These findings tend to discredit the idea that hydroxylated intermediates are involved in the biosynthesis of lipoic acid and support the idea that sulfur is introduced directly at the saturated carbons of octanoic acid as has been previously discussed.[2] This apparent lack of hydroxylated intermediates has been previously demonstrated in both biotin[11] and penicillin biosyntheses,[12] both being further examples of sulfur insertion at saturated carbons.

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(12) Aberhart, D. J. *Tetrahedron* **1977**, *33*, 1545–1559.
(13) White, R. H. *Biochemistry* **1978**, *17*, 3833–3840.

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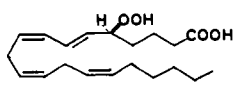
Simple Synthesis of the 11,12-Oxido and 14,15-Oxido Analogues of Leukotriene A and the Corresponding Conjugates with Glutathione and Cysteinylglycine, Analogues of Leukotrienes C and D

Sir:

Recent studies have led to the identification and synthesis of four of the naturally occurring "slow-reacting substances" (SRSs),[1,2] leukotriene C (**3**, RS = *S*-glutathionyl),[3,4] 11-*trans*-leukotriene C,[5] leukotriene D (**3**, RS = *S*-cysteinylglycyl), and leukotriene E (**3**, RS = cysteinyl).[3,5,6] These biologically active



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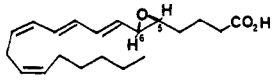

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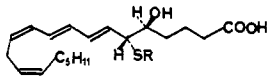

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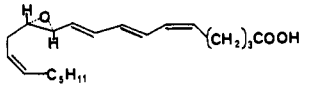

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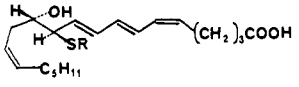

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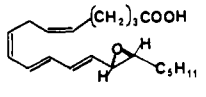

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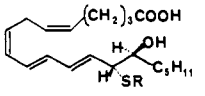

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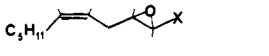

8 X = CHO
9 X = $(CH{=}CH)_2CHO$

(1) (a) Feldberg, W.; Kelaway, C. H. *J. Physiol. (London)* **1938**, *94*, 187. (b) Austen, K. *J. Immunol.* **1978**, *121*, 793. (c) Parker, C. W. *J. Allergy Clin. Immunol.* **1979**, *63*, 1.
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eicosanoids are of unusual interest in a number of areas of experimental medicine since they appear to be major agonists in various forms of immediate hypersensitivity, including asthma, allergic rhinitis, and urticaria.[7] They are formed biosynthetically from the precursor leukotriene A (**2**),[2] which in turn arises from (5*S*)-HPETE (**1**).[8,9] Since both (12*S*)-HPETE and (15*S*)-HPETE are known and can be generated enzymatically and since it is reasonable that these could be predecessors of epoxyeicosatetraenoic acids (EPETEs) analogous to leukotriene A (**2**), i.e., compounds **4** and **6**, respectively, it is obvious that two new families of sulfur-linked peptide conjugates (**5** and **7**) are in principle possible.[10] In view of the possibility that the EPETEs **4** and **6** and the peptide conjugates **5** and **7** might be naturally occurring, biologically active eicosanoids, we have undertaken the synthesis of these substances. The successful completion of this endeavor has made these compounds available both for biological study and for comparison with yet unidentified natural agonists. Such studies could also shed light on the biological role of naturally occurring HPETEs.[11]

The synthesis of the racemic methyl ester of the 11,12-oxido analogue (11,12-EPETE, **4**) of leukotriene A (**2**) started from undeca-2,5-diyn-1-ol[12] which was converted to the aldehyde **8** by the following sequence: (1) selective reduction of the 2,3 triple bond by using excess lithium aluminum hydride in ether at 23 °C[13] for 3 h to afford undeca-5-yn-*trans*-2-en-1-ol (96% yield), (2) epoxidation of the double bond by using 1.1 equiv of *m*-chloroperbenzoic acid in methylene chloride containing powdered sodium carbonate (98% yield), (3) cis hydrogenation of the triple bond by using 5% palladium-on-calcium carbonate catalyst and 10 equiv of triethylamine in tetrahydrofuran (THF) at 23 °C with 1 atmosphere of hydrogen (100% yield), and (4) oxidation of alcohol to aldehyde **8** (93%) by using in situ generated CrO_3·2Pyr in methylene chloride at 23 °C for 15 min.[14] The aldehyde **8**[14] was converted to the epoxy trienal **9** (88% yield) as described for the synthesis of **2**[3] with 1-lithio-4-ethoxybutadiene[15] as reagent, and finally **9** was converted to the methyl ester of **4** by sequential reaction in THF–hexamethylphosphoramide and dimethyl sulfoxide with the ylide from 5-(triphenylphosphonio)pentanoic acid[16] (at −78 to 0 °C over 2.5 h) followed by sodium bicarbonate and excess dimethyl sulfate at 23 °C for 1 h. After extractive isolation and chromatography on silica gel in the presence of triethylamine (1:1 hexane–ether solvent), (±)-**4**[14] [UV_{max} 269, 277, 288 nm (ε at 277 nm 40 000)] was obtained in 70% yield as the methyl ester[17]

