The synthesis of 11*R*- and 11*S*-HETE and of 11-*R*,*S*-HPETE methyl esters

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This paper is dedicated to Professor Leo Yaffe on the occasion of his 65th birthday

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Methyl 11*R*- and 11*S*-hydroxyeicosa-5*Z*,8*Z*,12*E*,14*Z*-tetraenoate (**17***R*, **17***S*) (11-HETE) and the corresponding 11-hydroperoxide **19** (11-HPETE) have been prepared from readily available starting materials. The yields were approximately 25% for 11*R*,*S*-HETE, and 5% each for 11*R*- and 11*S*-HETE.

Extensive 400 MHz ^{1}H nmr studies of **17** (nOe difference, 2D *J*-resolved) were undertaken to confirm the structure. Some conformational properties are discussed.

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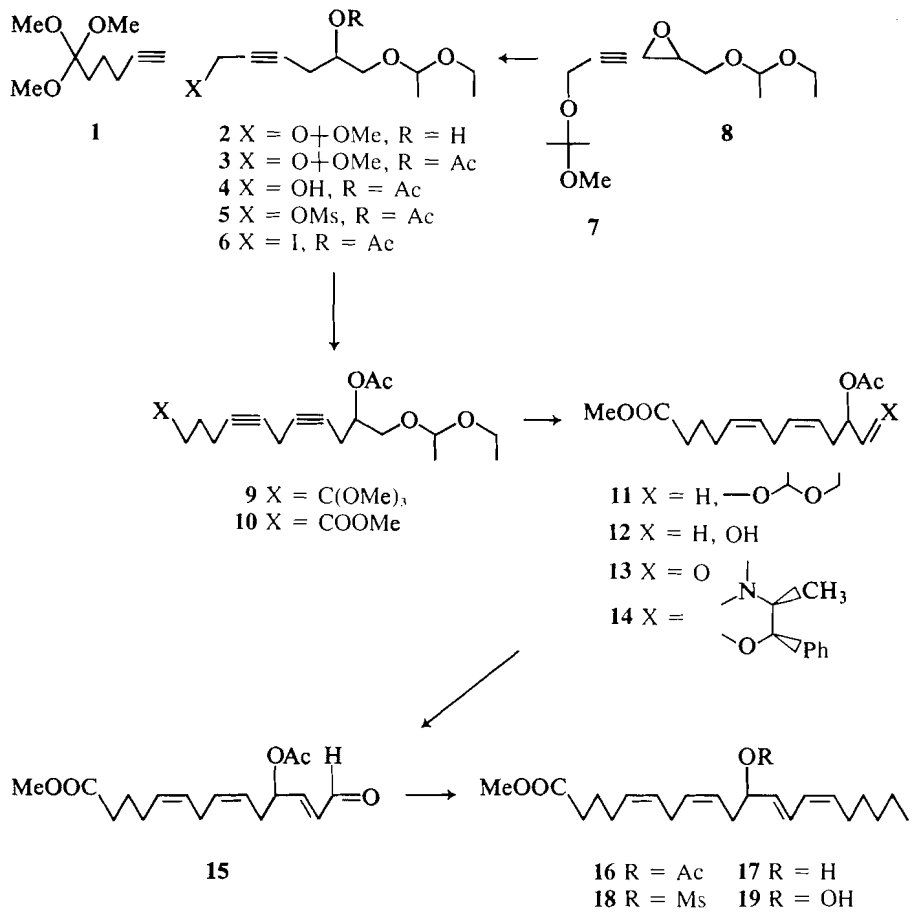
On a préparé les hydroxy-11*R* et 11*S* eicosatétraène-5*Z*,8*Z*,12*E*,14*Z* oate de méthyle (**17***R*,**17***S*) (H-11ETE) ainsi que l'hydroperoxyde-11 (**19**) (HP-11ETE) à partir de produits de départ facilement accessibles. Les rendements sont approximativement de 25% pour les H-11*R*,*S*ETE et de 5% chacun pour les H-11*R* et H-11*S* ETE.

On a fait appel à une étude poussée par rmn du ^{1}H à 400 MHz du composé **17** (différence de eOn, 2D résolu pour *J*) pour confirmer la structure. On discute de quelques propriétés conformationnelles.

[Traduit par le journal]

The total synthesis of enantiomerically pure 11-HETE has only recently been described (1–3). We wish to report full details of an expeditious synthesis of 11*R*- and 11*S*-HETE **17**, and of the corresponding 11-HPETE **19**.

Condensation of the ethoxyethylidene ether of glycidol (**8**) with the lithium anion of the methoxypropylidene ether of propargyl alcohol (**7**) gave adduct **2**, which was acetylated to provide **3**. Mild acid hydrolysis of **3**, followed by mesylation of the resulting alcohol **4**, gave **5** which provided iodide **6** upon treatment with sodium iodide.



