The lipoxygenase derived from potato tubers *in fact* was found to convert arachidonic acid into a mixture of products which included 5-HPETE (15% yield after correction for recovered arachidonic acid). The potato enzyme used was obtained simply by brief homogenization of potato tubers in pH 4.5 acetate buffer, filtration through gauze and precipitation with ammonium sulfate (50% saturation after a prior precipitation at 25% saturation), dissolution in pH 6.8 phosphate buffer, and dialysis as previously described.[12] The solution of lipoxygenase so obtained could be stored at 0 °C for up to 1 week with only minor loss of activity.

Preparative experiments with the enzyme were performed starting with an aqueous solution of ammonium arachidonate at pH 9 adding Triton X-100 (dispersant), Antifoam B and 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical (as radical trap), adjusting the pH to 6.4, adding enzyme solution, and stirring with oxygen for 12 min. Acidification to pH 4.0, extractive isolation with ether, and purification by thin layer chromatography on silica gel (5% CH_3OH, 25% hexane, 70% ether at 0 °C) afforded pure (*S*)-5-HPETE (**1**), identical chromatographically and by ^1H NMR with (±)-5-HPETE synthesized chemically as described above. Reduction of (*S*)-5-HPETE by cold aqueous sodium borohydride at pH 9 afforded (*S*)-5-HETE (chromatographically and spectroscopically identical with (±)-5-HETE synthesized chemically as described above). The absolute configuration of the enzymatically produced 5-HPETE and 5-HETE was shown to be *S* (as in **1** and **2**) by two different methods. The methyl ester of 5-HETE of enzymatic origin (made with ethereal diazomethane) was converted into the menthyloxycarbonyl derivative using the chloroformate of *l*-menthol[14] and pyridine for 3 h at 23 °C and then subjected to the sequence[15] (1) ozonolysis in methylene chloride at −20 °C; (2) oxidation with peracetic acid in ethyl acetate at 23 °C for 12 h; and (3) esterification with diazomethane in ether. The resulting menthyloxycarbonyl derivative of dimethyl 2-hydroxyadipate was characterized by gas chromatography (2% QF-1 fluorosilicone column at 185 °C) as the diastereomer of shorter retention time,[9a,16] thereby proving the *S* configuration at C-5 in **1** and **2**. The optical rotation measured for the methyl ester of **2** (*c* 0.99 in ethanol) was positive and increased with decreasing wavelength, e.g., $[\alpha]^{23}_{436}$ +12.42°, $[\alpha]^{23}_{D}$ +4.73°. The same dextrorotation with increasing value for decreasing wavelength has been observed previously for several alcohols having the dissymmetric unit corresponding to **6**.[17] The criterion of increasing dextrorotation as a function of decreasing wavelength in the range 589–436 nm is thus a simple and convenient indicator of chirality corresponding to **6** in an HETE methyl ester.

A lipoxygenase which converts arachidonic acid into 5-HPETE has also been found in tomato; however, the preparation using the potato[18] enzyme has been found to be cleaner and more convenient. Research is in progress on the action of a variety of other plant lipoxygenases on arachidonic acid.

By the use of radiolabeled arachidonic acid and the lipoxygenase of potato radiolabeled (*S*)-5-HPETE was readily prepared. This is now under study in the laboratory of Professor B. Samuelsson to check incorporation into SRS and other eicosanoids[2] in this series. The chemical conversion of (*S*)-5-HPETE to 5(*S*),6-oxido-7,9-*trans*-11,14-*cis*-eicosapentaenoic acid (**7**), the direct precursor of SRS, is described in a separate note.[19,20]

