# A Facile Synthesis and Enzymatic Resolution of Naturally Occurring Remotely Functionalized Alkylmethylmaleic Anhydrides from *Aspergillus wentii*: Aspergillus Acids A–D[1]

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**Abstract:** The first synthesis of four new naturally occurring remotely functionalized secondary mould metabolite anhydrides **1a–d** is described starting from *N*-*p*-tolyl citraconimide (**5**) in three to six steps and 20–65% overall yields. The condensation of triphenylphosphine-maleimide adduct **6** with aldehyde **4** furnished the *exo*-imide **7**, which after isomerization, hydrolysis, and acylation gave aspergillus acid A (**1a**) in 54% overall yield in four steps. The condensation of adduct **6** with aldehyde **15** similarly afforded the desired imide **17** in two steps. The acid-catalyzed hydrolysis of imide **17** directly furnished aspergillus acid B (**1b**), exposing the latent methyl ketone present as the terminal acetylene. Sodium borohydride induced chemoselective reduction of aspergillus acid B (**1b**) gave aspergillus acid C (**1c**), which upon acetic anhydride induced acylation, furnished aspergillus acid D (**1d**). A facile Amano PS catalyzed acylation of aspergillus acid C (**1c**) gave, in good yield, the desired (+)-aspergillus acid C (**1e**) in 70% ee and (–)-aspergillus acid D (**1f**) in 72% ee. In the present enzymatic reaction, the anhydride moiety presumably plays a crucial role in the substrate recognition, binding, and resolution process.

**Key words:** citraconimide, Wittig condensation, chemoselective reduction, aspergillus acid, enzymatic resolution

In the past decade, several structurally interesting compounds with dialkyl substituted maleic anhydride moieties have been isolated as bioactive natural products and were synthesized in view of their promising bioactivities;[2–4] of these, alkylmethylmaleic anhydrides are among the most popular (Figure 1).[5–15] One can surmise that nature might design these alkylmethylmaleic anhydrides by employing the condensation between pyruvic acid and other carboxylic acids. A specific example is that of chaetomellic acid A, which was isolated from *Chaetomella acutiseta*[8] (genesis pyruvic acid and palmitic acid).[16] Structure activity relationship studies have revealed that the hydrophilic dianion of chaetomellic acid A binds with the phosphate group of the enzyme and the hydrophobic tetradecyl group coils with the farnesyl chain thus deactivating the enzyme. Hence, such compounds highlighting the regiochemical dichotomy are known to be potent and highly specific inhibitors of ras-farnesyl-protein transferase (Ras-FPTase)[8,17] and presently chaetomellic acid A is of commercial interest as a bioactive natural product.[18] Assante et al., in 1979, isolated[9] four new secondary metabolites aspergillus acids A–D produced by the mould *Aspergillus wentii* when grown on a yeast–glucose medium; these natural products were also established to be derivatives of citraconic anhydride with remotely functionalized long hydrocarbon chains (Figure 1). On the basis of the Horeau method, the chiral centre in acids **1c** and **1d** has been assigned the *S* configuration.[9]

To date, the synthesis of these achiral/chiral natural products **1a–d** has not been reported. We believe that the remote functional groups on the hydrophobic long chain hydrocarbon units of these acids **1a–d** will anchor the binding process with target enzymes, resulting in a boost in activity.[17,19] The tremendous clinical potential of such compounds, as mentioned above, makes them attractive synthetic targets and the provision of a facile synthetic route to these molecules is an imperative task of current interest. In the past decade, we have in our group designed several bioactive natural and unnatural compounds using cyclic anhydrides as potential precursors[20] and we have also accomplished some important enzymatic resolutions.[21] In continuation of our earlier studies,[20,21] starting from maleimide **5**, herein we report the first synthesis of these naturally occurring acids **1a–d** formed by the elegant introduction of remote functional groups and an enzymatic resolution of acid **1c** (Schemes 1 and 2).

Aspergillus acid A (**1a**) is 2-(17-acetoxyheptadecyl)-3-methylmaleic anhydride while aspergillus acids B–D (**1b–d**) contain a 16-carbon chain with carbonyl, hydroxyl, and acetyl groups at carbon-15, respectively. In 1997, we developed elegant reaction conditions to couple citraconimide–triphenylphosphine adduct with aliphatic aldehydes leading to alkyl methyl substituted maleic anhydrides.[17c,22] We assumed that this coupling reaction would be useful for the preparation of the remotely functionalized anhydrides **1a–d**.

With this in mind we prepared the appropriate 17-acetoxyhexadecanal (**4**) in two steps starting from 1,17-heptadecanediol (**2**) via monoacetylation and Swern oxidation in 70% overall yield (Scheme 1). The triphenylphosphine-induced Wittig olefination of citraconimide **5** with acetoxyaldehyde **4** in refluxing acetic acid gave the corresponding *exo*-alkylidene succinimide **7** (*E*/*Z*, 90:10; $^1$H NMR spectroscopy) in 70% yield. The carbon–carbon double-bond migration from a trisubstituted exocyclic to a tetrasubstituted endocyclic was effected by triethylamine furnishing the desired maleimide **8** in 92% yield.

