Asymmetric synthesis of the northern segment of ephedradine C

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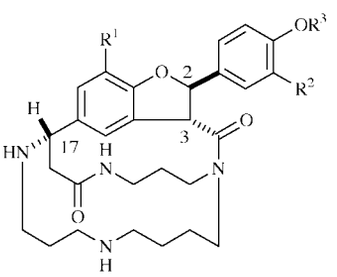
An asymmetric synthesis of the dihydrobenzofuran segment of ephedradine C has been achieved. Key steps include a chiral oxazolidinone-mediated aldol reaction to form a β-hydroxy ester, followed by a novel debenzylation and concomitant intramolecular cyclisation with iodotrimethylsilane. An asymmetric Michael reaction with a homochiral lithium amide was used to form the third and final chiral centre. The absolute stereochemistry of these three centres was confirmed by X-ray crystal-structure determinations.

Introduction

The ephedradines A, B, C and D (**1**–**4**) are components of the



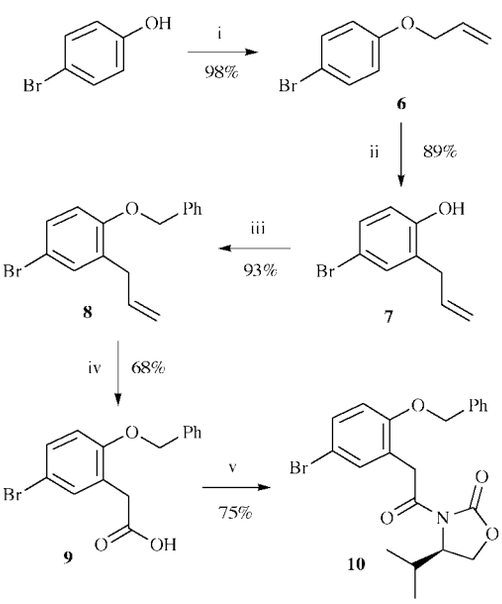
1: $R^1 = R^2 = R^3 = H$
2: $R^1 = R^3 = H$, $R^2 = OMe$
3: $R^1 = H$, $R^2 = OMe$, $R^3 = Me$
4: $R^1 = OMe$, $R^2 = R^3 = H$
5: $R^1 = R^2 = H$, $R^3 = Me$

crude drug 'mao-kon,' which is prepared from the underground parts of *Ephedra* plants, and has been used as an antiperspirant in Oriental medicine. They were all first isolated by Hikino and co-workers,[1–4] who established their structures by a combination of spectroscopic studies and a single-crystal X-ray analysis on the dihydrobromide salt of ephedradine A. They also demonstrated their ability to produce hypotension in rats.[5] The structures are characterised by a highly substituted dihydrobenzofuran nucleus which bridges a seventeen-membered lactam ring containing a spermine unit, with the absolute configuration at the three chiral centres being assigned as 2*R*,3*R*,17*S*. To date no total synthesis of any of the ephedradines has been published, although Wasserman *et al.*[6] have communicated a racemic synthesis of the related *O*-methylorantine **5**. Ephedradine C **3** was selected as the initial target and here we expand on our recent communication[7] of the first asymmetric synthesis of the suitably functionalised dihydrobenzo[*b*]furan segment with all three chiral centres in place.

Results and discussion

The enantiospecific synthesis of a dihydrobenzofuran, unsubstituted at the C-5 position, by the use of Evans aldol methodology[8] has been previously communicated.[9] However, early studies aimed at introducing suitable functionality at the C-5 position, such as acetals, silyl-protected alcohols and α,β-unsaturated esters, failed completely during the diastereoselective aldol reaction, with some decomposition of the ring substituent usually seen. Gratifyingly, the incorporation of a versatile bromine substituent could be successfully accomplished.

The required homochiral oxazolidinone **10** was readily prepared in five steps from 4-bromophenol (Scheme 1). Thus,



Scheme 1 *Reagents and conditions*: (i) allyl bromide, K_2CO_3, DMF, rt, 16 h; (ii) 223–230 °C, 2 h; (iii) $PhCH_2Br$, K_2CO_3, DMF, rt, 2.5 h; (iv) H_5IO_6, $RuCl_3 \cdot 3H_2O$, MeCN–CCl_4–water, rt, 16 h; (v) (a) Me_3CCOCl, Et_3N, Et_2O, −78 to 0 °C, 1 h; (b) (4*R*)-4-isopropyloxazolidin-2-one, BuLi, THF, −78 to 0 °C, 45 min.

4-bromophenol was alkylated with allyl bromide and potassium carbonate in a modification of a literature procedure,[10] in which DMF was used instead of acetone as the solvent, to give an almost quantitative yield of 1-allyloxy-4-bromobenzene **6**. This was followed by a Claisen rearrangement, brought about by heating at 230 °C for 2 h,[11] to give 2-allyl-4-bromophenol **7** in good yield. It was apparently important that purified ether **6** be used for this transformation to avoid its exothermic polymerisation on heating. An alternative method reported[12] for the Claisen rearrangement of this particular compound, using trifluoroacetic acid at room temperature, failed to produce a

