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A practical synthesis of enantiopure (*S*)-4-(4-hydroxybenzyl)-oxazolidin-2-one

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Abstract—A high yielding four-step synthesis of enantiopure 4-(4-hydroxybenzyl)-oxazolidin-2-one (*S*)-**1** from *N*-Boc-L-tyrosine is described. (*S*)-**1** is a key intermediate for the preparation of a number of polymer supported Evans' oxazolidin-2-ones that have been employed previously for solid supported asymmetric synthesis.

1. Introduction

There is currently much interest within the synthetic community directed towards the development of polymer supported chiral auxiliaries for the asymmetric synthesis of libraries of chiral compounds.[1] Within this area, a number of chiral polymer supported oxazolidin-2-ones derived from L-tyrosine have been described in which the chiral auxiliary fragment 4-(4-hydroxybenzyl)-oxazolidin-2-one (*S*)-**1** is attached to polymer support via its phenolic group.[2] These chiral polymers have been employed in asymmetric synthesis for a range of synthetic transformations including enolate alkylations,[2] aldol reactions,[3] Diels–Alder[4] and 1,3-dipolar cycloadditions.[5] As part of a research program directed towards the efficient use of chiral auxiliaries for asymmetric synthesis we required access to gram quantities of (*S*)-**1**. Consequently, we describe herein a facile four step synthesis that enables oxazolidin-2-one (*S*)-**1** to be prepared from *N*-Boc-L-tyrosine in good yield, using a synthetic protocol that proceeds via highly crystalline intermediates that do not require chromatography for purification.

2. Results and discussion

We required a synthesis of (*S*)-**1** that was high yielding and amenable to scale-up. A review of the literature revealed that five routes (**A**–**E**) to (*S*)-**1** had been reported previously, the details of which are described in Scheme 1.[6] Routes **A** and **B** involve a strategy in which the carboxylate and amino groups of L-tyrosine were protected as an ester and carbamate respectively. Subsequent reduction of the ester group with $NaBH_4$ affords an alkoxide that undergoes intramolecular cyclisation onto the carbonyl of the carbamate protecting group yielding oxazolidin-2-one (*S*)-**1**.[5,7] Route **C** was the shortest approach to (*S*)-**1** employing Evans' original conditions[8] for oxazolidin-2-one formation involving borane mediated reduction of the acid functionality of L-tyrosine, followed by treatment of the resultant amino-alcohol with diethyl carbonate under basic conditions.[3b] Route **D** employed *O*-benzyl-L-tyrosine that was reduced to the corresponding alcohol using $LiAlH_4$, followed by treatment with phosgene to afford an *O*-benzyl oxazolidin-2-one that was deprotected to (*S*)-**1** via hydrogenolysis.[3a] Finally, route **E** exploited *O*-benzyl-*N*-Boc-L-tyrosine as starting material that was reduced to its *N*-Boc-amino-alcohol, prior to *N*-Boc deprotection and treatment of the resulting amino-alcohol with phosgene to afford an *O*-benzyl-

