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THE DESIGN AND SYNTHESIS OF NOVEL CHAETOMELLIC ACID A ANALOGUES

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Abstract

Chaetomellic acid A is an alkyl dicarboxylic acid isolated from the fermentation of *Chaetomella acutiseta*. Chaetomellic acid A has been shown to be a potent, highly specific inhibitor of RAS farnesyl protein transferase (FPTase). The association between RAS proteins and cancer has made chaetomellic acid A a potential chemotherapeutic agent. Two novel chaetomellic acid A analogues have been prepared that incorporate aromatic rings in the alkyl tail. It is anticipated that these compounds will bind more tightly to the FPTase active site than the natural product due to intermolecular interactions between the aromatic rings in the tail and the aromatic amino acid residues that have been shown to line the enzyme pocket.

Keywords: Cancer, Chaetomellic acid A, Farnesyl protein transferase, Farnesyl pyrophosphate mimetics, RAS proteins

Introduction

Ras genes encode for RAS proteins which are initially found in the cell cytosol. In order to perform their function as a molecular switch for cell growth, RAS proteins must first become membrane bound. This occurs through a series of post-translational modifications (1-3). The key step in RAS membrane association is the addition of a fifteen carbon, farnesyl chain to the RAS protein catalyzed by the enzyme farnesyl protein transferase (FPTase). An intense interest in RAS proteins and FPTase has arisen since the discovery of mutant RAS proteins in approximately 30% of all human cancers (4). It has been shown that mutant RAS proteins that cannot be farnesylated, do not induce malignant transformation (5). Therefore, FPTase inhibitors have become attractive targets as potential chemotherapeutic agents.

Since its isolation in 1993 (6), chaetomellic acid A [**1**] has been synthesized via multiple routes (7-15) and shown to be a potent and highly specific inhibitor of FPTase (IC_{50} human FPTase = 55 nM). Chaetomellic acid A is a competitive inhibitor of FPTase, mimicking the enzymes natural substrate, farnesyl pyrophosphate (FPP). While most research in the area of FPP mimetics has focused on modifications to the biologically labile diphosphate "head" (16-21), manipulation of the hydrophobic farnesyl "tail" has also been shown to influence binding to the enzyme active site. For example, the presence of a benzoylbenzyl group in the "tail" of an FPP mimetic gives a slight increase (1.5-fold) in the binding affinity for FPTase (22). This data along with the publication of a crystal structure of FPTase (23,24), revealing a hydrophobic pocket lined with ten aromatic amino acid residues that accepts the terpenoid chain, has led to the hypothesis that the addition of aromatic rings into the hydrophobic "tail" will enhance the binding affinity of FPP analogues. To prove this hypothesis, two analogues of chaetomellic acid A have been prepared (Figure 1). One analogue incorporates one aromatic ring in the alkyl "tail" [**2**] and the other analogue incorporates two aromatic rings [**3**]. Molecular modeling studies show that both of these analogues, **2** and **3**, are similar in length to the natural product [**1**], 22.019 Å, 21.86 Å, and 22.031 Å respectively (25). It is anticipated that these compounds will be better FPTase inhibitors than chaetomellic acid A, thus illuminating the

