Supporting Information for:

Concise Synthesis of α -Amino Acids via Chiral Isoxazolines

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Experimental Section

General. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. THF and Et₂O were dried by passage through activated alumina columns and degassed by stirring under a dry N₂ atmosphere.¹ All reactions involving air- or moisture-sensitive compounds were performed under a dry N₂ atmosphere. BF₃•OEt₂, Et₃N, and (*i*-Pr)₂NH were distilled from CaH₂. Ac₂O was distilled from K₂CO₃. Precise concentrations of *n*-butyllithium and *t*-butyllithium solutions were determined by titration into diphenylacetic acid solution.² Purification by flash chromatography was carried out with E. Merck Silica Gel 60 (230-400 mesh) according to the procedure of Still, Kahn, and Mitra.³ ¹H and ¹³C NMR spectra were recorded in CDCl₃ at 500 MHz and 125 MHz, respectively, unless otherwise specified. Some ¹H NMR spectra, as noted in the text, were recorded at elevated temperatures in order to equilibrate rotamer signals. IR spectra were measured as thin films on NaCl plates. Melting points are uncorrected. Compounds found in the article text but not described in the Supporting Information (**14-16**, **20-36**, **38**, **42**, **43a**, **45-55**, **58**, **59**, **61-68**) were prepared using previously reported methods, and spectral data for these compounds were consistent with the literature reported values.^{4,5} 1-Bromo-2-(bromomethyl)naphthalene and 2-bromo-3-(bromomethyl)pyridine were prepared according to a literature reported procedure and the spectral data matched reported values.^{6,7} Compounds in the Supporting Information but not in the article text are numbered sequentially as **Sx**.

Grignard addition to isoxazolines:

(1*RS*)-1-[(3*SR*, 5*RS*)-3-Ethyl-3-(2-methylallyl)-isoxazolidin-5-yl]-ethanol (**39**):

A stirred solution of isoxazoline **23** (89 mg, 0.62 mmol, 1 eq) in 2 mL THF was cooled in

1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Timmers, F. J. *Organometallics*, **1996**, *15*, 1518-1520.

2) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879-1880.

3) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

4) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846-6847.

5) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *Synlett* **2004**, 1409-1413.

6) Smith, J. G.; Dibble, P. W.; Sandborn, R. E. *J. Org. Chem.* **1986**, *51*, 3762-3768.

7) Maiti, S.; Achari, B.; Mukhopadhyay, R.; Banerjee, A. K. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1769-1773.

a dry ice-acetone bath, and $\text{BF}_3 \cdot \text{OEt}_2$ (246 μL , 1.9 mmol, 3.1 eq) was added dropwise. After 30 min, 2-methylallylmagnesium chloride (3.9 mL of a 0.5 M solution in THF, 2.0 mmol, 3.2 eq) was added to the reaction mixture over 10 min. Following complete consumption of the starting material as indicated by TLC analysis, excess reagents were quenched with 2 mL H_2O , and the reaction was moved to an ice- H_2O bath, acidified by addition of 1 mL 1N HCl, and stirred with gradual warming to rt. The crude reaction mixture was diluted with 20 mL Et_2O , then extracted with 0.1 N HCl (3 x 5 mL). The combined aqueous extracts were neutralized with sat. aq. K_2CO_3 and extracted with Et_2O (3 x 10 mL). Combined organic extracts were dried, filtered, and concentrated. ^1H NMR analysis of the crude reaction mixture allowed for determination of the ratio of diastereomers. The crude residue was then purified by flash chromatography (1:2 hexanes:EtOAc), providing 118 mg of **39** as a colorless oil in 96% yield. Only the major diastereomer was used in subsequent transformations. IR: 3368, 2966, 1639, 1440 cm^{-1} ; ^1H NMR (400 MHz): δ 0.94 (t, 3H, $J = 7.5$), 1.16 (d, 3H, $J = 6.6$), 1.37-1.47 (m, 1H), 1.59-1.70 (m, 2H), 1.82 (s, 3H), 2.09-2.19 (m, 2H), 2.28 (d, 1H, $J = 13.9$), 3.61-3.69 (m, 1H), 3.81-3.88 (m, 1H), 4.72-4.75 (m, 1H), 4.86-4.89 (m, 1H); ^{13}C NMR (100 MHz): δ 9.00, 18.97, 24.35, 29.05, 42.22, 42.48, 68.00, 69.63, 86.45, 114.96, 142.42; HRMS (EI) calculated for $[\text{C}_{11}\text{H}_{21}\text{NO}_2]^+$: 199.1572, found: 199.1575.

(1RS)-1-((3SR, 5RS)-3-Allyl-3-phenyl-isoxazolidin-5-yl)-ethanol (37): Prepared using an analogous procedure to that described for **39**, starting from isoxazoline **26** (226 mg, 1.2 mmol) except that 2 additional eq of allylmagnesium chloride solution were added after 1 h. Purification by flash chromatography (1:1 hexanes:EtOAc) provided 206 mg of **37** as a colorless oil in 74% yield. IR: 3378, 3193, 2973, 1496 cm^{-1} ; ^1H NMR (400 MHz): δ 1.15 (d, 3H, $J = 6.5$), 2.04-2.13 (m, 1H), 2.34 (br s, 1H), 2.50-2.68 (m, 3H), 3.54-3.63 (m, 1H), 4.01-4.08 (m, 1H), 4.96-5.05 (m, 2H), 5.49-5.61 (m, 1H), 7.24-7.33 (m, 5H); ^{13}C NMR (100 MHz): δ 18.84, 41.86, 44.46, 69.43, 70.83, 86.01, 118.67, 126.10, 126.27, 127.30, 128.34, 133.45; HRMS (ESI) calcd. for $[\text{C}_{14}\text{H}_{19}\text{NO}_2 + \text{Na}]^+$: 256.1313, found: 256.1309.

(1RS)-1-[(3SR, 5RS)-3-Ethyl-3-(4-methylbenzyl)-isoxazolidin-5-yl]-ethanol (40): Prepared using an analogous procedure to that described for **39**, starting from isoxazoline **23** (212 mg, 1.5 mmol) except that 8 eq of 4-methylbenzylmagnesium chloride were used. Purification by flash chromatography (1:1 hexanes:EtOAc) provided 301 mg of **40** as a colorless oil in 83% yield. IR: 3204, 2965, 1456 cm^{-1} ; ^1H NMR (400 MHz): δ 1.00 (t, 3H, $J = 7.5$), 1.14 (d, 3H, $J = 6.2$), 1.33-1.46 (m, 1H), 1.50-1.62 (m, 2H), 2.17 (dd, 1H, $J = 7.7, 12.5$), 2.31 (s, 3H), 2.66 (d, 1H, $J = 13.9$), 2.86 (d, 1H, $J = 13.9$), 3.61-3.69 (m, 1H), 3.71-3.82 (m, 1H), 7.10 (s, 4H); ^{13}C NMR (100 MHz): δ 8.96, 18.99,

20.97, 28.79, 39.71, 41.03, 68.33, 69.59, 86.25, 128.85, 130.31, 134.08, 136.01; HRMS (ESI) calculated for $[C_{15}H_{23}NO_2 + H]^+$: 250.1807, found: 250.1815.

Reduction of isoxazolines and protection of resultant amine:

[(1*SR*, 3*RS*, 4*RS*)-1-Ethyl-3,4-dihydroxy-1-(2-methylallyl)-pentyl]-carbamic acid *tert*-butyl ester (S1**):** To a solution of isoxazolidine **39** (67 mg, 0.34 mmol, 1 eq) in 0.5 mL Et₂O cooled in an ice-H₂O bath was added LiAlH₄ (1.4 mL of a 1 M solution in Et₂O, 1.4 mmol, 4 eq) dropwise. When TLC analysis of the reaction indicated complete consumption of starting material, excess LiAlH₄ was decomposed using the Fieser procedure. The white salts were removed by filtration through celite and washed with copious THF. The filtrate was concentrated, and the remaining residue was dissolved in 2 mL EtOAc. BOC₂O (223 mg, 1.0 mmol, 3 eq) was added, and the pH was adjusted to 10 by addition of sat. aq. Li₂CO₃ solution. The biphasic reaction mixture was stirred at ambient temperature for 8 h, then diluted with 10 mL H₂O, and extracted with EtOAc (3 x 10 mL). The organic extracts were dried, filtered, and concentrated, and the crude residue was purified by flash chromatography (2:1 hexanes:EtOAc) providing 102 mg of **S1** as a white solid in 95% yield. mp = 93-95 °C; IR: 3348, 2966, 1681, 1518 cm⁻¹; ¹H NMR (400 MHz), major rotamer: δ 0.85 (t, 3H, *J* = 7.3), 1.15 (d, 3H, *J* = 5.9), 1.38 (s, 9H), 1.38-1.50 (m, 1H), 1.63-1.71 (m, 1H), 1.76 (s, 3H), 1.75-1.92 (m, 2H), 2.31 (d, 1H, *J* = 13.6), 2.62 (d, 1H, *J* = 13.6), 2.89 (br s, 1H), 3.29 (br s, 1H), 3.48-3.59 (m, 1H), 4.69 (s, 1H), 4.85 (s, 1H), 5.16 (br s, 1H); ¹³C NMR (100 MHz): δ 7.83, 19.42, 24.48, 28.33, 29.89, 38.75, 43.15, 57.31, 71.30, 72.45, 78.87, 115.55, 142.36, 155.06; HRMS (ESI) calcd for $[C_{16}H_{31}NO_4 + Na]^+$: 324.2151, found 324.2142.

