and calculated structure factors for $C_{27}H_{25}O_4Co$ (9 pages). Ordering information is given on any current masthead page.

Formation of an Allene Oxide from (8*R*)-8-Hydroperoxyeicosatetraenoic Acid in the Coral *Plexaura homomalla*

Alan R. Brash

Department of Pharmacology, Vanderbilt University Nashville, Tennessee 37232

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It has been known for two decades that the gorgonian coral *Plexaura homomalla* contains large amounts of prostaglandins of the A and E series,[1] yet the mechanism of biosynthesis of these compounds remains unresolved. There is strong circumstantial evidence that an allene oxide is formed via an (8*R*)-lipoxygenase pathway of arachidonic acid metabolism in *P. homomalla*[2-4] and that this transformation is a key step in the biosynthesis of the prostaglandins. This report describes the preparation of this unstable intermediate and establishes the structure as **2**.

In our initial investigations[3] we reported that the primary arachidonic acid metabolite (8*R*)-8-hydroperoxyeicosatetraenoic acid (8*R*-HPETE, **1**) is converted to a cyclopentenone **3** which had been detected previously in the coral *Clavularia viridis*[2] and to an α-ketol **4** (Scheme I). The α-ketol appears to be a hydrolysis product of the putative allene oxide, while the cyclic product is formed by a spontaneous rearrangement and ring closure. Notably, the cyclopentenone we isolated from incubations of *P. homomalla* has side chains in the cis configuration and is racemic,[3] and thus it is unlikely to be involved in the route to the prostaglandins.[5]

The first attempts to isolate **2** using acetone powder of coral were foiled by the comparatively low rate of conversion of 8*R*-HPETE. It was reasoned that a more prolonged reaction time was required than the 5 s used with related transformations in flaxseed,[6] and yet the rapid hydrolysis of the allene oxide ($t_{1/2} \approx 15$ s at 0 °C, pH 7.4)[7] had to be prevented. These conditions were attained by conducting the enzymic transformation at pH 6, 0 °C for 2 min, while vortexing the solution with pentane.[8] Under these circumstances the 8*R*-HPETE is metabolized, and nonpolar product(s) are extracted into the cold organic phase and protected from hydrolysis.

Normal phase HPLC of the extract at −15 °C revealed a single main nonpolar product.[9] The structure was assigned from (i) the conjugated diene chromophore (λ_{max} 239 nm in hexane), (ii) the ^{1}H NMR spectrum of the methyl ester derivative, and (iii) the rapid cyclization and hydrolysis of the product to cyclopentenone **3** and α-ketol **4**. The NMR data are particularly diagnostic (Figure 1),[10] the spectrum having many features in

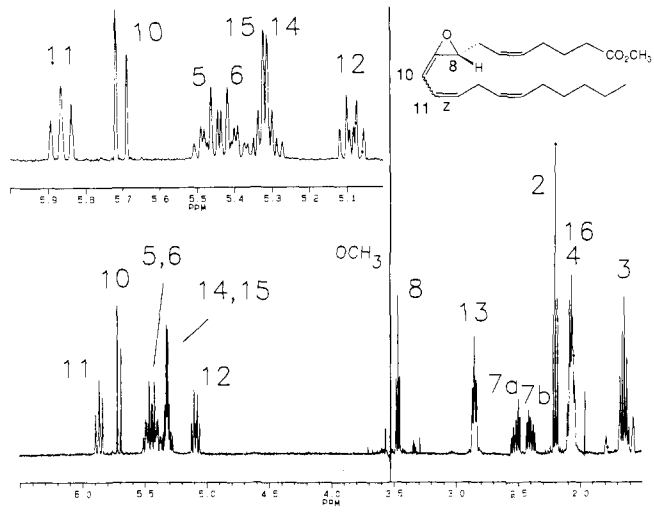
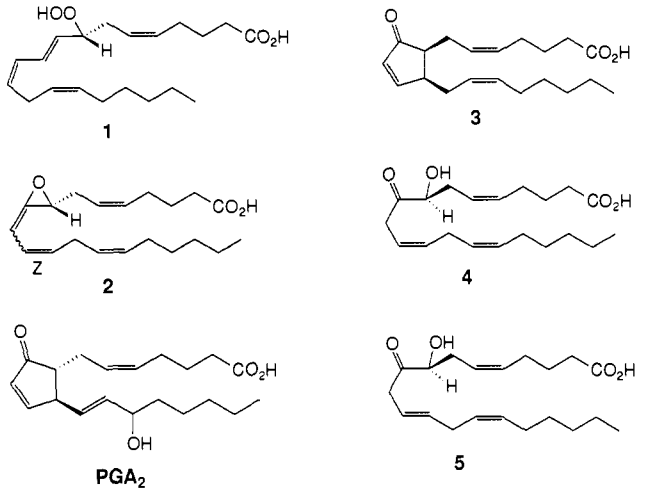


Figure 1. ^{1}H NMR (400 MHz) of **2**, methyl ester, in hexane-d_{14} at −50 °C.