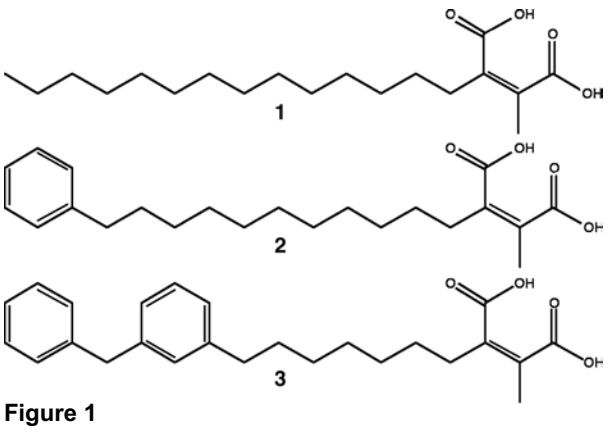
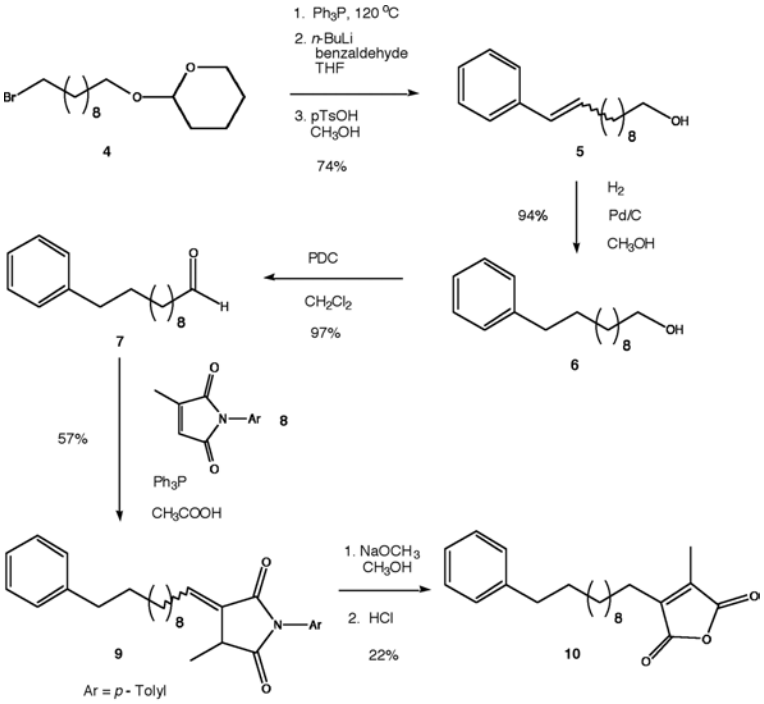


Figure 1



Scheme 1.

importance of nonbonding interactions in enzymatic recognition of the hydrophobic "tail".

Experimental

Tetrahydrofuran (THF) was distilled from sodium/ benzophenone immediately prior to use, while dichloromethane was freshly distilled from calcium hydride. All reactions in these solvents were conducted in oven-dried glassware under a positive pressure of nitrogen. Column chromatography was performed on 230-400 mesh silica gel. NMR spectra (^{1}H NMR at 300 MHz and ^{13}C NMR at 75 MHz) were recorded on a JEOL 300 MHz NMR spectrometer (JEOL-USA, Inc. Peabody, MA) with $CDCl_3$ solvent. High-resolution mass spectra were obtained on a Bruker BioTOF II mass spectrometer (Bruker Daltonics Inc. Billerica, MA) at the University of Minnesota Mass Spectrometry Service Laboratory. All starting chemicals were purchased from Aldrich (Milwaukee, WI) and used as received.

11-phenyl-10-undecen-1-ol [5]

A mixture of tetrahydropyran **4** (26) (3.42 g, 10.7 mmoles) and triphenylphosphine (3.33 g, 12.7 mmoles) was placed in a flame-dried 50 mL round-bottom flask fitted with a reflux condenser and stirred at 120°C for 1 hour. Upon generation of the phosphonium salt, the reaction mixture was cooled to 75°C and 30 mL of THF was added through the reflux condenser. The resulting solution was vigorously stirred and allowed to cool to room temperature. Once at room temperature, the solution was treated with *n*-BuLi (5.4 mL of a 2.5 M solution in hexanes, 13.5 mmol) to generate the ylide (red color). The mixture was allowed to stir for 5 minutes and then benzaldehyde was added dropwise (1.3 mL, 12.8 mmol). The Wittig reaction was allowed to stir for 1 hour and then subsequently quenched with 1 M HCl and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The crude oil obtained in this manner was placed in anhydrous methanol (20 mL) and treated with *p*-toluenesulfonic acid (246 mg, 1.29 mmol). The reaction mixture was allowed to stir overnight (15 hours) and then concentrated directly under vacuum to provide a yellow oil. Final purification by column chroma-tography (60:40 hexanes:ethyl acetate) afforded 11-phenyl-10-undecen-1-ol [**5**] as a 1.7:1.0 mixture of *cis*:*trans* isomers (1.93 g, 74%): ^{1}H NMR δ 7.39-7.14 (m, 5H), 6.41 (d, 1H, J = 11.8 Hz, *cis*), 6.38 (d, 1H, J = 15.7 Hz, *trans*), 6.22 (dt, 1H, J = 15.9, 6.6 Hz, *trans*), 5.66 (dt, 1H, J = 11.5, 7.4 Hz, *cis*), 3.63 (t, 2H, J = 6.6 Hz), 2.32 (m, 2H, *cis*), 2.20 (m, 2H, *trans*), 1.61-1.21 (m, 14H).

