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Asymmetric synthesis of (4*R*,5*R*)-cytoxazone and (4*R*,5*S*)-*epi*-cytoxazone

Stephen G. Davies,* Deri G. Hughes, Rebecca L. Nicholson, Andrew D. Smith and Angela J. Wright

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA

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(4*R*,5*R*)-Cytoxazone has been prepared in four steps and in 61% overall yield and >98% ee. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to *tert*-butyl (*E*)-3-(*p*-methoxyphenyl)prop-2-enoate and subsequent *in situ* diastereoselective enolate oxidation with (+)-(camphorsulfonyl)oxaziridine gave *tert*-butyl (2*R*,3*R*,α*R*)-2-hydroxy-3-(*p*-methoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate in >98% de. Subsequent *N*-benzyl deprotection to the primary β-amino ester *via* hydrogenolysis, oxazolidinone formation with C(2)-retention by treatment with diphosgene and chemoselective ester reduction furnishes (4*R*,5*R*)-cytoxazone. The synthesis of the C(5)-epimer, (4*R*,5*S*)-*epi*-cytoxazone in 44% overall yield, has also been completed *via* a protocol involving *N*-Boc protection of the primary β-amino ester, utilization of the *N*-Boc group to facilitate simultaneous C(2)-inversion and oxazolidinone formation, and subsequent reduction.

Introduction

Cytoxazone **1** is a microbial metabolite[1] isolated from *Streptomyces* sp.,[2] which has been identified as a selective modulator of T_H2 cytokine secretion. Due to its potent biological activity and relatively simple structure, the development of efficient asymmetric routes to cytoxazone and its stereoisomers has been the subject of intense synthetic interest. A variety of synthetic routes to **1** have been reported in 10% to 51% overall yield, including chemoenzymatic resolution,[3] imino 1,2-Wittig rearrangement,[4] addition of Grignard reagents to a protected imine,[5] Sharpless asymmetric dihydroxylation and regio- and stereoselective introduction of azide,[6,7] asymmetric aminohydroxylation[8] and asymmetric aldol reactions.[9] We have previously demonstrated that conjugate addition of a homochiral lithium amide to α,β-unsaturated esters and subsequent enolate oxidation with electrophilic oxygen sources allows the efficient synthesis of a range of *anti*-α-hydroxy-β-amino acid derivatives with high diastereoselectivity.[10] It was envisaged that this methodology would allow an efficient and stereoselective asymmetric synthesis of (4*R*,5*R*)-cytoxazone **1** *via* synthetic elaboration of the α-hydroxy-β-amino ester **2** derived from conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3** to a β-4-methoxyphenyl-α,β-unsaturated ester **4** and enolate hydroxylation (Fig. 1).

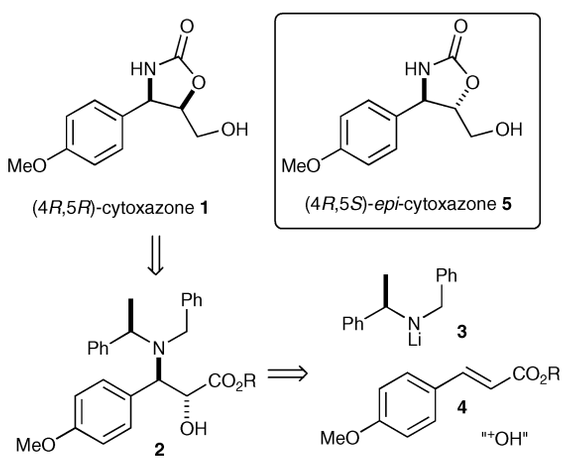

Fig. 1 Retrosynthetic analysis for **1** and **5**.

The realisation of this strategy, and the extension of this protocol to the synthesis of (4*R*,5*S*)-*epi*-cytoxazone **5** is described herein.

Results and discussion

Asymmetric synthesis of (4*R*,5*R*)-cytoxazone

Following the literature protocol,[10] conjugate addition of lithium amide (*R*)-**3** to *tert*-butyl (*E*)-3-(*p*-methoxyphenyl)-prop-2-enoate **6** and subsequent *in situ* diastereoselective enolate oxidation with (+)-(camphorsulfonyl)oxaziridine gave *anti*-α-hydroxy-β-amino ester (2*R*,3*R*,α*R*)-**7** in 79% yield and 98% de on a >3 mmol scale. The C(2)–C(3)-*anti*-configuration within α-hydroxy-β-amino ester **7** was assigned by analogy to the known *anti*-selectivity noted upon hydroxylation of related β-amino enolates. Having successfully installed the desired stereogenic centres required for the synthesis of cytoxazone, and with >3 mmol quantities of β-amino ester (2*R*,3*R*,α*R*)-**7** in hand, functional group manipulation of β-amino ester **7** to furnish the natural product was investigated. Initial attention was turned towards the efficient removal of the *N*-benzyl and *N*-α-methylbenzyl protecting groups, with hydrogenolysis using palladium hydroxide on carbon under 5 atmospheres of H_2 in MeOH affording the desired *anti*-α-hydroxy-β-amino ester-(2*R*,3*R*)-**8** in 96% yield and 98% de (Scheme 1).

Installation of the oxazolidinone functionality within cytoxazone was next investigated, with direct cyclisation of aminoalcohol **8** upon treatment with carbonyldiimidazole giving >70% conversion to oxazolidinone (4*R*,5*R*)-**9** on a trial scale, but less than 40% conversion on a mmol scale, furnishing (4*R*,5*R*)-**9** in 36% isolated yield. However, use of diphosgene for oxazolidinone formation proved satisfactory, giving oxazolidinone (4*R*,5*R*)-**9** in 88% isolated yield and in 98% de on a 2 mmol scale (Scheme 2).

