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A Synthesis of (*Z*)-Octadec-9-enedioic Acid

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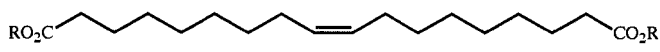
Abstract

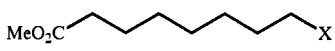
The monomethyl ester of azelaic acid was transformed into two fragments, namely [8-(methoxycarbonyl)octyl]triphenylphosphonium bromide and methyl 9-oxononanoate. A Wittig reaction between these two fragments produced dimethyl (*Z*)-octadec-9-enedioate and subsequent hydrolysis gave the title diacid. Interestingly, the same diacid was available *directly* from oleic acid in a published procedure which utilized a mutant strain of *Candida tropicalis*.

This paper emanates from an approach by Alcoa of Australia Ltd to groups at the University of Helsinki and The University of Western Australia to produce quantities of (*Z*)-octadec-9-enedioic acid (1). This diacid occurs in the sodium aluminate solutions formed in the Bayer process for the extraction of aluminium hydroxide from bauxite ore.

An obvious approach to the symmetrical diacid (1) is to employ a Wittig reaction to construct the crucial (*Z*)-alkene. This necessitates the aldehyde (2) and the phosphonium bromide (3), both potentially available from common azelaic acid. Thus, azelaic acid was first fully methylated and then selectively hydrolysed to yield the monomethyl ester (4).[1] Although the reduction of (4) to the desired alcohol (5) could be achieved with ethyl chloroformate/triethylamine/sodium borohydride,[2] the transformation went more smoothly with borane



(1) R = H
(7) R = Me



(2) X = CHO
(3) X = $CH_2P^+Ph_3\,Br^-$
(4) X = COOH
(5) X = CH_2OH
(6) X = CH_2Br
(8) X = $CHPPh_3$

[1] Rama Rao, A. V., Mysorekar, S. V., and Yadav, J. S., *Synth. Commun.*, 1987, **17**, 1339.
[2] Ishizumi, K., Koga, K., and Yamada, S.-i., *Chem. Pharm. Bull.*, 1968, **16**, 492.

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in tetrahydrofuran. Oxidation of the alcohol (5) to the aldehyde (2) was equally efficient with the chromium trioxide–nicotinic acid adduct[3] or with pyridinium chlorochromate. Likewise, bromination of the alcohol (5) easily gave (6)[4,5] and thence the phosphonium bromide (3).[6] Although toluene was an adequate solvent for this latter reaction, it proceeded better in *N*,*N*-dimethylformamide.

Finally, condensation of the aldehyde (2) with the phosphonium bromide (3) in aqueous dioxan with potassium carbonate as the base produced some of the desired diester (7) [contaminated by a little of the (*E*)-alkene].[7,8] However, the reaction was better done by first generating the ylide (8) under aprotic conditions and then adding the aldehyde (2)—a 54% yield of the (*Z*)-alkene (7) then resulted with little contamination by the (*E*)-isomer. Saponification of the diester (7) gave the diacid (1) as a white, microcrystalline solid, essentially pure (greater than 90%) by gas–liquid chromatography/mass spectrometry and ^{1}H and ^{13}C n.m.r. spectroscopy.

It interested us to compare the above preparation of the diacid (1) with its production *directly* from oleic acid by an oxidative process mediated by a yeast.[8–10] Thus, the growth of *Candida tropicalis* (mutant S_{76}) in an aerated broth containing copious amounts of oleic acid allowed for conversion into the desired diacid (1), isolated as its calcium salt. A simple workup, followed by column chromatography and recrystallization, then yielded the pure diacid (1). This literature method was certainly direct, allowed for the easy recovery of unreacted oleic acid, and provided gram quantities of (1) from several litres of culture.

Experimental

Experimental details have been given previously.[11]

Dimethyl Azelate

Azelaic acid (100 g, 532 mmol), conc. H_2SO_4 (5 ml) and dry methanol (400 ml) were processed[1] to produce a yellow oil which was distilled (75–105°C/0·4–0·5 mmHg) to give dimethyl azelate as a clear oil (92 g, 80%). ^{1}H n.m.r. (80 MHz) δ 1·09–1·78, m, 10H, CH_2; 2·25, t, J 6·9 Hz, 4H, CH_2CO_2; 3·63, s, 6H, Me. ^{13}C n.m.r. (50·3 MHz) δ 25·2, 29·2, 34·3, 7C, CH_2; 51·8, 2C, Me; 174·5, 2C, C=O.