Reaction of **6** with an anionic species generated from acetylenic orthoester **1** (2) by addition of one equivalent of butyllithium and one equivalent of cuprous iodide at −78°C gave orthoester **9** in what appeared to be a quantitative yield. This reaction requires some comment since approximately 30% of **9** was formed at −30°C within a few minutes, the balance of the reaction requiring a day at room temperature. The use of less CuI gave variable yields of **9**. Some hydrolysis of the acetate function was noted so that the reaction product was routinely reacetylated. Since tlc of the product showed two spots due to hydrolysis of orthoester **9** to ester **10**, probably in part on the tlc plate but perhaps during work-up, the product was submitted to very mild acid hydrolysis at this stage to give ester **10**.

Catalytic hydrogenation with Brown's nickel boride catalyst (4), followed by acid hydrolysis, gave alcohol **12**. Up to this point, all steps had proceeded seemingly in quantitative yield, as established by tlc and nmr, and no purification beyond extractions was necessary. Nevertheless, since the next few steps all involved sensitive compounds (**13**, **14**, and **15**) which were prone to decomposition upon standing, **12** was submitted to flash chromatography to remove very minor impurities which had accumulated over the 9-step sequence. The fact that the overall yield for the sequence was only ~50% was probably due to the relative volatility of the various intermediates. Certainly, chromatography at intermediate stages did not in any way enhance either yields or purity of alcohol **12**.

Although the simultaneous hydrolysis of the orthoester and ethoxyethylidene functions in **9** could be performed, it was noted that, in contrast to diolefins **11** and **12**, diacetylenes of type **9** or **10** were very fragile molecules which at times decomposed upon mere standing, or on exposure to silica gel.

Oxidation of **12** with dimethyl sulfoxide – oxalyl chloride using the recently described method of Swern and co-workers (5) gave aldehyde *R,S*-**13**. Treatment of *R,S*-**13** with *l*-ephedrine and 10 mol% pyridinium tosylate gave a mixture of diastereomeric ephedrine derivatives **14**, which were separated by flash chromatography.

The major isomers having the highest and second highest R_f-values had the 11*R* and 11*S* configurations, respectively (3). The minor isomers (~10% each) were not isolated, although, on larger runs, this could have easily been done. Hydrolysis of **14***R* and **14***S* gave **13***R* and **13***S*, each in approximately 20% yield, based on alcohol **12**.

Subsequent elaboration of the 12*E*,14*Z* diene systems follows that described for the *tert*-butyldimethylsilyl ether (2) corresponding to acetate **13** (3), and involves reaction of **13** with formylmethylenetriphenylphosphorane (6), followed by transformation of the *E*-α,β-unsaturated aldehyde **15** with triphenylhexylphosphonium bromide to give **16**. Treatment of tetraene acetate **16** thus obtained with methanolic sodium methoxide gave 11-HETE **17**, contaminated with 10–15% of its 14*E*-isomer, which was readily removed by flash chromatography.

When the same sequence was repeated with resolved aldehydes **13***R* and **13***S*, 11*R*-**17**, $[\alpha_D^{21}]$ 11.2° (10.97° (1)) and 11*S*-**17**, $[\alpha_D^{21}]$ −11.3° (CH_2Cl_2) were obtained.

Conversion to 11-HPETE **19** was accomplished in the following manner (7): **17** was transformed to mesylate **18** at −65°C by means of methanesulfonyl chloride/NEt_3. Addition of 90% hydrogen peroxide in ether gave hydroperoxide **19** in approximately 70% yield, contaminated with what appeared to be 30% of various isomers of 15-HPETE. Purification by hplc gave 11-HPETE **19** in 10–30% yield. Its 400 MHz ^{1}H nmr spectrum was virtually indistinguishable from that of **17**, except for the 11-proton, which appeared at 4.5 ppm, 0.3 ppm downfield from that of **17**. Its structure was confirmed by reduction of **19** (70% purity) with methanolic stannous chloride. Flash chromatography gave as major product **17**, identified by gc–ms of its trimethylsilyl ether. Its ^{1}H nmr was virtually identical to that of **17** described by Corey and Kang (1).

An extensive 400 MHz ^{1}H nmr study of **17** was undertaken to establish if the molecule has a conformational preference. This goal could not be achieved. However, a complete assignment was made as described in the following. The proton signals are sufficiently dispersed so that coupling connectivities between protons could be established by use of 1D homodecoupling experiments. Chemical shifts and coupling constants (except for $^3J_{18-19}$) were measured accurately from the 1D spectrum and 2D *J*-resolved spectra and are given in Table 1. The signals of protons H6, H8, H9, and H15 overlap (Fig. 1a); however, the separated signal for each proton could be observed from the nOe difference spectra (8). For example, when H14 was irradiated, the signal of H15 was enhanced while H6, H8, and H9 were not affected; the difference spectra washed out the signals of these latter protons, and only the signal of H15 is observed (Fig. 1b). Due to the spin echo nature of *J*-resolved 2D spectroscopy and the large applied resolution enhancement factor, the small coupling constants and the small differences in coupling constants can be observed and measured. The cross section plots (Fig. 1c) of the *J*-resolved 2D spectrum show well-resolved signals for all but the H8 and H9 olefinic protons. Because of the second order effect, the two latter protons produced the complex pattern depicted in the contour plot (Fig. 1d). The coupling constants $^3J_{5-6}$, $^3J_{8-9}$, $^3J_{12-13}$, and J_{14-15} are fully consistent with the configurations of the double bonds depicted in Fig. 1 (9).