With oxazolidinone (4*R*,5*R*)-**9** in hand, chemoselective reduction of the ester functionality to the alcohol was required to complete the synthesis of cytoxazone. Initial investigations utilised varying equivalents of $LiAlH_4$ over a range of temperatures for the reduction, with starting material being returned in each case. A broad range of reducing agents ($LiBH_4$,[11] Superhydride,[12] Red-Al[13] and DIBAL-H[14]) that have previously been shown to reduce *tert*-butyl esters were therefore screened

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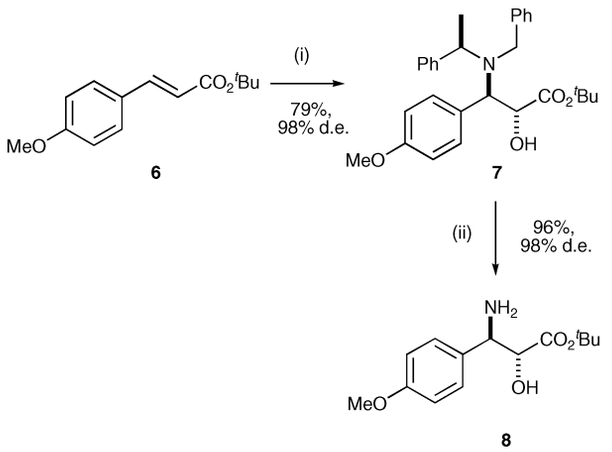
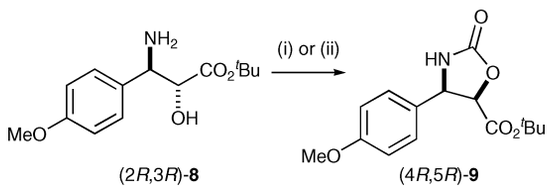


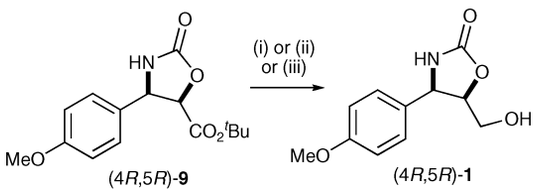
Scheme 1 *Reagents and conditions*: (i). lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3**, THF, −78 °C; then (+)-CSO, THF, −78 °C to rt; (ii). $Pd(OH)_2$ on C, H_2 (5atm.), MeOH.



(i) 36%, 98% d.e.
(ii) 88%, 98% d.e.

Scheme 2 *Reagents and conditions*: (i). CDI, DMAP, THF, rt; (ii). $Cl_3COCOCl$, activated charcoal, toluene, rt (1 hour) then Δ (4 hours).

for their suitability in this transformation. Reduction with $LiBH_4$ and Red-Al showed 20% and 50% conversion respectively to cytoxazone **1**, while Superhydride and DIBAL-H gave complete conversion to the cytoxazone **1** by ^{1}H NMR spectroscopic analysis of the crude reaction mixture, with chromatographic purification furnishing (4*R*,5*R*)-cytoxazone **1** in 70% and 75% yield respectively. As an alternative protocol, *in situ* conversion of the ester to the mixed anhydride and subsequent reduction, based upon the procedure reported by Boojamra *et al.*, was evaluated.[15] Oxazolidinone ester **9** was treated successively with TFA, ethyl chloroformate and $NaBH_4$ in diglyme, giving cytoxazone **1** in 92% isolated yield and 98% de with spectroscopic properties consistent with those reported in the literature {$[\alpha]_D^{25}$ −72.0 (*c* 1.0, MeOH), lit.[6] $[\alpha]_D^{25}$ −75.7 (*c* 1.0, MeOH)}. The ee of synthetic **1** was determined as >98% ee by ^{19}F NMR spectroscopic analysis of the esters derived from **1** and homochiral and racemic Mosher's acid chloride (Scheme 3). The formation of (4*R*,5*R*)-**1** as predicted is consistent with the initial *anti*-amino hydroxylation followed by oxazolidinone formation with retention of configuration at C(2).

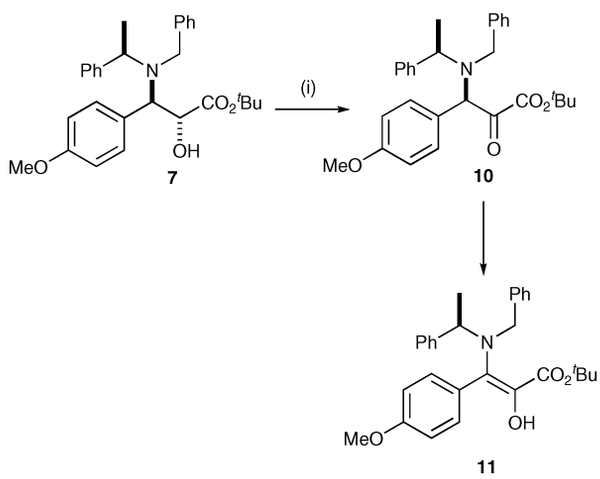


(i) Superhydride, 70%
(ii) DIBAL-H, 75%
(iii) TFA/EtOCOCl/$NaBH_4$, 92%

Scheme 3 *Reagents and conditions*: (i). Superhydride, THF, 0 °C to rt; (ii). DIBAL-H, DCM, 0 °C to rt; (iii) TFA, DCM, rt, 1 h; then $ClCO_2Et$ (1.5 eq.), THF, NEt_3, rt, 2 h; then $NaBH_4$, AcOH, diglyme, 0 °C.