Methyl Azelate (4)

Barium hydroxide octahydrate (61·5 g, 195 mmol) in methanol (1·40 litres) was used to convert[1] dimethyl azelate (83 g, 384 mmol) into a clear oil which was distilled under reduced pressure to give the monoester (4) as a clear oil (29·0 g, 37%). ^{1}H n.m.r. (80 MHz) δ

[3] Cossio, F. P., Lopez, M. C., and Palomo, C., *Tetrahedron*, 1987, **43**, 3963.
[4] Smith, L. M., Smith, R. G., Loehr, T. M., Daves, G. D., Jr, Daterman, G. E., and Wohleb, R. H., *J. Org. Chem.*, 1978, **43**, 2361.
[5] Wiley, G. A., Hershkowitz, R. L., Rein, B. M., and Chung, B. C., *J. Am. Chem. Soc.*, 1964, **86**, 964.
[6] Bestmann, H. J., Koschatzky, K. H., Schätzke, W., Süss, J., and Vostrowsky, O., *Liebigs Ann. Chem.*, 1981, 1705.
[7] Le Bigot, Y., Delmas, M., and Gaset, A., *Synth. Commun.*, 1982, **12**, 107.
[8] Yi, Z.-H., and Rehm, H.-J., *Appl. Microbiol. Biotechnol.*, 1989, **30**, 327.
[9] Yi, Z.-H., and Rehm, H.-J., *Appl. Microbiol. Biotechnol.*, 1988, **29**, 305.
[10] Yi, Z.-H., and Rehm, H.-J., *Appl. Microbiol. Biotechnol.*, 1988, **28**, 520.
[11] Rodriguez, E. B., and Stick, R. V., *Aust. J. Chem.*, 1990, **43**, 665.

1·09–1·81, m, 10H, CH_2; 2·13–2·41, m, 4H, CH_2CO_2; 3·59, s, Me. ^{13}C n.m.r. (50·3 MHz) δ 24·7, 28·9, 34·1, 7C, CH_2; 51·6, Me; 174·6, **C**OOMe; 179·5, COOH.

Methyl 9-Hydroxynonanoate (5)

(i) Ethyl chloroformate (10·9 g, 100 mmol) was added over a period of 30 min to the monoester (4) (20·2 g, 100 mmol) and triethylamine (10·1 g, 100 mmol) in tetrahydrofuran (150 ml) at −5°C, and the mixture was stirred for an additional 30 min at the same temperature. The mixture was filtered and washed with tetrahydrofuran (50 ml). The filtrate and the washings were added during 40 min to a solution of sodium borohydride (9·5 g, 250 mmol) in water (100 ml) at 10–15°C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h, then made acidic with dilute hydrochloric acid. The reaction mixture separated into two layers. The water layer was extracted with ether, the combined organic layers were washed with 2 M NaOH, 2 M HCl and water, then dried and evaporated. The residue was purified by flash chromatography to give the alcohol (5) (9·3 g, 50%).

(ii) Borane–methyl sulfide complex (8·4 ml, 84 mmol) was added dropwise to a stirred solution of methyl azelate (4) (15·0 ml, 74 mmol) in dry tetrahydrofuran (80 ml) at 0°C under argon. The solution was allowed to warm to room temperature, then kept overnight. Methanol (5 ml) was added and the solution was stirred for a further 1 h. The solvent was evaporated under reduced pressure and the residue extracted into ether, then washed with water, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions, then dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give the alcohol (5) as a clear oil (13·4 g).[12] ^1H n.m.r. (80 MHz) δ 1·06–1·78, m, 12H, CH_2; 2·22, t, J 6·9 Hz, CH_2CO_2; 3·50, t, J 6·3 Hz, C**H**$_2$OH; 3·56, s, Me. ^{13}C n.m.r. (50·3 MHz) δ 25·2, 26·0, 29·4, 29·5, 33·0, 34·4, 7C, CH_2; 51·8, Me; 62·8, CH_2OH; 174·7, C=O.

Methyl 9-Oxononanoate (2)

(i) The alcohol (5) (6·7 g, 35·6 mmol) and pyridine (27·7 g, 350 mmol) in dichloromethane (100 ml) under argon were added to a cooled (5°C) and stirred solution of the chromium trioxide–nicotinic acid adduct[3] (20·1 g, 90 mmol) in dichloromethane (150 ml). After 1 h the mixture was filtered through silica gel and eluted with dichloromethane. The resulting solution was washed with water, 6 M hydrochloric acid and 1 M sodium bicarbonate solution. Evaporation then gave the aldehyde (2) (5·9 g) as an oil.[13]

