Asymmetric synthesis of the left hand portion of the azinomycins

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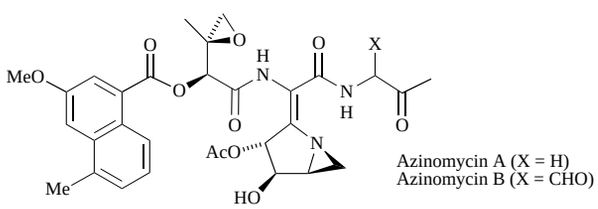
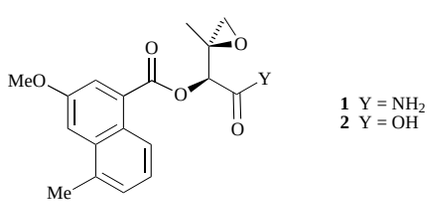
A nine step synthesis of the left hand portion of the azinomycins is described starting from 3,3-dimethylacrylic acid. The approach relies on a Sharpless asymmetric dihydroxylation (AD) reaction to install the requisite (2*S*,3*S*)-stereochemistry of epoxy alcohol 4. This epoxide is converted to crystalline amide derivative 12 whose structure and absolute stereochemistry have been unambiguously established using X-ray crystallography. Coupling of epoxy alcohol (2*S*,3*S*)-4 with naphthoyl chloride 16 and subsequent manipulations furnish epoxy amide (2*S*,3*S*)-1 identical in all respects with the natural material.

Introduction

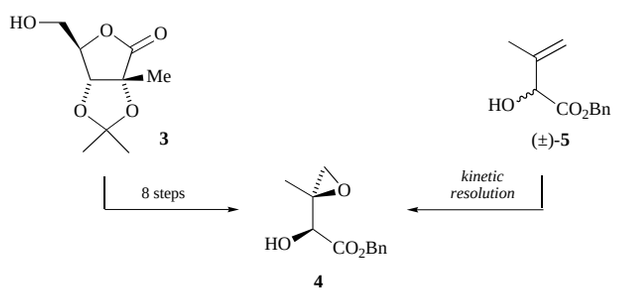
In 1986, azinomycins A and B were isolated from the culture broths of *Streptomyces griseofuscus* S42227 and were found to exhibit potent antitumour activity against a number of different tumour cell lines.[1] In addition, epoxy amide **1**, devoid of the





1-azabicyclo[3.1.0]hexane ring system, was isolated and later shown to also possess significant cytotoxic activity.[2] Armstrong *et al.* have established that azinomycin B causes interstrand cross-links in duplex DNA,[3] a process associated with many clinically important antitumour agents such as mitomycin C.[4] Not surprisingly, the important biological properties of the azinomycins coupled with their unique chemical structures have made them attractive targets for total synthesis. However, despite the development of a number of elegant approaches to various fragments of these natural products, a total synthesis of the azinomycins has not yet been realised.[2,5]

Our strategy to the azinomycins recognises the central amide bond as a key disconnection. Thus, the efficient preparation of carboxylic acid **2** is a key element of our planned synthesis. To accomplish this goal, we selected epoxy alcohol **4** as a key synthetic intermediate (Scheme 1). In addition to providing access to amide **1** and carboxylic acid **2**, we envisaged that it could be used to prepare a diverse array of synthetic analogues of the azinomycins for the development of structure–activity relationships. Two synthetic routes to epoxy alcohol **4** were described in the literature prior to our own investigations. Shibuya and coworkers converted D-(−)-fructose into protected γ-lactone **3**



Scheme 1

and subsequently used this compound to prepare homochiral **4** in a further eight steps (Scheme 1).[5b] More recently, an alternative approach to epoxy alcohol **4** has been developed by Konda *et al.* which relies upon a kinetic resolution step involving a Sharpless asymmetric epoxidation (SAE) reaction using L-(+)-diethyl tartrate.[5l] While this approach considerably reduces the number of steps required for the preparation of epoxide **4**, the SAE reaction proceeds in low yield (35%) and with only modest levels of asymmetric induction (73% ee). Further improvements to the enantioselectivity of this reaction have very recently been disclosed by Coleman *et al.* by use of L-(+)-diisopropyl tartrate.[5r]

In this paper, we disclose a short, practical asymmetric approach to epoxy alcohol **4**, and describe its conversion into primary amide **1** *via* carboxylic acid **2**.[6] Furthermore, in undertaking this work, we believe that we have identified some significant errors in the previously published routes to epoxy alcohol **4**.

Results and discussion

The approach we have adopted to homochiral epoxy alcohol **4** is based upon the asymmetric dihydroxylation methodology developed by Sharpless.[7] Commercially available 3,3-dimethylacrylic acid was converted into the corresponding benzyl ester **6** under phase transfer conditions.[8] Asymmetric dihydroxylation of this α,β-unsaturated ester using AD-mix-α gave diol (*R*)-**7** in 80% yield (Scheme 2).[9] Buffering of the reaction mixture by addition of sodium hydrogen carbonate was required to prevent ester hydrolysis. The enantiomeric excess of this diol was determined to be ≥95% ee by chiral HPLC analysis. The absolute configuration of this diol has been unambiguously established

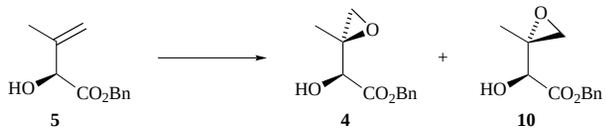
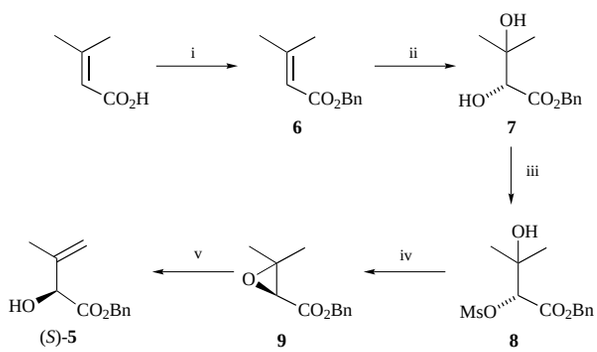


Table 1

Reaction conditions	4 : 10 [a]	Yield [b] (%)
m-CPBA, CH_2Cl_2, 0 °C	37 : 63	not determined
$VO(acac)_2$, Bu^{t}OOH, CH_2Cl_2, −20 °C ⟶ rt, 18 h	88 : 12	65
$Ti(OPr^i)_4$, Bu^{t}OOH, CH_2Cl_2, −20 ⟶ 0 °C, 24 h	87 : 13	51
$Mo(CO)_6$, Bu^{t}OOH, CH_2Cl_2, −20 ⟶ 40 °C	32 : 68	not determined
$Ti(OPr^i)_4$, D-(−)-DET, Bu^{t}OOH, CH_2Cl_2, −20 ⟶ 0 °C, 18 h	96 : 4	83
$Ti(OPr^i)_4$, L-(+)-DET, Bu^{t}OOH, CH_2Cl_2, −20 ⟶ 0 °C, 36 h	87 : 13	50

[a] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Isolated yield of epoxy alcohol **4** after column chromatography.



