A General Strategy for the Synthesis of Monohydroxy-eicosatetraenoic Acids: Total Synthesis of 5(*S*)-Hydroxy-6(*E*),8,11,14(*Z*)-eicosatetraenoic Acid (5-HETE) and 12(*S*)-Hydroxy-5,8,14(*Z*),10(*E*)-eicosatetraenoic Acid (12-HETE)

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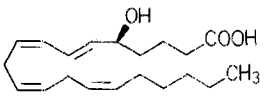
Stereocontrolled total syntheses of 5(*S*)-hydroxy-6(*E*),8,11,14(*Z*)-eicosatetraenoic acid (5-HETE) and 12(*S*)-hydroxy-5,8,14(*Z*),10(*E*)-eicosatetraenoic acid (12-HETE) via palladium(0)-copper(I) coupling technology are described.

Hydroxyeicosatetraenoic acids (HETE's) are a class of biologically important arachidonic acid metabolites, some of which have been implicated in inflammation and a number of other health-problems[1]. Their extremely low availability from natural sources coupled with the demand for these compounds for biological investigations prompted us to investigate possible synthetic strategies for their construction. In this communication we report an efficient entry into this family of compounds based on our recently introduced general strategy towards linear eicosanoids[2]. According to this strategy a conjugated *cis,trans* diene system is located in the target molecule and retrosynthetically disected at the central C—C bond, suggesting a terminal acetylene and a vinyl bromide as potential key intermediates. These key intermediates are then coupled by a palladium-copper catalyzed reaction[2,3] and the resulting enyne elaborated to the target. The approach, which provides for optically active or racemic products, is illustrated below with new and efficient synthesis of 5-HETE **(1)**[4] and 12-HETE **(2)**[5] in their natural forms.



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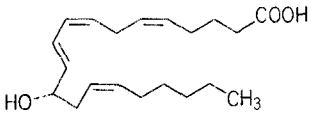

