lactone **11** (1.5 equiv of DBU, THF, 2 h, reflux) opens a route toward prostaglandins of the A series.[11] Treatment of **11** with *N*-bromoacetamide (1.2 equiv, aqueous acetone, 20 °C) yielded regio- and stereoselectively the bromohydrin **12** (83%, mp 76–77 °C) which was transformed (phenylbenzoyl chloride in pyridine then debromination with tri-*n*-butyl hydride) into a known[12] precursor **13** of F and E prostaglandins.

Thus, the vicinal alkylation of cyclopentadiene with (carbomethoxy)chloroketene has opened a general and extremely practical route to the prostaglandin hormones and their analogues. In our opinion the outstanding features of this synthesis are (a) *low cost* of starting material and reagent; (b) *high convergence*: two steps lead to the intermediate **4** common to virtually all classes of prostaglandins; therefore, the method is well suited for the preparation of analogues, even of the cis series; (c) *shortness*: e.g., six isolated steps from cyclopentadiene and **2** to the derivative of Corey aldehyde **13**; (d) *high stereoselectivity*; (e) possibility of an *early resolution*, e.g., on the acid derived from **7**.

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**Supplementary Material Available:** Crystallographic data for compounds **3** and **10** (4 pages). Ordering information is given on any current masthead page.

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## Stereospecific Total Synthesis of 11(*R*)-HETE (2), Lipoxygenation Product of Arachidonic Acid via the Prostaglandin Pathway

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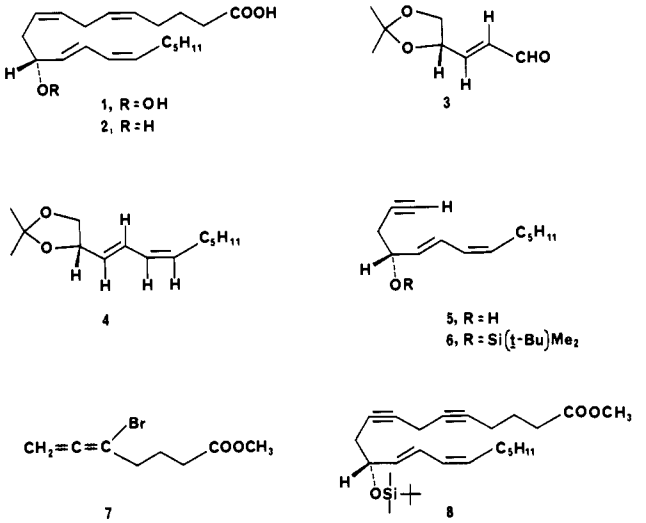
The initial step in the biosynthesis of prostaglandins is the oxidation of arachidonic acid by the 11(*R*)-lipoxygenase pathway to form the hydroperoxide **1**, 11(*R*)-HPETE, or the corresponding peroxyl radical.[1] The related 11(*R*)-hydroxy acid, 11(*R*)-HETE (**2**), which accompanies **1** as a coproduct (Chart I),[2] has been little studied despite the enormous level of research on the chemistry and synthesis of prostaglandins and the great interdisciplinary interest in biosynthetic matters.[3,4] We have been concerned recently with the development of a synthetic process which would make these key compounds readily available for chemical and biological studies. Reported herein is the first synthesis of 11-(*R*)-HETE (without the need for resolution) which is at the same time stereocontrolled, convergent, and illustrative of novel synthetic methodology. The process is applicable as well to the synthesis

Chart I




of 11(*S*)-HETE, and to the preparation of 11-HPETE, using the methodology previously described for the synthesis of 5- and 15-HPETE from the corresponding HETE's.[3,5]

The acetonide of D-glyceraldehyde (prepared from D-mannitol[6,7]) was converted into the *trans*-enal **3** in 75% overall yield by the following sequence: (1) reaction with 1 equiv of lithium ethoxyacetylide in tetrahydrofuran (THF) at −78 °C for 2 h and from −78 to 0 °C for 1 h; (2) hydrogenation (1 atm) of the acetylenic carbinol [obtained by extractive (basic) isolation] to the dihydro derivative using palladium-on-calcium carbonate catalyst (Lindlar) in hexane containing triethylamine (25 °C; reaction monitored by thin layer chromatography, TLC); (3) treatment of this product in wet methylene chloride with a trace of methanesulfonic acid at 25 °C for 30 min.[8] Wittig reaction of enal **3** with the ylide from *n*-hexyltriphenylphosphonium iodide and sodium methylsulfinyl carbanion in dimethyl sulfoxide[9] at 10 °C provided the *trans,cis*-diene **4** in 79% yield ($UV_{max}$ in hexane at 235 nm). Transformation of **4** to the acetylenic carbinol **5** was accomplished in 62% overall yield by the following sequence: (1) deketalization (0.005 N HCl in 4:1 acetonitrile–water at 23 °C for 26 h); (2) monotosylation at primary hydroxyl using 1 equiv of tosyl chloride in pyridine at −20 °C; (3) oxirane closure using 1,8-diazabicyclo[5.4.0]undec-7-ene in THF at 23 °C for 24 h; (4) reaction with lithium acetylide ethylenediamine complex (Aldrich Chemical Co.) at −20 °C in 3:1 hexamethylphosphoric triamide (HMPA)–THF (HMPA) THF for 12 h. Reaction of **5** with *tert*-butyldimethylsilyl chloride–imidazole in dimethylformamide at 25 °C for 4 h provided the corresponding silyl ether **6** in 94% yield. The ethynylation reaction used to prepare the homopropargylic alcohol **5** is noteworthy for its unprecedented position selectivity at the *nonallylic* position which depends on the use of HMPA as cosolvent. This methodology complements the use of organocopper reagents which favor allylic attack.