For conformationally labile molecules, nOe data do not present evidence to infer a conformational preference.[1] However, the nOe results when H13 and H14 were irradiated (nOe between H12 and H14, negligible nOe between H13 and H14) indicate that the protons H13 and H14 are *anti*, in perfect agreement with the value $^3J_{13-14}$ (9). The large nOe between H13 and H16 may suggest that the less sterically crowded conformation (C14—C15 bond *anti* to C16—C17 bond) is preferred. Positive and negative nOe were observed when protons H10 were saturated (see Table 2). Where dipole–dipole interaction is the dominant relaxation mechanism, alternating sign nOe is to be expected (10) in a series of neighboring protons. In fact, at least in one conformation, the protons H10b—H10a—H9—H8 are contiguous; for example when H10a was irradiated, the signal of proton H9 increased (positive effect) but the signal of proton H8 decreased (negative effect). The remaining nOe results may be satisfactorily interpreted in terms of the described structure.

Experimental[2]

Methoxyisopropylidene propargyl alcohol (7)

To a solution of propargyl alcohol (8.4 g, 150 mmol) in dry CH_2Cl_2 (400 mL) at 5°C under N_2 were added methoxypropene (11.9 g, 165 mmol) and pyridinium tosylate (3.77 g, 15 mmol). The reaction mixture was stirred at 5°C for 3.5 h; the product was then extracted with CH_2Cl_2 (2 × 500 mL); the CH_2Cl_2 extracts were washed with aqueous $NaHCO_3$ (4 × 50 mL), water (2 × 50 mL), and dried over $MgSO_4$.

[1]The nOe data confirm the assignment and are given in Table 2.

[2]For general procedures, see ref. 11.

TABLE 1. ^{1}H chemical shifts and coupling constants of **17**

Proton	δ(ppm)	J(Hz)
H2	2.197	H2–H3 = 7.3
H3	1.693	H3–H4 = 7.3
H4	2.067	H4–H5 = 7.3; H4–H6 = 1.3
H5	5.383	H5–H6 = 10.7; H5–H7 = 1.5
H6	5.509	H6–H7 = 7.2
H7	2.869	H7–H8 = 7.0; H7–H9≤1.0
H8	5.61	H8–H9 = 10.8; H8–H10a≤1.0; H8–H10b≤1.0
H9	5.58	H9–H10a = 7.1; H9–H10b = 6.5
H10a	2.463	H10a–H11 = 6.9; H10a–H10b = −14.0
H10b	2.377	H10b–H11 = 5.8
H11	4.195	H11–H12 = 6.0; H11–H13 = 1.4; H11–OH = 4.2
H12	5.781	H12–H13 = 15.2; H12–H14≤1.0
H13	6.801	H13–H14 = 11.1; H13–H15 = 1.1
H14	6.202	H14–H15 = 10.3; H14–H16≃1.3
H15	5.536	H15–H16 = 7.6
H16	2.259	H16–H17 = 7.4
H17	1.421	H17–H18 = 7.5
H18,H19	1.30	H19–H20 = 6.9
H20	0.969	
OCH_3	3.455	
OH	var	

The solvent was removed at atmospheric pressure and the product recovered by vacuum distillation (65°C, 43 Torr) in 70% yield; ^{1}H nmr (CCl_4) δ: 1.26 (s, 6H, $2CH_3$), 2.17 (t, 1H, $J \sim 2$ Hz, H—C≡C), 3.07 (s, 3H, OCH_3), 3.92 (d, 2H, $J \sim 2$ Hz, CH_2).

Ethoxyethylidene glycidol (8)

To a solution of glycidol (8.8 g, 120 mmol) in dry CH_2Cl_2 (400 mL) at 5°C under N_2 were added ethyl vinyl ether (17.3 g, 240 mmol) and pyridinium tosylate (3 g, 12 mmol). After half an hour the reaction mixture was warmed to room temperature and was stirred at 22°C for 3 h. Extraction with CH_2Cl_2 (2 × 500 mL) and washing of the CH_2Cl_2 extracts with aqueous $NaHCO_3$ (4 × 50 mL) and water (2 × 50 mL) gave, after drying over $MgSO_4$ and distillation, **8**, bp 75°C/20 Torr; ^{1}H nmr ($CDCl_3$) δ: 1.25 (t, 3H, $J = 7$ Hz, CH_2CH_3), 1.30 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 2.47–4.33 (m, 7H), 4.70 (q, 1H, $J \sim 6$ Hz, $CHCH_3$).

