A Facile Synthesis of Ras Farnesyl-Protein Transferase Inhibitor Chaetomellic Acid A[†,‡]

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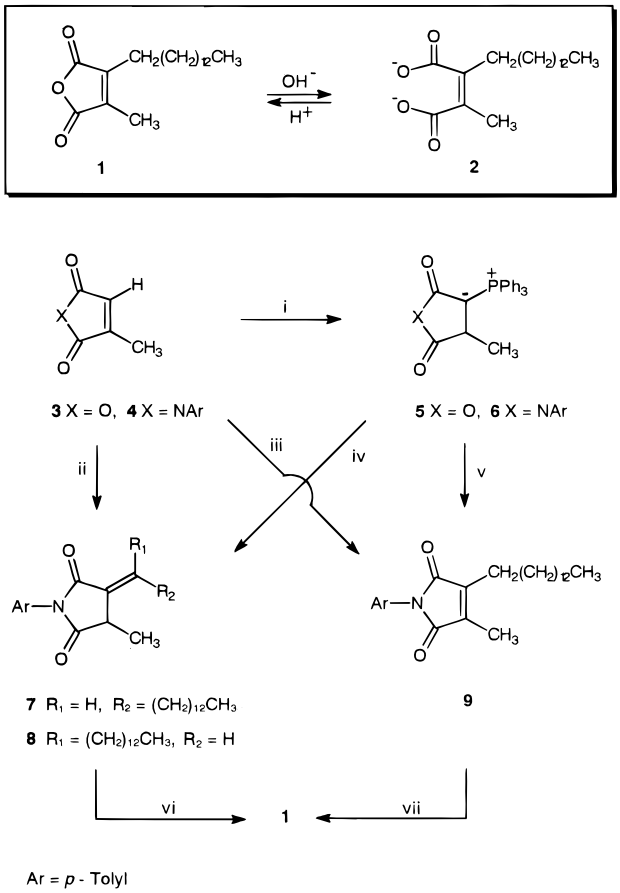
Chaetomellic acid A anhydride (**1**) has been recently isolated[1] from *Chaetomella acutiseta*, and the dianionic form **2** of **1** is a potent and highly specific inhibitor of ras farnesyl-protein transferase. The provision of facile synthetic approaches to this bioactive natural product, chaetomellic acid A anhydride (tetradecylmethylmaleic anhydride), is a task of current interest.[2−7] Five alternate syntheses of **1** have recently been reported.[2−6] The first biogenetic type four-step synthesis of **1** with 18% overall yield involves[2] the nonstereospecific aldol condensation of methyl palmitate with methyl pyruvate. The second three-step synthesis with 64% overall yield has been described[3] using photochemical doubly chemoselective cross coupling of myristyl cobaloxime with citraconic anhydride and diphenyl disulfide. The third five-step synthesis of **1** involves[4] a novel succinate to maleate oxidation with 83% overall yield. The fourth two-step stereospecific approach employs[5] reaction of organocuprates and acetylenedicarboxylate with 77% overall yield. Our recent three-step approach uses[6] condensation of tetradecylimidazopyridinium bromide and maleic anhydride with 62% overall yield. Now we herein report a novel and facile two-step approach to **1** via Wittig reaction of ylide adduct **6** with tetradecyl aldehyde.

The formation of ylide adducts from the reactions of triphenylphosphine (TPP) with maleic anhydride, maleimide, citraconic anhydride, and citraconimide was established[8] three decades ago. The phosphoranes generated from maleic anhydride and maleimide have been used for synthesis of butenolides,[9] furans,[9] intermediates to lysergic acid,[10] showdomycin,[11] quinoline derivatives,[12] and bioactive molecules.[13] The ylides methyl(triphenylphosphoranylidene)succinic anhydride (**5**) and methyl-*N*-*p*-tolyl(triphenylphosphoranylidene)succinimide (**6**) obtained from the citraconic anhydride (**3**) and citrconimide **4** were found to be more stable, as the preliminary attempts to condense them with benzaldehyde were unsuccessful.[8] We planned to study the reactivity of these ylides **5** and **6** with aliphatic aldehydes to design a facile approach to chaetomellic acid A anhydride (**1**) and develop a new convenient method to obtain the diverse menu of dialkyl-substituted maleic anhydrides.[14−17] All our attempts to condense **5** with tetradecanal in various solvents (acetic acid, pyridine, methanol, acetone, chloroform, and benzene) under reflux conditions met with failure. The relatively less stable citraconimide−TPP adduct **6** condensed very smoothly with tetradecanal in refluxing glacial acetic acid to yield a mixture of geometric isomers **7** plus **8** in 70% yield (Scheme 1), while there was no reaction in any other solvent from the above list. Since the isolated yield of adduct **6** was only 45−50%, we carried out a direct reaction of imide **4** with tetradecanal in the presence of TPP. A mixture of equivalent amounts of imide **4** and TPP and 1.5 equiv of 80% pure tetradecanal was refluxed in glacial acetic acid for 18 h; when the glacial acetic acid was distilled off in vacuo at 50 °C bath temperature, the reaction furnished exclu-

