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GENERAL METHOD OF SYNTHESIS FOR NATURAL LONG-CHAIN β-DIKETONES

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ABSTRACT.—Two general methods of synthesis have been developed for the preparation of long-chain β-diketones. The first relies on malonate-type alkylation of acid chlorides derived from fatty acids, while the second, more direct method, involves coupling and subsequent hydrolysis of long-chain acetylenes with acid chlorides of fatty acids.

β-Diketones with 31 carbon atoms and the diketone moiety disposed freely along this chain are ubiquitous components of many plant waxes (1-7).[2] Derivatives of these compounds such as hydroxyketones or diols also exist in many species (2,4). Suggestions that such compounds play an important role in the protection of grasses and leaves have been made (1,3). The interest of the agricultural sector in these compounds prompted us to investigate a general synthetic approach to structures **1**. Because of the availability and the low cost of fatty acids our design for any of the β-diketones originated with either fatty acids themselves or compounds readily available from them. We set out to prepare especially the natural products **1a** and **1d** and also compounds **1b** and **1c**, anticipating that their biological properties may be similar.

RESULTS AND DISCUSSION

We briefly investigated the conversion of acetylenes **2** to diketones **3** and the preparation of dienes **4** for a Diels-Alder/ozonolysis approach to the title compounds, since such strategy has been used by Franck[3] (8) and Nakane (9) (Scheme 1). The Wittig reactions of **3** and the yields of **4** were extremely low, and this project was abandoned even though the conversion of α-diketones into 1,3-dienes with stabilized Wittig reagents has been reported in low to moderate yields (10-12). The reactions of **3** with nonstabilized Wittig reagents produced complex mixtures of which **4** varied in amount (5-20%). Equally ineffective was a Simmons-Smith cyclopropanation of acetylenes **2** to cyclopropenes, although Simmons-Smith cyclopropanation of acetylenes was reported to afford cyclopropenes in low yield (4%) (13). We, therefore, turned to the acylation of terminal acetylenes with fatty acid chlorides and subsequent hydration of ynones **8** to the desired compounds. This method proved effective in the rapid preparation of title diketones. The alternate method we used was based on the acylation of methyl tet-

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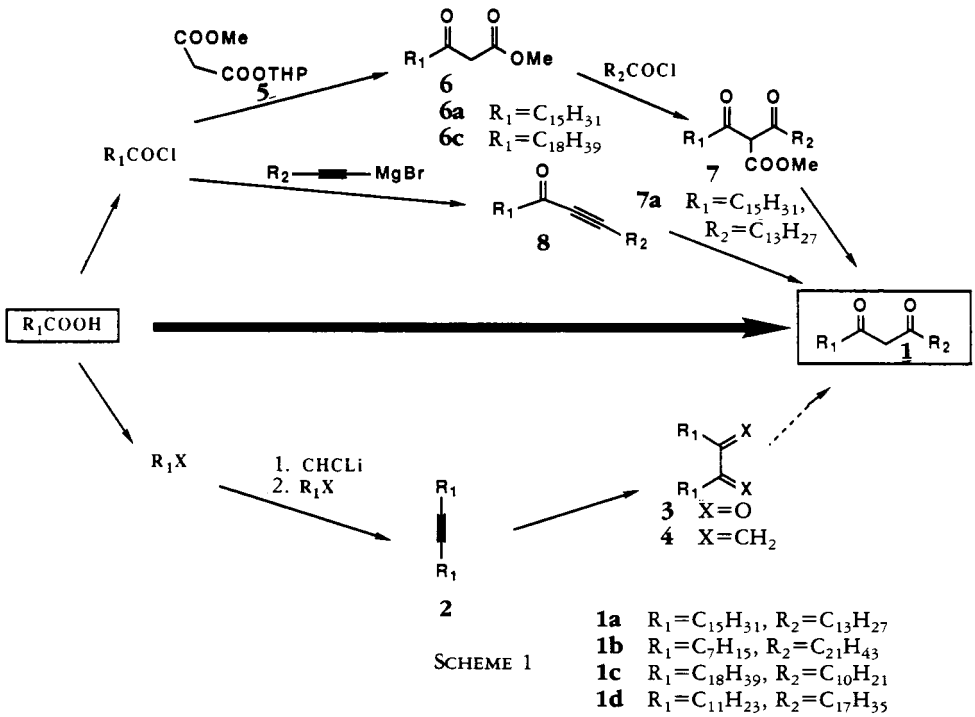
[2]Epicuticular wax of *Panicum virgatum* was shown to contain 69% (0.34% of plant weight) β-diketones. Epicuticular wax of *Eragrostis curvula* contains 47% diketones and 14% hydroxydiketones. Epicuticular waxes of *Secale cereale* and *Triticale hexaploide* contain 31-45% diketones. Epicuticular wax of *Poa ampla* contains 56% hydroxydiketones and 14% diketones. Epicuticular wax of *Triticum aestivum* (demar 4) contains 12% diketones. Epicuticular wax (seed and leaf) of *Avena sativa* contains 15% diketones and 12% hydroxydiketones.

