broad singlet), 3.63 (1 H, singlet, replaceable on addition of deuterium oxide), 4.31 (2 H, quartet, J = 7.0 Hz), 4.64 (1 H, singlet), 7.35 (10 H, singlet).

2-[Bis(carbethoxy)hydroxymethyl]cyclopentanone (8). Reaction of the pyrrolidine enamine of cyclopentanone[4] and diethyl ketomalonate by the procedure described for preparation of **5a** gave after distillation **8** as a colorless oil [79%, bp 98–100° (0.07 mm)]: ir (neat) 2.80 (m) and 5.75 μ (s); ^{1}H NMR δ 1.30 (3 H, triplet, J = 7.0 Hz), 1.33 (3 H, triplet, J = 7.0 Hz), 1.57–2.55 (6 H, multiplet), 3.24 (1 H, broad triplet, J = 8.0 Hz), 4.12 (1 H, broad singlet, replaceable on addition of deuterium oxide), 4.29 (2 H, quartet, J = 7.0 Hz), 4.38 (2 H, quartet, J = 7.0 Hz).

2-[Bis(carbethoxy)hydroxymethyl]cyclohexanone (9). Reaction of the pyrrolidine enamine of cyclohexanone[4] and diethyl ketomalonate by the procedure described for preparation of **5a** gave after distillation **9** as a colorless oil [77%, bp 125–127° (0.07 mm)]; ir (neat) 2.85 (m) and 5.75 μ (s); ^{1}H NMR δ 1.26 (3 H, triplet, J = 7.0 Hz), 1.30 (3 H, triplet, J = 7.0 Hz), 1.54–2.60 (8 H, multiplet), 3.34–3.82 (1 H, multiplet), 3.85–4.03 (1 H, broad singlet, replaceable on addition of deuterium oxide), 4.28 (4 H, quartet, J = 7.0 Hz).

α-Carbethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide (1a). To α-hydroxy-γ-keto diester **5a** (3.911 g, 15.0 mmol) was added a suspension of phosphorus pentoxide–methanesulfonic acid[5] (30 ml) and the mixture was heated to 50° for 5.2 hr, after which the mixture was cooled to 25° and added slowly to a mixture of water–ice (50:70 g). After stirring for 15 min, the yellow precipitate was filtered and dissolved in chloroform (60 ml). The aqueous filtrate was extracted with chloroform (15 ml). The chloroform solutions were combined and dried over anhydrous magnesium sulfate. Rotoevaporation of solvent and recrystallization from ether at −78° gave **1a** as a colorless solid (2.18 g, 74%, mp 83–84.5°): ir ($CHCl_3$) 5.65 (s), 5.86 (s), 6.01 (m), and 6.23 μ (s); ^{1}H NMR δ 1.37 (3 H, triplet, J = 7.0 Hz), 2.02 (3 H, doublet, J = 7.0 Hz), 2.42 (3 H, singlet), 4.37 (2 H, quartet, J = 7.0 Hz), 5.76 (1 H, quartet, J = 7.0 Hz); chemical ionization mass spectrum m/e 197.

α-Carbethoxy-β-methyl-γ-ethylidene-$\Delta^{\alpha,\beta}$-butenolide (1a) from Diethyl Ketomalonate and 3-Pentanone. To a stirred mixture of diethyl ketomalonate (1.44 ml, 9.42 mmol) and a suspension of phosphorus pentoxide–methanesulfonic acid (25 ml) was added 3-pentanone (0.5 ml, 4.72 mmol). After stirring for 1.5 hr at 25° another addition of 3-pentanone (0.5 ml, 4.72 mmol) was made. The mixture was stirred for another 1.5 hr and then heated to 50° for 9 hr, after which the mixture was cooled to 25° and added slowly to a mixture of water–ice (40:60 g) and stirred for 15 min. Extraction with chloroform (2 × 30 ml) followed by water wash (3 × 25 ml) of the chloroform layer, drying over anhydrous magnesium sulfate, rotoevaporation of solvent, and recrystallization from ether at −78° gave **1a** (19–23%).

