A cleavable linker strategy for optimizing the enolate alkylation reactions of a polymer-supported Evans' oxazolidin-2-one

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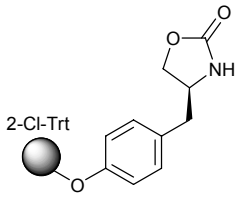
General procedure for carrying out TFA cleavage of 2-chlorotrityl polymer-supported oxazolidin-2-ones

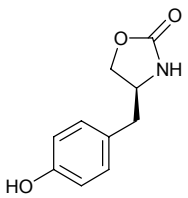
20 mg of resin was treated with a solution of CH_2Cl_2/trifluoroacetic acid/triisopropylsilane (94 :1 : 5) (4 mL) and the reaction swirled on an orbital shaker at room temperature for 30 min. The resin was then filtered off and washed sequentially with CH_2Cl_2 (5mL), THF (5mL) and MeOH (5mL). The organic solvent and washings were then combined together and solvent removed *in vacuo* to afford cleavage products whose mass was determined via weighing, and composition analysed *via* HPLC and/or ^{1}H NMR spectroscopy.

2-Cl-Trt-supported *N*-H-oxazolidin-2-one (*S*)-5



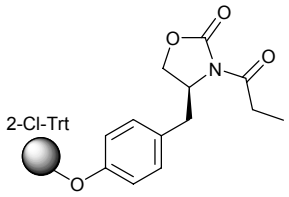
A solution of *NH*-oxazolidin-2-one (*S*)-**4** (695 mg, 3.6 mmol) in CH_2Cl_2/THF/DMF (50: 45: 5) was added to a suspension of preswollen 2-chlorotrityl chloride resin (1.00g, 1.20 mmol) in CH_2Cl_2/THF (1:1) (80 mL). Diisopropylethylamine (2.090 mL, 12.0 mmol) was then added and the reaction heated at 60 °C for 18 hours, after which time the reaction was cooled to room temperature and the resin removed *via* filtration. The resin was washed consecutively with CH_2Cl_2 (50mL), THF (50mL) and CH_2Cl_2/MeOH (50mL), and the resin dried thoroughly in a vacuum oven at 40 °C. The loading of resin (*S*)-**5** (IR, ν(C=O) = 1752cm^{-1}) was determined to be 1.16 mmolg^{-1} (97 %) *via* TFA cleavage to afford *O*H-*N*H-oxazolidin-2-one (*S*)-**4**.

(*S*)-4-(4-Hydroxy-benzyl)-oxazolidin-2-one 4



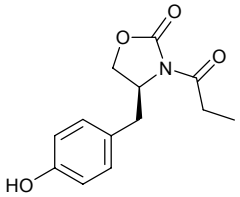
m.p. 179-181 °C (Lit.[1] m.p. 178-179 °C); $[\alpha]_D^{21}$ +12.1 (*c* 0.65, EtOH) (Lit.[1] $[\alpha]_D^{25}$ +11.8 (*c* 0.5, EtOH); ^{1}H NMR (d_4-MeOD, 300 MHz): δ 2.67 (2H, m, CH_AH_BAr), 4.01 (2H, m, CH_AH_BO, C*H*N), 4.27 (1H, m, CH$_A$$H_B$O), 6.64 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.95 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOH, 75.5 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=O); IR (KBr) ν_{max} (cm^{-1}): 3331 (broad O-H), 3140 (broad N-H), 1731 (C=O); MS (CI+) *m/z* (%) 211 (100) [M+NH_4^+]; HRMS (ES+) for $C_{10}H_{11}NO_3$ [M+NH_4]$^+$ Calc. 211.1077, Found 211.1079.

2-Cl-Trt-supported *N*-propionyl-oxazolidin-2-one (*S*)-6a



Lithium chloride (233 mg, 5.5 mmol), triethylamine (0.767 mL, 5.5 mmol) and propionic anhydride (1.10 mL, 5.5 mmol) were added to a suspension of preswollen polymer (*S*)-**5** (1.00g, 1.10 mmol) in THF (100 mL) and the reaction mixture refluxed for 16 hours. The reaction was cooled to room temperature, the resin removed *via* filtration and washed thoroughly with CH_2Cl_2 (10 mL), THF (10 mL), CH_2Cl_2 / MeOH (10 mL) and dried in a vacuum oven at 40 °C. The loading of polymer (*S*)-**6a** (IR, *v*(C=O) = 1780, 1700 cm^{-1}) was determined to be 1.05 mmol/g^{-1} using TFA cleavage to afford (*S*)-*N*-propionyl-4-(4-hydroxybenzyl)-oxazolidin-2-one.

