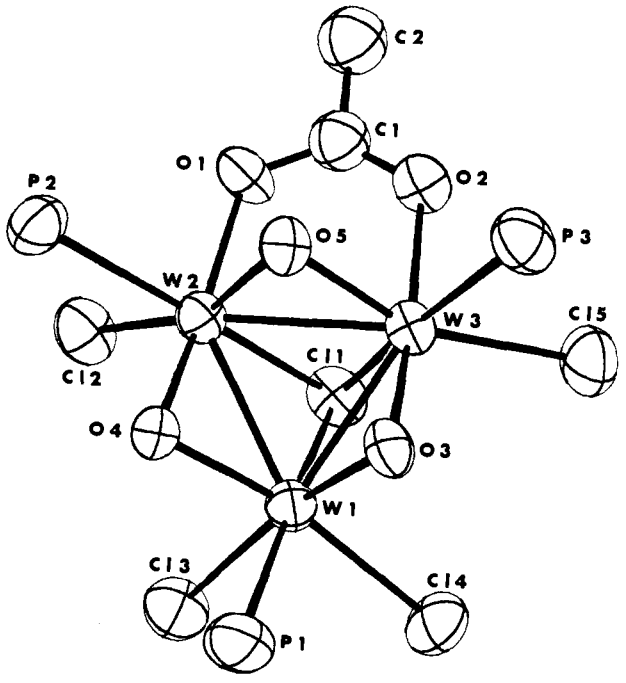

Figure 4. The $W_3O_3Cl_5(CH_3CO_2)(PBu^n_3)_3$ unit in compound **5**, omitting the *n*-Bu groups. Ellipsoids are shown at the 50% probability level.

Supplementary Material Available: Tables (11–V1) of atomic positional parameters for compounds **1–5** (4 pages). Ordering information is given on any current masthead page.

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(2) The first unambiguous example, the extremely unstable $[W_2Me_8]^{4-}$, was reported only in 1977.[3] The first compounds that are stable in the atmosphere at room temperature, $W_2(C_8H_8)_3$[4] and W_2(2-oxo-6-methylpyridine)$_4$,[5] were also reported very recently. Since then a few others similar to the oxopyridine complex have been described.[6]

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(10) Tables of atomic positional parameters are available as supplementary material. All structures are now refined to very low *R* values and the few additional modifications in the refinement procedures are not expected to affect any bond distances or angles significantly. Crystallographic data are as follows. **1**: space group *C2/c*; a = 18.297 (3), b = 9.192 (2), c = 19.042 (2) Å; β = 124.93 (1)°; Z = 4; R_F = 0.031, R_{wF} = 0.045 for 1741 reflections with $I > 3\sigma(I)$. **2**: space group $P2_1/n$; a = 9.150 (2), b = 12.029 (1), c = 14.245 (2) Å; β = 105.88 (2)°; Z = 2; R_F = 0.033, R_{wF} = 0.047 for 2082 reflections with $I > 3\sigma(I)$. **3**: space group *C2/c*; a = 24.702 (5), b = 10.024 (1), c = 22.822 (4) Å; β = 118.81 (2)°; Z = 4; R_F = 0.028, R_{wF} = 0.039 for 3261 reflections with $I > 3\sigma(I)$. **4**: space group $P2_1/n$; a = 23.103 (3), b = 13.254 (2), c = 16.781 (3) Å; β = 107.53 (1)°; Z = 4; R_F = 0.054, R_{wF} = 0.061 for 3517 reflections with $I > 3\sigma(I)$. **5**: space group $P2_1/n$; a = 12.056 (3), b = 20.248 (4), c = 23.977 (7) Å; β = 92.17 (2)°; Z = 4; R_F = 0.049, R_{wF} = 0.063 for 5729 reflections with $I > 3\sigma(I)$.

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(15) The staggered configuration rules out the existence of a δ bond and the W–W distance in this case is ~0.038 Å longer than those in **1**, **2**, and **3**. Whether **4** is paramagnetic with two unpaired electrons, as a simple analysis would suggest, remains to be determined. In any case, it appears that **4** provides a clear example of the strength of the conformational preference of the fused six-membered rings, which met no resistance in $Re_2Cl_4(dppe)_2$ but here apparently overcomes the resistance offered by the tendency toward δ bonding.

