Photochemical Transformations. Part 35.[1] A Simple Synthesis of Racemic Terrein

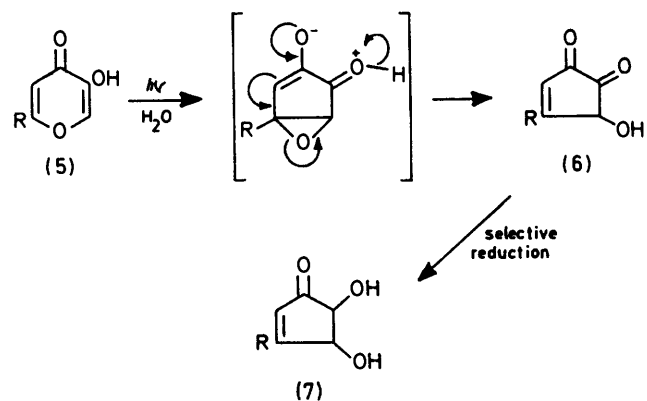By **Derek H. R. Barton** * and **Lumbertus A. Hulshof,** Chemistry Department, Imperial College, London SW7 2AY

Photochemical ring contraction in the presence of sodium cyanoborohydride of 5-hydroxy-2-[(E)-propenyl]-4-pyrone (11a), which was readily synthesised from kojic acid, gave (±)-terrein {trans-4,5-dihydroxy-3-[(E)-propenyl]cyclopent-2-enone} (1) as well as the (±)-isomer (12) with the hydroxy-groups cis.

THE mould metabolite terrein (1) [2-5] is sensitive to acid and to base. Its synthesis is, therefore, an interesting challenge. Although we had considered routes based on the established biosynthesis [6,7] of terrein, we finally devised a simple one-step synthesis based on photochemical ring contraction of the 3-hydroxy-4-pyrone nucleus (2). Precedent is found in the work of Shiozaki and Hiraoka.[8]

Preliminary studies showed (Scheme 1) that irradiation of the di-O-methyl derivative (3) of kojic acid in methanol gave 4-hydroxy-5,5-dimethoxy-3-methoxymethylcyclopent-2-enone (4) in reasonable yield. It was, however, difficult to hydrolyse and reduce this compound to obtain a terrein analogue with the correct functionality.
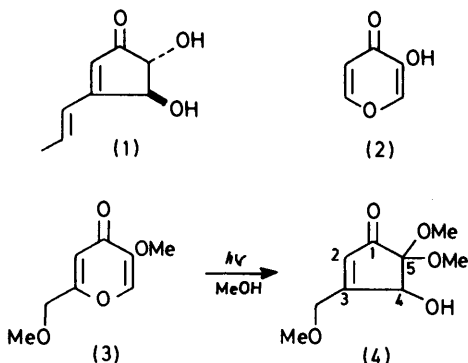
Consideration of the mechanism of formation of the cyclopentenone (4) (Scheme 2) suggested that if the

SCHEME 1

5-hydroxy-group of kojic acid were retained (5) then the intermediate (6) should be susceptible to selective

reduction (unconjugated carbonyl group more reactive) to give the correct (7) terrein functionality.

SCHEME 2

The best procedure appeared to be to introduce the propenyl group into kojic acid before the photochemical step. To this end kojic acid (8) was converted into 2-chloromethyl-5-hydroxy-4-pyrone (9) according to the procedure of Yabuta.[9] Subsequent treatment with triphenylphosphine in dry tetrahydrofuran afforded the phosphonio-derivative (10) in 89% yield. Following the method of Boden [10] a Wittig reaction (Scheme 3) was carried out with acetaldehyde and anhydrous potassium carbonate in dry tetrahydrofuran in the presence of a catalytic amount of dicyclohexyl-18-crown-6. In 95% maximum yield a mixture of 2-[(E)- and (Z)-propenyl]-5-hydroxy-4-pyrone (11a and b) was formed. From n.m.r. data the ratio was determined to be 5 : 1. Fractional recrystallisation from ethyl acetate at 0 °C allowed

[1] Part 34, A. G. M. Barrett, D. H. R. Burton, R. A. Russell and D. A. Widdowson, J.C.S. Perkin I, 1977, 631.

[2] H. Raistrick and G. Smith, Biochem. J., 1935, 29, 606.