Acetylenic alcohol 2

To protected propargyl alcohol **7** (7.7 g, 60 mmol) in dry THF (60 mL) at 5°C under N_2 was added first *n*-butyllithium (55 mmol) and then glycidol derivative **8** (7.3 g, 50 mmol) and dry HMPA (3 mL). The reaction mixture was brought to room temperature and was then stirred at 65°C for ~2.5 h. The solvents were removed at reduced pressure and the residue extracted with ether (2 × 300 mL); the ether extracts were washed with phosphate buffer (pH 4.5, 2 × 50 mL), water (3 × 50 mL), and dried over $MgSO_4$. Evaporation of the solvent yielded fairly pure **2** as an oil which was used as such without further purification; ^{1}H nmr ($CDCl_3$) δ: 1.20 (t, 3H, $J \sim 7$ Hz, CH_2CH_3), 1.32 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 1.35 (s, 6H, $2CH_3$), ~2.3–4.3 (m, 10H), 3.20 (s, 3H, OCH_3), 4.57–4.90 (m, 1H, OCHOEt); ms (*m/e*, 16 eV): 259 ($M^+ - CH_3$), 201 ($M^+ - CH_3CHOCH_2CH_3$), 171 ($M^+ - CH_2OCHCH_3OCH_2CH_3$), 141 ($Me_2(MeO)COCH_2C{\equiv}CCH_2^+$), 133 ($M^+ - 141$), 103 ($M^+ - 171$), 73 ($CH_3CHOCH_2CH_3^+$).

Acetate 3

To crude alcohol **2** (2.,7 g, 10 mmol) in anhydrous ether (50 mL) were added 4-dimethylaminopyridine (122 mg, 1 mmol) and acetic anhydride (1.9 mL, 20 mmol). The reaction mixture was stirred at room temperature for 1 h and was then extracted with ether (2 × 350 mL); the ether extracts were washed with aqueous $NaHCO_3$ (2 × 50 mL), water (3 × 50 mL), and dried over $MgSO_4$. Evaporation of the solvent, followed by azeotroping the excess acetic acid and acetic anhydride with toluene, yielded acetate **3**, which was used without further purification in the next step; ^{1}H nmr (CCl_4) δ: 1.05 (t, 3H, $J \sim 7$ Hz, CH_2CH_3), 1.18 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 1.18 (s, 6H, $2CH_3$), 1.90 (s, 3H, $COCH_3$), ~2.3–2.6 (m, 2H), 3.02 (s, 3H, OCH_3), ~3.1–5.0 (m, 8H); ms (*m/e*, 16 eV): 301 ($M^+ - CH_3$), 73 ($CH_3CHOCH_2CH_3^+$).

Propargylic alcohol 4

To acetate **3** (790 mg, 2.5 mmol) in methanol (20 mL) was added PPTS (25 mg); the reaction mixture was stirred at 5°C for ~1 h, and was then extracted with ether (2 × 350 mL); the ether extracts were washed with aqueous $NaHCO_3$. Evaporation of the solvent gave alcohol **4** as an oil, which was used as such for the following reaction; ^{1}H nmr ($CDCl_3$) δ: 1.18 (t, 3H, $J \sim 7$ Hz, CH_2CH_3), 1.28 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 2.07 (s, 3H, $COCH_3$), ~2.4–2.7 (m, 2H), ~3.1–5.2 (m, 9H); ms (*m/e*, 16 eV): 244 (M^+), 229 ($M^+ - CH_3$), 73 ($CH_3CHOCH_2CH_3^+$).

Mesylate 5

To alcohol **4** (454 mg, 1.86 mmol) in dry CH_2Cl_2 (10 mL) at 5°C, under N_2, were added triethylamine (1.3 mL, 9.3 mmol) and methanesulfonyl chloride (0.58 mL, 7.4 mmol). The reaction was over immediately (tlc); the reaction mixture was extracted with ether (2 × 175 mL); the ether extracts were washed with cold dilute aqueous HCl (2 × 30 mL), $NaHCO_3$ (3 × 30 mL), water (3 × 30 mL), and dried over $MgSO_4$. Mesylate **5**, thus obtained, was used without further purification for conversion into the corresponding iodide; ^{1}H nmr (CCl_4) δ: 1.05 (t, 3H, $J \sim 7$ Hz, CH_2CH_3), 1.08 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 1.92 (s, 3H, $COCH_3$), ~2.3–2.6 (m, 2H), 2.95 (s, 3H, SO_2CH_3), ~3.0–3.7 (m, 4H), ~4.4–5.0 (m, 4H).

