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SYNTHESIS OF CHAETOMELLIC ANHYDRIDE A, A POTENT INHIBITOR OF RAS PROTEIN FARNESYLTRANSFERASE

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Abstract – Chaetomellic anhydride A, a potent inhibitor of Ras protein farnesyltransferase, was synthesized in 61% yield over four steps from methyl propionate. The synthesis features palladium-catalyzed carboxylation reaction under Cacchi conditions, efficiently incorporating carbon monoxide generated *in situ* from acetic formic anhydride into β-carbomethoxyalkenyl triflate, and giving rise to the maleic anhydride motif of chaetomellic anhydride A. Noteworthy is the remarkable reactivity of the carboxylation reaction that takes place at room temperature despite the fact that common palladium-catalyzed carboxylations generally require rather harsh conditions. The scope of the method is also presented.

INTRODUCTION

Oncogenic studies have revealed that Ras protein is mutated in approximately 30% of human cancers, the mutation occurring via farnesylation of the protein catalyzed by a zinc metalloenzyme, protein farnesyltransferase (PFTase). As a result, PFTase inhibitors have received considerable attention in cancer chemotherapy due to their potential use as a new chemical substance that blocks oncogenic cell growth.[1,2] Intensive screening of natural and synthetic resources has led to the successful identification of a number of PFTase inhibitors: chaetomellic acid A (**1**) is a natural PFTase inhibitor produced by the coelomycete *Chaetomella acutiseta* and is obtained as chaetomellic anhydride A (**2**) that arises from facile dehydration of the maleic acid motif (Figure 1).[3] Because of its significant inhibitory activity

This Paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

toward recombinant human PFTase (IC_{50}=55 nM), acid **1** has become an attractive synthetic target in recent years.[4]

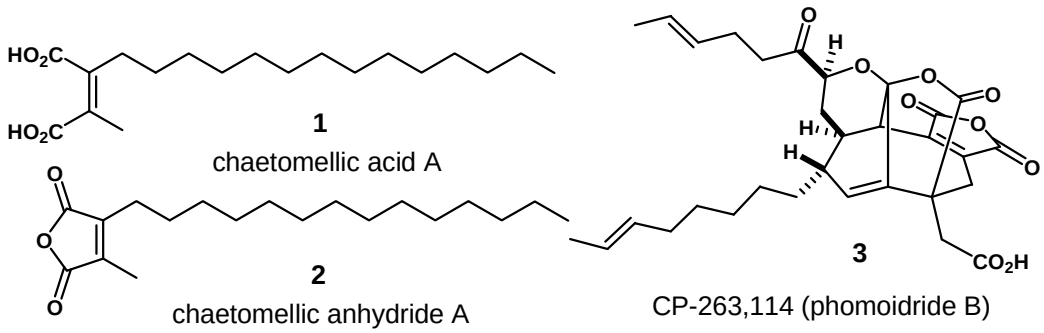


Figure 1. Natural farnesyltransferase inhibitors.

The prospect that PFTase inhibitors serve as potential anticancer agents has motivated us to establish an access to this class of molecules. Our recent efforts in this area have culminated in the synthesis of the fully functionalized core motif of (-)-CP-263,114 (phomoidride B) (**3**), which is one of the most structurally complex natural PFTase inhibitors.[5] In this context, we became interested in chaetomellic anhydride A (**2**) because it has a simple architecture and can easily be transformed into the bioactive dianion form of chaetomellic acid A (**1**) by mild saponification (i.e., pH > 7). We report herein an expeditious route to anhydride **2** employing a Pd-catalyzed carboxylation technique that would potentially provide an access to substituted maleic anhydrides, which widely constitute the structural motifs of bioactive nonadrides (Figure 2).[6]