(ii) Pyridinium chlorochromate (8·5 g, 40 mmol) and Celite were added in one portion to a solution of the alcohol (5) (4·99 g, 26·5 mmol) in dry dichloromethane (50 ml). The suspension was stirred for 2 h, then filtered through a plug of silica and eluted with petrol, then with ether. Evaporation of the solvent under reduced pressure gave the aldehyde (2) as a clear oil (4·52 g). ^1H n.m.r. (80 MHz) δ 1·00–1·81, m, 10H, CH_2; 2·25, t, J 7·5 Hz, CH_2CO_2; 2·38, m, C**H**$_2$CHO; 3·59, s, Me; 9·66, t, J 1·9 Hz, CHO. ^{13}C n.m.r. (50·3 MHz) δ 21·9, 24·8, 28·9, 29·2, 34·8, 43·9, 7C, CH_2; 51·4, Me; 174·2, **C**OOMe; 202·7, CHO.

Methyl 9-Bromononanoate (6)

Bromine (1·8 M in dichloromethane, 32·5 ml, 58 mmol) was added dropwise to an ice-cold solution of the alcohol (5) (10·0 g, 53·2 mmol), triphenylphosphine (15·3 g, 58·4 mmol) and pyridine (4·6 ml, 58·2 mmol) in dry dichloromethane (50 ml) stirred under argon. The resulting suspension was allowed to warm to room temperature and was stirred for a further 30 min. Air was bubbled through the suspension for 30 min, then the mixture was allowed to stand overnight. The suspension was filtered to remove pyridinium bromide, and silica gel was added to the filtrate. The solvent was evaporated under reduced pressure and the residue washed with petrol. The petrol extract was washed with 0·5 M aqueous sodium thiosulfate, 1 M hydrochloric acid, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions, then dried over magnesium sulfate and decolorized with activated carbon. The solvent was evaporated under reduced pressure to give the bromide (6) as a clear oil

[12] Lycan, W. H., and Adams, R., *J. Am. Chem. Soc.*, 1929, **51**, 625.
[13] Noller, C. R., and Adams, R., *J. Am. Chem. Soc.*, 1926, **48**, 1074.

(10·7 g).[14] ^{1}H n.m.r. (80 MHz) δ 1·15–2·03, m, 12H, CH_2; 2·31, t, J 6·9 Hz, CH_2CO_2; 3·41, t, J 6·9 Hz, CH_2Br; 3·66, s, Me.

[8-(Methoxycarbonyl)octyl]triphenylphosphonium Bromide (3)

(i) Toluene (110 ml) was introduced into a flask and 10 ml of the solvent was removed by distillation. Triphenylphosphine (13·1 g, 50 mmol) was added and again more toluene distilled. The bromide (6) (10·5 g, 42 mmol) was added and the mixture stirred at 110°C over 2 days. The toluene was then decanted and the oily residue dried (17·8 g).

(ii) The bromide (6) (10·6 g, 42·1 mmol) and triphenylphosphine (13·2 g, 50·5 mmol) in dry dimethylformamide (100 ml) were heated under reflux under argon for 3 h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel (EtOAc followed by 33% EtOH/EtOAc) to give the phosphonium bromide (3) as a pale yellow oil (16·3 g, 75%).[14] ^{1}H n.m.r. (80 MHz) δ 1·00–1·81, m, 12H, CH_2; 2·18, t, J 6·8 Hz, CH_2CO_2; 3·56, s, Me; 3·38–3·91, m, CH_2P; 7·41–8·00, m, 15H, Ph.

Dimethyl (Z)-Octadec-9-enedioate (7)

(i) The aldehyde (2) (3·50 g, 18·8 mmol), the phosphonium bromide (3) (11·6 g, 23·0 mmol) and potassium carbonate (3·9 g, 28 mmol) in dioxan (25 ml) and water (0·49 ml, 2·5 mmol) were stirred at 95°C over 2 days. Filtration and evaporation gave a residue which was subjected to flash chromatography to yield the alkene (7) (1·6 g, 25%) as an oil.[9] ^{13}C n.m.r. (50·3 MHz) δ 25·0, 27·02, 29·1, 29·7, 34·1, 14C, CH_2; 51·4, 2C, Me; 129·8, 2C, CH=(*Z*); 130·3, CH=(*E*); 174·3, 2C, C=O.

(ii) (A) Potassium hydride (50% in oil, 8 g) was washed with dry petrol, then with pentane. Excess solvent was driven off under an atmosphere of argon and hexamethyldisilazane (20 ml) and dry toluene (100 ml) were then added to the residue. The suspension was heated at 100°C for 3 h and the mixture filtered through a plug of Celite to give a pale yellow solution. Titration of three 1-ml aliquots against standard aqueous hydrochloric acid gave a determination of the concentration of the potassium hexamethyldisilylamide [$KN(SiMe_3)_2$] as 0·92 M.