Scheme 2 *Reagents and conditions*: (i) BnBr, KOH, Bu$^n_4$NBr, $CHCl_3$, H_2O, 99%; (ii) AD-mix-α, $NaHCO_3$, $MeSO_2NH_2$, Bu^{t}OH, H_2O, 80%; (iii) MsCl, CH_2Cl_2, Et_3N, 0 °C, 79%; (iv) Na_2CO_3, MeCN, 82 °C, 88%; (v) (±)-camphor-10-sulfonic acid (CSA), toluene, 110 °C, 77%

by X-ray crystallography,[5q] and is entirely in agreement with the model proposed by Sharpless.[7] Diol (*R*)-**7** was converted into allylic alcohol (*S*)-**5** in three steps involving selective mesylation, epoxide formation and subsequent acid catalysed ring opening of the epoxide (Scheme 2). Importantly, we have determined that no detectable racemisation occurs during this reaction sequence (see Experimental section).

A variety of oxidative methods have been examined for the stereocontrolled epoxidation of allylic alcohol (*S*)-**5**. Metal catalysed epoxidations using *tert*-butyl hydroperoxide, particularly those based upon vanadium(V) and titanium(IV), proved to be effective for this reaction (Table 1). Column chromatography allowed isolation of the desired diastereomer, (2*S*,3*S*)-**4** which was determined to be ⩾95% ee by chiral shift NMR analysis using (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. However, to our surprise, the optical rotation of our material, $[\alpha]_D^{20}$ 11.5 (*c* 1.9, EtOH) was different in both size and sign to the value originally reported by Shibuya, $[\alpha]_D^{20}$ −22.4 (*c* 0.13, EtOH).[5b] The confusion concerning the sign of the optical rotation of (2*S*,3*S*)-**4** is important because the value reported by Shibuya was later used by Konda to determine the sense of asymmetric induction in his kinetic resolution experiments employing racemic allylic alcohol **5** (Scheme 1).[5l] Konda concluded that the SAE reaction proceeded with unusual facial selectivity and required the use of L-(+)-diethyl tartrate to furnish (2*S*,3*S*)-**4**. We have examined the SAE reaction of *homochiral* (*S*)-**5** using both enantiomers of diethyl tartrate, and in contrast to Konda's observations, determined that the chirality of the substrate and reagent are matched when D-(−)-diethyl tartrate is used (Table 1).

In order to help resolve this confusion, we sought unambiguous proof concerning the absolute configuration of epoxy alcohol **4** prepared using our chemistry. This was accomplished by converting this epoxide into amide **12** by esterifying the hydroxy group with 1-naphthoyl chloride and coupling it with (*S*)-(−)-α-methylbenzylamine after cleavage of the benzyl ester by hydrogenation (Scheme 3). X-Ray crystallography was used to establish the relative stereochemical relationships within amide **12** (Fig. 1), and hence unambiguously determine the absolute configuration of epoxy alcohol **4**. From this study, we conclude that epoxide **4** made using our methodology possesses the (2*S*,3*S*)-stereochemistry and exhibits an optical rotation, $[\alpha]_D^{20}$ 11.5 (*c* 1.9, EtOH).

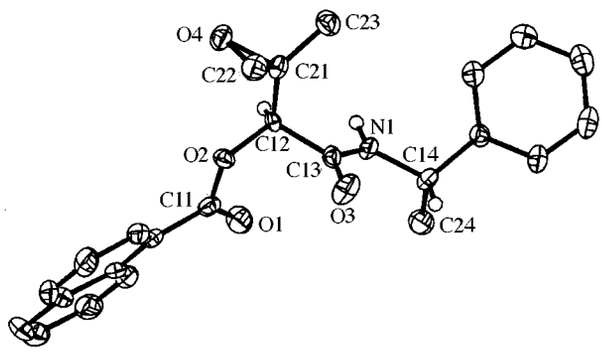
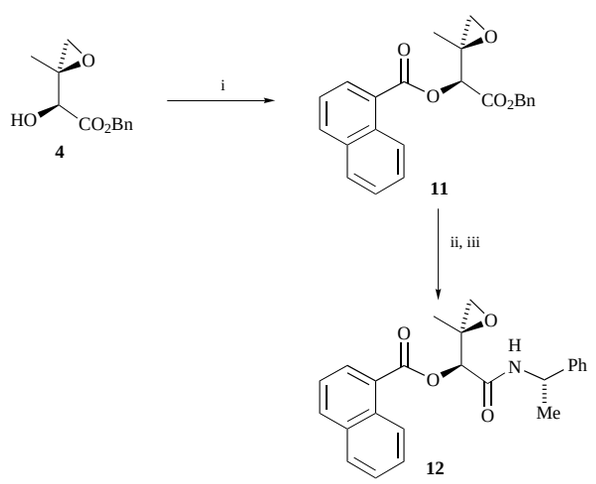


Fig. 1

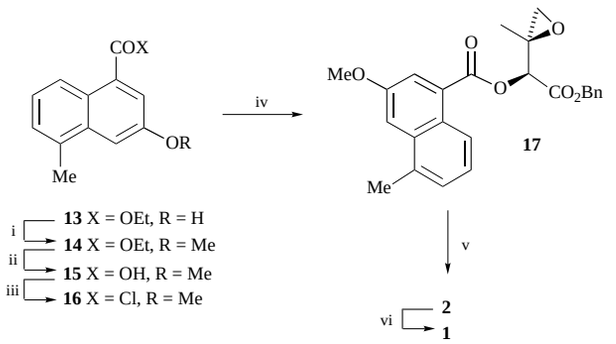


Scheme 3 *Reagents and conditions*: (i) 1-naphthoyl chloride, Et_3N, DMAP, CH_2Cl_2, 0 °C, 91%; (ii) 10% Pd/C, H_2, MeOH; (iii) (*S*)-(−)-α-methylbenzylamine, Et_3N, HOBt, PyBOP, DMF, 72% over two steps

Some further comments concerning the confusion in the literature are justified. We believe the optical rotation data reported by Shibuya and co-workers for epoxy alcohol **4** is incorrect but suggest that the material they prepared did possess the desired (2*S*,3*S*)-stereochemistry. While we are not in a position to speculate about the source of this error, it is pertinent to note that the optical rotation of carboxylic acid **2**, also reported in the same article describing the preparation of epoxy

alcohol **4**, has subsequently been corrected from $[\alpha]_D^{20}$ −15.2 (*c* 0.11, EtOH)[5b] to $[\alpha]_D$ 2.76 (*c* 1.08, EtOH).[5f] Having revised the sign of rotation reported by Shibuya for epoxy alcohol **4**, we suggest that Konda produced the (2*R*,3*R*)-enantiomer of **4** using L-(+)-diethyl tartrate in the SAE reaction and not the (2*S*,3*S*)-enantiomer as reported.[5l] This revision makes this chemistry consistent with the overwhelming majority of literature examples of kinetic resolution reactions employing the SAE reaction.[10] We believe that the results of Coleman should be revised on the same basis.[5r]

To complete the synthesis of epoxy amide **1**, we required the functionalised naphthoyl chloride **16**. This acid chloride was prepared from the known ethyl ester **13**[11] in a straightforward fashion (Scheme 4). Coupling of acid chloride **16** with epoxy