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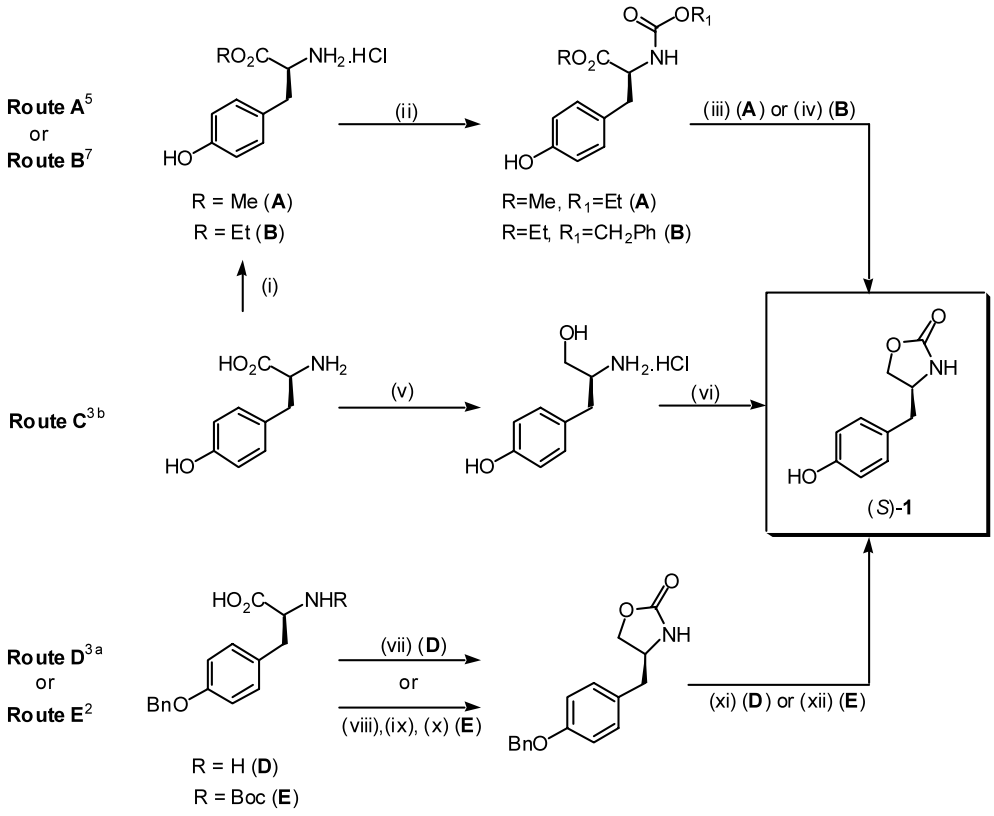
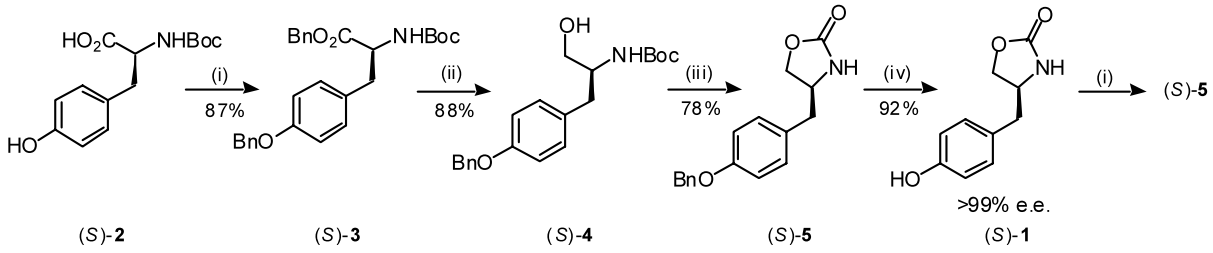


Scheme 1. *Reagents and conditions*: (i) $SOCl_2$, MeOH, >95% (**A**);[5] or EtOH, HCl (**B**);[7] (ii) (a) K_2CO_3, (b) EtOCOCl, $NaHCO_3$, >95%, (**A**);[5] or BnOCOCl, Na_2CO_3 (aq.), $CHCl_3$, (**B**);[7] (iii) (a) $NaBH_4$, THF, Δ, 82%; (b) K_2CO_3, toluene, Δ, 50% (**A**);[5] (iv) $NaBH_4$, LiI, THF, Δ, 90% (**B**);[7] (v) (a) $BH_3{\cdot}SMe_2$, $BF_3{\cdot}OEt_2$, THF, Δ; (b) 5 M NaOH (aq.), Δ; (c) 6 M HCl (aq.), 83% (three steps) (**C**);[3b] (vi) (a) $NaHCO_3$ (aq.), (b) $(EtO)_2CO$, K_2CO_3, 125°C, 86% (two steps) (**C**);[3b] (vii) (a) $LiAlH_4$, THF, 60°C, (b) $COCl_2$, toluene, 82% (two steps) (**D**);[3a] (viii) (a) ^{i}PrOCOCl, Et_3N, THF, (**E**), (b) $NaBH_4$ (**E**);[2] (ix) HCl, Et_2O–EtOAc, 25°C, 93% (**E**);[2] (x) $COCl_2$, KOH–K_2CO_3 (aq.), toluene, 0–25°C, 98% (**E**);[2] (xi) H_2, cat. Pd/C, EtOH (**D**);[3a] (xii) H_2, cat. Pd/C, MeOH–EtOAc, 25°C, 96% (**E**).[2]

oxazolidin-2-one that was once again deprotected to (*S*)-**1** under hydrogenolytic conditions.[2]