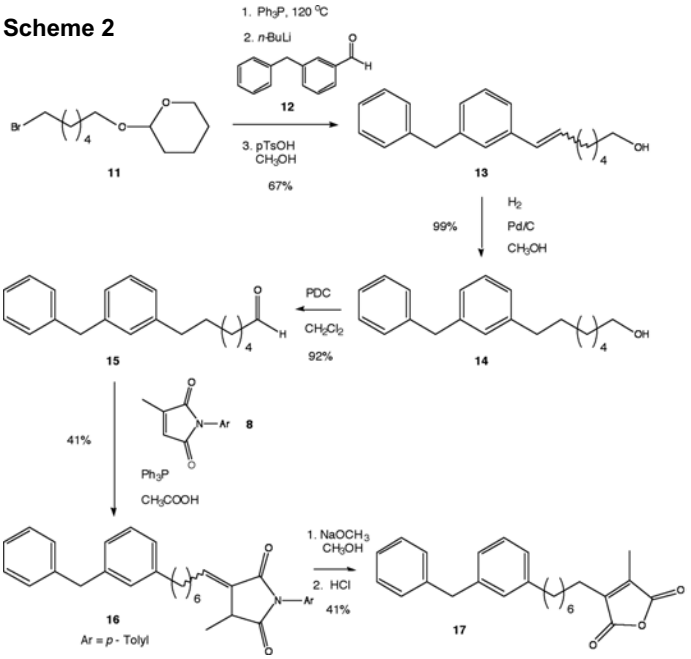
11-phenyl-1-undecanol [6]

A solution of alkene **5** (53 mg, 0.22 mmol) in anhydrous methanol (2 mL) was placed in a 5 mL round-bottom flask and treated with 5% palladium on carbon (43 mg, 0.020 mmol). The flask was placed under a hydrogen atmosphere by using a hydrogen balloon and allowed to stir for 3 hours. The reaction mixture was filtered through celite and silica gel (diethyl ether rinse) and concentrated *in vacuo* to afford 11-phenyl-1-undecanol [**6**] as a clear oil which solidifies to a white solid when placed in the freezer (50 mg, 94%): ^{1}H NMR δ 7.30-7.14 (m, 5H), 3.64 (t, 2H, J = 6.6 Hz), 2.60 (t, 2H, J = 7.7 Hz), 1.58 (m, 2H), 1.44 (br s, 1H), 1.37-1.22 (m, 16H); ^{13}C NMR δ 143.0, 128.5 (2C), 128.3 (2C), 125.6, 63.2, 36.1, 32.9, 31.6, 29.7-29.4 (6C), 25.8; HRMS calcd for $C_{17}H_{28}O$ $(M + Na)^+$ 271.397, found 271.2025.

11-phenyl-1-undecanal [7]

Alcohol **6** (720 mg, 2.90 mmol), pyridinium

Scheme 2



dichromate (PDC) (1.64 g, 4.35 mmol), and dichloromethane (25 mL) were placed in a flame-dried 50 mL round-bottom flask and allowed to stir overnight (17 hours). The resulting suspension was diluted with ether and filtered through a thin layer of celite and silica gel. The filtrate was concentrated under vacuum and purified by column chromatography (80:20 hexanes:ethyl acetate) to afford aldehyde **7** (690 mg, 97%): ^{1}H NMR δ 9.76 (t, 1H, *J* = 1.6 Hz), 7.32-7.12 (m, 5H), 2.60 (t, 2H, *J* = 7.4 Hz), 2.41 (dt, 2H, *J* = 1.9, 7.3 Hz), 1.67-1.54 (m, 2H), 1.28 (br s, 14H); ^{13}C NMR δ 203.1, 143.0, 128.5 (2C), 128.3 (2C), 125.6, 44.0, 36.1, 31.6, 29.6-29.2 (6C), 22.2.