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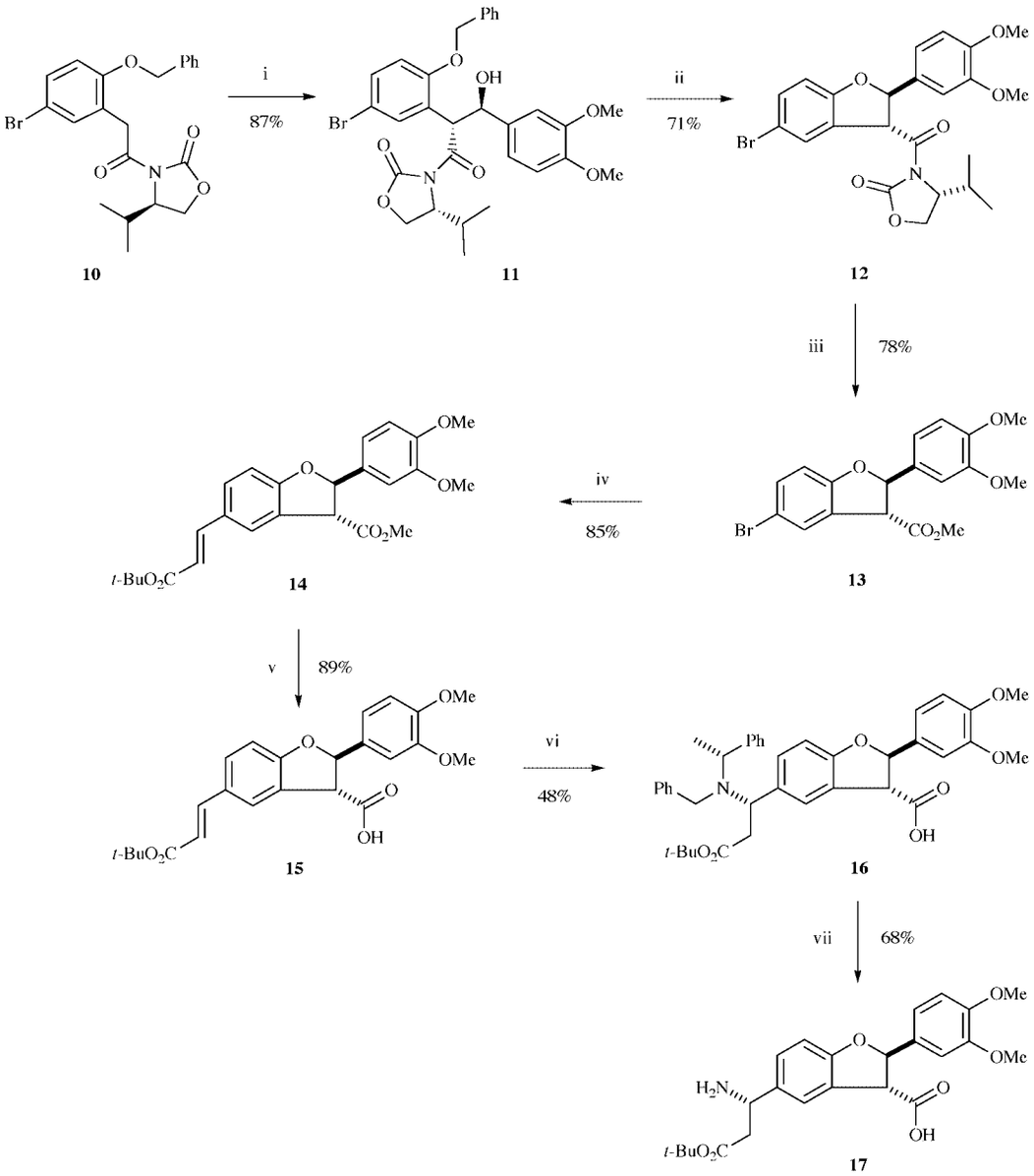


Scheme 2 *Reagents and conditions*: (i) (a) 9-BBN triflate, Pr^i_2NEt, CH_2Cl_2, 0 °C, 1 h; (b) 3,4-dimethoxybenzaldehyde, −78 °C to rt, 3 h; (ii) Me_3SiI, CH_2Cl_2, rt, 1 h; (iii) NaOMe, MeOH, 0 °C, 2 h; (iv) CH_2=$CHCO_2Bu^t$, Et_3N, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, sealed tube, 100 °C, 16 h; (v) $Ba(OH)_2 \cdot 8H_2O$, THF–MeOH, rt, 1 h; (vi) BuLi, (*R*)-(+)-*N*-benzyl-1-phenylethylamine, THF, −78 °C, 2 h; (vii) H_2, $Pd(OH)_2$ on C, MeOH–water–AcOH, 2 h.

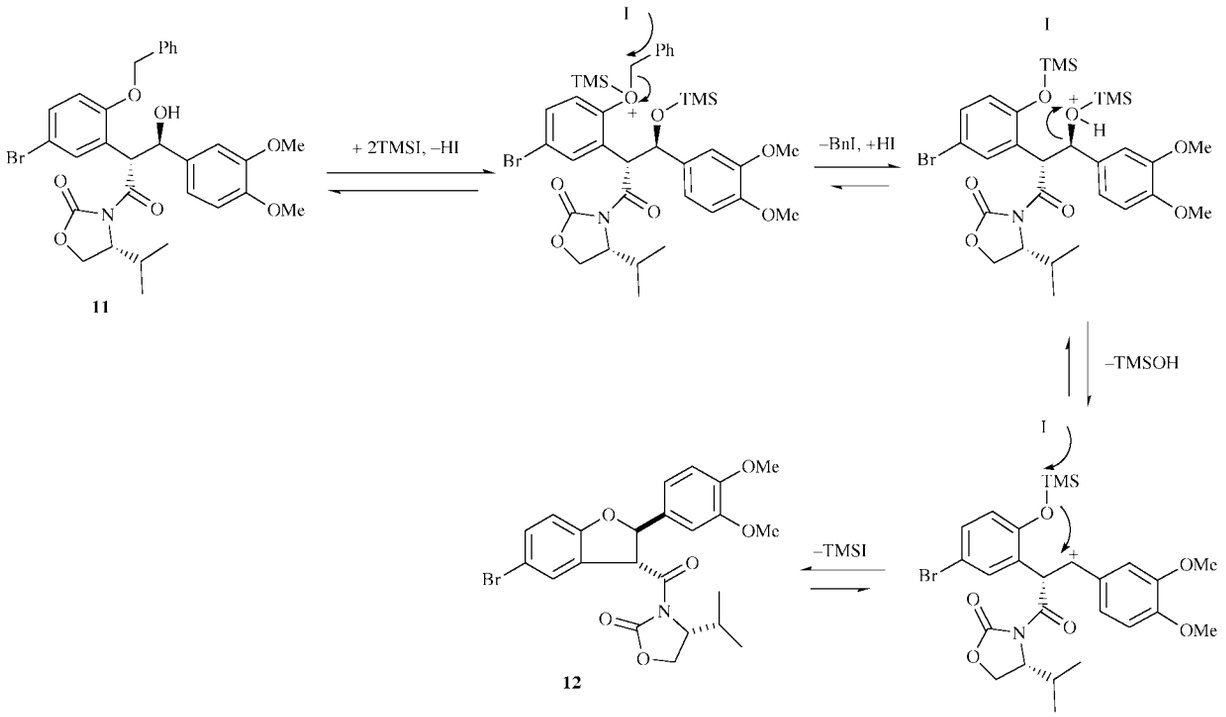
reaction in our hands. The phenolic group was then protected with benzyl bromide and potassium carbonate, using a similar modification to a literature[13] procedure as described above for **6**, to furnish 2-allyl-1-(benzyloxy)-4-bromobenzene **8**.

It was now required to oxidatively cleave the double bond of the allyl moiety in **8**. Although ozonolysis was considered, it was decided to utilise the method of Sharpless and co-workers,[14] which involved treating the alkene **8** in carbon tetrachloride–acetonitrile–water with sodium periodate (8 mole equiv.) and a catalytic quantity of ruthenium(III) chloride to give acid **9**. On larger scales, however, it was found to be more convenient to use periodic acid instead of sodium periodate, a modification described in a footnote by Chong and Sharpless,[15] which gave similar yields.