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(8) Satisfactory infrared and proton magnetic resonance (^1H NMR) spectra were obtained for a chromatographically homogeneous sample of each substance described herein. In addition mass spectral data were obtained for each substance except for the unstable hydroperoxides. The trans stereochemistry of the newly introduced double bond in **4** was clear from ^1H NMR data ($CDCl_3$): protons at C-7 and C-8 were farthest downfield; δ 6.62 (dd, J = 10.5, 15 Hz, 1 H) for H(7) and 5.99 (dd, J = 10.5, 10.5 Hz, 1 H) for H(8). See Gardner, H. W.; Weisleder, D. *Lipids* **1970,** *5,* 678; **1972,** *7,* 191. In addition the expected trans HC=CH bond was present in the IR spectrum at 985 cm^{-1}. Products **1, 2,** and **5** showed the same characteristic ^1H NMR peaks for the *cis,trans*-HC=CH—CH=CH– unit; for example, **5** had δ 6.54 (dd J = 10.5, 15 Hz, 1 H) for H(7) and 5.98 (dd, J = 10.5, 10.5 Hz, 1 H) for H(8).

(9) (a) Borgeat, P.; Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1976,** *251,* 7816. (b) Hydrogenation of the methyl ester **5** afforded methyl 5-hydroxyeicosanoate, the structure of which was clear from the mass spectrum. See Christopher, J. P.; Axelrod, B. *Biochem. Biophys. Res. Commun.* **1971,** *44,* 731.

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(16) A reference sample of the two diastereomers obtained from (±)-dimethyl 2-hydroxyadipate and the chloroformate of *l*-menthol showed two peaks under these gas chromatographic conditions. The mass spectra of the reference material and the product of degradation of **2** were identical.

(17) See: (a) Pattee, H. E.; Singleton, J. A. *J. Agric. Food Chem.* **1979,** *27,* 216. (b) Egmond, M. R.; Veldink, G. A.; Vliengenthart, J. F. G.; Boldingh, J. *Biochim. Biophys. Acta* **1975,** *409,* 399.

(18) Fresh Florida "red-skin" or Maine potatoes have been employed in our work.

(19) This research was assisted by a grant from the National Science Foundation. We are indebted to Mr. P. Malan of this department for helpful advice on the enzymic experiments.

(20) The results outlined in this paper were previously described in a lecture at the Karolinska Institutet, Stockholm, Sept 14, 1979.

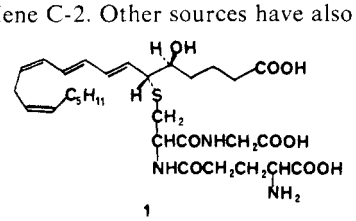
E. J. Corey,* John O. Albright
Alan E. Barton, Shun-ichi Hashimoto
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received October 17, 1979

Stereospecific Total Synthesis of a "Slow Reacting Substance" of Anaphylaxis, Leukotriene C-1

Sir:

"Slow reacting substance" (SRS), though known since 1938,[1] has only recently been characterized in terms of molecular structure.[2-5] We record here the first total synthesis of an SRS, leukotriene C-1 (**1**), isolated from mouse mast cell tumor,[6] along with variable amounts of a second less active SRS, leukotriene C-2. Other sources have also been used to



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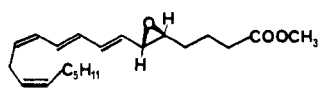

2

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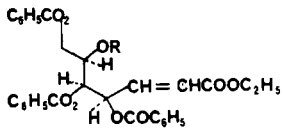
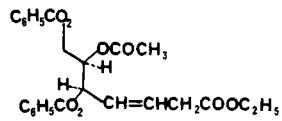
provide SRS,[7,8] but the purity and exact nature of such materials are unclear. The synthetic approach described herein is stereospecific, efficient, and provides the naturally occurring antipodal form of the leukotriene C-1 without the need for resolution. The unambiguous nature of the synthesis and the identity of synthetic and naturally derived leukotrienes provide the first rigorous proof of structure in all detail.

A key intermediate in the synthesis *and biosynthesis* of leukotriene C-1 is (−)-methyl *trans*-5(*S*),6(*S*)-oxido-7,9-*trans*-11,14-*cis*-eicosatetraenoate (**2**) (leukotriene A methyl ester[2,3]), which had previously been surmised to be a precursor (as the corresponding acid) of new eicosanoids[9] and synthesized[9] in racemic form. The synthesis of the Δ^9-cis stereoisomer of **2** (**14**) is also described herein. This substance and the (±)-5,6-*cis*-epoxide corresponding to **2**[9] were useful in determining the stereochemistry of the leukotrienes, which was unclear until the completion of this investigation.