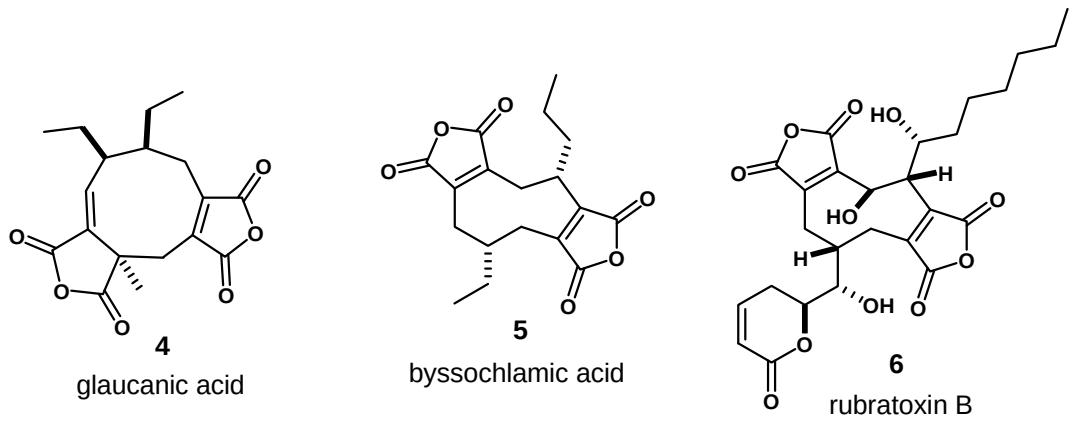


Figure 2. Bioactive natural maleic anhydrides.

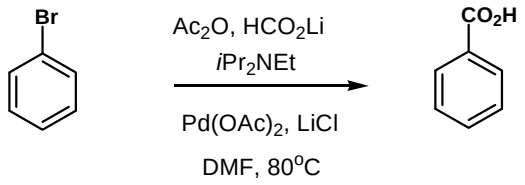
RESULTS AND DISCUSSION

Various means for synthesizing substituted maleic anhydrides have appeared in the literature, many of which rely on the transformation of alkynes and alkenes or the condensation of esters.[7] Those methods involve vicinal dialkylations of dimethyl acetylenedicarboxylate via 1,4-nucleophilic addition

reactions,[4n,7a] double carbonylation of acetylene-cobalt complexes,[7b,c] condensation of esters with α-ketoesters followed by dehydration,[4r] and Ni-catalyzed dicarboxylation of allenes.[4c]

Palladium-catalyzed carboxylation of β-carboalkoxyalkenyl triflates or halides, followed by cyclization of resultant maleic acid half-esters, is also particularly useful for this purpose, although it generally requires the use of highly toxic pressurized carbon monoxide (CO) gas.[8]

Recently, Cacchi and co-workers reported that aryl and vinyl halides or triflates could be carboxylated in the presence of palladium(0) catalyst by using acetic anhydride and lithium formate as the condensed source of CO, giving carboxylic acids in good yields.[9,10] Consequently, it occurred to us that the carboxylation of β-carbomethoxyalkenyl triflates with CO generated *in situ* under Cacchi conditions would provide half-esters, which, by subsequent cyclization, could be readily converted into substituted maleic anhydrides.

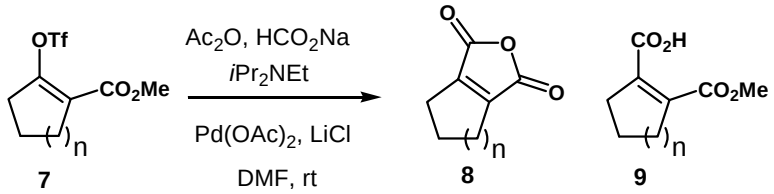


Scheme 1. Cacchi's carboxylation reaction.