[3] P. W. Clutterbuck, H. Raistrick, and F. Reuter, Biochem. J., 1937, 31, 987.

[4] J. F. Grove, J. Chem. Soc., 1954, 4693.

[5] D. H. R. Barton and E. Miller, J. Chem. Soc., 1955, 1028.

[6] A. J. Birch, A. Cassera, and A. R. Jones, Chem. Comm., 1965, 167.

[7] R. A. Hill, R. H. Carter, and J. Staunton, J.C.S. Chem. Comm., 1975, 380.

[8] M. Shiozaki and T. Hiraoka, Tetrahedron Letters, 1972, 4655; see also J. W. Pavlik and L. T. Pauliukonis, ibid., 1976, 1939.

[9] T. Yabuta, J. Chem. Soc., 1924, 575.

[10] R. M. Boden, Synthesis, 1975, 784.

isolation of analytically pure E-isomer (11a) in *ca.* 60% yield.

After preliminary experiments it was found that photolysis and reduction of the kojic acid derivative (11a) could be conveniently carried out as follows. A dilute solution of (11a) in water was irradiated at 0 °C for 33

(8) X = CH₂·OH
(9) X = CH₂Cl
(10) X = CH₂⁺PPh₃

(11a)   (11b)
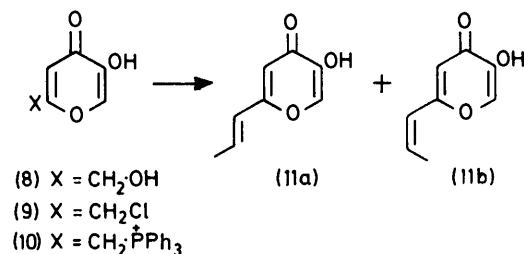
SCHEME 3

min. During the first 15 min of irradiation 2 mol. equiv. of sodium cyanoborohydride were added. After work-up a mixture of four components was obtained (yield 37%).

In 24.7% yield the less polar *cis*-4,5-dihydroxy-3-[(E)-propenyl]cyclopent-2-enone [($\pm$)-isoterrein] (12) was isolated by preparative t.l.c. Crystallisation from ether–acetone afforded an analytically pure sample, m.p. 88—89°. Fractional crystallisation of the second fraction from acetone–ether furnished in 1.4% yield the triol (14). Recrystallisation from acetone–ether gave an analytically pure sample, m.p. 101—102°. The mother liquor of the second fraction contained, according to n.m.r. data, a mixture of 69% of ($\pm$)-*trans*-4,5-dihydroxy-3-[(E)-propenyl]cyclopent-2-enone [($\pm$)-terrein]
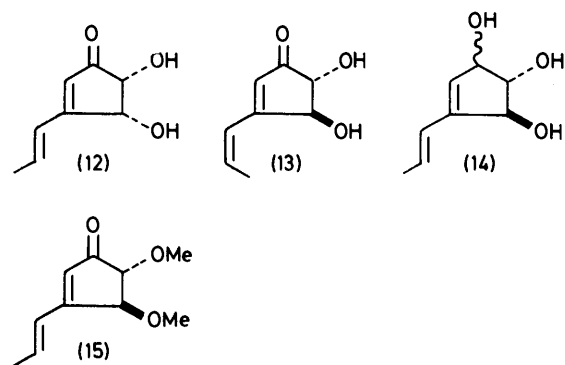
(1) and 31% of the Z-isomer (13) (7.5 and 3.4% overall yield, respectively).

Attempts to separate ($\pm$)-terrein (1) from this mixture *via* fractional crystallisation were only successful after seeding with ($\pm$)-terrein obtained as below.

The assignment of structure (12) was based upon the following considerations. The i.r. spectrum shows a strong band at 968 cm⁻¹ indicative of an E-configuration

in the side chain. The stereochemical relationship around C-4 and -5 was suggested to be *cis* on the basis of Boeseken titration results.[11] Confirmation was obtained from the reaction of (12) with triethylamine (see later). Furthermore the magnitude of the vicinal coupling constant ($J_{4,5}$ 6 Hz) [12] was in contrast with that for natural terrein (2.5 Hz).

The side-chain stereochemistry in (14) was derived from i.r. data ($\nu_{max.}$ 967 cm⁻¹), and the relationship at C-4 and -5 was demonstrated to be *trans* by the following experiments. When the *cis*-diol (12) was treated with sodium cyanoborohydride in water no conversion into (14) was observed. In contrast, a similar blank experiment with natural terrein afforded, after 1½ h, a mixture of optically active (14) and starting material (ratio *ca.* 1 : 2).