Iodide 6

To mesylate **5** (592 mg, 1.84 mmol) in acetone (10 mL) was added sodium iodide (1.1 g, 7.3 mmol); the reaction mixture was stirred for 1 h at room temperature and was then extracted with ether (2 × 200 mL); the ether extracts were washed with aqueous $NaHCO_3$ (1 × 100 mL, 1 × 50 mL), water (3 × 50 mL), and dried over $MgSO_4$. Iodide **6**, thus obtained, was used without further purification. On several occasions, evaporation of the ether resulted in decomposition of the iodide. This problem was remedied by use of CH_2Cl_2 as extraction solvent; ^{1}H nmr (CCl_4) δ: 1.10 (t, 3H, $J \sim 7$ Hz, CH_2CH_3), 1.18 (d, 3H, $J \sim 5$ Hz, $CHCH_3$), 1.95 (s, 3H, $COCH_3$), ~2.3–2.6 (m, 2H), ~3.2–3.7 (m, 6H), ~4.4–5.0 (m, 2H); ms (*m/e*, 16 eV): 339 ($M^+ - CH_3$), 265 ($M^+ - (OCHCH_3OCH_2CH_3)$).

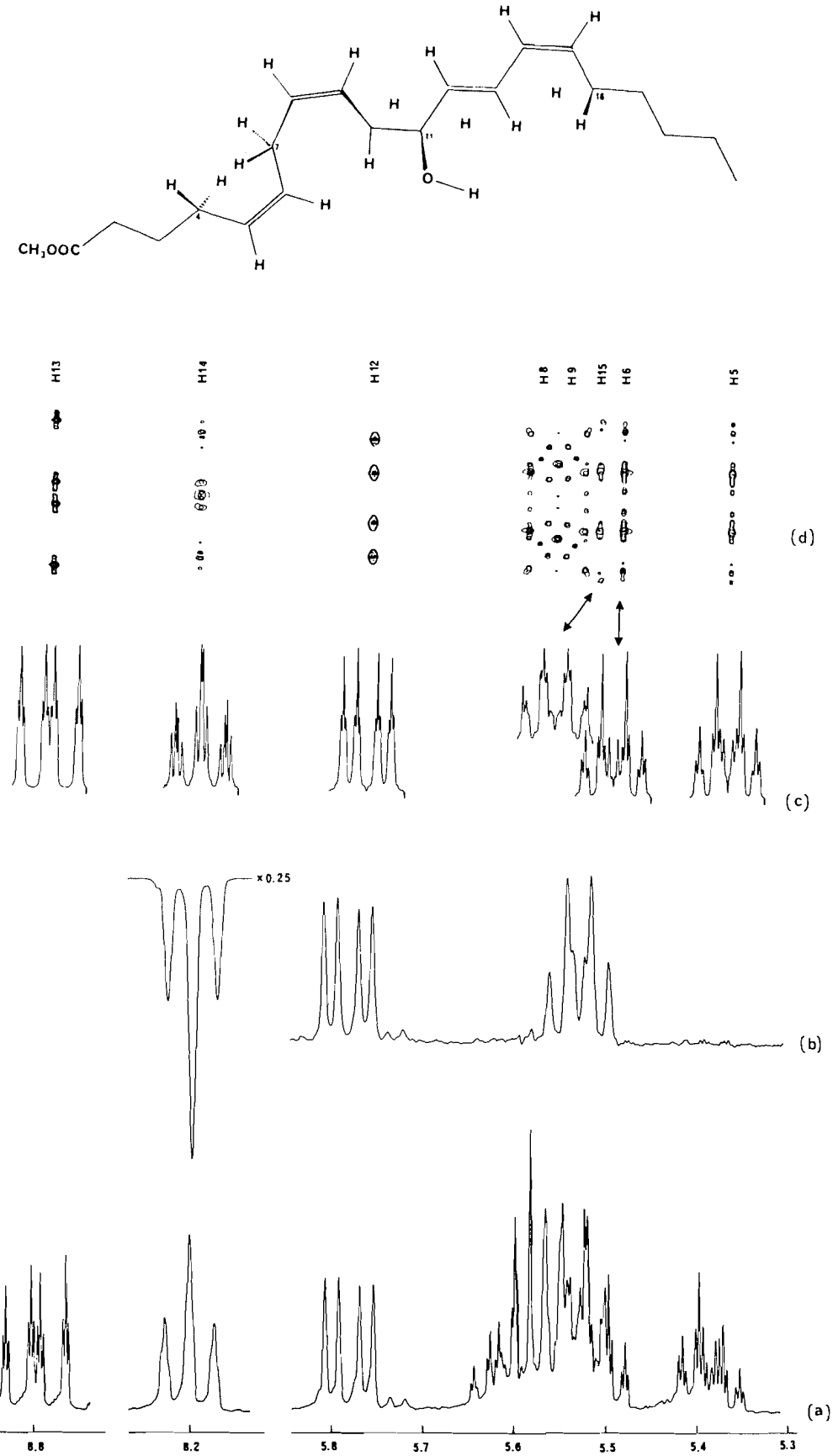


FIG. 1. Structure and examples of 400 HMz ^{1}H partial spectra of **17**; (a) 1D spectrum; (b) nOe difference spectrum; (c) cross section plots of the *J*-resolved ^{1}H 2D spectrum; (d) contour plots of the *J*-resolved ^{1}H 2D spectrum.