Scheme 4 *Reagents and conditions*: (i) NaH, DMF, MeI, 91%; (ii) MeOH, H_2O, LiOH, 92%; (iii) PCl_5, Et_2O, reflux, 99%; (iv) **4**, Et_3N, DMAP, CH_2Cl_2, 80%; (v) 10% Pd/C, H_2, MeOH; (iii) 35% NH_4OH, Et_3N, HOBt, PyBOP, DMF, 54% over two steps

alcohol **4** furnished ester **17** in 80% yield. Hydrogenation of the benzyl ester gave carboxylic acid **2**, which was converted directly to amide **1** by coupling with ammonium hydroxide. The spectroscopic and physical data for epoxy amide **1** prepared in this fashion are identical with those reported for the material isolated directly from the culture broths of *Streptomyces griseofuscus* S42227.[1b] Above all, the optical rotation of our material, $[\alpha]_D^{20}$ 54.3 (*c* 0.40, MeOH) was in very good agreement with the value reported for the natural material, $[\alpha]_D^{25}$ 48 (*c* 0.33, MeOH).[1b]

In summary, we have devised an efficient synthesis of the left hand portion of the azinomycins from commercially available 3,3-dimethylacrylic acid. Additional studies related to the synthesis and mechanism of action of the azinomycins and related analogues are ongoing and will be disclosed in due course.

Experimental

General

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of nitrogen. Anhydrous solvents were prepared in accordance with standard protocols, or alternatively purchased from Aldrich in Sure/Seal™ bottles. Sodium hydride was purchased as a 60% dispersion in mineral oil which was removed by repeated washing with light petroleum (bp 40–60 °C) prior to use. IR spectra were recorded (4000–600 cm^{-1}) on a Perkin-Elmer Paragon 1000 FT-IR spectrometer or a Nicolet Magna-550 FT-IR spectrometer, all with internal calibration. Spectra were recorded as thin films or Nujol mulls. NMR spectra were recorded on Bruker ACF-300, DPX 400 and DRX 400 spectrometers with either $SiMe_4$ or residual protic solvent as internal reference. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyser. Mass spectra and accurate masses were recorded under EI^+ or CI^+ conditions on a VG Analytical ZAB-E instrument at the EPSRC Mass Spectrometry Centre, University College, Swansea or under EI^+ conditions on a Kratos Profile HV-3 mass spectrometer. Optical rotations were determined on the sodium D-line (598 nm) using a PolAAr 2001 digital polarimeter or an Optical Activity digital polarimeter.

Benzyl 3-methylbut-2-enoate 6

To a stirred solution of 3,3-dimethylacrylic acid (14.04 g, 0.140 mol) and tetra-*n*-butylammonium bromide (3.77 g, 11.7 mmol) in chloroform (100 ml) at room temperature was added potassium hydroxide (8.51 g, 0.152 mol) in water (50 ml) followed by benzyl bromide (13.91 ml, 0.117 mol). The resulting two-phase mixture was heated at reflux for 18 h and, on cooling, water (150 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow liquid. Column chromatography (5% ethyl acetate–light petroleum) and subsequent bulb-to-bulb distillation (bp *ca.* 125 °C at 0.8 mmHg, lit.,[8] bp 106 °C at 0.06 mmHg) gave ester **6** as a colourless liquid (21.90 g, 99%); ν_{max}(thin film)/cm^{-1} 1718 (C=O), 1650 (olefinic C=C), 1498 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.40–7.23 (5H, m, ArH), 5.73 (1H, m, H-2), 5.13 (2H, s, CO_2CH_2Ph), 2.18 (3H, s, CH_3), 1.88 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 166.0 (s, C-1), 156.8 (s, C-3), 136.4 (s, ArC), 128.3 (d, ArCH), 127.9 (d, ArCH), 127.7 (d, ArCH), 115.7 (d, C-2), 65.0 (t, CO_2CH_2Ph), 27.0 (q, CH_3), 20.0 (q, CH_3); *m*/*z* (EI^+) 190 (M^+, 5%), 91 (100) (Found: M^+, 190.0990. $C_{12}H_{14}O_2$ requires 190.0990).

(2*R*)-Benzyl 2,3-dihydroxy-3-methylbutanoate 7

A stirred solution of AD-mix-α (110.52 g), methanesulfonamide (7.50 g, 78.9 mmol) and sodium hydrogen carbonate (19.89 g, 0.237 mol) in *tert*-butyl alcohol (300 ml) and water (300 ml) was prepared at room temperature. The reaction mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. Ester **6** (15.00 g, 78.9 mmol) was added in one portion and the orange heterogeneous slurry stirred at 0 °C for 60 h. Anhydrous sodium sulfite (118.42 g, 0.940 mol) was added at 0 °C and the reaction mixture allowed to warm to room temperature and stirred for 1 h. Ethyl acetate (200 ml) was added to the resulting green–brown mixture and, after separation of the layers, the aqueous phase was further extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were washed with 2 M aqueous potassium hydroxide (150 ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (10% ethyl acetate–light petroleum) provided benzyl alcohol (317 mg, 4%) as a colourless liquid; ν_{max}(thin film)/cm^{-1} 3333 (OH), 1607, 1496 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.25–7.13 (5H, m, ArH), 4.39 (2H, s, CH_2), 4.03 (1H, br s, OH); δ_C(100.6 MHz; $CDCl_3$) 140.7 (s, ArC), 128.1 (d, ArCH), 127.1 (d, ArCH), 126.7 (d, ArCH), 64.3 (t, CH_2). Further elution (30% ethyl acetate–light petroleum) gave a colourless oil which was further purified by bulb-to-bulb distillation (bp *ca.* 200 °C at 1.0 mmHg) to yield diol (2*R*)-**7** as a white crystalline solid (14.12 g, 80%), mp 35.5–37 °C; $[\alpha]_D^{20}$ −10.8 (*c* 1.0, EtOH); ν_{max}(thin film)/cm^{-1} 3461 (OH), 1733 (C=O), 1499 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.41–7.32 (5H, m, ArH), 5.27 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.21 (1H, d, *J* 12.1, CO_2CH_2Ph), 4.00 (1H, d, *J* 6.8, H-2), 3.24 [1H, br d, *J* 6.8, C-2(OH)], 2.61 [1H, br s, C-3(OH)], 1.26 (3H, s, CH_3), 1.17 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 172.7 (s, C-1), 134.9 (s, ArC), 128.5 (d, ArCH), 128.42 (d, ArCH), 128.38 (d, ArCH), 77.3 (d, C-2), 72.1 (s, C-3), 67.2 (t, CO_2CH_2Ph), 25.8 (q, CH_3), 24.8 (q, CH_3); *m*/*z* (CI^+) 242 ($M + NH_4^+$, 3%), 225 (MH^+, 1), 46 (100) (Found: $M + NH_4^+$, 242.1392. $C_{12}H_{20}NO_4$ requires 242.1392).

