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Stereocontrolled conversion of some optically active (4*S*,5*R*)-dihydroisoxazoles into acyclic 3-acetamido-1,2-diols

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Abstract—Optically active (4*S*,5*R*)-dihydroisoxazoles **5a**–**c** (90–91% ee) have been prepared by reaction of the epoxyketones **4a**–**c** with hydroxylamine. Reduction of compounds **5a** and **5b** using lithium aluminium hydride took place exclusively from the *Re* face to give (1*R*,2*S*,3*S*)-1,3-disubstituted-3-aminopropane-1,2-diols **6a** and **6b**. These amino-diols were characterised by *N*-acetylation and the stereochemical sense of the hydride reduction was confirmed by conversion of amides **7a** and **7b** into α-amino acid derivatives **10a** and **10b**.

1. Introduction

(4*S*,5*R*)-Dihydroisoxazoles have been shown to be versatile intermediates in synthesis through reduction of the heterocycle to form amino-diols of defined stereochemistry. Such chemistry has been utilised for the preparation of biologically important poly-hydroxylated amino-acids, amino-polyols and amino-sugars.[1–5]

The stereoselectivity of the reduction of (4*S*,5*R*)-dihydroisoxazoles with reagents such as lithium aluminium hydride has been attributed to the influence of the substituent at the 4-position.[6] *anti*-Stereochemistry between the newly-introduced amino moiety and the adjacent alcohol group may be achieved by direct reduction of the (4*S*,5*R*)-dihydroisoxazole.

(4*S*,5*R*)-Dihydroisoxazoles, in turn, may be prepared using a variety of methods including [3+2] cycloaddition chemistry.[7] Ito et al. reported the preparation of 4-hydroxy-Δ^2-isoxazolines via intramolecular ring opening of α,β-epoxy ketone oximes derived from α,β-epoxy ketones.[8] It was also shown that by increasing the equivalents of hydroxylamine the reaction would proceed directly to give racemic (4*S*/*R*,5*R*/*S*)-dihydroisoxazoles. However, only a narrow range of substrates have been examined. To date this approach has not been investigated using non-racemic epoxides. We envisaged that by employing optically active epoxy-ketones generated by Juliá-Colonna poly-amino acid catalysed reactions,[9–13] condensation with hydroxylamine and in situ intramolecular epoxide opening would generate the corresponding non-racemic heterocycles, which could be reduced to yield amino-diols and/or derivatives of defined stereochemistry (Scheme 1).

2. Results and discussion

The enones **3a**–**c** were epoxidised using urea–hydrogen peroxide complex and 1,8-diazabicycloundecene (DBU) in THF containing poly-L-leucine supported on silica, to yield enantio-enriched epoxides **4a**–**c** in high yields (Table 1).[14–16] The epoxides **4a**–**c** were reacted with hydroxylamine to afford the desired (4*S*,5*R*)-dihydroisoxazoles **5a**–**c** in good yields (Table 2). Chiral HPLC established that the reaction proceeded without loss of stereochemical integrity and the identity of compound **5b** was confirmed by X-ray analysis.[17]

The reduction of (4*S*,5*R*)-dihydroisoxazoles **5a** and **5b** was investigated using the method described by Rosini et al.[18] using 4 equiv. of lithium aluminium hydride in diethyl ether. Upon reduction of **5a**, a 7:1 mixture of the desired amino-diol **6a** and styrene glycol was obtained, as observed by ^{1}H NMR spectroscopy. It is possible that the glycol is formed by deprotonation of the hydroxyl group and cleavage of the (4*S*,5*R*)-dihydroisoxazole to form benzonitrile and α-hydroxy phenylacetaldehyde. The latter compound can then be reduced to give styrene glycol under the reaction conditions (Scheme 2). Benzonitrile (and/or benzylamine) was not observed in the reaction mixture; however, it is possible that this material was removed during the work-up procedure. Similarly the (4*S*,5*R*)-dihydroisoxazole **5b** gave a crude product comprising a mixture of **6b** (85%) and styrene glycol (15%).