TABLE 2. Nuclear Overhauser effects in **17**

Irradiated proton	Observed proton	% Area change[a]
H7	H4	5
	H6	4
	H8	4
	H10a	≤1
	H10b	≤1
H10a[b]	H8	~−2
	H9	~4
	H11	4
	H12	2.5
	H13	1.5
H10b[b]	H8	~5
	H9	~1
	H11	4
	H12	4
	H13	3
	H14	−1.5
H11	H9	~3
	H10a	~2
	H10b	~2
	H12	4
	H13	7.5
	OH	5.5
H13	H11	9
	H12	<1
	H14	<1
	H16	7
	OH	4
H14	H12	18
	H13	<1
	H15	20

[a]Positive value indicates an increase, negative value a decrease.
[b]Subsaturation decoupling level was used.

Ester ***10***

To acetylenic orthoester **1** (146 mg, 0.85 mmol) and CuI (161 mg, 0.85 mmol) in dry THF (1.5 mL) at −78°C under an argon atmosphere, was added dropwise *n*-butyllithium (0.51 mL, 0.81 mmol); after 15 min iodide **6** (250 mg, 0.71 mmol) in THF (1 mL) was added. The reaction mixture was brough to room temperature over a 0.5 h period, stirred at room temperature for 22 h, and added to aqueous pH 4 buffer (~20 mL); the product was extracted with ether (2 × 150 mL), the ether extracts were washed with H_2O (4 × 20 mL) and dried over $MgSO_4$. Evaporation of the solvents at reduced pressure, followed by a standard reacetylation, gave orthoester acetate **9** in about 85% yield.

Orthoester **9** was generally contaminated with some of its hydrolysis product, ester **10**, as could be seen by the ^1H nmr spectrum: 3.12 (s, OCH_3), 3.55 (s, CO_2CH_3).

To crude orthoester **9** (300 mg, 0.75 mmol) in MeOH/H_2O (4:0.1 mL) at 5°C was added PPTS (9 mg, 5%); after 4 h stirring at 5°C the reaction mixture was extracted with ether (2 × 170 mL), the ether extracts were washed with aqueous $NaHCO_3$ (3 × 40 mL), H_2O (3 × 30 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford ester **10** as an oil in quantitative yield; ^1H nmr (CCl_4) δ: 1.07 (t, 3H, J ~ 7 Hz, CH_2CH_3), 1.15 (d, 3H, J ~ 5 Hz, $CHCH_3$), ~1.5–2.6 (m, 8H), 1.90 (s, 3H, $COCH_3$), ~2.8–3.0 (m, 2H), ~3.0–5.0 (m, 6H), 3.50 (s, 3H, CO_2CH_3); ms (m/e, 70 eV): 263 (M^+ − $OCHCH_3OCH_2CH_3$), 203 (263 − AcOH).

Diolefin ***11***

To nickel acetate (0.5 g, 2 mmol) in a 2-necked flask equipped with a septum, was added 3 mL of 95% ethanol. The flask was connected to the hydrogenation apparatus and was flushed with hydrogen. The catalyst was produced by injecting 4 mL of a 0.5 *M* solution of sodium borohydride in 95% ethanol to the rapidly stirred solution of nickel acetate. The reaction vessel was reflushed with hydrogen and ethylene diamine (0.2 mL) was added. Hydrogenation was then initiated by introducing diacetylenic ester **10** (176 mg, 0.5 mmol) in ~1 mL ethanol via the septum. Hydrogen uptake was quantitative within an hour and then virtually ceased. The reaction mixture was filtered through Celite, the ethanol was removed under reduced pressure, and the residue extracted with ether (2 × 150 mL); the ether extracts were washed with H_2O (4 × 30 mL), dried over $MgSO_4$, and evaporated *in vacuo* to give di-olefinic ester **11** as an oil in 90% yield; ^1H nmr (CCl_4) δ: 1.28 (t, 3H, J ~ 7 Hz, CH_2CH_3), 1.35 (d, 3H, J ~ 5 Hz, $CHCH_3$), ~1.3–4.2 (m, 14H), 2.10 (s, 3H, $COCH_3$), 3.71 (s, 3H, CO_2CH_3), ~4.5–5.2 (m, 2H), ~5.3–5.7 (m, 4H, 2 CH=CH); ms (m/e, 70 eV): 311 (M^+ − OEt), 267 (M^+ − $OCHCH_3OCH_2CH_3$).

*Methyl 11-acetoxy-12-hydroxydodeca-5Z,8Z-dienoate (**12**)*

To acetal **11** (580 mg, 1.63 mmol) in MeOH (7 mL) was added PPTS (20 mg, 0.08 mmol); the reaction mixture was stirred at 35°C for 2 h and was then extracted with ether (2 × 160 mL); the ether extracts were washed with H_2O (1 × 70 mL, 5 × 30 mL) and dried over $MgSO_4$. Evaporation of the solvent, followed by flash chromatography (petroleum ether – ethyl acetate 5:4), gave pure alcohol **12**; ^1H nmr (CCl_4) δ: ~0.9–3.5 (m, 13H), 1.83 (s, 3H, $COCH_3$), 3.42 (s, 3H, CO_2CH_3), ~4.3–4.7 (m, 1H), ~4.9–5.4 (m, 4H, 2 CH=CH); ms (m/e, 70 eV): 224 (M^+ − AcOH), 206 (M^+ − AcOH − H_2O).