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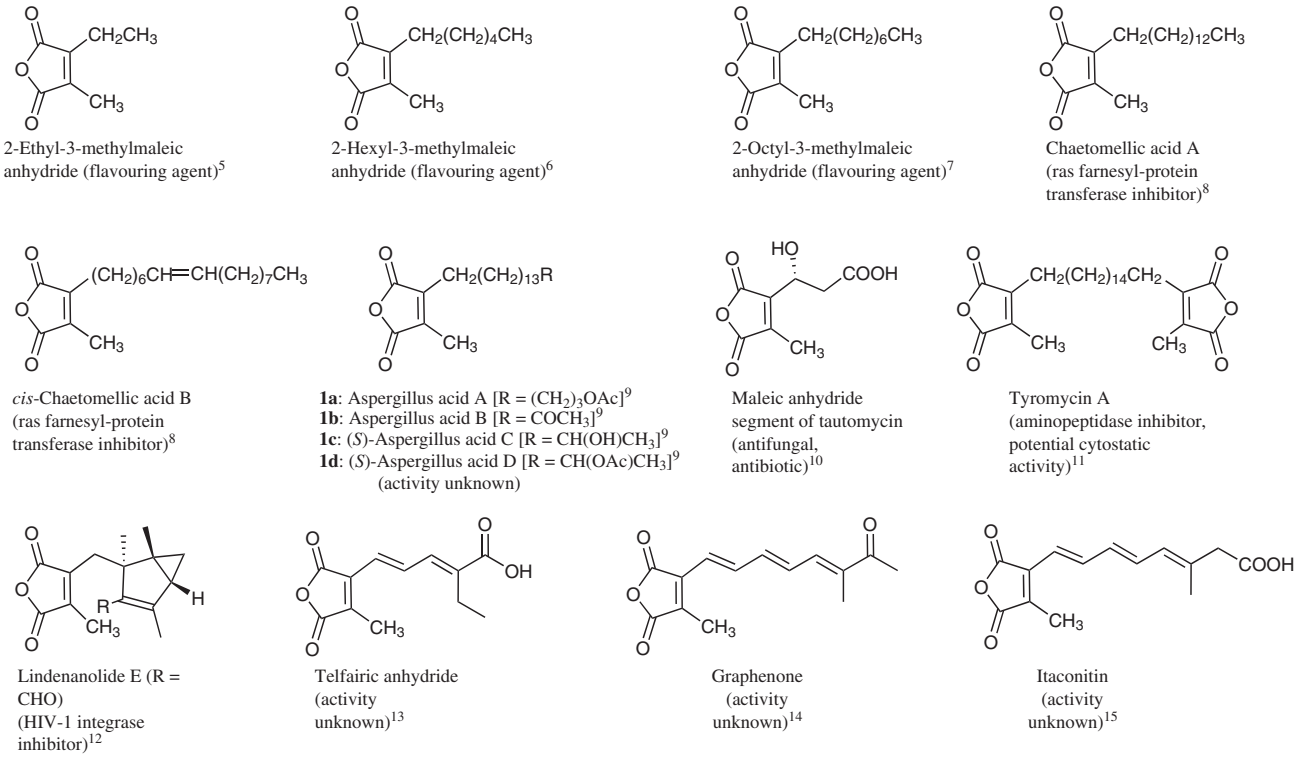
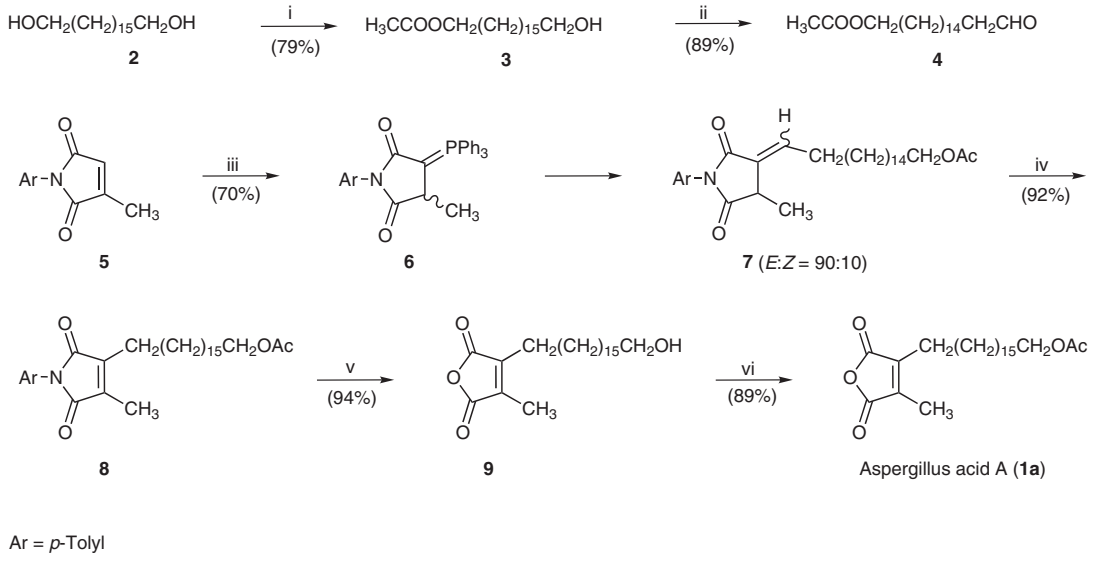



**Figure 1** Naturally occurring alkyl methyl substituted maleic anhydrides and their bioactivities

Base-catalyzed hydrolysis of maleimide **8** furnished the 2-(17-hydroxytetradecyl)-3-methylmaleic anhydride (**9**) in 94% yield. Acetic anhydride mediated acylation of anhydride **9** gave the naturally occurring aspergillus acid A (**1a**) in 89% yield. The analytical and spectral data obtained for acid **1a** were in complete agreement with the reported data[9] and the overall yield of **1a**, for the four steps, was 54%. The successful synthesis of **1a** proved that our present synthetic route would allow the preparation of chiral acids **1c** and **1d** via acid **1b**.

At this stage, we had two options for the synthesis of aspergillus acids B–D, (i) start with a suitable ω-substituted 16-carbon aldehyde, perform the selective remote functionalization, and then attempt a new enzymatic resolution, or (ii) directly design and start with a protected enantiomerically pure remotely functionalized 16-carbon aldehyde. We reasoned and chose the former, as the latter would involve (i) stoichiometric use of costly reagents for the enantioselective reduction of alkyl methyl ketone,[23,24] (ii) appropriate protection–deprotection of the secondary

