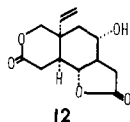
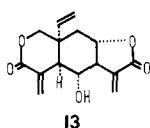


- (12) In order to confirm the stereochemistry of **11**, it was transformed by successive treatments with basic alumina and aqueous TFA and then heating at 160 °C into **12**, which proved to be identical with the bisnorvernolepin^{2,3} (**12**) derived from an authentic sample furnished by Professor Danishefsky, whom the authors thank for providing the sample and many NMR spectra.



- (13) (a) Decarboxylation occurred partially which was completed by the subsequent heating with methylenation. (b) J. Martin, P. C. Watts, and F. Johnson, *Chem. Commun.*, 27 (1970); (c) P. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 500 (1973).
- (14) Vernomenin (**13**) a congener of **1**, is largely absent (probably below 10%) owing to selective lactonization.



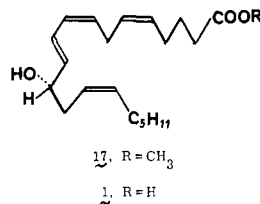
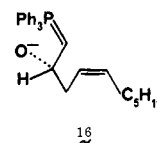
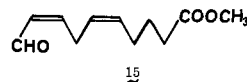
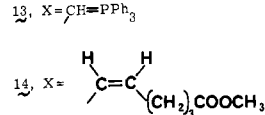
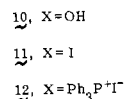
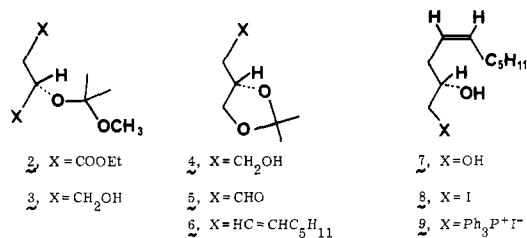
Minoru Isobe,* Hideo Iio, Tatsuhiko Kawai, Toshio Goto
Laboratory of Organic Chemistry, Faculty of Agriculture
Nagoya University, Chikusa, Nagoya 464, Japan
Received November 14, 1977

Total Synthesis of (*S*)-12-Hydroxy-5,8,14-*cis*,-10-*trans*-eicosatetraenoic Acid (Samuelsson's HETE)

Sir:

The title substance (**1**), commonly referred to by the discoverers' abbreviation HETE,^{1,2} is a biologically significant human metabolite of arachidonic acid. Although very little is known at present concerning the biological role(s) of HETE in cell function there can be little doubt that crucial findings will emerge from future studies of this compound and its immediate precursor, the corresponding hydroperoxide. Since the biosynthesis of these substances from arachidonic acid is not inhibited by aspirin or indomethacin,¹ in contrast to the prostaglandin endoperoxides PGG₂ and PGH₂, the formation of HETE is expected to be especially interesting in the case of human subjects receiving such medication. It is also noteworthy that very high levels of HETE have been observed in epidermal tissue of humans affected by the serious skin disease psoriasis.³ For these reasons and also because of the difficulty of obtaining material from natural sources in greater than submilligram quantities, we have developed the chemical synthesis of HETE described herein. The synthesis leads directly to the natural antipode without the need for resolution.

