Pergamon

Bioorganic & Medicinal Chemistry, Vol. 4, No. 6, pp. 881–883, 1996

0968-0896/96 $15.00 + 0.00

S0968-0896(96)00076-4

A Simple and Efficient Synthesis of the Ras Farnesyl-Protein Transferase Inhibitor Chaetomellic Acid A†

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Abstract—A simple and efficient synthesis of the ras farnesyl-protein transferase inhibitor chaetomellic acid A anhydride (**1**) is reported. The imidazopyridinium bromide **5** obtained from the reaction of 2-bromopalmitoyl chloride and 2-aminopyridine was reacted with maleic anhydride in the presence of NaOAc/AcOH to form **1** in 62% overall yield in three steps. Copyright © 1996 Elsevier Science Ltd

Introduction

Mutations of the ras protein are present in 30–50% of human colon and lung tumors and over 50% of pancreatic carcinomas.[1] For activity, ras is farnesylated by farnesyl-protein transferase at the C-terminal cysteine residue. Inhibition of farnesylation prevents ras membrane localization and blocks ras induced cell transformation.[2] Inhibition of farnesyl-protein transferase may thus block ras-dependent tumor growth. Chaetomellic acid A anhydride (**1**) has been recently isolated[3] from *Chaetomella acuttseta* by a group at Merck and they have discovered[3] that dianion **2** of **1** is a potent and highly specific inhibitor of ras farnesyl-protein transferase. To provide simple and efficient synthetic approaches to this bioactive natural product, chaetomellic acid A anhydride (tetradecylmethylmaleic anhydride) is a task of current interest.[4,5] Alkylmethylmaleic anhydrides are generally synthesized by condensation of ethyl monoalkylacetoacetate and sodium cyanide,[6] from the reaction of tricarbonyliridium halides and acetylenes,[7] by the pyrolysis of 1-ethoxy-1-alkenyl esters of pyruvic acid,[8] by the condensation of ethylpyruvate with the anions of α-phosphonatoesters[9,10] and by the addition of imidazopyridinium compounds to Michael acceptors.[11–13] The first reported,[4] biogenetic type four-step synthesis of **1** with 18% overall yield involves the non-stereospecific aldol condensation of methyl palmitate with methyl pyruvate as the key step. The second three-step synthesis with 64% overall yield has been described[5,14] using photochemical doubly chemoselective cross-coupling of myristyl cobaloxime with citraconic anhydride and diphenyl disulfide. We herein report a simple three-step synthesis of **1** with 59–62% overall yield by taking advantage of Baumann's elegant strategy[11–13] for the synthesis of disubstituted maleic anhydrides.

†NCL Communication no. 6234.

Results and Discussion

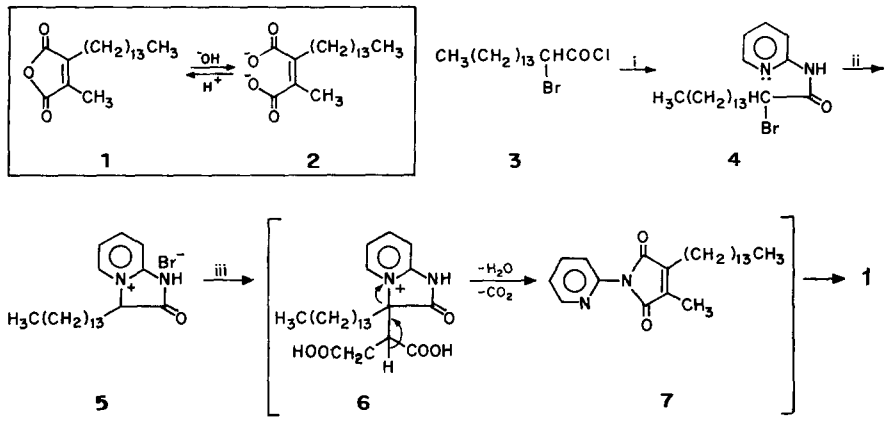
The reaction of freshly prepared 2-bromopalmitoyl chloride[15] with 2-aminopyridine in the presence of triethylamine in ether furnished the 2-bromopalmitamide derivative **4** in 94.5% yield. The bromoamide **4** on refluxing in *t*-BuOH underwent intramolecular cyclization to form the imidazopyridinium bromide **5** in 83.7% yield. The reaction of **5** with maleic anhydride in the presence of sodium acetate–acetic acid, under reflux conditions gave the chaetomellic acid A anhydride (**1**) in 78.4% yield via intermediate nitrogen ylide, Michael adduct **6** and imide **7**. The overall yield in three steps was 62%. It was also possible to repeat all the three steps in one pot. At the end of each step, the solvent used was removed under vacuum and the total contents were subjected to the next conditions without isolation and purification of intermediates **4** and **5**, to obtain **1** in 59% overall yield. It is known[3] that **1** in basic medium stays in the biologically active dianion form **2**.

In conclusion, we have reported a simple and efficient three-step synthesis of the ras farnesyl-protein transferase inhibitor chaetomellic acid A anhydride (**1**) with 59–62% overall yield (see Scheme 1).

Experimental

Satisfactory elemental analyses were obtained for compounds **1** and **4**.