Preliminary investigations into the synthesis of oxazolidin-2-one (*S*)-**1** using routes **A**–**C** proved unsatisfactory in our hands, both in terms of yield and reproducibility, primarily due to difficulties associated with the purification of non-crystalline polar intermediates containing unprotected phenolic substituents. Whilst these polarity problems could potentially be overcome in routes **D** and **E** using *O*-benzyl-L-tyrosine derivatives as substrates, the prospect of employing phosgene for oxazolidin-2-one ring formation on a large scale was unattractive. Consequently, we considered an alternative synthesis of (*S*)-**1** that would combine the relatively non-polar *O*-benzyl-L-tyrosine substrates employed in routes **D** and **E**, with the intramolecular alkoxide/*N*-carbamate cyclisation strategy for oxazolidin-2-one ring formation used in routes **A** and **B**. It was proposed that this strategy would enable (*S*)-**1** to be prepared in four steps from commercially available *N*-Boc-L-tyrosine,[9] without the necessity of using phosgene as a reagent for oxazolidin-2-one ring formation, according to the synthetic protocol described in Scheme 2.



Scheme 2. *Reagents and conditions:* (i) 3 equiv. BnBr, K_2CO_3, Bu_4NI (12.5 mol%), DMF; (ii) $LiAlH_4$, THF, 0°C→rt; (iii) NaH, THF; (iv) H_2, Pd/C, MeOH/EtOAc.

The carboxylate and phenolate functionalities of *N*-Boc-L-tyrosine (*S*)-**2** were *per*benzylated via treatment with K_2CO_3 and 3.0 equiv. of BnBr in DMF, in the presence of a catalytic amount of Bu_4NI, to afford *O*-benzyl-*N*-Boc-L-tyrosine benzyl ester (*S*)-**3** in 87% yield.[10] Subsequent reduction of (*S*)-**3** with $LiAlH_4$ in THF (0°C→rt) afforded *N*-Boc-*O*-benzyl-L-tyrosinol (*S*)-**4** in 88% yield.[11] Treatment of (*S*)-**4** with NaH in THF at room temperature resulted in intramolecular cyclisation of the resulting alkoxide onto the *N*-Boc-protecting group to afford (*S*)-4-(4-benzyloxybenzyl)-oxazolidin-2-one (*S*)-**5** as the sole product in 78% yield.[12] The enantiomeric excess of (*S*)-**5** was confirmed to be >99% e.e. via chiral HPLC analysis over a Chiralcel OD® stationary phase in comparison with a racemic sample of **5**. Finally, debenzylation of (*S*)-**5**, using the hydrogenolytic conditions of Burgess et al.,[2] was carried out using Pd/C in a mixed solvent of MeOH/EtOAc, to afford the target 4-(4-hydroxybenzyl)-oxazolidin-2-one (*S*)-**1** in an excellent 92% yield (Scheme 2). The enantiomeric excess of (*S*)-**1** was confirmed as >99% e.e. by conversion to (*S*)-**5** via treatment with excess benzyl bromide, K_2CO_3, and Bu_4NI in DMF, followed by chiral HPLC analysis as described. It should be noted that all of the intermediates in this synthetic protocol are *crystalline*, enabling purification at each step of the synthesis to be achieved via simple recrystallisation of the crude reaction products, thus enabling enantiopure (*S*)-**1** to be prepared in an overall 55% yield from *N*-Boc-L-tyrosine without recourse to chromatography.