The acid **9** was coupled with the lithium salt of (4*R*)-4-isopropyloxazolidin-2-one by activating the acid with pivaloyl chloride to give the homochiral imide **10**. It did not matter to the yield whether the usual 2.3 mole equiv. of the lithio oxazolidinone were used or only 1.05 mole equiv. Lithium chloride was also tried instead of butyllithium, as described by Ho and Mathre,[16] but none of the desired product was obtained.

The diastereoselective aldol reaction, using freshly prepared[17] 9-borabicyclo[3.3.1]nonane (9-BBN) triflate, then proceeded in high yield to give the expected *erythro* isomer **11** (Scheme 2), with no trace of other diastereomers as determined by ^{1}H NMR. As expected, the usual hydrogenolysis,[9] using Pd on C, of **11** followed by treatment with boron trifluoride–diethyl ether complex, led to the debrominated dihydrobenzofuran. However, treatment of **11** with iodotrimethylsilane (2.2 mole equiv.) led not only to debenzylation but also to concomitant intramolecular cyclisation to give the required *trans*-dihydrobenzofuran **12** as a single diastereomer in good yield. As far as can be ascertained, this is a novel method of dihydrobenzofuran ring formation. It should be noted that no significant dihydrobenzofuran product is seen with only 1.2 mole equiv. of iodotrimethylsilane, but an intermediate product with lower R_f-value is observed on TLC, which presumably is debenzylated material.

We postulate that the mechanism involves the attachment of two TMS groups to the oxygen atoms of the hydroxy group and the benzyl ether of **11** with the release of HI and iodide (Scheme 3). The latter then facilitates the cleavage of the



Scheme 3

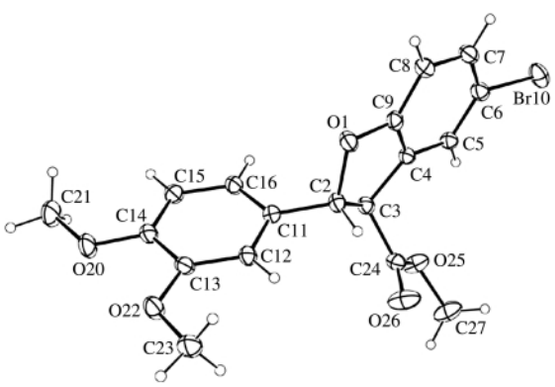


Fig. 1 ORTEP drawing of compound **13** with crystallographic numbering scheme.

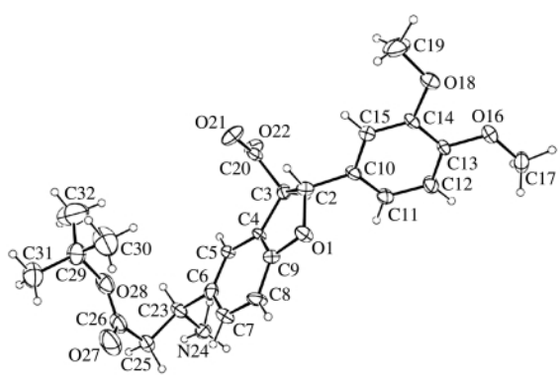


Fig. 2 ORTEP drawing of compound **17** with crystallographic numbering scheme.

benzyl group, forming benzyl iodide, whilst the HI protonates the TMS ether, promoting the loss of trimethylsilanol to give a resonance-stabilised carbocation. Ring closure now occurs with attack on the cation by the TMS ether, aided by the residual iodide ion, to form TMSI and only the thermodynamically more stable *trans*-dihydrobenzofuran **12**.

The oxazolidinone **12** was subsequently converted into the methyl ester **13** with sodium methoxide in methanol. It was only at this stage that suitable crystals could be obtained for X-ray crystal-structure determination. Fortunately, the presence of the heavy bromine atom enabled the absolute configuration to be determined. This was found to have the expected (2*R*,3*R*) configuration, as found in the natural product (Fig. 1).

Heck reaction[18] of **13** with *tert*-butyl acrylate gave the desired functionalised dihydrobenzofuran **14**. Optimum yields were obtained when 3 mole equiv. of acrylate and triethylamine were used and the reaction was performed in a sealed tube in the absence of solvent. Since the dihydrobenzofuran is sensitive to base-promoted ring opening, the methyl ester was hydrolysed to the acid **15** using the mild conditions of barium hydroxide in THF–MeOH.[6]

Asymmetric addition of the homochiral lithium amide of (*R*)-*N*-benzyl-1-phenylethylamine (4 mole equiv.) to the α,β-unsaturated ester **15** gave the β-amino ester **16**. Despite the fact that the free acid was used, ring opening of the dihydrobenzofuran gave the major by-product of this reaction. Reverse addition of the lithium amide to the acid did not improve yields.

Debenzylation of adduct **16** using Pd on C in acetic acid, or with $Pd(OH)_2$ on C in ethanol, led to low yields of deprotected material. However, the use of $Pd(OH)_2$ on C in a three-solvent system[19] gave good yields of deprotected amine **17**, although longer reaction times led to significant cleavage of the dihydrobenzofuran ring. The diastereoselectivity of the Michael addition was confirmed to be >98% by perfoming the reaction of **15** with the (*S*)-enantiomer of the lithium amide and deprotecting as described above. It was found by NMR that no visible trace of the other diastereomer was present in **17**.

The expected relative stereochemistry of **17** was confirmed by a single-crystal X-ray analysis (Fig. 2). Since compound **13** was found to possess the (2*R*,3*R*) configuration, then this means that the absolute configuration of **17** is (2*R*,3*R*,17*S*). Therefore, compound **17** contains all three chiral centres found in ephedradine C, and is suitably functionalised to allow the completion of the synthesis through introduction of the spermidine unit. This may be achievable by utilising similar chemistry to that of Wasserman *et al.*[6] who had an analogous intermediate in the synthesis of (±)-*O*-methylorantine.