The assignment of structure (13) is based on the fact that photoisomerisation of natural terrein gave a mixture of the *cis*-isomer (13) (46%) and unchanged terrein (1) (54%).

An improved preparation (35%) of ($\pm$)-isoterrein (12) was found in the irradiation of a dilute aqueous solution of (11a) for 35 min with the addition of 1 mol. equiv. of sodium borohydride during the first 15 min of reaction.

As mentioned above, pure ($\pm$)-terrein (1) could not at first be isolated from the photolysis–reduction sequence. The isomerisation of the readily available *cis*-isomer (12) was therefore examined. Treatment with triethylamine in water converted (12) into a mixture of starting material and ($\pm$)-terrein (1), which could be separated readily by t.l.c. A maximum yield of ($\pm$)-terrein (1) of 26% was obtained. Crystallisation from ether–acetone gave a pure specimen, m.p. 99—100°. ($\pm$)-Isoterrein (12) and ($\pm$)-terrein (1) differ in m.p., t.l.c. behaviour, and solution i.r. and n.m.r. spectra. Their mass spectra are essentially identical. The ($\pm$)-terrein corresponds in all respects with natural terrein.

During this work an elegant non-photochemical synthesis of ($\pm$)-terrein was reported by Auerbach and Weinreb.[13] The m.p. of their product was 87—89°, which is identical with that of our ($\pm$)-isoterrein (12). The last step in their synthesis is the treatment of the dimethyl ether (15) with dilute hydrochloric acid in order to remove the methyl groups. These are conditions which might well, through enolisation, convert the less stable ($\pm$)-terrein into the more stable ($\pm$)-isoterrein (12) which, in any case, crystallises more easily. We sent a specimen of ($\pm$)-isoterrein, m.p. 88—89°, to Professor Weinreb, who compared it with his ($\pm$)-terrein of m.p. 87—89°. The two compounds differed in t.l.c. behaviour. Professor Weinreb writes ' The m.p. discrepancy is undoubtedly due to the fact that our ($\pm$)-terrein was not fully purified. The fact that our ($\pm$)-terrein and your ($\pm$)-isoterrein melt at the same temperature is probably coincidence '.

[11] J. Böeseken, *Adv. Carbohydrate Chem.*, 1949, **4**, 189; J. Böeseken and H. Couvert, *Rev. Trav. chim.*, 1921, **40**, 354.

[12] See C. M. Strunz and A. S. Court, *J. Amer. Chem. Soc.*, 1973, **95**, 3000.
[13] J. Auerbach and S. M. Weinreb, *J.C.S. Chem. Comm.*, 1974, 298.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. N.m.r. spectra were recorded with a Varian T60 instrument (tetramethylsilane as internal standard). I.r. spectra were obtained with a Perkin-Elmer 257 grating spectrometer. U.v. spectra were recorded with a Unicam SP 800 spectrometer. Optical activity was measured with a Perkin-Elmer 141 polarimeter. Mass spectra were run with an A.E.I. MS9 high resolution spectrometer.

4-Hydroxy-5,5-dimethoxy-3-methoxymethylcyclopent-2-enone (4) (with K. TORSSEL).—A solution of 5-methoxy-2-methoxymethyl-4-pyrone [14] (3) (1.8 g, 10.6 mmol) in methanol (260 ml) was irradiated in a Rayonet Reactor with sixteen 75 W 3 100 Å lamps for 20 h. Almost complete conversion was observed. The solution was evaporated *in vacuo* leaving a yellow oil which was separated by preparative t.l.c. (silica; chloroform–methanol, 1.15 : 1), giving *compound* (4) as a broad band close to the solvent front. Recrystallised from cyclohexane–carbon tetrachloride (1 : 3) this (0.6 g, 28%) had m.p. 90—91°, $\nu_{max.}$ (CHCl₃) 3 100m and 1 720s cm⁻¹, δ (CDCl₃) 6.14 (1 H, dt, J 1.4 and 1.8 Hz), 4.61br (1 H, s), 4.35br (2 H, s), 3.51 (3 H, s), 3.47 (6 H, s), and 3.00 (OH, d, J 8 Hz), *m/e* 202 (Found: C, 53.45; H, 6.9. C₉H₁₄O₅ requires C, 53.45; H, 7.0%).