(B) [8-(Methoxycarbonyl)octyl]triphenylphosphonium bromide (3) (12·3 g, 23·9 mmol) was dissolved in dry 1,3-dimethylpyrimidin-2-one (65 ml) under argon and then tetrahydrofuran (150 ml) was added. The solution was chilled to −10°C whereupon a precipitate began to form. Excess $KN(SiMe_3)_2$ (60 ml, 55 mmol) was added, generating a deep orange colour. The aldehyde (2) (3·70 g, 20 mmol) was added dropwise to the mixture with the aid of a small amount of dry toluene (1 ml), whereupon the orange colour was nearly discharged. The mixture was then allowed to stir for a further 10 min. The solvent was evaporated under reduced pressure and the residue extracted with petrol. The extract was washed with water, 1 M HCl, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions, then dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a pale yellow oil (3·2 g). This oil was purified by flash chromatography (10% EtOAc/petrol) to give the dimethyl ester (7) as a clear oil (1·81 g, 54%). ^{1}H n.m.r. (80 MHz) δ 1·03–1·81, m, 24H, CH_2; 1·81–2·13, m, 4H, C**H**$_2$CH=; 25·28, t, J 6·9 Hz, 4H, CH_2CO_2; 3·63, s, 6H, Me; 5·19–5·41, m, 2H, CH=.

(Z)-Octadec-9-enedioic Acid (1)

(i) The dimethyl ester (7) (3·31 g, 9·74 mmol) was dissolved in ethanol (25 ml) containing sodium hydroxide (20%; 5·8 ml, 29 mmol) and the mixture stirred at room temperature for 2·5 h. The solvent was evaporated under reduced pressure and the residue acidified with 1 M HCl. This mixture was extracted with ether, and the extract washed with saturated aqueous sodium chloride solution, then dried over magnesium sulfate. The solvent was evaporated under reduced pressure to give a clear oil (3·30 g) which solidified upon standing overnight. Recrystallization then gave the diacid (1) as a white powder (2·05 g, 67%), m.p. 52–55°C (Et_2O/petrol). A small portion was taken and recrystallized again to give a white powder, m.p.

[14] Tranchepain, I., Le Berre, F., Duréault, A., Le Merrer, Y., and Depezay, J. C., *Tetrahedron*, 1989, **45**, 2057.

61–67°C (petrol; lit.[15,16] 67–68°C). ^{1}H n.m.r. (300 MHz) δ 1·20–1·40, 1·55–1·70, 1·90–2·05, 3m, 24H, CH_2; 2·32, t, J 7·5 Hz, 4H, CH_2CO_2; 5·30–5·37, m, 2H, CH=. ^{13}C n.m.r. (75·5 MHz) δ 24·6, 27·1, 29·0, 29·1, 29·6, 34·0, 14C, CH_2; 129·8, 2C, CH=; 180·2, 2C, C=O.

(ii) Two 2-litre conical flasks were each charged with 300 ml of EL-medium,[9] 7·5 g of calcium carbonate and 9 ml of oleic acid. The sterile broths were then inoculated with *Candida tropicalis* (mutant S_{76}) and the flasks incubated at 30°C at a shaking speed of 150 r.p.m. for 42 h. The contents of the two flasks were then combined, acidified to pH 1 and filtered through a plug of Celite. The filtrate was extracted with diethyl ether, and the ether extract was extracted with 1 M sodium hydroxide solution. The combined aqueous extracts were acidified to pH 1 and the resultant solution was extracted with ether. The organic extract was dried over anhydrous magnesium sulfate, and the ether evaporated under reduced pressure to give a pale yellow oil. This oil was purified by flash chromatography (20% EtOAc/petrol followed by 2% AcOH/EtOAc) to give the diacid (1) as a pale yellow oil (1·16 g, 6·6%) which crystallized. The 300-MHz ^{1}H and 75-MHz ^{13}C n.m.r. spectra of this material were identical to those recorded for the material produced synthetically. A small portion was taken and recrystallized to give a white powder, m.p. 64–66°C. Also recovered from the flash chromatography was oleic acid (12·4 g) as a clear oil.

Acknowledgments

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[15] Seoane, E., Arnó, M., Pedro Llinares, J. R., and Sánchez Parareda, J., *Chem. Ind. (London)*, 1978, 165.
[16] Dupont, G., Dulou, R., and Cohen, J., *Bull. Soc. Chim. Fr.*, 1956, 55.