Aldehyde ***13***

To a solution of oxalyl chloride (74 mg, 0.58 mmol) in dry methylene chloride (3 mL) at ~55°C, under argon, was added dimethylsulfoxide (91 mg, 1.16 mmol, in 0.75 mL CH_2Cl_2); after 2 min, alcohol **12** (150 mg, 0.53 mmol) in 1 mL CH_2Cl_2 was added. Stirring at −55°C was continued for an additional 15 min and triethylamine (267 mg, 2.64 mmol) added. After 5 min the reaction was warmed to room temperature, water was added, and the mixture was extracted with ether (2 × 150 mL); the ether extracts were washed with water (4 × 25 mL), dried over $MgSO_4$, and evaporated to give aldehyde **13** as an oil. It was used as such in the subsequent resolution with ephedrine or Wittig reaction with formylmethylenetriphenylphosphane; ^1H nmr (CCl_4) δ: ~1.2–3.0 (m, 10H), 2.20 (s, 3H, $COCH_3$), 3.67 (s, 3H, CO_2CH_3), 5.00 (t, J ~ 6 Hz, 1H), ~5.2–5.7 (m, 4H, 2 CH=CH), 9.57 (s, 1H, CHO); ms (m/e, 70 eV): 282 (M^+), 222 (M^+ − AcOH).

l-*Ephedrine derivative* ***14*** *of aldehyde* ***13***

A solution of aldehyde **13** (230 mg, 0.82 mmol), *l*-ephedrine (269 mg, 1.63 mmol), and PPTS (20 mg, 10 mol%) in dry methylene chloride (4 mL) was stirred under N_2 at 40°C for 3 h and at room temperature for 5 h to effect a complete conversion of **13** to **14**. The CH_2Cl_2 was evaporated to yield the two desired ephedrine derivatives **14***R* and **14***S* which were separated by slash chromatography (petroleum ether – ethyl acetate 10:2, 20% yield of each); ^1H nmr ($CDCl_3$) δ of **14***S* (lower R_f): 0.53 (d, 3H, J = 7 Hz, CH_3), ~1.1–3.0 (m, 10H), 1.90 (s, 3H, $COCH_3$), 2.30 (s, 3H, NCH_3), 3.47 (s, 3H, CO_2CH_3), 3.85 (d, 1H, J = 4 Hz), ~4.7–5.4 (m, 7H), 7.13 (s, 5H, C_6H_5); of **14***R* (higher R_f): 0.57 (d, 3H, J = 7 Hz), ~1.1–3.0 (m, 10H), 2.03 (s, 3H $COCH_3$), 2.20 (s, 3H, NCH_3), 3.50 (s, 3H, CO_2CH_3), 3.75 (d, 1H, J = 2 Hz), ~4.7–5.5 (m, 7H), ~7.0–7.4 (m, 5H, C_6H_5); ms (m/e, 70 eV): 429 (M^+), 398 (M^+ − OCH_3), 176 (cyclic—NMeCHMeCHPhOCH—$^+$).

*Aldehydes 14*R *and 14*S

To ephedrine derivative **14***R* (125 mg, 0.29 mmol) in MeOH (5 mL) was added 1 mL aqueous 0.5 *N* HCl. The solution was stirred at 33°C for ~4 h and was then extracted with ether (2 × 150 mL); the ether extracts were washed with dilute aqueous HCl (1 × 50 mL, 1 × 20 mL), water (4 × 20 mL), and dried over $MgSO_4$. Evaporation of the solvent gave crude aldehyde **13***R* in ~90% yield; it was used without further purification in the subsequent Wittig reaction. An identical procedure was used to produce **13***S*.

*Methyl 11-acetoxy-14-oxo-tetradeca-5Z,8Z,12E-trienoate (**15**)*

The aldehyde **13** (85 mg, 0.30 mmol) in dry DMF (2 mL) under Ar was added formylmethylenetriphenylphosphorane (100 mg, 0.33 mmol). The reaction mixture was stirred at 42°C for 4 h and was then extracted with ether (2 × 150 mL). The ether extracts were washed with water (4 × 20 mL) and dried over $MgSO_4$; evaporation of the solvent followed by flash chromatography (petroleum ether – ethyl acetate 12:3) gave α,β-unsaturated aldehyde **15** as an oil in ~50% yield; ^{1}H nmr (CCl_4) δ: ~1.4–2.9 (m, 10H), 2.00 (s, 3H, $COCH_3$), 3.53 (s, 3H, CO_2CH_3), ~5.0–5.7 (m, 4H, CH=CH), 6.0 (ABXY octet, 1H, C13, $J_{13,12}$ = 16, $J_{13,14}$ = 7, $J_{13,11}$ = 1 Hz), 6.60 (ABXq, 1H, C12, $J_{12,13}$ = 16, $J_{12,11}$ = 4 Hz), 9.43 (d, 1H J = 7 Hz, CHO); ms (m/e, 70 eV): 248 (M^+ – AcOH).