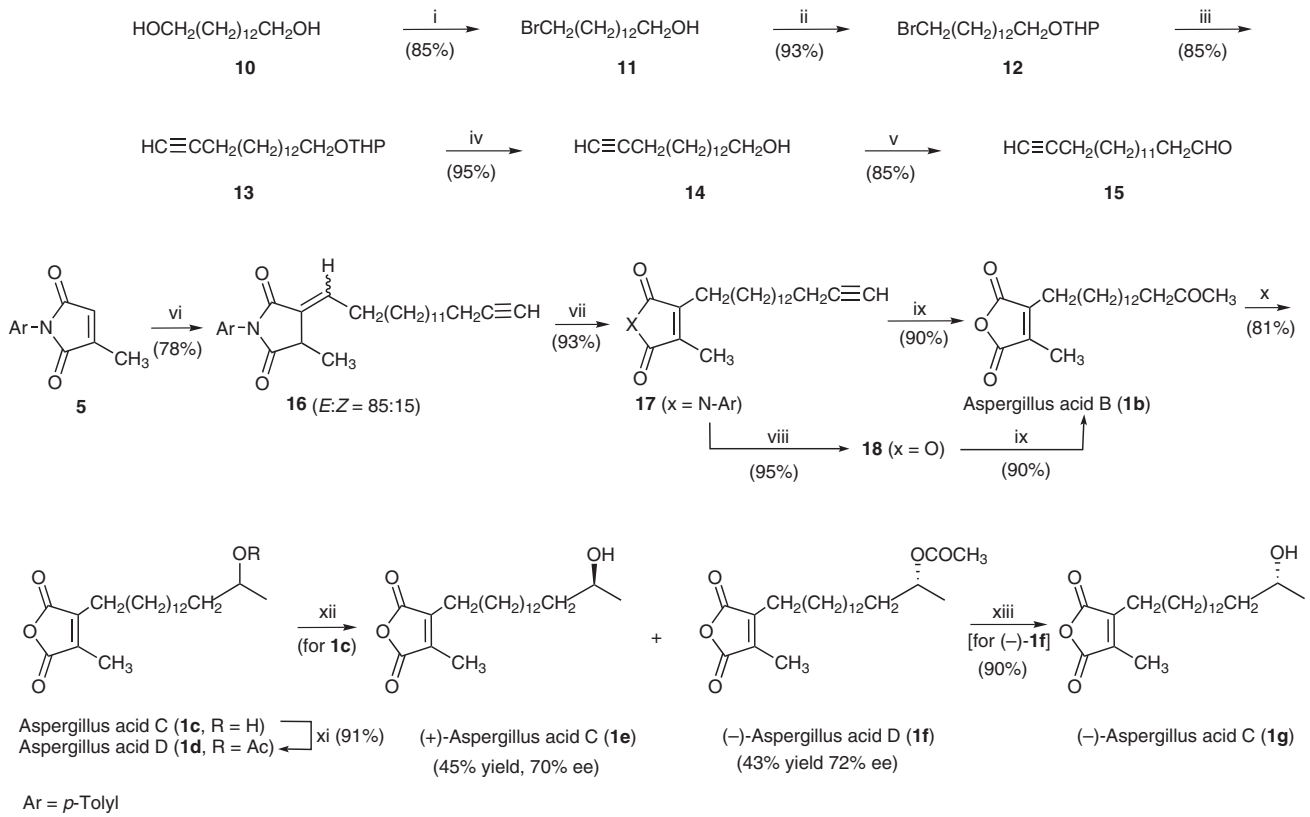



**Scheme 1** *Reagents and conditions*: (i) $Ac_2O$ (0.98 equiv), py, r.t., 6 h; (ii) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, –60 °C, 90 min; (iii) $PPh_3$, AcOH, **4**, reflux, 18 h; (iv) $Et_3N$, THF, reflux, 48 h; (v) (a) KOH (30% aq), THF–MeOH (1:2), reflux, 12 h, (b) $H^+$/HCl; (vi) $Ac_2O$, py, r.t., 8 h.

alcohol moiety, and (iii) possible loss of enantiomeric purity during the course of the total synthesis.

In our efforts to functionalize the remote carbon in accordance with the established structures of the target molecules, we envisaged a Markovnikov hydration of a terminal acetylene as the key step in the synthesis of these mould metabolites **1b–d**. In this context, 1,14-tetradecane diol (**10**) was transformed in two steps to the ω-bromo-*O*-THP protected alcohol **12** via the corresponding bromohydrin in 79% overall yield. The bromo compound **12** was then converted using standard functional group interconversions to the desired aldehyde **15** in three steps (69%) with incorporation of an acetylene unit at the terminal position of the chain (Scheme 2). The overall yield of aldehyde **15** for the five steps was 54%. Wittig condensation of aldehyde **15** with the imide–triphenylphosphine adduct generated in situ from citraconimide **5** proceeded smoothly in refluxing acetic acid to yield the *exo*-imide **16** (*E*/*Z*, 85:15; $^1$H NMR spectroscopy) in 78% yield with the carbon–carbon triple bond intact. Subsequently, triethylamine efficiently catalyzed the isomerization of the exocyclic trisubstituted carbon–carbon double bond in *exo*-alkylidene succinimide **16** to afford the tetrasubstituted endocyclic maleimide **17** in 93% yield. To complete the synthesis of the second metabolite in the series, we were now left with two important tasks, converting the maleimide **17** to the anhydride and exposing the latent methyl ketone present as the terminal acetylene. Both steps were achieved in one pot in 90% yield upon treatment of imide **17** with a mixture of acetic acid and 6 M sulfuric acid (2:1) at 100 °C. Under these conditions, the imide was hydrolyzed to the anilic acid, which subsequently underwent ring-closure to the anhydride; simultaneous addition of a water molecule to the carbon–carbon triple bond in a Markovnikov fashion led to the generation of an alkyl methyl ketone, thus furnishing the natural product **1b**. We were also able to successfully isolate the intermediate acetylinic anhydride **18** by carrying out base-catalyzed hydrolysis of the corresponding maleimide **17**. The anhydride **18** on acid-catalyzed hydration gave the desired aspergillus acid B (**1b**) in 90% yield. The overall yield of aspergillus acid B for the three steps was 65%.