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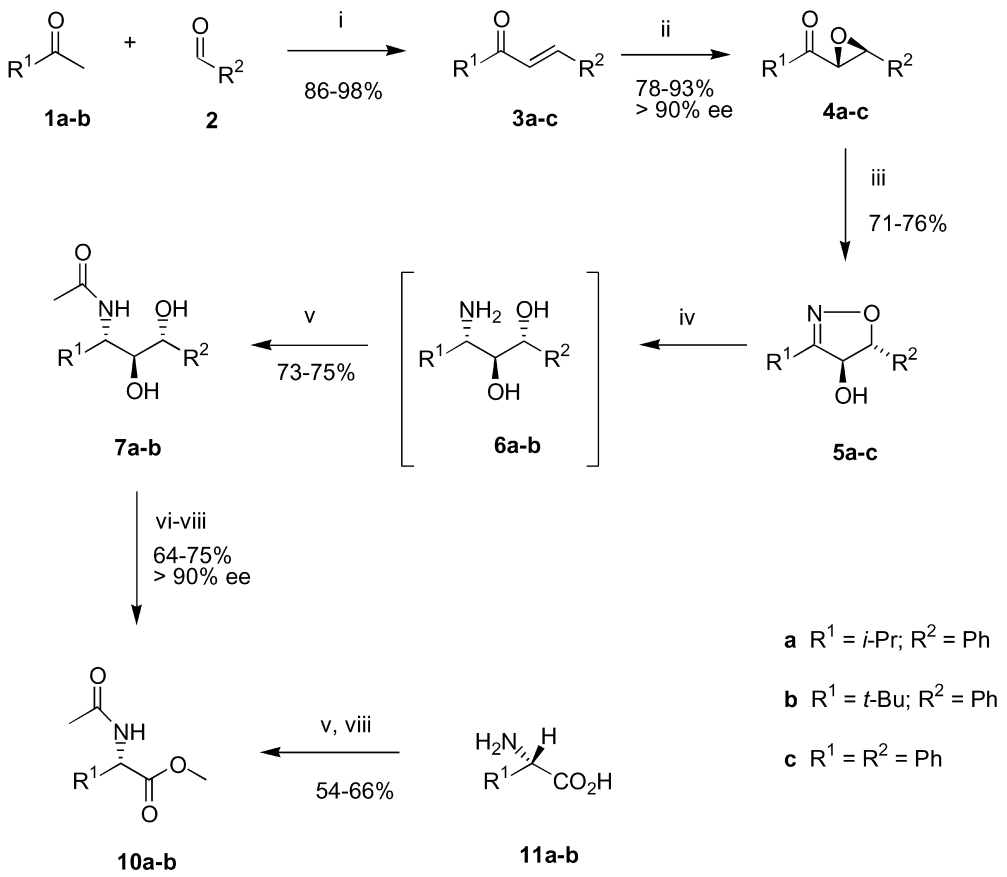


Scheme 1. *Reagents and conditions*: (i) $Ba(OH)_2$, EtOH, 90°C; (ii) Poly-L-leucine-1,3-diaminopropane adsorbed onto silica (PLL–SiO_2), DBU, urea–H_2O_2, THF; (iii) $NH_2OH{\cdot}HCl$, pyridine, EtOH, 90°C; (iv) $LiAlH_4$, THF, rt; (v) Ac_2O, pyridine, rt; (vi) $NaIO_4$ on silica, rt, DCM; (vii) CrO_3, H_2SO_4, acetone, 0°C; (viii) $TMSCHN_2$, hexane, MeOH, rt.

Table 1. The epoxidation of selected enones

Product	R^1	R^2	ee (%)[a]	Yield (%)[b]	Time (h)
4a	*i*-Pr	Ph	90	78	24
4b	*t*-Bu	Ph	91	84	18
4c	Ph	Ph	95	93	3

[a] Determined by chiral HPLC.
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate).

Table 2. Heterocyclisation reaction

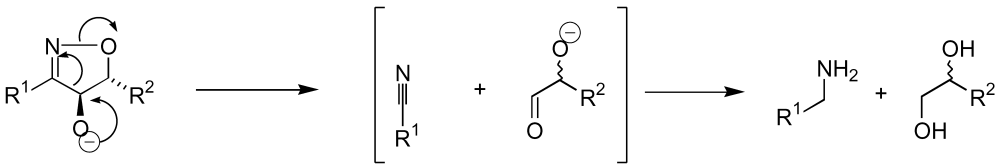
Product	R^1	R^2	ee (%)[a]	Yield (%)[b]	Time (h)
5a	*i*-Pr	Ph	89	73	14
5b	*t*-Bu	Ph	92	76	10
5c	Ph	Ph	94	71	13

[a] Determined by chiral HPLC.
[b] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate).

