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Peter T. Bell, and William A. Donaldson

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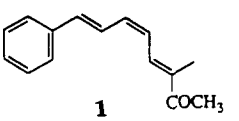
SYNTHESIS OF LIGNARENONE B

PETER T. BELL and WILLIAM A. DONALDSON*

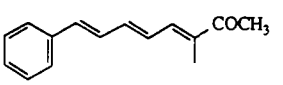
Department of Chemistry, Marquette University, 535 North 14th Street, Milwaukee, Wisconsin 53233

ABSTRACT.—The synthesis of the recently isolated ϖ-phenyl conjugated trienone, lignarenone B [**2**] was achieved, beginning from 5-phenyl-2,4-pentadienoic acid.

Recently, two new polyenes, lignarenones A [**1**] and B [**2**], were isolated from the mantles of the Mediterranean bullomorph mollusc *Scaphander lignaruis* (Scaphandridae) (1). The structures of **1** and **2** were assigned solely on the basis of their spectroscopic data. These compounds may possess alarm pheromone properties as they are structurally similar to the known alarm pheromone, 3-methylnavenone B (2,3). As part of our interest in the synthesis of linear polyenes (4,5), we herein report the first total synthesis of **2**.

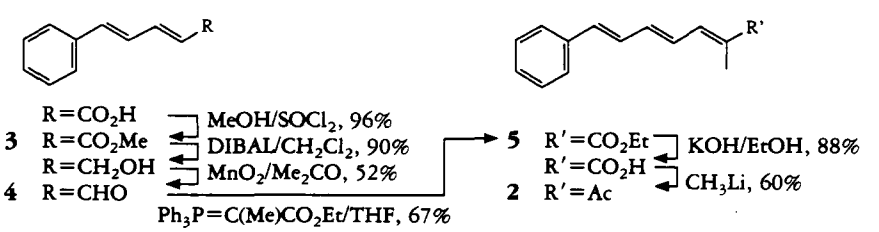


1



2

The sequence for the synthesis of lignarenone B is illustrated in Scheme 1. Methyl 5-phenyl-*E,E*-2,4-pentadienoate [**3**] has previously been prepared from the reaction of cinnamaldehyde with methyl triphenylphosphoranylideneacetate (6). For our purposes **3** was prepared by esterification of commercially available 5-phenyl-2,4-pentadienoic acid ($SOCl_2$/MeOH). Although the reduction of **3** to 5-phenyl-2,4-pentadien-1-ol by $LiAlH_4$ has been reported (7), we found that in our hands this reaction resulted in the formation of a mixture of dienol and two additional products with mol wt of 162. These two other products presumably arise via further hydride addition to the dienol (8). Reduction of **3** (DIBAL 2 equiv/CH_2Cl_2) (6) followed by oxidation (MnO_2/Me_2CO) (7) gave 5-phenyl-2,4-pentadienal [**4**]. Purification of **4** by cc gave the *E,E* isomer in >95% isomeric purity, as determined by nmr and gc-ms analysis. Notably, PDC oxidation of the dienol gave a mixture of isomeric 5-phenyl-2,4-pentadienals as evidenced by two aldehyde signals in the nmr spectrum (6). Reaction of **4** with (carboethoxyethylidene) triphenylphosphorane gave the unsaturated ester **5**. The structure of **5** was assigned the *E,E,E* stereochemistry on the basis of 2D nmr analysis. Off-diagonal correlation between the C-2 methyl signal (δ 2.00) and an olefinic signal at δ 7.26 facilitated assignment of H-3. The 2D NOESY spectrum of **5** exhibited no off-diagonal correlation between the same signals, thus indicating their trans relationship. Hydrolysis of **5** gave the acid **6**. Finally, treatment of **6** with



SCHEME 1

methyllithium (3.6 equiv), followed by quench with TMSiCl and aqueous acid workup (9), gave **2**. The nmr spectra of lignarenone B, kindly provided by Dr. A. Spinella, were identical with those of the product prepared in the above fashion. This chemical synthesis thus confirms the structural assignment of the natural product.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The 300 MHz ^{1}H-nmr and 75 MHz ^{13}C-nmr spectra of all compounds were obtained in $CDCl_3$ solutions using a GE 300 Omega Spectrometer. The chemical shifts are reported in ppm downfield from TMS; all couplings are in Hz. Analysis by gc-ms was performed on a Hewlett Packard 5890 equipped with a 5970 mass selective detector. Melting points were obtained with a Mel-Temp apparatus and are uncorrected. Spectrograde solvents were used without any further purification unless otherwise noted. Dry THF was obtained by distillation from potassium benzophenone ketyl and dry CH_2Cl_2 by distillation from P_2O_5. Chromatography was performed with Si gel 62 (60–200 mesh) as supplied by Aldrich Chemical Co.