(((1*SR*, 3*RS*, 4*RS*)-1-Allyl-3,4-dihydroxy-1-phenyl-pentyl)-carbamic acid benzyl ester (S2**):** Prepared using an analogous procedure to that described for **S1**, starting from isoxazolidine **37** (35.3 mg, 0.15 mmol) with the following exception. After filtration of salts and concentration of filtrate, the resultant residue was dissolved in 0.6 mL 5:1 THF:H₂O. To this stirred solution was added Li₂CO₃ (33 mg, 0.45 mmol, 3 eq). Benzyl chloroformate (65 μ L, 0.45 mmol, 3 eq) was added dropwise, and the reaction was stirred at rt for 3 h. Standard workup and purification by flash chromatography (1:1 hex: EtOAc) provided 38 mg of **S2** as a colorless oil in 68% yield. IR: 3341, 2971, 1704, 1496, 1267 (cm⁻¹); ¹H NMR (400 MHz), major rotamer: δ 1.10 (d, 3H, *J* = 5.9), 2.07-2.36 (m, 3H), 2.49 (br s, 1H), 2.81 (d, 2H, *J* = 7.3), 3.47-3.58 (m, 2H), 4.98-5.12 (m, 4H), 5.49-5.65 (m, 1H), 5.63 (br s, 1H), 7.21-7.26 (m, 2H), 7.27-7.39 (m, 8H); ¹³C NMR (100

MHz): δ 19.07, 42.98, 43.83, 59.64, 66.50, 70.78, 72.36, 119.37, 125.28, 125.44, 125.65, 126.83, 128.05, 128.35, 133.11, 136.39, 144.16, 155.42. HRMS (EI): calcd for $[C_{22}H_{27}NO_4 + Na]^+$: 392.1838, found: 392.1831.

[(1*S*R, 3*R*S, 4*R*S)-1-Ethyl-3,4-dihydroxy-1-(4-methyl-benzyl)-pentyl]-carbamic acid *tert*-butyl ester (S3**):** Prepared using an analogous procedure to that described for **S1**, starting from isoxazolidine **40** (173 mg, 0.69 mmol). Purification by flash chromatography (2:1 hexanes:EtOAc) provided 205 mg of **S3** as a white solid in 85% yield. mp 121-122 °C; IR: 3357, 2972, 1713, 1513, 1167 cm^{-1} ; 1H NMR: δ 0.94 (t, 3H, $J = 7.4$), 1.17 (d, 3H, $J = 6.1$), 1.35-1.42 (m, 1H), 1.44 (s, 9H), 1.71 (dd, 1H, $J = 8.9$, 15.0), 1.73-1.81 (m, 1H), 1.89 (d, 1H, $J = 15.1$), 2.26 (br s, 1H), 2.30 (s, 3H), 2.80 (d, 1H, $J = 13.6$), 3.17 (d, 1H, $J = 13.4$), 3.51-3.60 (m, 2H), 4.86 (br s, 1H), 7.03 (d, 2H, $J = 8.1$), 7.07 (d, 2H, $J = 8.1$); ^{13}C NMR (100 MHz): δ 7.84, 19.49, 20.92, 28.39, 28.96, 37.96, 40.65, 57.89, 71.27, 72.45, 78.79, 128.63, 130.43, 134.33, 135.73, 154.95; HRMS (ESI) calcd for $[C_{20}H_{33}NO_4 + Na]^+$: 374.2307, found: 374.2301.

Preparation of β,β -amino acids:

3-*tert*-Butoxycarbonylamino-3-ethyl-5-methyl-hex-5-enoic acid (56**):** To a stirred solution of the protected amine diol **S1** (32 mg, 0.11 mmol, 1 eq) in 1.1 mL 1:1 CH_3CN-H_2O was added $NaIO_4$ (46 mg, 0.22 mmol, 2 eq). After 1 h, TLC analysis indicated complete consumption of the amine diol. The reaction mixture was diluted with 5 mL H_2O and extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (1 x 5 mL), dried, filtered, and concentrated. The crude residue was redissolved in 0.5 mL *t*-BuOH, and 2-methyl-2-butene (548 μ L, 5.2 mmol, 47 eq) was added. A solution of $NaClO_2$ (92 mg, 1.0 mmol, 9 eq) and KH_2PO_4 (105 mg, 0.77 mmol, 7 eq) in 1 mL H_2O was added dropwise, and the reaction mixture was stirred at rt for 3 h. The reaction mixture was subsequently diluted with 5 mL H_2O and extracted with EtOAc (4 x 5 mL). The combined organic extracts were dried, filtered, concentrated, and the crude residue was purified by flash chromatography (5:1 CH_2Cl_2 :EtOAc with 1% AcOH) to provide 21 mg of **56** as a colorless oil in 71% yield. IR: 2974, 1710, 1168 cm^{-1} ; 1H NMR (50 °C): δ 0.90 (t, 3H, $J = 7.6$), 1.42 (s, 9H), 1.74-1.80 (m, 2H), 1.79 (s, 3H), 2.46 (d, 1H, $J = 13.9$), 2.57 (d, 1H, $J = 13.7$), 2.65 (d, 1H, $J = 14.9$), 2.84 (d, 1H, $J = 14.9$), 4.76 (d, 1H, $J = 0.7$), 4.91 (d, 1H, $J = 0.8$), 4.95 (br s, 1H); ^{13}C NMR (100 MHz): δ 7.99, 24.37, 28.20, 29.25, 40.01, 42.42, 56.66, 79.30, 116.10, 141.47, 154.76, 176.56; HRMS (ESI) calcd for $[C_{14}H_{25}NO_4 + Na]^+$: 294.1681, found: 294.1691.

3-Benzyloxycarbonylamino-3-phenyl-hex-5-enoic (60): Prepared using an analogous procedure to that described for **56**, starting from **S2** (60 mg, 0.16 mmol). Purification by flash chromatography (5:1 CH₂Cl₂:EtOAc with 1% AcOH) provided 47 mg of **60** as a colorless oil in 87% yield. IR: 3061, 1714, 1496, 1246 cm⁻¹; ¹H NMR (50 °C): δ 2.77 (dd, 1H, *J* = 7.9, 13.6), 2.97 (dd, 1H, *J* = 6.6, 13.6), 3.13 (d, 1H, *J* = 14.9), 3.30 (d, 1H, *J* = 14.9), 5.02-5.12 (m, 4H), 5.40-5.49 (m, 1H), 5.74 (br s, 1H), 7.21-7.34 (m, 10H); ¹³C NMR (note: some signals coincide): δ 41.49, 44.38, 58.82, 66.53, 120.08, 125.17, 128.02, 128.39, 132.19, 136.43, 142.75, 154.94, 176.00; HRMS (ESI) calcd for [C₂₀H₂₁NO₄ + Na]⁺: 362.1368, found: 362.1370.

(3-tert-Butoxycarbonylamino-3-4-methylbenzyl)-pentanoic acid (57): Prepared using an analogous procedure to that described for **56**, starting from **S3** (40 mg, 0.12 mmol). Purification by flash chromatography (5:1 CH₂Cl₂:EtOAc with 1% AcOH) provided 35 mg of **57** as a colorless oil in 90% yield. IR: 2975, 1709, 1513, 1166 cm⁻¹; ¹H NMR (50 °C): δ 0.96 (t, 3H, *J* = 7.6), 1.46 (s, 9H), 1.69 (q, 2H, *J* = 7.3), 2.31 (s, 3H), 2.67 (d, 1H, *J* = 14.6), 2.77 (d, 1H, *J* = 14.6), 2.98 (d, 1H, *J* = 13.7), 3.09 (d, 1H, *J* = 13.7), 4.60-4.90 (br s, 1H), 7.07 (s, 4H); ¹³C NMR (100 MHz): δ 7.92, 21.01, 24.27, 28.40, 39.50, 40.07, 57.27, 79.33, 128.80, 130.54, 133.51, 136.13, 154.77, 176.62; HRMS (ESI) calcd for [C₁₈H₂₇NO₄ + Na]⁺: 344.1838, found: 344.1840.

