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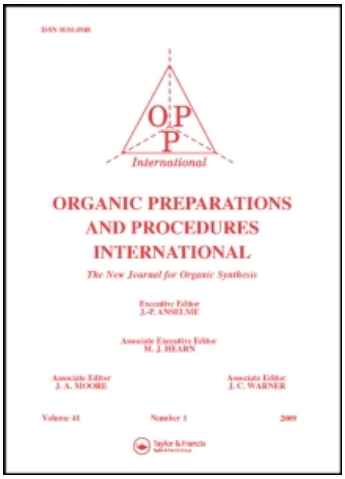

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A SHORT SYNTHESIS OF (11Z, 15Z)-EICOSADIENOIC ACID, A COMPOUND OF MARINE SPONGE ORIGIN

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A SHORT SYNTHESIS OF (11Z,15Z)-EICOSADIENOIC ACID, A COMPOUND OF MARINE SPONGE ORIGIN

Submitted by (05/04/92)

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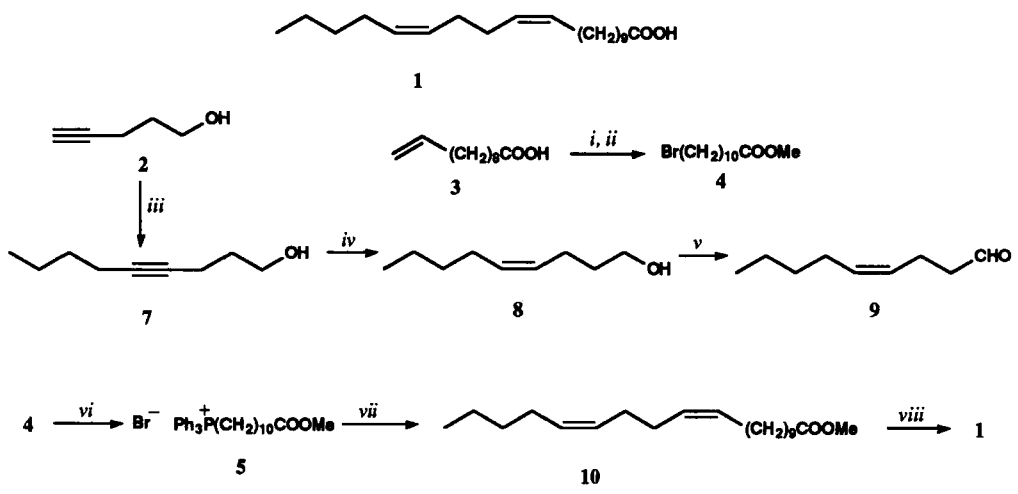
The chemical investigation of marine organisms has resulted in the isolation and characterization of a number of unusual compounds[1-3] of diverse biological activities. This has provided great impetus to the studies of their metabolism and biosynthesis. Their low natural abundance makes their syntheses of great importance. Among the various types of marine products, the ubiquitous phospholipids occupy an important position. Recently, Carballeira *et al.*[2] isolated a new compound, (11Z,15Z)-eicosadienoic acid (**1**) from Caribbean sponge, *Amphimedon complanata*. To the best of our knowledge, there is no report of its synthesis. We herein report a practical and stereoselective synthesis of this compound relying on the "building block" approach.

From a retrosynthetic perspective, the easily available acetylenic alcohol **2** seems to be ideally suited for its derivatization to the necessary 1,5-alkadienic unit present in **1**. The bifunctional alcohol was used earlier in the preparation[4] of other classes of active compounds *viz* pheromones, jasmonoids and a prostaglandin synthon. The other notable feature was utilization of yet another commercially available substance *viz*. 10-undecenoic acid (**3**) for the preparation of the C_{11}–synthon (**5**) required for the synthesis. Hydrogen bromide was added to **3** and the product was esterified.[5] Subsequent treatment of the resulting bromoester (**4**) with triphenylphosphine in refluxing acetonitrile afforded the



i) HBr, Br_2O_2, *ii*) MeOH/H^+, *iii*) $LINH_2$, *n*-BuBr (6), *iv*) H_2/P(2) Ni, *v*) PCC, *vi*) PPh_3
vii) $NaCH_2S(O)CH_3$, (9), *viii*) Alc./KOH; H^+

known[6] phosphonium salt (**5**). Pyridinium chlorochromate (PCC)[7] oxidation of (4Z)-nonenol (**8**), prepared[8] from **2**, yielded the aldehyde (**9**)[9]. Stereoselective Wittig Z-olefination was performed by treating aldehyde (**9**) with phosphorane of **5**, using sodium dimsyl as base and DMSO-THF(1:1) as solvent system to furnish (Z,Z)-C_{20}-dienoate (**10**) whose stereochemical purity was assayed to be 95% through GLC analysis. Its IR spectrum was devoid of a characteristic *trans*-olefinic band at 960-980 cm^{-1} region, while the PMR signal width due to the olefinic protons was found to be 10Hz. This indicated the (Z) stereochemistry of both of the disubstituted olefins in **10**. Further confirmation of this was accomplished on the basis of the ^{13}C chemical shifts of four allylic carbon atoms (δ 27.2 and 27.4), characteristic for internal (Z)-double bonds. The expected values for the (E)-isomer is about 5 ppm downfield[10,11] *i.e.* δ 32. The spectral data of **10** were identical with the reported values[2]. Alkaline hydrolysis of **10** followed by acidification completed the formal synthesis of **1**.

EXPERIMENTAL SECTION

IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 783 spectrophotometer. The PMR spectra were obtained on AC-200 MHz Bruker NMR spectrometer in $CDCl_3$ using TMS as internal standard and the values were expressed in δ scale(ppm). GLC analysis was carried out on a Shimadzu GC-7A chromatograph fitted with a flame ionization detector and glass column containing 10% Silar on gas chrom Q 80-100 mesh. Mass spectra were taken using Shimadzu GC-MS QP-1000A spectrometer. All the anhydrous reactions were carried out under argon atmosphere using freshly distilled anhydrous solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4.