Reaction of the 2,3,5-tribenzoyl derivative of D-(−)-ribose[10] with 1.1 equiv of ethoxycarbonylmethylenetriphenylphosphorane[11] and a trace of benzoic acid[12] in dimethoxyethane (DME) at reflux for 4 h afforded the α,β-unsaturated ester **3** (as a mixture of *E* and *Z* isomers in a ratio of 86:14, R_f values 0.82 and 0.65 by TLC analysis[13] using 10:1 methylene chloride–methanol) as a colorless oil in 96% yield after chromatography on silica gel (elution with 4:1 methylene chloride–methanol).[14] Acetylation of **3** (10 equiv of acetic anhydride containing a trace of sulfuric acid at 23 °C for 3 h) produced the oily monoacetate **4** (100%) which, upon treatment with



3 R=H
4 R=OAc



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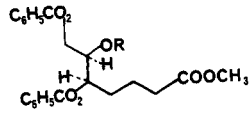
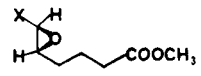


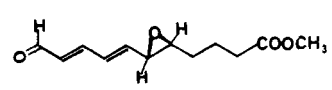
6 R=H
7 R=Tos



8 X=CH$_2$OH
9 X=CHO

excess powdered 95% zinc amalgam[15] in ether saturated with dry hydrogen chloride at 15 °C for 6 h, gave the deoxygenated β,γ-unsaturated ester **5** (colorless oil, mixture of *E* and *Z* isomers, R_f 0.49 and 0.51 using 20:1 methylene chloride–methanol, ratio 85:15) in 93% yield. Catalytic hydrogenation of **5** (10% Pd/C catalyst, 1 atm of H_2 in methanol at 23 °C) provided the oily dihydro derivative (100%) which, upon exposure to 0.005% dry hydrogen chloride in methanol at 23 °C for 72 h, produced the monohydroxy methyl ester dibenzoate **6**, $[\alpha]^{25}_D$ +11.4° (*c* 0.90, $CHCl_3$), in 99% yield. The monotosylate **7**, $[\alpha]^{25}_D$ +34.5° (*c* 1.72, $CHCl_3$), prepared from **6** using 1.2 equiv of tosyl chloride in dry pyridine (conc solution) at 23 °C for 6 h and at 50 °C for 3 h (98% yield), upon treatment with 5 equiv of potassium carbonate in methanol at 23 °C for 2 h, led cleanly to the trans epoxide **8**, $[\alpha]^{24}_D$ −37.4° (*c* 0.27, in $CHCl_3$), as a colorless oil in 98% yield.[16,17] Oxidation of the epoxy primary alcohol **8** using excess Collins reagent[18] in methylene chloride at 23 °C for 15 min afforded the epoxy aldehyde **9**, $[\alpha]^{25}_D$ +68.6° (*c* 0.31, $CHCl_3$), in 96% yield.[19]

Reaction of the epoxy aldehyde **9** with 1-lithio-4-ethoxybutadiene[20] at −78 °C in tetrahydrofuran (THF) for 1 h afforded, after quenching with aqueous sodium bicarbonate and extractive isolation, the secondary alcohol resulting from nucleophilic addition to formyl which without purification was treated with 1.2 equiv of methanesulfonyl chloride and 1.4 equiv of triethylamine in methylene chloride at −45 °C for 15 min and then pH 7.0 phosphate buffer at −45 to 0 °C. After extraction, rapid chromatography, and recrystallization from 1:1 ether–hexane, the dienal ester **10**,[21] mp 36 °C, $[\alpha]^{25}_D$



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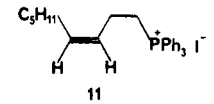
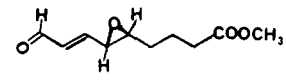