***N*-*p*-tolylsuccinimide [9]**

A mixture of aldehyde **7** (210 mg, 0.854 mmol), triphenylphosphine (235 mg, 0.896 mmol), and citraconimide **8** (27) (180 mg, 0.896 mmol) was placed in glacial acetic acid (5 mL) and heated to reflux with stirring overnight (17 hours). The acetic acid was removed under reduced pressure and the resulting oil was purified by column chromatography (85:15 hexanes:ethyl acetate). A 6.1:1.0 mixture of *E*:*Z* isomers of *N*-*p*-tolylsuccinimide **9** was obtained (210 mg, 57%): ^{1}H NMR δ 7.33-7.16 (m, 9H), 6.94 (dt, 1H, *J* = 2.2, 8.0 Hz, *E*), 6.24 (dt, 1H, *J* = 1.9, 7.7 Hz, *Z*), 3.51-3.42 (m, 1H, *E*), 3.42-3.32 (m, 1H, *Z*), 2.93-2.79 (m, 2H, *Z*), 2.64 (t, 2H, *J* = 7.4 Hz), 2.41 (s, 3H), 2.40-2.21 (m, 2H, *E*), 1.72-1.58 (m, 2H), 1.54 (d, 3H, *J* = 7.4 Hz, *E*), 1.49 (d, 3H, *J* = 7.4 Hz, *Z*), 1.33 (br s, 14H).

Anhydride [10]

Sodium metal (130 mg, 5.65 mmol) and anhydrous methanol (10 mL) were mixed together to generate a 0.565 M solution of sodium methoxide *in situ*. Succinimide **9** (170 mg, 0.394 mmol) was placed in a 10 mL round-bottom flask and subsequently treated with the freshly prepared 0.565 M sodium methoxide solution (5.0 mL, 2.8 mmol). The resulting mixture was heated at reflux for 2 hours and then the methanol solvent was removed under vacuum. The resulting residue was acidified with 3 M HCl, extracted with diethyl ether, and concentrated. The crude yellow oil was purified by column chromatography (80:20 hexanes:ethyl acetate) to afford pure anhydride **10** (30 mg, 22%): ^{1}H NMR δ 7.31-7.13 (m, 5H), 2.60 (t, 2H, *J* = 7.4 Hz), 2.45 (t, 2H, *J* = 7.4 Hz), 2.06 (s, 3H), 1.67-1.51 (m, 2H), 1.37-1.23 (m, 16H); ^{13}C NMR δ 166.4, 166.0, 144.9, 143.0, 140.5, 128.5 (2C), 128.3 (2C), 125.6, 36.1, 31.6, 29.6, 29.6, 29.6, 29.5, 29.5, 29.4, 29.2, 27.7, 24.5, 9.6; HRMS calcd for $C_{22}H_{30}O_3$ $(M + Na)^+$ 365.466, found 365.2096.

Alkenol [13]

In a similar procedure as described above for 11-phenyl-10-undecen-1-ol [**5**], THP ether **11** (26) (1.58 g, 5.96 mmol) and triphenyl phosphine (1.87 g, 7.13 mmol) were stirred for 1 hour at 120°C. The phosphonium salt was diluted with THF (20 mL) and treated with *n*-BuLi (2.9 mL of a 2.5 M solution in hexanes, 7.2 mmol). Generation of the ylide was followed by the addition of a solution of 3-(phenylmethyl)benzaldehyde **12** (28) (1.3 g, 6.6 mmol) in THF (10 mL) via cannula. The reaction was allowed to stir for 2 hours and worked-up as described above for compound **5**. The crude product was diluted in anhydrous methanol (100 mL) and treated with *p*-toluenesulfonic acid (1.15 g, 6.05 mmol). Purification by column chromatography (65:35 hexanes:ethyl acetate) provided pure alkenol **13** as a 2.6:1.0 mixture of *cis*:*trans* isomers (1.11 g, 67%): ^{1}H NMR δ 7.38-7.03 (m, 9H), 6.42 (d, 1H, *J* = 11.8 Hz, *cis*), 6.39 (d, 1H, *J* = 15.7 Hz, *trans*), 6.23 (dt, 1H, *J* = 15.7, 6.6 Hz, *trans*), 5.67 (dt, 1H, *J* = 11.5, 7.4 Hz, *cis*), 4.01 (s, 2H, *cis*), 4.00 (s, 2H, *trans*), 3.66 (t, 2H, *J* = 6.6 Hz, *trans*), 3.63 (t, 2H, *J* = 6.6 Hz, *cis*), 2.33 (m, 2H, *cis*), 2.24 (m, 2H, *trans*), 1.68-1.32 (m, 6H).