Reaction of the diethyl ester of (*S*)-(-)-malic acid (natural form) with 2-methoxypropene⁴ under catalysis by a trace of phosphorous oxychloride⁵ at 23 °C for 1 h afforded the protected ester **2**⁶ (100%) which underwent reduction to **3** (LiAlH₄ in THF, reflux, 5 h, 79%) and cyclization (BF₃·Et₂O in ether at 23 °C for 2 h) to give the 1,2-acetonide of 1,2,4-butanetriol **4**⁷ (86%), [α]_D²⁵ -1.86° (*c* 1.6, CH₃OH). Collins oxidation⁷ of **4** produced the aldehyde **5** which was transformed into the *cis* olefin **6** [α]_D²⁰ +23.8° (*c* 1.8, CHCl₃), by reaction with 1-hexyldienetriphenylphosphorane in THF (30 min at -78 °C, 30 min at 0 °C, and 3 h at 25 °C)⁷ (68% overall yield from **4**). The diol **7** (from **6** and 1 N hydrochloric acid in THF at 47 °C for 3 h) was converted to the primary mesitylenesulfonate (1 equiv of sulfonyl chloride in ether-pyridine at -20 °C for 1 h and 0 °C for 32 h), and thence to the iodo alcohol **8** (96%) with sodium iodide in acetone in darkness at 25 °C for 70 h, and finally to the phosphonium iodide **9** (triphenyl-



phosphine in benzene at 40 °C for 5 days in darkness, 86%).

A second component for the convergent synthesis of **1**, the aldehyde **15**, was prepared as follows. 5-Tetrahydropyranyloxy-3-pentyn-1-ol (**10**)⁸ was converted via sequential reaction with *p*-toluenesulfonyl chloride-pyridine and sodium iodide in acetone to the iodide **11** (90%) and thence with 3 equiv of triphenylphosphine in acetonitrile at 25 °C for 96 h (in the presence of precipitated calcium carbonate) into the acetylenic phosphonium salt **12** (70%). Hydrogenation of **12** over palladium/calcium carbonate afforded the corresponding *cis* ethylenic phosphonium salt (97%) which upon reaction with 1 equiv of *n*-butyllithium in THF (to generate ylide **13**) and further treatment with methyl 4-formylbutyrate⁹ produced the *cis,cis* diene **14** (72%). Cleavage of the tetrahydropyranyl group in **14** (methanol containing *p*-toluenesulfonic acid, 1 h at 25 °C, 94%) and oxidation of the resulting alcohol with excess activated manganese dioxide¹⁰ in ether led cleanly to the easily isomerizable *cis,cis* aldehyde **15** which was used immediately in the final coupling step because of its lability.¹¹

The coupling of the aldehyde **15** and the phosphonium reagent **9** was effected via the β -oxido ylide derived from the latter.^{7,12} Reaction of **9** (rigorously dried by repeated azeotropic distillation of solvent from a toluene-THF solution) with 2 equiv of methyllithium in THF solution at -78 °C for 5 min and -25 °C for 30 min afforded the deep red oxido ylide **16**. The solution was diluted with 10 vol of toluene, cooled to -78 °C and treated with the aldehyde **15** at that temperature for 5 min and at -30 °C for 1 min. Hexamethylphosphoric amide (4 equiv) was added to accelerate elimination of triphenylphosphine oxide and the reaction mixture was allowed to warm over 2 h from -30 to -10 °C. Extractive isolation and chromatography on silica gel (petroleum ether-ether for development) afforded as the major reaction products the methyl ester **17** and triphenylphosphine oxide. The structure of **17** was completely corroborated by spectral data, especially important being the ¹H NMR spin-decoupled spectra which showed a single *trans* double bond between carbons 10 and 11, and the UV spectrum¹ (found, λ_{max} 237 nm (ϵ 32 800)). The ¹H NMR spectra of synthetic **17** and the methyl ester (CH₂N₂) of naturally derived HETE were identical, as were the mass spectra¹³

and thin layer chromatographic mobility.¹⁴ Further, coupled gas chromatographic-mass spectral measurements of the trimethylsilyl ether-methyl ester derivative of synthetic and naturally derived HETE gave identical results, both with regard to GC retention time and mass spectrum.^{1,14} Since ¹H NMR data for **1** and **17** have not previously been reported, some of the characteristic peaks for **17** are presented here (CDCl₃ as solvent): H-10, 6.55 (d of d, $J_{10,11} = 15$ Hz and $J_{9,10} = 10$ Hz); H-9, 5.95 (t, $J_{8,9} = J_{9,10} = 10.5$ Hz); H-11, 5.70 (d of d, $J_{10,11} = 15$ Hz and $J_{11,12} = 6$ Hz); H-(5,6,8,14,15), 5.3–5.5 (m); H-12, 4.2 (q, $J_{11,12} = J_{12,13} = 6$ Hz); COOCH₃, 3.65 (s); H-7, 2.90 (br t); H-2, 2.30 (t, $J_{2,3} = 6$ Hz); and H-20, 0.87 ppm (br t).