Scheme I



(1) Weinheimer, A. J.; Spraggins, R. L. *Tetrahedron Lett.* **1969**, *59*, 5185-5188. Light, R. J.; Samuelsson, B. *Eur. J. Biochem.* **1972**, *28*, 232-240. Schneider, W. P.; Hamilton, R. D.; Rhuland, L. E. *J. Am. Chem. Soc.* **1972**, *94*, 2122-2123.

(2) Corey, E. J.; Lansbury, P. T., Jr.; Yamada, Y. *Tetrahedron Lett.* **1985**, *26*, 4171-4174. Corey, E. J.; d'Alarcao, M.; Matsuda, S. P. T.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 289-290. Corey, E. J.; Matsuda, S. P. T. *Tetrahedron Lett.* **1987**, *28*, 4247-4250. Corey, E. J.; Matsuda, S. P. T.; Nagata, R.; Cleaver, M. B. *Ibid.* **1988**, 2555-2558.

(3) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. M. *J. Biol. Chem.* **1987**, *262*, 15829-15839.

(4) For references to analogous reactions in plants, see: Hamberg, M. *Biochim. Biophys. Acta* **1987**, *920*, 76-84. Baertschi, S. W.; Ingram, C. D.; Harris, T. M.; Brash, A. R. *Biochemistry* **1988**, *27*, 18-24. Crombie, L.; Morgan, D. O. *J. Chem. Soc., Chem. Commun.* **1988**, 558-560.

(5) The cyclopentenone product **3** from *Clavularia viridis* and other sources is named pre-clavulone A by Professor Corey and co-workers,[2] although there is not yet evidence for the precursor-product relationship.

(6) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3382-3386.

(7) This is an estimate, based on the measured half-life of (9*Z*,13*S*,15*Z*)-12,13-epoxy-9,11,15-octadecatrienoic acid ($t_{1/2}$ = 16 s at 0 °C, pH 7.4).[6]

(8) Conditions for 1 mL incubation: to *P. homomalla* acetone powder, 10 mg/mL in pH 6 phosphate at 0 °C, is added 8*R*-HPETE (200 μg in 20 μL EtOH), with vortexing for 2 min with 2 mL of pentane, centrifugation for 2 min at 10000 g, and collection of $\approx$ 1 mL of pentane (yield of **2**: $\approx$ 5-10%).

(9) Altex Ultrasphere silica column (4.5 × 0.46 cm), solvent system: hexane/diethyl ether/glacial acetic acid (100/10/0.01 by vol) for **2** and hexane/diethyl ether (100:3 v/v) for the methyl ester derivative. Temperature, −15 °C; flow rate, 3 mL/min; retention time $\approx$ 1.5 min.

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common with the other allene oxides we have characterized.[6] From the coupling constants, the 5,11,14 double bonds are known to be cis, a significant point in relation to subsequent experiments. The chirality at C-8 was determined following hydrogenation (H_2/PtO_2 in hexane, 10 min at −15 °C). The major product was identified as (*S*)-8-hydroxyeicosanoate,[11] which (given that the priority order is reversed on hydrogenation) indicates that the allene oxide is of the 8*R* configuration. Minor products included methyl eicosanoate, (*RS*)-9-hydroxyeicosanoate, the 8-oxo and 9-oxo analogues, and small amounts 8,9-diol.

An interesting facet of the biphasic enzymic reaction is that the recoveries are better if the mixture is emulsified, although this is not required with an analogous reaction in flaxseed. Notably, the allene oxide is likely to be a substrate for additional enzymic transformations in the intact tissue, and this may entail its biosynthesis in a "protected" hydrophobic millieu.

