An expeditious synthesis of chaetomellic anhydrides A and B, and analogues

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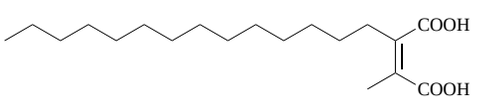
Chaetomellic anhydrides A and B and analogues have been prepared in one step by Barton radical decarboxylation; namely, irradiation of thiohydroxamic esters derived from carboxylic acids, in the presence of citraconic anhydride.

The *ras* oncogen has been reported to be expressed in many human tumours and tumour cell lines.[1] The activity of the product of *ras* oncogen, Ras (a GTP-binding protein), can be correlated with the addition of a C_{15} farnesyl unit to Ras by protein-farnesyl transferase (PFTase) and it is this addition which is essential for its association with cell membranes and promotion of cell transforming activity.[2]

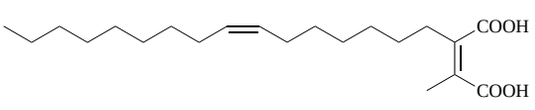
PFTase inhibitors were found to reduce the number of phenotypes of cells transformed by Ras, in cell culture and animal models,[3] which stimulated an extensive research program for the design of potent inhibitors of this enzyme.[4]

In the search for *ras* protein-farnesyl transferase inhibitors, chaetomellic acids A **1**, and B **2** were isolated from fermentation extracts of the coleomycete *Chaetomellia acutiseta*.[5] Their inhibitory activity in the farnesyl pyrophosphate binding to mammalian PFTase is in the nM concentration range, probably because the diacids act as stable pyrophosphate mimics.



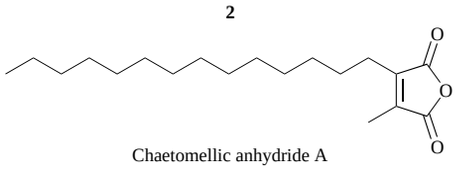
Chaetomellic acid A

1



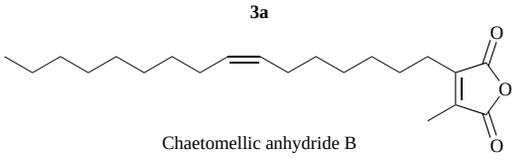
Chaetomellic acid B

2



Chaetomellic anhydride A

3a

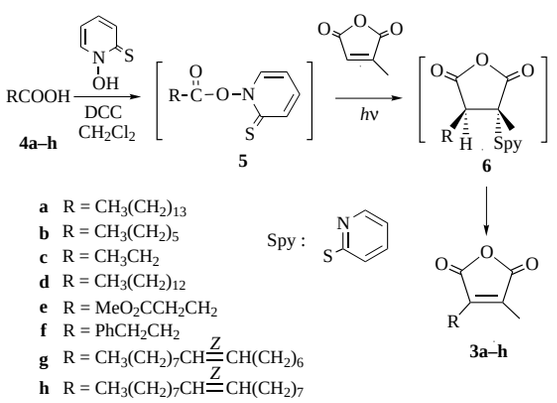


Chaetomellic anhydride B

3g

Because of their potent inhibitory activity, chaetomellic acids have been the object of considerable synthetic effort. Thus, several approaches have been reported for the total synthesis of chaetomellic acids: by non-stereospecific aldol/elimination,[6] cobalt-mediated radical coupling,[7] a malonic ester-type synthesis[8] and finally addition of organocuprates to alkynes.[9]

Herein we report a further, more efficient one-step synthesis of chaetomellic acids, by way of Barton radical decarboxylation.[10,11] Thus, the readily available pentadecanoic acid **4a** was converted into its thiohydroxamic ester **5**, by the DCC coupling method (Scheme 1). Irradiation *in situ* with a tungsten light



a R = $CH_3(CH_2)_{13}$
b R = $CH_3(CH_2)_5$
c R = CH_3CH_2
d R = $CH_3(CH_2)_{12}$
e R = $MeO_2CCH_2CH_2$
f R = $PhCH_2CH_2$
g R = $CH_3(CH_2)_7CH{=}^{Z}CH(CH_2)_6$
h R = $CH_3(CH_2)_7CH{=}^{Z}CH(CH_2)_7$