Attempts to purify the crude mixtures containing **6a** and **6b** by flash chromatography were unsuccessful, therefore the amino-diols **6a** and **6b** were mono-acetylated, using 1.1 equiv. of acetic anhydride in pyridine, to give the amides **7a** and **7b** in yields of 73 and 75% (over two steps), respectively, after column chromatography. The structure of compound **7a** was confirmed by X-ray crystallography.[19] Reduction of the diphenyl compound **5c** proceeded less cleanly and this reaction was not investigated further.

The diols **7a** and **7b** were cleaved using sodium periodate on silica (1.2 mmol/g), then oxidised using Jones' reagent, to give the *N*-acetylated amino acids which were subsequently converted into the corresponding methyl esters **10a** and **10b** (overall yields 64 and 75%, respectively). Authentic samples of **10a** and **10b** were also prepared from the commercially available amino acids. GC analysis of the compounds **10a** and **10b**, showed that the configuration of the amino acids obtained from the oxidative cleavage of the protected amino-diols corresponded predominantly to the L-form of the derivatised commercial amino acids **10a** (90% ee), **10b** (91% ee). Thus, the reductions of the (4*S*,5*R*)-dihydroisoxazoles **6a** (89% ee) and **6b** (90% ee) appear to take place in *anti*-fashion under complete stereocontrol, since the optical purities of the starting materials and the corresponding amino acid derivatives **10a** (90% ee) and **10b** (91% ee) match within experimental error.

In summary, optically active (4*S*,5*R*)-dihydroisoxazoles **5a–c** are readily formed from the appropriate enones. Reduction of representative examples of these (4*S*,5*R*)-dihydroisoxazoles takes place with a high degree of stereocontrol to yield (after acetylation) chiral *N*-acetyl amino diols **7a–b** both in a state of high diastereomeric purity.



R^1 = ^{i}Pr, ^{t}Bu, Ph

R^2 = Ph

Scheme 2.

3. Experimental

3.1. General

Melting points were measured used a Reichert-Jung Thermovar hot-stage microscope and are uncorrected. Microanalyses were determined using a Carlo Elba elemental analyser. Nominal and accurate mass spectra were recorded on a VG7070E, CIPOS, Kratos Profile HV3 and TRIO1000 using electron ionisation (EI^+) and chemical ionisation (CI^+). Optical rotations ($[\alpha]_D$) were measured at ambient temperature (22±3°C) from chloroform solutions using a 0.1 dm path length cell, on a Optical Activity Ltd AA-1000 polarimeter and are recorded in units of 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded, with NaCl discs in Nujol using a Perkin–Elmer 881 infrared spectrophotometer, over a range of 4000–800 cm^{-1}. All ^{1}H NMR spectra were recorded unless otherwise specified, as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Bruker Avance 400 MHz spectrometer or a Bruker 250 MHz spectrometer. Chemical shifts are quoted in parts per million; *J*-values are given in Hz. The ^{13}C NMR spectra were recorded on the same instruments at 100 MHz (using tetramethylsilane as an internal standard). Chiral high performance liquid chromatography was conducted using a Chiralpak AD column (Daicel Chemical Industries), 0.4625 cm. Thin layer chromatography was performed on aluminium backed silica gel 60 F_{254} plates in a variety of solvent systems. The plates were visualised by application of CAM, $KMnO_4$ or ninhydrin and baked with a heat gun. Flash column chromatography was conducted with ICN silica 32-63, 60 Å. Enones **3a** and **3b** were prepared according to the literature.[20] Commercially available amino acids (**11a**–**b**) were *N*-acetylated using literature procedures.[21]