The Triphenylphosphonio-derivative (10).—A mixture of the chloromethylpyrone (9) [9] (10.7 g) and triphenylphosphine (31.9 g) was refluxed in dry, distilled tetrahydrofuran (350 ml) for 4 days. After cooling to room temperature the precipitate was filtered off (20.7 g). Continued reflux of the filtrate for another 7 days gave a second crop of (10) (4.4 g); total yield 25.1 g (89%), m.p. >270° (decomp.), δ [(CD₃)₂SO] 8.1—7.6 (16 H, m), 6.37 (1 H, d, J_{PH} 2.8 Hz), and 5.43 (2 H, d, J_{PH} 16 Hz).

5-Hydroxy-2-[(E)- and (Z)-propenyl-4-pyrone] (11a *and* b).—Following the method of Boden,[10] freshly distilled acetaldehyde (0.9 g, 20.5 mmol), b.p. 21°, was added to a mixture of the phosphonio-derivative (10) (2.1 g, 5 mmol), powdered potassium carbonate (anhydrous) (1.4 g, 10 mmol), and dicyclohexyl-18-crown-6 (Fluka) (50 mg) in dry, distilled tetrahydrofuran (75 ml). The solution was stirred at room temperature for 43 h. After 10 min a yellow colour had appeared which steadily changed to orange. Work-up involved addition of water (*ca.* 100 ml), three-fold extraction with ether, and acidification of the aqueous layer followed by extraction three times with chloroform. The combined organic extracts were washed with water, dried (MgSO₄), and evaporated, giving clean material (0.72 g, 95%) which according to n.m.r. data consisted of a mixture of *E*- and *Z*-isomers (5 : 1). The isomers migrated separately in analytical t.l.c. (silica; chloroform–methanol, 12.5 : 1) with $R_F(Z) > R_F(E)$. Recrystallisation from ethyl acetate at 0 °C allowed the isolation of 60% of pure E-*isomer* (11a), m.p. 160—164°, $\nu_{max.}$ (CHBr₃) 3 430m, 3 000w, 1 680m, 1 650sh,m, 1 620s, 1 407m, 1 390s, 1 260s, 1 220s, 965s (*E*-CH=CH),[5] 907s, and 859s cm⁻¹, $\lambda_{max.}$ (H₂O) 280 (ε 18 500) and 221 nm (ε 18 500), δ (CHCl₃) 7.77 (1 H, s), 7.0—6.0 (2 H, m), 6.27 (1 H, s), and 2.02 (3 H, dd, J 6 and 1 Hz), *m/e* 152, 137, 124, 123, and 95 (Found: C, 63.3; H, 5.3. C₈H₈O₃ requires C, 63.15; H, 5.25%).

(±)-*cis*-4,5-*Dihydroxy*-3-[(E)-*propenyl*]*cyclopent-2-enone* [(±)-*Isoterrein*] (12), *its* trans-*Isomer* [(±)-*Terrein*] (1), *its* trans,Z-*Isomer* (13), *and* (±)-5-[(E)-*Propenyl*]*cyclopent-4-*

ene-r-1,t-2,3-triol (14).—Portions (each *ca.* 62 mg, 0.41 mmol) of compound (11a) were dissolved in water (100 ml each). The resulting solution were irradiated at 0 °C in a Pyrex apparatus for 33 min with a high-pressure mercury lamp (125 W) while nitrogen was bubbled through. During the first 15 min sodium cyanoborohydride (2 mol. equiv.) was introduced. Work-up of three photoreactions involved extraction with ethyl acetate (3 × 150 ml) followed by continuous extraction with ethyl acetate for 24 h. The combined extracts were washed with brine (*ca.* 50 ml),dried (MgSO₄), and evaporated. The residue was subjected to preparative t.l.c. (silica; chloroform–methanol, 12.5 : 1) allowing isolation of two bands, one (A) with R_F value slightly higher than and the other (B) with the same R_F value as that of natural terrein. All the starting material had been consumed.