11

−27.3° (*c* 1.97, $CHCl_3$), λ^{EtOH}_{max} 273 nm (e 27 000), was obtained in 63% overall yield from **9**. Reaction of the phosphonium iodide **11**[9] with 1 equiv of *n*-butyllithium in THF at −78 °C for 15 min gave the corresponding ylide[9] which after addition of 12 equiv of hexamethylphosphoric amide was allowed to react with slightly less than 1 equiv of the aldehyde **10** at −78 °C for 5 min to provide, after extractive isolation and rapid chromatography on silica gel in the presence of triethylamine, the epoxy tetraene ester **2**, $[\alpha]^{25}_D$ −21.9° (*c* 0.32, cyclohexane), λ^{MeOH}_{max} 269, 278, 289 nm (ϵ_{278} 40 000), as a pale yellow oil in 56% yield.

The isomeric epoxy tetraene ester **14** was also synthesized from epoxy aldehyde **9** as follows. Reaction of the *tert*-butyl-



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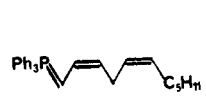

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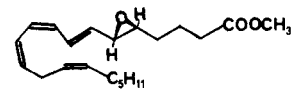
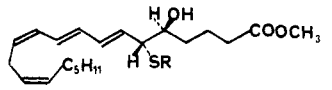


14

imine of trimethylsilylacetaldehyde with 1 equiv of *sec*-butyllithium in ether at −78 °C for 45 min generated the α-lithio derivative[22] which was cooled to −110 °C and allowed to react with 0.9 equiv of **9** at −110 °C for 15 min and at −78 °C for 30 min and finally quenched with pH 7 phosphate buffer. Extractive isolation and chromatography on silica gel gave the enal ester **12** as a colorless oil, $[\alpha]^{25}_D$ −23.4° (*c* 0.7, $CHCl_3$), λ^{EtOH}_{max} 228 nm (ϵ 16 000), in 46% yield. The ylide **13** was generated from the corresponding phosphonium mesylate[23] by reaction with 1 equiv of lithium diisopropylamide in THF at −95 °C for 15 s and treated with 20 equiv of cold (ca. −60 °C) hexamethylphosphoric amide in THF for 10 s with stirring (bath at −95 °C) and then the aldehyde **12** was added. After 20 min at −95 °C, the reaction mixture was quenched with pH 7 buffer and the product was isolated by extraction and chromatographed rapidly on silica gel in the presence of triethylamine to give methyl *trans* 5(*S*),6(*S*)-oxido-7-*trans*-9,11,14-*cis*-eicosatetraenoate (**14**) admixed with the isomer **2** as an oil (~25% yield), λ^{MeOH}_{max} 266, 276, 286 nm (ϵ_{276} 40 000). The R_f values of **14** and **2** were the same in several solvents (e.g., 0.48 on silica gel using 1:1 ether–hexane containing triethylamine),[24] and consequently purification of **14** was not possible at this stage. The presence of two geometrical isomers at the 9,10 double bond is clear from ^1H NMR data on the mixture compared with pure **2** and from study of further reactions. An investigation of the coupling of ylide **13** with several model aldehydes (e.g., crotonaldehyde) reveals that the reaction produces cis and trans coupling products even under conditions which normally lead to >95% cis isomer.[25] The mixture of **14** and **2** was nonetheless found to be useful in the preparation of the 9,10-cis stereoisomer of leukotriene C-1 since purification could be effected in the next step (vide infra).