γ-Lactone of (2-Hydroxy-2-cyclohexeneylidene)carbethoxyacetic Acid (10). Reaction of α-hydroxy-γ-keto diester **9** and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave after crystallization from ether at −78° **10** (84%; mp 108–110°): ir ($CHCl_3$) 5.65 (s), 5.87 (s), 6.04 (m), and 6.20 μ (s); ^{1}H NMR δ 1.38 (3 H, triplet, J = 7.0 Hz), 1.90 (2 H, quintet, J = 6.0 Hz), 2.49 (2 H, quartet, J = 6.0 Hz), 3.09 (2 H, triplet, J = 6.0 Hz), 4.36 (2 H, quartet, J = 7.0 Hz), 6.18 (1 H, triplet, J = 6.0 Hz); electron impact mass spectrum m/e 208.0761.

Attempted Synthesis of γ-Lactone of (2-Hydroxy-2-cyclopenteneylidene)carbethoxyacetic Acid. Reaction of α-hydroxy-γ-keto diester **8** and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave an uncharacterized polymeric substance.

α-Carbethoxy-β-methyl-γ-(1-phenylmercaptoethyl)-$\Delta^{\beta,\gamma}$-butenolide (11). To a stirred suspension of $\Delta^{\alpha,\beta}$-butenolide **1a**, (0.34 g, 1.74 mmol), phenyl mercaptan (177 μl, 1.72 mmol), ether (0.2 ml), and methanol (70 μl) was added triethylamine (2 μl, 0.014 mmol). After 0.5 hr, rotoevaporation of solvent and crystallization from methylene chloride–ether at −10° gave **11** (0.429 g, 81%, mp 90.5–93.0°): ir ($CHCl_3$) 5.61 (s), 5.81 (m), and 6.02 μ (m); ^{1}H NMR δ 1.37 (3 H, triplet, J = 7.0 Hz), 1.47 (3 H, doublet, J = 7.0 Hz), 2.17 (3 H, singlet), 3.70 (1 H, doublet of quartets, J = 7.0, J_{ab} = 2.0 Hz), 4.38 (2 H, quartet, J = 7.0 Hz), 4.94 (1 H, doublet, J_{ab} = 2.0 Hz) [decoupling experiment—irradiation of doublet at δ 4.94 (H_a) results in collapse of doublet of quartets at δ 3.70 (H_b) to a quartet (J = 7.0 Hz) and irradiation of doublet of quartets at δ 3.70 (H_b) results in collapse of doublet at δ 4.94 (H_a) to a singlet]; electron impact mass spectrum m/e 306.

Anal. Calcd for $C_{16}H_{18}H_4S$: C, 62.74; H, 5.92; O, 20.89; S, 10.45. Found: C, 62.66; H, 5.99.

α-Carbethoxy-β-phenyl-γ-benzylidene-$\Delta^{\alpha,\beta}$-butenolide (1b). Reaction of 1,3-diphenylacetone, diethyl ketomalonate, and phosphorus pentoxide–methanesulfonic acid by the procedure described for preparation of **1a** gave after silica gel column chromatography with benzene–petroleum ether (1:1 by volume), followed by crystallization from ether at −78°, **1b** (31%, mp 104–106°): ir ($CHCl_3$) 5.65 (s), 5.84 (s), 6.10 (m), 6.21 (m), 6.31 (m), and 6.38 μ (m); ^{1}H NMR δ 1.17 (3 H, triplet, J = 7.0 Hz), 4.22 (2 H, quartet, J = 7.0 Hz), 6.11 (1 H, singlet), 7.38 (8 H, multiplet), 7.78 (2 H, multiplet); electron impact mass spectrum m/e 320.

Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03; O, 19.98. Found: C, 75.15; H, 4.99.

Acknowledgment. This work was supported by the National Institutes of Health (Grant CA16624-02).

Registry No.—**1a**, 57346-36-8; **1b**, 57346-37-9; **2a**, 57346-38-0; **2b**, 57346-39-1; **3a**, 96-22-0; **3b**, 102-04-5; **4**, 609-09-6; **5a**, 57379-34-7; **6a**, 13654-48-3; **6b**, 13750-57-7; **6d**, 10321-68-3; **8**, 57362-19-3; **9**, 57346-40-4; **10**, 57346-41-5; **11**, 57346-42-6; cyclopentanone pyrrolidine enamine, 7148-07-4; cyclohexanone pyrrolidine enamine, 1125-99-1.