Scheme 1[a]



[a] (i) PPh_3, AcOH, Δ, 2 h. (ii) PPh_3, AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h. (iii) (a) condition ii, (b) Δ, 140−150 °C, 30 min. (iv) AcOH, $CH_3(CH_2)_{12}CHO$, reflux, 18 h. (v) (a) condition iv, (b) Δ, 140−150 °C, 30 min. (vi) (a) CH_3ONa/CH_3OH, reflux, 2 h, (b) H^+/HCl. (vii) (a) $KOH/H_2O/CH_3OH/THF$, reflux, 2 h, (b) H^+/HCl.

† Dedicated to Honourable Professor Georg Wittig on the occasion of his 100th birthday.

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sively the mixture of **7** plus **8** in 71% yield (E:Z = 85:15, by integration of vinylic proton in ^{1}H NMR) via **6**. When the acetic acid was distilled off under normal atmospheric pressure at 140−150 °C bath temperature, and the oily residue was further heated at the same temperature for the next 30 min, the above reaction directly gave maleimide derivative **9** via **6** and **7** plus **8** in 91% yield, thus offering both condensation and the isomerization of double bond (exo to endo) in one pot. The mixture of **7** plus **8** on treatment with sodium methoxide in methanol under reflux conditions followed by acidification directly gave cheatomellic acid A anhydride (**1**) in 62% yield. The disubstituted maleimide **9** on alkaline hydrolysis under reflux conditions in a THF−methanol−water mixture as the solvent system followed by acidification gave **1** in 98% yield, thus providing **1** in two steps (**4** → **9** → 1) with 89% overall yield. It is known[1] that **1** in basic medium stays in the biologically active dianionic form **2**.

In summary, we have demonstrated for the first time that the citraconimide−TPP adduct **6** condenses with aliphatic aldehyde (tetradecanal), providing a facile two-step synthesis of chaetomellic acid A anhydride (**1**) with 89% overall yield and access to analogues of **1**, hence a new convenient and efficient method to model a variety of other dialkyl-substituted maleic anhydride derivatives.

Experimental Section

Melting points are uncorrected. Column chromatographic separations were done on ACME silica gel (60−120 mesh). Triphenylphosphine, citraconic anhydride, and tetradecanal were obtained from Aldrich. The citraconimide **4** was obtained[18] in quantitative yield from citraconic anhydride (**3**) via dehydration of mixture of corresponding regioisomers of maleanilic acids.

Methyl(triphenylphosphoranylidene)succinic Anhydride (5) and Methyl-*N*-*p*-tolyl(triphenylphosphoranylidene)succinimide (6). These were prepared using literature procedures.[8] **5**: mp 180−181 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 0.82 (d, J = 7 Hz, 3H), 3.36 (q, J = 8 Hz, 1H), 7.30−7.80 (m, 15H). **6**: mp 98−102 °C; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ 1.15 (d, J = 7 Hz, 3H), 3.10 (s, 3H), 3.85−4.20 (m, 1H), 7.30−7.80 (m, 19H).