As an initial investigation of the feasibility of maleic anhydride formation, several cyclic β-carbomethoxyalkenyl triflates **7a-d** were subjected to CO insertion reaction (Table 1). Cyclic triflates **7a-d** were each treated with a mixture of acetic anhydride, formic salt,[11] LiCl, and *i*Pr_2NEt in the presence of $Pd(OAc)_2$ in DMF at room temperature.[12] As expected, enol triflates were consumed within reasonable reaction times to produce maleic anhydrides and/or half-esters as the major products in various ratios depending on the ring size of the substrate used. It should be noted, however, that the present reactions smoothly took place *even at room temperature* despite the fact that Pd-catalyzed carboxylations generally require rather harsh conditions (e.g., heating at 80 °C). The progress of the reactions was easily monitored by TLC, indicating that 5- and 6-membered ring triflates **7a** and **7b** mainly gave half-esters. Half-ester **9b** produced from triflate **7b** could be transformed into corresponding maleic anhydride **8b** with azeotropic dehydration in the presence of TsOH, whereas 5-membered half-ester **9a** derived from **7a** yielded no maleic anhydride under the same conditions, resulting in its recovery (entries 1 and 2). In contrast, 7- and 8-membered ring substrates **7c** and **7d** were found to readily provide maleic anhydrides **8c** and **8d**, respectively, along with unstable intermediates (*vide infra*) that completely disappeared during an acidic aqueous work-up due to their susceptibility to hydrolysis and high propensity for cyclization (entries 3 and 4). The inefficiency in cyclizing the 5- and 6-ring half-esters derived from **7a** and **7b** is reasonably

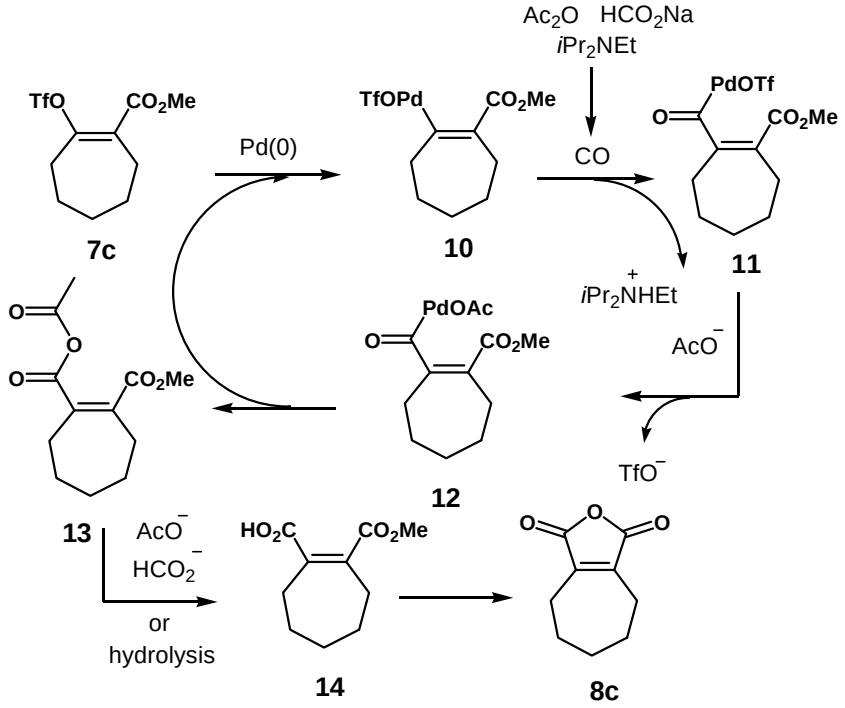
attributable to the high degree of ring strain of the bicyclic anhydrides compared to that of the larger carbocycles.

Table 1. Pd-catalyzed carboxylation reaction of β-carbomethoxyalkenyl triflates.



entry	substrate		time	yield (%)
1	**a**	n=1	1.5 h	**9a** (79)[a]
2	**b**	n=2	9.5 h	**8b** (86)[a]
3	**c**	n=3	50 min	**8c** (82)[b]
4	**d**	n=4	55 min	**8d** (90)[b]

a) overall yield after azeotropic dehydration.
b) after acidic aqueous work-up.