(16) In keeping with this, Sharp and Schrock[7] found ν_{W-W} of 260 cm^{-1} whereas, for $W_2(mhp)_4 \cdot CH_2Cl_2$, a ν_{W-W} of 295 cm^{-1} was found.[5]

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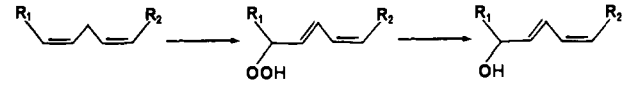
Controlled Chemical Synthesis of the Enzymatically Produced Eicosanoids 11-, 12-, and 15-HETE from Arachidonic Acid and Conversion into the Corresponding Hydroperoxides (HPETE)

Sir:

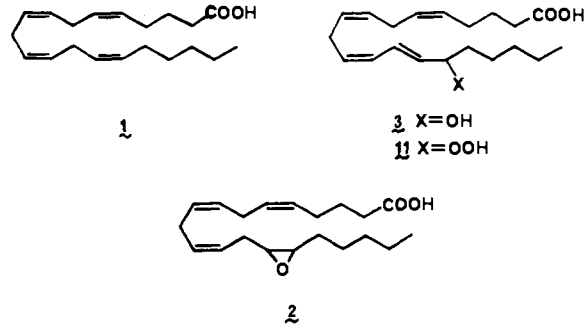
Arachidonic acid (**1**) serves as the biological precursor of a growing family of physiologically active eicosanoids[1,2] which includes not only the prostaglandins and their further transformation products (thromboxanes, prostacyclines, etc.) but also lipoxygenase-derived hydroperoxides and alcohols (HPETE's and HETE's, respectively).[3-7] Although the lipoxygenase type of oxidation of *cis,cis*-1,4-dienes (Scheme I)

Scheme I



can in principle be effected by singlet oxygen ($^1\Delta g$ state), the reaction of this reagent with polyunsaturated acids is so nonselective (leading to mixtures of all of the expected "ene" oxidation products)[8] as to be preparatively useless. In this communication we describe an approach to the synthesis of three biologically interesting HETE's by methods which are suitable for multigram laboratory preparation and which illustrate useful new synthetic methodology as well.

The one-step conversion of arachidonic acid into the 14,15-epoxide (**2**) in 98% yield by internal oxygen transfer has recently been described.[9] Reaction of **2** with 5 equiv of the



1

3 X=OH
11 X=OOH

2

reagent prepared from isopropylcyclohexylamine and methylmagnesium bromide (1:1) in tetrahydrofuran (THF) at 0 °C for 10 min and then 0–23 °C for 2 h and 23 °C for 3.5 h was very clean and afforded, after quenching with saturated aqueous sodium dihydrogen phosphate, extractive isolation with ether, concentration, and simple chromatographic sepa-

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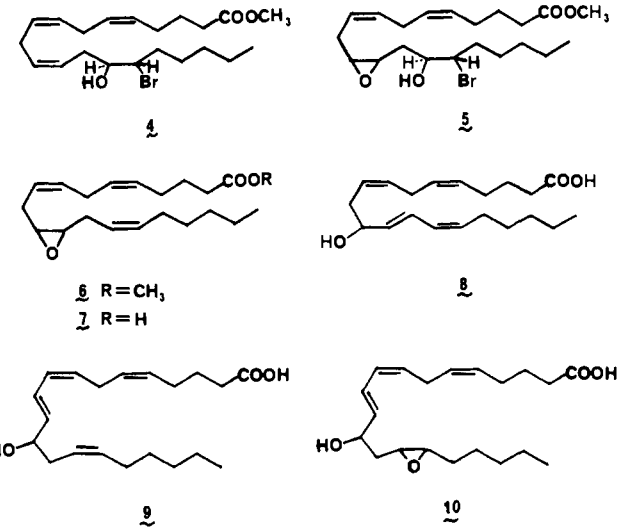
ration on silica gel, a 70% yield of pure 15-HETE (**3**), identified by comparison with authentic material[10] both as the free acid and methyl ester (CH_2N_2).[11] The use of the magnesium derivative of isopropylcyclohexylamine (MICA) was found to be remarkably effective for the epoxide → allylic alcohol conversion and definitely superior to other reagents previously employed for this purpose, including lithium diethylamide, lithium diisopropylamide, and diethylaluminum 2,2,6,6-tetramethylpiperidide.[12] Under the conditions outlined above the 12,13-epoxide of linoleic acid is converted by MICA in THF into 13-hydroxy-*cis*-9,*trans*-11-octadecanoic acid in 87% yield.[13]