Allene oxides are known to undergo a facile rearrangement to cyclopentenones.[12] Recently it was shown that allene oxides with a cis olefin in conjugation with the epoxyene will form a cyclopentenone with cis geometry of the side chains, whereas with a trans bond, ring closure leads to side chains in the trans configuration.[12c] We detected an 11-cis to 11-trans isomerization of the α-ketol product **4** to **5** in incubations of *P. homomalla*.[13] The [1-^{14}C]α-ketol **4** was converted to **5** (yield: 26%) during a 20-min incubation at room temperature (pH 8, 3 mg/mL acetone powder). A pertinent question is whether **5** also arises from an allene oxide with an 11-trans double bond. From an incubation containing α-ketols **4** and **5** in the ratio of 85:15, 11-cis:11-trans, the cyclopentenone **3** was found to be 98.5% cis geometry. Thus, the allene oxide precursor is predicted to have almost exclusively an 11-cis double bond,[12] in accord with the direct structural analysis. There does remain, however, the possibility that the allene oxide **2** is a substrate for this type of transformation under the natural conditions of biosynthesis. Other mechanisms of biosynthesis involving lipoxygenase metabolism of the cyclopentenone **3**[2] or the allene oxide **2**[14] have been proposed.

PGA_2 and PGE_2 have the 8*R* configuration at the juncture of the top side chain, and therefore it is highly significant that the lipoxygenase pathway in *P. homomalla* forms an 8*R*-hydroperoxide, and, as shown here, the 8*R*-HPETE is converted to an 8*R*,9-epoxyallene (Scheme I). The biosynthetic pathway must include a cyclization of the allene oxide with retention of configuration at C-8, and, either during the cyclization or in a later isomerization, a cyclic product with a trans geometry of the side chains must be formed. Another mechanism involving the 15-lipoxygenase metabolism of 8*R*-HPETE to 8,15-DiHPETE prior to formation of an allene oxide[2] is as yet not substantiated by the experimental results.[3]

Acknowledgment. The cooperation of the Department of Development & Natural Resources of the Cayman Islands in collection of samples of *P. homomalla* is gratefully acknowledged and Dr. David G. Anderson for collections in Florida. Professor Thomas M. Harris and Steven Baertschi participated in many invaluable discussions and provided the excellent NMR data. I also thank Dr. Jin K. Cha for helpful discussions, Christiana Ingram for contributions to the α-ketol analyses, and Dr. Ian A. Blair for providing the excellent mass spectrometry facilities. This work is supported by NIH grants DK-35275 and ES-00267.

(10) ^{1}H NMR of **2**, methyl ester (400 MHz, in hexane-d_{14} at −50 °C) was assigned from the 2-D COSY and decoupling experiments with peaks at δ 5.865 for H11 (t, $J_{10,11} = J_{11,12} = 11$ Hz, 1 H), 5.70 for H10 (d, 1 H), 5.55–5.37 for H5 and 6 (m, $J_{5,6} = 11$ Hz, 2 H), 5.365–5.270 for H14 and 15 (m, $J_{14,15} = 10.5$ Hz, 2 H), 5.085 for H12 (dt, $J_{11,12} = 11$ Hz, $J_{12,13} = 7$ Hz, 1 H), 3.525 for OCH_3 (s, 3 H), 3.465 for H8 (t, $J_{7,8} = 5.5$ Hz, 1 H), 2.85 for H13 (t, $J_{12,13} = J_{13,14} = 7$ Hz, 2 H), 2.575–2.485 for H7a and 2.43–2.36 for H7b (m, $J_{6,7} = 7$ Hz, $J_{7a,7b} = 15$ Hz, 2 H), 2.20 for H2 (t, 2 H), 2.10–2.03 for H4 and H16 (m, 4 H), 1.65 for H3 (p, 2 H), with H17–20 obscured by the residual CHD and CHD_2 in the hexane.

(11) Benzyl 8-hydroxyeicosanoate was resolved on a 25 × 0.46 cm Chiralcel OB column (Baker): solvent, 1% isopropyl alcohol in hexane; flow rate, 0.3 mL/min; 8*S* enantiomer at 17.2 mL (96% of area) and 8*R* at 20.0 mL (4%). Note that hydrogenation changes the R and S assignment of the 8-hydroxyl; thus, 8*R*-HETE is converted to (*S*)-8-hydroxyeicosanoic acid.