Reaction of epoxy tetraene **2** in a minimum of methanol with a variety of sulfhydryl compounds (2–3 equiv) and triethylamine (3–4 equiv) at 25 °C for ~4 h resulted in good yields of the product of S_N2 displacement by nucleophilic sulfur at C-6 to form derivatives of structure **15**. These products characteristically show λ^{MeOH}_{max} 280 nm (ϵ ~40 000) and ^1H NMR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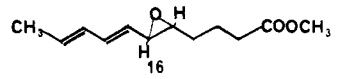
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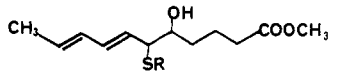
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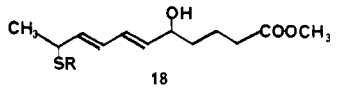
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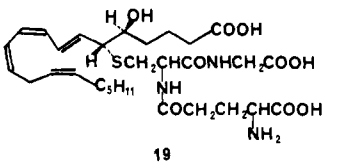
peaks characteristic of C=C—CH_2—C=C at δ 2.9-3.1, but no peak for an allylic carbinol proton [C=C—C*H*(OH)] in the 4.1-4.25-ppm region. Preliminary studies with the model epoxy ester **16** had shown unambiguously that the reaction with RSH-Et_3N-CH_3OH afforded exclusively S_N2 displacement at C-6 to give **17** whereas reaction with RSH-lithium perchlorate-CH_3OH yielded the isomeric product type having structure **18.** The structures of **17** and **18** (easily separated by chromatogrphy with the latter being the more polar, e.g., for R = $CH_2CH_2COOCH_3$) were determined by ^1H NMR analysis with spin decoupling which also served to provide valuable chemical-shift data. A single coupling product was obtained from the reaction of **2** with *N*-trifluoroacetylglutathione dimethyl ester[26] (2 equiv) and triethylamine (3 equiv) in methanol at 23 °C for 4 h in 80% yield. The homogeneity of the product, λ_{max}^{MeOH} 270, 280, 290 nm (ε 32 000, 40 000, 31 000), was demonstrated by high pressure liquid chromatography (HPLC) (cyanopropyl μ-Porasil column of Waters Associates, Inc., with 80:20:1 hexane-methylene chloride-isopropyl alcohol).[27] Selective hydrolysis of the *N*-trifluoroacetyl triester in 0.03 M potassium carbonate 0.03 M potassium bicarbonate in 95:5 water-methanol at 23 °C for 12 h proceeded quantitatively as determined by reversed-phase HPLC analysis (Waters Associates μ-Porasil-C_{18} reversed-phase column using 65:35 methanol-water containing 0.1% acetic acid buffered to pH 5.6 with ammonium hydroxide) to afford a single product, **1**, λ_{max}^{MeOH} 270, 280, 290 nm (ε 32 000, 40 000, 31 000), homogeneous by reversed-phase HPLC analysis.[28] This synthetic product (**1**) was indistinguishable from leukotriene C-1 of natural origin[2] in terms of ultraviolet absorption,[2] chromatographic behavior by reversed-phase HPLC,[2] rate and product of reaction with soybean lipoxygenase,[2] and biological activity.[29]

The glutathione conjugate **1** could also be made from **2** by the following sequence: (1) reaction with glutathione (3 equiv) and triethylamine (12 equiv) in a minimum of methanol at 23 °C for 4 h to give a single coupling product as determined by reversed-phase HPLC (same ultraviolet absorption as **1**); and (2) hydrolysis of the monoester so obtained using 0.1 M potassium carbonate in 98:2 water-methanol at 23 °C for 3 h. The product was identical with **1** prepared via the *N*-trifluoroacetyl trimethyl ester of **1**.

Reaction of the mixture of **14** and **2** obtained as described above with glutathione and triethylamine in methanol, followed by methyl ester cleavage (0.1 M potassium carbonate as above), afforded, in addition to **1** (derived from **2**), a new conjugate (**19**) which could be separated from **1** by reversed-phase HPLC. This substance was easily distinguished from leukotriene C-1 by its ultraviolet maximum (277 vs. 280 nm for **1**) and reversed-phase HPLC analysis: retention times for **19,** leukotriene C-1, and leukotriene C-2 were 23.5, 25, and 28.5 min, respectively, under the conditions cited above. Structure **19** is thus excluded for leukotrienes C-1 and C-2.