The 11,12-epoxide of arachidonic acid, a critical intermediate for the synthesis of 11- and 12-HETE and an interesting compound in its own right, could be synthesized selectively from the readily available **2** as follows. Treatment of the methyl ester of epoxide **2** at 5 °C in acetic acid–saturated aqueous potassium bromide–THF (20:3:4) for 12 h afforded after extractive isolation a 95% yield of a mixture of bromohydrins consisting of **4** and the position isomer (14-bromo, 15-hydroxyl



substitution) in a ratio of ~2:1 (R_f values found for **4** and the position isomer by TLC on silica gel using hexane–ether (4:1) were 0.15 and 0.19, respectively). The mixture of **4** and the position isomer was oxidized using excess anhydrous *tert*-butyl hydroperoxide in dry benzene in the presence of 0.75 equiv of vanadyl acetylacetonate (Alpha Division of Thiokol Co.)[14] at 23 °C for 120–130 min, quenched with dimethyl sulfide (23 °C, 30 min), and subjected to extractive isolation and chromatography on silica gel to afford the epoxy bromohydrin **5** in 63% overall yield from the ester of **2.** The position isomer of **4** is largely unchanged at minimum time and is readily separated from **5** by chromatography and recycled to **2** by base.

The conversion of **5** into the desired 11,12-oxide **6** by elimination of the elements of hydroxyl and bromine, a step which had been anticipated to be straightforward, presented formidable problems. Unexpectedly the reaction of **5** or various derivatives of **5** (e.g., mesylate, *p*-bromobenzenesulfonate, tosylate, benzoate, nitrite) with any of a number of reducing agents (zinc, Rieke zinc,[15] magnesium, lithium dialkylcuprates, and various other metal–halogen exchange reagents) led to mixtures of **6** and 20–50% $\Delta^{14,15}$-trans isomer, as well as to a number of byproducts in varying amount depending on the reagent. Nonselective elimination was also observed using a simpler substrate, threo bromohydrin obtained from the epoxide of methyl oleate (KBr in HOAc). The problem of effecting stereospecific conversion of threo bromohydrin into cis olefin was finally solved by the use of a new process which should have general utility because of the mildness and simplicity of the conditions involved.

To a solution of the epoxy bromohydrin **5** and 2 equiv of dry pyridine in methylene chloride at 0 °C was added slowly a solution of 1.1 equiv of trifluoromethanesulfonic anhydride in methylene chloride (with stirring throughout) and after 40 min a solution of 10 equiv of hexamethylphosphorous triamide in the same solvent was added over a few minutes. After 30 min at 0 °C, the product was isolated by dilution with ether, washing (ice–water, saturated aqueous copper sulfate, saturated aqueous sodium chloride), concentration, and simple chromatographic separation on a column of silica gel to afford in 85% yield the 11,12-epoxide of methyl arachidonate (**6**) as a colorless oil.[16] Analysis by TLC using silver nitrate impregnated plates indicated a purity of ~95% for the 11,12-epoxide **6,** the major contaminant being the 14,15-trans isomer. The structure of **6** was proved by the sequence (1) hydrogenation (H_2, Pd/C in ethyl acetate) to the saturated epoxy ester and (2) cleavage by aqueous periodic acid at 23 °C to give *n*-nonanal and methyl 10-formyldecanoate, both fully characterized by ^1H NMR, IR, mass spectral, and gas chromatographic data. The hexamethylphosphorous triamide promoted elimination of vicinal bromo triflates when applied to the threo bromohydrin from methyl oleate afforded pure methyl oleate in >90% yield.

Saponification of the epoxy ester **6** occurred cleanly using ~10 equiv of lithium hydroxide in dimethoxyethane–water (2.5:1) at 23 °C for 15 h to give the epoxy acid **7** as a colorless oil (100%).[17] Reaction of the epoxy acid **7** with 5 equiv of MICA in THF at 0 °C for 0.5 h and 23 °C for 3.5 h afforded, after isolation as described above for 15-HETE (**3**), 70% of a mixture of 11-HETE (**8**) and 12-HETE (**9**) (ratio 1:1.5) which could be separated chromatographically.[18] The structures of **8** and **9** were established by ^1H NMR and mass spectral data (and in the case of **9** comparison with authentic material[19]).