The completion of the 20-carbon chain was effected by a new and highly selective procedure for carbon–carbon bond formation with generation of a 1,4-diyne unit. While the coupling of a nucleophilic acetylide with a propargylic halide leads to allene

(1) See: Hamberg, M.; Svensson, J.; Wakabayaski, T.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 345 and references cited therein.
(2) See: Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1967**, *242*, 5344.
(3) In a previous paper from these laboratories the concurrent synthesis of (±)-11- and (±)-12-HETE from 11,12-epoxyarachidonic acid has been described: Corey, E. J.; Marfat, A.; Falck, J. R.; Albright, J. O. *J. Am. Chem. Soc.* **1980**, *102*, 1433.
(4) For nonselective oxidation of arachidonic acid by $Cu^{2+}$–$H_2O_2$ and singlet oxygen see: (a) Baeynaems, J. M.; Oates, J. A.; Hubbard, W. C. *Prostaglandins* **1980**, *19*, 87. (b) Porter, N. A.; Wolf, R. A.; Pagels, W. R.; Marnett, L. J. *Biochem. Biophys. Res. Commun.* **1980**, *92*, 349. The latter paper also deals with the question of whether **1** or the corresponding peroxyl radical (or both) are predecessors of prostaglandins.
(5) Corey, E. J.; Albright, J. O.; Barton, A. E.; Hashimoto, S. *J. Am. Chem. Soc.* **1980**, *102*, 1435.
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(7) For a synthesis of the acetonide of L-glyceraldehyde (starting material for 11(*R*)-HETE), see: Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1939**, *61*, 761.
(8) Satisfactory infrared, ultraviolet, proton magnetic resonance, and mass spectral data were obtained on chromatographically purified samples of each intermediate. All reactions were conducted under an atmosphere of argon, and intermediates were stored under argon in frozen benzene at −20 °C or below. All intermediates were obtained as colorless liquids.
(9) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

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or mixtures of allene and acetylene, our studies indicate that the corresponding coupling of metal acetylide with an *allenic* bromide or iodide under the proper conditions can lead to 1,4-diynes in high yield. This process, which will be discussed in more general terms in a separate paper, has been applied to the synthesis of 11(*R*)-HETE (**2**) as follows. The acetylenic diene **6** in THF at −45 °C was converted to the lithio derivative (1 equiv of *n*-butyllithium) and thence to a mixed Gilman reagent with 1.1 equiv of cuprous cyanide in THF–HMPA at −20 °C. After 10 min, methyl 5-bromo-5,6-heptadienoate (**7**)[10] in THF was added and the mixture (final ratio of HMPA to THF 1.1:1) was stirred at 4 °C for 12 h and 23 °C for 48 h. Extractive isolation and chromatography on silica gel gave pure coupled diyne **8** in 89% yield.[11] Conversion of **8** to the methyl ester of **2** was cleanly effected by selective hydrogenation (Lindlar catalyst in hexane–triethylamine, 1 atm of $H_2$) to the corresponding *cis,cis,trans,-cis*-tetraene and desilylation[12] using tetra-*n*-butylammonium fluoride in THF at 25 °C; the methyl ester of **2** showed $[\alpha]^{25}_D$ +10.97° (*c* 1.0, $CH_2Cl_2$); $UV_{max}$ (hexane) 235 nm; $^1H$ NMR spectrum ($CDCl_3$, 80 MHz) $\delta$ 6.54 (dd, $J$ = 10.8, 15.0 Hz, 1 H), 5.96 (br t, $J$ = 10.8 Hz, 1 H), 5.1–5.8 (m, 6 H), 4.22 (q, $J$ = 7.0 Hz, 1 H), 3.66 (s, 3 H), 2.79 (t, $J$ = 5.1 Hz, 2 H), 2.32 (t, $J$ = 7.0 Hz, 2 H) 1.1–2.2 (m, 14 H), 0.88 (t, $J$ = 6 Hz, 3 H). This ester is best stored in frozen benzene under argon in the presence of a trace of 4-hydroxy-2,2,6,6-tetramethylpiperidinoxy free radical at <−20 °C.[13] 11(*R*)-HETE is readily obtained from the ester by saponification at 25 °C in the absence of air, acidification, and extractive isolation;[3] it is relatively unstable to storage compared to the methyl ester.