Triethylsilyl protection of isoxazolines:

(5RS)-3-Ethyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (S4): A solution of isoxazoline **23** (891 mg, 6.2 mmol, 1 eq) in 40 mL THF was cooled with stirring in an ice-H₂O bath. To this solution was added DMAP (76 mg, 0.6 mmol, 0.1 eq) and Et₃N (956 μ L, 6.8 mmol, 1.1 eq) and the mixture was stirred with continued cooling. Triethylsilyl triflate (1.6 mL, 6.8 mmol, 1.1 eq) was added dropwise to this mixture, and the reaction was monitored by TLC. Upon complete consumption of the starting material, the excess reagents were quenched with 100 mL water, and the resultant mixture was extracted with Et₂O (3 x 75 mL). The combined extracts were washed with brine (1 x 75 mL), dried over MgSO₄, filtered, concentrated, and purified by flash chromatography (9:1 hexanes: EtOAc) to afford 1.6 g **S4** as a colorless oil in 99% yield. IR: 2954, 2875, 1456, 1104, 1009 cm⁻¹; ¹H NMR (400 MHz): δ 0.60 (q, 6H, *J* = 7.9), 0.93 (t, 9H, *J* = 7.9), 1.08 (d, 3H, *J* = 6.2), 1.14 (t, 3H, *J* = 7.5), 2.32 (q, 2H, *J* = 7.6), 2.75-2.89

(m, 2H), 3.87-3.94 (m, 1H), 4.43-4.50 (m, 1H); ^{13}C NMR (100 MHz): δ 4.79, 6.69, 10.83, 17.85, 21.13, 37.32, 68.53, 82.80, 159.65; HRMS (ESI) calcd. for $[\text{C}_{13}\text{H}_{27}\text{NO}_2\text{Si} + \text{Na}]^+$: 280.1709, found: 280.1704.

(5RS)-3-Isobutyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (S5): Prepared using an analogous procedure to that described for **S4**, starting from isoxazoline **14** (850 mg, 5.0 mmol). Purification by flash chromatography afforded 1.4 g **S5** as a colorless oil in 99% yield. IR: 2954, 1455, 1102, 1007 cm^{-1} ; ^1H NMR (400 MHz): δ 0.58 (q, 6H, $J = 7.9$), 0.90-0.95 (m, 15H), 1.08 (d, 3H, $J = 6.2$), 1.82-1.93 (m, 1H), 2.18 (d, 2H, $J = 7.3$), 2.73-2.86 (m, 2H), 3.86-3.94 (m, 1H), 4.46 (ddd, 1H, $J = 5.3$, 8.4, 13.7); ^{13}C NMR (100 MHz) some signals coincide: δ 4.80, 6.75, 17.88, 22.43, 26.08, 36.55, 37.76, 68.38, 82.77, 158.00; HRMS (ESI) calcd. for $[\text{C}_{15}\text{H}_{31}\text{NO}_2\text{Si} + \text{Na}]^+$: 308.2022, found: 308.2018.

(5RS)-3-Phenyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (S6): Prepared using an analogous procedure to that described for **S4**, starting from isoxazoline **26** (570 mg, 3.0 mmol). Purification by flash chromatography afforded 908 mg **S6** as a colorless oil in 99% yield. IR: 2952, 2873, 1596, 1445, 1355, 1106 cm^{-1} ; ^1H NMR (400 MHz): δ 0.60 (q, 6H, $J = 7.9$), 0.94 (t, 9H, $J = 7.9$), 1.14 (d, 3H, $J = 6.2$), 3.17-3.30 (m, 2H), 3.96-4.03 (m, 1H), 4.64-4.70 (m, 1H), 7.35-7.40 (m, 3H), 7.63-7.68 (m, 2H); ^{13}C NMR (100 MHz): 4.82, 6.73, 18.00, 35.48, 68.64, 84.17, 126.55, 128.56, 129.57, 129.84, 156.32; HRMS (ESI) calcd for $[\text{C}_{17}\text{H}_{27}\text{NO}_2\text{Si} + \text{Na}]^+$: 328.1709, found: 328.1703

C4 alkylation of isoxazolines:

(4RS, 5RS)-4-(2-Bromo-benzyl)-3-ethyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (69): A solution of $(i\text{-Pr})_2\text{NH}$ (379 μL , 2.7 mmol, 1.5 eq) in 10 mL THF was stirred with cooling in an ice- H_2O bath. To the cooled solution was added n -butyllithium (1.29 mL of a 2.17 M solution in hexanes, 2.79 mmol, 1.55 eq) dropwise over 10 min. After 20 min, the clear, colorless solution was cooled in a dry ice-acetone bath. A 2 mL THF solution of isoxazoline **S4** (463 mg, 1.8 mmol, 1 eq) was then added

over 15 min. After stirring with continued cooling for 90 min, a 2 mL THF solution of 2-bromobenzyl bromide (1.4 g, 5.4 mmol, 3 eq) was added over 15 min. The reaction was monitored by TLC for consumption of starting material. After 2 h, excess reagents were quenched by the addition of 5 mL H₂O and the resulting mixture was placed in an ice-H₂O bath. The biphasic mixture was partitioned with 30 mL H₂O and 30 mL Et₂O. The aqueous layer was extracted with Et₂O (3 x 15 mL), and the combined organic extracts were washed with brine (1 x 20 mL), dried, filtered, and concentrated. GC and ¹H NMR analysis of the crude residue indicated that the product was a single regioisomer and a single diastereomer. Purification of the crude residue by flash chromatography (9:1 hexanes:EtOAc) provided 620 mg of **69** as a colorless oil in 81% yield. IR: 2953, 2875, 1468, 1145, 1098, 1007 cm⁻¹; ¹H NMR (400 MHz): δ 0.45 (q, 6H, *J* = 7.9), 0.83 (t, 9H, *J* = 7.9), 0.85 (d, 3H, *J* = 6.6) 1.18 (t, 3H, *J* = 7.5), 2.17-2.28 (m, 1H), 2.43-2.53 (m, 1H), 2.62 (dd, 1H, *J* = 10.6, 13.6), 3.19 (dd, 1H, *J* = 4.8, 13.6), 3.48-3.53 (m, 1H), 3.55-3.61 (m, 1H), 4.16 (t, 1H, *J* = 4.8), 7.10 (ddd, 1H, *J* = 2.2, 7.5, 7.6), 7.18-7.26 (m, 2H), 7.54 (dd, 1H, *J* = 1.1, 8.1); ¹³C NMR (100 MHz): δ 4.70, 6.74, 11.00, 17.99, 19.85, 37.83, 49.11, 68.12, 87.16, 124.52, 127.55, 128.50, 131.56, 133.11, 137.47, 161.98; HRMS (ESI) calcd for [C₂₀H₃₂BrNO₂Si + Na]⁺: 448.1283, 450.1263, found: 448.1283, 450.1271.

(4RS, 5RS)-4-(2-Bromo-benzyl)-3-isobutyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (71): Prepared using an analogous procedure to that described for **69**, starting from isoxazoline **S5** (380 mg, 1.33 mmol). Purification by flash chromatography (9:1 CH₂Cl₂:hexanes) provided 466 mg of **71** as a colorless oil in 77% yield. IR: 2954, 1464, 1238, 1147, 1099, 1009 cm⁻¹; ¹H NMR (400 MHz): δ 0.45 (q, 6H, *J* = 7.6), 0.81-0.87 (m, 12H), 0.90 (d, 3H, *J* = 6.6), 0.96 (d, 3H, *J* = 6.6), 1.90-2.03 (m, 1H), 2.14-2.27 (m, 2H), 2.62 (dd, 1H, *J* = 10.6, 13.6), 3.19 (dd, 1H, *J* = 4.6, 13.6), 3.41-3.47 (m, 1H), 3.52-3.60 (m, 1H) 4.13 (dd, 1H, *J* = 4.6, 5.7), 7.10 (ddd, 1H, *J* = 2.2, 7.5, 7.5), 7.17-7.26 (m, 2H), 7.54 (dd, 1H, *J* = 1.1, 7.7); ¹³C NMR (100 MHz): δ 4.75, 6.79, 18.16, 22.00, 23.27, 16.10, 35.22, 37.98, 49.61, 68.07, 87.39, 124.51, 127.61, 128.57, 131.69, 133.54, 137.49, 160.10; HRMS (ESI) calcd for [C₂₂H₃₆BrNO₂Si + Na]⁺: 476.1596, 478.1576, found: 476.1596, 478.1577.