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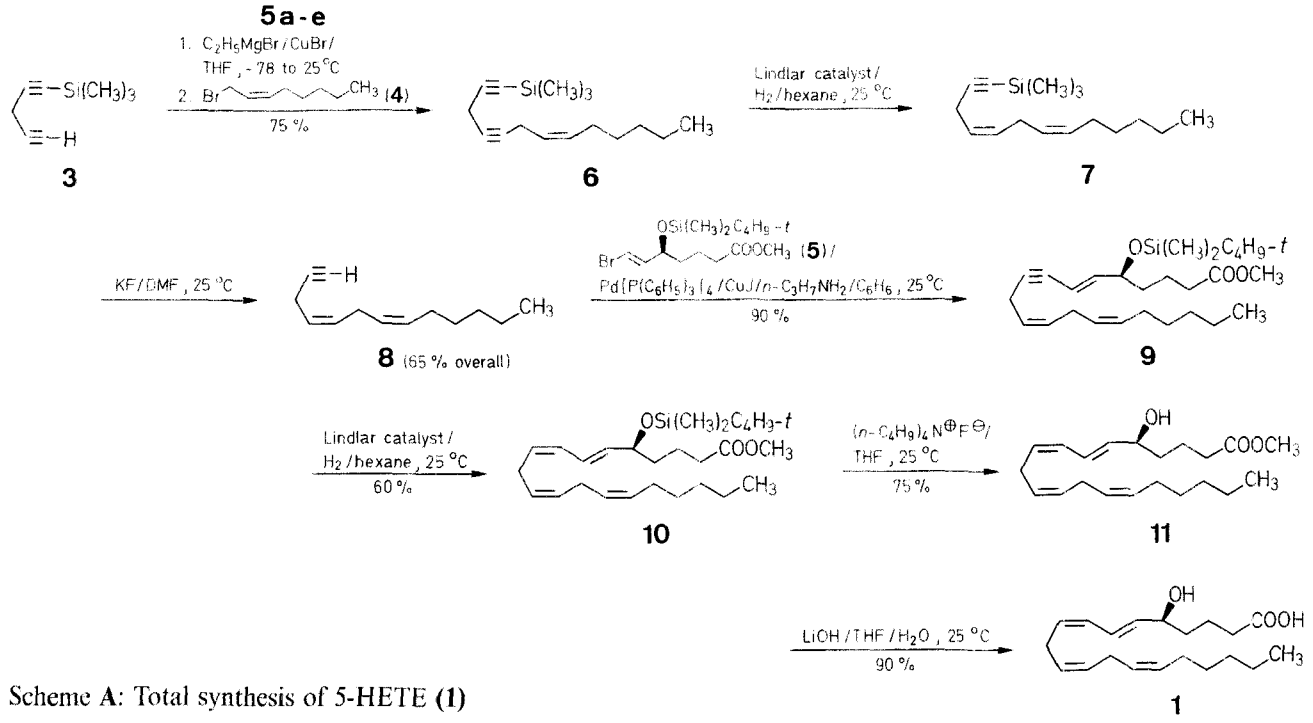
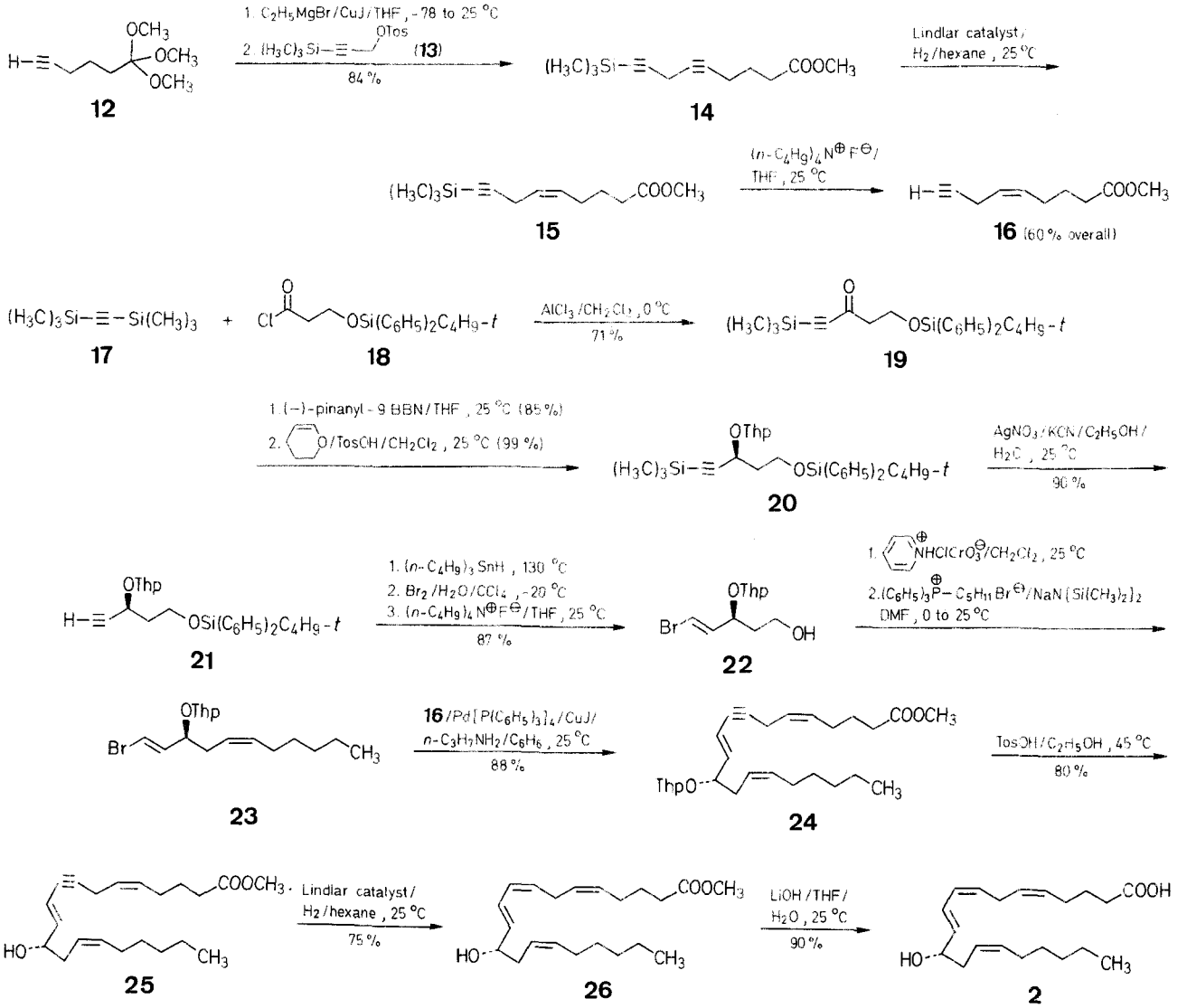
5(*S*)-HETE was synthesized from the known fragments **3**[6], **4**[7], and **5**[2] as depicted in Scheme **A**. Thus, conversion of acetylene **3** to its magnesium derivative (1.1 eq. ethylmagnesium bromide, 0.1 eq. copper(I) bromide, tetrahydrofuran $-78 \rightarrow 25\,^{\circ}C$) followed by alkylation with allyl bromide **4** (1.2 eq., $-78 \rightarrow 25\,^{\circ}C$) led to compound **6** in 75% yield. Selective hydrogenation of **6** using Lindlar catalyst (hydrogen, hexane, 25 °C) afforded monoacetylene **7** which was desilylated (2.0 eq. potassium fluoride, dimethylformamide, 25 °C) leading to the key intermediate terminal acetylene **8** in 65% overall yield. Coupling[2,3] of **8** with an excess of the readily accessible vinyl bromide **5** (1.5 eq.) in the presence of tetrakis[triphenylphosphine]palladium (0.06 eq.), copper(I) iodide (0.16 eq.) and *n*-propylamine (1.3 eq.) in benzene at 25 °C furnished the enyne **9** in 90% yield (based on **8**). Lindlar hydrogenation of **9** (hydrogen, hexane, 25 °C) led to the methyl ester silyl ether **10** (60%) from which the protecting groups were sequentially removed to afford 5(*S*)-HETE methyl ester **(11)** (1.5 eq. tetra-*n*-butylammonium fluoride, tetrahydrofuran, 25 °C, 75% yield) and 5(*S*)-HETE **(1)** (3.0 eq. lithium hydroxide, tetrahydrofuran + water, 3 + 1, 25 °C, 90% yield).