(*S*)-*N*-propionyl-4-(4-hydroxybenzyl)-oxazolidin-2-one

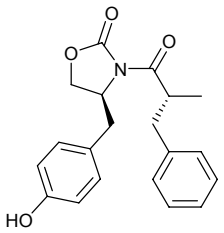


m. p. 135–136 °C; $[\alpha]_D^{21}$ + 43 (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.14 (3H, t, *J* 7.0 Hz, CH_3), 2.66 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH$_B$Ar), 2.89 (2H, m, CH_2CH$_3$), 3.13 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$$H_B$Ar), 4.12 (2H, m, C$H_AH_B$O), 4.55 (1H, m, C*H*N), 4.78 (1H, br. s, O*H*), 6.73 (2H, app. d, *J* 8.5 Hz, H-*o*-OAr*H*), 7.00 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*); ^{13}C NMR (d_4-MeOD, 75.5 MHz): δ 9.2 (CH_3), 30.4 (CH_2), 37.8 (CH_2), 56.8 (CH), 68.1 (CH_2), 116.9 (CH), 127.8 (C), 132.0 (CH), 156.0 (C=O), 158.1 (C), 176.1(C=O); IR (KBr) ν_{max} (cm^{-1}): 3331 (broad O-H), 1756 (C=O), 1709 (C=O); MS (CI+, NH_3) *m/z* (%) 267 (52) [M+NH_4^+], 91 (100); HRMS (ES+) for $C_{13}H_{15}NO_4$ [M+NH_4]$^+$ Calc. 267.1339, Found 267.1343.

Solid phase enolate alkylation reaction – optimised method for formation of (*S,αR*)-10a

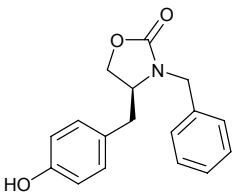
Polymer (*S*)-**6a** (150 mg, 1.05 mmolg^{-1}) (sealed within an IRORI minikan^{TM}) was preswelled in THF (8 mL) at 0 °C for 30 minutes under a nitrogen atmosphere. LHMDS (10 equiv., 1.0 M in THF) was then added dropwise and the reaction was stirred for 30 minutes at 0^{o}C before the solvent and excess base were removed *via* cannula. The resin was then resuspended in fresh pre-chilled THF (10mL) at 0 ^{o}C under nitrogen, followed by dropwise addition of benzyl bromide (535 mg, 20 equiv.). The resultant suspension was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over a period of 20 minutes. The reaction was quenched by addition of phosphate buffer solution (5 mL, pH 7), the IRORI minkan^{TM} recoverd and the resultant resin (*S,αR*)-**10a** washed thoroughly using CH_2Cl_2 (10 mL), CH_2Cl_2 /MeOH (10 mL) and THF (10 mL). TFA cleavage of 20 mg of the resultant resin (*S,αR*)-**10a**, followed by ^{1}H NMR spectroscopic analysis of the resultant cleavage products revealed the presence of (4*S*)-4-(4-hydroxybenzyl)-3-((2*R*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one **9a** (75%, 97% de), (*S*)-*HN*-4-(4-hydroxybenzyl-oxazolidin-2-one **4** (22%) and (*S*)-*N*-benzyl-4-(4-hydroxybenzyl)-oxazolidin-2-one **7** (3%).

(4*S*)-4-(4-Hydroxy-benzyl)-3-((2*R*)-2-methyl-3-phenyl-propionyl)-oxazolidin-2-one 9a



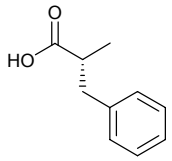
m. p. 142-143 °C; $[\alpha]_D^{21}$ + 79 (*c* 1.35, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (3H, d, *J* 7.0 Hz, C*H*$_3$), 2.44 (1H, dd, *J* 13.5, 9.5 Hz, C*H*$_A$H$_B$Ar), 2.58 (1H, dd, *J* 13.0, 7.5 Hz, CH(CH$_3$)*H*$_A$H$_B$), 2.83 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$*H*$_B$Ar), 3.06 (1H, dd, *J* 13.0, 7.0 Hz, CH(CH$_3$)H$_A$*H*$_B$), 4.03 (3H, m, C*H*$_A$*H*$_B$O, C*H*CH$_3$), 4.52 (1H, m, C*H*N), 5.83 (1H, br. s, O*H*), 6.65 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.75 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.06-7.19 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 17.3 (CH_3), 37.1 (CH_2), 40.1 (CH), 40.3 (CH_2), 55.6 (CH), 66.5 (CH_2), 116.3 (CH), 126.9 (C), 128.8 (CH), 129.6 (CH), 129.8 (CH), 131.0 (CH), 139.5 (C), 153.9 (C=O), 155.8 (C), 177.3 (C=O); IR (KBr) ν_{max} (cm^{-1}): 3345 (O-H), 1771 (C=O), 1719 (C=O); MS (CI+, NH_3) m/z (%) 340 (100) [M+H$^+$], 357 (98) [M+NH_4^+]; HRMS (ES+) for $C_{20}H_{21}NO_4$ [M+H]$^+$ Calc. 340.1543, Found 340.1542.