3.1.1. 2-Methyl-1-[(2*R*,3*S*)-3-phenyl-oxiranyl)-propan-1-one (4a).[14] To a solution of (*E*)-4-methyl-1-phenyl-pent-1-en-3-one (**3a**) (3 g, 17.2 mmol) in anhydrous THF (100 mL) was added successively poly-L-leucine adsorbed onto silica (6.0 g), urea hydrogen peroxide (1.94 g, 20.7 mmol) and 1,8-diazabicyclo(5,4,0)undec-7-ene (3.85 mL, 25.8 mmol). The mixture was stirred at room temperature for 24 h. The mixture was filtered and the polymer washed with ethyl acetate. Water (150 mL) was added to the filtrate. The mixture was extracted with ethyl acetate (3×100 mL) and the combined extracts washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure to afford a pale yellow oil (2.78 g). Flash chromatography of the residue over silica gel with hexane/ethyl acetate (9:1) as the eluent afforded 2-methyl-1-[(2*R*,3*S*)-3-phenyl-oxiranyl)-propan-1-one (**4a**) (2.56 g, 78%, 90% ee [chiral HPLC-hexane/ethanol (9:1)]) as a white solid, mp 46°C (from ethanol); (found: C, 76.2; H, 7.6. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4 %); $[\alpha]_D$=−110 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 1710 (C=O) and 1230 (C–O); δ_H (250 MHz, $CDCl_3$) 1.04 (3H, d, *J*=6.9 Hz, CH_3), 1.08 (3H, d, *J*=6.9 Hz, CH_3), 2.83 (1H, hept, *J*=6.9 Hz, C*H*(CH_3)$_2$), 3.62 (1H, d, *J*=1.7 Hz, COCH), 3.94 (1H, d, *J*=1.7 Hz, C*H*Ph), 7.26–7.60 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.3, 18.1 (2×CH_3), 37.0 (*C*H(CH_3)$_2$), 58.4 (*C*HPh), 61.9 (CO*C*H), 125.7, 129.0, 129.1 (ArCH), 135.4 (ArC*ipso*), 208.7 (C=O); *m/z* (CI^+) 191 (66%) $[M+H^+]$ and 208 (24%) $[M+NH_4]^+$.

3.1.2. 2-Dimethyl-1-[(2*R*,3*S*)-3-phenyl-oxiranyl]-propan-1-one (4b).[14] Using the above method and compound (**3b**) as starting material 2,2-dimethyl-1-[(2*R*,3*S*)-3-phenyl-oxiranyl]-propan-1-one (**4b**) (2.78 g, 84%, 91% ee [chiral HPLC-hexane/ethanol (9:1)]) was obtained as a white solid, mp 59°C (from hexane) (lit.,[22] 68–70°C); (found: C, 76.6; H, 8.0. $C_{13}H_{16}O_2$ requires C, 76.4; H, 7.9%); $[\alpha]_D$=−194 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 1707 (C=O) and 1245 (C–O); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, 3×CH_3), 3.85 (1H, d, *J*=1.7 Hz, COCH), 3.86 (1H, d, *J*=1.7 Hz, C*H*Ph), 7.24–7.58 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 25.7 (3CH_3), 43.6 (*C*Me$_3$) 59.1, 59.3 (CO*C*H, *C*HPh), 125.7, 128.7, 128.9 (ArCH), 135.7 (ArC*ipso*), 208.1 (C=O); *m/z* (CI^+) 205 (38%) $[M+H]^+$ (found: $[M+H]^+$, 205.1226. $C_{13}H_{16}O_2$ requires $[M+H]^+$, 205.1229).

3.1.3. Phenyl-[(2*R*,3*S*)-3-phenyl-oxiranyl]-methanone (4c).[14] Using the above method and compound (**3c**) as starting material phenyl-[(2*R*,3*S*)-3-phenyl-oxiranyl]-methanone (**4c**) (4.32 g, 93%, 95% ee [chiral HPLC-hexane/ethanol (9:1)]) was obtained as a white solid, mp 90°C (from ethanol) (lit.,[22] 94–96°C from ethanol); (found: C, 80.2; H, 5.4. $C_{15}H_{12}O_2$ requires C, 80.3; H, 5.4%); $[\alpha]_D$=−200 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 1687 (C=O) and 1271 (C–O); δ_H (250 MHz, $CDCl_3$) 4.08 (1H, d, *J*=1.9 Hz, COCH), 4.31 (1H, d, *J*=1.9 Hz, C*H*Ph), 7.32–8.07 (10H, m, 2×Ph); δ_C (100 MHz, $CDCl_3$) 59.7 (CO*C*H), 61.4 (*C*HPh), 126.2, 128.8, 129.2, 129.3, 129.4, 134.3 (2ArCH) 134.4, 135.9 (2ArC*ipso*), 193.5 (C=O), *m/z* (CI^+) 225 (28%) $[M+H^+]$.