Synthesis of (4*R*,5*S*)-*epi*-cytoxazone

With the asymmetric synthesis of (4*R*,5*R*)-cytoxazone **1** complete, further investigations focused upon the preparation of 5-*epi*-cytoxazone. As the introduction of the hydroxyl functionality into *anti*-α-hydroxy-β-amino ester **7** *via* conjugate addition/hydroxylation is substrate controlled, the *syn*-epimer cannot be synthesised *via* direct oxidation of the β-amino enolate formed *in situ* from conjugate addition. Epimerisation of the existing hydroxyl stereocentre of *anti*-α-hydroxy-β-amino ester **7** was therefore investigated for the synthesis of 5-*epi*-cytoxazone. An oxidation/reduction protocol was first attempted, with stereoselective reduction of an α-keto-β-amino ester proposed as a route to the required *syn*-α-hydroxy-β-amino ester. Oxidation of *anti*-α-hydroxy-β-amino ester **7** under standard Swern conditions[16] returned only starting material, while oxidation with *o*-iodooxybenzoic acid proved successful, giving the desired α-keto-β-amino ester **10**. However, α-keto-β-amino ester **10** underwent rapid tautomerisation to enol (α*R*)-**11**, limiting the synthetic utility of this strategy (Scheme 4).

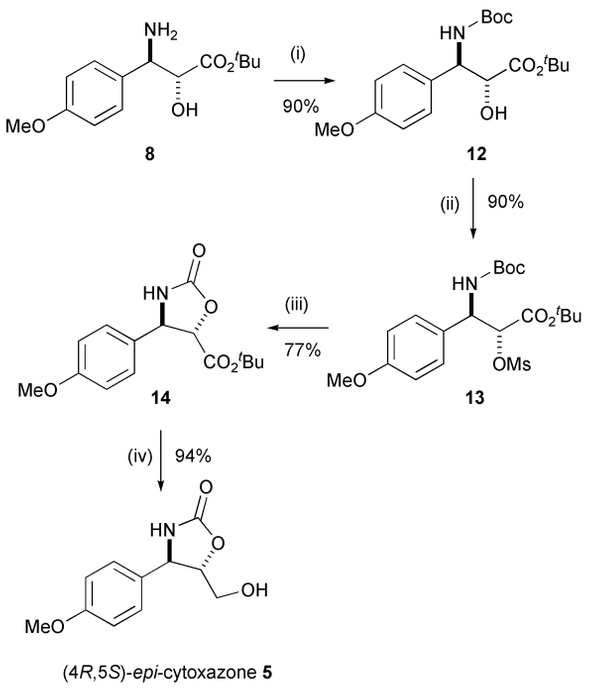


Scheme 4 *Reagents and conditions*: (i). *o*-iodooxybenzoic acid, DMSO, rt.

As an alternative approach, a procedure for the inversion of the C(2)-hydroxyl stereocentre within *anti*-α-hydroxy-β-amino ester **7** was examined. Although direct C(2)-inversion of *anti*-α-hydroxy-β-amino ester **7** under Mitsunobu conditions[17] returned only starting material, it was proposed that intramolecular inversion using neighbouring group participation of an *N*-Boc protected *anti*-α-hydroxy-β-amino ester would lead directly to oxazolidinone formation.[18] Following this hypothesis, secondary *N*-Boc species **12** was prepared by selective *N*-protection of primary amino *anti*-α-hydroxy-β-amino ester **8** in 90% yield. Treatment of **12** with methanesulfonyl chloride in DCM allowed formation of the C(2)-mesylate **13** in 90% yield, which upon heating in DMF gave the desired *trans*-(4*R*,5*S*)-oxazolidinone **14** as a single diastereoisomer in 77% isolated yield. Subsequent reduction with Superhydride gave (4*R*,5*S*)-*epi*-cytoxazone **5** in 94% yield and 98% de, with comparable spectroscopic properties to those described in the literature {$[\alpha]_D^{20}$ +28.6 (*c* 1.0, MeOH), lit.[6] $[\alpha]_D^{25}$ +28.8 (*c* 0.59, MeOH)} (Scheme 5).

Conclusions

In conclusion, we have shown that homochiral (4*R*,5*R*)-cytoxazone **1** may be prepared in four steps and in 61% overall yield *via* an efficient protocol that compares well to the other published synthetic routes (10% to 51% yield) to this natural product. The synthesis of (4*R*,5*R*)-cytoxazone **1** involves a protocol involving conjugate addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide **3** and subsequent *in situ* diastereoselective enolate oxidation, followed by hydrogenolysis, oxazolidinone formation and reduction. (4*R*,5*S*)-*epi*-Cytoxazone has been prepared in 44% overall yield by a strategy involving intramolecular *N*-Boc participation to facilitate oxazolidinone



Scheme 5 *Reagents and conditions*: (i). Boc_2O, $NaHCO_3$, MeOH, rt, sonication; (ii). MsCl, NEt_3, DCM, 0 °C to rt; (iii). DMF, 60 °C; (iv). Superhydride, DCM, 0 °C to rt.

formation and simultaneous C(2)-hydroxyl inversion, and subsequent deprotection. The synthetic strategy detailed herein is equally applicable to the synthesis of the (4*S*,5*S*)- and (4*S*,5*R*)-stereoisomers of cytoxazone using the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide, and the application of this strategy to a variety of related natural products is currently underway.