Determination of enantiomeric purity of (2*R*)-diol 7

To a stirred solution of diol **7** (500 mg, 2.23 mmol), triethylamine (0.47 ml, 3.35 mmol) and 4-dimethylaminopyridine (27.2 mg, 0.223 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere was added 1-naphthoyl chloride (0.35

ml, 2.34 mmol) dropwise. The mixture was stirred at 0 °C for 2 h and then water (50 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a pale brown oil. Column chromatography (5→20% ethyl acetate–light petroleum) provided (2*R*)-benzyl 3-hydroxy-3-methyl-2-(1-naphthoyloxy)butanoate as a colourless oil (750 mg, 89%); $[\alpha]_D^{20}$ 22.9 (*c* 1.0, EtOH); ν_{max}(thin film)/cm^{-1} 3508 (OH), 1721 (C=O), 1594, 1577, 1500 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.85 (1H, d, *J* 8.6, ArH), 8.21 (1H, dd, *J* 7.3, 1.3, ArH), 8.04 (1H, d, *J* 8.0, ArH), 7.88 (1H, dd, *J* 8.0, 1.5, ArH), 7.60–7.47 (3H, m, ArH), 7.37–7.28 (5H, m, ArH), 5.30 (1H, d, *J* 12.3, CO_2CH_2Ph), 5.25 (1H, s, H-2), 5.24 (1H, d, *J* 12.3, CO_2CH_2Ph), 2.67 (1H, br s, OH), 1.40 (3H, s, CH_3), 1.39 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 168.8 (s, C=O), 166.7 (s, C=O), 135.1 (s, ArC), 133.9 (d, ArCH), 133.8 (s, ArC), 131.4 (s, ArC), 130.4 (d, ArCH), 128.63 (d, ArCH), 128.58 (d, ArCH), 128.5 (d, ArCH), 128.4 (d, ArCH), 128.0 (d, ArCH), 126.4 (d, ArCH), 126.3 (s, ArC), 125.7 (d, ArCH), 124.5 (d, ArCH), 79.0 (d, C-2), 71.5 (s, C-3), 67.4 (t, CO_2CH_2Ph), 26.3 (q, CH_3), 26.1 (q, CH_3); *m*/*z* (CI$^+$) 396 (M + NH_4^+, 37%), 379 (MH^+, 13), 224 (100) (Found: MH^+, 379.1545. $C_{23}H_{23}O_5$ requires 379.1545). This ester was found to be ≥95% ee by HPLC analysis using a Chiralcel OD column (10% propan-2-ol–*n*-hexane; 1.0 ml min^{-1}) [t_R 14.3 min (major); 17.3 min (minor)]. The corresponding racemic ester was prepared and used as a standard in this analysis.

(2*R*)-Benzyl 3-hydroxy-2-(methanesulfonyloxy)-3-methylbutanoate 8

To a stirred solution of diol (2*R*)-**7** (14.06 g, 62.8 mmol) and triethylamine (13.10 ml, 94.2 mmol) in dry dichloromethane (100 ml) at 0 °C under a nitrogen atmosphere was added methanesulfonyl chloride (5.10 ml, 65.9 mmol) dropwise. The reaction mixture was stirred at 0 °C for 3 h and then saturated aqueous sodium hydrogen carbonate (100 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 100 ml). The combined organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Column chromatography (10% ethyl acetate–dichloromethane) provided initially (2*R*)-benzyl 2,3-bis-(methanesulfonyloxy)-3-methylbutanoate as a white crystalline solid (1.20 g, 5%), mp 37.5–39.5 °C; $[\alpha]_D^{20}$ 16.5 (*c* 1.0, EtOH); ν_{max}(thin film)/cm^{-1} 1755 (C=O), 1609, 1588, 1499 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.37–7.32 (5H, m, ArH), 5.29 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.26 (1H, s, H-2), 5.21 (1H, d, *J* 12.1, CO_2CH_2Ph), 3.07 (3H, s, OSO_2CH_3), 2.89 (3H, s, OSO_2CH_3), 1.68 (6H, s, 2 × CH_3); δ_C(100.6 MHz; $CDCl_3$) 165.7 (s, C-1), 134.3 (s, ArC), 128.8 (d, ArCH), 128.7 (d, ArCH), 128.6 (d, ArCH), 88.2 (s, C-3), 80.2 (d, C-2), 68.0 (t, CO_2CH_2Ph), 40.3 (q, OSO_2CH_3), 38.7 (q, OSO_2CH_3), 23.9 (q, CH_3), 23.5 (q, CH_3); *m*/*z* (CI$^+$) 398 (M + NH_4^+, 3%), 208 (100) (Found: M + NH_4^+, 398.0943. $C_{14}H_{24}NO_8S_2$ requires 398.0943). Further elution (10% ethyl acetate–dichloromethane) then gave mesylate (2*R*)-**8** as a white crystalline solid (14.97 g, 79%), mp 57.5–59 °C; $[\alpha]_D^{20}$ 21.5 (*c* 1.0, EtOH); ν_{max}(thin film)/cm^{-1} 3529 (OH), 1751 (C=O), 1609, 1588, 1499 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.42–7.27 (5H, m, ArH), 5.30 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.23 (1H, d, *J* 12.1, CO_2CH_2Ph), 4.85 (1H, s, H-2), 3.04 (3H, s, OSO_2CH_3), 2.48 (1H, br s, OH), 1.31 (3H, s, CH_3), 1.30 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 167.4 (s, C-1), 134.6 (s, ArC), 128.74 (d, ArCH), 128.67 (d, ArCH), 128.6 (d, ArCH), 83.0 (d, C-2), 71.5 (s, C-3), 67.8 (t, CO_2CH_2Ph), 38.7 (q, OSO_2CH_3), 25.7 (q, CH_3), 25.4 (q, CH_3); *m*/*z* (CI$^+$) 320 (M + NH_4^+, 10%), 303 (MH^+, 1%), 108 (100) (Found: M + NH_4^+, 320.1168. $C_{13}H_{22}NO_6S$ requires 320.1168).

(2*S*)-Benzyl 2,3-epoxy-3-methylbutanoate 9

A stirred suspension of mesylate (2*R*)-**8** (13.89 g, 46.0 mmol) and anhydrous sodium carbonate (48.75 g, 0.460 mol) in dry acetonitrile (100 ml) was heated at reflux under a nitrogen atmosphere for 48 h. The resulting pale yellow heterogeneous mixture was quenched with water (100 ml) and extracted with dichloromethane (3 × 100 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow liquid. Column chromatography (10% ethyl acetate–light petroleum) gave epoxide (2*S*)-**9** (8.38 g, 88%) as a colourless liquid; $[\alpha]_D^{20}$ 3.54 (*c* 1.2, EtOH); ν_{max}(thin film)/cm^{-1} 1752 (C=O), 1588, 1498 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.39–7.30 (5H, m, ArH), 5.24 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.19 (1H, d, *J* 12.1, CO_2CH_2Ph), 3.36 (1H, s, H-2), 1.40 (3H, s, CH_3), 1.35 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 167.8 (s, C-1), 135.0 (s, ArC), 128.1 (d, ArCH), 128.0 (d, ArCH), 66.3 (t, CO_2CH_2Ph), 59.6 (s, C-3), 58.7 (d, C-2), 23.7 (q, CH_3), 17.7 (q, CH_3); *m*/*z* (CI$^+$) 224 (M + NH_4^+, 100%) (Found: M + NH_4^+, 224.1287. $C_{12}H_{18}NO_3$ requires 224.1287).