10-Carbomethoxydecyltriphenylphosphonium Bromide (5).- A mixture of triphenylphosphine (30 g) and **4** (28 g) in acetonitrile (150 mL) was refluxed for 40 hrs. The solvent was removed and the residue was washed with hot petroleum ether (3x 40 mL) to afford 38 g (70%) of **5**, mp. 109-111°;

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PMR ($CDCl_3$): δ 1.2-1.7 (m, 16H), 2.3 (t, *J* = 8Hz, 2H), 3.5-3.8 (t, *J* = 5Hz, 2H, overlapped with a singlet at 3.71, 3H), 7.8 (m, 15H).

Anal. Calcd. for $C_{30}H_{38}BrPO_2$: C, 66.54; H, 7.07; Br, 14.76. Found: C, 66.71; H, 6.84; Br, 14.38

(4Z)-Non-4-enal (9).- To a stirred suspension of PCC (2.6 g, 0.012 mol) in CH_2Cl_2 (40 mL), a solution of alkenol (**8**) (1.15 g, 0.008 mol) in CH_2Cl_2 (10 mL) was added. The mixture was stirred at room temperature for 3 hrs (monitored by TLC). Dry ether (50 mL) was added and the precipitate was removed by filtration through florisil column. The filtrate was concentrated under vacuum to afford 0.9 g (80%) of **9**. IR (film): 2720, 1720; PMR ($CDCl_3$): δ 0.91 (t, *J* = 5Hz, 3H), 1.2-1.4 (m, 4H), 2.0-2.5 (m, 6H), 5.3-5.5 (m, 2H), 9.8 (t, *J* = 1Hz, 1H). The aldehyde was used as such in the next step without further purification.

(11Z,15Z)-Eicosa-11,15-dienoic Acid (1).- A suspension of NaH (0.46 g of 50% dispersion, 0.0096 mol) in DMSO (20 mL) was stirred at 65-70° until the evolution of hydrogen ceased (45 min.). The resulting light green dimsyl solution was transferred with a cannula to an ice cold solution of salt (**5**) (5.4 g, 0.01 mol) in mixture of THF (40 mL) and DMSO (10 mL). The reaction mixture was then stirred for 30 min. and the resulting dark red solution was cooled (-20°) and the aldehyde (**9**) (0.9 g, 0.0064 mol) in DMSO (10 mL) was added over 10 min. The mixture was stirred for 1 hr at -30° and 5 hrs at an ambient temperature. Workup furnished a residue which was purified by column chromatography through silica gel eluting with 0-10% ethyl acetate in hexane to obtain 1.3 g. (63%) of pure dienic ester (**10**). An analytical sample was prepared by preparative thin layer chromatography. GLC: 180° 40 mL N_2/min: R_t = 6.8 min; bp. 194-196°/4mm n_D^{24} 1.4640; IR (film): 3005, 1720, 1445, 1150; PMR ($CDCl_3$): δ 0.9 (bt, 3H), 1.2-1.6 (m, 18H), 1.9-2.2 (m, 8H), 2.3 (t, *J* = 6Hz, 2H), 3.68 (s, 3H), 5.3-5.5 (m, 4H); MS: m/z 322(M^+); ^{13}C NMR: δ 13.9, 22.3, 24.9, 26.9, 27.2, 27.4, 29.2, 29.4, 29.7, 31.6, 34.1, 51.4, 129.2, 129.7, 130.3, 130.7 and 174.3.

Anal. Calcd. for $C_{21}H_{38}O_2$: C, 78.20; H, 11.87. Found: C, 78.41; H, 11.72

The above ester (1.0 g, 0.003 mol) was hydrolyzed with alcoholic KOH followed by acidification to obtain 0.82 g (85%) of acid (I) after workup as colorless viscous oil; n_D^{24} 1.4784; IR (film): 3400 (broad), 1720, 1450; PMR ($CDCl_3$): δ 0.9 (br s, 3H), 1.2-1.7 (m, 18H), 1.9-2.2 (m, 8H), 2.3 (t, *J* = 6Hz, 2H), 4.1 (s, 1H, D_2O exchangeable), 5.3-5.5 (m, 4H); MS: m/z 308(M^+).

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Found: C, 78.01; H, 11.93

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CONVENIENT SYNTHESIS OF 2-PHENETHYL ALCOHOL BY HYDROLYSIS OF 2-BROMOETHYLBENZENE UNDER PHASE TRANSFER CONDITIONS†

Submitted by (08/18/92)

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The flowery odor of 2-phenethyl alcohol gives it a significant commercial value in the synthetic perfumes industry. However, traces of impurities have undesirable effects on the alcohol's rosy odor, rendering it unsuitable as a perfume grade alcohol. Most commercial preparations of 2-phenethyl alcohol involve the Friedel-Crafts reaction of benzene and ethylene oxide[1]. This method suffers from the disadvantage of producing bibenzyl and ethylene oxide polymers as by-products which necessitates further purification of the alcohol in order to achieve a fragrance grade product. Furthermore, this process has an overall selectivity of only about 66% and requires a large excess of $AlCl_3$ over ethylene oxide in order to obtain significant yields of 2-phenethyl alcohol. Moreover, benzene, ethylene oxide and aluminum chloride cause environmental problems. Another commercially feasible method for the production of 2-phenethyl alcohol is based on the hydrogenation of styrene oxide[1]. Limitations of this method include that the cost of the epoxide and the further purification necessary to meet perfume grade specifications. We report here a new process