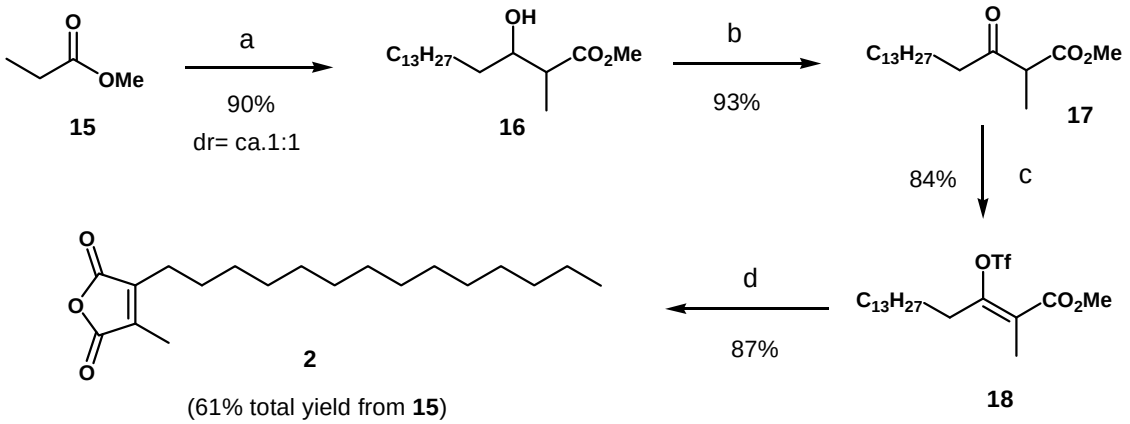


Scheme 2. Mechanism of maleic anhydride formation.

Quite interestingly, applying a nonaqueous work-up enabled the successful isolation of mixed acetic anhydride **13** from 7-membered ring substrate **7c**:[13] after starting triflate **7c** had been completely consumed, the reaction mixture was diluted with dry Et_2O and filtered through a short plug of

Celite/Florisil. Then the filtrate was concentrated *in vacuo* to give a mixture of two compounds detectable by TLC, both of which were visualized using UV light and stained with $KMnO_4$ solution. Rapid and careful chromatography of the mixture afforded highly labile anhydride **13** and cyclized product **8c**. The successful isolation of **13** in this case indicates that the carboxylations proceed through an intermediacy of the mixed acetic anhydride, which supports Cacchi's mechanistic proposal.[9a] A plausible mechanism is thus reasonably assumed for the present reaction: anhydride **13** generated via acylpalladium intermediate **12** is deacetylated by nucleophilic attack of an acetate and/or a formate anion in the reaction mixture, or hydrolyzed by moisture, yielding corresponding half-ester **14** that then undergoes rapid cyclization to afford maleic anhydride **8c** (Scheme 2).

The present procedure allowed us to devise an expeditious route to chaetomellic anhydride A (**2**) (Scheme 3). We initiated the synthesis with β-hydroxy ester **16,** which was prepared by aldol condensation of methyl propionate (**15**) with pentadecanal. Compound **16** was oxidized with PCC to produce β-keto ester **17** in 93% yield, which, upon treatment with NaH in refluxing toluene followed by the addition of triflic anhydride at 0 °C, selectively gave (*Z*)-β-carbomethoxyalkenyl triflate **18** in 84% yield.[14] Although triflation could be carried out by enolizing **17** with potassium hexamethyldisilazide and subsequent treatment of the resultant enolate with phenyl triflimide, this procedure led to a somewhat low yield owing to the production of undesired (*E*)-triflate isomer (70% yield, *Z*/*E* = ca. 3:1). Then, triflate **18** was subjected to the key anhydride-forming reaction to furnish chaetomellic anhydride A (**2**) in 87% yield.[15] This synthesis enabled a highly efficient four-step access to target **2** in 61% overall yield from commercially available ester **15**.



Reagents and conditions: (a) LDA, $C_{14}H_{29}CHO$, THF, -78 °C, 90%; (b) PCC, CH_2Cl_2, rt; (c) NaH, 85 °C, toluene, then Tf_2O, 0 °C, 84%; (d) Ac_2O, HCO_2Na, *i*-Pr_2NEt, cat. $Pd(OAc)_2$, LiCl, DMF, rt, 87%.

Scheme 3. Synthesis of chaetomellic anhydride A.