3.1.4. (4*S*,5*R*)-4-Hydroxy-3-isopropyl-5-phenyl-4,5-dihydro-isoxazole (5a). To a stirring ethanolic solution (90 mL) of 2-methyl-1-[(2*R*,3*S*)-3-phenyl-oxiranyl)-propan-1-one (**4a**) (8.71 g, 0.046 mol) was added hydroxylamine hydrochloride (9.55 g, 0.137 mol) and pyridine (14.8 mL, 0.183 mol) and the mixture stirred at reflux (90°C) for 14 h. The reaction mixture was acidified by

addition of 2 M aqueous HCl (80 mL), diluted with water (400 mL) and extracted with diethyl ether (4×100 mL). The combined organic extracts were washed with saturated aqueous copper sulfate solution (2×200 mL), water (2×100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford a brown oil (8.63 g). Flash chromatography of the residue over silica gel with hexane/ethyl acetate (4:1) as the eluent afforded (4*S*,5*R*)-4-hydroxy-3-isopropyl-5-phenyl-4,5-dihydro-isoxazole **5a**. (6.82 g, 73%, 89% ee [chiral HPLC-hexane/ethanol (9:1)]) as a white solid; mp 73–74°C (from hexane/diethyl ether); (found: C, 70.3; H, 7.4; N, 6.8. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); $[\alpha]_D$=+284 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3276 (OH) and 1623 (C=N); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J*=6.8 Hz, CH_3), 1.20 (3H, d, *J*=6.8 Hz, CH_3), 2.41 (1H, br. s, OH), 2.85 (1H, hept, *J*=6.8 Hz, C*H*(CH_3)$_2$), 4.92 (1H, d, *J*=4.1 Hz, C*H*OH), 5.29 (1H, d, *J*=4.1 Hz, C*H*Ph), 7.24–7.44 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.7, 20.5 (2×CH_3), 26.4 ($CH(CH_3)_2$), 85.4 (CHOH), 88.9 (*C*HPh), 125.4, 128.2, 128.8 (ArCH), 138.1 (ArC*ipso*), 163.8 (C=N); *m*/*z* (CI^+) 206 (100%) $[M+H]^+$ (found: $[M+H]^+$, 206.1184. $C_{12}H_{15}NO_2$ requires $[M+H]^+$, 206.1181).

3.1.5. (4*S*,5*R*)-3-*tert*-Butyl-4-hydroxy-5-phenyl-4,5-dihydro-isoxazole (5b). Using the above method and compound **4b** as starting material (4*S*,5*R*)-3-*tert*-butyl-4-hydroxy-5-phenyl-4,5-dihydro-isoxazole (**5b**) (4.32 g, 76%, 92% ee [chiral HPLC-hexane/ethanol (9:1)]) was obtained as a white solid, mp 75°C (from hexane/diethyl ether); (found: C, 71.1; H, 7.8; N, 6.4. $C_{13}H_{17}NO_2$ requires C, 71.2; H, 7.8; N, 6.4%); $[\alpha]_D$=+191 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3284 (OH) and 1624 (C=N); δ_H (400 MHz, $CDCl_3$) 1.26 (9H, s, $3CH_3$), 2.17 (1H, d, *J*=9.0 Hz, OH), 4.92 (1H, dd, *J*=9.0 Hz, 2.9 Hz C*H*OH), 5.34 (1H, d, *J*=2.9 Hz, C*H*Ph), 7.24–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 28.8 ($3CH_3$), 33.0 (*C*Me_3) 85.0 (CHOH), 89.3 (*C*HPh), 125.3, 128.2, 128.8 (ArCH), 137.9 (ArC*ipso*), 165.8 (C=N); *m*/*z* (CI^+) 220 (100%) $[M+H]^+$ (found: $[M+H]^+$, 220.1345. $C_{13}H_{17}NO_2$ requires $[M+H]^+$, 220.1337).

3.1.6. (4*S*,5*R*)-4-Hydroxy-3,5-diphenyl-4,5-dihydro-isoxazole (5c). Using the above method and compound **4c** as starting material (4*S*,5*R*)-4-hydroxy-3,5-diphenyl-4,5-dihydro-isoxazole (**5c**) (6.42 g, 71%, 94% ee [chiral HPLC-hexane/ethanol (9:1)]) was obtained as a white solid, mp 166–168°C (from ethanol); (found: C, 75.0; H, 5.5; N, 5.8. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.9%); $[\alpha]_D$=+159 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3299 (OH) and 1634 (C=N); δ_H (400 MHz, $CDCl_3$) 1.57 (1H, s, OH), 5.38 (1H, d, *J*=3.2 Hz, C*H*OH), 5.56 (1H, d, *J*=3.2 Hz, C*H*Ph), 7.30–7.85 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 85.0 (CHOH), 90.6 (*C*HPh), 125.7, 127.5, 128.2, 128.8, 129.3, 129.3 (2ArCH), 130.8, 138.1 (2×ArC*ipso*), 157.6 (C=N); *m*/*z* (CI^+) 240 (100%) $[M+H^+]$.