12-HETE could also be synthesized from bromohydrin **5** by the following sequence: (1) reaction with potassium carbonate in methanol to afford quantitatively the 11,12:14,15-bis epoxide of methyl arachidonate; (2) saponification to the diepoxy acid; (3) reaction with MICA to afford the 14,15-oxide of 12-HETE (**10**); and (4) deoxygenation of the epoxide with potassium selenocyanate in methanol[20] at reflux to form **9** (30% overall yield).

Finally we report the first method for the conversion of an HETE into the corresponding HPETE. Reaction of the methyl ester of 15-HETE in methylene chloride at −42 °C with 1.1 equiv of methanesulfonyl chloride and 2.2 equiv of triethylamine for 10 min affords the ester mesylate which is then allowed to react at −42 °C with 10 equiv of *tert*-butyl dimethylhydroperoxide for 10 min. Extractive isolation affords the *tert*-butyldimethylsilyl derivative of the methyl ester of 15-HPETE contaminated by only trace amounts of two isomeric impurities. After chromatographic purification, desilylation (1:1:1 acetic acid–water–THF, 20 °C, 1 h) and saponification (dimethoxyethane–water–lithium hydroxide, 20 °C), (±)-15-HPETE (**11**) was obtained as a colorless oil spectroscopically and chromatographically identical with material produced by the action of soybean lipoxygenase on arachidonic acid.[3]

The studies outlined above demonstrate effective and selective chemical syntheses of a number of important eicosanoids. In addition they illustrate three new synthetic methods which fill critical gaps in previous chemical knowledge.[21]

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(16) This and other new substances described herein were fully characterized by IR, ^1H NMR, and mass spectroscopy.
(17) With the development of this synthesis selective conversions of arachidonic acid into the 5,6-, 11,12-, and 14,15-oxides are now available as described in this communication and ref 9.
(18) Separated by high pressure liquid chromatography [Waters Associates μ-Porasil column using heptane–isopropyl alcohol (200:1)]. The trans configuration of the 10,11 double bond in the 12-HETE methyl ester synthesized by the present method is clear from (1) its identity (^1H NMR, IR, mass spectrum, chromatographic mobility) with methyl ester of 12-HETE (**9**) synthesized by the previously described[19] unambiguous route and (2) the ^1H NMR spectrum (in $CDCl_3$) which shows peaks at δ 6.55 (dd, $J_{10,11}$ = 15, $J_{9,10}$ = 10.5 Hz, 1 H) for H(10), 5.95 (dd, $J_{8,9} = J_{9,10}$ = 10.5 Hz, 1 H) for H(9), and 5.70 (dd, $J_{10,11}$ = 15, $J_{11,12}$ = 6 Hz, 1 H) for H(11). See Gardner, H. W.; Weisleder, D. *Lipids* **1970**, *5*, 678; **1972**, *7*, 191. The trans configuration of the 12,13 double bond in synthetic 11-HETE (**8**) and its methyl ester is similarly indicated by ^1H NMR data. **8** methyl ester (in $CDCl_3$): δ 5.64 (dd $J_{12,13}$ = 15.4, $J_{11,12}$ = 6.5 Hz, 1 H) for H(12) and 6.54 (dd, $J_{12,13}$ = 15.4, $J_{13,14}$ = 10.6 Hz, 1 H) for H(13).
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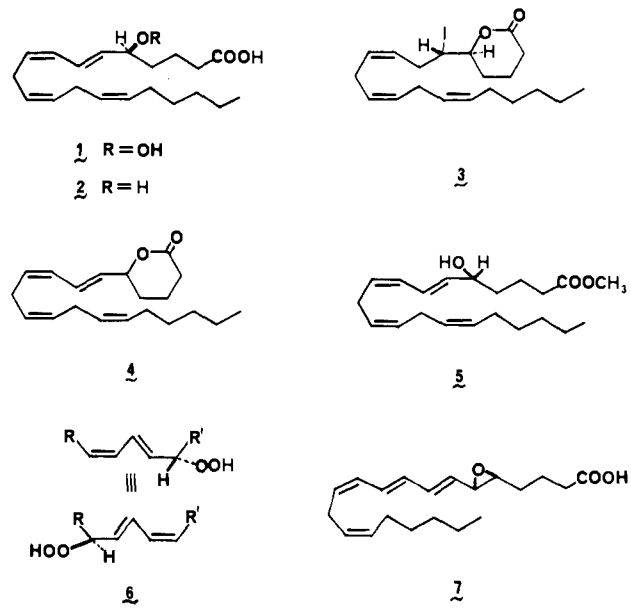
Chemical and Enzymic Syntheses of 5-HPETE, a Key Biological Precursor of Slow-Reacting Substance of Anaphylaxis (SRS), and 5-HETE