(2*S*)-Benzyl 2-hydroxy-3-methylbut-3-enoate 5

A stirred mixture of epoxide (2*S*)-**9** (8.25 g, 40.0 mmol) and (±)-camphor-10-sulfonic acid (1.86 g, 8.02 mmol) in dry toluene (70 ml) was heated at reflux under a nitrogen atmosphere for 4 h. On cooling, the heterogeneous mixture was filtered and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (5% ethyl acetate–light petroleum) gave allylic alcohol (2*S*)-**5** (6.35 g, 77%) as a colourless oil; $[\alpha]_D^{20}$ 71.7 (*c* 1.1, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 3468 (OH), 1738 (C=O), 1652 (olefinic C=C), 1498 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.39–7.28 (5H, m, ArH), 5.23 (1H, d, *J* 12.3, CO_2CH_2Ph), 5.19 (1H, d, *J* 12.3, CO_2CH_2Ph), 5.12 (1H, m, =CH_2), 5.00 (1H, m, =CH_2), 4.61 (1H, s, H-2), 3.28 (1H, br s, OH), 1.70 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 173.1 (s, C-1), 141.7 (s, C-3), 135.1 (s, ArC), 128.4 (d, ArCH), 128.3 (d, ArCH), 128.0 (d, ArCH), 114.9 (t, =CH_2), 74.8 (d, C-2), 67.3 (t, CO_2CH_2Ph), 17.7 (q, CH_3); *m*/*z* (CI$^+$) 224 (M + NH_4^+, 6%), 207 (MH^+, 1), 108 (100) (Found: M + NH_4^+, 224.1287. $C_{12}H_{18}NO_3$ requires 224.1287). Allylic alcohol (2*S*)-**5** was found to be ≥95% ee by HPLC analysis using a Chiralcel OD column (1% propan-2-ol–*n*-hexane; 0.7 ml min^{-1}) [t_R 26.4 min (major); 28.9 min (minor)]. (2*R*)-**5** was prepared and used as a standard in this analysis.

(2*S*,3*S*)-Benzyl 3,4-epoxy-2-hydroxy-3-methylbutanoate 4

(a) Using vanadyl acetylacetonate–*tert*-butyl hydroperoxide. To a stirred solution of allylic alcohol (2*S*)-**5** (500 mg, 2.43 mmol) and vanadyl acetylacetonate (64.3 mg, 0.243 mmol) in dry dichloromethane (30 ml) at −20 °C under a nitrogen atmosphere was added a solution of anhydrous *tert*-butyl hydroperoxide (5–6 M in *n*-decane, 0.97 ml, *ca*. 4.85 mmol) dropwise causing a colour change from dark green to dark brown. The reaction mixture was allowed to warm to 0 °C and stirred for 18 h during which time the colour turned to orange. After quenching with water (50 ml), the organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Azeotropic removal of the excess *tert*-butyl hydroperoxide with toluene (50 ml) gave a yellow oil which was determined to be an 88 : 12 mixture of the (2*S*,3*S*) : (2*S*,3*R*) diastereomers by ^{1}H NMR spectroscopy. Column chromatography (20% ethyl acetate–light petroleum) provided epoxy alcohol (2*S*,3*S*)-**4** as a white crystalline solid (350 mg, 65%) and as a single diastereomer, mp 35–36.5 °C; $[\alpha]_D^{20}$ 11.5 (*c* 1.9, EtOH); ν_{max}(thin film)/cm^{-1} 3468 (OH), 1740 (C=O), 1499 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 7.39–7.28 (5H, m, ArH), 5.27 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.20 (1H, d, *J* 12.1, CO_2CH_2Ph), 4.01 (1H, s, H-2), 3.47 (1H, br s, OH), 2.83 (1H, d, *J* 4.8, H-4), 2.59 (1H, d, *J* 4.8, H-4), 1.28 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 171.8 (s, C-1), 134.9 (s, ArC), 128.55 (d, ArCH), 128.48 (d, ArCH), 128.3 (d, ArCH), 73.8 (d, C-2), 67.4 (t, CO_2CH_2Ph), 56.8 (s, C-3), 51.6 (t, C-4), 17.0 (q, CH_3); *m*/*z* (CI$^+$) 240 (M + NH_4^+, 15%), 223 (MH^+, 1), 74 (100) (Found: C, 64.74; H, 6.11. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%) (Found:

M + NH_4^+, 240.1236. $C_{12}H_{18}NO_4$ requires 240.1236). Chiral shift ^{1}H NMR analysis (400 MHz; $CDCl_3$) was performed using epoxy alcohol (2*S*,3*S*)-**4** (3.1 mg) and (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (20.6 mg). Epoxy alcohol (2*R*,3*R*)-**4** was prepared and used as a standard for comparison purposes in this analysis. Integration of the methyl resonances at δ_H 1.26 [(2*R*,3*R*)] and δ_H 1.25 [(2*S*,3*S*)] revealed an ee ≥95%.

(b) Using titanium(IV) isopropoxide–D-(−)-diethyl tartrate–*tert*-butyl hydroperoxide. To a stirred mixture of allylic alcohol (2*S*)-**5** (5.00 g, 24.3 mmol) and activated 4 Å molecular sieves (2.00 g) in dry dichloromethane (50 ml) at −20 °C under a nitrogen atmosphere was added titanium(IV) isopropoxide (1.07 ml, 3.64 mmol) and D-(−)-diethyl tartrate (900 mg, 4.37 mmol). The reaction mixture was stirred at −20 °C for 40 min, followed by dropwise addition of a solution of anhydrous *tert*-butyl hydroperoxide (5–6 M in *n*-decane, 9.71 ml, *ca*. 48.6 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 18 h. Water (100 ml) was added and the reaction medium was allowed to warm to room temperature whereupon stirring was continued for a further 30 min. The heterogeneous mixture was then filtered through a pad of Celite, the organic layer separated and the aqueous layer extracted with dichloromethane (3 × 100 ml). The combined organic phases were washed rapidly with a solution of 10% sodium hydroxide in brine (5 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Azeotropic removal of the excess *tert*-butyl hydroperoxide with toluene (100 ml) gave a pale yellow oil which was found to be a 96:4 mixture of the (2*S*,3*S*):(2*S*,3*R*) diastereomers by ^{1}H NMR spectroscopy. Column chromatography (20% ethyl acetate–light petroleum) provided epoxy alcohol (2*S*,3*S*)-**4** (4.47 g, 83%) as a white crystalline solid and a single diastereomer; $[\alpha]_D^{20}$ 13.4 (*c* 1.9, EtOH). Spectroscopic data were identical with those described above.

(c) Using titanium(IV) isopropoxide–L-(+)-diethyl tartrate–*tert*-butyl hydroperoxide. To a stirred mixture of allylic alcohol (2*S*)-**5** (500 mg, 2.43 mmol) and activated 4 Å molecular sieves (500 mg) in dry dichloromethane (30 ml) at −20 °C under a nitrogen atmosphere was added titanium(IV) isopropoxide (0.11 ml, 0.364 mmol) and L-(+)-diethyl tartrate (90.0 mg, 0.437 mmol). The reaction mixture was stirred at −20 °C for 40 min, followed by dropwise addition of a solution of anhydrous *tert*-butyl hydroperoxide (5–6 M in *n*-decane, 0.97 ml, *ca*. 4.85 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 36 h. Water (50 ml) was added and the reaction medium was allowed to warm to room temperature whereupon stirring was continued for a further 30 min. Work-up and purification as described in (b) above gave epoxy alcohol (2*S*,3*S*)-**4** (270 mg, 50%) as a white crystalline solid after purification. ^{1}H NMR spectroscopy prior to column chromatography determined that the crude product consisted of an 87:13 mixture of the (2*S*,3*S*):(2*S*,3*R*) diastereomers. Spectroscopic data were identical with those described above.