3.1.7. (1*R*,2*S*,3*S*)-3-Amino-4-methyl-1-phenyl-pentane-1,2-diol (6a). A two-necked flask was charged with a solution of (4*S*,5*R*)-4-hydroxy-3-isopropyl-5-phenyl-4,5-dihydro-isoxazole **5a** (1.0 g, 4.88 mmol) in anhydrous THF (10 mL). The solution was stirred under an atmosphere of nitrogen and cooled to 0°C. A solution of $LiAlH_4$ in diethyl ether (1 M, 19.5 mL, 19.5 mmol) was added dropwise to the reaction mixture which was then allowed to warm to room temperature. After 1.5 h the reaction was quenched by the careful addition of aqueous solution of sodium hydroxide (20% aq. soln., 75 mL). The aqueous layer was extracted with diethyl ether (3×75 mL) and the combined organic phase was washed with brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to afford a mixture of (1*R*,2*S*,3*S*)-3-amino-4-methyl-1-phenyl-pentane-1,2-diol **6a** and styrene glycol (ratio 7:1 by ^1H NMR) as a white solid (1.0 g); ν_{max} (Nujol)/cm^{-1} 3394 (1° NH_2) and 3309 (2×OH); δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, *J*=6.9 Hz, CH_3) 0.87 (3H, d, *J*=6.9 Hz, CH_3), 2.20 (1H, heptd, *J*=6.9, 3.0 Hz, (C*H*(CH_3)$_2$), 2.73 (1H, dd, *J*=8.5, 3.0 Hz, C*H*NH_2), 3.22 (1H, app. t, *J*=8.5 Hz, C*H*OH), 3.47 (1H, dd, *J*=11.3, 8.3 Hz, styrene glycol), 3.57 (1H, dd, *J*=1.3, 3.5 Hz, styrene glycol), 4.53 (1H, d, *J*=8.5 Hz, C*H*Ph), 4.61 (1H, dd, *J*=8.1, 3.5 Hz, styrene glycol), 7.21–7.45 (10H, m, 2×Ph, diol and styrene glycol); δ_C (100 MHz, $CDCl_3$) 13.9 and 18.6 (2×CH_3), 28.0 (*C*H(CH_3)$_2$), 61.1 ($CHNH_2$), 68.0 (styrene glycol), 73.8 (CHOH), 74.5 (styrene glycol), 79.8 (*C*HPh), 124.9, 126.2, 127.1, 127.4, 128.1, 128.3 (2×ArCH, diol and styrene glycol), 141.0, 141.7 (2×ArC*ipso*, diol and styrene glycol); *m*/*z* (CI^+) 210 (100%) $[M+H]^+$ (found: $[M+H]^+$, 210.1498. $C_{13}H_{21}NO_2$ requires $[M+H]^+$, 210.1494).

3.1.8. (1*R*,2*S*,3*S*)-3-Amino-4,4-dimethyl-1-phenyl-pentane-1,2-diol (6b). Using the above method with compound **5b** as starting material (1*R*,2*S*,3*S*)-3-amino-4,4-dimethyl-1-phenyl-pentane-1,2-diol **6b** and styrene glycol (ratio 6:1 by ^1H NMR) was obtained as a white solid (0.98 g), ν_{max} (Nujol)/cm^{-1} 3408 (1° NH_2) and 3286 (2° OH); δ_H (400 MHz, $CDCl_3$) 0.88 (9H, s, 3×CH_3), 2.55 (1H, d, *J*=8.3 Hz, C*H*NH_2), 3.30 (1H, app. t, *J*=8.3 Hz, C*H*OH), 3.42 (1H, dd, *J*=11.3, 8.3 Hz, styrene glycol), 3.53 (1H, dd, *J*=11.3, 3.4 Hz, styrene glycol), 4.46 (1H, d, *J*=8.3 Hz, C*H*Ph), 4.57 (1H, dd, *J*=8.3, 3.4 Hz, styrene glycol), 7.14–7.38 (10H, m, 2×Ph, diol and styrene glycol); δ_C (100 MHz, $CDCl_3$) 25.8 (3×CH_3), 34.1 (*C*Me_3), 63.5 ($CHNH_2$), 67.0 (styrene glycol), 73.5 (styrene glycol), 74.1 (CHOH), 78.5 (*C*HPh), 124.8, 126.7, 126.8, 126.9, 127.1, 127.3 (2ArCH, diol and styrene glycol) 140.0, 140.5 (2×ArC*ipso*, diol and styrene glycol); *m*/*z* (CI^+) 224 (100%) $[M+H]^+$ (found: $[M+H]^+$, 224.1651. $C_{13}H_{21}NO_2$ requires $[M+H]^+$, 224.1651).