(4RS, 5RS)-4-(2-Bromo-benzyl)-3-phenyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (73): Prepared using an analogous procedure to that described for **69**, starting from isoxazoline **S6** (458 mg, 1.50 mmol). Purification by flash chromatography (9:1 CH₂Cl₂:hexanes) provided 650 mg of **73** as a colorless oil in 91% yield. IR: 2952, 2873, 1444, 1350, 1146, 1100, 1006 cm⁻¹; ¹H NMR (400 MHz): δ 0.44 (q, 6H, *J* = 7.8), 0.83 (t, 9H, *J* = 7.9), 0.87 (d, 3H, *J* = 6.2), 2.67 (dd, 1H, *J* = 11.2, 13.8), 3.30 (dd, 1H, *J* = 4.6, 13.8), 3.65-3.73 (m, 1H), 4.02-4.08 (m, 1H), 4.34 (dd, 1H, *J* = 3.3,

5.5), 7.06-7.11 (m, 1H), 7.17-7.23 (m, 2H), 7.37-7.41 (m, 3H), 7.54 (dd, 1H, $J = 0.9, 7.9$), 7.80-7.85 (m, 2H); ^{13}C NMR (100 MHz, some resonances coincide): δ 4.71, 6.77, 18.10, 38.26, 47.23, 68.12, 88.02, 124.57, 127.15, 127.54, 128.56, 128.77, 129.88, 132.20, 133.12, 137.28, 159.56; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{32}\text{BrNO}_2\text{Si} + \text{Na}]^+$: 496.1283, 498.1263, found: 496.1287, 498.1270.

(4RS, 5RS)-4-(1-Bromo-naphthalen-2-ylmethyl)-3-ethyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (75): Prepared using an analogous procedure to that described for **69**, starting from isoxazoline **S4** (312 mg, 1.21 mmol), except that 1-bromo-2-(bromomethyl)-naphthalene was used instead of 2-bromobenzyl bromide. Purification by flash chromatography (9:1 CH_2Cl_2 :hexanes) provided 438 mg of **75** as a colorless oil in 76% yield. IR: 2952, 2873, 1457, 1143, 1099, 1007 cm^{-1} ; ^1H NMR (400 MHz): δ 0.27 (q, 6H, $J = 7.9$), 0.70 (t, 9H, $J = 7.9$), 0.84 (d, 3H, $J = 6.2$), 1.20 (t, 3H, $J = 7.5$), 2.21-2.32 (m, 1H), 2.45-2.56 (m, 1H), 2.89 (dd, 1H, $J = 10.6, 13.6$), 3.44 (dd, 1H, $J = 4.9, 13.4$), 3.54-3.61 (m, 1H), 3.61-3.68 (m, 1H), 4.27 (t, 1H, $J = 4.6$), 7.30 (d, 1H, $J = 8.4$), 7.50 (ddd, 1H, $J = 1.3, 6.6, 8.1$), 7.58 (ddd, 1H, $J = 1.1, 6.8, 8.8$), 7.74 (d, 1H, $J = 8.4$), 7.80 (d, 1H, $J = 8.1$), 8.29 (d, 1H, $J = 8.8$); ^{13}C NMR (100 MHz): δ 4.61, 6.65, 11.08, 17.93, 19.97, 38.99, 49.43, 68.02, 87.14, 124.42, 126.34, 127.22, 127.57, 127.82, 128.06, 128.69, 132.64, 133.55, 135.78, 162.11; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{34}\text{BrNO}_2\text{Si} + \text{Na}]^+$: 498.1440, 500.1420, found: 498.1447, 500.1433.

2-Bromo-3-[(4RS, 5RS)-3-ethyl-5-((1RS)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazol-4-ylmethyl]-pyridine (77): Prepared using an analogous procedure to that described for **69**, starting from isoxazoline **S4** (514 mg, 1.8 mmol) but 2-bromo-3-(bromomethyl)-pyridine was used instead of 2-bromobenzyl bromide. Purification by flash chromatography (3:1 hexanes:EtOAc) provided 651 mg of **77** as a colorless solid in 85% yield. mp = 129-131 $^{\circ}\text{C}$; IR: 2971, 1557, 1404, 1051 cm^{-1} ; ^1H NMR (400 MHz): δ 0.43 (q, 6H, $J = 7.9$), 0.83 (t, 9H, $J = 8.1$), 0.88 (d, 3H, $J = 6.6$), 1.21 (t, 3H, $J = 7.5$), 2.20-2.31 (m, 1H), 2.45-2.55 (m, 1H), 2.61 (dd, 1H, $J = 10.6, 13.9$), 3.16 (dd, 1H, $J = 4.4, 13.9$), 3.53-3.60 (m, 1H), 3.64-3.71 (m, 1H), 4.14 (dd, 1H, $J = 4.0, 5.1$), 7.22 (dd, 1H, $J = 4.8, 7.3$), 7.52 (dd, 1H, $J = 1.8, 7.3$), 8.27 (dd, 1H, $J = 2.2, 4.8$); ^{13}C NMR (100 MHz): δ 4.67, 6.71, 10.97, 17.71, 19.79, 36.85, 48.39, 67.23, 86.90, 122.84, 134.97, 139.37, 144.46, 148.44, 161.63; HRMS (ESI) calcd for $[\text{C}_{19}\text{H}_{31}\text{BrN}_2\text{O}_2\text{Si} + \text{Na}]^+$: 449.1236, 451.1216, found: 449.1249, 451.1367.

(4*RS*, 5*RS*)-4-(2-Bromo-5-methoxy-benzyl)-3-ethyl-5-((1*RS*)-1-triethylsilanyloxy-ethyl)-4,5-dihydro-isoxazole (79): Prepared using an analogous procedure to that described for **69**, starting from isoxazoline **S4** (309 mg, 1.2 mmol) but 1-bromo-2-bromomethyl-4-methoxybenzene was used instead of 2-bromobenzyl bromide. Purification by flash chromatography (9:1 hexanes:EtOAc) provided 425 mg of **79** as a white solid in 78% yield. mp = 44-46 °C; IR: 2953, 2875, 1594, 1572, 1472, 1243, 1100, 1007 cm⁻¹; ¹H NMR (400 MHz): δ 0.43 (q, 6H, *J* = 7.9), 0.84 (t, 9H, *J* = 7.9), 0.87 (d, 3H, *J* = 6.2), 1.19 (t, 3H, *J* = 7.5), 2.18-2.28 (m, 1H), 2.42-2.53 (m, 1H), 2.56 (dd, 1H, *J* = 10.6, 13.6), 3.15 (dd, 1H, *J* = 4.6, 13.4), 3.48-3.53 (m, 1H), 3.57-3.64 (m, 1H), 3.75 (s, 3H), 4.18 (dd, 1H, *J* = 4.4, 5.1), 6.65 (dd, 1H, *J* = 2.9, 8.8), 6.73 (d, 1H, *J* = 2.9), 7.41 (d, 1H, *J* = 8.8); ¹³C NMR (100 MHz): δ 4.71, 6.75, 11.04, 18.01, 19.86, 38.04, 49.12, 55.37, 68.09, 87.04, 113.93, 114.81, 117.40, 133.64, 138.37, 158.89, 162.04; HRMS (ESI) calcd for [C₂₁H₃₄BrNO₃Si + Na]⁺: 478.1389, 480.1369, found: 478.1387, 480.1367.

Preparation of isoxazolidines:

Isoxazolidine 70. A solution of isoxazoline **69** (218 mg, 0.51 mmol, 1 eq) in 5 mL THF was stirred with cooling in a dry ice-acetone bath. To this solution was added *t*-BuLi (617 μ L of a 1.7 M solution in pentane, 1.1 mmol, 2 equiv), and the reaction mixture was stirred with monitoring by TLC. After 90 min, TLC analysis indicated complete consumption of the starting material, and excess reagents were quenched with 1 mL H₂O. The reaction was then moved to an ice-water bath, and 5 mL ether and 2 mL 3N HCl solution were added to remove of the triethylsilyl group. This biphasic reaction mixture was stirred for 12 h with gradual warming to rt, then partitioned with 10 mL of H₂O and 10 mL of Et₂O. The aqueous layer was neutralized with sat. aq. K₂CO₃, then extracted with Et₂O (4 x 10 mL). The combined organic extracts were combined, dried, filtered, and concentrated. Purification of the crude residue by flash chromatography (1:2 hexanes:EtOAc) provided 104 mg of **70** as a colorless oil in 87% yield. IR: 3214, 2966, 2927, 1458, 1135, 1074 cm⁻¹; ¹H NMR (400 MHz): δ 0.81 (t, 3H, *J* = 7.5), 1.27 (d, 3H, *J* = 6.2), 1.82-2.01 (m, 2H), 2.71-2.77 (m, 1H), 2.87 (d, 1H, *J* = 16.5), 3.17 (dd, 1H, *J* = 8.4, 16.8), 3.49 (t, 1H, *J* = 6.6), 3.83-3.89 (m, 1H), 7.17-7.23 (m, 1H), 7.24-7.29 (m, 3H); ¹³C NMR (100 MHz): δ 9.19, 19.19, 30.16, 35.58, 52.80, 68.60, 82.30, 96.06, 123.80, 125.12, 127.36, 128.59, 142.11, 143.61; HRMS (ESI) calcd for [C₁₄H₁₉NO₂ + Na]⁺: 256.1313, found: 256.1318.