(12) (a) Grimaldi, J.; Bertrand, M. *Tetrahedron Lett.* **1969**, *38*, 3269–3272. Grimaldi, J.; Bertrand, M. *Bull. Soc. Chim. Fr.* **1971**, 957–962. (b) For recent work and further references, see: Doutheau, A.; Sartoretti, J.; Gore, J. *Tetrahedron* **1983**, *39*, 3059–3065. Doutheau, A.; Gore, J.; Diab, J. *Ibid.* **1985**, *41*, 329–338. (c) Kim, S. J.; Cha, J. K. *Tetrahedron Lett.* **1988**, *29*, 5613–5616.

(13) The ^{1}H NMR (400 MHz) of **5** in $CDCl_3$ was assigned by 2-D COSY and decoupling experiments with peaks at δ 5.61–5.54 for H12 and 5.56–5.48 for H11 (m, $J_{11,12} = 15.2$ Hz), at 5.65–5.45 for H5 and 5.45–5.35 for H6 (m, $J_{5,6} = 10.2$ Hz), at 5.50–5.40 for H15 and 5.40–5.30 for H14 (m, $J_{14,15} = 10.8$ Hz), with other resonances at 4.29 for H8 (dd, 1 H), 3.23 for H10 (m, 2 H), 2.79 for H13 (m, 2 H), 2.65–2.55 for H7a and 2.45–2.35 for H7b (m, 2 H), 2.37 for H2 (t, 2 H), 2.13 for H4 (q, 2 H), 2.02 for H16 (q, 2 H), 1.73 for H3 (p, 2 H), 1.40–1.30 for H17 (m, 2 H), 1.37–1.25 for H18 and H19 (m, 4 H), and 0.88 for H20 (t, 3 H). On normal phase and reversed phase HPLC, **5** chromatographed immediately after **4**, and the two isomers gave essentially identical mass spectra. The absolute configuration of **5** was measured using a method described before[3] as a 40% enantiomeric excess of the 8*S* configuration; the 11-*cis* α-ketol **4** recovered from the same incubation was 54% enantiomeric excess of 8*S*.

(14) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. M. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.*, *19* Raven Press: New York, 1989; in press.

Asymmetric Allylboration with *B*-Allyl-2-(trimethylsilyl)borolane

Robert P. Short and Satoru Masamune*

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

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Stereoselective addition of an acetate unit to the prostereogenic[1] carbonyl carbon of an aldehyde is achieved by a variety of aldol reactions.[2] A synthetic equivalent of this fundamental carbon–carbon bond-forming process is asymmetric allylboration, for which several chiral reagents have been devised in recent years.[3] The magnitude of asymmetric induction achieved by these reagents lies, with few exceptions, in the range 70–90% ee (see Table I) for representative (achiral) substrates.[4] In our synthetic studies on polyketide natural products we have been faced with a problem of raising the enantioselectivity of allylboration to 95% ee or higher so as to gain stereochemical control of the reaction sufficient for double asymmetric synthesis.[3e-f,5] We describe herein the preparation of homochiral (*R* and *S*)-*B*-allyl-2-(trimethylsilyl)-borolanes (*R*)-**1** and (*S*)-**1**, reagents which possess high reactivity and meet the above demand for enantioselectivity. In practice, **1** is generated in situ from its air-stable precursor, the synthesis of which is simple and practical. Of particular interest is the mechanistic course of this asymmetric reaction effected by the monosubstituted borolane derivative **1** of C_1 symmetry rather than the disubstituted analogues of C_2 symmetry (e.g., *trans*-2,5-dimethylborolane) reported earlier from these laboratories.[6]

(1) Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

(2) (a) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24 and references cited therein. (b) Masamune, S.; Sato, T.; Kim, B. M.; Wollmann, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 8279.

(3) (a) Herold, T.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 768. (b) Hoffmann, R. W. *Pure Appl. Chem.* **1988**, *60*, 123. (c) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (d) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (e) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (f) Roush, W. R.; Banfi, L. *J. Am. Chem. Soc.* **1988**, *110*, 3979.

(4) The reagent described in ref 3f exhibits excellent enantioselectivity (>95% ee) but suffers from low reactivity and thus may not be a practical reagent for natural product synthesis.

(5) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. For studies on double asymmetric allylboration, see: (b) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (c) Roush, W. R.; Palkowitz, A. D. *J. Am. Chem. Soc.* **1987**, *109*, 953. (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319.

(6) Masamune, S. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH: 1986; p 49.

0002-7863/89/1511-1892$01.50/0