Experimental

General

All reactions involving organometallic or other moisture sensitive reagents were performed under an atmosphere of dry nitrogen using standard vacuum line techniques. All glassware was flame-dried and allowed to cool under vacuum. In all cases, the reaction diastereoselectivity was assessed by peak integration in the ^{1}H NMR spectrum of the crude reaction mixture. THF was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. DCM was distilled under an atmosphere of dry nitrogen from calcium hydride. Et_2O was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl. Water was distilled. All other solvents were used as supplied (Analytical or HPLC grade), without prior purification. All organometallic reagents were used as supplied. All other reagents were used as supplied, without prior purification. Reactions were dried with $MgSO_4$. Thin layer chromatography (TLC) was performed on aluminium sheets coated with 60 F_{254} silica. Sheets were visualised using UV light, iodine, phosphomolybdic acid (PMA) solution, or $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica. Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker DPX 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz), Bruker AV 400 (^{1}H: 400 MHz and ^{13}C: 100 MHz), or where stated on a Bruker DPX 200 (^{1}H: 200 MHz and ^{13}C: 50 MHz) or AMX 500 (^{1}H: 500 MHz and ^{13}C: 125 MHz) in the deuterated solvent stated. All chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Coupling constants are quoted twice, each being recorded as observed in the spectrum without averaging. Residual signals from the solvents were used as an internal reference. Infrared spectra were recorded on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer using either a $CHCl_3$ cell ($CHCl_3$) or a KBr disc (KBr). Only the characteristic peaks are quoted. Low-resolution mass spectra (*m*/*z*) were recorded on VG MassLab 20–250 or Micromass Platform 1 spectrometers and high-resolution mass spectra (HRMS) on a Micromass Autospec 500 OAT spectrometer. Techniques used were chemical ionisation (CI, NH_3), atmospheric pressure chemical ionisation (APCI) using partial purification by HPLC with methanol : acetonitrile : water (40 : 40 : 20) as eluent or electrospray ionisation (ESI). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are quoted in g 100 mL^{-1}. Melting points were recorded on a Leica VMTG Galen III apparatus and are uncorrected. Elemental analyses were performed by the microanalysis service of the Inorganic Chemistry Laboratory, Oxford.

Preparation of (2*R*,3*R*,α*R*)-*tert*-butyl 2-hydroxy-3-(*p*-methoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)-propanoate 7. BuLi (2.5 M in hexanes, 2.6 mL, 6.4 mmol) was added dropwise to a stirred solution of the (*R*)-α-*N*-methylbenzyl-*N*-benzylamine (1.4 g, 6.8 mmol) in THF (40 mL) at –78 °C. After thirty minutes a solution of (*E*)-**6** (1.0 g, 4.2 mmol) in THF (40 mL) at −78 °C was added dropwise *via* cannula. After a further two hours solid (+)-CSO (1.6 g, 6.8 mmol) was added and the mixture warmed to rt overnight before being partitioned between 10% aqueous citric acid solution and DCM. The combined organic layers were dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on silica (30–40 petroleum : Et_2O, 9 : 1) gave (2*R*,3*R*,α*R*)-**7** as a colourless oil (1.54 g, 79%). $[\alpha]_D^{25}$ −2.5 (*c* 1.9, $CHCl_3$); ν_{max} ($CHCl_3$) 3020 (O–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.22 (9H, s, C(*Me*)$_3$), 2.76 (1H, br s, O*H*), 3.79 (1H, d, *J* 15.0, NCH_A), 3.80 (3H, s, O*Me*), 4.11 (1H, d, *J* 15.0, NCH_B), 4.16 (1H, d, *J* 3.3, C(3)*H*), 4.20 (1H, q, *J* 6.8, C(α)*H*), 4.38 (1H, d, *J* 3.3, C(2)*H*), 6.85 (2H, d, *J* 8.9, Ar$_{ortho}$*H*), 7.40 (2H, d, *J* 8.9, Ar$_{meta}$*H*), 7.17–7.49 (10H, m, Ph*H*); δ_C (100 MHz, $CDCl_3$) 13.9 (C(α)*Me*), 27.7 (C(*Me*)$_3$), 52.2 (*C*(α)H), 55.2 (*C*H$_2$), 57.1 (O*Me*), 65.2 (*C*(3)H), 73.4 (*C*(Me)$_3$), 82.1 (*C*(2)H), 113.2, 113.3 (*Ar*$_{ortho}$, C$_6$H$_4$–OMe), 126.6, 126.8 (*Ph*$_{para}$), 127.9, 128.0, 128.1, 128.2, 130.2 (*Ph*$_{ortho}$, *Ph*$_{meta}$, *Ar*$_{para}$, C$_6$H$_4$–OMe) 130.9, 131.0 (*Ar*$_{meta}$, C$_6$H$_4$–OMe), 141.9, 144.2 (*Ph*$_{ipso}$), 158.9 (*Ar*$_{ipso}$, C$_6$H$_4$–OMe), 172.1 (*C*O); *m*/*z* (APCI$^+$) 462 (MH$^+$, 2%), 195 (100); HRMS (CI) $C_{29}H_{36}NO_4^+$ requires 462.2644; found 462.2642.