3-Benzyl-4-(4*S*)-(4-hydroxy-benzyl)-oxazolidin-2-one 7



$[\alpha]_D^{21}$ + 14 (*c* 0.7, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.51 (1H, dd, *J* 13.5, 9.5 Hz, CH_AH$_B$Ar), 2.92 (1H, dd, *J* 13.5, 3.5 Hz, CH$_A$$H_B$Ar), 3.69 (1H, m, C*H*N), 3.94 (1H, dd, *J* 8.5, 6.0 Hz, CH_AH$_B$O), 4.05 (2H, m, CH$_A$$H_BO, NCH_AH_B$), 4.80 1H, d, *J* 15.0, NCH$_A$$H_B$), 6.71 (2H, app. d, *J* 8.5 Hz, *o*-OAr*H*), 6.82 (2H, app. d, *J* 8.5 Hz, *m*-OAr*H*), 7.16 – 7.33 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 37.8 (CH_2), 46.7 (CH_2), 55.8 (CH), 67.5 (CH_2), 116.3 (CH), 127.1 (C), 128.5 (CH), 128.6 (CH), 129.3 (CH), 130.5 (CH), 136.1 (C), 155.8 (C=O), 159.2 (C); IR (Thin film) ν_{max} (cm^{-1}): 3365 (broad O-H), 1742 (C=O); MS (CI+, NH_3) m/z (%) 301 (100) [M+NH_4^+], 284 (40) [M+H^+]; HRMS (ES+) for $C_{17}H_{17}NO_3$ [M+H]$^+$ Calc. 284.1281, Found 284.1278.

(*R*)-2-benzyl-propionic acid 11a



H_2O_2 (50mg, 10 equiv.) was added to preswollen resin **10a** (130 mg) in THF (10 mL) at 0 °C, followed by dropwise addition of LiOH (16mg, 5 equiv.) in H_2O (0.2 mL). The resultant suspension was shaken using an orbital shaker for 4 hours, then the resin filtered off and washed thoroughly with CH_2Cl_2 (5 mL) and THF (5 mL). All washings were collected and evaporated to dryness, and the resultant cleavage products redissolved in EtOAc (10 mL) followed by H_2O (10 mL). The aqueous layer was acidified to pH 1.0 using 2.0 N HCl (aq.), saturated with sodium chloride, before being extracted with EtOAc (10 mL). The combined organic fractions were then dried with $MgSO_4$, filtered and solvent removed *in vacuo* to afford (*R*)-2-benzyl-propionic acid **11a** (16 mg, 0.1 mmol, 67% yield) and in 97% ee as determined by chiral HPLC analysis using a ChiralCel OJ column.

^{1}H NMR ($CDCl_3$, 300 MHz): $[\alpha]_D^{21}$ -25.0 (*c* 1.0, $CHCl_3$) (Lit.[2] $[\alpha]_D^{21}$ for (*S*)-**11a** +20.6 (*c* 0.87, $CHCl_3$)); δ 1.15 (3H, d, *J* 7.0 Hz, CH_3), 2.63 (1H, dd, *J* 13.5, 8.0 Hz, CH_AH$_B$Ph), 2.73 (1H, m, C*H*), 3.05 (1H, dd, *J* 13.5, 8.0 Hz, CH$_A$$H_B$Ph), 7.11-7.30 (5H, br. m, Ar*H*); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.4 (CH_3), 40.1 (CH_2), 40.9 (CH), 126.3 (CH), 127.2 (CH), 128.8 (CH), 139.2 (C), 182.4 (C=O). Chiral HPLC conditions: ChiralCel

OJ column, 98% *n*-Hexane, 2 % isopropyl alcohol, 0.1% TFA, 1 ml/min. (*R*)-**11a** t_R 9.5 min, (*S*)-**11a** t_R 10.8 min.

References

(1) Faita, G.; Paio, A.; Ouadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron*, **2001**, *57*, 8313.

(2) Kotake, T.; Hayashi, Y; Rajesh, S.; Mukai, Y.; Takiguchi, Y.; Kimura, T.; Kiso, Y.; *Tetrahedron*, **2005**, *61*, 3819.