Isoxazolidine 72. Prepared using an analogous procedure to that described for **70**, starting from isoxazoline **71** (214 mg, 0.47 mmol). Purification by flash chromatography (1:1 hexanes:EtOAc) provided 85 mg of **72** as a colorless oil in 69% yield. IR: 3348, 2954, 1723, 1459, 1366, 1134 cm^{-1} ; ^1H NMR (400 MHz): δ 0.70 (d, 3H, $J = 6.6$), 0.88 (d, 3H, $J = 6.6$), 1.26 (d, 3H, $J = 6.6$), 1.52-1.63 (m, 1H), 1.79-1.84 (m, 2H), 2.71-2.78 (m, 1H), 2.87 (d, 1H, $J = 16.8$), 3.21 (dd, 1H, $J = 8.2, 16.6$), 3.48 (t, 1H, $J = 6.2$), 3.81-3.88 (m, 1H), 7.17-7.31 (m, 4H); ^{13}C NMR: δ 19.11, 23.66, 24.63, 25.07, 35.55, 45.90, 53.84, 68.62, 81.71, 95.62, 124.33, 125.19, 127.20, 128.49, 141.76, 144.22; HRMS (ESI) calcd for $[\text{C}_{16}\text{H}_{23}\text{NO}_2 + \text{H}]^+$: 262.1807, found: 262.1803.

Isoxazolidine 74. Prepared using an analogous procedure to that described for **70**, starting from isoxazoline **73** (308 mg, 0.65 mmol). Purification by flash chromatography (3:2 hexanes:EtOAc) provided 162 mg of **74** as a colorless oil in 84% yield. IR: 3362, 2971, 1719, 1446, 1071 cm^{-1} ; ^1H NMR (400 MHz): δ 1.25 (d, 3H, $J = 6.6$), 3.00 (dd, 1H, $J = 2.2, 16.9$), 3.16 (1H, ddd, $J = 2.2, 6.6, 8.4$), 3.41 (dd, 1H, $J = 8.4, 16.8$), 3.65 (t, 1H, $J = 6.6$), 3.81-3.88 (m, 1H), 7.08-7.13 (m, 1H), 7.19-7.23 (m, 2H), 7.26-7.32 (m, 4H), 7.35-7.39 (m, 3H); ^{13}C NMR (100 MHz) some signals coincide: δ 19.25, 35.66, 58.57, 68.80, 84.30, 96.58, 125.15, 125.37, 125.92, 127.02, 127.75, 128.44, 128.93, 141.73, 144.41; HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{19}\text{NO}_2 + \text{Na}]^+$: 304.1313, found: 304.1308.

Isoxazolidine 76. Prepared using an analogous procedure to that described for **70**, starting from isoxazoline **75** (279 mg, 0.59 mmol). Purification by flash chromatography (1:1 EtOAc:hexanes) provided 152 mg of **76** as a colorless oil in 86% yield. IR: 3403, 2966, 2874, 1625, 1513, 1457, 1378, 1141, 1077 cm^{-1} ; ^1H NMR (400 MHz): δ 0.72 (t, 3H, $J = 7.3$), 1.31 (d, 3H, $J = 6.6$), 2.02-2.11 (m, 1H), 2.36-2.45 (m, 1H), 2.83-2.89 (m, 1H), 2.96 (d, 1H, $J = 16.8$), 3.30 (dd, 1H, $J = 8.4, 16.9$), 3.48 (t, 1H, $J = 6.8$), 3.89-3.96 (m, 1H), 7.29 (d, 1H, $J = 8.1$), 7.41-7.50 (m, 2H), 7.76 (d, 1H, $J = 8.4$), 7.84 (d, 1H, $J = 8.1$), 8.17 (d, 1H, $J = 8.1$); ^{13}C NMR (100 MHz): δ 9.12, 19.37, 30.33, 35.56, 53.86, 68.54, 84.02, 95.28, 123.23, 124.07, 125.26, 126.35, 128.72, 129.55, 129.63, 133.57, 137.69, 139.58; HRMS (ESI) calcd for $[\text{C}_{18}\text{H}_{21}\text{NO}_2 + \text{Na}]^+$: 306.1470, found: 306.1466.

Isoxazolidine 78. Prepared using an analogous procedure to that described for **70**, starting from isoxazoline **77** (68 mg, 0.16 mmol) with the following exception. After consumption of starting material was observed by TLC analysis, the excess reagents were quenched with H₂O only. Standard workup and purification by flash chromatography (1:1 hexanes:EtOAc) provided 41 mg of **78** as a colorless oil in 73% yield. IR: 2956, 2875, 1773, 1580, 1456, 1098 cm⁻¹; ¹H NMR: δ 0.63 (q, 6H, *J* = 7.9), 0.77 (t, 3H, *J* = 7.6), 0.97 (t, 9H, *J* = 7.9), 1.26 (d, 3H, *J* = 6.3), 1.8 (br s, 1H), 2.12-2.21 (m, 1H), 2.87 (d, 1H, *J* = 16.8), 2.93-2.99 (m, 1H), 3.13 (dd, 1H, *J* = 8.4, 16.7), 3.60 (br s, 1H), 4.01-4.07 (m, 1H), 5.92 (br s, 1H), 7.09-7.17 (m, 1H), 7.49 (d, 1H, *J* = 7.3), 8.52 (d, 1H, *J* = 4.9); ¹³C NMR: δ 4.97, 6.87, 9.18, 20.03, 27.42, 34.23, 50.40, 70.65, 80.39, 94.60, 122.68, 132.75, 135.67, 149.50, 163.53; HRMS (ESI) calcd for [C₁₉H₃₂N₂O₂Si + Na]⁺: 371.2131, found: 371.2124.

Isoxazolidine 80. Prepared using an analogous procedure to that described for **70**, starting from isoxazoline **79** (170 mg, 0.37 mmol). Purification by flash chromatography (1:4 hexanes:EtOAc) provided 90 mg of **80** as a colorless oil in 93% yield. IR: 3212, 2965, 2929, 1607, 1495, 1254, 1142, 1082 cm⁻¹; ¹H NMR (400 MHz): δ 0.80 (t, 3H, *J* = 7.5), 1.26 (d, 3H, *J* = 6.6), 1.78-1.99 (m, 2H), 2.70-2.75 (m, 1H), 2.82 (d, 1H, *J* = 16.8), 3.13 (dd, 1H, *J* = 8.4, 16.8), 3.49 (t, 1H, *J* = 6.6), 3.77 (s, 3H), 3.81-3.89 (m, 1H), 6.71 (d, 1H, *J* = 2.2), 6.79 (dd, 1H, *J* = 2.4, 8.4), 7.16 (d, 1H, *J* = 8.4); ¹³C NMR (100 MHz): δ 9.23, 19.17, 30.22, 35.66, 53.28, 55.33, 68.53, 81.71, 96.13, 109.88, 113.67, 124.48, 135.70, 143.81, 160.35; HRMS (ESI) calcd for [C₁₅H₂₁NO₃ + Na]⁺: 286.1419, found: 286.1416.

Preparation of CBz-protected amine diols:

[(1*R*S, 2*R*S)-2-((1*R*S, 2*R*S)-1,2-Dihydroxy-propyl)-1-ethyl-indan-1-yl]-carbamic acid benzyl ester (S7**):** Prepared using an analogous procedure to that described for **S2**, starting from from isoxazolidine **70** (64 mg, 0.28 mmol). Purification by flash chromatography (1:1 hexanes:EtOAc) provided 81 mg of **S7** as a colorless oil in 79% yield. IR: 3405, 3030, 2969, 1694, 1504, 1456, 1256, 1069 cm⁻¹; ¹H NMR (C₆D₆, 40 °C): δ 0.76 (t, 3H, *J* = 7.4), 1.25 (d, 3H, *J* = 6.3), 1.85 (d, 1H, *J* = 9.0), 2.04-2.13 (m, 1H),

2.44 (dd, 1H, $J = 10.4, 15.3$), 2.70 (dd, 1H, $J = 7.8, 15.4$), 2.83 (br s, 1H), 2.90 (dd, 1H, $J = 9.9, 17.9$), 3.50 (ddd, 1H, $J = 1.7, 5.0, 9.5$), 3.65-3.71 (m, 1H), 4.58 (br s, 1H), 4.75 (br s, 1H), 4.85 (d, 1H, $J = 12.2$), 4.89 (d, 1H, $J = 12.2$), 6.97-7.18 (m, 9H); ^{13}C NMR (100 MHz) some signals coincide: δ 9.31, 20.97, 28.73, 33.70, 46.96, 66.75, 68.62, 69.22, 75.13, 122.97, 124.70, 126.78, 128.05, 128.16, 128.47, 136.13, 143.02, 144.56, 156.09; HRMS (ESI) calcd for $[\text{C}_{22}\text{H}_{27}\text{NO}_4 + \text{Na}]^+$: 392.1838, found: 392.1842.