Preparation of (2*R*,3*R*)-*tert*-butyl 2-hydroxy-3-amino-3-(*p*-methoxyphenyl)propanoate 8. Pearlman's catalyst (0.5 g) was added to a solution of **7** (1.5 g, 3.0 mmol) in degassed MeOH (10 mL) and stirred vigorously under five atmospheres of H_2 gas for 24 hours. The reaction mixture was then filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to afford the crude product as a yellow solid. Purification *via* flash column chromatography on silica (Et_2O : MeOH, 9 : 1) gave (2*R*,3*R*)-**8** as a colourless solid (0.77 g, 96%); $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24%; found C, 63.00; H, 7.79; N, 5.54%; $[\alpha]_D^{25}$ −1.2 (*c* 2.1, $CHCl_3$); mp 111–114 °C; ν_{max} (KBr) 3366 (N–H), 3287 (O–H), 1734 (C=O); δ_H (500 MHz, $CDCl_3$), 1.35 (9H, s, C(*Me*)$_3$), 2.28 (3H, br s, NH_2 and O*H*), 3.77 (3H, s, O*Me*), 4.21 (1H, d, *J* 3.6, C(2)*H*), 4.31 (1H, d, *J* 3.6, C(3)*H*), 6.83 (2H, d, *J* 8.9, Ar$_{ortho}$*H*), 7.24 (2H, d, *J* 8.9, Ar$_{meta}$*H*); δ_C (125MHz, $CDCl_3$) 27.8 (C*Me*$_3$), 57.4 (O*Me*), 74.8 (*C*Me$_3$), 77.2 (*C*(3)H), 82.5 (*C*(2)H), 113.4, 113.6 (*Ar*$_{ortho}$), 128.3, 128.4 (*Ar*$_{meta}$), 132.8 (*Ar*$_{para}$), 158.9 (*Ar*$_{ipso}$), 171.6 (*C*O); *m*/*z* (APCI$^+$) 268 (MH$^+$, 12%), 195 (100); HRMS (CI) $C_{14}H_{22}NO_4^+$ requires 268.1549, found 268.1542.

Preparation of (4*R*,5*R*)-4-(*p*-methoxyphenyl)-5-*tert*-butoxy-carbonyl oxazolidin-2-one 9. (i). With CDI; to a solution of **8** (100 mg, 0.40 mmol) in THF (3 mL) were added carbonyl diimidazole (100 mg, 0.60 mmol) and DMAP (10 mg, 0.08

mmol). The reaction mixture was stirred for 24 h at rt before addition of saturated aqueous NH_4Cl (2 mL). The aqueous phase was extracted with EtOAc (3 × 5 mL), washed with brine (10 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (Et_2O) gave (4*R*,5*R*)-**9** as a colourless solid (42 mg, 36%).

(ii). With diphosgene; diphosgene (0.29 mL, 2.39 mmol) was added dropwise to a stirred suspension of **8** (580 mg, 2.17 mmol) and activated charcoal (100mg) in toluene (20 mL) and the mixture stirred for 1 h at rt before refluxing for 4 h. After recooling to rt, the mixture was filtered through Celite® and concentrated *in vacuo* to yield a crude product which was washed with saturated aqueous NH_4Cl (20 mL), extracted with EtOAc (3 × 20 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (Et_2O) gave (4*R*,5*R*)-**9** as a colourless solid (550 mg, 88%); $[\alpha]_D^{25}$ −1.3 (*c* 1.8, $CHCl_3$), mp 153–155 °C; ν_{max} (KBr) 1778 (C=O, oxazolidinone), 1744 (C=O, ester); δ_H (400 MHz, $CDCl_3$) 1.07 (9H, s, CMe_3), 3.80 (3H, s, O*Me*), 5.11 (1H, d, *J* 9.3, C(5)*H*), 5.15 (1H, d, *J* 9.3, C(4)*H*), 5.99 (1H, br s, N*H*), 6.88 (2H, d, *J* 8.8, $Ar_{ortho}H$), 7.24 (2H, d, *J* 8.8, $Ar_{meta}H$); δ_C (100 MHz, $CDCl_3$) 29.0 (CMe_3), 50.6 (*C*(4)H), 55.4 (O*Me*), 77.9 (*C*Me_3), 83.0 (*C*(5)H), 114.1 (Ar_{ortho}), 127.9 (Ar_{meta}), 128.7 (Ar_{para}), 158.4 (Ar_{ipso}), 160.4 (N*C*O), 165.3 (*C*O); *m*/*z* (APCI$^+$) 294 (MH^+, 90%), 238 (100); HRMS (CI) $C_{15}H_{20}NO_5^+$ requires 294.1341, found 294.1352.

Preparation of (4*R*,5*R*)-4-(*p*-methoxyphenyl)-5-hydroxymethyl oxazolidin-2-one 1[6]**.** (i). DIBAL-H (1.0 M in hexanes, 0.85 mL, 0.85 mmol) was added dropwise to a solution of **9** (25 mg, 0.09 mmol) in DCM (2 mL) at 0 °C. The resulting solution was allowed to warm to rt over 6 h before the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on silica (Et_2O : MeOH, 99 : 1) gave **1** as a colourless solid (15 mg, 75%).

(ii). Superhydride (1.0 M in THF, 0.85 mL, 0.85 mmol) was added dropwise to a solution of **9** (25 mg, 0.09 mmol) in THF (2 mL) at 0 °C. The resulting solution was allowed to warm to rt over 6 h before the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on silica (Et_2O : MeOH, 99 : 1) gave **1** as a colourless solid (14 mg, 70%).