The methyl ester **17** was observed to be weakly dextrorotatory, $[\alpha]^{25}_D +1.50^\circ$ (c 0.2, CHCl₃). Hydrolysis of the ester **17** with aqueous alcoholic base readily afforded the corresponding free acid **1** (HETE).

The synthesis of HETE described above not only allows the preparation of larger amounts of this substance, but it also confirms completely the original¹ structural and stereochemical assignment.¹⁵

References and Notes

- (1) M. Hamberg and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 3400 (1974).
- (2) M. Hamberg, J. Svensson, and B. Samuelsson, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 3824 (1974).
- (3) S. Hammerström, M. Hamberg, B. Samuelsson, E. A. Duell, M. Stawiski, and J. J. Voorhees, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 5130 (1975).
- (4) M. S. Newman and M. C. Vander Zwan, *J. Org. Chem.*, **38**, 2910 (1973).
- (5) A. F. Klug, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972).
- (6) Satisfactory infrared, ¹H NMR, and mass spectral data were obtained for all synthetic intermediates.
- (7) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Am. Chem. Soc.*, **93**, 1490 (1971).
- (8) Prepared from the lithio derivative of propargyl alcohol and excess ethylene oxide in THF at -78°C for 2 h and 12 h at 25°C in 80% yield. See R. F. Borch, A. J. Evans, and J. J. Wade, *J. Am. Chem. Soc.*, **99**, 1612 (1977).
- (9) Prepared by Rosenmund reduction of the acid chloride of monomethyl glutarate using palladium/charcoal and 1 equiv of 2,6-lutidine in THF (1 atm H₂, 1 h at 25°C); see A. W. Burgstahler and L. O. Weigel, and C. G. Schaefer, *Synthesis*, 967 (1976).
- (10) See, A. J. Fatiadi, *Synthesis*, 65 (1976). The manganese dioxide used was prepared from manganous chloride and permanganate (see p. 67).
- (11) The α , β -cis aldehyde **15** showed $J = 8$ Hz for CH-CHO and $J = 10$ Hz for protons α and β to formyl; upon standing at 25°C the ¹H NMR spectrum indicated gradual formation of the more stable α , β -trans aldehyde.
- (12) See E. J. Corey, P. Ulrich, and A. Venkateswarlu, *Tetrahedron Lett.*, 3231 (1977), and references cited therein.
- (13) The ¹H NMR and mass spectra of the methyl ester of naturally derived HETE (from blood platelets) were provided by Drs. T. K. Schaaf and J. Eggler of the Charles Pfizer Co.
- (14) We are indebted to Drs. Bengt Samuelsson and Sven Hammerström of the Karolinska Institutet, Stockholm, for making TLC and GC-mass spectral comparisons.
- (15) We are grateful to the National Science Foundation for financial assistance.

E. J. Corey,* Haruki Niwa, Jochen Knolle

Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received November 11, 1977

Crown Ether Model Systems for the Study of Photoexcited-State Response to Oriented Perturbers. How Does a Naphthalene Derivative Respond to an Alkali Metal Cation in Its π Face?