[3]The ozonolysis of 1,4-dienes has been successfully tried in the synthesis of polyketides and ozonolysis of symmetrical dihydrobenzenes to yield formylacetates has been accomplished.



SCHEME 1

rahydropyranylmalonate[4] (14) [**5**] with the requisite acyl chloride (15). On acidic workup the resulting malonate yielded through decarboxylation ketoesters **6** which were acylated to diketoesters **7** in good yields (16). The decarbomethoxylation of **7** with LiI (17) gave the β-diketones. The sequence **5**↦**6**↦**7**↦**1** could be carried through without purification, since the final products readily formed copper complexes from which the pure diketones could be recovered by treatment with dilute HCl. Thus, the title compounds **1** were prepared by two different approaches, each of which is amenable to a large scale synthesis.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The ir spectra were determined on a Perkin-Elmer 710B spectrophotometer calibrated with a film of polystyrene. ^{1}H-nmr spectra were recorded with Varian EM-390 or Bruker WP 270 S4 spectrometer using TMS as an internal standard. ^{13}C-nmr spectra were obtained on a Bruker NR-80 instrument using TMS as an internal standard. Mass spectra were obtained by the use of a Varian MAT 112 magnetic sector instrument operating at 70 eV. Solvents used were dried and purified by standard methods.

METHOD A: MALONATE ALKYLATION.—*Preparation of methyl 3-oxoalkanoates* [**6**].—See below for yield and spectral data of individual compounds.

Sodium hydride (0.02 eq) was added to a stirred solution of methyl (2-tetrahydropyranyl) malonate [**5**][4] (0.01 eq) in dry C_6H_6 (15 ml) at room temperature. After 30 min the appropriate acid chloride[5] (0.011 eq, neat) was added in portions (caution: caused foaming), and the stirring was continued for another hour. The reaction mixture was then diluted with C_6H_6 (20 ml) and quenched with H_2O (100 ml) and 6 N HCl until pH4. The layers were separated, and the aqueous layer was extracted with C_6H_6 (2×20 ml). The organic layers were combined, and glacial HOAc (ca 2.0 ml) was added. The mixture was refluxed

[4]This mixed ester was prepared in 3 steps starting from malonic acid by diesterification of malonic acid (MeOH, HCl), followed by partial hydrolysis (KOH, MeOH), and further protection with 3,4-dihydro-2H-pyran in acidic medium.

[5]Prepared by treatment of the corresponding carboxylic acid with $SOCl_2$ in DMF for 48 h.

for 45 min and washed with saturated $NaHCO_3$ (2×50 ml), brine (2×50 ml), dried (Na_2SO_4), and solvent evaporated to yield crude **6** (95%), which was used in the next step without further purification.

Preparation of methyl 2,2-diacylethanoate [**7**].—Sodium hydride (0.02 eq) was added to a stirred solution of **8** (0.01 eq) in dry C_6H_6 (15 ml) at room temperature. After 30 min the appropriate acid chloride[5] (0.01 eq, neat) was added in portions. The stirring was continued for 1 h. The reaction mixture then was diluted with C_6H_6 (20 ml) and quenched with H_2O (100 ml) and 6 N HCl until pH4. The layers were separated, and the aqueous layer was extracted with C_6H_6 (2×20 ml). The organic layers were combined and washed with brine (2×100 ml), dried (Na_2SO_4), and solvent evaporated to give crude carbomethoxydiketones [**7**].