2.1. X-Ray crystal structure of 4-(4-benzyloxybenzyl)-oxazolidin-2-one 5

4-(4-Benzyloxybenzyl)-oxazolidin-2-one (*S*)-**5** was sufficiently crystalline for an X-ray crystal structure to be determined, the results of which are depicted in Figure 1. Packing within the unit cell was dominated by hydrogen bonding between the carbonyl group of one oxazolidin-2-one molecule to the N–H group of an adjacent oxazolidin-2-one affording long hydrogen-bonded 'ladders' in which the 4-aryl substituents of each oxazolidin-2-one molecule are alternately staggered orthogonal to the plane of the hydrogen bonded ladder. This hydrogen bonded ladder structural motif has been observed previously in the solid state structures of (*S*)-4-(chlorophenylmethyl)-oxazolidin-2-one[13] and (*S*)-4-benzyl-oxazolidin-2-one[14] as detailed in the CCDC database.[15]

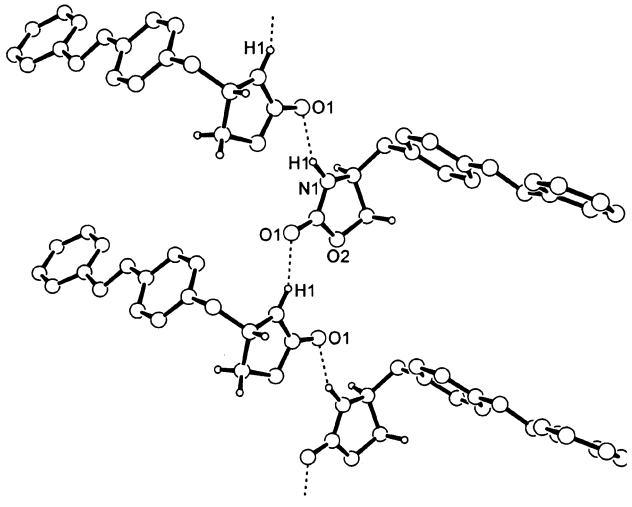


Figure 1. X-Ray crystal structure plot illustrating intermolecular hydrogen bonding between molecules of (*S*)-**5** in the solid state.

3. Conclusion

A high yielding four step synthesis of enantiopure 4-(4-hydroxybenzyl)-oxazolidin-2-one (*S*)-**1** from *N*-Boc-L-tyrosine via crystalline intermediates is described. (*S*)-**1** is a key intermediate for the preparation of a number of polymer supported Evans' oxazolidin-2-ones that have been employed previously for solid supported asymmetric synthesis.

4. Experimental

Anhydrous THF was obtained via distillation under nitrogen from sodium benzophenone ketyl. All commercial reagents were used without purification unless stated otherwise. Reactions were monitored by TLC on Whatman aluminium backed UV_{254} silica gel plates. Melting points were measured on a Büchi 535 melting point apparatus and are uncorrected. Specific rotations were measured with an AA-10 automatic polarimeter from Optical Rotations Ltd. Proton and carbon magnetic resonance spectra (^1H and ^{13}C NMR) were recorded on a Bruker 300 MHz spectrometer. The assignment of ^{13}C NMR data was assisted by DEPT experiments. Mass spectra were carried out at Swansea, University of Wales (Finnigan MAT 8340 instrument). High Performance Liquid Chromatography was performed on SP Thermo Separation products spectra SERIES and Spectra Physics Systems using a Chiralcel OD® column obtained from Fisher Scientific supplies.

4.1. *O*-Benzyl-*N*-Boc-L-tyrosine benzyl ester {(*S*)-3-(4-benzyloxyphenyl)-2-tert-butoxycarbonyl amino-propionic acid benzyl ester} 3