(d) Using titanium(IV) isopropoxide–*tert*-butyl hydroperoxide. To a stirred mixture of allylic alcohol (2*S*)-**5** (500 mg, 2.43 mmol) and activated 4 Å molecular sieves (500 mg) in dry dichloromethane (30 ml) at −20 °C under a nitrogen atmosphere was added titanium(IV) isopropoxide (0.11 ml, 0.364 mmol). The reaction mixture was stirred at −20 °C for 40 min, followed by dropwise addition of a solution of anhydrous *tert*-butyl hydroperoxide (5–6 M in *n*-decane, 0.97 ml, *ca*. 4.85 mmol). The reaction mixture was allowed to warm to 0 °C and stirred for 24 h. Water (50 ml) was added and the reaction medium was allowed to warm to room temperature whereupon stirring was continued for a further 30 min. The heterogeneous mixture was then filtered through a pad of Celite and the organic layer separated. The aqueous layer was extracted with dichloromethane (3 × 100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. Azeotropic removal of the excess *tert*-butyl hydroperoxide with toluene (50 ml) gave a pale yellow oil which was found to be a 87:13 mixture of the (2*S*,3*S*):(2*S*,3*R*) diastereomers by ^{1}H NMR spectroscopy. Column chromatography (20% ethyl acetate–light petroleum) provided epoxy alcohol (2*S*,3*S*)-**4** (273 mg, 51%) as a white crystalline solid and a single diastereomer. Spectroscopic data were identical with those described above.

(2*S*,3*S*)-Benzyl 3,4-epoxy-3-methyl-2-(1-naphthoyloxy)-butanoate 11

To a stirred solution of epoxy alcohol (2*S*,3*S*)-**4** (1.00 g, 4.50 mmol), triethylamine (0.94 ml, 6.76 mmol) and 4-dimethylaminopyridine (55.0 mg, 0.451 mmol) in dry dichloromethane (30 ml) at 0 °C under a nitrogen atmosphere was added 1-naphthoyl chloride (0.71 ml, 4.73 mmol) dropwise. The reaction mixture was stirred at 0 °C for 2 h then water (100 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Column chromatography (20% ethyl acetate–light petroleum) provided epoxy ester (2*S*,3*S*)-**11** as a colourless oil (1.53 g, 91%); $[\alpha]_D^{20}$ −11.7 (*c* 1.1, EtOH); ν_{max}(thin film)/cm^{-1} 1752 (C=O), 1722 (C=O), 1594, 1576, 1499 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.91 (1H, d, *J* 8.5, ArH), 8.25 (1H, dd, *J* 7.3, 1.3, ArH), 7.92 (1H, d, *J* 8.0, ArH), 7.77 (1H, d, *J* 8.0, ArH), 7.53 (1H, m, ArH), 7.46–7.33 (4H, m, ArH), 7.29–7.22 (3H, m, ArH), 5.30 (1H, d, *J* 12.1, CO_2CH_2Ph), 5.29 (1H, s, H-2), 5.21 (1H, d, *J* 12.1, CO_2CH_2Ph), 2.94 (1H, d, *J* 4.8, H-4), 2.61 (1H, d, *J* 4.8, H-4), 1.44 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 167.3 (s, C=O), 166.0 (s, C=O), 134.9 (s, ArC), 133.9 (d, ArCH), 133.5 (s, ArC), 131.2 (s, ArC), 130.6 (d, ArCH), 128.39 (d, ArCH), 128.36 (d, ArCH), 128.2 (d, ArCH), 128.1 (d, ArCH), 127.8 (d, ArCH), 126.2 (d, ArCH), 125.5 (s, ArC), 125.4 (d, ArCH), 124.3 (d, ArCH), 75.2 (d, C-2), 67.2 (t, CO_2CH_2Ph), 55.0 (s, C-3), 51.7 (t, C-4), 17.8 (q, CH_3); *m*/*z* (CI^+) 394 (M + NH_4^+, 10%), 377 (MH^+, 15), 116 (100) (Found: MH^+, 377.1389. $C_{23}H_{21}O_5$ requires 377.1389).

(1*S*)-*N*-(1-Phenylethyl)-(2*S*,3*S*)-3,4-epoxy-2-(1-naphthoyloxy)-butanamide 12

To a stirred solution of epoxy ester (2*S*,3*S*)-**11** (618 mg, 1.64 mmol) in dry methanol (50 ml) was added 10% palladium on carbon (92.7 mg, 15% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 2 h at room temperature. The black heterogeneous reaction mixture was filtered through a pad of Celite and the filtrate concentrated *in vacuo* to give a colourless oil (427 mg) which was then dissolved in dry *N*,*N*-dimethylformamide (50 ml). To this stirred solution at 0 °C was successively added (*S*)-(−)-α-methylbenzylamine (0.24 ml, 1.85 mmol), triethylamine (0.50 ml, 3.62 mmol), 1-hydroxybenzotriazole (250 mg, 1.85 mmol) and PyBOP (962 mg, 1.85 mmol). After the mixture had been warmed to room temperature and stirred for 18 h, toluene (25 ml) and ethyl acetate (50 ml) were added. The resulting solution was successively washed with 5% hydrochloric acid (50 ml), water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a brown semi-solid. Column chromatography (30% ethyl acetate–light petroleum) provided amide (1′*S*,2*S*,3*S*)-**12** as a white solid (461 mg, 72%) which was crystallised (ethyl acetate–*n*-hexane) to give white needles, mp 127.5–129.5 °C; $[\alpha]_D^{20}$ −36.6 (*c* 1.0, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3290 (NH), 1724 (ester C=O), 1653 (amide C=O), 1593, 1585, 1495 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.89 (1H, dd, *J* 8.8, 0.9, ArH), 8.26 (1H, dd, *J* 7.2, 1.3, ArH), 8.03 (1H, d, *J* 8.2, ArH), 7.87 (1H, dd, *J* 8.1, 1.4, ArH), 7.61–7.46 (3H, m, ArH), 7.33–7.20 (5H, m, ArH), 6.46 (1H, br d, *J* 8.0, NH), 5.19 [1H, m, NHC*H*(CH_3)Ph], 5.19 (1H, s, H-2), 3.02 (1H, d, *J* 4.5, H-4), 2.77 (1H, d, *J* 4.5, H-4), 1.52 [3H, d, *J* 7.0, NHCH(CH_3)Ph], 1.44 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 166.0 (s, C=O), 165.8 (s, C=O), 143.0 (s, ArC), 134.0 (d, ArCH), 133.8 (s, ArC), 131.4 (s, ArC), 130.7 (d, ArCH), 128.7 (d, ArCH), 128.6 (d, ArCH), 128.1 (d, ArCH),

127.4 (d, ArCH), 126.4 (d, ArCH), 126.1 (s, ArC), 126.0 (d, ArCH), 125.7 (d, ArCH), 124.5 (d, ArCH), 76.2 (d, C-2), 56.1 (s, C-3), 53.5 (t, C-4), 49.0 [d, NH*C*H(CH_3)Ph], 22.1 [q, NHCH(*C*H_3)Ph], 17.6 (q, CH_3); *m/z* (CI^+) 390 (MH^+, 100%) (Found: C, 74.33; H, 5.91%; N, 3.70%. $C_{24}H_{23}NO_4$ requires C, 74.02%; H, 5.95; N, 3.60%) (Found: MH^+, 390.1705. $C_{24}H_{24}NO_4$ requires 390.1705).