(iii). Mixed anydride route; **9** (50 mg, 0.17 mmol) was treated with TFA (1.8 mL) in DCM (0.2 mL) at rt for 1 h before the volatiles were removed *in vacuo* to yield a colourless solid. The residue was coevaporated with DCM–toluene (1 : 1) and MeOH–toluene (1 : 1). The residue (50 mg, 0.28 mmol) was treated with ethyl chloroformate (28 mg, 0.26 mmol) and NEt_3 (26 mg, 0.26 mmol) in THF (5 mL) at rt and allowed to warm to rt for 2h, before the addition of $NaBH_4$ (1.02 mL, 0.5 M in diglyme, 0.51 mmol) at 0 °C. The resulting solution was allowed to warm to rt over 6 h before the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 5 mL), dried, filtered and concentrated *in vacuo*. Purification *via* column chromatography on silica (Et_2O : MeOH, 99 : 1) gave **1** as a colourless solid (35 mg, 92%) with spectroscopic data comparable to the literature; $[\alpha]_D^{25}$ −72.0 (*c* 1.0, MeOH) {lit.[6] $[\alpha]_D^{25}$ −75.7 (*c* 1.0, MeOH)}; δ_H (400 MHz, acetone) 3.17–3.27 (2H, br m, CH_2), 3.81 (3H, s, O*Me*), 3.86 (1H, br s, O*H*), 4.82 (1H, ddd, *J* 4.2, *J* 8.2, *J* 8.4, C(5)*H*), 5.03 (1H, d, *J* 8.2, C(4)*H*), 6.95 (2H, d, *J* 8.8, $Ar_{ortho}H$), 6.97 (1H, br s, N*H*), 7.25 (2H, d, *J* 8.8, $Ar_{meta}H$); δ_C (125 MHz, acetone) 55.6 (O*Me*), 57.8 (*C*5), 62.5 (*C*H_2), 81.5 (*C*4), 114.7 (Ar_{ortho}), 129.1 (Ar_{meta}), 130.3 (Ar_{para}), 159.6 (*C*O), 160.7 (Ar_{ipso}).

Preparation of (3*R*,α*R*)-*tert*-butyl 2-oxo-3-(*p*-methoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)propanoate 10 and (α*R*)-*tert*-butyl 2-hydroxy-3-(*p*-methoxyphenyl)-3-(*N*-benzyl-*N*-α-methylbenzylamino)prop-2-enoate 11. Compound **7** (100 mg, 0.22 mmol) and IBX (67 mg, 0.24 mmol) were stirred in DMSO (5 mL) for 16 h. H_2O (10 mL) was added and the mixture extracted with DCM (3 × 5 mL), washed with H_2O (5 × 5 mL) dried, filtered and concentrated *in vacuo* to yield a crude product. ^{1}H 400 MHz NMR spectroscopic analysis obtained immediately after work-up showed the predominance of ketone **10**; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.8, *C*(α)*Me*), 1.29 (9H, s, C(*Me*)$_3$), 3.79 (3H, s, O*Me*), 3.97 (1H, d, *J* 15.5, NCH_A), 4.14 (1H, d, *J* 15.5, NCH_B), 4.20 (1H, q, *J* 6.8, C(α)*H*), 5.33 (1H, s, C(3)*H*), 7.14–7.50 (14H, m, Ar*H*, Ph*H*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 27.5 (C(*Me*)$_3$), 51.2 (*C*(α)H), 55.2 (*C*H_2), 59.6 (O*Me*), 67.4 (*C*(3)H), 73.4 (*C*(Me)$_3$), 114.0, 114.3 (Ar_{ortho}), 126.3, 126.4, 126.7, 127.0, 127.2, 127.5, 128.0, 128.1, 128.2, 128.4 (Ph_{ortho}, Ph_{meta}, Ph_{para}, Ar_{para}) 131.0, 131.3 (Ar_{meta}), 142.2, 144.3 (Ph_{ipso}), 159.4 (*C*O), 160.9 (Ar_{ipso}), 196.5 (*C*(2)O); After standing for 2.5 h the ketone **10** had tautomerised to the enol form **11**; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, C(*Me*)$_3$), 1.60 (3H, d, *J* 6.9, *C*(α)*Me*), 3.80 (3H, s, O*Me*), 3.97 (1H, d, *J* 15.7, NCH_A),4.05 (1H, d, *J* 15.7, NCH_B), 4.87 (1H, q, *J* 6.9, C(α)*H*), 6.75–7.50 (14H, m, Ar*H*, Ph*H*); δ_C (100 MHz, $CDCl_3$) 18.4 (C(α)*Me*), 27.6 (C(*Me*)$_3$), 48.3 (*C*(α)H), 55.3 (*C*H_2), 58.7 (O*Me*), 73.4 (*C*(Me)$_3$), 112.9 (*C*2), 114.0, 114.3 (Ar_{ortho}), 127.0, 127.1, 127.2, 127.4, 127.5, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 128.9, 129.0 (Ph_{ortho}, Ph_{meta}, Ph_{para}, Ar_{meta}, Ar_{para}) 132.6 (*C*3), 140.7, 143.4 (Ph_{ipso}), 159.6 (Ar_{ipso}), 166.8 (*C*O).