Scheme 1

(500 W) of the thiohydroxamic ester **5**, in the presence of citraconic anhydride (5 equiv.), during 30 min, gave an intermediate addition product **6** which, without isolation, undergoes complete β-elimination after flash chromatography on silica gel to furnish chaetomellic anhydride A **3a** (70%). In order to understand the course of the β-elimination, the thiohydroxamic ester was isolated and irradiated in the presence of citraconic anhydride in $CDCl_3$. Analysis of the reaction mixture was followed by NMR spectroscopy and showed the co-existence of the addition product **6a** as the only isomer, and of the chaetomellic anhydride **3a** in the ratio 3:1 after irradiation for 30 min. After the mixture had been stirred for 3 days the addition product **6a** had completely disappeared and only signals for the β-elimination product were observed in the NMR spectrum. The rapid elimination of the 2-pyridylthio group of the intermediate **6** on silica, which proceeds by *syn* elimination, established the *trans* stereochemical relationship of the pyridylthio and the alkyl substituents, resulting from the *trans* addition of the radical to citraconic anhydride.[7,12]

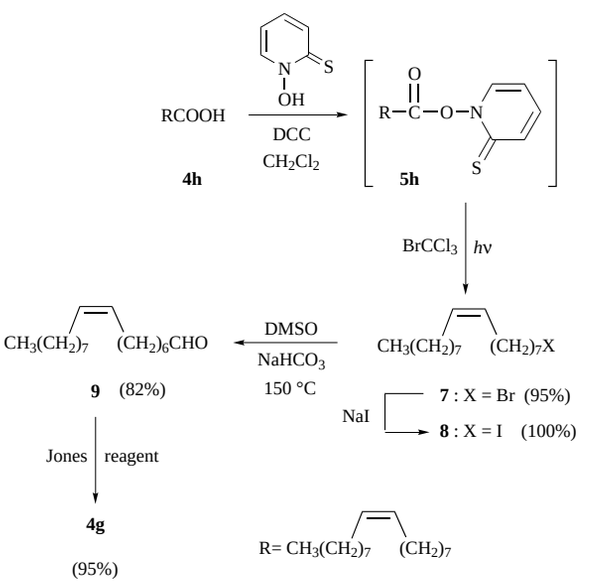
Other 2,3-dialkylmaleic anhydrides were prepared: these include the naturally occurring 2-hexyl-3-methylmaleic anhydride **3b** (isolated from the essential oil of *Agropyrum repens* rhizome)[13] and 2-ethyl-3-methylmaleic anhydride **3c** (from the volatile oil of *Paederia foetida* L.,[14] and from fruits of *Sambucus nigra* L.).[15] The results are given in Table 1.

For the synthesis of chaetomellic anhydride B, we first prepared the heptadecenoic acid **4g** by a more practical approach than that reported in the literature,[16] namely decarboxylation of the corresponding thiohydroxamic ester **5h** derived from oleic acid **4h** in the presence of $BrCCl_3$ to give the bromo compound

Table 1

Entry	Acid	% Product (yield)	
1	**4a**	Chaetomellic A	**3a** (70)
2	**4b**		**3b** (69)
3	**4c**		**3c** (46)
4	**4d**		**3d** (65)
5	**4e**		**3e** (74)
6	**4f**		**3f** (75)
7	**4g**	Chaetomellic B	**3g** (60)
8	**4h**		**3h** (72)

7.[17] Subsequent iodination and oxidation[18] furnished the heptadecenal **9**, which was then treated with Jones reagent to provide the corresponding acid **4g** in 74% overall yield (Scheme 2). Thus, the radical decarboxylation of heptadecenoic and



Scheme 2

oleic acids, was carried out in the presence of a large excess (10 equiv.) of citraconic anhydride to prevent intramolecular radical cyclisation, and provided the chaetomellic anhydride B **3g**, and its analogue **3h** in 60 and 72% yields, respectively.

In summary, we have described an efficient one-step total synthesis of chaetomellic anhydrides and their analogues from readily available carboxylic acids. The mild conditions of the reaction, and the easy elimination of the pyridylthio group in **6** makes the decarboxylation a new route to the rapid synthesis of diverse PFTase inhibitor analogues.