Chemoselective reduction of the ketone carbonyl in **1b** was now necessary to obtain the corresponding hydroxyl compound **1c**. In our hands, sodium borohydride reduction of **1b** in organic solvents under a variety of conditions failed to provide us with the required chemoselectivity. We always observed the reduction of the anhydride carbonyl as well as the ketone moiety and obtained a mixture of the corresponding butyrolactones **19a/19b** (26:74) with




**Scheme 2** *Reagents and conditions*: (i) HBr (47% aq), toluene, reflux, 96 h; (ii) DHP, PPTS (cat.), $CH_2Cl_2$, r.t., 4 h; (iii) NaC≡CH, THF, HMPA, –78 °C to r.t., 40 h; (iv) *p*-TsOH, MeOH, r.t., 2 h; (v) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, –60 °C, 90 min; (vi) $PPh_3$, AcOH, **15**, reflux, 24 h; (vii) $Et_3N$, THF, reflux, 48 h; (viii) (a) KOH (30% aq), THF–MeOH (1:2), reflux, 12 h, (b) $H^+$/HCl; (ix) 6 M $H_2SO_4$–AcOH (1:2), 100 °C, 8 h; (x) (a) NaOH (aq), THF, 50 °C, 2 h, (b) $NaBH_4$, 0 °C to r.t., 3 h, (c) $H^+$/HCl; (xi) $Ac_2O$, py, r.t., 12 h; (xii) Amano PS, vinyl acetate, hexane–benzene (2:1), 45 °C, 72 h; (xiii) (a) NaOH (aq), THF, 50 °C, 4 h, (b) $H^+$/HCl.

the remote hydroxyl functional group (Scheme 3). The structural assignment of regioisomers **19a** and **19b** was deduced on the basis of $^1$H NMR signals for the vinylic methyl group. As expected, the β-methyl group signal in the major isomer **19b** appeared at 2.02 ppm, while the α-methyl group in the minor isomer **19a** appeared at 1.83 ppm. Finally, the desired chemoselectivity was obtained by carrying out a sodium borohydride reduction of the corresponding di-sodium salt of **1b** followed by quenching the reaction with dilute hydrochloric acid to afford, exclusively, the natural product **1c** in 81% yield. We believed that the hydroxy anhydride **1c** was a potential precursor for the synthesis of the macrocyclic lactone skeleton via intramolecular lactonization pathway. Acetylation of hydroxy anhydride **1c** with acetic anhydride–pyridine furnished the fourth metabolite in the series, **1d**, in 91% yield. The overall yield of aspergillus acid C was 53% (four steps) and that of aspergillus acid D was 48% (five steps). The analytical and spectral data obtained for natural products **1b–d** were in complete agreement with the reported data.[9]

The conversion of methyl alkyl ketones to enantiomerically pure secondary alcohols using Baker's yeast and other microorganisms is known to be unsatisfactory[24,25] and enzymatic resolution is a better option in such cases. We felt that the presence of a remote anhydride moiety in aspergillus acid C would improve the recognition and binding of the substrate acids **1c/1d** during resolution and hence we systematically studied both the enzyme-catalyzed hydrolysis of (±)-**1d** and the enzyme-catalyzed acylation of (±)-**1c** using vinyl acetate as an acyl donor. The biphasic Amano PS catalyzed hydrolysis of (±)-**1d** proceeded rather slowly and after a prolonged reaction time (seven days), we observed only 8–10% of the hydrolyzed product (by $^1$H NMR spectroscopy). Following our earlier observation,[21a] we performed the Amano PS catalyzed acylation of (±)-**1c** in hexane–benzene (2:1) and observed a very clean acylation at 45 °C to obtain the acids (+)-**1e** (45%) and (–)-**1f** (43%), after separation by column chromatography. The base-catalyzed hydrolysis of (–)-aspergillus acid D (**1f**) furnished (–)-aspergillus acid C (**1g**) in 90% yield. $^1$H NMR spectra of the MTPA derivatives[26] of both (+)-aspergillus acid C (**1e**) and (–)-aspergillus acid C (**1g**) showed a very clean separation of the two diastereomeric methoxy group singlet signals, revealing that the acids (+)-**1e** and (–)-**1g** formed in 70% ee and 72% ee, respectively. To the best of our knowledge[27] this is the first enzymatic resolution of a secondary alcohol coupled with a maleic anhydride moiety.

In summary, a facile route for the synthesis of four new secondary metabolites **1a–d** has been described in three to five steps in very good overall yields. In the present synthesis, a terminal acetylene group is employed to bring about an elegant means of remote functionalization; the chemoselective sodium borohydride reduction and Amano PS catalyzed enzymatic resolution are both noteworthy. The Amano PS catalyzed enzymatic resolution of (±)-**1c** gave the (+)-aspergillus acid C (**1e**) in 45% yield and 70% ee and (–)-aspergillus acid D (**1f**) in 43% yield and 72% ee. We feel that the present approach is general in nature and will be useful for the design of several analogues of these metabolites for structure activity relationship studies.

Stereochemical assignments are based on the optical rotation of known compounds.[9] Amano PS-1360 U was obtained from Amano Pharmaceuticals, Japan. The activity of the lipase powder used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder.[28] Mps are uncorrected. NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a Brucker AC 200, MSL 300, and MSL 500 NMR spectrometers. FT-IR spectra were recorded on a FT-IR-8300 Shimadzu spectrometer. Column chromatographic separations were done on ACME silica gel (60–120 mesh/100–200 mesh). Commercially available 1,14-tetradecanediol, $Cl(CO)_2Cl$, $PPh_3$, dihydropyran, $Ac_2O$, sodium acetylide, DCC, and (*R*)-Mosher's acid were used. Petroleum ether (PE) with a bp range 60–80 °C was used.

**17-Acetoxyheptadecan-1-ol (3)**

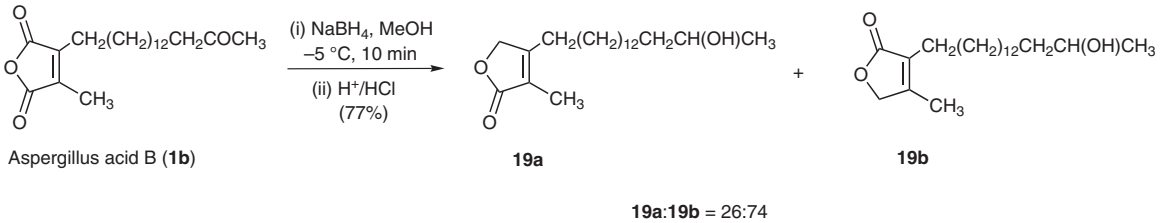
$Ac_2O$ (0.92 mL, 9.80 mmol) was added to a cool (ice bath) solution of 1,17-heptadecanediol (**2**)[29] (2.72 g, 10.00 mmol) in anhyd pyridine (10 mL) with stirring. The reaction mixture was allowed to warm to r.t., stirred for a further 6 h, then poured into ice-water (30 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with a solution of $CuSO_4$ (5% aq, 30 mL), $H_2O$ (30 mL), brine (30 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 8:2) to give **3**; yield: 2.48 g (79%); white solid; mp 60–61 °C.