19

The epoxide **2** has also allowed the synthesis of the analogues of **1** having the sulfur of cysteine and cysteinyl glycine attached to C-6 rather than glutathione. These substances (actually prepared at an earlier date than **1**, using analogous procedures) were found to be distinctly different (reversed-phase HPLC,[30] biological activity) from leukotrienes C-1 and C-2.[31]

As a result of the investigations described herein, pure synthetic SRS, leukotriene C-1, is now available in multigram amounts (as opposed to a few micrograms from natural sources). Further the detailed structure has been established unambiguously.[32]

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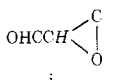
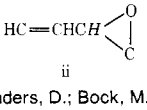
(13) All R_f values given herein were obtained using thin layer chromatography on silica gel plates.
(14) Infrared, proton magnetic resonance, and mass spectral (and where appropriate ultraviolet spectral) data were obtained using purified, chromatographically homogeneous samples of each synthetic intermediate, and were in agreement with the assigned structure.
(15) For preparation see Elphimoff-Felkin, I.; Sarda, P. *Tetrahedron Lett.* **1972,** 725.
(16) The trans epoxy ester **8** was shown to be different from the stereoisomeric cis epoxy ester which was synthesized (as the racemate) for comparison by oxidation of methyl 7-hydroxy-*cis*-5-heptenoate with peracetic acid.
(17) ^1H NMR (80 MHz) data for **8** (δ in $CDCl_3$): 3.56 (dd, $J_{a,b}$ = 13, $J_{6,7}$ = 2.2 Hz, 1 H) (H_a of CH_2OH), 3.87 (dd, $J_{a,b}$ = 13, $J_{6,7}$ = 3.9 Hz, 1 H) (H_b of CH_2OH). IR (cm^{-1} in CCl_4): 3450 (OH), 1730 ($COOCH_3$).
(18) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968,** 3363.
(19) ^1H NMR (80 MHz) data for **9** (δ in $CDCl_3$): 9.01 (d, $J_{6,7}$ = 6.1 Hz, 1 H) (formyl H), 3.14 (dd, $J_{6,7}$ = 6.1, $J_{5,6}$ = 2.0 Hz, 1 H) (i).


i

(20) Wollenberg, R. H. *Tetrahedron Lett.,* **1978,** 717. We are indebted to Dr. Wollenberg for a sample and spectra of the precursor reagent, 1-tributylstannyl-4-ethoxybutadiene.
(21) ^1H NMR (80 MHz) data for **10** (δ in $CDCl_3$): 9.57 (d, $J_{10,11}$ = 7.8 Hz, 1 H) (formyl H), 3.21 (dd, $J_{6,7}$ = 7.2, $J_{5,6}$ = 2.0 Hz, 1 H) (ii), 2.91 (td, $J_{4,5}$ = 5.9, $J_{5,6}$ = 2.0 Hz, 1 H) (iii). IR (cm^{-1} in CCl_4): 1730 ($COOCH_3$), 1675, 1635 (*E,E*)-dienal)).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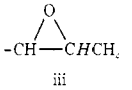
iii

(22) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976,** 7.
(23) The phosphonium salt was prepared from the corresponding mesylate and triphenylphosphine in concentrated solution in acetonitrile. *cis,cis*-2,5-Undecadien-1-ol was prepared by Lindlar reduction of the corresponding diyne prepared according to Eiter, K.; Lieb, F.; Disselnkötter, Oediger, H. *Justus Liebigs Ann. Chem.* **1978,** 658, and converted to the mesylate by reaction with 1.2 equiv of methanesulfonyl chloride and 1.5 equiv of triethylamine at −20° for 0.5 hr followed by extractive isolation.
(24) Because of the instability of the tetraene epoxides **2** and **14** under acidic conditions, silica gel must be deactivated by triethylamine before chro-