Scheme **A**: Total synthesis of 5-HETE **(1)**



Scheme **B**: Total synthesis of 12(*S*)-HETE **(2)**

The synthesis of 12(*S*)-HETE **(2)** is outlined in Scheme **B**. In this sequence, the requisite fragments were defined as the terminal acetylene **16** and vinyl bromide **23**. Thus, coupling of the acetylenic orthoester **12**[8] via its Grignard reagent (1.1 eq. ethylmagnesium bromide, 0.1 eq. copper(I) bromide, tetrahydrofuran, $-78 \rightarrow 25\,^{\circ}C$) with tosylate **13** (1.2 eq., $-78 \rightarrow 25\,^{\circ}C$) proceeded smoothly to furnish, after acidic work-up product **14** in 84% yield. Selective reduction of **14** under Lindlar conditions followed by desilylation, as described for **7** → **8** above, furnished key intermediate **16** (60% overall yield) via **15**. For the synthesis of **23**, the acid chloride **18**[9] was reacted with bis[trimethylsilyl]acetylene **(17)** in the presence of aluminium chloride (1.1 eq., dichloromethane, 0 °C) to afford, in 71% yield, ynone **19**. Enantioselective reduction of **19** with (−)-pinanyl-9-BBN[10] (1.2 eq., tetrahydrofuran, 25 °C, 85% yield and ≥ 95 e.e.)[11] furnished, after tetrahydropyranylation (1.5 eq. dihydropyran, *p*-toluenesulfonic acid catalyst, dichloromethane, 25 °C, 99% yield) compound **20** from which the trimethylsilyl group was removed (excess silver nitrate/potassium cyanide, aqueous ethanol, 25 °C, 90% yield) leading to **21**. Addition of tri-*n*-butyltin hydride (1.5 eq., neat, 130 °C) followed by brominolysis (1.5 eq. bromine, carbon tetrachloride, −20 °C, 87% overall) and desilylation (1.5 eq. tetra-*n*-butylammonium fluoride, tetrahydrofuran, 25 °C, 95%) gave the hydroxyvinyl bromide **22** which was oxidized to the corresponding aldehyde (1.4 eq. pyridinium chlorochromate, dichloromethane, 25 °C) and condensed with the ylid derived from pentyltriphenylphosphonium bromide (1.5 eq.) and sodium bis[trimethylsilyl]amide[12] (1.45 eq., dimethyoxyethane, 0–25 °C, 72%) leading cleanly to the desired key intermediate **23**. The coupling of **16** with **23** proceeded smoothly under the palladium-copper catalyzed conditions prescribed above for **5** + **8** and furnished **24** in 88% yield. Finally, removal of the tetrahydropyranyl group (*p*-toluenesulfonic acid catalyst, ethanol, 45 °C, 80%) followed by selective Lindlar-type hydrogenation of the resulting compound **25** led to 12(*S*)-HETE methyl ester **26** (75% yield) from which 12(*S*)-HETE **(2)** was generated (90% yield) by alkaline hydrolysis as described above for 5(*S*)-HETE **(1)**.