Experimental

Mps were obtained on a Reichert Thermovar hot stage and are uncorrected. Proton and carbon NMR spectra were obtained using either a Bruker AM360 or a Bruker AC250 or a Bruker DPX400 spectrometer. *J*-Values are given in hertz. Mass spectra were recorded on a Quattro 1 operating in an electrospray (ES) mode. IR spectra were recorded on a Nicolet 205 FT-IR spectrometer, for samples either as thin films between sodium chloride discs or in potassium bromide discs. (Note that only the strongest peaks from the mass spectra and IR spectra are reported below.) Optical rotations were obtained at 22 °C using a Perkin-Elmer 241 polarimeter. $[\alpha]_D$-Values are given in 10^{-1} deg cm^2 g^{-1}. Elemental analysis for carbon, hydrogen, and nitrogen was performed by Butterworth Laboratories Ltd. Analytical TLC was conducted either on precoated silica gel 60 F_{254} plates (Merck) or on precoated aluminium oxide 60 F_{254} neutral (type E) aluminium sheets (Merck). Visualisation of the plates was accomplished by using UV light and/or iodine and/or aq. potassium permanganate. Chromatography was conducted either on silica gel 60, 220–440 mesh (Fluka) or aluminium oxide 90, activity II–III (Merck) under low pressure. Solutions were evaporated on a Büchi rotary evaporator under reduced pressure. All starting materials were obtained from commercial sources and used as received unless otherwise indicated. Triethylamine and *N*,*N*-diisopropylethylamine were distilled from calcium hydride. 3,4-Dimethoxybenzaldehyde was purified by dry flash chromatography ($CHCl_3$) and dried overnight under high vacuum. Petroleum spirit refers to that fraction having a boiling range of 60–80 °C.

1-Allyloxy-4-bromobenzene 6[10]

To a stirred mixture of 4-bromophenol (100.0 g, 0.578 mol) and anhydrous potassium carbonate (95.86 g, 0.694 mol) in anhydrous DMF (400 mL), under argon, was added allyl bromide (55.0 mL, 0.636 mol) and the mixture was stirred overnight at room temperature. The mixture was then partitioned between water (2 L) and petroleum spirit (2 L). The aqueous layer was further extracted with more petroleum spirit (1 L), and the combined organic extracts were dried ($MgSO_4$), and evaporated. The residue was purified by dry flash chromatography (silica gel; 0–5% Et_2O–petroleum spirit) to give **6** (120.3 g, 98%) as a *colourless oil*; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.37 (2H, m, ArH), 6.80 (2H, m, ArH), 6.03 (1H, m, C=CHC), 5.40 (1H, dq, *J* 17.3 and 1.6, CH=CC), 5.29 (1H, dq, *J* 9.2 and 1.4, CH=CC), 4.51 (2H, dt, *J* 5.3 and 1.6, CCH_2O).

2-Allyl-4-bromophenol 7[11]

1-Allyloxy-4-bromobenzene **6** (11.63 g, 54.6 mmol) was heated at 230 °C under nitrogen for 2 h. After cooling, the reaction mixture was purified by flash chromatography (silica gel; 20% EtOAc–petroleum spirit) to give **7** (10.4 g, 89%) as a *pale brown oil*; δ_H (250 MHz; $CDCl_3$; Me_4Si) 7.24–7.20 (2H, m, ArH), 6.70 (1H, m, ArH), 5.98 (1H, m, C=CHC), 5.21 (1H, td, *J* 1.5 and 0.5, CH=CC), 5.15 (1H, dq, *J* 7.9 and 1.5, CH=CC), 4.96 (1H, s, OH), 3.37 (2H, d, *J* 6.3, C=CCH_2).

2-Allyl-1-(benzyloxy)-4-bromobenzene 8[12]

To a stirred solution of 2-allyl-4-bromophenol **7** (2.12 g, 9.94 mmol) in anhydrous DMF (12 mL) was added anhydrous potassium carbonate (1.65 g, 11.9 mmol), followed by benzyl bromide (1.30 mL, 10.9 mmol), and the mixture was stirred at room temperature under nitrogen for 3 h. The mixture was then partitioned between water (100 mL) and 50% Et_2O–petroleum spirit (100 mL). The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel; 0–2% Et_2O–petroleum spirit) to give **8** (2.81 g, 93%) as a *colourless oil*; δ_H (250 MHz; $CDCl_3$; Me_4Si) 7.41–7.24 (7H, m, ArH), 6.77 (1H, m, ArH), 5.97 (1H, m, C=CHC), 5.11 (1H, m, CH=CC), 5.06 (2H, s, PhCH_2O), 5.04 (1H, m, CH=CC), 3.40 (2H, d, *J* 6.7, C=CCH_2).

2-(Benzyloxy)-5-bromophenylacetic acid 9

To a mixture of 2-allyl-1-benzyloxy-4-bromobenzene **8** (2.48 g, 8.18 mmol) in CCl_4–MeCN–H_2O (2:2:3; 56 mL) was added sodium periodate (10.50 g, 49.1 mmol), then ruthenium(III) chloride trihydrate (47.7 mg, 0.182 mmol), and the mixture was stirred vigorously for 15 h. More sodium periodate (3.50 g, 16.4 mmol) was added and the mixture was stirred for a further 3 h before being partitioned between water (200 mL) and methylene dichloride (200 mL). The aqueous layer was further extracted with more methylene dichloride (2 × 200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel; 3–5% MeOH–CH_2Cl_2) to give **9** (1.78 g, 68%) as a *cream solid*; δ_H (250 MHz; $CDCl_3$; Me_4Si) 7.36–7.29 (7H, m, ArH), 6.79 (1H, m, ArH), 5.05 (2H, s, PhCH_2O), 3.67 (2H, s, CH_2CO).