matography. Since these compounds are also air sensitive,[9] they were stored under argon in frozen benzene containing 4-hydroxy-2,2,6,6-tetramethylpiperidinooxy free radical as antioxidant.
(25) These studies which will be published separately show (from ^{1}H NMR data) that the cis double bond in conjugation with the ylide retains its configuration during ylide generation and coupling, an important finding for this and other applications.
(26) The *N*-trifluoroacetyl derivative of glutathione dimethyl ester was obtained by reaction of the tetramethyl ester of the disulfide form of glutathione (Watanabe, T.; Kohno, K.; Noda, K.; Hayashi, K. Japanese Patent 6 820 166, 1968; *Chem. Abstr.* **1969**, *70*, 58286j) with trifluoroacetic anhydride and powdered sodium carbonate in methylene chloride with stirring at 0 °C for 30 min, followed by isolation and disulfide cleavage using triphenylphosphine in 2:1 dimethoxyethane–water at 23 °C for 3 h.
(27) In contrast four stereoisomeric products were obtained (as expected) by reaction of *N*-trifluoroacetylglutathione methyl ester with the mixture of 5,6-cis and 5,6-trans isomers of (±)-**2** synthesized as described earlier;[9] these were readily separated by HPLC with one component corresponding to the product from (−)-**2**.
(28) Hydrolysis of the mixture of stereoisomeric[27] *N*-trifluoroacetyl trimethyl esters afforded a mixture of **1** and 3 stereoisomers which was readily resolved by reversed-phase HPLC.
(29) Superimposible lines were obtained in extensive dose-response studies using synthetic **1** and leukotriene C-1 with guinea pig ileum as test tissue.[2,5]
(30) Reversed-phase HPLC retention times were in the order cys analogue ≫ cys gly analogue > **1**, as expected.
(31) The attachment of a glutathione moiety at C-6 in leukotriene C-1 rather than cys or cys gly units has also been demonstrated by amino acid determination.[4]
(32) The research at Harvard was assisted by a grant from the National Science Foundation, NIH postdoctoral fellowships to D.C. and A.M., a research fellowship to G.G. from the Takeda Chem. Ind. Ltd., and a NATO fellowship to C.M. The work in Stockholm was supported by a grant from the Swedish Medical Research Council (Project 03X-217).

E. J. Corey,* David A. Clark, Giichi Goto
Anthony Marfat, Charles Mioskowski
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Bengt Samuelsson, Sven Hammarström
Department of Chemistry, Karolinska Institutet
S-104 01 Stockholm, Sweden
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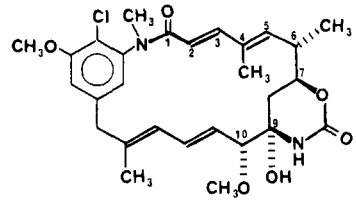
Total Synthesis of (−)-*N*-Methylmaysenine

Sir:

The first total synthesis of a maytansenoid, (±)-*N*-methylmaysenine, (±)-**1**, was recently reported from these labo-



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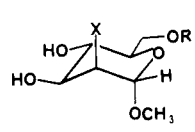
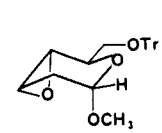
ratories.[1,2] We now describe a synthetic route to *N*-methylmaysenine which yields this substance in the natural optically active (levo) form without the need of resolution. The individual steps in the synthesis proceed in very good yields and the various chiral centers are established with high stereochemical efficiency.

Commercially available tri-*O*-acetyl-D-glucal (Pfanstiehl Laboratories, Inc.) was transformed into the epoxy trityl (Tr) ether **5** in 62% overall yield by a sequence of steps which were readily conducted on a 0.5-mol scale. The acetyl groups of tri-*O*-acetyl-D-glucal were cleaved by methanolysis (2 M solution of triacetate in dry methanol containing as catalyst 0.05 mol of sodium methoxide at 23 °C for 1.5 h), and the resulting solution of unsaturated triol was treated with 1.05 equiv of mercuric acetate for 2.5 h at 23 °C to effect methoxy mercuration. The mercuration product **2** was obtained as a crystalline solid by filtration through Celite, concentration under reduced pressure to ~25% of the original volume, and filtration; further concentration of the filtrate afforded a second crop of crystals (total yield 75%).[3] Reaction of a solution of **2** in methanol (1.3