The described synthesis of 5(*S*)-HETE **(1)** and 12(*S*)-HETE **(2)** demonstrate further the generality and scope of the palladium-copper-based general approach to linear eicosanoids and make these biomolecules readily available for further investigations.

All new compounds were characterized by full spectroscopic and analytical and/or exact mass data. Yields refer to spectroscopically and chromatographically homogeneous materials.

Coupling of Vinyl Bromide 5 with Acetylene 8; Preparation of Compound 9:

To a solution (0.6 ml, dry degassed benzene) of vinyl bromide **5** (110 mg, 0.314 mmol) is added *n*-propylamine (0.03 ml, 0.38 mmol) followed by tetrakis[triphenylphosphine]palladium (22 mg, 0.018 mmol) at 25 °C under argon. The mixture is stirred under these conditions for 45 min before acetylene **8** (165 mg, 0.94 mmol) in dry, degassed benzene (2 ml) and copper(I) iodide (10 mg, 0.005 mmol) are sequentially added. Stirring for 12 h at 25 °C, dilution with ether (25 ml), and washing with saturated ammonium chloride solution and brine give a solution which is dried with magnesium sulfate and evaporated leading to an oily product. Flash column chromatography (silica, ether/petroleum ether, 1:1) affords enyne **9** as a colorless oil; yield: 122 mg (90%); R_f: 0.21 (silica, ether/petroleum ether, 1:1). H.R.M.S.: *m/e* = 447.3272 ($M^+ + 1$); calc. for $C_{27}H_{46}H_3Si$: 446.3204.

I.R. (neat): ν = 3020, 2960, 2860, 1745, 1250, 835 cm^{-1}.

U.V. (CH_3OH): λ_{max} = 225 nm.

^{1}H-N.M.R. ($CDCl_3$, 250 MHz): δ = 6.01 (dd, J = 15.9 Hz, 5.6 Hz, 1 H, olefinic); 5.64 (m, 2 H, olefinic); 5.40 (m, 3 H, olefinic); 4.15 (dt, J = 5.0 Hz, 1.0 Hz, 1 H, C<u>H</u>—O); 3.64 (s, 3 H, $COOC\underline{H}_3$); 3.01 (d, J = 6.0 Hz, allylicpropargylic, 2 H); 2.75 [t, J = 6.0 Hz, 2 H, (bis) allylic]; 2.28 (t, J = 7.0 Hz, 2 H, $C\underline{H}_2COOCH_3$); 2.01 (m, 2 H, allylic); 1.70–1.20 (m, 10 H, $C\underline{H}_2$); 0.85 (m, 12 H, $C\underline{H}_3$, $SiC(C\underline{H}_3)_3$); 0.04 and 0.02 ppm [singlets, 3 H each, $Si(C\underline{H}_3)_2$].