3.1.9. *N*-[(1*S*,2*S*,3*R*)-2,3-Dihydroxy-1-isopropyl-3-phenyl-propyl]-acetamide (7a). Acetic anhydride (74 μL, 0.78 mmol) was added to a solution of crude (1*R*,2*S*,3*S*)-3-amino-4,4-dimethyl-1-phenyl-pentane-1,2-diol **6a** (151 mg, 0.72 mmol) in pyridine (0.81 mL). The solution was stirred under nitrogen at room temperature overnight. The reaction was quenched by addition of 2 M aqueous HCl (3.7 mL) and water (10 mL). This solution was extracted with ethyl acetate (3×25 mL) and the combined organic extracts were washed with saturated copper sulfate solution and water, dried (Na_2SO_4) and evaporated under reduced pressure to afford a yellow oil (150 mg). Flash chromatography of the residue over silica gel with hexane-ethyl acetate (3:1) as the eluent afforded *N*-[(1*S*,2*S*,3*R*)-2,3-dihydroxy-1-isopropyl-3-phenyl-propyl]-acetamide **7a** (132 mg, 73% over two steps) as a white solid; mp 135°C; (found: C, 66.7; H, 8.4; N, 5.5. $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%);

$[\alpha]_D$=−46 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3390 (2° OH) and 3260 (CO*NH*), 1670 (*CO*NH); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J*=6.8 Hz, CH_3) 0.95 (3H, d, *J*=6.8 Hz, CH_3), 1.72 (3H, s, CH_3CO), 2.21 (1H, heptd, *J*=6.7, 4.9 Hz, C*H*$(CH_3)_2$), 2.60 (1H, br. s, OH), 3.36 (1H, br. s, OH), 3.92 (1H, ddd, *J*=9.4, 7.0, 4.9 Hz, C*H*NH_2), 3.95–4.01 (1H, br. m, C*H*OH), 4.79 (1H, d, *J*=3.2 Hz, C*H*Ph), 5.21 (1H, d, *J*=9.4 Hz, NH) 7.24–7.42 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.3 and 20.4 ($2CH_3$), 23.0 (CH_3), 27.9 (*C*H$(CH_3)_2$), 56.4 ($CHNH_2$), 75.1 (CHOH), 75.8 (*C*HPh), 126.2, 127.6, 128.6 (ArCH), 141.4 (ArC*ipso*), 171.6 (C=O); *m*/*z* (CI^+) 252 (100) $[M+H]^+$ (found: $[M+H]^+$, 252.1598. $C_{14}H_{21}NO_3$ requires $[M+H]^+$, 252.1600).

3.1.10. *N*-[(1*S*,2*S*,3*R*)-1-*tert*-Butyl-2,3-dihydroxy-3-phenyl-propyl]-acetamide (7b). Using the above method and compound **6b** as starting material *N*-[(1*S*, 2*S*, 3*R*)-1-*tert*-butyl-2,3-dihydroxy-3-phenyl-propyl]-acetamide (**7b**) (140 mg, 75% over two steps) was obtained as a white solid; mp 156°C; (found: C, 67.5; H, 8.4; N, 4.8. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%); $[\alpha]_D$=−34 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3392 (2° OH) and 3286 (CO*NH*), 1652 (*CO*NH); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, 3×CH_3), 1.73 (3H, s, CH_3), 3.87 (1H, dd, *J*=10.0, 5.8 Hz, CHNH), 4.07 (1H, app. t, *J*=5.8 Hz, CHOH), 4.66 (1H, d, *J*=5.8 Hz, CHPh), 5.60 (1H, d, *J*=10.0 Hz, NH), 7.22–7.45 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 23.1 (CH_3), 27.3 ($3CH_3$), 34.4 (*C*Me_3), 60.8 (CHNH), 74.7 (CHOH), 76.5 (*C*HPh), 126.4, 127.9, 128.7 (ArCH), 141.8 (ArC*ipso*), 171.1 (C=O); *m*/*z* (CI^+) 266 (97%) $[M+H]^+$ (found: $[M+H]^+$, 266.1750. $C_{15}H_{23}NO_3$ requires $[M+H]^+$, 266.1756).