Preparation of β-diketones [**1**].—To a solution of **7** (0.01 eq) in 50 ml of DMF, under N_2, $LiI\cdot 2H_2O$ (0.011 eq) (17) was added and the mixture refluxed for 4 h. Then H_2O (30 ml) was added, and the mixture was acidified with 3 N HCl. An orange solid was separated, which was dissolved in Et_2O. The organic layer was washed with 3 N HCl, brine, dried ($CaCl_2$), and solvent evaporated. The crude was purified by column chromatography [on SiO_2, hexane-EtOAc (99:1)] to give average an overall yield of 65% of pure diketones [**1**].

METHOD B: YNONE HYDROLYSIS.—To a stirred solution of acid chloride[5] (0.01 eq) in dry Et_2O at −78° the alkynylmagnesium iodide (prepared by slow addition at 0° of CH_3MgI to the corresponding terminal alkyne in dry Et_2O and further reflux for 1 h), (0.01 eq) in Et_2O was added dropwise under N_2. After the addition was completed, the cooling bath was removed and the mixture allowed to reach room temperature. The stirring was continued for 1 h. The mixture was diluted with Et_2O and quenched with saturated NH_4Cl solution. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine (2×20 ml), dried ($MgSO_4$), and solvent evaporated to yield 90% of crude unsaturated ketone [**8**] [ir (KBr plate, neat) 220, 1665 cm^{-1}]. The crude product was dissolved in HOAc (4 ml) and 6 ml of a solution of $HgSO_4$ [prepared from concentrated H_2SO_4 (10.5 ml), H_2O (39.5 ml), and red HgO (2.0 g)] was added. The mixture was then refluxed for 2 h. After cooling, treatment with 6 N HCl (15 ml) (to destroy mercuric complexes), extraction with Et_2O (3×20 ml), quick filtration through SiO_2, and evaporation of solvent gave 50% of pure diketone [**1**].[6]

SPECTRAL DATA AND YIELDS.—**1a**:[6] Yield (method A): 70%; ir (neat) 2920, 2850, 1715, 1605, 1470 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.87 (m, 6H), 1.25 (broad, 44H), 1.56 (m, 4H), 2.28 (t, 3.5H), 2.48 (t, 0.5H), 3.48 (s, 0.4H), 5.45 (s, 0.8H), ≧ 11 (OH variable 0.8H); ^{13}C nmr ($CDCl_3$) δ 14.17 (CH_3), 22.75, 23.49, 25.79, 29.12, 29.40, 29.72, 31.96, 38.45, 43.80 (keto form), 62.15 (CH_2 keto), 99.02 (enolic CH), 194.51 (enolic form); ms *m/z* (rel. int.) 464 (M+) (2), 446 (4), 281 (6), 253 (8), 239 (8), 211 (35), 100 (85), 71 (50), 57 (100); hrms *m/z* 464.4528 ($C_{31}H_{60}O_2$ requires 464.4593).

1b: Yield (Method A): 65%; (Method B): 70%; ir (neat) 2920, 2850, 1710, 1610, 1470, 1260, 910, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.81 (m, 6H), 1.25 (broad, 44H), 1.54 (m, 4H), 2.22 (t, 3.5H), 2.43 (t, 0.5H), 3.47 (s, 0.2H), 5.41 (s, 0.9H), ≧ 11 (OH variable 0.9H); ^{13}C nmr ($CDCl_3$) δ 13.96 (CH_3), 22.60, 23.40, 25.71, 28.94, 29.04, 29.18, 29.28, 29.41, 29.63, 30.24, 31.60, 31.89, 38.39, 43.74 (keto form), 57.20 (CH_2 keto), 98.97 (enolic CH), 194.58 (enolic form), 204.10 (keto form); ms *m/z* (rel. int.) 464 (M+) (6), 446 (5), 365 (7), 337 (3), 323 (4), 304 (7), 184 (45), 169 (30), 127 (50), 100 (75), 57 (100); hrms *m/z* 464.4575 ($C_{31}H_{60}O_2$ requires 464.4593).