Further studies on **1** and **2** and the biomimetic synthesis of prostaglandins are underway and will be reported in due course.[14]

(10) Methyl 5-bromo-5,6-heptadienoate (7) was synthesized in 76% yield by reaction of methyl 7-(trimethylsilyl)-5-heptynoate with 1 equiv of bromine in methylene chloride at −78 °C.

(11) An obvious route to **8** involving the ethynylation of the epoxide corresponding to diol derivative **4** using the lithio acetylide from 5,8-nonadiynoate ion (or ester) was foiled by the acidity of the 1,4-diyne unit and consequent instability of the ethynylating reagent.

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(14) This research was assisted financially by grants from the National Science Foundation and the National Institutes of Health

## $^{13}C$ Magic Angle NMR Study of the Isomerization of *cis*- to *trans*-Polyacetylene

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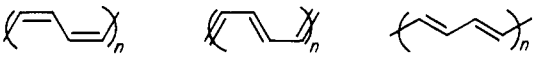
Polyacetylene occupies a central position in the burgeoning field of conducting polymers.[1] In spite of the discovery of several other polymers dopable to high conductivity,[2-7] polyacetylene continues to be the prototypical model, and efforts to understand its electrical properties are viewed as necessary for rational design of new systems. Such understanding requires a knowledge of the microstructure; unfortunately the insolubility of polyacetylene has made the acquisition of this knowledge difficult.

The isomerization of the as-formed cis-transoid isomer (**1**) to the trans-transoid isomer (**3**) has been studied by IR[8,9] and ESR spectroscopy.[10] The individual isomers have also been examined



1 2 3

by $^{13}C$ magic angle NMR spectroscopy.[11] We now report a study of the isomerization process by a combination of IR and NMR spectroscopy and a discrepancy in composition as measured by the two techniques.

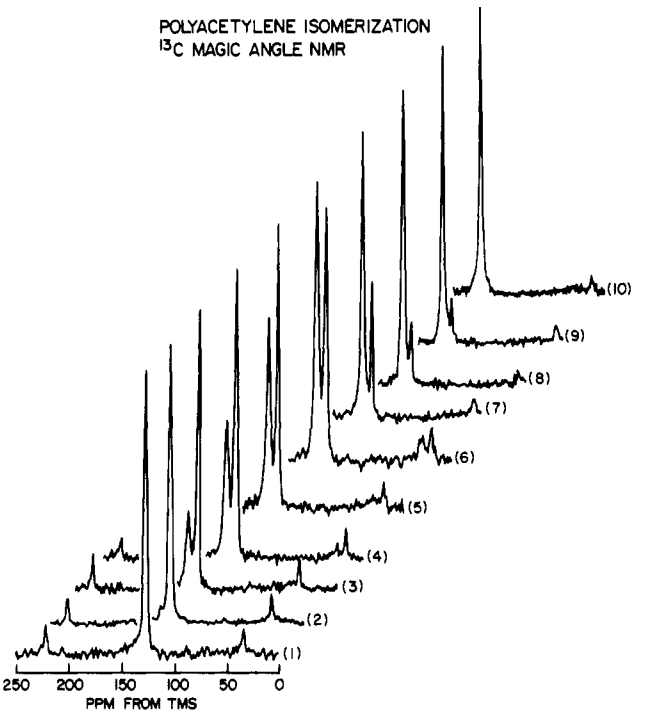



**Figure 1.** 22.63-MHz carbon-13 NMR spectra of a 12 mg initially high cis content polyacetylene as isomerization progresses to the trans form. Proton enhanced cross-polarization conditions: repetition time = 1 s; contact time = 1 ms, with resonant radio frequency field of 8 and 32 G for protons and carbons, respectively; proton decoupling power = 12 G; no. of scans ~50000 per spectrum; spinning speed = 2.2–2.5 KHz. Spectra are arbitrarily normalized to the larger of the two peaks. Percent trans determined from IR absorption ratio (740 vs. 1010 $cm^{-1}$)[8] and the corresponding thermal history for each spectrum: (1) 32% (25 °C, 1.5 days); (2) 47% (25 °C, 9 days); (3) 47% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 1 h); (4) 52% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 2 h); (5) 51% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 4 h); (6) 48% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 7.5 h); (7) 59% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 22.8 h); (8) 54% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 47 h); (9) 85% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 64 h); (10) 94% (25 °C, 11 days; 78 °C, 1 h; 100 °C, 64 h; 200 °C, 21 min).

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