3-(phenylmethyl)benzeneheptanol [14]

Alkenol **13** (110 mg, 0.393 mmol), 5% palladium on carbon (120 mg, 0.0569 mmol), and methanol (4 mL) were stirred under a hydrogen atmosphere in a similar procedure as described for 11-phenyl-1-undecanol [**6**] above. Standard work-up provided alcohol **14** as a clear oil (420 mg, 83%): ^{1}H NMR δ 7.37-7.18 (m, 6H), 7.09-7.01 (m, 3H), 4.00 (s, 2H), 3.65 (t, 2H, *J* = 6.6 Hz), 2.61 (t, 2H, *J* = 7.4 Hz), 1.80 (br s, 1H), 1.70-1.53 (m, 2H), 1.38 (br s, 8H); ^{13}C NMR δ 143.1, 141.4, 141.1, 129.2, 129.1 (2C), 128.5 (2C), 128.5, 126.4, 126.3, 126.1, 63.1, 42.1, 36.0, 32.9, 31.5, 29.4 (2C), 25.7; HRMS calcd for $C_{20}H_{26}O$ $(M + Na)^+$ 305.414, found 305.1875.

3-(phenylmethyl)benzeneheptanal [15]

Following the procedure described above for the preparation of aldehyde **7**, alcohol **14** (110 mg, 0.390 mmol), PDC (220 mg, 0.585 mmol), and dichloromethane (5 mL) were allowed to stir for 19 hours. Upon standard work-up and purification by column chromatography (80:20 ethyl acetate:hexanes), pure aldehyde **15** was isolated as a clear oil (100 mg, 92%): ^{1}H NMR δ 9.80 (t, 1H, *J* = 1.7 Hz), 7.41-7.25 (m, 6H), 7.15-7.08 (m, 3H), 4.06 (s, 2H), 2.67 (t, 2H, *J* = 7.4 Hz), 2.45 (dt, 2H, *J* = 1.7, 7.3 Hz), 1.76-1.64 (m, 4H), 1.47-1.39 (m, 4H); ^{13}C NMR δ 202.8, 143.0, 141.5, 141.2, 129.3, 129.1 (2C), 128.6 (2C), 128.6, 126.5, 126.3, 126.2, 44.0, 42.1, 36.0, 31.4, 29.2 (2C), 22.2.

***N*-*p*-tolylsuccinimide [16]**

Following the same procedure used to prepare *N*-*p*-tolylsuccinimide **9**, a mixture of aldehyde **15** (270 mg, 0.964 mmol), triphenylphosphine (265 mg, 1.01 mmol), and citraconimide **8** (27) (203 mg, 1.01 mmol) was placed in glacial acetic acid (8 mL) and heated to reflux with stirring overnight (21 hours). The acetic acid was removed under reduced pressure. The resulting oil was purified by column chromatography (90:10 hexanes:ethyl acetate) and a 6.4:1.0 mixture of *E*:*Z* isomers of *N*-*p*-tolylsuccinimide **16** was obtained (181 mg, 41%): ^{1}H NMR δ 7.38-7.23 (m, 10H), 7.12-7.06 (m, 3H), 6.96 (dt, 1H, *J* = 2.2, 8.0 Hz, *E*), 6.25 (dt, 1H, *J* = 1.9, 8.0 Hz, *Z*), 4.03 (s, 2H, *E*), 4.02 (s, 2H, *Z*), 3.52-3.42 (m, 1H, *E*), 3.44-3.34 (m, 1H, *Z*), 2.97-2.83 (m, 2H, *Z*), 2.65 (t, 2H, *J* = 7.4 Hz), 2.43 (s, 3H, *E*), 2.42 (s, 3H, *Z*), 2.40-2.24 (m, 2H, *E*), 1.75-1.61 (m, 2H), 1.56 (d, 3H, *J* = 7.4 Hz, *E*), 1.51 (d, 3H, *J* = 7.4 Hz, *Z*), 1.49-1.37 (m, 6H).