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(7) See: (a) Austen, K. F. *Harvey Lect.* **1978**, *73*, 93. (b) Austen, K. F. In "Immediate Hypersensitivity"; Bach, M. K., Ed., Marcel Dekker: New York, **1978**.
(8) The pathway arachidonic acid → **1** → **2** → leukotriene B was first proposed by one of us (E.J.C.) in March 1977; see: (a) Corey, E. J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748. (b) Borgeat, P.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3213. (c) Corey, E. J.; Niwa, H.; Falck, J. R.; Mioskowski, C.; Arai, Y.; Marfat, A. *Adv. Prostaglandin Thromboxane Res.* **1980**, *6*, 19. (d) Rådmark, O.; Malsten, C.; Samuelsson, B.; Goto, G.; Marfat, A.; Corey, E. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 954.
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(10) An analogous series originating from the currently unknown 8-HPETE is also possible in principle.
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(12) Eiter, K.; Lieb, F.; Disselnkötter, H.; Oediger, H. *Justus Liebigs Ann. Chem.* **1978**, 658.
(13) All temperatures in °C.
(14) Satisfactory infrared, ultraviolet, proton magnetic resonance, and mass spectral data were obtained.
(15) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717.
(16) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1979**, *91*, 5675.
(17) The newly created cis double bond was generated with 90% selectivity (i.e., cis/trans = 9:1) as indicated by chromatographic analysis.

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(colorless oil), showing ^{1}H NMR peaks at δ 3.34 (s, 3 H, OCH_3), 3.13 (dd, J = 7.6, 1.9 Hz, 1 H at C-11), and 2.82 (td, J = 5.1, 1.9 Hz, 1 H at C-12).

A simple synthesis of 14,15-EPETE (**6**) as the methyl ester from (15*S*)-HPETE[11a,18] was effected as follows.[9] The methyl ester of (15*S*)-HPETE (formed from the acid by using CH_2N_2 in ether at 0 °C) in 1:1 methylene chloride–ether at −110 to −105 °C was treated with 5 equiv of 1,2,2,6,6-pentamethylpiperidine[9] and 2 equiv of trifluoromethanesulfonic anhydride for 45 min, quenched (at −105 °C) with pentane–triethylamine, and isolated extractively (with the cold aqueous phase at ca. pH 9). The crude product consisted of the desired methyl ester of **6** and the 15-ketone, arising from simple dehydration of 15-HPETE in a ratio of 2:1. Because the chromatographic separation of this mixture was not easy, it was treated with sodium borohydride in dimethoxyethane at 0 °C to reduce the ketone and then chromatographed on silica gel by using 7:3 pentane–ether containing triethylamine[9,19] to afford the pure methyl ester of **6** (40%)[14] [UV_{max} (in CH_3OH as for **4**) 268, 279, 288 nm (ϵ at 279 nm 40 000); $[\alpha]^{23}_D$ −5.0° (*c* 0.3, cyclohexane containing 0.2% triethylamine)]; ^{1}H NMR data were in accord with **6** although not very characteristic.