Experimental

All the reactions were carried out under an argon atmosphere. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 MHz spectrometer. Chemical shifts (δ) are expressed in ppm from Me_4Si as internal standard. Mass spectra were recorded on a Kratos MS 50 instrument at 70 eV or CI (NH_3). IR spectra were recorded on a Nicolet (impact 400D) FT IR. All reagents were obtained from commercial suppliers and used without further purification. Methylene dichloride was distilled from CaH_2. Flash chromatography was effected on silica (Merck Kieselgel 60, 230–400 mesh) with mixtures of ethyl acetate and hexane as eluents. TLC analyses were performed on thin-layer analytical plates 60F254 (Merck). Elementary analyses were carried out in the Institu de Chimie des Substances Naturelles, Gif-s-Yvette.

General procedure

Note: Since the *N*-hydroxypyridine-2-thiones are somewhat sensitive to daylight, it is advisable to cover the reaction flasks with aluminium foil.

DCC (2.2 mmol) was added under argon to a solution of the carboxylic acid **4a–h** (2 mmol) and 2-mercaptopyridine *N*-oxide (2.2 mmol) in dry CH_2Cl_2 (10 cm^3). The mixture was then stirred at room temperature for 2 h after which citraconic anhydride (10 mmol; except for heptadecenoic and oleic acids, 20 mmol) was then added to it; the aluminium foil was removed and the mixture was irradiated with a tungsten lamp (500 W) at 10–15 °C for 30 min. After this the mixture was filtered to remove the urea and then evaporated under reduced pressure. The residue was dissolved in diethyl ether (100 cm^3) and the solution washed with 5% aqueous $NaHCO_3$ (50 cm^3), water (50 cm^3) and brine (50 cm^3) and then dried ($MgSO_4$). After the mixture had been evaporated under reduced pressure the excess of citraconic anhydride was removed in high vacuum, and the residue subjected to flash chromatography on silica with ethyl acetate–hexane (1:9) as the eluent to yield compounds **3a–h**.

3-Tetradecyl-4-methylfuran-2,5-dione (chaetomellic anhydride A) 3a. *m/z* (CI) 309 (MH^+); ν_{max}(neat)/cm^{-1} 1850, 1823, 1769, 1673, 922 and 735; δ_H($CDCl_3$) 2.43 (2 H, t, vinyl CH_2), 2.05 (3 H, s, vinyl CH_3), 1.56 (2 H, m), 1.26 (22 H, m) and 0.86 (3 H, t, alkyl CH_3); δ_C($CDCl_3$) 166.2, 165.8, 144.7, 140.4, 31.9, 29.6 to 29.1 (9 CH_2), 27.5, 24.3, 22.6, 14.0 (alkyl CH_3) and 9.4 (4-CH_3); δ_H and δ_C spectral results were in agreement with literature values.[5]

3-Hexyl-4-methylfuran-2,5-dione 3b. *m/z* (CI) 197 (MH^+); ν_{max}(neat)/cm^{-1} 1850, 1826, 1769, 1673, 923 and 740; *m/z* (CI) 197 (M^+); δ_H($CDCl_3$) 2.42 (2 H, t, vinyl CH_2), 2.04 (3 H, s, vinyl CH_3), 1.54 (2 H, m), 1.27 (6 H, m) and 0.85 (3 H, t, alkyl CH_3); δ_C($CDCl_3$) 166.4, 165.8, 144.7, 140.4, 31.3, 29.0, 27.5, 24.4, 22.4, 11.9 (alkyl CH_3) and 9.4 (4-CH_3); δ_H and δ_C spectral results were in agreement with literature values.[13]

3-Ethyl-4-methylfuran-2,5-dione 3c. *m/z* (CI) 141 (MH^+); ν_{max}(neat)/cm^{-1} 1844, 1769, 1673 (weak), 930 and 738; δ_H($CDCl_3$) 2.5 (2 H, q, vinyl CH_2), 2.04 (3 H, s, vinyl CH_3) and 1.23 (3 H, t, alkyl CH_3); δ_C 166.2, 165.7, 145.6, 140.1, 29.3, 11.9 (alkyl CH_3) and 9.3 (4-CH_3); δ_H and δ_C spectral results were in agreement with literature values.[14,15]

4-Methyl-4-tridecylfuran-2,5-dione 3d. *m/z* (CI) 295 (MH^+); ν_{max}(neat)/cm^{-1} 1855, 1823, 1769, 1673, 922 and 735; δ_H($CDCl_3$) 2.41 (2 H, t, vinyl CH_2), 2.03 (3 H, s, vinyl CH_3), 1.54 (2 H, m), 1.23 (20 H, m) and 0.84 (3 H, t, alkyl CH_3); δ_C 166.2, 165.8, 144.7, 140.4, 31.9, 29.6 to 29.1 (8 CH_2), 27.5, 24.4, 22.6, 14.0 (alkyl CH_3) and 9.4 (4-CH_3) (Found: C, 73.26; H, 10.23. $C_{18}H_{30}O_3$ requires C, 73.46; H, 10.20%).