CONCLUSION

In summary, we have established an efficient route to chaetomellic anhydride A (**2**) via maleic anhydride formation under Cacchi's CO insertion conditions. We also found evidence of an intermediacy of the mixed acetic anhydride in the carboxylation reactions, which supports the mechanistic rationale previously proposed by Cacchi and co-workers. The expeditiousness of the present synthesis allowed us to produce chaetomellic anhydride A (**2**) in a large quantity and thus, the method for elaborating maleic anhydride motifs established here will provide a foundation for synthesizing various substituted maleic anhydrides.

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11. Cacchi has established the superior reactivity of lithium salt (HCO_2Li) in carboxylation reactions. Sodium formate (HCO_2Na), however, was used as the formic salt throughout this study because of ease of availability.
12. **A typical procedure for maleic anhydride formation:** A mixture of HCO_2Na (143 mg, 2.1 mmol), Ac_2O (130 μL, 1.4 mmol), and *i*-Pr_2NEt (245 μL, 1.4 mmol) was stirred at rt for 1 h. To this mixture were added triflate **7d** (221 mg, 0.7 mmol) in DMF (1.0 mL + 0.5 mL x 2 used for rinsing),

$Pd(OAc)_2$ (7.9 mg, 0.035 mmol), and LiCl (89 mg, 2.1 mmol) sequentially, and the stirring was continued for another hour. The mixture was poured into a separatory funnel where it was partitioned between 2 *N* HCl and Et_2O. Then, the organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (Et_2O/hexane=1:3 v/v) to give maleic anhydride **8d** as a colorless oil. IR (neat) ν 1771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.68-2.63 (m, 4H), 1.86-1.79 (m, 4H), 1.60-1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 144.3, 25.8, 25.3, 22.9; MS *m/z*: 180 (M^+), 108 (100%); HRMS (EI) calcd for $C_{10}H_{12}O_3$ (M^+): 180.0786, found: 180.0789.

13. NMR data of mixed acetic anhydride **13**: ^1H NMR (300 MHz, $CDCl_3$) δ 3.56 (s, 3H), 2.63-2.58 (m, 1H), 2.49-2.38 (m, 3H), 2.09 (s, 3H), 1.90-1.59 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 167.0, 157.0, 133.0, 116.4, 51.9, 29.9, 26.4, 26.3, 26.0, 24.6, 21.4.
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15. **Synthesis of chaetomellic anhydride A (2)**: By applying the same protocol as that described above (note 12) to triflate **18** (1.59 g, 3.58 mmol), two materials consisting of desired anhydride **2** and its unstable precursor, a mixed acetic anhydride, were produced. Therefore, the mixture was diluted with CH_2Cl_2 followed by adding silica gel (ca. 20 g) to ensure complete cyclization of the precursor, yielding anhydride **2** as the sole product. Following filtration, concentration and purification by silica gel column chromatography (CH_2Cl_2) gave chaetomellic anhydride A (**2**) (935 mg, 87%) as a colorless oil, which solidified in a refrigerator (at ~3°C) as a waxy solid. **Chaetomellic anhydride A:** IR (neat) ν: 1771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (t, 2H, *J*=7 Hz), 2.07 (s, 3H), 1.63-1.54 (m, 2H), 1.34-1.25 (m, 22H), 0.88 (t, 3H, *J*=7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 165.7, 144.6, 140.3, 31.9, 29.7-29.2 (9 peaks), 27.6, 24.5, 22.7, 14.1, 9.5; MS *m/z*: 308 (M^+), 126 (100%); HRMS (EI) calcd for $C_{19}H_{32}O_3$ (M^+) *m/z*: 308.2351, found: 308.2355. The data are in full agreement with those reported.[4a,f,m] **Mixed acetic anhydride:** ^1H NMR (300 MHz, $CDCl_3$) δ 3.57 (s, 3H), 2.25 (t, 2H, *J*=8 Hz), 2.09 (s, 3H), 1.88 (s, 3H), 1.37-1.16 (m, 24H), 0.88 (t, 3H, *J*=7 Hz).