Preparation of (2*R*,3*R*)-*tert*-butyl 2-hydroxy-3-(*p*-methoxyphenyl)-3-(*N*-*tert*-butoxy-carbonylamino)propanoate 12. A solution of **8** (0.30 g, 1.1 mmol), Boc_2O (0.26 g, 1.2 mmol) and $NaHCO_3$ (0.19 g, 2.2 mmol) in MeOH (5 mL) was sonicated for 12h. The reaction mixture was concentrated *in vacuo* and partitioned between saturated aqueous NH_4Cl and Et_2O, the combined organic extracts were dried, filtered and concentrated *in vacuo* to yield a crude product. Purification *via* flash column chromatography on silica (30–40 petroleum : Et_2O, 1 : 1) afforded (2*R*,3*R*)-**12** as a colourless oil (0.37 g, 90%); $[\alpha]_D^{25}$ −1.5 (*c* 3.8, $CHCl_3$); ν_{max} ($CHCl_3$) 3020 (O–H), 1710 (br, 2 × C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (9H, s, N–*Boc*), 1.47 (9H, s, C(*Me*)$_3$), 3.30 (1H, br s, O*H*), 3.78 (3H, s, O*Me*), 4.46 (1H, br s, N*H*), 5.01 (1H, d, *J* 8.8, C(2)*H*), 5.57 (1H, d, *J* 8.8, C(3)*H*), 6.83 (2H, d, *J* 8.7, $Ar_{ortho}H$), 7.26 (2H, d, *J* 8.7, $Ar_{meta}H$); δ_C (100 MHz, $CDCl_3$) 27.9 (Boc–CMe_3), 28.4 (CMe_3), 55.2 (*C*(3)H), 55.7 (O*Me*), 73.1 (Boc–*C*Me$_3$), 79.7 (*C*Me$_3$), 83.4 (*C*(2)H), 113.6, 113.8 (Ar_{ortho}), 129.0, 129.1 (Ar_{meta}), 129.4 (Ar_{para}), 154.9 (Boc-*C*O), 159.3 (Ar_{ipso}), 171.0 (*C*O); *m*/*z* (APCI$^+$) 368 (MH^+ 2%) 195 (100); HRMS (CI) $C_{19}H_{28}NO_6Na^+$ requires 390.1893, found 390.1881.

Preparation of (2*R*,3*R*)-*tert*-butyl 2-methanesulfonyloxy-3-(*p*-methoxyphenyl)-3-(*N*-tert-butoxy-carbonylamino)propanoate 13. Methanesulfonyl chloride (0.09 mL, 1.13 mmol) was added to a stirred solution of **12** (395 mg, 1.08 mmol) and NEt_3 (0.21 mL, 1.51 mmol) in DCM (20 mL) at 0 °C and stirred for 40 minutes, before warming to rt. After stirring for 24 h, the reaction mixture was quenched with H_2O (10 mL), extracted with DCM (4 × 20 mL), washed with brine, dried, filtered and concentrated *in vacuo* to yield the crude product. Purification *via* flash column chromatography on silica (30–40 °C petroleum : Et_2O, 1 : 1) afforded **13** as a pale yellow oil (432 mg, 0.97 mmol, 90%); $[\alpha]_D^{25}$ −18.2 (*c* 2.0, $CHCl_3$); ν_{max} (thin film) 1749 (C=O ester), 1712 (C=O carbamate); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, N-*Boc*), 1.43 (9H, s, C(*Me*)$_3$), 3.14 (3H, s, SO_2Me), 3.78 (3H, s, O*Me*), 5.21–5.22 (2H, m, N*H* & C(2)*H*), 5.43 (1H, d, *J* 3.2, C(3)*H*), 6.82–6.86 (2H, m, $Ar_{ortho}H$), 7.28 (2H, d, *J* 8.3, $Ar_{meta}H$); δ_C (100 MHz, $CDCl_3$) 27.8 (Boc-CMe_3), 28.3 (CMe_3), 39.1 (SO_2Me), 54.6 (*C*(3)H), 55.2 (O*Me*), 79.2 (*C*(2)H), 80.3 (Boc-*C*Me$_3$), 83.8 (*C*Me$_3$), 113.9 (Ar_{ortho}), 127.9 (Ar_{para}), 129.3 (Ar_{meta}), 154.8 (Ar_{ipso}), 159.6 (Boc-*C*O), 165.5 (*C*O); *m*/*z* (CI$^+$)

468 (MNa^+, 100%), 366 (25), 334 (40), 273 (40); HRMS (CI) $C_{20}H_{31}NO_8SNa^+$ requires 468.1668, found 468.1662.

Preparation of (4*R*,5*S*)-4-(*p*-methoxyphenyl)-5-*tert*-butoxycarbonyl oxazolidin-2-one 14. A solution of **13** (370 mg, 0.83 mmol) in DMF (20 mL) was warmed to 60 °C for 18 h, then cooled to rt. After stirring for a further 24 h, the reaction mixture was diluted with water, extracted with DCM (5 × 20 mL), dried, filtered and concentrated *in vacuo* to yield a crude product (330 mg). Purification by column chromatography on silica (30–40 °C petroleum : Et_2O, 1 : 1) afforded **14** as a white solid (187 mg, 0.64 mmol, 77%); mp 104–105 °C (pentane–Et_2O); $[a]_D^{22}$ +94.7 (*c* 0.55, MeOH); ν_{max} (KBr disc) 1771 (C=O ester), 1726 (C=O oxazolidin-2-one); δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C(*Me*)$_3$), 3.81 (3H, s, O*Me*), 4.58 (1H, d, *J* 5.7, C(2)*H*), 4.86 (1H, d, *J* 5.7, C(3)*H*), 6.66 (1H, s, N*H*), 6.90–6.93 (2H, m, $Ar_{ortho}H$), 7.26–7.28 (2H, m, $Ar_{meta}H$); δ_C (100 MHz, $CDCl_3$) 27.9 (C*Me*$_3$), 55.3 (O*Me*), 58.9 (*C*(3)H), 80.9 (*C*(2)H), 83.6 (*C*Me$_3$), 114.5 (Ar_{ortho}), 127.3 (Ar_{meta}), 131.1 (Ar_{para}), 15.83 (N*C*O), 160.0 (*C*O), 167.3 (Ar_{ipso}); *m*/*z* (ES^-) 292 ($M - H^+$, 100%); HRMS (ES−) $C_{15}H_{19}NO_5 - H^+$ requires 292.1185, found 292.1177.