3-Methoxycarbonylethyl-4-methylfuran-2,5-dione 3e. *m/z* (CI) 199 (MH^+); ν_{max}(neat)/cm^{-1} 1845, 1769, 1741, 1670, 920, 902 and 740; δ_H($CDCl_3$) 3.7 (3 H, s, OCH_3), 2.73 (4 H, 2 t, CH_2CH_2) and 2.13 (3 H, s, vinyl CH_3); δ_C 172.0, 165.8, 165.5, 142.1 (2 ethylenic Cs), 51.9 (OCH_3), 30.7 and 19.8 (CH_2) and 9.6 (4-CH_3).

3-Methyl-4-phenethylfuran-2,5-dione 3f. *m/z* (CI) 217 (MH^+); ν_{max}(neat)/cm^{-1} 1825, 1760, 1670, 936, 890, 759, 730 and 705; δ_H($CDCl_3$) 7.38 to 7.10 (5 H, m, Ar), 2.87 (2 H, t, A_2B_2 system), 2.73 (2 H, t, A_2B_2 system) and 1.67 (3 H, s, 3-CH_3); δ_C 165.8, 165.6, 142.8, 141.5, 139.4, 128.5, 128.2, 126.5, 33.2, 26.3 and 8.8 (Found: C, 72.61; H, 5.64. $C_{13}H_{12}O_3$ requires C, 72.22; H, 5.55%).

(*Z*)-3-Hexadec-7-enyl-4-methylfuran-2,5-dione, chaetomellic anhydride B 3g. *m/z* (CI) 335 (MH^+); ν_{max}(neat)/cm^{-1} 3010, 1857, 1769, 1675, 923, 766 and 738; δ_H($CDCl_3$) 5.35 (2 H, m, ethylenic H), 2.43 (2 H, t, vinyl CH_2), 2.04 (3 H, s, vinyl CH_3), 1.95 (4 H, m), 1.55 (2 H, m), 1.23 (18 H, m) and 0.85 (3 H, t, alkyl CH_3); δ_C 166.1, 165.5, 144.7, 140.3, 130.7, 129.9, 32.6, 32.4, 31.9, 29.7 to 27.5 (8 CH_2), 24.4, 22.6, 14.1 (alkyl CH_3) and 9.5 (4-CH_3); δ_H and δ_C spectral results were in agreement with literature values.[5]

(*Z*)-3-Heptadec-8-enyl-4-methylfuran-2,5-dione 3h. *m/z* (CI) 366 ($M + NH_4^+$); ν_{max}(neat)/cm^{-1} 3010, 1857, 1769, 922 and

740; δ_H($CDCl_3$) 5.31 (2 H, m, ethylenic H), 2.42 (2 H, t, vinyl CH_2), 2.04 (3 H, s, vinyl CH_3), 1.97 (4 H, m), 1.54 (2 H, m), 1.25 (20 H, m) and 0.85 (3 H, t, alkyl CH_3); δ_C 166.1, 165.2, 144.7, 140.4, 130.1, 129.6, 32.6, 31.9, 29.7 to 29.0 (7 CH_2), 27.5, 27.2, 27.1, 24.4, 22.7, 14.1 (alkyl CH_3) and 9.4 (4-CH_3) (Found: C, 76.03; H, 10.38. $C_{22}H_{36}O_3$ requires C, 75.86; H, 10.35%).