X-Ray crystallographic data for (1′*S*,2*S*,3*S*)-12

Crystal data for $C_{24}H_{23}NO_4$, *M*r = 389.43, orthorhombic, space group $P2_12_12_1$, $a = 4.7091(12)$, $b = 11.712(3)$, $c = 36.709(8)$ Å, $V = 2024.6(9)$ Å^3, $Z = 4$, $D_c = 1.278$ Mg m^{-3}, μ(Mo-Kα) = 0.087 mm^{-1}, $F(000) = 824$, $T = 150(2)$ K, crystal size 0.30 × 0.08 × 0.06 mm. All crystallographic measurements were made on a Delft Instruments FAST area detector diffractometer positioned at the window of a rotating anode generator with Mo-Kα radiation ($\lambda = 0.710\,69$ Å) by following procedures described elsewhere.[12] The cell parameters were determined by least-squares refinement of diffractometer angles for 250 reflections within $1.83 \leqslant \theta \leqslant 25.02°$. The data were corrected for Lorentz and polarisation factors but not for absorption. The structure was solved by direct methods (SHELXS86)[13] and refined by full-matrix least-squares on F^2 using all unique data with intensities greater than 0 (SHELXL93).[14] The non-hydrogen atoms were all anisotropic. The hydrogen atoms were included in calculated positions (riding model). Final R_1 and wR_2 values are 0.0443 [1497 data with $I > 2\sigma(I)$] and 0.0987 (all 3071 data, 264 parameters) respectively. The diagram was drawn using SNOOPI.[15] Sources of scattering factor data are given in reference 14. The calculations were done on a 200 MHz personal computer. The detailed crystallographic results for this study have been deposited with the Cambridge Crystallographic Data Centre and are available on request.

Ethyl 3-methoxy-5-methyl-1-naphthoate 14

To a stirred solution of ethyl 3-hydroxy-5-methyl-1-naphthoate **13**[11] (5.38 g, 23.4 mmol) in dry *N*,*N*-dimethylformamide (70 ml) at room temperature under a nitrogen atmosphere was added sodium hydride (730 mg, 30.4 mmol) which resulted in the solution turning green. The mixture was stirred for 30 min and then methyl iodide (2.91 ml, 46.7 mmol) was added causing a further colour change to red–brown. After stirring for a further 30 min, the reaction mixture was quenched with water (70 ml) and extracted with ethyl acetate (3 × 70 ml). The combined organic extracts were washed with water (5 × 70 ml), dried (Na_2SO_4) and concentrated *in vacuo* to provide a dark brown semi-solid. Column chromatography (2% ethyl acetate–light petroleum) provided ester **14** (5.21 g, 91%) as a white crystalline solid, mp 74.5–77 °C; ν_{max}(Nujol)/cm^{-1} 1711 (C=O), 1601, 1576, 1510 (aromatic C=C); δ_H(300 MHz; $CDCl_3$) 8.61 (1H, m, ArH), 7.80 (1H, d, *J* 2.6, ArH), 7.41 (1H, d, *J* 2.6, ArH), 7.36–7.30 (2H, m, ArH), 4.45 (2H, q, *J* 7.0, $CO_2CH_2CH_3$), 3.94 (3H, s, OCH_3), 2.64 (3H, s, Ar-CH_3), 1.44 (3H, t, *J* 7.0, $CO_2CH_2CH_3$); δ_C(75.5 MHz; $CDCl_3$) 167.5 (s, C=O), 156.0 (s, ArC), 134.4 (s, ArC), 133.1 (s, ArC), 130.0 (s, ArC), 127.6 (d, ArCH), 126.9 (s, ArC), 124.8 (d, ArCH), 124.0 (d, ArCH), 121.4 (d, ArCH), 107.7 (d, ArCH), 61.2 (t, $CO_2CH_2CH_3$), 55.5 (q, OCH_3), 20.1 (q, Ar-*C*H_3), 14.4 (q, $CO_2CH_2CH_3$); *m/z* (CI^+) 262 (M + NH_4^+, 100%), 245 (MH^+, 16) (Found: C, 74.10; H, 6.97%. $C_{15}H_{16}O_3$ requires C, 73.75; H, 6.60%) (Found: MH^+, 245.1178. $C_{15}H_{17}O_3$ requires 245.1178).

3-Methoxy-5-methyl-1-naphthoic acid 15

To a stirred solution of ester **14** (5.10 g, 20.9 mmol) in a mixture of methanol (150 ml) and water (30 ml) at room temperature was added lithium hydroxide (4.39 g, 0.105 mol) and the reaction mixture stirred for 18 h. Ethyl acetate (100 ml) was added and the organic phase separated. The aqueous layer was acidified to pH 1 with 2 M aqueous hydrochloric acid and extracted with ethyl acetate (3 × 70 ml). The combined organic layers were washed with brine (100 ml), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting pale yellow solid was washed with *n*-hexane (100 ml) to give acid **15** (4.16 g, 92%) as a white crystalline solid, mp 180–183 °C (lit.,[16] mp 179–180 °C), which was used without further purification; ν_{max}(Nujol)/cm^{-1} 3400–2400 (OH), 1682 (C=O), 1601, 1512 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 11.75 (1H, br s, OH), 8.81 (1H, d, *J* 7.8, ArH), 8.05 (1H, d, *J* 1.5, ArH), 7.54 (1H, s, ArH), 7.41–7.37 (2H, m, ArH), 3.99 (3H, s, OCH_3), 2.69 (3H, s, Ar-CH_3); δ_C(100.6 MHz; $CDCl_3$) 172.8 (s, C=O), 156.0 (s, Ar-C), 134.6 (s, ArC), 133.3 (s, ArC), 127.9 (s, ArC), 127.8 (d, ArCH), 127.2 (s, ArC), 125.3 (d, ArCH), 124.1 (d, ArCH), 122.8 (d, ArCH), 109.5 (d, ArCH), 55.7 (q, OCH_3), 20.2 (q, Ar-*C*H_3). Spectroscopic data were in accordance with the reported values of Onda *et al.*[16]