(*R*)-(−)-3-[2-(Benzyloxy)-5-bromophenylacetyl]-4-isopropyloxazolidin-2-one 10

To a stirred solution of 2-benzyloxy-5-bromophenylacetic acid **9** (0.5252 g, 1.64 mmol) in anhydrous diethyl ether (18 mL), cooled to −78 °C under argon, was added by syringe anhydrous triethylamine (0.239 ml, 1.71 mmol), followed by trimethylacetyl chloride (0.211 mL, 1.71 mmol). The resulting thick white mixture was then warmed to 0 °C and stirred for 1 h before recooling to −78 °C. Meanwhile, to a stirred solution of (4*R*)-4-isopropyloxazolidin-2-one (0.2220 g, 1.72 mmol) in THF (4 mL) at −78 °C under argon, was added by syringe, over a period of 10 min, a 1.6 M solution of butyllithium in hexanes (1.07 mL, 1.71 mmol), keeping the temperature ≤−70°C. The resulting mixture was then transferred dropwise by cannula to the flask containing the mixed anhydride. The resulting mixture was stirred at −78 °C for 15 min, then allowed to warm to 0 °C and stirred for a further 30 min before quenching with saturated aq. NH_4Cl (10 mL). The mixture was then partitioned between water (45 mL) and diethyl ether (15 mL). The organic layer was washed with saturated aq. NaCl (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; 25% EtOAc–petroleum spirit) to give **10** (0.5303 g, 75%) as a *colourless solid*; mp 69–74 °C; $[\alpha]_D$ −51.6 (*c* 1.0 in CH_2Cl_2) (Found: C, 58.5; H, 5.0; N, 3.35. $C_{21}H_{22}BrNO_4$ requires C, 58.3; H, 5.1; N, 3.2%); ν_{max} (KBr)/cm^{-1} 2959, 1778, 1712, 1497, 1452, 1391, 1375, 1363, 1346, 1312, 1297, 1277, 1255, 1235, 1206; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.36–7.28 (7H, m, ArH), 6.79 (1H, d, *J* 8.7, ArH), 5.05 (1H, d, *J* 11.7, PhC*H*O), 5.00 (1H, d, *J* 11.7, PhC*H*O), 4.31 (1H, d, *J* 17.5, CHCON), 4.31 (1H, m, NCH), 4.18 (1H, d, *J* 17.5, CHCON), 4.14 (1H, dd, *J* 9.1 and 3.0, CO_2CH), 4.07 (1H, t, *J* 9.1, CO_2CH), 2.29 (1H, m, Me_2CH), 0.85 (3H, d, *J* 7.1, CCH_3), 0.77 (3H, d, *J* 7.0, CCH_3); δ_C (90.6 MHz; $CDCl_3$; Me_4Si) 170.3 (C*C*ON), 155.8 (Ar), 154.2 (NCOO), 136.6 (Ar), 133.9 (CH), 131.2 (CH), 128.6 (CH), 128.0 (CH), 127.3 (CH), 125.7 (Ar), 113.4 (CH), 112.9 (Ar), 70.3 (CH_2), 63.4 (CH_2), 58.6 (CH), 37.2 (CH_2), 28.4 (CH), 17.9 (CH_3), 14.6 (CH_3); *m*/*z* (ES^+) 434/432 (18/16%, $[M + H]^+$), 391 (100).

(4*R*)-(+)-3-{(2*R*,3*R*)-2-[2-(Benzyloxy)-5-bromophenyl]-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoyl}-4-isopropyloxazolidin-2-one 11

To a stirred solution of (*R*)-(−)-3-[2-(benzyloxy)-5-bromophenylacetyl]-4-isopropyloxazolidin-2-one **10** (13.58 g, 31.4 mmol) in anhydrous methylene dichloride (330 mL), cooled to 0 °C under argon, was added by cannula over a period of 15 min a solution of 9-BBN triflate (9.34 g, 34.6 mmol) in anhydrous methylene dichloride (120 mL), keeping the temperature below 1 °C. The mixture was then stirred at 0 °C for

10 min before the dropwise addition, over a period of 5 min, of distilled *N*,*N*-diisopropylethylamine (9.14 mL, 52.5 mmol), keeping the temperature below 2 °C. The mixture was stirred at 1 °C for 1 h, then cooled to −78 °C. A solution of 3,4-dimethoxybenzaldehyde (5.74 g, 34.5 mmol) in anhydrous methylene dichloride (120 mL), stored over 4 Å molecular sieves for 1 h, was then added over a period of 33 min by cannula, keeping the temperature below −75 °C. The mixture was stirred at this temperature for 1 h, then at room temperature for 2 h, before quenching with 10% aq. NaH_2PO_4 (600 mL). The mixture was extracted with diethyl ether (800 + 400 mL) and the combined organic extracts were washed with saturated aq. NaCl (200 mL) and evaporated. The residue was dissolved in methanol (810 mL), cooled to 0 °C, and 30% aq. hydrogen peroxide (160 mL) was added. The mixture was stirred for 140 min in an ice–water-bath, then concentrated *in vacuo*. The resulting aqueous residue was partitioned between diethyl ether (500 mL) and water (400 mL), and the aqueous layer was further extracted with diethyl ether (300 mL). The combined organic extracts were washed with saturated aq. NaCl (200 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; 35% EtOAc–petroleum spirit) to give **11** (16.35 g, 87%) as a *white solid*; mp 65–69 °C; $[\alpha]_D$ +81.3 (*c* 1.0 in CH_2Cl_2) (Found: C, 60.3; H, 5.25; N, 2.5. $C_{30}H_{32}BrNO_7$ requires C, 60.2; H, 5.4; N, 2.3%); ν_{max} (KBr)/cm^{-1} 3501, 2963, 1782, 1694, 1593, 1517, 1487, 1464, 1453, 1385, 1235, 1202, 1154, 1139, 1120, 1101, 1057, 1025, 974, 859, 807, 752, 740, 697, 647; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.46 (1H, d, *J* 2.5, ArH), 7.39–7.27 (6H, m, ArH), 6.73 (1H, d, *J* 8.8, ArH), 6.71 (1H, m, ArH), 6.62–6.60 (2H, m, ArH), 5.80 (1H, d, *J* 6.0, CHCON), 5.23 (1H, d, *J* 6.0, C*H*OH), 4.92 (1H, d, *J* 11.6, PhC*H*O), 4.72 (1H, d, *J* 11.6, PhC*H*O), 4.35 (1H, m, NCH), 4.09–4.07 (2H, m, CO_2CH_2), 3.80 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 2.33 (1H, m, Me_2CH), 0.86 (3H, d, *J* 7.0, CCH_3), 0.65 (3H, d, *J* 6.8, CCH_3); δ_C (90.6 MHz; $CDCl_3$; Me_4Si) 173.4 (C*C*ON), 157.1 (Ar), 153.1 (NCOO), 148.9 (Ar), 148.8 (Ar), 137.0 (Ar), 134.3 (Ar), 132.6 (CH), 131.9 (CH), 128.8 (CH), 128.2 (CH), 127.7 (CH), 125.9 (Ar), 119.6 (CH), 114.2 (CH), 113.1 (Ar), 110.9 (CH), 109.9 (CH), 75.0 (CHOH), 71.1 (PhCH_2O), 63.2 (CO_2CH_2), 58.7 (NCH), 56.2 (OCH_3), 56.0 (OCH_3), 50.0 (*C*HCON), 28.3 (*C*HMe_2), 18.4 (C*C*H$_3$), 14.5 (C*C*H$_3$); *m*/*z* (ES$^+$) 582/580 (11/12%, $[M - H_2O + H]^+$), 393 (13), 391 (47), 167 (100), 130 (34).

