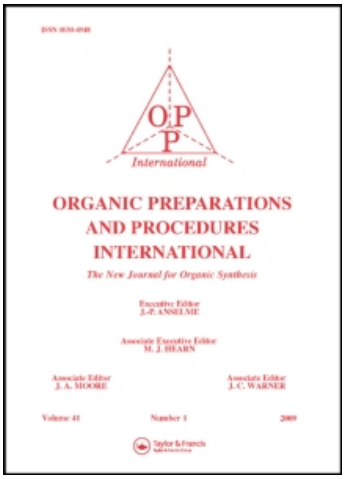

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A SHORT AND CONVENIENT SYNTHESIS OF 12-OXO-E-10-DODECENOIC ACID (TRAUMATIN)

Bruce J. Gaede[a]
[a] Monsanto Agricultural Company, St Louis, MO

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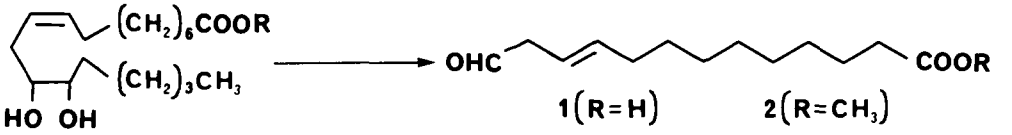
8. The yield was based on LAH because LAH is the limiting reagent.

A SHORT AND CONVENIENT SYNTHESIS OF 12-OXO-E-10-DODECENOIC ACID (TRAUMATIN)

Submitted by (10/24/86) Bruce J. Gaede

Monsanto Agricultural Company
800 North Lindbergh Blvd.
St. Louis, MO 63167

Traumatin (1) is a cleavage product of oxidized unsaturated C_{18} fatty acids from plants,[1-3] which has been implicated as a "wound hormone".[3] Most of the synthetic effort directed at 1 has centered on cleavage of fatty acid or ester diols (Eq. 1);[4] only recently has the first practical synthesis of 1 appeared (Eq. 2).[5] This latter route, which provides 1 in five steps from 10-undecenoic acid in 11% overall yield, suffers from the necessity of preparing the C_{10} aldehyde 3 by batch ozonolysis of the methyl ester of 10-undecenoic acid. This procedure exposes the worker to



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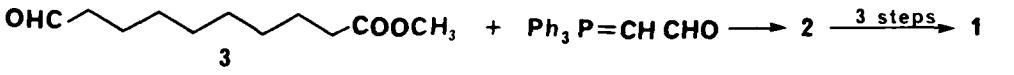
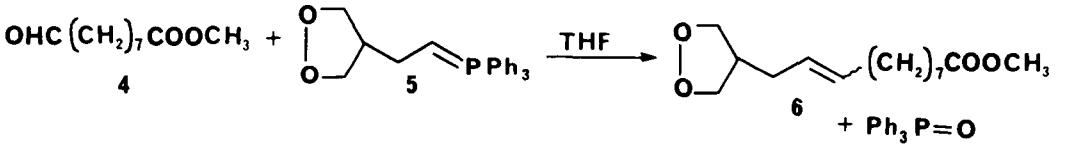
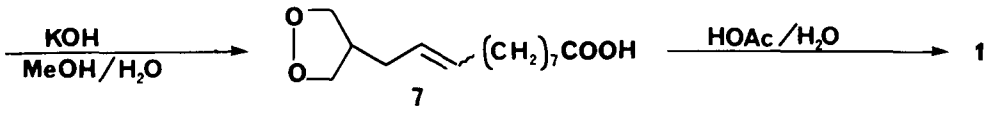


(2)

potential hazards in preparing larger quantities of the corresponding ozonide in concentrated solution at ambient temperature, and in the unpredictable decomposition of the ozonide to form 3.[6] The synthesis reported here provides multigram quantities of traumatin from a readily available starting material in four steps and 30% overall yield.

The synthesis proceeded as shown below. The starting C_9-aldehyde-ester 4, could be easily prepared from inexpensive and readily available





aleuritic acid by periodate cleavage, purification by simple acid-base extraction, and esterification with diazomethane.[7] Conversion to the C_{12}-compound 6 was achieved by three-carbon homologation via a Wittig reaction.[8] It was imperative for the success of this reaction that the phosphonium bromide precursor to 5 be prepared according to a specific procedure.[9] No attempt was made to separate the acetal ester 6 from the triphenylphosphine oxide. Rather, the ester was hydrolyzed in hot potassium hydroxide solution[5] to give the unstable acetal-acid 7, which was purified by acid-base extraction. Hydrolysis of the acetal and isomerization of the double bond in hot acetic acid gave traumatin (1);

the E-isomer was the only product observed. After chromatography and recrystallization the product was obtained as a white solid.