IR ($CHCl_3$): 3447, 1726 cm$^{-1}$.

$^1$H NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 26 H), 1.50–1.70 (m, 5 H), 2.05 (s, 3 H), 3.64 (t, *J* = 6 Hz, 2 H), 4.05 (t, *J* = 6 Hz, 2 H).

**17-Acetoxyheptadecan-1-al (4)**

A solution of $Cl(CO)_2Cl$ (0.88 mL, 10.00 mmol) in anhyd $CH_2Cl_2$ (5 mL) was placed in a two-necked round-bottom flask and kept under argon at –60 °C. A solution of DMSO (1.42 mL, 20.00 mmol) in anhyd $CH_2Cl_2$ (5 mL) was added dropwise over a period of 5 min.




Aspergillus acid B (**1b**) **19a** **19b**

**19a**:**19b** = 26:74

**Scheme 3**

Alcohol **3** (1.57 g, 5.00 mmol) in anhyd $CH_2Cl_2$ (5 mL) was added dropwise over a period of 5 min and stirred at –60 °C for 90 min. $Et_3N$ (4.17 mL, 30.00 mmol) was added, the reaction mixture was allowed to warm to r.t., and stirred for a further 45 min. The reaction was quenched by the addition of $H_2O$ (20 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were washed with $H_2O$ (20 mL), brine (20 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **4**; yield: 1.39 g (89%); thick oil.

IR ($CHCl_3$): 2716, 1740, 1729 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.28 (br s, 24 H), 1.50–1.75 (m, 4 H), 2.05 (s, 3 H), 2.43 (dt, *J* = 8, 2 Hz, 2 H), 4.05 (t, *J* = 6 Hz, 2 H), 9.77 (s, 1 H).

**Hexadec-15-yne-1-al (15)**

Prepared from **14** (1.50 g, 6.30 mmol) using the same procedure as described for **4**; yield: 1.26 g (85%); thick oil.

IR (neat): 3310, 2718, 2116, 1726, $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.28 (br s, 20 H), 1.45–1.80 (m, 2 H), 1.94 (br s, 1 H), 2.19 (t, *J* = 7 Hz, 2 H), 2.43 (t, *J* = 7 Hz, 2 H), 9.77 (s, 1 H).

**(±)-2-Heptadec-(17-acetoxy)ylidene-3-methyl-*N*-(*p*-tolyl)succinimide (7)**

A mixture of citraconimide **5** (603 mg, 3.00 mmol) and $PPh_3$ (0.95 g, 3.60 mmol) in glacial AcOH (15 mL) was stirred at r.t. for 1 h. Aldehyde **4** (1.31 g, 4.20 mmol) in glacial AcOH (7 mL) was added and the reaction was refluxed with stirring for 18 h. AcOH was distilled off in vacuo at 50 °C and the residue was dissolved in EtOAc (30 mL). The organic layer was washed successively with $H_2O$ (15 mL), an aq solution of $NaHCO_3$ (15 mL), brine (15 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **7**; yield: 1.04 g (70%); yellow solid; mp 60–61 °C.

IR ($CHCl_3$): 1771, 1713, 1672 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 24 H), 1.50–1.70 (m, 4 H), 1.52 (d, *J* = 8 Hz, 3 H), 2.05 (s, 3 H), 2.20–2.40 (m, 2 H), 2.38 (s, 3 H), 3.46 (q, *J* = 8 Hz, 1 H), 4.05 (t, *J* = 6 Hz, 2 H), 6.25 (dt, *J* = 8, 2 Hz, 0.1 H), 6.92 (dt, *J* = 8, 2 Hz, 0.9 H), 7.15–7.30 (m, 4 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 16.4, 20.9, 21.1, 25.8, 28.5, 29.1, 29.4–29.5 (12 × $CH_2$), 37.4, 64.5, 126.1, 129.3, 129.6, 130.5, 138.3, 140.5, 145.0 (*Z*-*C*H=C), 168.8, 171.1, 177.3.

Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52; N, 2.81. Found: C, 74.93; H, 9.33; N, 2.86.

**(±)-2-Hexadec-(15-yne)ylidene-3-methyl-*N*-(*p*-tolyl)succinimide (16)**

Prepared from **5** (603 mg, 3.00 mmol) using the same procedure as described for **7**; yield: 985 mg (78%); thick oil.

IR ($CHCl_3$): 3306, 2116, 1771, 1713, 1672 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.29 (br s, 18 H), 1.45–1.65 (m, 4 H), 1.52 (d, *J* = 6 Hz, 3 H), 1.94 (t, *J* = 2 Hz, 1 H), 2.18 (dt, *J* = 7, 2 Hz, 2 H), 2.25–2.35 (m, 2 H), 2.38 (s, 3 H), 3.45 (q, *J* = 6 Hz, 1 H), 6.23 (dt, *J* = 8, 2 Hz, 0.15 H), 6.91 (dt, *J* = 8, 2 Hz, 0.85 H), 7.10–7.30 (m, 4 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 16.4, 18.3, 21.1, 28.4–29.4 (12 × $CH_2$), 37.5, 68.0, 84.7, 126.2, 129.3, 129.6, 130.5, 138.4, 140.5, 144.4 (*Z*-*C*H=C), 168.8, 177.3.

Anal. Calcd for $C_{28}H_{39}NO_2$: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.81; H, 9.36; N, 3.27.

**2-Heptadec-(17-acetoxy)yl-3-methyl-*N*-(*p*-tolyl)maleimide (8)**

A solution of **7** (994 mg, 2.00 mmol) in THF (3 mL) and $Et_3N$ (3 mL) was stirred under reflux for 48 h, then the reaction was allowed to cool to r.t. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **8**; yield: 915 mg (92%); white solid; mp 70–71 °C.

IR ($CHCl_3$): 1736, 1707 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 26 H), 1.50–1.70 (m, 4 H), 2.05 (s, 6 H), 2.37 (s, 3 H), 2.46 (t, *J* = 6 Hz, 2 H), 4.05 (t, *J* = 6 Hz, 2 H), 7.15–7.30 (m, 4 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 8.7, 20.8, 20.9, 23.7, 25.8, 28.1, 28.5, 29.1, 29.2, 29.4, 29.5 (9 × $CH_2$), 64.5, 125.5, 129.3, 129.4, 137.0, 137.1, 141.2, 170.7, 170.9, 171.0.