Potassium carbonate (29.59 g, 214.5 mmol), benzyl bromide (15.3 mL, 128.7 mmol) and tetrabutylammonium iodide (1.98 g, 5.4 mmol) were added to a solution of *N*-Boc-L-tyrosine (*S*)-**2** (12.1 g, 42.9 mmol) in DMF (150 mL). The mixture was stirred for 48 h at rt followed by addition of water (200 mL) and extraction with ethyl acetate (3×150 mL). The organic fractions were combined, washed with 1N HCl and brine, dried over sodium sulphate, and the solvent removed in vacuo to afford a dark orange oil that was recrystallised (Et_2O/petrol) to afford a crystalline solid (17.23 g, 87%). Mp 85–86°C, lit.[16] 74–75°C; $[\alpha]_D^{21} = -7.9$ (*c* 29.7, EtOAc); lit.[16] = −8.0 (*c* 10, DMF); ^1H NMR ($CDCl_3$, 300 MHz): δ 1.41 (9H, s, $OC(CH_3)_3$), 2.98 (2H, d, $J = 5.65$ Hz, $C_6H_4CH_2$), 4.52 (1H, m, C*H*), 4.89 (1H,

d, $J=8.3$ Hz, NH), 4.95 (2H, s, PhCH_2OAr), 5.06 (2H, m, CH_2O), 6.76 (2H, app d, Ar-H, $J=8.6$ Hz), 6.87 (2H, app d, Ar-H, $J=8.6$ Hz), 7.21–7.38 (10H, bm, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 28.3 (CH_3), 37.4 (CH_2), 54.5 (CH), 67.0 (C), 70.0 (CH_2), 79.9 (CH_2), 114.9 (CH), 127.9 (CH), 128.6 (CH), 130.4 (CH_2), 130.5 (CH), 135.2 (C), 137.0 (C), 155.1 (C), 157.8 (C), 171.80 (C); m/z (CI^+) 462 (MH^+, 41%).

4.2. *O*-Benzyl-*N*-Boc-L-tyrosinol {(*S*)-[1-(4-Benzyloxybenzyl)-2-hydroxyethyl]-carbamic acid *tert*-butyl ester} 4

A solution of ester (*S*)-**3** (9.72 g, 21.1 mmol) in THF (40 mL) was added to a vigorously stirred solution of $LiAlH_4$ (31.6 mL, 1.0 M, 31.6 mmol) in THF at 0°C over a period of 45 min (**CAUTION** evolution of hydrogen). The reaction mixture was then stirred at rt for 1 h before quenching via dropwise addition of aqueous potassium hydroxide solution (85 mL, 10%). The resulting solution was filtered through a pad of Celite® to remove the gelatinous white precipitate, before being extracted with ethyl acetate. The organic layers were combined, washed with brine (3×20 mL), dried with magnesium sulphate, and the solvent removed in vacuo to afford the title compound (6.62 g, 18.5 mmol, 88%) as a cream powder. Mp 102–103°C, lit.[17] 108–109°C; $[\alpha]_D^{21}=-18.0$ (c 17.4, EtOAc), lit.[17] $=-17.0$ (c 10.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.33 (9H, s, OC(CH_3)$_3$), 2.68 (2H, d, $C_6H_4CH_2$, $J=6.8$ Hz), 3.43 (1H, dd, CH_AH_BOH, $J=10.9$ Hz, 5.3 Hz), 3.55 (1H, dd, CH_AH_BOH, $J=10.9$ Hz, 3.8 Hz), 3.72 (1H, m, N-CH), 4.72 (1H, bs, NH), 4.95 (2H, s, PhCH_2OAr), 6.83 (2H, app d, Ar-H, $J=8.5$ Hz), 7.04 (2H, app d, Ar-H, $J=8.5$ Hz), 7.18–7.37 (5H, bm, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 27.3 (CH_3), 35.5 (CH_2), 52.8 (CH), 63.1 (C), 68.9 (CH_2), 78.6 (CH_2), 114.9 (CH), 126.0 (CH), 126.4 (CH), 126.9 (CH), 127.5 (CH), 129.1 (CH), 129.3 (C), 155.2 (C), 156.5 (C); m/z (EI^+) 357 (MH^+, 39%).