[(1*R*, 2*R*)-2-((1*R*, 2*R*)-1,2-Dihydroxy-propyl)-1-isobutyl-indan-1-yl]-carbamic acid benzyl ester (S8**):** Prepared using an analogous procedure to that described for **S2**, starting from isoxazolidine **72** (82 mg, 0.32 mmol). Purification by flash chromatography (1:1 hexanes:EtOAc) provided 90 mg of **S8** as a colorless oil in 71% yield. IR: 3407, 2953, 1698, 1498, 1455, 1242 cm^{-1} ; ^1H NMR (C_6D_6 , 40 $^\circ\text{C}$): δ 0.63 (d, 3H, $J = 6.6$), 1.01 (d, 3H, $J = 6.6$), 1.27 (d, 3H, $J = 6.3$), 1.60-1.68 (m, 1H), 1.80 (d, 1H, $J = 9.8$), 1.88 (dd, 1H, $J = 5.9, 14.2$), 2.39 (dd, 1H, $J = 10.3, 15.4$), 2.72 (dd, 1H, $J = 7.9, 15.5$), 2.93 (br d, 1H, $J = 9.8$), 3.00-3.07 (m, 1H), 3.52 (ddd, 1H, $J = 1.5, 5.1, 9.8$), 3.65-3.73 (m, 1H), 4.55 (br s, 1H), 4.73 (br s, 1H), 4.85 (d, 1H, $J = 12.2$), 4.89 (d, 1H, $J = 12.0$), 6.97-7.15 (m, 9H); ^{13}C NMR (100 MHz) some signals coincide: δ 18.10, 20.76, 24.11, 24.94, 33.73, 43.67, 47.34, 66.66, 68.38, 68.75, 75.04, 123.17, 124.63, 126.47, 127.99, 128.11, 128.41, 136.05, 142.66, 145.29, 155.89; HRMS (ESI) calcd for $[\text{C}_{24}\text{H}_{31}\text{NO}_4 + \text{Na}]^+$: 420.2151, found: 420.2146.

[(1*R*, 2*R*)-2-((1*R*, 2*R*)-1,2-Dihydroxy-propyl)-1-phenyl-indan-1-yl]-carbamic acid benzyl ester (S9**):** Prepared using an analogous procedure to that described for **S2**, starting from isoxazolidine **74** (35 mg, 0.12 mmol). Purification by flash chromatography (2:1 EtOAc:hexanes) provided 37 mg of **S9** as a colorless oil in 74% yield. IR: 3316, 1700, 1520, 1255 cm^{-1} ; ^1H NMR (C_6H_6 , 50 $^\circ\text{C}$): δ 0.60 (d, 3H, $J = 6.1$), 1.90-2.10 (br s, 1H), 2.68 (dd, 1H, $J = 7.1, 15.1$), 2.85-2.95 (br s, 1H), 3.21 (dd, 1H, $J = 11.2, 14.9$), 3.46 (dd, 1H, $J = 5.9, 11.7$), 3.70 (ddd, 1H, $J = 6.1, 12.5, 18.6$), 3.82 (br s, 1H), 4.83 (d, 1H, $J = 12.2$), 5.00 (d, 1H, $J = 12.5$), 7.01-7.38 (m, 14 H); ^{13}C NMR (100 MHz): δ 19.36, 33.98, 54.13, 66.56, 67.57, 68.56, 70.94, 124.03, 126.20, 126.78, 127.01, 127.87, 127.93, 128.01, 128.06, 128.14, 128.37, 136.36, 141.96, 142.53, 147.08, 155.31; HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{27}\text{NO}_4 + \text{Na}]^+$: 440.1838, found: 440.1842.

[(1*R*, 2*R*)-2-((1*R*, 2*R*)-1,2-Dihydroxy-propyl)-1-ethyl-2,3-dihydro-1H-cyclopenta[a]naphthalen-1-yl]-carbamic acid benzyl ester (S10**):** Prepared

using an analogous procedure to that described for **S2**, starting from isoxazolidine **76** (70 mg, 0.25 mmol). Purification by flash chromatography (2:1 EtOAc:hexanes) provided 66 mg of **S10** as a colorless oil in 63% yield. IR: 3397, 2967, 1684, 1235 cm^{-1} ; ^1H NMR, major rotamer: δ 0.62 (br s, 3H), 1.27 (d, 3H, $J = 6.1$), 1.93 (br s, 1H), 2.51-2.64 (m, 1H), 2.71 (br s, 1H), 2.76-2.87 (m, 2H), 3.03-3.17 (m, 1H), 3.57 (d, 1H, $J = 8.3$), 3.73 (br s, 1H), 3.88 (br s, 1H), 4.96 (br s, 2H), 5.31 (br s, 1H), 7.14-7.33 (m, 6H), 7.38-7.47 (m, 2H), 7.72 (d, 1H, $J = 8.1$), 7.84 (d, 1H, $J = 8.1$), 8.12 (d, 1H, $J = 8.3$); ^{13}C NMR (100 MHz) some resonances coincide: δ 9.08, 21.04, 32.52, 35.08, 46.88, 66.56, 68.40, 71.33, 75.54, 122.41, 122.95, 124.68, 126.37, 127.83, 128.03, 128.41, 129.31, 129.61, 129.80, 133.41, 136.30, 141.50, 155.98; HRMS (ESI) calcd for $[\text{C}_{26}\text{H}_{29}\text{NO}_4 + \text{Na}]^+$: 442.1994, found: 442.2000.

S11

[(6*RS*, 7*RS*)-6-((1*RS*, 2*RS*)-1,2-Dihydroxy-propyl)-7-ethyl-6,7-dihydro-5*H*-[1]pyrindin-7-yl]-carbamic acid benzyl ester (S11**):** Prepared using an analogous procedure to that described for **S2**, starting from isoxazolidine **78** (43 mg, 0.12 mmol) with the following exception. After protection of the amine was complete as indicated by TLC analysis, 1 eq of a 1 M TBAF solution in THF was added to the reaction mixture to remove the triethylsilyl group. After 1 h the reaction mixture was diluted with 5 mL brine, and extracted 3 x 5 mL with EtOAc. The combined organic extracts were then dried, filtered and concentrated. Purification of the crude residue by flash chromatography (2:1 EtOAc:hexanes) provided 22 mg of **S11** as a colorless oil in 49% yield. IR: 3288, 2965, 1699, 1496, 1266 cm^{-1} ; ^1H NMR, major rotamer: δ 0.74 (t, 3H, $J = 7.2$), 1.26 (d, 3H, $J = 6.6$), 1.87 (d, 1H, $J = 8.8$), 2.23-2.41 (m, 2H), 2.54-3.00 (m, 3H), 3.43-3.57 (m, 2H), 3.76-3.85 (m, 1H), 4.92 (d, 1H, $J = 12.2$), 5.00 (d, 1H, $J = 12.0$), 5.15 (br s, 1H), 7.09-7.15 (m, 1H), 7.24-7.36 (m, 5H), 7.48-7.55 (m, 1H), 8.44 (d, 1H, $J = 4.9$); ^{13}C NMR (acetone- d_6): δ 9.12, 21.13, 32.38, 32.92, 45.85, 55.57, 66.18, 68.06, 76.02, 123.16, 128.34, 128.51, 129.18, 132.42, 138.59, 139.12, 148.68, 156.22, 164.37; HRMS (ESI) calcd for $[\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_4]^+$: 393.1790, found: 393.1791.

S12

[(1*RS*, 2*RS*)-2-((1*RS*, 2*RS*)-1,2-Dihydroxy-propyl)-1-ethyl-5-methoxy-indan-1-yl]-carbamic acid benzyl ester (S12**):** Prepared using an analogous procedure to that described for **S2**, starting from isoxazolidine **80** (54 mg, 0.21 mmol). Purification by flash chromatography (2:1 EtOAc:hexanes) provided 54 mg of **S12** as a colorless oil in 65% yield. IR: 3398, 1934, 1693, 1606, 1492, 1251 cm^{-1} ; ^1H NMR (C_6D_6): δ 0.82 (t, 3H, $J = 7.4$), 1.30 (d, 3H, $J = 6.1$), 1.91 (d, 1H, $J = 9.5$), 2.02-2.11 (m, 1H), 2.37 (dd, 1H, $J = 10.4, 15.5$), 2.66 (dd, 1H, $J = 7.8, 15.6$), 2.95 (br s, 1H, overlaps with peak at $\delta = 2.98$), 2.98 (dd, 1H, $J = 9.8, 17.8$), 3.33 (s, 3H), 3.55 (ddd, 1H, $J = 3.4, 4.9, 9.8$), 3.68-3.75 (m,

1H), 4.71 (br s, 1H), 4.87 (d, 1H, $J = 12.2$), 4.91 (d, 1H, $J = 12.2$), 4.96 (br s, 1H), 6.58 (d, 1H, $J = 2.2$), 6.67 (dd, 1H, $J = 2.3, 8.4$), 6.84 (d, 1H, $J = 8.3$), 6.98-7.20 (m, 5H); ^{13}C NMR (C_6D_6): δ 9.99, 21.71, 29.18, 34.30, 48.34, 55.29, 67.23, 69.17, 69.57, 75.94, 110.25, 113.95, 124.51, 127.96, 128.98, 128.99, 137.34, 137.87, 145.51, 156.87, 161.03; HRMS (ESI) calcd for $[\text{C}_{23}\text{H}_{29}\text{NO}_5 + \text{Na}]^+$: 422.1943, found: 422.1939.