2, X = HgOAc, R = H
3, X = R = H
4, X = H, R = Tr



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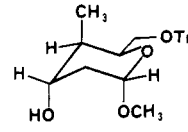

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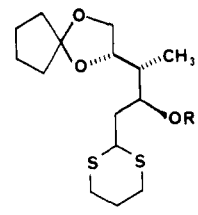
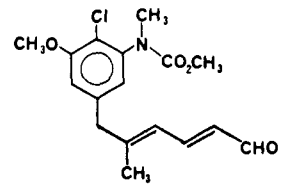


7, R = H
8, R = MEM



9

M) with 1.5 equiv of sodium chloride (15 min at 23 °C) produced a solution of the corresponding chloromercurial which was cooled to 0 °C and treated with a slight excess (1.05 equiv) of sodium borohydride in isopropyl alcohol. After 30 min at 0 °C, methanol was removed under reduced pressure, the residue was suspended in ethyl acetate with rapid stirring, treated with a slight excess of 12 *N* hydrochloric acid and then with excess solid sodium bicarbonate to neutralize the slightly acidic mixture, dried over molecular sieve (4 Å), filtered through Celite, and evaporated in vacuo to afford triol **3** (99%) after drying over P_2O_5 at 23 °C for 48 h, at 55 °C for 16 h, and at 100 °C for 1 h. The thoroughly dried triol **3** upon treatment with 1.1 equiv of trityl chloride in dry pyridine (1.25 mL/g of **3** at 23 °C for 16 h) afforded, after recrystallization of crude product from ether–methylene chloride–pentane (40 to −20 °C), the trityl ether diol **4**, mp 142–144 °C, $[\alpha]^{25}_D$ +43° (*c* 3.04, $CHCl_3$).[4] A solution of the diol **4** in hexamethylphosphoric triamide (HMPT, 4.7 mL/g of **4**) was added to a suspension of sodium hydride (4 equiv) in HMPT (4 mL/g of **4**) at 5 °C and the mixture was brought to 23 °C for 30 min and diluted with 0.5 vol. of tetrahydrofuran (THF). After cooling to −25 °C, the disodium derivative of **4** was treated with triisopropylbenzenesulfonylimidazole (1.1 equiv based on **4**) in THF (3 mL/g of sulfonyl reagent) with stirring at −25 °C for 1 h and −25 to −5 °C for 3 h. Filtration of the reaction mixture through Celite after dilution with ether, concentration under reduced pressure, and extractive isolation (Darco treatment) afforded a crude product which yielded 75% epoxide **5**, mp 101–102 °C, $[\alpha]^{25}_D$ +40° (*c* 4.22, $CHCl_3$), by crystallization from ether–pentane and an additional 15% by chromatography of the mother liquors (90% total yield of **5**). Reaction of the epoxide **5** with 2.8 equiv of methyllithium and 0.57 equiv of cuprous iodide in 2:1 ether–toluene at −78 °C for 48 h and −45 °C for 48 h afforded 95% **6**, mp 125–126 °C (from ether–pentane), $[\alpha]^{25}_D$ +36° (*c* 4.2, $CHCl_3$).[6] Treatment of **6** with 5 equiv of propane-1,3-dithiol in 1:6 chloroform–12 N hydrochloric acid at 0 °C for 15 min resulted in cleavage of the pyranose ring and the trityl ether to give 96% trihydroxyalkyl-1,3-dithiane, mp 107–108 °C, $[\alpha]^{25}_D$ −16.9° (*c* 3.0, $CHCl_3$), which was selectively protected by reaction with 1.6 equiv of 1-ethoxycyclopentene and 0.04 equiv of boron trifluoride etherate in THF (15 mL/g of triol) at −30 °C for 30 min to give the ketal dithiane **7**, mp 62–63 °C (from ether–hexane), $[\alpha]^{25}_D$ −28.8 °C (*c* 1.0, $CHCl_3$), in 86% yield. For complete protection **7** was treated with 3 equiv of β-methox-

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