An efficient synthesis of (±)-piliformic acid †

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An easy, four-step access to naturally occurring (±)-(*E*)-2-hexylidene-3-methylsuccinic acid (piliformic acid, **1**) with 49% overall yield has been described *via* Wittig reaction of methyl(triphenylphosphoranylidene)succinimide **7** with hexanal followed by acid-induced hydrolysis of the formed succinimide derivatives (*E*)-**8** plus (*Z*)-**9**.

Introduction

Piliformic acid (2-hexylidene-3-methylsuccinic acid, **1**) was identified[1] in 1985 as a metabolite of several closely related fungi of the Xylariaceous genera. It was isolated in small quantities from *Hypoxylon deustum*, while it was obtained in substantial quantities as the major metabolite of the dung fungus *Poronia piliformis* and also from four members of the morphologically related *Xylaria* genus, *X. polymorpha*, *X. longipes*, *X. mali* and *X. hypoxylon*, which grow on dead and decaying wood. In nature, piliformic acid **1** exists in *laevo*, *dextro* and racemic forms, although the absolute stereochemistry has not been determined. The structural assignment of piliformic acid **1** has been done on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. On the basis of ^{1}H NMR data the carbon–carbon double bond in **1** has been assigned (*E*)-geometry and this has been further confirmed by comparison with a synthetic sample. Until now only one, four-step synthesis of this natural product **1** is known,[1] from Anderson and Edwards, starting from Meldrum's acid *via* condensation of ethyl 3-oxooctanoate with ethyl 2-bromopropionate to obtain diethyl 2-hexanoyl-3-methylsuccinate, followed by its sodium borohydride reduction to give the ethyl ester of paraconic acid, which on treatment with sodium ethoxide followed by alkaline hydrolysis furnishes **1** in 1.75% overall yield. They examined a number of possible routes for the synthesis of diacid **1** and reported that attempts to condense hexanal with diethyl methylsuccinate using potassium *tert*-butoxide or sodium hydride as base and the attempted reaction of 1,2-bis(ethoxycarbonyl)-propylidene(triphenyl)phosphorane with hexanal in refluxing benzene met with failure. Recently the biosynthesis of piliformic acid **1** has been studied[2] and the provision of a simple synthetic approach to this natural product is a challenging task of current interest. In our studies towards the synthesis of the bioactive natural product chaetomellic acid A,[3–5] we have developed conditions[4] for the condensation of the methyl-(triphenylphosphoranylidene)succinimide **7**[6] with aliphatic aldehydes and now we herein report yet another application of this condensation reaction to complete an efficient synthesis of (±)-piliformic acid **1** (Scheme 1).

Results and discussion

The reaction of *p*-toluidine **2** with citraconic anhydride[7] **3** in diethyl ether at room temperature furnished a mixture[8] of methylmaleanilic acids (*α*-methyl : *β*-methyl = 9 : 1) in 95% yield. This mixture of regioisomers **4** plus **5** on treatment with acetic anhydride–sodium acetate gave the citraconimide **6** in 90% yield. A mixture of equimolar amounts of imide **6** and triphenylphosphine (TPP) on refluxing with 1.5 equivalents of hexanal in glacial acetic acid for 10 h yielded a combination of geometric isomers **8** and **9** as a thick oil in 83% yield, *via* an adduct **7**. The integral values for vinylic protons in the ^{1}H NMR spectrum of this mixture of geometric isomers (*E*)-**8** and (*Z*)-**9** revealed that they are formed in an 85 : 15 ratio. Several reaction conditions were tried for hydrolysis of **8** plus **9** to obtain (*E*)-plus (*Z*)-piliformic acids, and without the concomitant isomerisation of trisubstituted exocyclic to tetrasubstituted endocyclic double bond in the **8** plus **9** mixture, and the best results were obtained with a combination of acetic acid and conc. hydrochloric acid. The mixture of isomers **8** plus **9** on refluxing with conc. hydrochloric acid and glacial acetic acid (1 : 1) for 60 h furnished only the required mixture of (*E*)- and (*Z*)-piliformic acids in 98% yield with the same ratio and without migration of the carbon–carbon double bond. Recrystallisation of this mixture from excess of hot water gave the desired pure (*E*)-isomer in more than 70% yield. The analytical and spectral data obtained for **1** were in agreement with the reported data.[1,2]

In summary, we have demonstrated an efficient 4-step synthesis of naturally occurring (±)-piliformic acid **1** with a 49% overall yield.