Preparation of cis- β -proline analogs:

(1*RS*, 2*RS*)-1-Benzyloxycarbonylamino-1-ethyl-indan-2-carboxylic acid (**81**):

Prepared using an analogous procedure to that described for **56**, starting from amine diol **S7** (38 mg, 0.10 mmol). Purification by flash chromatography (5:1 CH_2Cl_2 :EtOAc with 1% HOAc) provided 25 mg of **81** as a colorless oil in 84% yield. IR: 3313, 2967, 1714, 1506, 1457, 1253, 1069 cm^{-1} ; ^1H NMR (C_6H_6 , 50 $^\circ\text{C}$): δ 0.83 (t, 3H, $J = 7.3, 14.6$), 2.12-2.21 (m, 1H), 2.22-2.34 (m, 1H), 3.02-3.10 (m, 1H), 3.34-3.39 (m, 2H), 4.95 (m, 2H), 5.65-6.20 (br s, 1H), 7.10-7.35 (m, 9H); ^{13}C NMR: δ 8.38, 29.68, 34.07, 51.98, 66.55, 68.84, 123.99, 124.53, 126.55, 127.95, 128.07, 128.35, 128.56, 136.26, 141.57, 142.84, 155.23, 177.65; HRMS (ESI) calcd for $[\text{C}_{20}\text{H}_{21}\text{NO}_4]^+$: 362.1368, found: 362.1366. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is best stored as the carboxylate salt or as an ester. For example, a portion of crude **81** (7.2 mg, 0.02 mmol, 1 eq) was converted to the methyl ester by treatment with TMSCHN_2 (106 μL of a 2 M solution in Et_2O , 10 eq) in 600 μL benzene/MeOH (3:1) at rt. After 5 min, the reaction was concentrated, then purified by passage through a plug of silica (9:1 hex:EtOAc) to provide 5 mg of the corresponding methyl ester as a colorless oil in 68% yield. ^1H NMR: δ 0.84 (d, 3H, $J = 7.3$), 2.28 (br s, 2H), 3.08 (dd, 1H, $J = 10.2, 17.6$), 3.30-3.45 (m, 2H), 3.62 (s, 3H), 4.93 (d, 1H, $J = 12.2$), 5.00 (d, 1H, $J = 12.2$), 5.83 (br s, 1H), 7.23-7.43 (m, 9H).

(1*RS*, 2*RS*)-1-Benzyloxycarbonylamino-1-isobutyl-indan-2-carboxylic acid (**82**):

Prepared using an analogous procedure to that described for **56**, starting from amine diol **S8** (45 mg, 0.11 mmol). Purification by flash chromatography (5:1 CH_2Cl_2 :EtOAc with 1% HOAc) provided 40 mg of **82** as a colorless oil in 98% yield. IR: 3352, 2955, 1700, 1652, 1250 cm^{-1} ; ^1H NMR (C_6H_6 , 50 $^\circ\text{C}$): δ 0.76 (d, 3H, $J = 6.6$), 0.82 (d, 3H, $J = 6.8$), 1.55-1.61 (m, 1H), 2.06-2.18 (m, 1H), 2.74 (dd, 1H, $J = 10.0, 18.1$), 3.26-3.34 (m, 2H), 4.98 (m, 2H), 6.90-7.34 (m, 9H); ^{13}C NMR: δ 24.09, 24.26, 24.52, 34.27, 44.46, 52.44, 66.52, 68.32, 124.47, 126.39, 127.58, 127.94, 128.14, 128.28, 128.33, 128.54,

135.95, 143.40, 154.76, 177.74; HRMS (ESI) calcd for $[C_{22}H_{25}NO_4 + Na]^+$: 390.1681, found: 390.1676. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is best stored as the carboxylate salt or as an ester. For example, a portion of crude **82** (18.1 mg, 0.049 mmol) was converted to the methyl ester as described for **81** to provide 14 mg of the corresponding methyl ester as a colorless oil in 75% yield. 1H NMR: δ 0.83 (d, 3H, J = 6.6), 0.87 (d, 3H, J = 6.6), 1.57-1.64 (m, 1H), 2.15 (br dd, 1H, J = 4.9, 13.9), 2.19-2.29 (m, 1H), 3.06-3.13 (m, 1H), 3.28-3.37 (m, 2H), 3.64 (s, 3H), 4.91 (d, 1H, J = 12.2), 5.00 (d, 1H, J = 12.2), 6.02 (br s, 1H), 7.20-7.32 (m, 8H), 7.45 (br s, 1H).

(1SR, 2RS)-1-Benzyloxycarbonylamino-1-phenyl-indan-2-carboxylic acid (83): Prepared using an analogous procedure to that described for **56**, starting from amine diol **S9** (23 mg, 0.05 mmol). Purification by flash chromatography (5:1 CH_2Cl_2 :EtOAc with 1% HOAc) provided 14 mg of **83** as a colorless oil in 82% yield. IR: 3328, 3031, 1702, 1497, 1347, 1239 cm^{-1} ; 1H NMR (C_6H_6 , 50 $^{\circ}C$): δ 3.18-3.26 (m, 1H), 3.43-3.49 (m, 2H), 4.90-4.96 (m, 2H), 6.95-7.40 (m, 14H); ^{13}C NMR (100 MHz) some signals coincide: δ 34.51, 58.10, 66.76, 70.30, 124.31, 125.32, 126.19, 126.46, 127.30, 127.75, 127.96, 128.28, 136.10, 141.42, 142.32, 144.17, 154.70, 176.39; HRMS (ESI) calcd for $[C_{24}H_{21}NO_4 + Na]^+$: 410.1368, found: 410.1370. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is best stored as the carboxylate salt or as an ester. For example, a portion of crude **83** (4.5 mg, 0.01 mmol) was converted to the methyl ester as described for **81** to provide 3.2 mg of the corresponding methyl ester as a colorless oil in 67% yield. 1H NMR: δ 3.16 (dd, 1H, J = 7.1, 14.5), 3.33 (dd, 1H, J = 7.0, 10.6), 3.42 (dd, 1H, J = 10.6, 14.5), 3.62 (s, 3H), 4.88 (br d, 1H, J = 11.7), 5.01 (br s, 1H), 7.02 (br s, 1H), 7.24-7.57 (m, 13H).

(1RS, 2RS)-1-Benzyloxycarbonylamino-1-ethyl-2,3-dihydro-1H-cyclopenta[a]naphthalene-2-carboxylic acid (84): Prepared using an analogous procedure to that described for **56**, starting from amine diol **S10** (52 mg, 0.13 mmol). Purification by flash chromatography (5:1 CH_2Cl_2 :EtOAc with 1% HOAc) provided 39 mg of **84** as a colorless oil in 79% yield. IR: 2967, 1710, 1344, 1229 cm^{-1} ; 1H NMR, major rotamer: δ 0.61 (br s, 3H), 2.28-2.66 (m, 2H), 2.91-3.67 (m, 3H), 4.50-4.99 (m, 2H), 6.47 (br s, 1H), 6.87-7.41 (m, 6H), 7.39-7.46 (m, 2H), 7.49 (br s, 1H), 7.84 (d, 1H, J = 7.1), 8.11 (d, 1H, J = 9.3); ^{13}C NMR (100 MHz): δ 8.55, 32.96, 34.42, 51.31, 66.93, 71.60, 122.61, 122.89, 124.76, 126.28, 127.62, 127.75, 128.06, 129.08, 129.46, 129.73, 133.51, 134.83, 135.79, 140.79, 156.88, 176.90; HRMS (ESI) calcd for $[C_{24}H_{23}NO_4 + Na]^+$: 412.1525, found: 412.1519. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is

best stored as the carboxylate salt or as an ester. For example, a portion of crude **84** (8.8 mg, 0.02 mmol) was converted to the methyl ester as described for **81** to provide 6.8 mg of the corresponding methyl ester as a colorless oil in 73% yield. ¹H NMR, major rotamer: δ 0.65 (t, 3H, $J = 7.4$), 2.50-2.61 (m, 1H), 2.62 (br s, 1H), 3.19 (br s, 1H), 3.56 (br s, 5H), 5.09 (br s, 2H), 5.36 (br s, 1H), 7.10-7.36 (m, 6H), 7.38-7.45 (m, 2H), 7.74 (d, 1H, $J = 8.3$), 7.84 (d, 1H, $J = 7.8$), 8.14 (d, 1H, $J = 8.3$).