Anal. Calcd for $C_{31}H_{47}NO_4$: C, 74.81; H, 9.52; N, 2.81. Found: C, 74.65; H, 9.41; N, 2.92.

**2-Hexadec-(15-yne)yl-3-methyl-*N*-(*p*-tolyl)maleimide (17)**

Prepared from **16** (945 mg, 2.25 mmol) using the same procedure as described for **8**; yield: 880 mg (93%); white solid; mp 71–72 °C.

IR ($CHCl_3$): 3308, 2116, 1709 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.27 (br s, 20 H), 1.40–1.70 (m, 4 H), 1.94 (t, *J* = 2 Hz, 1 H), 2.05 (s, 3 H), 2.18 (dt, *J* = 7, 2 Hz, 2 H), 2.37 (s, 3 H), 2.46 (t, *J* = 7 Hz, 2 H), 7.23 (br s, 4 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 8.9, 18.4, 21.1, 23.8, 28.2–29.6 (12 × $CH_2$), 68.0, 84.8, 125.7, 129.3, 129.6, 137.1, 137.4, 141.3, 170.9, 171.2.

Anal. Calcd for $C_{28}H_{39}NO_2$: C, 79.76; H, 9.32; N, 3.32. Found: C, 79.62; H, 9.25; N, 3.20.

**2-Heptadec-(17-hydroxy)yl-3-methylmaleic Anhydride (9)**

To a solution of imide **8** (745 mg, 1.50 mmol) in THF–MeOH (1:2, 12 mL) was added an aq solution of KOH (30%; 10 mL) and the reaction mixture was heated under reflux for 12 h with stirring. The reaction mixture was concentrated in vacuo, the residue was acidified with dilute HCl, and extracted with $Et_2O$ (3 × 50 mL). The organic layer was washed with $H_2O$ (50 mL), brine (50 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **9**; yield: 516 mg (94%); white solid; mp 63 °C.

IR ($CHCl_3$): 3404, 1765, 1707 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.25 (br s, 26 H), 1.50–1.70 (m, 5 H), 2.07 (s, 3 H), 2.45 (t, *J* = 6 Hz, 2 H), 3.64 (t, *J* = 4 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 9.4, 24.3, 25.7, 27.5, 29.1, 29.3–29.5 (11 × $CH_2$), 32.7, 62.9, 140.4, 144.7, 165.8, 166.2.

Anal. Calcd for $C_{22}H_{38}O_4$: C, 72.09; H, 10.45. Found: C, 71.97; H, 10.36.

**2-Hexadec-(15-yne)yl-3-methylmaleic Anhydride (18)**

Prepared from **17** (210 mg, 0.50 mmol) using the same procedure described for **9**; yield: 157 mg (95%); thick oil.

IR ($CHCl_3$): 3314, 2116, 1765, 1713 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 20 H), 1.45–1.65 (m, 4 H), 1.94 (t, *J* = 2 Hz, 1 H), 2.07 (s, 3 H), 2.19 (dt, *J* = 6, 2 Hz, 2 H), 2.46 (t, *J* = 6 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ = 9.5, 18.4, 24.4, 27.6, 28.5, 28.7, 29.1, 29.2, 29.4–29.5 (6 × $CH_2$), 29.7, 68.0, 84.8, 140.4, 144.8, 165.9, 166.3.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.01; H, 9.63.

**2-Heptadec-(17-acetoxy)yl-3-methylmaleic Anhydride (Aspergillus Acid A, 1a)**

To a stirred solution of alcohol **9** (366 mg, 1.00 mmol) in pyridine (4 mL) was added $Ac_2O$ (0.47 mL, 5 mmol) and the reaction mixture was kept in the dark at r.t. for 8 h. The reaction mixture was poured into $H_2O$ (20 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with an aq solution of $CuSO_4$ (20 mL), $H_2O$ (20 mL), brine (20 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **1a**; yield: 363 mg (89%); white solid; mp 43–44 °C (lit.[9] mp 45–46 °C).

IR ($CHCl_3$): 1857, 1774, 1726, 1472, 1250 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 26 H), 1.45–1.70 (m, 4 H), 2.05 (s, 3 H), 2.07 (s, 3 H), 2.45 (t, *J* = 6 Hz, 2 H), 4.05 (t, *J* = 6 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 9.4, 20.9, 24.4, 25.9, 27.5, 28.6, 29.2–29.6 (12 × $CH_2$), 64.6, 140.4, 144.7, 165.8, 166.2, 171.1.

Anal. Calcd for $C_{24}H_{40}O_5$: C, 70.55; H, 9.87. Found: C, 70.61; H, 10.00.

**2-Hexadec-(15-acetoxy)yl-3-methylmaleic Anhydride (Aspergillus Acid D, 1d)**

Prepared from **1c** (106 mg, 0.30 mmol) using the same procedure described for **1a**; yield: 108 mg (91%); thick oil.

IR ($CHCl_3$): 1767, 1732 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.20 (d, *J* = 8 Hz, 3 H), 1.26 (br s, 22 H), 1.40–1.70 (m, 4 H), 2.03 (s, 3 H), 2.07 (s, 3 H), 2.46 (t, *J* = 7 Hz, 2 H), 4.89 (sext, *J* = 6 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$, 125 MHz): δ = 9.4, 19.8, 21.2, 24.3, 25.3, 27.5, 29.1, 29.3–29.4 (9 × $CH_2$), 35.8, 70.9, 140.4, 144.6, 165.8, 166.2, 170.7.

Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71. Found: C, 70.09; H, 9.82.

**14-Bromotetradecan-1-ol (11)**

To a mixture of diol **10** (3.45 g, 15.00 mmol) and toluene (60 mL) was added concd HBr (48% aq solution; 2 mL, 17.65 mmol). The heterogeneous mixture was stirred and heated at reflux for 48 h. A second portion of HBr (0.75 mL, 6.62 mmol) was added and the reaction mixture was heated at reflux for a further 48 h. When the starting diol had been completely consumed (TLC), the reaction mixture was allowed to cool to r.t., and the phases were separated. The organic layer was diluted with EtOAc (60 mL) and washed with NaOH (1 M; 40 mL), brine (40 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo to afford a thick oil, which was purified by column chromatography (PE–EtOAc, 8:2) to give **11**; yield: 3.74 g (85%); white solid; mp 52–54 °C.