EXPERIMENTAL SECTION

The 60 MHz ^1H NMR spectra were obtained on a Varian EM-360 instrument in $CDCl_3$. Chemical shifts are reported in ppm (δ) from internal TMS. The 360 MHz ^1H and 90 MHz ^{13}C NMR spectra were obtained on a Bruker WM-360 instrument operating in the pulsed Fourier transform mode using the same solvent and reference. Coupling constants are in Hz. Mass spectra were obtained on a Finnigan Model 4500 instrument. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA 30366.

12-(1,3-Dioxolan-2-yl)-9-dodecenoic Acid (7).- A suspension of 19.95 g (0.045 mole) of 2-(1,3-dioxolan-2-yl)ethyltriphenylphosphonium bromide (5)[9] in 100 ml of dry tetrahydrofuran was cooled to -25 to -30° under nitrogen and treated with 17.3 ml (0.045 mole) of a 2.6 M solution of n-butyllithium in hexane. The alkyllithium was added dropwise at a rate such that the internal temperature remained below -25°. The resulting red-brown cloudy solution was stirred 0.5 hr, whereupon a solution of 5.59 g (0.03 mole) of 9-oxononanoic acid methyl ester (4)[7] in 20 ml of dry tetrahydrofuran was added dropwise over 10 min at -25°. The resulting yellow mixture was allowed to come to room temperature overnight. The tan suspension was poured into 750 ml of water and extracted three times with 200 ml of ether. The combined ethereal extracts were washed with 250 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to give 11.57 g of crude 6 and triphenylphosphine oxide as a yellow semisolid. This mixture was mixed with 20 ml of methanol, 20 ml of water, and 3.3 g (0.05 mole) of potassium hydroxide pellets, and the mixture was refluxed 1 hr. After cooling, the reaction was diluted with 300 ml of water and extracted three times with 100 ml of ether. The combined ethereal extracts were washed with 50 ml of 1% aqueous potassium hydroxide, and the aqueous fractions were combined and acidified with conc. hydrochloric acid. The acidified aqueous phase

was extracted three times with 150 ml of ether. The combined ethereal extracts were washed with 50 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated to give 4.67 g of crude 7 as a yellow oil; no attempt was made to purify the oil, which was used directly.

12-(1,3-Dioxolan-2-yl)-9-dodecenoic acid methyl ester (6) was purified for characterization by radial thin layer chromatography using 4:1 hexane-ethyl acetate on a 4 mm silica gel plate and a Harrison Research Model 7924T Chromatotron. The crude material from a 0.0225 mole scale reaction was eluted to give 2.57 g (63%) of 6 contaminated with 6.4 mole percent of triphenylphosphine (by ^{1}H NMR). ^{1}H NMR (60 MHz): δ 5.48 (m, 2H), 4.93 (t, J = 4, 1H), 3.95 (b, 4H), 3.68 (s, 3H), 2.6-1.0 (m, 18H). Mass spectrum: CI (isobutane): m/e 271 $(M + 1)^+$; EI (70 ev): m/e 269 $(M-1)^+$, 239, 183, 73.

Anal. Calcd. for $C_{15}H_{26}O_4$ (+6.4 mole % of Ph_3P): C, 67.64; H, 9.44

Found: C, 67.98; H, 9.54

Traumatin (1).- The crude 7 from the procedure above was refluxed under nitrogen in 50 ml of 1:1 acetic acid-water. After 40 min, an aliquot revealed the absence of 7 (R_f 0.37, silica gel, 1:1 hexane-ethyl acetate containing 1% acetic acid). The mixture was cooled after 75 min and poured into 250 ml of saturated sodium chloride solution. The solution was extracted three times with 100 ml of ether, and the combined ethereal extracts were washed twice with 60 ml of water and twice with 50 ml of saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to give 5.81 g of impure yellow solid. This material was chromatographed on a Waters Prep-500 instrument using two silica gel cartridges and a mobile phase of 1:1 hexane-ethyl acetate containing 1% acetic acid. Pure 1 was obtained at 1.5-1.9 column volumes as 3.0 g of yellow solid, mp. 56-62°. Recrystal-

lization from cyclohexane-ether gave 2.2 g of a white solid, mp. 65-66°, lit.[10] mp. 65-66°. ^{1}H NMR (360 MHz): δ 11.2 (b, 1H), 9.51 (d, J = 8, 1H), 6.89 (dt, J = 15, 7, 1H), 6.15 (dd, J = 15, 8, 1H), 2.35 (m, 4H), 1.73-1.20 (m, 12H). ^{13}C NMR (90 MHz): δ 194.2, 179.5, 159.1, 132.7, 33.8, 32.5, 28.83, 28.81, 18.78, 28.70, 27.5, 24.4. Mass spectrum: CI (isobutane): m/e 213 $(M+1)^+$; EI (70 ev): m/e 212, 194, 166, 138, 123, 112, 98.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50

Found: C, 67.58; H, 9.40

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