

## **A Facile Synthesis of (10Z,15Z)-Eicosa-10,15-dienoic Acid, a Marine Natural Product**

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## A FACILE SYNTHESIS OF (10Z,15Z)-EICOSA-10,15-DIENOIC ACID, A MARINE NATURAL PRODUCT

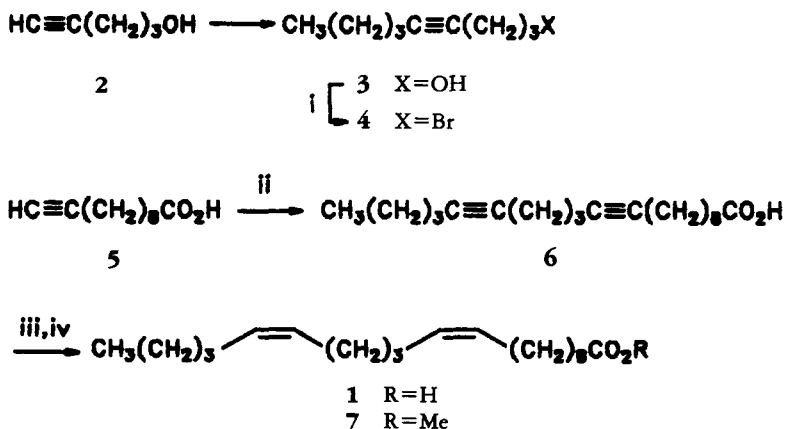
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ABSTRACT.—A short synthesis of (10Z,15Z)-eicosa-10,15-dienoic acid, a marine natural product, has been achieved by alkylation of the terminal acetylene of 10-undecynoic acid with an acetylenic bromide followed by *cis*-hydrogenation.

Extensive research in the field of marine natural products chemistry has led to the isolation of several rare fatty acids of varied structural features, giving rise to speculation on the possibility of newer biological phenomena occurring in the marine world. One such compound, (10Z,15Z)-eicosa-10,15-dienoic acid (**1**), was recently isolated from the Mediterranean opisthobranch, *Haminaea templadoi* (1). 1,6-Dienic fatty acids like **1** are observed primarily in the marine field and less frequently from other types of organisms. An extensive bioassay of **1** required its availability in large quantities. In view of this, we carried out a short, stereoselective synthesis of this compound using operationally simple reactions and commercially available materials. This constitutes the first synthesis of **1** (Scheme 1).

The (10Z)-olefinic unit of **1** was available from 10-undecynoic acid and the (15Z)-olefin was obtained from 4-pentyn-1-ol (**2**). Alcohol **3** (2,3), prepared from **2** by bromination (PPh<sub>3</sub>, Br<sub>2</sub>/pyridine), furnished bromide **4**. Treatment of the dilithio salt of 10-undecynoic acid **5** (4) with the bromide **4** at -50° in THF/HMPA yielded the C-alkylated product **6** in 68% yield. Treatment of **6** by *cis*-hydrogenation (5) produced the title compound [**1**]. The identity of **1** was established from its spectral data and by combustion analysis. The eims data of its methyl ester **7** were comparable with those values reported (1). The (Z)-geometry of **1** was deduced from the absence of the trans-olefinic ir band at 960–980 cm<sup>-1</sup> and the <sup>13</sup>C-nmr signals of the allylic carbon atoms (6,7) of **7**. The isomeric purity of **1** as 98% was established by a



i) Ph<sub>3</sub>P.Br<sub>2</sub>/Pyridine/CH<sub>2</sub>Cl<sub>2</sub>; ii) *n*-BuLi/HMPA/THF, **4**;  
 iii) H<sub>2</sub>/P-2 Ni/EtOH/H<sub>2</sub>NCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>; iv) MeOH/H<sup>+</sup>.

SCHEME 1. Synthetic Scheme for (10Z,15Z)-Eicosa-10,15-dienoic Acid.

capillary gc (stationary phase, OV-17) analysis of its methyl ester 7.

## EXPERIMENTAL

**GENERAL EXPERIMENTAL PROCEDURES.**—All bps are uncorrected. Ir spectra were scanned on a Perkin-Elmer spectrophotometer model 783. The  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra were recorded in  $\text{CDCl}_3$  on a Bruker AC-200 200 MHz instrument. Gc analyses were carried out on a Shimadzu GC-7A gas chromatograph fitted with a glass column. Mass spectra were recorded on a Shimadzu QP-1000A GC-MS mass spectrometer. All anhydrous reactions were carried out under an Ar atmosphere using freshly distilled solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous  $\text{Na}_2\text{SO}_4$ .