4.3. (*S*)-4-(4-Benzyloxybenzyl)-oxazolidin-2-one 5

A solution of alcohol (*S*)-**4** (5.2 g, 14.54 mmol) in THF (50 mL) was added to a suspension of sodium hydride (1.45 g, 36.4 mmol) in THF (200 mL) over a period of 20 min, stirred for 12 h, then quenched with a saturated solution of aqueous ammonium chloride (70 mL). The reaction mixture was then extracted with ethyl acetate (3×25 mL), the organic layers combined, washed with aqueous hydrochloric acid (100 mL, 5% solution), saturated $NaHCO_3$ solution (100 mL), and brine (100 mL), and then dried over magnesium sulphate. The solvent was then removed in vacuo to yield the title compound (3.12 g, 78%) as a white crystalline solid. Mp 133-134°C, lit.[7] 136–138°C; $[\alpha]_D^{21}=-85.1$ (c 50.5, EtOAc), lit.[7] $=-84.8$ (c 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.82 (2H, m, $C_6H_4CH_2$), 4.05 (1H, m, N-CH), 4.15 (1H, dd, CH_AH_BO, $J=8.5$ Hz, 5.5 Hz), 4.39 (1H, app t, $CHCH_AH_BO$, $J=8.5$ Hz), 4.98 (2H, s, PhCH_2OAr), 5.05 (1H, bs, NH), 6.87 (2H, app d, Ar-H, $J=8.5$ Hz), 7.02 (2H, app d, Ar-H, $J=8.5$ Hz), 7.25–7.38 (5H, bm, Ar-H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 41.2 (CH_2), 54.6 (CH), 70.3 (CH_2), 70.8 (CH_2), 116.7 (CH), 128.3 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 130.9 (C), 137.7 (C), 158.7 (C), 160.6 (C); m/z (EI^+) 283 (MH^+, 8%); HPLC: Chiralcel OD® column, solvent = hexane/isopropyl alcohol (80:20), flow rate = 1 mL/min, retention times = (*S*)-**5** = 28.7 min, (*R*)-**5** = 35.2 min.

4.4. (*S*)-4-(4-Hydroxy-benzyl)-oxazolidin-2-one 1

Oxazolidin-2-one (*S*)-**5** (2.00 g, 7.1 mmol) and Pd/C (5%) (744 mg, 0.35 mmol) were placed in a dry Schlenk tube under a hydrogen atmosphere. A mixture of methanol/ethyl acetate (1:1, 30 mL) was added via syringe. The resulting mixture was stirred at rt for 12 h, filtered through a pad of Celite®, which was washed thoroughly with ethyl acetate. The combined organic solvent was then removed in vacuo to yield (*S*)-**1** (1.25 g, 6.5 mmol, 92%) as a white powder. Mp 179–181°C, lit.[7] 175–178°C; $[\alpha]_D^{21}=-12.3$ (c 6.5, MeOH), lit.[5a] $=-11.8$ (c 5.0, EtOH); ^{1}H NMR (MeOD, 300 MHz): δ 2.67 (2H, m, $C_6H_4CH_2$), 4.01 (2H, m, O-CH_AH_B, CH), 4.27 (1H, m, O-CH_AH_B), 6.64 (2H, app d, Ar-H, $J=8.5$ Hz), 6.95 (2H, app d, Ar-H, $J=8.5$ Hz); ^{13}C NMR (MeOD, 75 MHz): δ 41.4 (CH_2), 55.6 (CH), 70.8 (CH_2), 116.8 (CH), 128.6 (CH), 130.9 (C), 157.9 (C), 162.7 (C); m/z (EI^+) 193 (MH^+, 5%); HRMS (ES^+) for $C_{10}H_{11}NO_3$ $[M+NH_4]^+$ requires 211.1077, Found 211.1079.

4.5. Determining the enantiomeric excess of (*S*)-1 via conversion to (*S*)-5

Potassium carbonate (2.96 g, 2.15 mmol), benzyl bromide (0.153 mL, 1.29 mmol) and tetrabutylammonium iodide (20 mg) were added to a solution of (*S*)-**1** (83 mg, 0.43 mmol) in DMF (1.5 mL). The mixture was stirred for 48 h at rt followed by addition of water (20 mL) and extraction with ethyl acetate (3×15 mL). The organic fractions were combined, washed with 1N HCl and brine, dried over sodium sulphate, and the solvent removed in vacuo to afford (*S*)-**5** (115 mg, 0.41 mmol) as a crystalline solid which was analysed via chiral HPLC using a Chiralcel OD® column and shown to be >99% e.e.

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