References and Notes

(1) For a review of the chemistry of butenolides, see Y. Shyamsunder Rao, *Chem. Rev.*, **64**, 353 (1964).
(2) M. Alguero, J. Bosch, J. Castaner, J. Castella, J. Castells, R. Metres, J. Pascual, and F. Serratoso, *Tetrahedron*, **18**, 1381 (1962).
(3) R. B. Woodward and G. B. Singh, *J. Am. Chem. Soc.*, **71**, 7581 (1949); **72**, 1428, 5351 (1950); R. B. Woodward and G. B. Singh, *Nature (London)*, **165**, 928 (1950).
(4) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963), and references cited therein.
(5) Recently, Eaton and co-workers have demonstrated that an uncharacterized reagent composed of a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid was effective in the preparation of cyclopentanones by the intramolecular acylation of olefin acids and the preparation of amides by the Beckmann rearrangement: P. E. Eaton, G. R. Carlson, and J. T. Lee, *J. Org. Chem.*, **38**, 4071 (1973).
(6) It has been suggested that the cytotoxicity of sesquiterpene lactones may depend upon the ability of these compounds to react with biological thiols [S. M. Kupchan, D. C. Fessler, M. A. Eakin, and T. J. Giacobbe, *Science*, **168**, 376 (1970)]; however, a more recent report reveals that an attempt to find a direct correlation between the rate of cysteine addition and cytotoxicity was unsuccessful [S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971)].
(7) Diethyl ketomalonate (**4**) is commercially available; however, **4** may be conveniently prepared in at least 100-g amounts by nitrogen tetroxide oxidation of diethyl malonate: E. Gilman and T. B. Johnson, *J. Am. Chem. Soc.*, **50**, 3341 (1928).
(8) J. J. Looker, *J. Org. Chem.*, **31**, 2973 (1966).

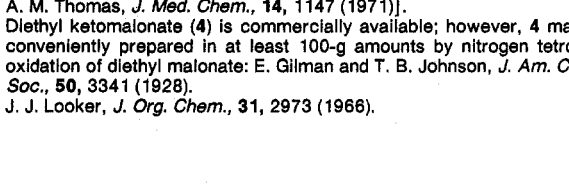
A Convenient Synthesis of a Hydrindan Precursor to Strigol

Lloyd J. Dolby* and Gunnar Hanson[1]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received August 5, 1975

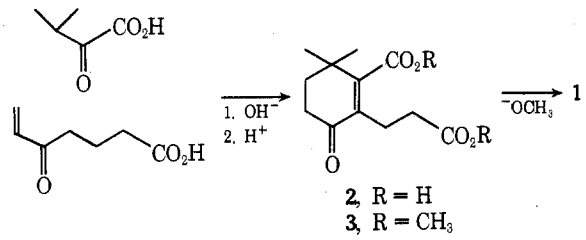
Strigol, a potent seed germination stimulant for the root parasite witchweed (*Striga lutea* Lour), has been an interesting synthetic problem since the structure of this material was reported in 1972.[2] Three syntheses which differ only in the construction of the hydrindan portion of strigol have been reported.[3,4] The ideal hydrindan precursor is the β-



1 strigol

keto ester 1, which was the key intermediate in the first synthesis of strigol.[3]

Our synthesis of the β-keto ester 1 is outlined below. Two known compounds, dimethylpyruvic acid[5] and 5-oxo-6-heptenoic acid,[6] are condensed in aqueous base to give 70–80% yields of the dibasic acid 2, which is converted to the methyl ester in quantitative yield by diazomethane. Diester 3 is cyclized to the nicely crystalline β-keto ester 1 in 98% yield by the action of sodium methoxide in methanol.



2, R = H
3, R = CH_3

This route to the hydrindan portion of strigol is much shorter than those previously reported and the yields are quite good. Moreover, the starting materials, dimethylpyruvic acid and 5-oxo-6-heptenoic acid, are easily obtained. Dimethylpyruvic acid may be conveniently prepared by an azlactone synthesis as described many years ago.[5] We prepared 5-oxo-6-heptenoic acid in modest yield by acylating ethylene with glutaric anhydride and aluminum chloride, although it and its esters have been prepared by other routes.[6-9] The crude material from the Friedel–Crafts acylation is quite satisfactory for the condensation with dimethylpyruvic acid.