(*Z*)-1-Bromoheptadec-8-ene 7[17]

To a solution of oleic acid **4h** (20 mmol, 5.64 g), and 2-mercaptopyridine *N*-oxide (22 mmol, 2.8 g), in dry CH_2Cl_2 (50 cm^3), DCC (22 mmol, 4.53 g) was added. The mixture was stirred at room temperature under argon for 1 h after which the *N*,*N*′-dicyclohexylurea was filtered off and washed with dry CH_2Cl_2 under aluminium foil protection. The CH_2Cl_2 was removed from the mixture *in vacuo* at room temperature with light protection (aluminium foil) and the residue was taken up in $BrCCl_3$ (40 cm^3). The mixture was irradiated with a tungsten lamp (500 W) at 10–15 °C for 30 min after which the $BrCCl_3$ was removed *in vacuo* and the residue dissolved in diethyl ether (100 cm^3). The solution was washed with water (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica with hexane as the eluent, to give the bromo compound as a colourless oil (6.03 g, 95%); *m*/*z* (CI) 316–318 (MH^+); ν_{max}(neat)/cm^{-1} 3010, 1660 and 725; δ_H($CDCl_3$) 5.34 (2 H, m, ethylenic H), 3.38 (2 H, t, CH_2Br), 2.03 (4 H, m), 1.83 (2 H, m), 1.43 (2 H, m), 1.31 (18 H, m) and 0.87 (3 H, t, CH_3); δ_C 130.0, 129.6, 33.7, 32.8, 32.6, 31.9, 29.7, 29.6, 29.5, 29.3, 29.0, 28.7, 28.1, 27.2, 27.1, 22.7 and 14.1.

(*Z*)-8-Heptadecenal 9

To a solution of (*Z*)-1-bromoheptadec-8-enal **7** (17.35 mmol, 5.5 g) in dry acetone (100 cm^3) was added sodium iodide (34.7 mmol, 5.2 g); the stirred mixture was heated under reflux for 2 h and then allowed to cool. It was then filtered and concentrated by removal of acetone *in vacuo*. The residue was taken up in CH_2Cl_2 and the solution washed with water and brine, dried ($MgSO_4$) and concentrated. The crude iodo compound **8** was added to a stirred mixture of DMSO (50 cm^3) and sodium hydrogen carbonate (8.7 g) at 150 °C under argon. After 15 min the mixture was rapidly cooled and then poured into water (100 cm^3). The aqueous solution was extracted with diethyl ether (4 × 50 cm^3). The combined extracts were washed with water, dried ($MgSO_4$), filtered and concentrated. The residue was subjected to flash chromatography on silica with hexane–ethyl acetate (95:5) as eluent to give the aldehyde **9** as a colourless oil (3.6 g, 82%); *m*/*z* (CI) 252 (M^+); ν_{max}(neat)/cm^{-1} 1741 and 725; δ_H($CDCl_3$) 9.78 (1 H, t, CHO), 5.33 (2 H, m, ethylenic H), 2.42 (2 H, dt, CH_2CHO), 2.01 (4 H, m), 1.63 (2 H, m), 1.29 (18 H, m) and 0.88 (3 H, t, CH_3); δ_C 202.6, 130.0, 129.5, 43.8, 31.84, 29.7 to 27.0 (9 CH_2), 22.6, 22.0 and 14.0 (Found: C, 70.37; H, 12.28. $C_{17}H_{32}O{\cdot}1/2H_2O$ requires C, 70.16; H, 12.64%).

(*Z*)-8-Heptadecenoic acid 4g[16]

To a solution of the aldehyde **9** (1.02 mmol, 257 mg) in acetone (5 cm^3), Jones reagent (1.6 cm^3, 2 equiv.) was added dropwise. After the mixture had been stirred for 9 h at room temperature, additional Jones reagent (0.8 cm^3, 1 equiv.) was added to the mixture and stirring continued overnight at room temperature. Propan-2-ol (3 cm^3) was added to the mixture which was then stirred for 1 h. After this the mixture was diluted with diethyl ether and filtered through Celite. The filtrate was evaporated under reduced pressure and the residue subjected to flash chromatography on silica with hexane–ethyl acetate (9:1) to give the heptadecenoic acid **4g** as a colourless oil (258 mg, 95%); *m*/*z* (CI) 268 (M); ν_{max}(neat)/cm^{-1} 3500–2500 (acid ν_{OH}), 1714 and 732; δ_H($CDCl_3$) 5.32 (2 H, m, ethylenic H), 2.35 (2 H, t, CH_2CO_2H), 2.02 (4 H, m), 1.64 (2 H, m), 1.30 (18 H, m) and 0.88 (3 H, t, CH_3); δ_C 180.2, 130.1, 129.6, 34.1, 31.9, 29.8–27.1 (10 CH_2), 24.6, 22.7 and 14.1.

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