1c: Yield (Method A): 68%; ir (neat) 2920, 2850, 1715, 1610, 1470, 910, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.90 (m, 6H), 1.22 (broad, 44H), 1.54 (m, 4H), 2.20 (t, 3.5H), 2.43 (t, 0.45H), 3.47 (s, 0.3H), 5.41 (s, 0.9H), ≧ 11 (OH variable 0.8H); ^{13}C nmr ($CDCl_3$) δ 13.99 (CH_3), 22.61, 24.67, 25.70, 28.61, 29.27, 29.41, 29.63, 30.31, 31.84, 34.08, 38.39, 43.75 (keto form), 57.25 (CH_2 keto), 98.97 (enolic CH), 194.56 (enolic form); ms *m/z* (rel. int.) 464 (M+) (17), 446 (14), 338 (14), 323 (17), 281 (20), 226 (30), 211 (30), 169 (50), 100 (100), 71 (35), 57 (75); hrms *m/z* 464.4613 ($C_{31}H_{60}O_2$ requires 464.4593).

1d: Yield (Method A): 68%; ir (neat) 2920, 2860, 1710, 1640, 1470, 1260, 905, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 0.90 (m, 6H), 1.20 (broad, 44H), 1.54 (m, 4H), 2.26 (t, 3.5H), 2.43 (t, 0.5H), 3.47 (s, 0.4H), 5.40 (s, 0.8H), ≧ 11 (OH variable 0.8H); ^{13}C nmr ($CDCl_3$) δ 14.70 (CH_3), 22.70, 25.74, 29.35, 29.64, 30.82, 31.92, 34.06, 38.39, 43.80 (keto form), 57.10 (CH_2 keto), 103.10 (enolic CH), 196.56 (enolic form), 205.00 (keto form); ms *m/z* (rel. int.) 464 (M+) (11), 324 (10), 309 (12), 267 (25), 225 (20), 183 (30), 100 (70), 83 (25), 71 (45), 57 (100); hrms *m/z* 464.4594 ($C_{31}H_{60}O_2$ requires 464.4593).

6a: Yield: 95%; ir (neat) 2950, 2870, 1715, 1470, 1100, 1040, 920, 725 cm^{-1}. ^1H nmr ($CDCl_3$) δ

[6]The spectral and chromatographic data for diketone **1a** matched nicely with those reported in the literature for this natural product (19). A successful tlc comparison was made with an authentic sample kindly provided by Prof. Moyna of the Universidad de la Republica, Montevideo, Uruguay.

0.90 (m, 3H), 1.20 (broad, 24H), 1.48 (m, 2H), 2.42 (m, 2H), 3.39 (s, 2H), 3.66 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 13.95 (CH_3), 22.57, 23.42, 28.95, 29.26, 29.55, 31.80, 42.97 (α CH_2), 48.92 (α CH_2), 52.13 (OCH_3), 192.30, 202.70; ms *m/z* (rel. int.) 312 (M+) (5), 239 (11), 162 (12), 151 (12), 129 (25), 116 (100), 57 (25); hrms *m/z* 312.2672 ($C_{19}H_{36}O_3$ requires 312.2664).

6c: Yield: 94%; ir (neat) 2950, 2870, 1715, 1470, 1080, 1040, 900, 720 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.90 (m, 3H), 1.20 (broad, 30H), 1.50 (m, 2H), 2.28 (t, 0.5H), 2.44 (t, 1.5H), 3.39 (s, 2H), 3.66 (s, 3H); ^{13}C nmr ($CDCl_3$) δ 13.99 (CH_3), 22.61, 23.46, 28.99, 29.29, 29.60, 31.83, 43.00 (α CH_2), 48.95 (α CH_2), 52.17 (OCH_3), 207.09; ms *m/z* (rel. int.) 354 (M+) (13), 298 (18), 281 (14), 162 (20), 129 (25), 116 (100), 69 (35), 57 (65); hrms *m/z* 354.3133 ($C_{22}H_{42}O_3$ requires 354.3133).

7a: Ir (neat) 2940, 2850, 1720, 1470, 1240, 1040, 900 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 0.90 (m, 6H), 1.23 (broad, 44H), 1.50 (m, 4H), 2.32 (m, 2.8H), 2.51 (m, 1.2H), 3.42 (s, 1H), 3.74 (m, 3H); ms *m/z* (rel. int.) 522 (M+) (7), 504 (10), 339 (34), 311 (38), 239 (35), 211 (98), 71 (57), 57 (100); hrms *m/z* 522.4726 ($C_{33}H_{62}O_4$ requires 522.4648).

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