3.1.11. (*S*)-2-Acetylamino-3-methyl-butyric acid methyl ester (10a). Sodium periodate on silica (1.2 mmol/g, 300 mg, 0.36 mmol) was added to a solution of *N*-[(2*S*,3*R*)-2,3-dihydroxy-1-isopropyl-3-phenyl-propyl]-acetamide (**7a**) (30 mg, 0.12 mmol) in dichloromethane (0.75 mL). The mixture was allowed to stir for 4 h at room temperature under an atmosphere of nitrogen. The mixture was filtered and the solid residue washed with dichloromethane (2×1 mL). The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was redissolved in acetone (1 mL). A solution of freshly prepared Jones' reagent (1.36 M, 0.11 mL, 0.14 mmol) was added at 0°C, and the mixture was allowed to stir for 70 min at 0°C. The mixture was filtered and washed with (3×1 mL) acetone. The solution was diluted with water (2.5 mL), extracted with ethyl acetate (5×5 mL) and the combined organic phase was dried with $MgSO_4$ and evaporated under reduced pressure. The residue (15 mg, 0.1 mmol) was redissolved in methanol/toluene (1:3, 1 mL) and a solution of $TMSCHN_2$ in hexane (2 M, 150 μL, 0.3 mmol) was added and allowed to stir for 3 h at room temperature under an atmosphere of nitrogen. To this mixture was added acetic acid (0.1 mL) and the solvent was removed under reduced pressure to afford (*S*)-2-acetylamino-3-methyl-butyric acid methyl ester (**10a**) (13 mg, 64%, 90% ee [chiral GC-Lipodex E, 130°C, dichloromethane]) as a white solid, mp 61–62°C (from ethyl acetate) (lit.,[23] 68–69°C from ethyl acetate/petroleum ether); (found: C, 55.4; H, 8.8; N, 8.1. $C_8H_{15}NO_3$ requires C, 55.5; H, 8.7; N, 8.1%); $[\alpha]_D$=−27 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3273 (CO*NH*), 1739 (COOMe) 1638 (*CO*NH); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, d, *J*=6.9 Hz, CH_3), 0.95 (3H, d, *J*=6.9 Hz, CH_3), 2.09 (3H, s, CH_3C=O), 2.18 (1H, heptd, *J*=6.9, 5.2 Hz, C*H*$(CH_3)_2$), 3.78 (3H, s, CH_3O), 4.63 (1H, dd, *J*=8.1, 5.2 Hz, C*H*NH), 6.24 (1H, d, *J*=8.1 Hz, NH); δ_C (100 MHz, $CDCl_3$) 18.1 and 19.2 (2×CH_3), 23.6 (*C*H_3C=O), 32.0 (*C*H$(CH_3)_2$), 52.2 (CH_3O), 57.6 (CHNH), 170.7 and 173.8 (2×C=O); *m*/*z* (CI^+) 174 (100%) $[M+H]^+$ (found: $[M+H]^+$, 174.1133. $C_8H_{16}NO_3$ requires $[M+H]^+$, 174.1130).

3.1.12. (*S*)-2-Acetylamino-3,3-dimethyl-butyric acid methyl ester (10b). Using the above method and compound **7b** as starting material (*S*)-2-acetylamino-3,3-dimethyl-butyric acid methyl ester (**10b**) (15 mg, 75%, 91% ee [chiral GC-Lipodex E, 120°C, dichloromethane]) was obtained as a white solid; (found: C, 57.6; H, 9.1; N, 7.5. $C_9H_{17}NO_3$ requires C, 57.7; H, 9.15; N, 7.5%); $[\alpha]_D$=−36 (*c* 1, $CHCl_3$); ν_{max} (Nujol)/cm^{-1} 3268 (CO*NH*), 1752 (COOMe) 1643 (*CO*NH); δ_H (400 MHz, $CDCl_3$) 0.98 (9H, s, 3×CH_3), 2.09 (3H, s, CH_3C=O), 3.78 (3H, s, CH_3O), 4.53 (1H, d, *J*=9.6 Hz, C*H*NH), 6.08 (1H, br. d, NH); δ_C (100 MHz, $CDCl_3$) 23.8 (*C*H_3C=O), 26.8 ($3CH_3$), 35.0 (*C*Me_3), 52.2 (CH_3O), 60.3 (CHNH), 170.3 and 172.9 (2C=O); *m*/*z* (CI^+) 188 (100%) $[M+H]^+$ (found: $[M+H]^+$, 188.1288. $C_9H_{17}NO_3$ requires $[M+H]^+$, 188.1287).

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