Experimental Section[10]

5-Oxo-6-heptenoic Acid. A mixture of aluminum chloride (66.7 g, 0.5 mol), glutaric anhydride (28.5 g, 0.25 mol), and methylene chloride (1 l.) was placed in a 2-l. three-necked flask equipped with a gas inlet tube, a drying tube, and a mechanical stirrer. Ethylene (44 g, 1.57 mol) was bubbled in during 4.5 hr with vigorous stirring, after which the reaction mixture was poured over a mixture of 5% hydrochloric acid (900 ml) and ice. The organic layer was separated and the aqueous portion was extracted once with ether (300 ml). The organic extracts were separately washed with water and evaporated under reduced pressure. The combined residues were warmed on the steam bath for 10 min with 100 ml of 10% potassium carbonate solution which resulted in a bright yellow suspension. This mixture was washed with ether until a colorless ether extract was obtained. The aqueous portion was acidified with hydrochloric acid and extracted with ether. The dried (Na_2SO_4) ether solution was evaporated to leave an orange oil (5.2 g, 14%) which crystallized on storage. A similar run gave a 34% yield of material with satisfactory spectroscopic properties. The material was triturated with carbon tetrachloride and collected. A sample of the crystalline material was purified by short-path distillation to produce a clear oil which gave crystalline material, mp 44–46°, after exposure to air (lit.[6] mp of the hydrate 45–46.5°): ir ν_{max} ($CHCl_3$) 1710, 1685, 1618 cm^{-1}; ^1H NMR 1.97 (p, 2 H, J = 7 Hz), 2.44 (t, 2 H, J = 7 Hz), 2.70 (t, 2 H, J = 7 Hz), 5.8–6.6 ppm (m, 3 H).

4,4-Dimethyl-2-(2-carboxyethyl)cyclohex-2-en-1-one-3-carboxylic Acid (2). A solution of dimethylpyruvic acid (1.23 g, 0.0106 mol) and 5-oxo-6-heptenoic acid (1.509 g, 0.0106 mol) in 31.5 ml of 1.5 N aqueous potassium hydroxide was heated on the steam bath for 2 hr. The cooled solution was acidified with concentrated hydrochloric acid and the crystalline material (1.68 g) was collected by filtration. The ^1H NMR spectrum of this material was identical with that of the purified substance. The filtrate was extracted with ether to afford an additional 0.411 g of crude diacid 2 which was contaminated with ca. 50% by weight of dimethylpurivic acid as judged by its ^1H NMR spectrum. The total yield of crude diacid 2 (2.0 g) was 79%. The crude material was recrystallized from water to yield needles, mp 205–206.5°, with slight previous softening. Impure diacid is more conveniently recrystallized from ethyl acetate. The purified material showed ^1H NMR (Me_2SO-d_6–$CDCl_3$) 1.26 (s, 6 H), 1.95 (q, 2 H, J = 6 Hz), 2.2–2.7 ppm (m, 6 H); ir ν_{max} (KBr) 1710, 1635 cm^{-1}; mass spectrum m/e calcd for $C_{12}H_{16}O_5$, 240.100; found, 240.100.

4,4-Dimethyl-2-(2-carbomethyoxyethyl)-3-carbomethoxycyclohex-2-enone (3). A sample of dibasic acid 2 in tetrahydrofuran was treated with excess ethereal diazomethane. The solvent was evaporated and the residue was sublimed to give a quantitative yield of 3: mp 47–49°; ^1H NMR 1.23 (s, 6 H), 1.90 (t, 2 H, J = 7 Hz), 2.40–2.7 (m, 6 H), 3.65 ppm (s, 3 H); ir ν_{max} ($CHCl_3$) 1730, 1675, 1619 cm^{-1}; uv λ_{max} (EtOH) 237 nm (ε 12360); mass spectrum m/e calcd for $C_{14}H_{20}O_5$, 268.131; found, 268.129.