Band A gave (±)-*isoterrein* (12) (24.7%). Recrystallisation from acetone–ether gave sample, m.p. 88—89°, $\nu_{max.}$ (CHCl₃) 3 530m, 3 395m, 2 910m, 1 710s, 1 640s, 1 577s, 1 442m, 1 395m, 1 378m, 1 343m, 1 306m, 1 283m, 1 118s, 1 103sh,s, 1 078s, 968s (*E*-CH=CH),[5] and 870m cm⁻¹, $\lambda_{max.}$ (abs. EtOH) 272.5 nm (ε 24 500), δ [(CD₃)₂CO] 6.73 (1 H, m, with J 6 Hz in fine splitting), 6.62 (1 H, s), 6.00 (1 H, s), 4.58 (2 H, ABq, J_{AB} 6 Hz, $\Delta\nu_{AB}$ 51.6 Hz), 3.80 (OH, exchangeable), and 2.03 (3 H, d, J 6 Hz), *m/e* 154, 139, 121, and 79 (Found: C, 62.45; H, 6.6. C₈H₁₀O₃ requires C, 62.3; H, 6.55%).

Band B afforded a second fraction (12.3%) which according to spectral data consisted of three other products. Crystallisation from acetone–ether gave the *triol* (14) (1.4%). Recrystallisation from acetone–ether afforded a sample, m.p. 101—102°, $\nu_{max.}$ (Nujol) 3 280s, 1 310m, 1 183m, 1 135m, 1 128m, 1 055s, 1 026m, 1 006m, 967s (*E*-CH=CH),[5] 879m, and 857m cm⁻¹, $\lambda_{max.}$ (abs. EtOH) 234 nm (ε 20 800), δ [(CDCl₃)₂SO] 6.17 (2 H, m), 5.73 (1 H, m), 4.6—3.5 (6 H, m), and 1.88 (3 H, d, J 5 Hz), *m/e* 156, 123, 95, and 81 (Found: C, 61.45; H, 7.7. C₈H₁₂O₃ requires C, 61.5; H, 7.75%).

The i.r. and n.m.r. spectra of the mother liquor indicated that compounds (1) and (13) were present. From the n.m.r. spectrum (see for details under the photolysis of natural terrein) the ratio was determined to be 69 : 31, respectively. Thus (1) had been formed in 7.5% and (13) in 3.4% yield. Seeding with analytically pure (±)-terrein gave more crystalline (±)-terrein (1), identical with material obtained from equilibration of the *cis*-isomer (12) (see below).

Boric Acid Titrations by the Method of Böeseken.—By the usual procedure [11] (±)-isoterrein gave 35.6% of the theoretical titration value for production of alkali. Natural (±)-terrein gave only 21.5%.

Treatment of (±)-Isoterrein (12) *with Sodium Cyanoborohydride.*—A solution of isoterrein (12) (10.5 mg, 0.068 mmol) and sodium cyanoborohydride (4.3 mg, 0.068 mmol) in water (2 ml) was stirred for 20 h at room temperature. Analytical t.l.c. (silica; chloroform–methanol, 12.5 : 1) indicated that no conversion had taken place.

Reaction of Natural Terrein with Sodium Cyanoborohydride. —A solution of natural terrein (30.0 mg, 0.195 mmol) and the cyanoborohydride (12.3 mg, 0.195 mmol) in water (3.5 ml) was stirred at room temperature for 1½ h. Analytical t.l.c. (silica; chloroform–methanol 12.5 : 1) indicated no materials of different R_F value from that of natural terrein. N.m.r. and u.v. spectra showed the presence of a mixture of starting material (1) and compound (14) (*ca.* 2 : 1 from u.v. data).

[14] J. W. Armit and T. J. Nolan, *J. Chem. Soc.*, 1931, 3023; A. Beelik, *Adv. Carbohydrate Chem.*, 1956, **11**, 145.