(4*R*)-(−)-3-{[(2*R*,3*R*)-5-Bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl]carbonyl}-4-isopropyloxazolidin-2-one 12

To a stirred solution of (4*R*)-(+)-3-{(2*R*,3*R*)-2-[2-(benzyloxy)-5-bromophenyl]-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoyl}-4-isopropyloxazolidin-2-one **11** (6.10 g, 10.2 mmol) in anhydrous methylene dichloride (400 mL) under argon was added dropwise, over a period of 3 min, iodotrimethylsilane (3.2 mL, 22.5 mmol) and the resulting red-brown solution was stirred at room temperature for 77 min. Methanol (100 mL) was then added and the mixture was stirred for 10 min. The solvents were evaporated off and the residue was purified by flash chromatography (silica gel; 2–4% EtOAc–CH_2Cl_2 then 70–80% Et_2O–hexane) to give **12** (3.56 g, 71%) as a *colourless solid*; mp 61–63 °C; $[\alpha]_D$ −235.8 (*c* 1.0 in CH_2Cl_2) (Found: C, 56.55; H, 5.0; N, 3.1. $C_{23}H_{24}BrNO_6$ requires C, 56.3; H, 4.9; N, 2.9%); ν_{max} (KBr)/cm^{-1} 2963, 1778, 1697, 1518, 1472, 1387, 1374, 1302, 1261, 1206, 1160, 1142, 1111, 1026, 811; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.41 (1H, fine m, ArH), 7.33 (1H, dd, *J* 8.4 and 2.1, ArH), 6.90 (1H, dd, *J* 8.2 and 1.9, ArH), 6.86 (1H, d, *J* 1.9, ArH), 6.83 (1H, d, *J* 8.2, ArH), 6.80 (1H, d, *J* 8.4, ArH), 6.22 (1H, d, *J* 6.6, CHO), 5.64 (1H, d, *J* 6.6, CHCON), 4.52 (1H, m, NCH), 4.35 (1H, t, *J* 9.2, CO_2CH), 4.30 (1H, dd, *J* 9.2 and 3.5, CO_2CH), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 2.32 (1H, m, Me_2CH), 0.91 (3H, s, CCH_3), 0.85 (3H, s, CCH_3); δ_C (90.6 MHz; $CDCl_3$; Me_4Si) 170.0 (C*C*ON), 158.6 (Ar), 153.8 (NCOO), 149.5 (Ar), 149.3 (Ar), 132.5 (CH), 132.0 (Ar), 128.0 (CH), 127.0 (Ar), 118.8 (CH), 112.6 (Ar), 111.6 (CH), 111.2 (CH), 109.3 (CH), 86.2 (CH), 63.8 (CH_2), 58.7 (CH), 55.9 (CH_3), 54.4 (CH), 28.4 (CH), 17.8 (CH_3), 14.8 (CH_3); *m*/*z* (ES$^+$) 509/507 (64/74%, $[M + NH_4]^+$), 492/490 (12/13, $[M + H]^+$), 214 (16), 195 (24), 172 (16), 152 (21), 147 (26), 130 (100), 118 (79).

(−)-Methyl (2*R*,3*R*)-5-bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylate 13

To a solution of (4*R*)-(−)-3-{[(2*R*,3*R*)-5-bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-yl]carbonyl}-4-isopropyloxazolidin-2-one **12** (0.1062 g, 0.217 mmol) in anhydrous methanol (5 mL), cooled under nitrogen to 0 °C, was added dropwise a 30 wt% solution of sodium methoxide in methanol (41.3 μL, 0.217 mmol), and the mixture was stirred at 0 °C for 2 h. The mixture was then partitioned between 0.05 M aq. HCl (15 mL) and diethyl ether (20 mL). The organic layer was washed with saturated aq. NaCl (10 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; 25% EtOAc–petroleum spirit) to afford **13** (66.6 mg, 78%) as a *white solid*; mp 95.5–96 °C (from EtOAc–hexane); $[\alpha]_D$ −92.0 (*c* 1.0 in CH_2Cl_2) (Found: C, 55.1; H, 4.4. $C_{18}H_{17}BrO_5$ requires C, 55.0; H, 4.4%); ν_{max} (KBr)/cm^{-1} 2957, 2835, 1735, 1605, 1594, 1521, 1467, 1440, 1432, 1348, 1330, 1295, 1284, 1261, 1244, 1232, 1205, 1167, 1144, 1118, 1064, 1031, 998, 964, 896, 856, 842, 824, 813, 763, 662, 647; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.47 (1H, fine m, ArH), 7.34 (1H, m, ArH), 6.94 (1H, dd, *J* 8.4 and 2.1, ArH), 6.89 (1H, d, *J* 2.1, ArH), 6.85 (1H, d, *J* 8.4, ArH), 6.78 (1H, d, *J* 8.5, ArH), 6.05 (1H, d, *J* 8.0, CHO), 4.28 (1H, d, *J* 8.0, C*H*CO_2Me), 3.88 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.84 (3H, s, OCH_3); δ_C (90.6 MHz; $CDCl_3$; Me_4Si) 170.6 (C*C*OO), 158.3 (Ar), 149.3 (Ar), 132.5 (CH), 132.3 (Ar), 128.1 (CH), 126.2 (Ar), 118.4 (CH), 112.6 (Ar), 111.4 (CH), 111.2 (CH), 108.9 (CH), 86.3 (CH), 55.9 (CH_3), 55.3 (CH_3), 52.9 (CH); *m*/*z* (ES$^-$) 393/391 (32/35%, $[M - H]^-$), 367 (100), 281 (40), 255/253 (53/39, $[M - (MeO)_2C_6H_3 - 2H]^-$).

(−)-Methyl (2*R*,3*R*)-5-[2-(*tert*-butoxycarbonyl)vinyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylate 14

Into a 15 mL pressure tube were placed (−)-methyl (2*R*,3*R*)-5-bromo-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylate **13** (0.4672 g, 1.19 mmol), palladium(II) acetate (5.4 mg, 0.024 mmol), tri(*o*-tolyl)phosphine (22.4 mg, 0.074 mmol), *tert*-butyl acrylate (0.522 mL, 3.56 mmol) and anhydrous triethylamine (0.497 mL, 3.57 mmol). The tube was flushed with argon, capped, and heated at 100 °C for 16 h. After cooling, the mixture was partitioned between water (20 mL) and diethyl ether (40 mL). The organic layer was washed with saturated aq. NaCl (15 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (alumina; 40–70% CH_2Cl_2–hexane) to give **14** (0.4470 g, 85%) as a *yellow oil*; $[\alpha]_D$ −121.7 (*c* 1.0 in CH_2Cl_2) (Found: C, 68.2; H, 6.25. $C_{25}H_{28}O_7$ requires C, 68.2; H, 6.4%); ν_{max} (film)/cm^{-1} 2975, 2838, 1740, 1700, 1633, 1606, 1517, 1467, 1464, 1439, 1391, 1367, 1328, 1240, 1151, 1113, 1027, 982, 907, 859, 817, 762, 735, 703; δ_H (360 MHz; $CDCl_3$; Me_4Si) 7.56 (1H, d, *J* 15.9, C=C*H*CO_2Bu^t), 7.55 (1H, s, ArH), 7.41 (1H, d, *J* 8.3, ArH), 6.95 (1H, dd, *J* 8.3 and 2.0, ArH), 6.90–6.88 (2H, m, ArH), 6.86 (1H, d, *J* 8.3, ArH), 6.25 (1H, d, *J* 15.9, CH=CCOO), 6.09 (1H, d, *J* 7.8, CHO), 4.29 (1H, d, *J* 7.8, C*H*CO_2Me), 3.88 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 1.53 [9H, s, $C(CH_3)_3$]; δ_C (125.8 MHz; $CDCl_3$; Me_4Si) 170.8 (*C*O_2Me), 166.6 (C=C*C*OO), 160.8 (Ar), 149.3 (*C*OMe × 2), 143.1 (*C*H=CCO), 132.3 (Ar), 130.6 (CH), 128.2 (Ar), 125.0 (Ar), 124.6 (CH), 118.4 (CH), 117.8 (C=*C*HCO), 111.2 (CH), 110.2 (CH), 108.9 (CH), 86.5 (CH),