IR ($CHCl_3$): 3393 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 20 H), 1.50–1.70 (m, 3 H), 1.86 (quint, *J* = 7 Hz, 2 H), 3.42 (t, *J* = 7 Hz, 2 H), 3.65 (t, *J* = 7 Hz, 2 H).

**14-Bromo-1-(tetrahydropyranyloxy)tetradecane (12)**

To a solution of **11** (3.30 g, 11.26 mmol) in anhyd $CH_2Cl_2$ (20 mL) were added dihydropyran (1.54 mL, 16.90 mmol) and PPTS (28 mg, 0.11 mmol). The reaction mixture was stirred at r.t. for 4 h. The reaction was diluted with $CH_2Cl_2$ (15 mL) the reaction mixture was washed with a sat. aq solution of $NaHCO_3$ (15 mL), brine (15 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **12**; yield: 3.95 g (93%); thick oil.

IR ($CHCl_3$): 1462, 1215 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.27 (br s, 20 H), 1.45–1.75 (m, 6 H), 1.75–2.00 (m, 4 H), 3.41 (t, *J* = 7 Hz, 2 H), 3.30–3.60 (m, 2 H), 3.65–3.95 (m, 2 H), 4.58 (t, *J* = 2 Hz, 1 H).

**1-Tetrahydropyranyloxypentadec-15-yne (13)**

A sodium acetylide slurry in xylene (18%, 0.84 g, 17.50 mmol) and THF (20 mL) under argon was cooled to –78 °C, and a solution of **12** (3.30 g, 8.75 mmol) in HMPA (10 mL) and THF (4 mL) was slowly injected into the reaction mixture with stirring. The reaction mixture was allowed to warm to r.t. and stirred for a further 40 h. The reaction was slowly quenched by the addition of a sat. solution of $NaHCO_3$ (5%, 15 mL), then a solution of $NH_4OAc$ (15 mL) was added to dissolve the white precipitate formed. The reaction mixture was extracted with EtOAc (3 × 30 mL), the combined organic layers were washed with $H_2O$ (25 mL), brine (25 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give **13**; yield: 2.40 g (85%); thick oil.

IR ($CHCl_3$): 3310, 2118, 1466, 1454 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.27 (br s, 20 H), 1.40–1.65 (m, 8 H), 1.94 (t, *J* = 2 Hz, 1 H), 2.18 (dt, *J* = 7, 2 Hz, 2 H), 3.30–3.60 (m, 3 H), 3.65–3.95 (m, 3 H), 4.58 (t, *J* = 2 Hz, 1 H).

**Hexadec-15-yn-1-ol (14)**

To a solution of **13** (2.19 g, 6.80 mmol) in MeOH (20 mL) was added *p*-TsOH·$H_2O$ (129 mg, 0.68 mmol) and the reaction mixture was stirred for 2 h at r.t. $NaHCO_3$ (500 mg) was added and the reaction mixture was stirred for a further 30 min. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo. The residue was diluted with $H_2O$ (20 mL) and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with $H_2O$ (30 mL), a sat. solution of $NaHCO_3$ (30 mL), brine (30 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 8:2) to give **14**; yield: 1.54 g (95%); white solid; mp 35 °C.

IR ($CHCl_3$): 3381, 3310, 2116, 1464, 1433 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.28 (br s, 20 H), 1.45–1.75 (m, 5 H), 1.95 (t, *J* = 2 Hz, 1 H), 2.18 (dt, *J* = 7, 2 Hz, 2 H), 3.64 (t, *J* = 6 Hz, 2 H).

**2-Hexadec-(15-oxo)yl-3-methylmaleic Anhydride (Aspergillus Acid B, 1b)**

A solution of **17** (632 mg, 1.50 mmol) in AcOH (6 mL) and $H_2SO_4$ (6 M; 3 mL) was heated at 100 °C for 8 h with stirring. The reaction mixture was allowed to cool to r.t., concentrated in vacuo, the residue was diluted with $H_2O$ (20 mL), and extracted with EtOAc (3 × 30 mL). The combined organic extract was washed successively with $H_2O$ (30 mL), brine (30 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 8:2) to give **1b**; yield: 473 mg (90%); white solid; mp 43–44 °C (lit.[9] mp 43 °C).

IR ($CHCl_3$): 1765, 1713 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.26 (br s, 20 H), 1.45–1.65 (m, 4 H), 2.07 (s, 3 H), 2.14 (s, 3 H), 2.42 (t, *J* = 8 Hz, 2 H), 2.45 (t, *J* = 8 Hz, 2 H).

$^{13}C$ NMR ($CDCl_3$, 50 MHz): δ = 9.5, 23.8, 24.4, 27.6, 29.1–29.4 (10 × $CH_2$), 29.8, 43.8, 140.4, 144.7, 165.9, 166.3, 209.4.

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.81; H, 9.90.

**2-Hexadec-(15-hydroxy)yl-3-methylmaleic Anhydride (Aspergillus Acid C, 1c)**

A solution of **1b** (350 mg, 1.00 mmol) in aq NaOH (30%, 5 mL) and THF (5 mL) was stirred for 2 h at 50 °C. The reaction mixture was cooled to 0 °C and then $NaBH_4$ (76 mg, 2.00 mmol) was added in one portion. The reaction mixture was allowed to warm to r.t. and stirred for 3 h. The reaction mixture was concentrated in vacuo, acidified by the slow addition of dilute HCl, extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with $H_2O$ (30 mL), brine (30 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 8:2) to give **1c**; yield: 285 mg (81%); white solid; mp 51–52 °C (lit.[9] mp 50 °C).

IR ($CHCl_3$): 3398, 1765 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.18 (d, *J* = 8 Hz, 3 H), 1.26 (br s, 22 H), 1.45–1.65 (m, 4 H), 2.07 (s, 3 H), 2.45 (t, *J* = 7 Hz, 2 H), 3.80 (sext, *J* = 6 Hz, 1 H).