Lindlar Hydrogenation of Compound 25. Synthesis of 12(*S*)-HETE Methyl Ester (26):

Enyne **25** (20 mg, 0.062 mmol) is dissolved in hexane (2 ml) and hydrogenated in the presence of quinoline (10 µl) over Lindlar catalyst (2 mg) and 1 atm hydrogen at 25 °C for 1.5 h. Dilution with ether (10 ml), filtration through florisil, evaporation, and flash column chromatography furnished 12(*S*)-HETE methylester **(26)**; yield: 15 mg, (75%) and unreacted starting material; yield: (3 mg, (15%). Product **26**; colorless oil; R_f: 0.32 (silica, 20% ethyl acetate in petroleum ether.

H.R.M.S.: *m/e* = 334.2485 (M^+); calc. for $C_{21}H_{34}O_3$: 334.2499.

I.R. (neat): ν = 3420, 3020, 2960, 2940, 2860, 1745, 1250 cm^{-1}.

U.V. (CH_3OH): λ_{max} = 235 nm.

^{1}H-N.M.R. ($CDCl_3$, 250 MHz): δ = 6.55 (dd, J = 15.1 Hz, 10.8 Hz, 1 H, olefinic); 5.98 (t, J = 10.8 Hz, 1 H, olefinic); 5.72 (dd, J = 15.1 Hz, 6.8 Hz, 1 H, olefinic); 5.62–5.32 (m, 5 H, olefinic); 4.21 (m, 1 H, C<u>H</u>O); 3.65 (s, 3 H, $COOC\underline{H}_3$); 2.92 [t, J = 6.0 Hz, 2 H, (bis) allylic]; 2.30 (m, 4 H, $C\underline{H}_2COOCH_3$, allylic); 2.05 (m, 4 H, allylic); 1.90–1.20 (m, 9 H, $C\underline{H}_2$, O<u>H</u>); 0.85 ppm (t, J = 7.0 Hz, 3 H, $C\underline{H}_3$)

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[1] For some recent reviews, see:
Samuelsson, B. *Science* **1983**, *220*, 568.
Samuelsson, B. *Angew. Chem.* **1983**, *95*, 854; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 805.
Corey, E.J. *Experientia* **1982**, *38*, 1259.
Hammarstrom, S. *Ann. Rev. Biochem.* **1983**, *52*, 355.

[2] Nicolaou, K.C., Webber, S.E., *J. Am. Chem. Soc.* **1984**, *106*, 5734.

[3] Sonogashira, K., Tohda, Y., Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
Ratovelomana, V., Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.

[4] For previous synthesis of 5-HETE see:
Rokach, J., Adams, J., Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185 (racemic).
Zamboni, R., Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999 (optically active).

[5] For previous synthesis of 12-HETE see:
Corey, E.J., Kyler, K., Raju, N. *Tetrahedron Lett.* **1984**, *25*, 5115 (racemic).
Corey, E.J., Niwa, H., Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942 (optically active).

[6] Verkruijsse, H.D., Hasselaar, M. *Synthesis* **1979**, 292.

[7] Prepared from the corresponding acetylenic alcohol by Lindlar hydrogenation followed by treatment with tetrabromomethane/triphenylphosphine: Petasis, N.A. *Ph. D. Thesis*, University of Pennsylvania, 1983, pp. 44.

[8] Just, G., Luthe, C. *Tetrahedron Lett.* **1982**, *23*, 1331.

[9] Acid chloride **18** was prepared from 1,3-propanediol by (1) monosilylation (1.1 eq. *t*-butylchlorodiphenylsilane, 2.0 eq. imidazole, dimethylformamide, 25 °C); (2) Jones oxidation (acetone, 0 °C), and (3) chloride formation (1.1 eq oxalyl chloride, 1.1 eq pyridine, dichloromethane, 0–25 °C) in 60% overall yield.

[10] Midland, M.M., McDowell, D.C., Hatch, R.L., Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

[11] e.e. Determined by the Mosher ester method: Dale, J.A., Dull, D.L., Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

[12] Bestmann, H.J., Stransky, W., Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694.