5,5-Dimethyl-8-carbomethoxybicyclo[4.3.0]non-1(6)-ene-2,7-dione (1). The diester 3 (0.20 g) was heated under reflux for 2 hr in a nitrogen atmosphere with 2 ml of 0.78 N sodium methoxide in methanol. The cooled solution was treated with 0.1 g of acetic acid and diluted with 1% hydrochloric acid. The crystalline material was collected by filtration and the aqueous portion was extracted with ether. The combined product was dried to give 0.173 g (98%) of 1. A sample was crystallized from methanol and sublimed to give an analytical sample, mp 136.8–141°. The material is clearly a mixture of tautomers (ca. 1:1) in chloroform solution as previously indicated: ^1H NMR ($CDCl_3$) 1.32, 1.38 (s, 6 H), 1.96 m, 4 H), 2.67 (q, 2 H, J = 7 Hz), 2.92 (m, 1 H), 3.28 (s, 1 H), 3.49 (m, 1 H), 3.78, 3.83 ppm (s, 3 H); ir ν_{max} ($CHCl_3$) 1740, 1715, 1680 sh, 1615, 1548 cm^{-1}; uv λ_{max} (EtOH) 222 nm (ε 9170), 256 (7590), 325 (6478); mass spectrum m/e calcd for $C_{13}H_{16}O_4$, 236.105; found, 236.103.

Registry No.—1, 51799-98-5; 2, 57304-91-3; 3, 57304-92-4; dimethylpyruvic acid, 759-05-7; 5-oxo-6-heptenoic acid, 6934-67-4; glutaric anhydride, 108-55-4; ethylene, 74-85-1; diazomethane, 334-88-3; sodium methoxide, 124-41-4.

References and Notes

(1) NSF Undergraduate Research Participant.
(2) C. E. Cook, L. P. Whichard, M. E. Wall, G. H. Egley, P. Coggon, P. A. Luhan, and A. T. McPhail, *J. Am. Chem. Soc.*, **94**, 6198 (1972).
(3) J. B. Heather, R. S. D. Miltol, and C. J. Shih, *J. Am. Chem. Soc.*, **96**, 1976 (1974).
(4) G. A. MacAlpine, R. A. Raphael, A. Shaw, A. W. Taylor, and H. Wild, *J. Chem. Soc., Chem Commun.*, 834 (1974).
(5) G. R. Ramage and J. L. Simonsen, *J. Chem. Soc.*, 532 (1935).
(6) S. Umezawa, Japanese Patent 1713 (1962); *Chem Abstr.*, **58**, 7833*a* (1963).
(7) G. P. Vig, A. S. Dhindsa, A. K. Vig, and O. P. Chugh, *J. Indian Chem. Soc.*, **49**, 163 (1972).
(8) L. B. Barkley, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *J. Am. Chem. Soc.*, **78**, 4111 (1956).
(9) N. Nazarov and S. I. Savyalov, *J. Gen. Chem. USSR* (*Engl. Transl.*), **23**, 1703 (1953).
(10) Infrared spectra were measured with either Beckman IR-5A or IR-7 infrared spectrophotomers. Proton magnetic resonance spectra were determined at 100 MHz with a Varian Model XL-100 spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to tetramethylsilane internal standard. In the presentation of the ^1H NMR spectra the following notations are used: s = singlet, d = doublet, t = triplet, q = quartet, p = pentuplet, and m = multiplet.

Synthesis of a Useful Spin Labeled Probe, 1-Oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine

Elmer J. Rauckman, Gerald M. Rosen,* and Mohamed B. Abou-Donia

Department of Physiology and Pharmacology, Duke University Medical Center, Durham, North Carolina 27710

Received September 3, 1975

In our continuing study of the cholinergic receptor we found it necessary to prepare a variety of spin labeled analogues of acetylcholine, one of which required the preparation of 1-oxyl-4-carboxyl-2,2,6,6-tetramethylpiperidine (1). Unfortunately, the preparation of 1 proved to be of great difficulty because the nitroxyl group is sensitive to many synthetically useful techniques.

* Fellow of the Neurological Disease and Stroke Institute of the National Institutes of Health No. NS2697.