3-(*E*/*Z*)-Tetradecylidene-4-methyl-*N*-*p*-tolylsuccinimides (7/8). A mixture of citraconimide **4** (402 mg, 2 mmol), triphenylphosphine (524 mg, 2 mmol), and tetradecanal (636 mg, 3 mmol, 80% purity) in glacial acetic acid (10 mL) was refluxed with stirring for 18 h. Acetic acid was distilled off in vacuo at 50 °C, and the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine 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 ether and ethyl acetate (9:1) gave a mixture of **7** plus **8** (**7**:**8** = 85:15 by ^{1}H NMR): 560 mg (71% yield); mp 53−57 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.9 (t, J = 8 Hz, 3H), 1.30 (bs, 20H), 1.45−1.60 (m, 2H), 1.53 (d, J = 10 Hz, 3H), 2.20−2.35 (m, 2H), 2.40 (s, 3H), 3.30−3.55 (m, 1H), 6.25 (dt, J = 4 and 10 Hz, 0.15H), 6.93 (dt, J = 4 and 10 Hz, 0.85H), 7.20 (d, J = 13 Hz, 2H), 7.30 (d, J = 13 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 16.4, 21.6, 22.7, 28.4−29.7 (10 × CH_2), 32.0, 37.5, 126.2 (2-carbons, see proton-coupled ^{13}C NMR data), 129.6, 130.8, 138.2, 140.3, 168.7, 177.2; the signals for the C-4 methyl carbon, the C-4 carbon, and the proton bearing olefinic carbon from the corresponding (*Z*)-isomer appeared at δ 16.2, 39.5, and 144.1, respectively; proton-coupled ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.8−38.0 (complex pattern, proton bearing saturated carbons), 126.3 (d), 126.4 (s), 129.8 (d), 130.8 (s), 138.4 (s), 140.6 (d), 168.9 (s), 177.4 (s); MS (*m*/*e*) 397, 242, 229, 216, 203, 133, 118, 107, 95, 91, 81, 67, 55; IR ($CHCl_3$) ν_{max} 1705, 1665 cm^{-1}. Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89. Found: C, 78.67; H, 9.96.

Similarly the adduct **6** with tetradecanal under the same set of conditions gave a mixture of **7** plus **8** in 70−75% yield.

***N*-*p*-Tolylchaetomellic Acid A Imide (9).** The imide **9** was prepared using the same procedure as described for the preparation of **7** plus **8**, except that the acetic acid was distilled off slowly over a period of 15 min at 140−150 °C bath temperature and the oily residue was further heated with stirring for 30 min at same bath temperature. **9**: 720 mg (91% yield); mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 200 Hz) δ 0.90 (t, J = 7 Hz, 3H), 1.30 (bs, 22H), 1.60 (m, 2H), 2.06 (s, 3H), 2.38 (s, 3H), 2.47 (t, J = 7 Hz, 2H), 7.24 (bs, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.0, 14.3, 21.3, 22.9, 24.0, 28.4, 29.5−29.9 (9 × CH_2), 32.1, 125.9 (2-carbons), 129.8, 137.3, 137.4, 141.5, 171.0, 171.3; MS (*m*/*e*) 397, 382, 294, 228, 215, 203, 183, 149, 107, 91, 81, 67, 57; IR (Nujol) ν_{max} 1710, 1690, 1650 cm^{-1}. Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89. Found: C, 78.72; H 9.77.

Similarly the adduct **6** with tetradecanal under the same set of conditions gave imide **9** in 88−90% yield.

Chaetomellic Acid A Anhydride (1). (**a**) A mixture of **7** plus **8** (100 mg) in a solution of sodium methoxide (100 mg) in methanol (5 mL) was refluxed for 2 h with stirring. The methanol was removed in vacuo. The residue was acidified with dilute HCl and ether extracted (10 mL × 2), and the organic layer was washed with water and brine and dried over Na_2SO_4. Concentration in vacuo followed by silica gel column chromatographic purification of the residue furnished pure **1** (thick oil): 48 mg (62% yield). (**b**) To the solution of imide **9** (100 mg) in a THF−methanol mixture (6 mL, THF:MeOH = 1:2) was added a solution of KOH (300 mg) in water (1 mL), and the reaction mixture was refluxed for 2 h with stirring. The solvent mixture was removed in vacuo, and the residue was acidified with dilute HCl. Repetition of the above workup procedure followed by silica gel column chromatographic purification furnished pure **1**: 76 mg (98% yield); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, J = 7 Hz, 3H), 1.15−1.45 (bs, 22H), 1.56 (m, 2H), 2.07 (s, 3H), 2.45 (t, J = 7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.6, 14.3, 22.9, 24.6, 27.7, 29.0−31.0 (9 × CH_2), 32.1, 140.6, 144.9, 166.0, 166.4; MS (*m*/*e*) 308, 290, 206, 191, 168, 150, 136, 126, 115, 105, 95, 91, 81, 69; IR (neat) ν_{max} 2960, 2940, 2925, 2860, 1770, 1680 cm^{-1}. Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.72; H, 10.39. IR, ^{1}H NMR, ^{13}C NMR, and mass data are in agreement with literature[1] values.

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Supporting Information Available: ^{1}H NMR spectra of **1**, **4**, **7** plus **8**, and **9** and ^{13}C NMR and mass spectra of **1**, **7** plus **8**, and **9** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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