5-Phenyl-E,E-*2,4-pentadienal* [**4**].—Compound **4** was prepared from **3** via reduction (DIBAL 2 equiv/CH_2Cl_2) followed by oxidation (MnO_2/Me_2CO) according to literature procedures (7,8). The crude product was purified in two batches by chromatography using hexanes-EtOAc (9:1) as eluent to give **4** as a yellow-orange oil which solidified only upon refrigeration (i.e., mp ca. 0°) (52%). The ^{1}H-nmr spectrum for **4** is consistent with one of the isomers reported in the literature (5). ^{1}H nmr δ 9.64 (d, J = 8.1, 1H), 7.55–7.24 (m, 6H), 7.08–6.96 (m, 2H), 6.29 (dd, J = 8.0, 15.1, 1H); ir (CCl_4) 3032, 2808, 2737, 1688, 1622, 1152, 1109 cm^{-1}; gc-ms *m/z* [M]$^+$ 158 (52), 129 (100), 77 (31).

Ethyl 2-methyl-7-phenyl-E,E,E-*2,4,6-heptatrienoate* [**5**].—To a stirred suspension of (carboethoxyethylidene)triphenylphosphorane (1.7 g, 4.8 mmol) in dry THF (20 ml) was added **4** (0.51 g, 3.2 mmol). The reaction mixture was stirred at room temperature for 3 days, and then the solvent was evaporated. Purification of the residue by chromatography using hexanes-EtOAc (9:1) as eluent followed by recrystallization from 95% EtOH gave **5** as a yellow solid (0.52 g) (67%): mp 77–79°; ^{1}H nmr δ 7.46–7.24 (m, 6H), 6.94 (dd, J = 10.2, 15.6, 1H), 6.72 (dd, J = 9.7, 14.9, 1H), 6.71 (d, J = 15.7, 1H), 6.63 (dd, J = 10.9, 14.9, 1H), 4.24 (q, J = 7.0, 2H), 2.00 (narrow d, J = ca. 1, 3H), 1.32 (t, J = 7.1, 3H); ^{13}C(^{1}H) nmr δ 168.3, 139.3, 138.0, 136.9, 135.6, 128.7, 128.6, 128.2, 128.16, 127.3, 126.7, 60.6, 14.3, 12.8; ir (CCl_4) 3030, 2982, 1705, 1500 cm^{-1}; hreims *m/z* 242.1302 (calcd for $C_{16}H_{18}O_2$, 242.1307). *Anal.* calcd for $C_{16}H_{18}O_2 \cdot \frac{1}{3}H_2O$: C 77.40, H 7.57; found C 77.11, H, 7.51.

3-Methyl-8-phenyl-E,E,E-*3,5,7-octatrien-2-one* [**2**] *(lignarenone B).*—To a heterogeneous mixture of KOH (2.0 g, 34 mmol), H_2O (20 ml), and **5** (0.65 g, 2.7 mmol) was added sufficient 95% EtOH for the reaction mixture to become homogeneous. The mixture was stirred at room temperature for 24 h, cooled in an ice-H_2O bath, and cautiously acidified with 1.0 M HCl. The acidic solution was extracted with CH_2Cl_2, the combined organic extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 7-phenyl-*E,E,E*-2,4,6-heptatrienoic acid [**6**] as a pale yellow gum (0.50 g) (88%): ^{1}H nmr δ 12.0 (br s, CO_2H), 7.46–7.24 (m, 6H), 6.94 (dd, J = 10.3, 15.4, 1H), 6.73 (d, J = 15.4, 1H), 6.74 (dd, J = 10.3, 15.0, 1H), 6.62 (dd, J = 10.9, 15.2, 1H), 2.00 (narrow d, J = ca. 1 Hz, Me). This compound was used in the next step without further purification. To a stirred solution of **6** (0.50 g, 2.3 mmol) in dry THF (16 ml) cooled in an ice-H_2O bath, a solution of CH_3Li (6.0 ml, 8.4 mmol, 1.4 M) in Et_2O was rapidly added via syringe. The reaction mixture turned from yellow to dark purple and was stirred at this temperature for 2 h. The reaction was quenched at 0° by rapid addition of chlorotrimethylsilane (6 ml), during which the dark purple color turned to yellow. The reaction mixture was allowed to come to room temperature, 1 M aqueous HCl (16 ml) was added, and the biphasic mixture was stirred for an additional 0.5 h. The mixture was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Purification of the residue by chromatography using hexanes-EtOAc (9:1) as eluent gave **2** as a yellow oil (0.30 g) (60%): ^{1}H nmr δ 7.50–7.43 (br d, J = 7.8, 1H), 7.40–7.26 (m, 4H), 7.13 (d, J = 10.3, 1H), 6.95 (dd, J = 15.6, 9.8 Hz, 1H), 6.79–6.64 and 6.73 (m, and d, respectively, J = 15.6, total 3H), 2.36 (s, Ac), 1.92 (s, Me); ^{13}C(^{1}H) nmr δ 199.4, 140.0, 139.1, 136.6, 136.3, 136.2, 128.7, 128.6, 128.4, 128.3, 126.7, 25.6, 11.6; ir (CCl_4) 3030, 2976, 2870, 1710, 1664 cm^{-1}; gc-ms *m/z* [M]$^+$ 212 (100), 197 (44), 169 (76), 154 (65), 153 (48), 141 (64), 128 (65), 115 (60), 91 (83). The ^{1}H- and ^{13}C-nmr spectra of this product match those of authentic lignarenone B (1). Hreims *m/z* 212.1195 (calcd for $C_{15}H_{16}O$, 212.1202).

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