*Methyl 11-acetoxyeicosa-5Z,8Z,12E,14Z(E)-tetraenoate (**16**)*

To *n*-hexyltriphenylphosphonium bromide (107 mg, 0.25 mmol) in dry THF (3 mL) at room temperature under an argon atmosphere and was added *n*-butyllithium (0.18 mmol); after 15 min, the reaction mixture was cooled to −78°C, and aldehyde **15** (46 mg, 0.15 mmol) in THF (1 mL) was added dropwise via syringe. The reaction was over immediately; it was warmed up rapidly by immersion into a 20°C water bath, poured into pH 4 buffer (50 mL), and extracted with ether (2 × 150 mL). The ether extracts were washed with water (4 × 30 mL), dried over $MgSO_4$, and evaporated to give acetate **16** contaminated with some of its 14*E* isomer.

*Methyl 11-hydroxyeicosa-5Z,8Z,12E,14Z-tetraenoate (**17**)*

Crude acetate **16** (49 mg, 0.13 mmol) in dry methanol (4 mL) containing a catalytic amount of sodium methoxide was stirred at room temperature for 0.5 h, and was then neutralized with strong acidic resin (AM-120 H^+). Removal of the resin, followed by evaporation of the methanol, gave alcohol **17** contaminated with its 14*E* isomer. The latter was removed by flash chromatography (petroleum ether – ethyl acetate 9:2); ms (m/e, 70 eV): trimethylsilylether: 406 (M^+), 283 (M^+ – CH=CHCH=CH$(CH_2)_4CH_3$), 225 ($(Me)_3SiOCHCH$=CHCH=CH$(CH_2)_4CH_3$).

*Methyl 11-hydroperoxyeicosa-5Z,8Z,12E,14Z-tetraenoate (**19**)*

To alcohol **17** (10 mg, 0.030 mmol) in dry CH_2Cl_2 (1.6 mL) under an argon atmosphere at −65°C was added triethylamine (0.017 mL, 0.12 mmol), the methanesulfonyl chloride (0.0035 mL, 0.045 mmol). After 0.5 h, 90% hydrogen peroxide (0.04 mL, 1.6 mmol) was added in 0.5 mL ether at −81°C. After 15 min, water was added and the reaction mixture extracted with ether–pentane (2:1) (60 mL); the ether–pentane extracts were washed with cold water (10 × 10 mL), dried over $MgSO_4$, and evaporated to yield hydroperoxide **19** contaminated with ~30% of its 15-hydroperoxy isomers (^{1}H nmr evidence only).

Purification by hplc was carried out using a straight-phase column (Altex Ultra-Sil), and petroleum ether – ethyl acetate as solvent system. The hydroperoxide mixture decomposed on the column, giving first a less polar material, then **19**, followed (shoulder) by other hydroperoxides (15-HPETE's). Only 10–30% of **19** could be isolated.

The crude mixture of HPETE's (1 mg, 70% **19**, 30% others by 400 MHz ^{1}H nmr) was reduced with $SnCl_2$ (12 mg) in 0.5 mL methanol for 2 min at room temperature. Extraction with ether–pentante 1:1, and washing with pH 4 buffer and water gave, after drying, a mixture. Separation by hplc, using the same column and petroleum ether – ethyl acetate (10:1) gave, as the major product, **17**.

*Experimental section for ^{1}H nmr of **17***

The solution of **17** (~10^{-2} *M*) was made up in C_6D_6, and degassed through 5 cycles of freeze–pump–thaw. The ^{1}H spectra were obtained on the Brüker WH-400 located at the "Laboratoire Régional de RMN" at the Université de Montréal. The 1D FID were accumulated with 16K data points and zero-filled before being Fourier transformed to obtain a digital resolution better than 0.1 Hz. The steady-state nOe difference spectra were obtained by subtraction of FID or transformed spectra; transients were collected after preirradiation (10–12 s) at selective frequencies and recycled to average the drift effect. For the protons H10a and H10b, subsaturation power levels were used to achieve partial selectivity; for other protons, complete saturation power levels were used. The T_1 of the protons obtained by nonselective inversion recovery were in the range of 0.8 to 2 s.

The 2D *J* spectra were obtained with the automated Brüker program. Because of the memory storage limit, the window of f_2 dimension only covers the downfield part of the spectra (1100 Hz), the frequency offset was carefully chosen to avoid the foldover problem. The digital resolution is 0.268 Hz after zero-filling in both f_1 and f_2. A Gaussian resolution enhancement function is applied in both t_1 and t_2 directions before doing the Fourier transform.

The coupling constants are calculated directly by first order analysis for the well-dispersed proton signals and from the simulated spectra using the standard PANIC program from the Brüker software package.

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