3-Methoxy-5-methyl-1-naphthoyl chloride 16

To a stirred solution of acid **15** (4.10 g, 19.0 mmol) in dry diethyl ether (50 ml) at room temperature under a nitrogen atmosphere was added phosphorus pentachloride (3.96 g, 19.0 mmol) and the reaction mixture was heated at reflux for 2 h. Concentration *in vacuo* provided acid chloride **16** (4.41 g, 99%) as a yellow solid, mp 93–96 °C, which was used without further purification; ν_{max}(Nujol)/cm^{-1} 1751 (C=O), 1599, 1582, 1506 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.44 (1H, dd, *J* 8.2, 1.5, ArH), 8.16 (1H, d, *J* 2.6, ArH), 7.52 (1H, d, *J* 2.2, ArH), 7.41–7.35 (2H, m, ArH), 3.97 (3H, s, OCH_3), 2.65 (3H, s, Ar-CH_3); δ_C(100.6 MHz; $CDCl_3$) 167.4 (s, C=O), 155.7 (s, ArC), 134.4 (s, ArC), 133.6 (s, ArC), 131.8 (s, ArC), 128.3 (d, ArCH), 126.5 (d, ArCH), 126.2 (s, ArC), 126.0 (d, ArCH), 123.2 (d, ArCH), 110.7 (d, ArCH), 55.8 (q, OCH_3), 20.2 (q, Ar-*C*H_3); *m/z* (EI^+) 236 [M^+(^{37}Cl), 26%], 234 [M^+(^{35}Cl), 54], 199 (100) (Found: M^+, 234.0451. $C_{13}H_{11}ClO_2$ requires 234.0448).

(2*S*,3*S*)-Benzyl 3,4-epoxy-2-(3-methoxy-5-methyl-1-naphthoyloxy)-3-methylbutanoate 17

To a stirred solution of epoxy alcohol (2*S*,3*S*)-**4** (1.00 g, 4.50 mmol), triethylamine (0.94 ml, 6.76 mmol) and 4-dimethylaminopyridine (55.0 mg, 0.451 mmol) in dry dichloromethane (20 ml) at 0 °C under a nitrogen atmosphere was added a solution of acid chloride **16** (1.11 g, 4.73 mmol) in dry dichloromethane (20 ml) dropwise. The reaction mixture was stirred at 0 °C for 4 h and then water (100 ml) was added. The organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 50 ml). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. Column chromatography (20% ethyl acetate–light petroleum) provided epoxy ester (2*S*,3*S*)-**17** as a colourless oil (1.52 g, 80%); $[\alpha]_D^{20}$ −6.71 (*c* 0.16, EtOH) (lit.,[5b] $[\alpha]_D^{20}$ −12.3 (*c* 0.16, EtOH); ν_{max}(thin film)/cm^{-1} 1753 (C=O), 1728 (C=O), 1603, 1501 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.58 (1H, m, ArH), 7.89 (1H, d, *J* 2.6, ArH), 7.46 (1H, d, *J* 2.5, ArH), 7.40–7.37 (2H, m, ArH), 7.36–7.28 (5H, m, ArH), 5.33 (1H, d, *J* 12.3, CO_2CH_2Ph), 5.25 (1H, d, *J* 12.3, CO_2CH_2Ph), 5.24 (1H, s, H-2), 3.94 (3H, s, OCH_3), 2.98 (1H, d, *J* 4.7, H-4), 2.69 (1H, d, *J* 4.7, H-4), 2.65 (3H, s, Ar-CH_3), 1.46 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 167.4 (s, C=O), 166.1 (s, C=O), 155.9 (s, ArC), 135.1 (s, ArC), 134.4 (s, ArC), 133.2 (s, ArC), 128.7 (d, ArCH), 128.5 (d, ArCH), 128.3 (d, ArCH), 128.2 (s, ArC), 127.8 (d, ArCH), 126.9 (s, ArC), 125.2 (d, ArCH), 123.8 (d, ArCH), 122.1 (d, ArCH), 108.5 (d, ArCH), 75.5 (d, C-2), 67.5 (t, CO_2CH_2Ph), 55.6 (q, OCH_3), 55.3 (s, C-3), 52.0 (t, C-4), 20.1 (q), 18.0 (q). Spectroscopic data were in accordance with the reported values of Shibuya *et al.*[5b]

(2*S*,3*S*)-3,4-Epoxy-2-(3-methoxy-5-methyl-1-naphthoyloxy)-3-methylbutanamide 1

To a stirred solution of epoxy ester (2*S*,3*S*)-**17** (355 mg, 0.845 mmol) in dry methanol (50 ml) was added 10% palladium on carbon (53.3 mg, 15% w/w) and the suspension stirred under a hydrogen atmosphere (1 atm) for 2 h at room temperature. The

black heterogeneous reaction mixture was filtered through a pad of Celite and the filtrate concentrated *in vacuo* to give crude carboxylic acid **2** as a colourless oil (269 mg) which was then dissolved in dry *N*,*N*-dimethylformamide (50 ml). To this stirred solution at 0 °C was successively added 35% aqueous ammonia (0.10 ml, 2.06 mmol), triethylamine (0.26 ml, 1.86 mmol), 1-hydroxybenzotriazole (128 mg, 0.948 mmol) and PyBOP (494 mg, 0.950 mmol). After the mixture had been warmed to room temperature and stirred for 18 h, toluene (25 ml) and ethyl acetate (50 ml) were added. The resulting solution was successively washed with 5% hydrochloric acid (50 ml), water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow–brown semi-solid. Column chromatography (50% ethyl acetate–light petroleum) provided epoxy amide (2*S*,3*S*)-**1** as a white crystalline solid (150 mg, 54%); mp 148–150.5 °C (lit.,[1b,5f] mp 153–154 °C); $[\alpha]_D^{20}$ 54.3 (*c* 0.40, MeOH) [lit.,[1b] $[\alpha]_D^{25}$ 48 (*c* 0.33, MeOH); lit.,[5a] $[\alpha]_D^{23}$ 47.5 (*c* 0.32, MeOH); lit.,[5f] $[\alpha]_D^{20}$ 45.2 (*c* 0.31, MeOH)]; ν_{max}(Nujol)/cm^{-1} 3449 (NH), 3300 (NH), 1726 (ester C=O), 1672 (amide C=O), 1603, 1578, 1510 (aromatic C=C); δ_H(400 MHz; $CDCl_3$) 8.62 (1H, m, ArH), 7.89 (1H, d, *J* 2.6, ArH), 7.44 (1H, d, *J* 2.5, ArH), 7.36–7.32 (2H, m, ArH), 6.26 (1H, br s, NH), 6.14 (1H, br s, NH), 5.21 (1H, s, H-2), 3.95 (3H, s, OCH_3), 3.00 (1H, d, *J* 4.5, H-4), 2.77 (1H, d, *J* 4.5, H-4), 2.65 (3H, s, Ar-CH_3), 1.54 (3H, s, CH_3); δ_C(100.6 MHz; $CDCl_3$) 169.1 (s, C=O), 165.6 (s, C=O), 155.9 (s, ArC), 134.4 (s, ArC), 133.2 (s, ArC), 128.1 (s, ArC), 127.8 (d, ArCH), 126.9 (s, ArC), 125.2 (d, ArCH), 123.8 (d, ArCH), 122.1 (d, ArCH), 108.4 (d, ArCH), 75.9 (d, C-2), 55.9 (s, C-3), 55.6 (q, OCH_3), 53.2 (t, C-4), 20.1 (q), 17.7 (q). Spectroscopic data were in accordance with the reported values of Yokoi *et al.*[1b]

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