$^{13}C$ NMR ($CDCl_3$, 75 MHz): δ = 9.0, 23.0, 24.0, 25.4, 27.1, 28.8, 29.2–29.3 (9 × $CH_2$), 38.9, 67.5, 140.2, 144.3, 165.5, 165.9.

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.62; H, 10.36.

**4-(15′-Hydroxyhexadecyl)-3-methyl-2(5*H*)-furanone (19a) and 3-(15′-Hydroxyhexadecyl)-4-methyl-2(5*H*)-furanone (19b)**

Anhydride **1b** (35 mg, 0.10 mmol) was dissolved in MeOH (4 mL). $NaBH_4$ (10 mg, 0.26 mmol) was added to the above solution at –5 °C and stirred for 10 min. The reaction was then quenched by the slow addition of dilute HCl and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed successively with $H_2O$ (15 mL), brine (15 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 8:2) to give **19b** and **19a**.

**19a**

Yield: 7 mg (21%); white solid; mp 72–73 °C (lit.[9] mp 72–74 °C).

IR (nujol): 3500, 1765 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.19 (d, *J* = 6 Hz, 3 H), 1.30 (br s, 22 H), 1.40–1.60 (m, 4 H), 1.83 (s, 3 H), 2.41 (t, *J* = 8 Hz, 2 H), 3.80 (sext, *J* = 6 Hz, 1 H), 4.66 (s, 2 H).

Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found: C, 74.39; H, 11.22.

**19b**

Yield: 19 mg (56%); white solid; mp 53–54 °C (lit.[9] mp 53–55 °C).

IR (nujol): 3472, 1734 $cm^{-1}$.

$^1H$ NMR ($CDCl_3$, 200 MHz): δ = 1.19 (d, *J* = 6 Hz, 3 H), 1.30 (br s, 22 H), 1.40–1.60 (m, 4 H), 2.02 (s, 3 H), 2.25 (t, *J* = 7 Hz, 2 H), 3.80 (sext, *J* = 6 Hz, 1 H), 4.62 (s, 2 H).

Anal. Calcd for $C_{21}H_{38}O_3$: C, 74.51; H, 11.31. Found: C, 74.62; H, 11.29.

**Amano PS Catalyzed Acylation of (±)-1c**

A solution of alcohol (±)-**1c** (176 mg, 0.50 mmol) in *n*-hexane–benzene (2:1; 9 mL) was added to Amano PS lipase (100 mg) followed by vinyl acetate (0.23 mL, 2.50 mmol). The reaction mixture was stirred at 45 °C for 72 h and then allowed to cool to r.t. The enzyme was removed by filtration, and washed with EtOAc. The organic layer was dried ($Na_2SO_4$), concentrated in vacuo, and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give (+)-**1e** and (–)-**1f**.

**(+)-1e**

Yield: 79 mg (45%); white solid; mp 52 °C; $[\alpha]_{589}^{20}$ +1.3 (*c* 1.0, $CHCl_3$) {lit.[9] [α] +1.83 (*c* 0.38, $CHCl_3$)}.

Analytical and spectral data obtained were identical with **1c**.

**(–)-1f**

Yield: 85 mg (43%); thick oil; $[\alpha]_{589}^{20}$ +2.0 (*c* 1.0, $CHCl_3$) {lit.[9] (+)-**1f** [α] +2.70 (*c* 0.22, $CHCl_3$)}.

Analytical and spectral data obtained were identical with **1d**.

**(–)-(*R*)-2-Hexadec-(15-hydroxy)yl-3-methylmaleic Anhydride (1g)**

A solution of acetate (–)-**1f** (60 mg, 0.15 mmol) in an aq solution of NaOH (30%; 3 mL) and THF (3 mL) was stirred for 4 h at 50 °C. The reaction mixture was cooled to r.t., concentrated in vacuo, acidified by the addition of dilute HCl, and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed successively with $H_2O$ (15 mL), brine (15 mL), and dried over $Na_2SO_4$. The organic phase was concentrated in vacuo and the residue was purified by column chromatography (PE–EtOAc, 9:1) to give (–)-**1g**.

Yield: 48 mg (90%); thick oil; $[\alpha]_{589}^{20}$ –1.4 (*c* 1.0, $CHCl_3$).

Analytical and spectral data obtained were identical with **1c**.

**MTPA Ester; General Procedure**

To a solution of (*R*)-Mosher's acid (15 mg, 0.06 mmol), alcohol (+)-**1e** or (–)-**1g** (18 mg, 0.05 mmol) and DMAP (cat.) in anhyd $CH_2Cl_2$ (3 mL) was added a solution of DCC (12 mg, 0.06 mmol) in anhyd $CH_2Cl_2$ (2 mL) at 0 °C. The reaction mixture was allowed to warm to r.t. and stirred for 8 h. The urea formed was removed by filtration, the organic phase was concentrated in vacuo, and the residue was purified by column chromatography (PE–EtOAc, 9.5:0.5) to give the MTPA ester as a thick oil in quantitative yield.

**MTPA Ester of (+)-(*S*)-2-Hexadec-(15-hydroxy)yl-3-methylmaleic Anhydride (1e)**

$^1H$ NMR ($CDCl_3$, 500 MHz): δ = 1.15–1.35 (m, 25 H), 1.55–1.70 (m, 4 H), 2.07 (s, 3 H), 2.45 (t, *J* = 10 Hz, 2 H), 3.55 (s, 0.45 H), 3.57 (s, 2.55 H), 5.16 (sext, *J* = 5 Hz, 1 H), 7.35–7.43 (m, 3 H), 7.50–7.55 (m, 2 H).

**MTPA Ester of (–)-(*R*)-2-Hexadec-(15-hydroxy)yl-3-methylmaleic Anhydride (1g)**

$^1H$ NMR ($CDCl_3$, 500 MHz): δ = 1.20–1.35 (m, 25 H), 1.50–1.63 (m, 4 H), 2.07 (s, 3 H), 2.45 (t, *J* = 10 Hz, 2 H), 3.55 (s, 2.58 H), 3.57 (s, 0.42 H), 5.14 (sext, *J* = 5 Hz, 1 H), 7.35–7.43 (m, 3 H), 7.50–7.55 (m, 2 H).

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