80.3 (CMe_3), 55.9 ($OCH_3 \times 2$), 55.1 (CH_3), 52.8 (CH), 28.2 [$C(CH_3)_3$]; *m/z* (ES^+) 441 (21%, $[M + H]^+$), 385 (100, $[M - CMe_3 + 2H]^+$), 367 (95, $[M - OCMe_3]^+$), 335 (23).

(2*R*,3*R*)-(−)-5-[2-(*tert*-Butoxycarbonyl)vinyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylic acid 15

To a stirred solution of (−)-methyl (2*R*,3*R*)-5-[2-(*tert*-butoxycarbonyl)vinyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylate **14** (0.4213 g, 0.956 mmol) in a mixture of anhydrous THF (2 mL) and anhydrous methanol (2 mL), under nitrogen, was added barium hydroxide octahydrate (0.3325 g, 1.05 mmol) and the mixture was stirred at room temperature for 1 h. Ethyl acetate (30 mL) was then added, followed by 0.05 M aq. HCl (45 mL), making the mixture pH 4. The aqueous layer was separated, and extracted further with ethyl acetate (30 mL). The combined organic extracts were washed with saturated aq. NaCl (20 mL), dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography (silica gel; 5–7% MeOH–CH_2Cl_2) to afford **15** (0.3640 g, 89%) as a *white solid*; mp 108–111 °C; $[\alpha]_D$ −351.9 (*c* 1.0 in CH_2Cl_2) (Found: C, 66.5; H, 6.0. $C_{24}H_{26}O_7 \cdot 0.4H_2O$ requires C, 66.5; H, 6.2%); ν_{max} (KBr)/cm^{-1} 2975, 2934, 1736, 1702, 1663, 1632, 1605, 1518, 1490, 1465, 1441, 1421, 1392, 1369, 1328, 1261, 1238, 1154, 1111, 1027, 982, 947, 918, 855, 814, 763; δ_H (250 MHz; DMSO-d_6; Me_4Si) 7.66 (1H, s, ArH), 7.58 (1H, d, *J* 8.4, ArH), 7.52 (1H, d, *J* 15.9, C=C*H*CO_2Bu^t), 6.99–6.89 (4H, m, ArH), 6.31 (1H, d, *J* 15.9, CH=CCOO), 5.97 (1H, d, *J* 7.6, CHO), 4.30 (1H, d, *J* 7.6, C*H*CO_2H), 3.74 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 1.47 [9H, s, $C(CH_3)_3$]; δ_C (90.6 MHz; DMSO-d_6; Me_4Si) 172.1 (C*C*OO), 165.7 (C=C*C*OO), 160.5 (Ar), 148.8 (Ar), 143.5 (*C*H=CCO), 132.6 (Ar), 130.0 (CH), 127.5 (Ar), 127.0 (Ar), 124.7 (CH), 118.4 (CH), 116.6 (C=*C*HCO), 111.6 (CH), 109.7 (CH), 109.4 (CH), 87.2 (CH), 79.5 (CMe_3), 55.5 (CH_3), 55.4 (CH_3), 55.1 (CH), 27.8 (CH_3); *m/z* (ES^+) 427 (19%, $[M + H]^+$), 371 (100, $[M - CMe_3 + 2H]^+$), 353 (38, $[M - OCMe_3]^+$), 235 (26), 194 (22).

(2*R*,3*R*)-(−)-5-{(1*S*)-1-[(1*R*)-*N*-Benzyl-1-phenylethylamino]-2-(*tert*-butoxycarbonyl)ethyl}-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylic acid 16

A solution of (*R*)-(+)-*N*-benzyl-1-phenylethylamine (1.2018 g, 5.69 mmol) in anhydrous THF (5 mL) was stored over 3 Å molecular sieves for 30 min, then cooled under nitrogen to 0 °C. A 1.6 M solution of butyllithium in hexanes (2.86 mL, 4.58 mmol) was added dropwise over a period of 4 min, whilst the mixture was stirred and maintained at a temperature of 0 ± 3 °C. The resulting red solution was stirred at this temperature for 20 min, then cooled to −78 °C. A solution of (2*R*,3*R*)-(−)-5-[2-(*tert*-butoxycarbonyl)vinyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylic acid **15** (0.5143 g, 1.21 mmol) in anhydrous THF (3 mL) was added dropwise over a period of 20 min, keeping the temperature below −75 °C, and the mixture was stirred at this temperature for a further 2 h. Saturated aq. NH_4Cl (2.5 mL) was then added and the mixture was allowed to warm to 3 °C before being partitioned between saturated aq. NaCl (40 mL) and ethyl acetate (40 mL). The aqueous layer was further extracted with ethyl acetate (2 × 40 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica gel; 2% MeOH–CH_2Cl_2) to afford **16** (0.3685 g, 48%) as a *colourless solid*; mp 70–71 °C; $[\alpha]_D$ −35 (*c* 0.1 in CH_2Cl_2); ν_{max} (film)/cm^{-1} 2971, 2932, 2834, 1726, 1610, 1516, 1489, 1454, 1368, 1260, 1140, 1028, 816, 751, 700; δ_H (360 MHz; DMSO-d_6; Me_4Si) 7.42–7.22 (12H, m, ArH), 6.95–6.91 (3H, m, ArH), 6.85 (1H, d, *J* 8.3, ArH), 5.89 (1H, d, *J* 7.5, CHO), 4.28 (1H, d, *J* 7.5, C*H*CO_2H), 4.15 (1H, m, NC*H*C-CO_2Bu^t), 3.97 [1H, m, PhC*H*(Me)N], 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.62 (2H, s, PhCH_2N), 2.59 (1H, m, C*H*CO_2-Bu^t), 2.36 (1H, m, C*H*CO_2Bu^t), 1.16 [9H, s, $C(CH_3)_3$], 1.15 (3H, d, *J* 6.8, CH_3CN); δ_C (100.6 MHz; DMSO-d_6; Me_4Si) 172.5 (*C*O_2H), 170.7 (C*C*O_2Bu^t), 158.2 (Ar), 149.3 (Ar), 144.9 (Ar), 142.3 (Ar), 134.2 (Ar), 133.2 (Ar), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.5 (Ar), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.8 (CH), 125.3 (CH), 118.9 (CH), 112.1 (CH), 110.2 (CH), 109.1 (CH), 86.5 (CHO), 80.0 (*C*Me_3), 60.0 (COCH$_2$*C*HN), 57.2 (Ph*C*HN), 56.0 (OCH_3), 55.8 (OCH_3), 55.4 (*C*HCO_2H), 50.7 (Ph*C*H_2), 38.7 (CO*C*H_2), 27.9 [$C(CH_3)_3$], 16.4 (CH_3); *m/z* (ES^+) 638 (6%, $[M + H]^+$), 427 (100, $[M - PhCH(Me)NHBn + H]^+$), 371 (19, $[M - PhCH(Me)NHBn - CMe_3 + 2H]^+$), 327 (13, $[M - PhCH(Me)NHBn - CO_2CMe_3 + 2H]^+$), 212 (66, $[PhCH(Me)NHBn + H]^+$).