Sir:

The hydroperoxide (*S*)-5-HPETE (**1**) is the first intermediate[1,2] in a recently recognized series of biosynthetic processes which lead from arachidonic acid to a number of biologically active compounds, including **7** (leukotriene A) and the slow-reacting substance of anaphylaxis (SRS).[1c,3-7] In this communication we describe a simple chemical synthesis of **1** and the corresponding alcohol (**2**) in racemic form and also a straightforward enzymic preparation of the 5-(*S*)-chiral forms of **1** and **2**.

As previously described, the iodo lactone **3** is easily available from arachidonic acid in 86% yield (8 equiv of KI, 15 equiv of I_2, 5 equiv of $KHCO_3$ in 1:2 aqueous tetrahydrofuran (THF) at 0 °C for 18 h). Reaction of **3** with 2.5 equiv of 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene at 23 °C for 7 h produced the unsaturated lactone **4**[8] (72–85% yield), λ_{max} in ether 235



nm (ϵ 28 000), which was transformed into the methyl ester of (±)-5-HETE (**5**), λ_{max} in CH_3OH 235 nm (ϵ 28 600), by treatment with 6 equiv of triethylamine in methanol at 23 °C for 30 min (82% overall yield from iodo lactone **3**). The mass spectrum of the trimethylsilyl ether of **5** was identical with that previously reported for natural material obtained from rabbit leukocytes.[9] Saponification of **5** proceded quantitatively using lithium hydroxide in dimethoxyethane–water at 23 °C to afford (±)-5-HETE (**2**).

Reaction of the methyl ester of (±)-5-HETE in methylene chloride at −65 °C with 1.5 equiv of methanesulfonyl chloride and 1.8 equiv of triethylamine for 30 min produced a solution of the 5-mesylate which was cooled to −110 °C and treated with 50 equiv of dry hydrogen peroxide in ether (3 M) for a reaction time of 15 min. After quenching, extractive isolation, and thin layer chromatography on silica gel, the methyl ester of (±)-**1** was obtained in ~50% yield.[10] Saponification of the methyl ester was effected using a large excess of lithium hydroxide and hydrogen peroxide in dimethoxyethane–water (1:1) at 23 °C for 1.5 h to give after TLC purification on silica gel (with 95:5 CH_2Cl_2–CH_3OH for elution) pure (±)-5-HPETE (**1**). Treatment of (±)-**1** with diazomethane in ether afforded cleanly the corresponding methyl ester. Reduction of (±)-**1** with sodium borohydride in water at pH 9 produced (±)-5-HETE (**2**).

With synthetic 5-HETE and 5-HPETE in hand as chromatographic references, the possibility that various plant-derived lipoxygenases might be capable of converting arachidonic acid into 5-HPETE could readily be tested. The lipoxygenase of potato tubers was especially interesting for study since it has been reported to convert linoleic acid almost exclusively (95%) into 9-(*S*)-hydroperoxyoctadeca-*trans*-10,*cis*-12-dienoic acid.[11,12] The strong tendency to attach oxygen at the point nearest to the carboxylic function contrasts, for example, with the much studied soybean lipoxygenase which converts linoleic acid mainly into 13-(*S*)-hydroperoxyoctadeca-*cis*-9,*trans*-11-dienoic acid and arachidonic acid into 15-(*S*)-HPETE.[13] A highly significant (but previously unnoted) stereochemical pattern also emerges from previous studies on the stereochemistry of the hydroperoxides produced from plant lipoxygenases. Thus, soybean-, corn-, and potato-derived lipoxygenases generate the dissymmetric 1,5-disubstituted penta-*trans*-2,*cis*-4-dien-1-ol unit with the absolute configuration depicted in **6**, i.e., with *S* chirality at the oxygenated carbon atom. Obviously, it is this absolute stereochemical specificity which is required for the formation of (*S*)-5-HPETE from arachidonic acid.

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