(1RS, 2RS)- 1-Benzylloxycarbonylamino-1-ethyl-5-methoxy-indan-2-carboxylic acid (85): Prepared using an analogous procedure to that described for **56**, starting from amine diol **S12** (69 mg, 0.20). Purification by flash chromatography (5:1 CH₂Cl₂:EtOAc with 1% HOAc) provided 68 mg of **85** as a colorless oil in 67% yield. IR: 3347, 2964, 1716, 1494, 1251 cm⁻¹; ¹H NMR (acetone-d₆), major rotamer: δ 0.84 (t, 3H, $J = 7.3$), 2.20-2.27 (m, 1H), 2.30-2.38 (m, 1H), 3.03-3.12 (m, 1H), 3.30-3.39 (m, 2H), 3.77 (s, 3H), 4.89 (d, 1H, $J = 12.9$), 4.92 (d, 1H, $J = 12.7$), 6.61 (br s, 1H), 6.75 (dd, 1H, $J = 2.6, 8.4$), 6.78 (br s, 1H), 7.25-7.38 (m, 5H); ¹³C NMR (acetone-d₆): δ 8.96, 35.38, 52.39, 55.66, 66.21, 66.43, 68.22, 110.21, 113.20, 126.52, 128.68, 128.76, 129.31, 129.37, 136.95, 138.67, 144.58, 161.08, 175.31; HRMS (ESI) calcd for [C₂₁H₂₃NO₅ + Na]⁺: 392.1474, found: 392.1468. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is best stored as the carboxylate salt or as an ester. For example, a portion of crude **85** (9.4 mg, 0.03 mmol) was converted to the methyl ester as described for **81** to provide 6.5 mg of the corresponding methyl ester as a colorless oil in 68% yield. ¹H NMR (C₆D₆), major rotamer: δ 0.82 (t, 3H, $J = 7.3$), 2.29 (br s, 1H), 2.45 (br s, 1H), 2.69 (dd, 1H, $J = 7.7, 15.5$), 3.20 (t, 1H, $J = 8.1$), 3.29 (s, 3H), 3.30 (s, 3H), 4.94 (d, 1H, $J = 12.5$), 5.03 (d, 1H, $J = 12.5$), 5.96 (br s, 1H), 6.57 (br s, 1H), 6.70 (dd, 1H, $J = 2.2, 8.3$), 6.98-7.07 (m, 3H), 7.11-7.19 (m, 2H), 7.29-7.37 (m, 1H).

(6RS, 7RS)-7-Benzylloxycarbonylamino-7-ethyl-6,7-dihydro-5H-[1]pyrindine-6-carboxylic acid (86): Prepared using an analogous procedure to that described for **56**, starting from amine diol **S11** (30 mg, 0.08 mmol). Purification by flash chromatography (4:1 EtOAc:CH₂Cl₂ with 1% HOAc) provided 24 mg of **86** as a colorless oil in 86% yield. IR: 3288, 295, 1717, 1497, 1225 cm⁻¹; ¹H NMR, major rotamer: δ 0.74 br s, 3H), 1.95 (br s, 1H), 2.10-2.54 (m, 1H), 2.77-3.14 (m, 3H), 4.61-5.12 (m, 2H), 6.08 (br s, 1H), 6.68-7.05 (m, 1H), 7.10-7.37 (m, 5H), 7.61 (br s, 1H), 8.41 (br s, 1H); ¹³C NMR: δ 7.98, 30.65, 31.83, 51.34, 66.48, 67.10, 122.92, 123.12, 127.84, 128.30, 133.07, 135.86, 136.49, 147.43, 155.55, 161.50, 175.28; HRMS (ESI) calcd for [C₁₉H₂₀N₂O₄ + Na]⁺: 341.1501, found: 341.1496. This compound is acid-sensitive, likely due to instability of the Cbz protecting group caused by steric crowding. For this reason, it is best stored as

the carboxylate salt or as an ester. For example, a portion of crude **86** (9.1 mg, 0.03 mmol) was converted to the methyl ester as described for **81** to provide 9.5 mg of the corresponding methyl ester as a colorless oil in 99% yield. ^1H NMR, major rotamer: δ 0.78 (t, 3H, $J = 7.4$), 1.85-1.92 (m, 1H), 2.44-2.53 (m, 1H), 3.08-3.17 (m, 1H), 3.32 (br d, 1H, $J = 15.1$), 3.46 (s, 3H), 3.58 (br s, 1H), 5.00 (s, 2H), 5.59 (br s, 1H), 7.15 (br s, 1H), 7.24-7.31 (m, 4H), 7.55 (br s, 1H), 8.40 (d, 1H, $J = 4.6$).

NOE studies:

(1RS)-Acetic acid 1-((3SR, 4RS, 5RS)-2-acetyl-3-allyl-4-ethyl-3-isobutyl-isoxazolidin-5-yl)-ethyl ester (S13): Crude isoxazolidine **44b** (225 mg, 0.63 mmol, 1 eq) was dissolved in 3 mL DMF. To this solution was added Ac_2O (600 mL, 6.3 mmol, 10 eq) and $(i\text{-Pr})_2\text{NEt}$ (330 mL, 1.89 mmol, 3 eq). The reaction was irradiated in a conventional microwave oven at 20% power 10 x 15 sec, then partitioned with 15 mL Et_2O and 15 mL H_2O . The aqueous layer was extracted with Et_2O (3 x 15 mL), and the combined organic extracts were washed with 0.1 N HCl (2 x 20 mL) and brine (1 x 20 mL), then dried and concentrated. GC, mass spectrometric, and crude ^1H NMR analysis indicated the presence of both a mono-acetylated isoxazolidine and a di-acetylated isoxazolidine, each as a single diastereomer. Flash chromatography (3:1 hexanes: EtOAc) provided 45 mg of the di-acetylated product **S13** as a colorless oil in 22% yield (the mono-acetylated product, N-acetylated, was isolated in 44% yield). ^1H NMR: δ 0.92-0.97 (m, 9H), 1.34 (d, 3H, $J = 6.6$), 1.44-1.53 (m, 2H), 1.57-1.65 (m, 1H), 1.67-1.75 (m, 1H), 2.05 (s, 3H), 2.06 (s, 3H), 2.25 (dd, 1H, $J = 7.8, 14.7$), 2.31 (dd, 1H, $J = 6.8, 14.7$), 2.36-2.42 (m, 1H), 2.98 (dd, 1H, $J = 6.6, 14.7$), 3.77 (dd, 1H, $J = 2.2, 10.0$), 5.02-5.11 (m, 3H), 5.67-5.76 (m, 1H).

An NOE difference experiment on **S13** showed the key enhancements as indicated:

(1RS)-Acetic acid 1-[(3RS, 5RS)-2-acetyl-3-methyl-3-isobutyl-isoxazolidin-5-yl]-ethyl ester (S14): To a solution of **48** (38 mg, 0.13 mmol, 1 eq) in 1.3 mL DMF was added DMAP (0.8 mg, 0.007 mmol, 0.05 eq), Et_3N (55 μL , 0.39 mmol, 3 eq), and Ac_2O (38 μL , 0.39 mmol, 3eq). After 1 h, the mixture was diluted with 7 mL H_2O and

extracted with EtOAc (3 x 5 mL). The organic layer was washed with 0.1 N HCl (2 x 5 mL), brine (1 x 7 mL), dried, and concentrated to provide 26 mg of **S13** as a colorless oil in 74% yield. IR: 2955, 1738, 1651, 1372 cm^{-1} ; ^1H NMR: δ 0.91 (d, 3H, $J = 6.6$), 0.95 (d, 3H, $J = 6.6$), 1.27 (d, 3H, $J = 6.6$), 1.55 (s, 3H), 1.68-1.75 (m, 1H), 1.83 (dd, 1H, $J = 7.0$, 14.3), 1.91 (dd, 1H, $J = 5.1$, 13.9), 2.01 (dd, 1H, $J = 5.5$, 12.8), 2.02 (s, 3H), 2.07 (s, 3H), 2.17 (t, 1H, $J = 10.6$), 4.10-4.15 (m, 1H), 4.97-5.04 (m, 1H); ^{13}C NMR (100 MHz): δ 16.92, 21.48, 22.72, 23.60, 25.19, 25.21, 25.50, 44.16, 46.59, 65.92, 69.88, 79.97, 170.65, 230.03; HRMS (ESI) calcd for $[\text{C}_{14}\text{H}_{25}\text{NO}_4 + \text{Na}]^+$: 294.1681, found: 294.1678.

An NOE difference experiment on **S14** showed the key enhancements as indicated:

An NOE difference experiment on **S15** showed the key enhancements as indicated:

S

Spectrum acquired at 50 °C

mixture of rotamers

mixture of rotamers