Experimental

Mps were taken on a Buchi melting point B-540 apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker AC 200 NMR spectrometer (200 MHz). The ^{13}C NMR spectrum was recorded on a Bruker MSL 300 NMR spectrometer (75 MHz). Mass spectra were recorded on a Finnigan Mat 1020 mass spectrometer at 70 eV. The FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer, and microanalyses were carried out on a Carlo-Erba instrument. Column chromotographic separations were done on ACME silica gel (60–120 mesh). TPP and hexanal were obtained from Aldrich Chemical Co. Petroleum spirit refers to the fraction with distillation range 60–80 °C.

N-(*p*-Tolyl)-α- and -β-methylmaleanilic acids 4 + 5

To a constantly stirred solution of citraconic anhydride **3** (3.92 g, 3.5 mmol) in diethyl ether (25 mL) at rt was added a solution of *p*-toluidine **2** (3.75 g, 3.5 mmol) in diethyl ether (25 mL), dropwise over a period of 10 min. The reaction mixture was stirred at rt for 50 min and the precipitated product was filtered off, washed with diethyl ether (10 mL × 2), and dried *in vacuo* to obtain a mixture of the α- and β-isomers in the ratio 9 : 1

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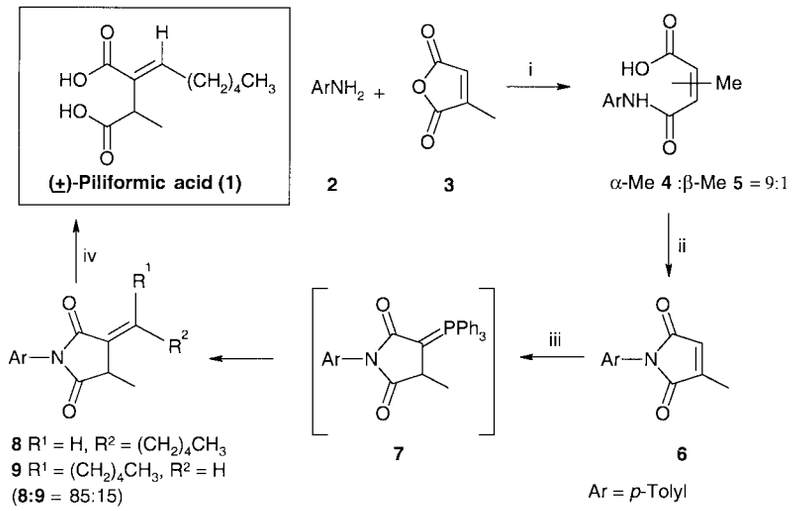

Scheme 1 *Reagents, conditions and yields*: (i) Et_2O, rt, 1 h (95%); (ii) Ac_2O–NaOAc, water-bath, 60–65 °C, 1 h (90%); (iii) TPP, AcOH, hexanal, reflux, 10 h (83%); (iv) (a) AcOH, conc. HCl, reflux, 60 h (98%); (b) recrystallisation from excess of hot water, (*E*)-isomer (70%).

(7.29 g, 95%); mp 195–199 °C. The above mixture of acids on recrystallisation from methanol gave exclusively the α-isomer **4**, mp 201 °C; IR (Nujol) ν_{max} 3400, 1715, 1660, 1620 cm^{-1}.

N-(*p*-Tolyl)citraconimide 6

A mixture of the methylmaleanilic acids **4** plus **5** (2.2 g, 10 mmol) in Ac_2O (15 mL) and fused NaOAc (0.1 g) was heated in a water-bath at 60–65 °C for 1 h. The reaction mixture was allowed to reach rt and was poured into ice-cold water (200 mL). The formed precipitate was filtered off, washed with excess of water, and vacuum dried to give **6** (1.82 g, 90%), mp 115–116 °C (from EtOH); IR (Nujol) ν_{max} 1710, 1685 cm^{-1}; ^1H NMR δ_H 2.18 (d, *J* 2 Hz, 3 H), 2.38 (s, 3 H), 6.47 (q, *J* 2 Hz, 1 H), 7.20 (d, *J* 10 Hz, 2 H), 7.27 (d, *J* 10 Hz, 2 H); MS *m*/*z* 201 (M^+, 100%), 186 (7), 172 (13), 157 (30), 144 (27), 132 (32), 117 (40), 104 (28), 91 (22), 86 (13), 77 (26), 68 (31), 57 (3).