Anhydride [17]

Following the same procedure used to synthesize anhydride **10**, anhydride **17** was prepared from succinimide **16**. 15 mL of a freshly prepared 0.87 M sodium methoxide solution was added to succinimide **16** (181 mg, 0.389 mmol) and the mixture was heated at reflux for 3 hours. Removal of methanol under vacuum, acidification with 3 M HCl, and diethyl ether extraction provided a yellow oil which was purified by column chromatography (90:10 hexanes:ethyl acetate) to afford pure anhydride **17** (60 mg, 41%): ^{1}H NMR δ 7.33-7.15 (m, 6H), 7.05-6.98 (m, 3H), 3.97 (s, 2H), 2.57 (t, 2H, *J* = 7.7 Hz), 2.44 (t, 2H, *J* = 7.4 Hz), 2.06 (s, 3H), 1.66-1.50 (m, 4H), 1.38-1.28 (m, 6H); ^{13}C NMR δ 166.3, 166.0, 144.8, 142.9, 141.4, 141.1, 140.5, 129.2, 129.0 (2C), 128.5 (2C), 128.4, 126.4, 126.2, 126.1, 42.0, 35.9, 31.4, 29.4, 29.2, 29.2, 27.6, 24.5, 9.6; HRMS calcd for $C_{25}H_{28}O_3$ $(M + Na)^+$ 399.483, found 399.1915.

Results and Discussion

The preparation of anhydrides **10** (Scheme 1) and **17** (Scheme 2) were accomplished using similar reaction sequences. The synthesis of anhydride **10** began with 10-bromo-1-(tetrahydropyranyloxy) decane **4**, which was prepared in two known steps from commercially available 1,10-decanediol (26). Bromide **4** was subsequently converted to a phosphorus ylide upon treatment with triphenylphosphine followed by *n*-butyllithium. Addition of benzaldehyde to the ylide provided the desired Wittig product in high yield. The coupling proceeded smoothly except for one problem. Under the Wittig reaction conditions, some cleavage of the tetrahydropyranyl ether protecting group was observed. The resulting Wittig product was therefore not purified, but carried directly into the deprotection step. Treatment with *p*-toluenesulfonic acid converted all of the Wittig product to alkenol **5**, providing a 74% yield over the two steps. Alkenol **5** was isolated as a 1.7:1.0 mixture of *cis*:*trans* isomers (29) that was converted to a single compound, alcohol **6**, upon hydrogenation over palladium on carbon. With alcohol **6** in hand, a procedure previously developed to convert tetradecanol to chaetomellic anhydride A was employed to prepare anhydride **10** (7). Alcohol **6** was transformed to aldehyde **7** using a chromium oxidation. The aldehyde was condensed with known citraconimide **8** (27) under acidic conditions to yield

N-*p*-tolylsuccinimide **9** as a 6.1:1.0 mixture of *E* and *Z* isomers (29). Treatment of the mixture with sodium methoxide in methanol followed by acidification resulted in the preparation of anhydride **10** in moderate yield.

Anhydride **17** was prepared using the same sequence as described above for anhydride **10**. There are only two differences in the synthetic sequences. First, anhydride **17** was synthesized from a shorter bromotetrahydropyranyl ether. Commerically available 1,6-hexanediol was used instead of 1,10-decanediol as a starting material to prepare 6-bromo-1-(tetrahydropyranyloxy)hexane **11** (26). Second, the Wittig reagent prepared from bromide **11** was coupled with 3-(phenylmethyl)benzaldehyde (**12**) instead of benzaldehyde. Aldehyde **12** was prepared in three steps from commercially available 3-bromobenzaldehyde (28). The Wittig product was deprotected and hydrogenated to alcohol **14** as described above. Once obtained, alcohol **14** was converted to anhydride **17** following the three step protocol established in synthesizing anhydride **10** from alcohol **6**.

Conclusion

In summary, two chaetomellic acid A analogues have been prepared, analogue **10**, incorporating one aromatic ring, and analogue **17**, incorporating two aromatic rings. Both of these compounds were prepared in eight linear steps with overall yields of 7.5% and 7.6% respectively. Although synthesized in the anhydride form, for bioassaying purposes, compounds **10** and **17** are chaetomellic acid A analogues. It has been shown that under typical assay conditions (pH 7.5), chaetomellic anhydride A opens up to the biologically active dicarboxylate form of chaetomellic acid A with no loss of FPTase activity (6). The same results should hold true for chaetomellic anhydride analogues **10** and **17**. Under basic bioassay conditions, they will be converted to the diacid salts of compounds **2** and **3** (Figure 1) *in situ*. In this manner, compounds **10** and **17** will serve as useful probes to investigate the importance of non-bonding interactions in enzymatic recognition of the hydrophobic "tail".

Acknowledgment

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