Natural Terrein (1).—Extensive fractionation showed
($\pm$)-terrein [3] (from the collection of the late Professor H.
Raistrick) to be pure; m.p. 125—127°, $[\alpha]_D^{25}$ +163.3°,
$[\alpha]_{578}^{25}$ +169.2°, $[\alpha]_{546}^{25}$ +185.9°, $[\alpha]_{436}^{25}$ +139.3° (c 0.97 in
H_2O); $[\alpha]_D^{24}$ +42.9°, $[\alpha]_{578}^{24}$ +41.0°, $[\alpha]_{546}^{24}$ +30.0°, $[\alpha]_{436}^{24}$
—392.9° (c 0.48 in Me_2CO), $\nu_{max.}$ ($CHCl_3$) 3 590m, 3 400m,
2 996w, 2 936w, 2 910w, 2 850w, 1 705s, 1 638s, 1 570s,
1 443m, 1 382m, 1 335m, 1 098s, 1 073s, 1 013m, 967s, and
900m cm^{-1}, δ [$(CD_3)_2CO$] 7.2—6.2 (1 H, m centred at
δ 6.72, fine splitting with J 6 Hz), 6.53 (1 H, s), 5.95 (1 H, s),
4.75 and 4.08 (2 H, broad singlets), and 1.92 (3 H, d, J 6 Hz)
(OH chemical shifts dependent on concentration), $\lambda_{max.}$
(abs. EtOH) 275 nm (ε 21 200), m/e 154, 139, 121, and 79.

Photolysis of Natural Terrein (1).—A solution of natural
terrein (1) (62.0 mg, 0.403 mmol) in water (100 ml) was
irradiated for 3 h under the conditions described above, then
lyophilized. Analytical t.l.c. (silica; chloroform—methanol,
12.5 : 1) showed that only material with the same R_F value
as that of starting material was present. The n.m.r.
spectrum indicated the presence of the isomer (13) in 46%
yield {signals due to terrein itself and furthermore δ [$(CD_3)_2$-
CO] 6.32 (1 H, s), 6.27 (1 H, s), 6.09 (1 H, s), and 1.96 (3 H,
d. J 6 Hz)}.

Photolysis–Reduction of Compound (11a) *with Sodium
Borohydride*.—Portions (each ca. 62 mg, 0.41 mmol) of
compound (11a) were dissolved in water (100 ml each).
The solutions were irradiated in a Pyrex glass apparatus
cooled in ice for 35 min with a high-pressure mercury lamp
(125 W) while nitrogen was bubbled through. During the
first 15 min 1 mol. equiv. of sodium borohydride was intro-
duced. After irradiation three solutions were combined.
Work-up involved extraction with ethyl acetate (3 × 150
ml) followed by continuous extraction with ethyl acetate for
24 h. The combined extracts were washed with brine
(ca. 50 ml), dried (Na_2SO_4), and evaporated. The residue

was subjected to preparative t.l.c. (silica; chloroform–
methanol, 12 : 5 : 1), which showed that all the starting
material had been consumed. Two fractions were isolated,
one (A) with R_F value slightly higher than and the other (B)
with the same R_F value as that for natural terrein. Frac-
tion A gave ($\pm$)-isoterrein (12) (34.7%).

($\pm$)-*trans-4,5-Dihydroxy-3-[(E)-propenyl]cyclopent-2-en-
one[($\pm$)-Terrein]* (1).—In a typical experiment a solution
of ($\pm$)-isoterrein (12) (133.8 mg, 0.869 mmol) in water (30
ml) was treated with triethylamine (28 mg, 0.280 mmol).
Stirring at room temperature for 3 days followed by evapor-
ation at room temperature afforded a residue which,
according to t.l.c., consisted of starting material and a
product which migrated at the same rate as natural terrein.
Preparative t.l.c. (silica; chloroform–methanol, 12.5 : 1)
gave starting material (40.4 mg, 30%) and semisolid ($\pm$)-
terrein (1) (20.9 mg, 16%). Crystallisation (twice) from
ether–acetone gave a sample, m.p. 99—100°, $\nu_{max.}$ ($CHCl_3$)
3 590m, 3 400m, 2 996w, 2 936w, 2 910w, 2 850w, 1 705s,
1 638s, 1 570s, 1 443m, 1 382m, 1 335m, 1 098s, 1 073s,
1 013m, 967s, and 900m cm^{-1}, $\lambda_{max.}$ (abs. EtOH) 275 nm
(ε 21 100), δ [$(CD_3)_2CO$] 7.2—6.2 (1 H, m, centred at δ 6.72,
fine splitting with J 6 Hz), 6.53 (1 H, s), 5.95 (1 H, s), 4.39
(2 H, ABq, J_{AB} 2.5 Hz, $\Delta\nu_{AB}$ 39.9 Hz), and 1.92 (3 H, d, J
6 Hz), m/e 154, 139, 121, and 79 (Found: C, 62.15; H, 6.35.
$C_8H_{10}O_3$ requires C, 62.3; H, 6.55%).