The *S*-glutathione conjugates of **4** and **6** (**5** and **7**, RS = *S*-glutathionyl) were prepared as described previously for the conversion of leukotriene A (**2**) to leukotriene C (**3**, RS = *S*-glutathionyl).[3] The methyl ester of **4** or **6** was treated in a minimum of methanol containing **4** equiv of triethylamine with 2 equiv of *N*-(trifluoroacetyl)glutathione dimethyl ester at 23 °C for 4 h, and the resulting product [UV_{max} (in CH_3OH) 268, 277 (ϵ 40 000), 288 nm] was purified by reversed-phase (RP) chromatography [RP-high-performance liquid chromatography (high-performance LC)] with a Waters Associates μ-Bondapak C_{18} column with 65:35:0.1 CH_3OH–H_2O–HOAc buffered to pH 5.6 by the addition of 2.0 M NH_4OH. From racemic **4** methyl ester, as expected, two separable diasteromeric peptide conjugates were obtained in equal amounts whereas **6** (optically active) gave only a single conjugate. Each tripeptide conjugate was deprotected by exposure to 25 equiv of 1.0 M lithium hydroxide in 5:1 dimethoxyethane–water at 0 °C for 30 min and 23 °C for 12 h, and purification was effected by RP-high-performance LC as described above. Retention volumes (R_v) of the two diastereomers of **5** (RS = glutathionyl) were almost identical (4.8), and that of **7** (RS = glutathionyl) was 5.5[20] (leukotriene C = 6.4).

The *S*-cysteinylglycyl conjugates were obtained from the methyl esters of **4** and **6** in a similar way[5] by using *N*-(trifluorocysteinyl)glycine methyl ester[5] for forming the dipeptide conjugate and purifying the final deprotected products by RP-high-performance LC; R_v values were 6.2 and 6.8 for the two diasteromers **5** (RS = *S*-cysteinylglycyl) and 7.7 for **7** (RS = *S*-cysteinylglycyl) (leukotriene C = 6.4).

Arachidonic acid has in the past several years emerged as one of nature's most versatile substrates for the synthesis of important natural products, recalling such celebrated molecules as squalene, δ-aminolevulinic acid, and shikimic acid. It seems not unreasonable that this efficiency might extend to pathways via EPETEs to peptide conjugates such as **5** and **7**. With the successful synthesis of these substances by efficient and simple routes, the stage is now set for the study of their biological properties and a search to determine their presence or absence in living systems. These investigations will be reported in due course.[21]

(18) Baldwin, J. E.; Davies, D. I.; Hughes, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 115.

(19) For the synthesis of the peptide S-conjugates **7**, this purification of **6** methyl ester was unnecessary.

(20) Each of the S-conjugates **5** and **7** showed UV_{max} (CH_3OH) at 270, 280 (ϵ 40 000), and 290 nm.

(21) This research was assisted financially by the National Science Foundation and the National Institutes of Health.

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Tantalum–Neopentylidene Hydride and Tantalum–Neopentylidyne Hydride Complexes[1]

Sir:

α-Hydride elimination is the name given to the postulated intramolecular formation of an alkylidene–hydride complex from an alkyl complex. So far, however, there is no unambiguous example of such a reaction.[2] Since we have prepared various "d^0"[3] tantalum–neopentylidene complexes,[4] we thought we might be able to prepare analogous neopentylidene hydride complexes by reducing Ta(V)–neopentyl complexes by two electrons, a process which formally involves an "α-elimination" reaction. Another version of "α elimination" might be the conversion of a d^2 neopentylidene complex to a neopentylidyne hydride complex. We report here several examples of such reactions along with one reduction which yields a "d^2" neopentylidene complex which is stable toward formation of an alkylidyne–hydride complex.

The reduction of $Ta(CH_2CMe_3)Cl_4$ with 2 equiv of 0.4% sodium amalgam in ether/tetrahydrofuran in the presence of 5 equiv of PMe_3 under N_2 or Ar gives **1a** as beige crystals (eq 1) in moderate

$$Ta(CR_2CMe_3)Cl_4 + 2Na/Hg + 5PMe_3 \xrightarrow{\text{ether/THF}} Ta(CRCMe_3)(R)Cl_2(PMe_3)_3 \quad (1)$$

1a, R = H
1b, R = D

yield.[5] An analogous reduction of $Ta(CD_2CMe_3)Cl_4$ gave **1b**. The infrared spectrum of **1a** shows two medium strength peaks at 2440 and 1730 cm^{-1} which shift to 1805 and 1270 cm^{-1} in **1b**. The former we assign to the ν_{CH_α} stretch of a distorted neopentylidene ligand (one with a large Ta–C_α–C_β angle[4,6]). The latter, broader peak we assign to ν_{TaH}.