Sir:

Crown ether naphthalene derivatives **1**,¹ **2**, and **3** have been designed as model systems for the study of the geometric requirements of perturber-chromophore interactions. In this report² the changes in the emission properties of **1** caused by

Table I. Emission Quantum Yields^a and Lifetimes of 1,5-Naphtho-22-crown-6 (**1**) in Alcohol Glass^a at 77 K with Alkali Metal Chloride Salts Added in 5:1 Molar Excess (Crown at 1.00×10^{-4} F)

Salt added	ϕ_f^b	τ_f , ns	ϕ_p^b	τ_p , s
None	0.11	35	0.17	2.2
NaCl	0.075	29	0.13	2.1
KCl	0.061	27	0.12	2.2
RbCl	0.018	<i>c</i>	0.19	1.6
CsCl	0.0015	<i>c</i>	0.34	0.42

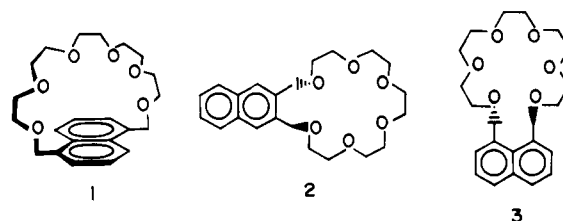
^a See note 4. ^b ϕ_f and ϕ_p are relative to naphthalene in ref 7a. ^c ϕ_f was too low to allow reliable measurement of τ_f .

Table II. Estimates^{a,b} of Rate Constants for Excited-State Processes of 1,5-Naphtho-22-crown-6 (**1**) in Alcohol Glass^c at 77 K with Alkali Metal Chloride Salts Added in 5:1 Molar Excess (Crown at 1.00×10^{-4} F)

Salt added	$10^{-6}k_f$	$10^{-6}k_{nr}$	$10^2k_p^d$	k_{dt}^d
None	3.1	25	8.7	0.37
NaCl	2.6	32	6.7	0.41
KCl	2.3	35	5.8	0.39
RbCl	1 ^e	52	12.	0.50
CsCl	1 ^e	670	81.	1.57

^a All rate constants in s^{-1} . ^b $k_f = \phi_f\tau_f^{-1}$; $k_{nr} = (1 - \phi_f)\tau_f^{-1}$; $k_p = \phi_p(1 - \phi_f)^{-1}\tau_p^{-1}$; $k_{dt} = \tau_p^{-1} - k_p$. ^c See note 4. ^d With $\phi_f + \phi_{isc} = 1.0$ assumed. ^e Estimated from 77 K UV absorption spectra.

alkali metal cations held near the face of the naphthalene π system are described and compared to earlier results with **2** and **3**.³ This study illustrates the extent to which external heavy-atom perturbation is dependent on the orientation of the perturber.



The fluorescence and phosphorescence quantum yields (ϕ_f and ϕ_p , respectively) and lifetimes (τ_f and τ_p , respectively) of pure **1** were measured in alcohol glass⁴ at 77 K and the effects of added Na⁺, K⁺, Rb⁺, and Cs⁺ chloride⁵ salts determined (see Table I). In the cases of Rb⁺ and Cs⁺ perturbation, ϕ_f is decreased to the extent that reliable measurement of τ_f is not feasible with the equipment available to us. Plots of ϕ_f and also ϕ_p vs. the mole fraction of added salt showed that the emission observed when a 5-fold excess of salt is present is that of completely complexed, and therefore specifically perturbed, crown **1**, and not that due to a small fraction of free **1**. Table II lists estimates of the rate constants for fluorescence (k_f), nonradiative decay of the singlet excited state (k_{nr}), phosphorescence (k_p), and nonradiative decay of the triplet state (k_{dt}).^{6,7}

Perturbation by a light cation (K⁺) of **1**,⁸ **2**, and **3** (pictured in the upper portion of Figure 1) causes real but not overpowering changes in all rate constants. Holding a light cation in the face of the π system does not increase the overall perturbing capability of the cation as compared with its effect when held at the side or end of the naphthalene chromophore.

Heavy-cation perturbation (by Cs⁺) gives an interesting pattern shown in the lower part of Figure 1. The rate constants for processes involving singlet-triplet interchanges (k_{dt} , k_p ,