Preparation of (4*R*,5*S*)-4-(*p*-methoxyphenyl)-5-hydroxymethyl oxazolidin-2-one 5. Superhydride (1.0 M in THF, 2.05 mL, 2.05 mmol) was added dropwise to a solution of **14** (150 mg, 0.51 mmol) in THF (20 mL) at 0 °C. The resulting solution was allowed to warm to rt over 6 h before the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc (3 × 15 mL), dried, filtered and concentrated *in vacuo*. Purification *via* flash column chromatography on silica (Et_2O : MeOH, 99 : 1) gave **5** (107 mg, 94%) as a colourless solid; mp 158–160 °C (MeOH–Et_2O); $[a]_D^{23}$ +28.6 (*c* 1.0, MeOH); δ_H (500 MHz, CD_3OD) 3.69 (1H, dd, *J* 4.5, *J* 12.5, CH_A), 3.79 (3H, s, O*Me*), 3.82 (1H, dd, *J* 3.5, *J* 12.5, CH_B), 4.32 (1H, ddd, *J* 3.5, *J* 4.5, *J* 6.5, C(5)*H*), 4.75 (1H, d, *J*6.5, C(4)*H*), 6.96 (2H, d, *J* 8.5, $Ar_{ortho}H$), 7.30 (2H, d, *J* 8.5, $Ar_{meta}H$); δ_C (125MHz, CD_3OD) 55.9 (O*Me*), 58.7 (*C*5), 62.6 (*C*H_2), 87.0 (*C*4), 115.6 (Ar_{ortho}), 128.8 (Ar_{meta}), 133.7 (Ar_{para}), 160.8 (*C*O), 161.5 (Ar_{ipso}).

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References and notes

1 H. Kakeya, M. Morishita, H. Koshino, T. Morita, K. Kobayashi and H. Osada, *J. Org. Chem.*, 1999, **64**, 1052.
2 H. Kakeya, M. Morishita, K. Kobinata, M. Osono, M. Ishizuka and H. Osada, *J. Antibiot.*, 1998, **51**, 1126.
3 Z. Hamersak, E. Ljubovic, M. Mercep, M. Mesic and V. Sunjic, *Synthesis*, 2001, **13**, 1989.
4 O. Miyata, H. Asai and T. Naito, *Synlett*, 1999, **12**, 1915.
5 A. Madham, A. R. Kumar and B. V. Rao, *Tetrahedron: Asymmetry*, 2001, **12**, 2009.
6 Y. Sakamoto, A. Shiraishi, J. Seonhee and T. Nakata, *Tetrahedron Lett.*, 1999, **40**, 4203.
7 M. Seki and K. Mori, *Eur. J. Org. Chem.*, 1999, 2965.
8 S. Milicevic, R. Matovic and R. N. Saicic, *Tetrahedron Lett.*, 2004, **45**, 955.
9 P. H. Carter, J. R. LaPorte, P. A. Scherle and C. P. Decicco, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1237.
10 A. N. Chernaga, M. E. Bunnage, S. G. Davies and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2373.
11 D. Ma, T. Zhang, G. Wang, A. P. Kozikowski, N. E. Lewin and P. M. Blumberg, *Bioorg. Med. Chem. Lett.*, 2001, **10**, 99.
12 P. Deprez, J. Royer and H-P. Husson, *Tetrahedron*, 1993, **49**, 3781.
13 S. Harashima, O. Oda, S. Amemiya and L. Kojima, *Tetrahedron*, 1991, **47**, 2773.
14 M. M. Kabat, L. M. Garofalo, A. R. Daniewski, S. D. Hutchings, W. Liu, M. Okabe, R. Radinov and Y. Zhou, *J. Org. Chem.*, 2001, **66**, 6141.
15 C. G. Boojamra, R. C. Lemoine, J. C. Lee, R. Léger, K. A. Stein, N. G. Vernier, A. Magon, O. Lomovskaya, P. K. Martin, S. Chamberland, M. D. Lee, S. J. Hecker and V. J. Lee, *J. Am. Chem. Soc.*, 2001, **123**, 870.
16 T. T. Tidwell, *Org. React.*, 1990, **39**, 297.
17 M. E. Bunnage, S. G. Davies and C. J. Goodwin, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2385.
18 For another recent application of this strategy see : M. E. Bunnage, A. J. Burke, S. G. Davies, N. L. Millican, R. L. Nicholson, P. M. Roberts and A. D. Smith, *Org. Biomol. Chem.*, 2003, 3708. For a related protocol for C(2)-inversion of α-hydroxy-β-amino esters see reference 17.