NMR studies (^{1}H, ^{31}P,[7] and ^{13}C[8]) suggest this formulation is correct. The ^{1}H NMR spectrum (270 MHz, −20 °C) of **1a** shows an eight line resonance due to Ta–H at δ 10.00 (J_{HP_A} = 17.7 Hz, J_{HP_B} = 101.9 Hz, J_{HP_C} = 91.0 Hz) which is further split due to coupling to the neopentylidene α-hydrogen atom (J_{HH_α} = 1.5 Hz). The signal for the neopentylidene α-hydrogen atom (a broadened doublet) is found at δ 0.24. Both are absent in **1b**. The ^{13}C NMR spectrum contains a signal for the neopentylidene α-carbon atom at δ 216 with J_{CH_α} = 72 Hz and J_{CP} = 6.4 Hz. The low value for J_{CH_α} also suggests that this neopentylidene ligand is highly

(1) Multiple Metal–Carbon Bonds. 18. Part 17 in press.

(2) (a) The best evidence for a process of this sort is Green's isolation of $[W(\eta^5\text{-}C_5H_5)_2(CD_2PPhMe_2)(D)]^+$ from the reaction of $[W(\eta^5\text{-}C_5H_5)_2(\eta^2\text{-}C_2H_4)(CD_3)]^+$ with $PPhMe_2$.[2b] He proposes that "$[W(\eta^5\text{-}C_5H_5)_2(CD_3)]^+$" is in equilibrium with $[W(\eta^5\text{-}C_5H_5)_2(CD_2)(D)]^+$: (b) Cooper, N. J.; Green, M. L. H. *J. Chem. Soc., Dalton Trans.* **1979**, 1121–1127, and references therein.

(3) By "d^0" we mean Nb- or Ta-alkylidene complexes containing three anionic ligands such as chlorides, alkyl groups, etc.[4] If one draws an analogy between an alkylidene and an oxo ligand (O^{2-}), then the metal is d^0. In order to be consistent, we must call alkylidyne ligands trianions.

(4) Schrock, R. R. *Acc. Chem. Res.* **1979**, *12*, 98–104.

(5) Anal. Calcd for $TaC_{14}H_{38}Cl_2P_3$: C, 30.51; H, 6.95. Found: C, 30.37; H, 7.01.

(6) (a) There is good evidence that a neopentylidene ligand is often severely distorted in some "d^0" alkylidene complexes toward a "neopentylidyne" ligand with a pseudo-bridging H_α between C_α and the metal.[4,6b] This distortion seems severe when "softer" ligands are present (η^5-C_5R_5, Br, PR_3) and comparatively mild when "harder" ligands are present (OR,[6c] O[6d]). (b) Schultz, A. J.; Williams, J. M.; Schrock, R. R.; Rupprecht, G. A.; Fellmann, J. D. *J. Am. Chem. Soc.* **1979**, *101*, 1593–1595. (c) Schrock, R.; Rocklage, S.; Wengrovius, J.; Rupprecht, G.; Fellmann, J. *J. Mol. Catal.* **1980**, *8*, 73–83. (d) Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Missert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515–4516.

(7) ^{31}P{^{1}H} NMR (ppm from H_3PO_4, toluene-d_8, 109.29 MHz, −30 °C) showed a 12-line ABC spectrum with peaks at −26.2 (A), −17.5 (B), and −4.1 (C) with $J_{P_AP_C}$ = 115.0 Hz, $J_{P_BP_C}$ = 51.1 Hz, and $J_{P_AP_B}$ = 29.3 Hz. Selectively decoupling the PMe_3 protons yields a 24-line pattern with J_{P_AH} = 17.3 Hz, J_{P_BH} = 101.0 Hz and J_{P_CH} = 90.6 Hz.

(8) ^{13}C NMR (ppm from Me_4Si, toluene-d_8, 67.89 MHz, −15 °C, gated ^{1}H decoupled): 216.0 (d of octet, J_{CP} ≈ 6.4 Hz, J_{CH} = 72 Hz, $CHCMe_3$), 46.23 (s, $CHCMe_3$), 34.13 (q, J_{CH} = 124 Hz, $CHCMe_3$), 22.82 (qd, J_{CP} = 24.82 Hz, J_{CH} ≈ 131 Hz, PMe_3(A)), 18.76 (qd, J_{CP} = 26.85 Hz, J_{CH} ≈ 131 Hz, PMe_3(B)), 16.26 (qd, J_{CP} = 20.69 Hz, J_{CH} ≈ 131 Hz, PMe_3(C)).

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