***N*-(2-Pyridyl)-α-bromopalmitamide (4).** To a solution of 2-aminopyridine (3.76 g, 40 mmol) and triethylamine (4.04 g, 40 mmol) in dry ether (150 mL) at room temperature was added α-bromopalmitoyl chloride[15] (14.2 g, 40 mmol) in dry ether (25 mL) in a dropwise fashion over a period of 1 h under vigorous stirring. The reaction mixture was further stirred for 4 h at



Scheme 1. (i) 2-Aminopyridine, TEA, Et_2O, rt; (ii) *t*-BuOH, reflux; (iii) maleic anhydride, NaOAc, AcOH, reflux.

room temperature. The yellow colour suspension was filtered and washed with ether (30 mL × 3). The filtrate was concentrated and the residue was chromatographed on silica gel; the elution with a mixture of petroleum ether and diethyl ether (80:20) gave 15.53 g of the *N*-(2-pyridyl)-α-bromopalmitamide (**4**) with 94.5% yield, mp 37–38 °C. IR (neat): ν 3250, 1690, 1650, 1600, 1590 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J=7$ Hz), 1.15–1.40 (br s, 22H), 1.50 (m, 2H), 1.90–2.30 (m, 2H), 4.40 (t, 1H, $J=7$ Hz), 7.10 (dt, 1H, $J=7$ and 2 Hz), 7.75 (dt, 1H, $J=7$ and 2 Hz), 8.23 (br d, 1H, $J=9$ Hz), 8.35 (dd, 1H, $J=7$ and 2 Hz), 9.40 (br s, 1H).

3-Tetradecyl-2-oxo-3*H*-imidazo[1,2-*a*]pyridinium bromide (5). A solution of α-bromopalmitamide, **4** (14.39 g, 35 mmol) in *t*-BuOH (25 mL) was refluxed for 27 h with constant stirring. The *t*-BuOH was removed under reduced pressure and the thick yellow oil obtained was stirred with dry ether (100 mL) at room temperature for 1 h. The resulting solid was filtered, washed with ether (30 mL × 3) and dried under vacuum to give 12.04 g of crude 3-tetradecyl-2-oxo-3*H*-imidazo[1,2-*a*]pyridinium bromide (**5**) with 83.7% yield, mp 104–8 °C. IR (nujol): ν 3320, 1765, 1660, 1590 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J=7$ Hz), 1.15–1.40 (br s, 22H), 1.40–1.55 (m, 2H), 2.35 (m, 2H), 5.85 (t, 1H, $J=7$ Hz), 7.58 (t, 1H, $J=7$ Hz), 7.80 (d, 1H, $J=7$ Hz), 8.35 (t, 1H, $J=7$ Hz), 8.78 (d, 1H, $J=7$ Hz), 13.00 (s, 1H).

Chaetomellic acid A anhydride (tetradecylmethylmaleic anhydride) (1). A mixture of imidazopyridinium bromide **5** (12.33 g, 30 mmol), maleic anhydride (2.94 g, 30 mmol) and sodium acetate (2.49 g, 30 mmol) in 98% acetic acid (50 mL) was refluxed for 5 h with constant stirring. The reaction mixture was concentrated under vacuum and the resulting residue was dissolved in ether. The ether layer was washed with water, brine and dried over sodium sulfate. Concentration of organic layer followed by silica gel column chromatographic purification with a mixture of petroleum ether and diethyl ether (90:10) gave 7.24 g of chaetomellic acid A anhydride (**1**) with 78.4% yield. IR (neat): ν 2960, 2940, 2925, 2860, 1770, 1680, 1460, 1290, 1130, 930, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, 3H, $J=7$ Hz), 1.15–1.45 (br s, 22H), 1.56 (m, 2H), 2.07 (s, 3H), 2.45 (t, 2H, $J=7.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): 9.60, 14.25, 22.85, 24.60, 27.74, 29.00–31.00 ($9 \times CH_2$), 32.09, 140.62, 144.91, 166.03, 166.42 ppm.

One pot synthesis of chaetomellic acid A anhydride (1). To a solution of 2-aminopyridine (3.76 g, 40 mmol) and triethylamine (4.04 g, 40 mmol) in dry ether (150 mL) at room temperature was added α-bromopalmitoyl chloride (14.2 g, 40 mmol) in dry ether (25 mL) in a dropwise fashion over a period of 1 h under vigorous stirring. The reaction mixture was further stirred for 4 h at room temperature and the solvent ether was removed under vacuum on a rotavapour. The total residue was dissolved in *t*-BuOH (30 mL) and refluxed for 27 h with constant stirring. The *t*-BuOH was removed under reduced pressure and the thick yellow oil obtained was reacted with maleic anhydride (3.92 g, 40 mmol) in the presence of sodium acetate (8.28 g, 40 mmol) and 98% acetic acid (60 mL), under reflux for 5 h with constant stirring. Removal of acetic acid under vacuum followed by usual work up and silica gel column chromatographic purification furnished 7.27 g of chaetomellic acid A anhydride (**1**) with 59% yield.

Acknowledgement

We are grateful to Dr K. N. Ganesh, Head, Division of Organic Chemistry (Synthesis), for constant encouragement.

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(*Received in Japan* 18 *January* 1996; *accepted* 13 *March* 1996)