Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4071-4072, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0767-R

A Cobaloxime-Mediated Synthesis of the Ras Farnesyl-Protein Transferase Inhibitor Chaetomellic Acid A

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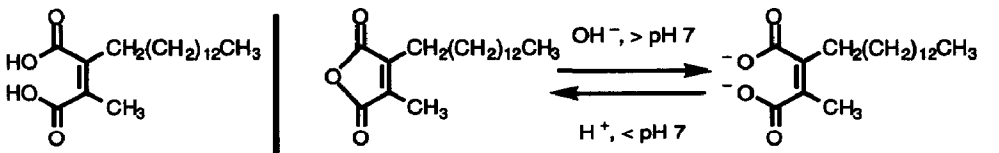
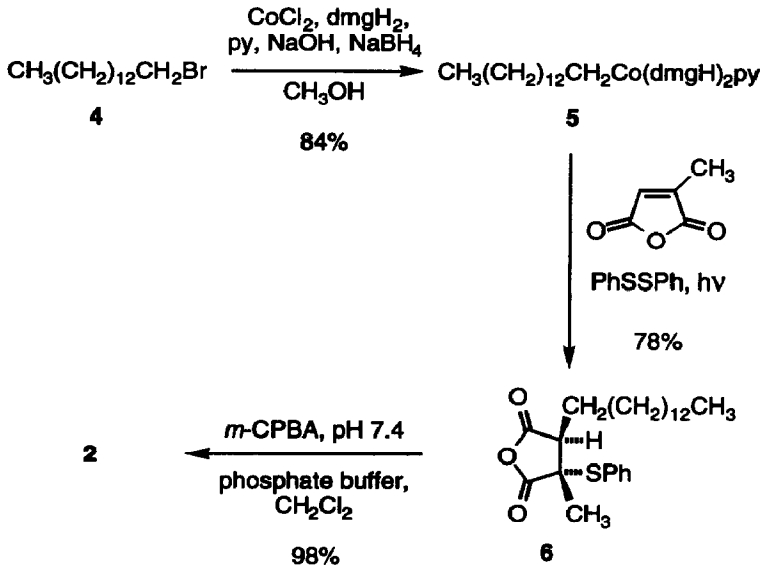
Abstract: A short and efficient synthesis of chaetomellic acid A anhydride (**2**) is reported utilizing a doubly chemoselective cross coupling of myristyl cobaloxime with citraconic anhydride and diphenyl disulfide as the key step. Sulfide oxidation followed by syn elimination provides **2** in 64% overall yield starting from myristyl bromide. Basic hydrolysis of **2** is known to provide chaetomellic acid A dianion (**3**), the biologically active form.

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 (FPTase) at the C-terminal cysteine residue. Inhibition of farnesylation prevents Ras membrane localization and blocks Ras-induced cell transformation.[2] Inhibition of FPTase may thus block Ras-dependent tumor growth. Chaetomellic acid A (**1**) was recently characterized through spectroscopic studies of the anhydride (**2**) isolated from *Chaetomella acutiseta* by a group at Merck.[3] Aqueous base (pH 7.5) hydrolysis of **2** readily forms the dianion (**3**).[3a] Acidification of aqueous solutions of **3** produces **2**, which is also the major form obtained by attempts at isolation of **1**.[3a] The apparent biologically active form is **3** which has been shown to be a potent Ras FPTase inhibitor (IC_{50} = 55 nM).[2] The first reported synthesis of "chaetomellic acid A", isolated and characterized as **2**, used a non-stereospecific aldol/elimination sequence, requiring separation of a 1:1 diastereomeric mixture of aldol adducts and a subsequent 4:3:0.5 mixture of regio- and diastereoisomeric alkenes after elimination, to provide **2** in ~18% overall yield for 4 steps starting from methyl palmitate.[3c]



Chaetomellic Acid A (**1**) | Chaetomellic Acid A Anhydride (**2**) | Chaetomellic Acid A Dianion (**3**) (*Biologically Active Form*)

We report here a high-yielding stereospecific synthesis of **2** using a cobalt-mediated radical cross coupling strategy.[4] Oxidative addition of $py(dmgH)_2Co^-$, generated in situ, with myristyl bromide (**4**) under standard cobaloxime-forming conditions provided myristyl-cobaloxime **5** in 84% yield after chromatography on silica gel.[5] Photolysis of an anaerobic CH_3CN solution of **5** (20 mM), citraconic anhydride (20 equiv, 400 mM) and PhSSPh (1.05 equiv, 21mM) provided **6** in 78% yield after chromatography on silica gel.[5,6] Oxidation of the sulfide in **6** to the sulfoxide with meta-chloroperoxybenzoic acid at 0 °C, with in situ syn elimination under the reaction conditions (or at ambient temperature during work-up), provided chaetomellic acid A anhydride **2** in 98% yield.[5] Facile elimination of the intermediate sulfoxide establishes the *trans* stereochemical relationship of the thiophenyl and myristyl substitutents in **6**, which is the predicted stereochemistry based on steric effects.[4] The synthetic strategy described here can easily be adapted to the synthesis of diverse chaetomellic acid A analogs. Cobaloximes can be prepared from primary and secondary alkyl bromides, iodides, or alcohol sulfonate esters. The exceptionally mild reaction conditions should be compatible with virtually all common organic functional groups.



Acknowledgment. This research was supported by NSF CHE 8806805 and a fellowship from the U.S. Department of Education GAANN Program (R.M.S.).

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3. (a) Singh, S. B.; Zink, D. L.; Liesch, J. M.; Goetz, M. A.; Jenkins, R. G.; Nallin-Omstead, M.; Silverman, K. C.; Bills, G. F.; Mosley, R. T.; Gibbs, J. B.; Albers-Schonberg, G.; Lingham, R. B. *Tetrahedron* **1993**, *49*, 5917-5926. (b) Lingham, R. B.; Silverman, K. C.; Bills, G. F.; Cascales, C.; Sanchez, M.; Jenkins, R. G.; Gartner, S. E.; Martin, I.; Diez, M. T.; Pelaez, F.; Mochales, S.; Kong, Y. L.; Burg, R. W.; Meinz, M. S.; Huang, L.; Nallin-Omstead, M.; Mosser, S. D.; Schaber, M. D.; Omer, C. A.; Pompliano, D. L.; Gibbs, J. B.; Singh, S. B. *Applied Microbiology and Biotechnology* **1993**, *40*, 370-374. (c) Singh, S. B. *Tetrahedron Lett.* **1993**, *34*, 6521-6524.
4. For previous work on this type of synthetic strategy, applied to the synthesis of butenolides, see: Branchaud, B. P.; Slade, R. M.; Janisse, S. K. *Tetrahedron Lett.* **1993**, *34*, 7885-7888.
5. Myristyl bromide (1-bromotetradecane) and citraconic anhydride (methylmaleic anhydride) were obtained from Aldrich and used as received. Compound **5** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and high resolution MS. Compound **6** was characterized by ^{1}H NMR, ^{13}C NMR, MS and high resolution MS. Compound **2** was characterized by ^{1}H NMR, ^{13}C NMR, IR, MS and high resolution MS.
6. All photolyses were performed in Pyrex tubes in deoxygenated CH_3CN under Ar or N_2. Visible light photolysis was provided by two 300W incandescent light bulbs held 4-5 inches from the tube. Reactions were maintained at 15 °C with a circulating constant temperature bath over the duration of the photolysis (10 hr).

(*Received in USA* 23 *March* 1994; *accepted* 15 *April* 1994)