(±)-(*E*/*Z*)-2-Hexylidene-3-methyl-*N*-(*p*-tolyl)succinimides 8 + 9

A mixture of the citraconimide **6** (1.51 g, 7.5 mmol), TPP (1.97 g, 7.5 mmol) and hexanal (1.13 g, 11.25 mmol) in glacial acetic acid (20 mL) was refluxed with stirring for 10 h. Acetic acid was distilled off *in vacuo* at 50 °C and the residue was dissolved in ethyl acetate (50 mL). The organic layer was washed successively with water (15 mL) and brine (15 mL), and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* followed by silica gel column chromatographic purification of the residue using a mixture of petroleum spirit and ethyl acetate (9 : 1) gave **8** plus **9** (**8** : **9** = 85 : 15, by ^1H NMR) as a thick oil (1.78 g, 83%); IR (neat) ν_{max} 1771, 1710, 1672 cm^{-1}; ^1H NMR δ_H 0.92 (t, *J* 6.0 Hz, 3 H), 1.25–1.45 (m, 4 H), 1.45–1.70 (m, 2 H), 1.48 (d, *J* 6.0 Hz, 0.45 H, *Z*-isomer), 1.53 (d, *J* 6.0 Hz, 2.55 H), 2.20–2.38 (m, 1.70 H), 2.39 (s, 3 H), 2.75–2.95 (m, 0.3 H, *Z*-isomer), 3.30–3.55 (m, 1 H), 6.23 (dt, *J* 8.0 and 3.0 Hz, 0.15 H, *Z*-isomer), 6.92 (dt, *J* 8.0 and 3.0 Hz, 0.85 H), 7.21 (d, *J* 8.0 Hz, 2 H), 7.29 (d, *J* 8.0 Hz, 2 H); MS *m*/*z* 286 (MH^+, 100%), 230 (10), 147 (24), 106 (9), 91 (15), 81 (19), 77 (10), 73 (47), 55 (10) (Calc. for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.83; H, 8.07; N, 5.02%).

(±)-(*E*)-Piliformic acid 1

A mixture of **8** plus **9** (1.10 g, 3.86 mmol) was dissolved in glacial acetic acid plus concentrated hydrochloric acid (1 : 1; 100 mL) and the solution was refluxed for 48 h. Additional conc. HCl (25 mL) was added to the reaction mixture, which was further refluxed for 12 h, concentrated *in vacuo* and the obtained residue was dissolved in 5% aq. sodium bicarbonate (25 mL). The aqeous layer was washed with ethyl acetate (2 × 15 mL) and acidified with dil. HCl. The acidified aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the organic layer was washed successively with water (15 mL) and brine (15 mL), and dried over Na_2SO_4. Concentration of the organic layer *in vacuo* gave mixture of (*E*)- plus (*Z*)-piliformic acids (0.81 g, 98%). The mixture of acids was recrystallised from excess of hot water (120 mL) to obtain pure (*E*)-piliformic acid **1** (0.57 g, 70%), mp 155 °C (from H_2O); IR (Nujol) ν_{max} 1717, 1678, 1637 cm^{-1}; ^1H NMR δ_H 0.90 (t, *J* 6.0 Hz, 3 H), 1.15–1.47 (m, 7 H), 1.47–1.65 (m, 2 H), 2.05–2.40 (m, 2 H), 3.58 (q, *J* 8.0 Hz, 1 H), 7.03 (t, *J* 8.0 Hz, 1 H), 11.00–12.50 (br s, 2 H) [in the (*E* + *Z*)-isomer mixture, the signals for the vinylic proton and allylic methylene protons from the *Z*-isomer appeared at δ 6.23 and δ 2.63, respectively]; ^{13}C NMR ($CDCl_3$) δ_C 13.9, 15.3, 22.4, 28.1, 28.7, 31.4, 37.6, 131.4, 147.1, 172.4, 180.7; MS *m*/*z* 214 (M^+, 2%), 196 (22), 168 (38), 139 (27), 125 (100), 112 (100), 99 (60), 95 (100), 91 (24), 81 (91), 67 (84), 55 (58) (Calc. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.74; H, 8.72%).

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