(2*R*,3*R*)-(−)-5-[(1*S*)-1-Amino-2-(*tert*-butoxycarbonyl)ethyl]-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylic acid 17

A mixture of (2*R*,3*R*)-(−)-5-{(1*S*)-1-[(1*R*)-*N*-benzyl-1-phenylethylamino]-2-(*tert*-butoxycarbonyl)ethyl}-2-(3,4-dimethoxyphenyl)-2,3-dihydrobenzofuran-3-carboxylic acid **16** (0.7730 g, 1.21 mmol) and palladium(II) hydroxide on carbon powder (20% Pd; 0.3833 g) in a mixture of methanol (12 mL), water (1.2 mL) and acetic acid (0.3 mL) was stirred vigorously under an atmosphere of hydrogen for 2 h. The catalyst was removed by filtration, and washed well with methanol. The combined filtrates were evaporated, and the residue was purified by flash chromatography [silica gel; CH_2Cl_2–MeOH–NH_3(aq); 85 : 15 : 1.5 to 80 : 20 : 2] to afford **17** (0.3634 g, 68%) as a *white solid*; mp 215–219 °C (from MeOH–EtOAc–isohexane †); $[\alpha]_D$ −89 (*c* 0.1 in CH_2Cl_2) (Found: C, 64.5; H, 6.6; N, 2.9. $C_{24}H_{29}NO_7 \cdot 0.1H_2O$ requires C, 64.7; H, 6.6; N, 3.15%); ν_{max} (film)/cm^{-1} 3363, 2972, 1724, 1586, 1516, 1491, 1369, 1261, 1158, 1027, 816; δ_H (400 MHz; DMSO-d_6; Me_4Si) 7.78 (1H, s, ArH), 7.11 (1H, d, *J* 8.2, ArH), 6.93 (1H, d, *J* 8.4, ArH), 6.92 (1H, s, ArH), 6.88 (1H, dd, *J* 8.4 and 2.0, ArH), 6.76 (1H, d, *J* 8.2, ArH), 5.97 (1H, d, *J* 8.1, CHO), 4.28 (1H, dd, *J* 9.3 and 6.0, NCHCCO$_2$), 4.01 (1H, d, *J* 8.1, C*H*CO_2H), 3.74 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 2.85 (1H, dd, *J* 15.0 and 6.0, $CHCO_2$), 2.77 (1H, dd, *J* 15.0 and 9.3, $CHCO_2$), 1.24 [9H, s, $CO_2C(CH_3)_3$]; δ_C (100.6 MHz; DMSO-d_6; Me_4Si) 173.3 (C*C*O_2H), 169.2 (C*C*O_2Bu^t), 159.1 (Ar), 149.2 (Ar), 149.0 (Ar), 134.3 (Ar), 130.7 (Ar), 129.5 (Ar), 129.1 (CH), 124.1 (CH), 119.0 (CH), 112.1 (CH), 110.2 (CH), 108.3 (CH), 88.1 (CHO), 80.7 (*C*Me_3), 57.6 (*C*HCO_2H), 56.0 (OCH_3), 55.8 (OCH_3), 51.9 (CHN), 41.6 (CO*C*H_2), 27.9 [$C(CH_3)_3$]; *m/z* (ES^+) 887 (6%, $[2M + H]^+$), 427 (100, $[M - NH_2]^+$), 371 (11, $[M - NH_2 - CMe_3 + H]^+$), 327 (5, $[M - NH_2 - CO_2CMe_3 + H]^+$).

Crystal-structure determination of 13‡

Crystal data. $C_{18}H_{17}BrO_5$, $M = 393.242$, orthorhombic, $a = 11.094(2)$, $b = 28.750(2)$, $c = 5.363(3)$ Å, $V = 1711(1)$ Å^3, $T = 294$ K, space group $P2_12_12_1$, $Z = 4$, $\mu = 3.50$ mm^{-1}, 3820 reflections measured, 3219 unique, which were all used in the refinement. The final agreement statistics are: $R = 0.045$ [based on 2600 reflections with $I \geq 2\sigma(I)$], $wR = 0.115$. During refinement the Flack *x* parameter refined to a value of 0.003 indicating that the correct absolute configuration had been chosen.

Crystal-structure determination of 17‡

Single crystals of compound **17** were grown from methanol–methylene dichloride and mounted on a glass fibre for transfer to the diffractometer.

Crystal data. $C_{24}H_{29}NO_7$, $M = 443.501$, orthorhombic, $a = 11.799(4)$, $b = 25.651(6)$, $c = 7.991(6)$ Å, $V = 2419(3)$ Å^3, $T = 294$ K, space group $P2_12_12_1$, $Z = 4$, $\mu = 0.70$ mm^{-1}, 2482

† A commercial mixture of isomeric C_6H_{14} hydrocarbons.

‡ CCDC reference number 207/397. See http://www.rsc.org/suppdata/p1/a9/a909816j for crystallographic files in .cif format.

unique reflections measured, of which 2 were suppressed as being unsuitable for inclusion during refinement. The final agreement statistics are: $R = 0.069$ [based on 885 reflections with $I \geq 2\sigma(I)$], $wR = 0.166$.

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