**1-BROMO-4-NONYNE [4].**—To a solution of triphenylphosphine (6.17 g, 0.024 mol) in  $\text{CH}_2\text{Cl}_2$  (50 ml),  $\text{Br}_2$  (4.3 ml, 5.5 M solution in  $\text{CCl}_4$ , 0.024 mol) was added. After 0.5 h, compound 3 (3.0 g, 0.021 mol) and pyridine (1.9 ml, 0.024 mol) in  $\text{CH}_2\text{Cl}_2$  (20 ml) were added at  $0^\circ$ . After stirring for 3 h, most of the solvent was removed under reduced pressure, with the residue diluted with *n*-hexane (200 ml) and the solution passed through a 6" pad of neutral alumina (gr. II). After concentration, the residue was distilled to obtain pure 4 (3.15 g, 72.8%); bp  $100^\circ$  10 Torr; ir (film)  $\nu$  max  $2210\text{ cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.87 (3H, br t), 1.2–1.6 (6H, m), 1.9–2.5 (4H, m), 3.54 (2H, t,  $J=7$  Hz); *anal.* found C, 53.32; H, 7.35; Br, 39.33%.  $\text{C}_9\text{H}_{15}\text{Br}$  requires C, 53.22; H, 7.44; Br, 39.34%.

**10,15-EICOSADIENOIC ACID [6].**—To a magnetically stirred solution of 5 (1.82 g, 0.01 mol) in THF (20 ml) was added a solution of *n*-BuLi (13.75 ml, 1.6 M in hexane, 0.022 mol) at  $-70^\circ$ . After 0.5 h, HMPA (5 ml) was added at  $-50^\circ$  followed by the bromide 4 (2.23 g, 0.011 mol) in THF (10 ml). Stirring was continued for 8 h at the same temperature and the reaction was quenched with dilute HCl (2 N). Isolation by cc ( $\text{SiO}_2$ , 0–30% EtOAc in hexane) furnished pure 6 (2.06 g, 68%); ir (film)  $\nu$  max 3500–3000,  $1710\text{ cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.87 (3H, br t), 1.42 (18H, br s), 1.9–2.5 (10H, m), 8.7 (1H, s,  $\text{D}_2\text{O}$  exchangeable); *anal.* found C, 78.84; H, 10.71.  $\text{C}_{20}\text{H}_{32}\text{O}_2$  requires C, 78.89; H, 10.60%.

(10Z,15Z)-EICOSA-10,15-DIENOIC ACID [1].—Following a known general procedure (5), compound 6 (2.0 g, 6.6 mmol) was semi-hydrogenated in EtOH (30 ml) over P-2 Ni catalyst in the presence of ethylene diamine (0.12 ml) to furnish pure 1 (1.94 g, 95.6%) after cc ( $\text{SiO}_2$ , 0–5% MeOH in  $\text{CHCl}_3$ ); ir (film)  $\nu$  max 3500–3000, 1710,  $1645\text{ cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.90 (3H, br t), 1.45 (18H, br s), 1.9–2.5 (10H, m), 5.2–5.6 (4H, m), 8.7 (1H, s,  $\text{D}_2\text{O}$  exchangeable); *anal.* found C, 77.74; H, 11.88%.  $\text{C}_{20}\text{H}_{36}\text{O}_2$  requires C, 77.86; H, 11.76%; ms  $m/z$  308  $[\text{M}]^+$ .

**METHYL ESTER [7].**—Esterification of the above compound with MeOH/ $\text{H}^+$  afforded 7 as an oil; gc (OV-17, 50 m, i.d. 0.25 mm; split (1:100); FID;  $\text{N}_2$  2 ml/min, 180–250°, 4° min.),  $R$ , 11.97 min, 98%; ir  $\nu$  max 3010, 1740, and 1640 (film)  $\text{cm}^{-1}$ ;  $^1\text{H}$  nmr ( $\text{CDCl}_3$ )  $\delta$  0.88 (3H, br t), 1.46 (18H, br s), 2.0–2.2 (8H, m), 2.30 (2H, t,  $J=7.5$  Hz), 3.60 (3H, s), 5.3–5.4 (4H, m);  $^{13}\text{C}$  nmr  $\delta$  13.99, 22.31, 22.64, 24.93, 26.88, 27.17, 29.21, 29.66, 31.89, 34.08, 51.37, 129.52, 130.11, 174.26; *anal.* found C, 78.31; H, 9.83%.  $\text{C}_{21}\text{H}_{38}\text{O}_2$  requires C, 78.20; H, 9.92%; ms  $m/z$  322  $[\text{M}]^+$ .

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