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New syntheses of enantiopure 2-methyl isoserines

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Abstract—Herein we describe the synthesis of the two enantiomerically pure 3-amino-2-hydroxy-2-methylpropionic acids—(*S*)- and (*R*)-α-methyl isoserines—starting from the chiral diols (*S*)- and (*R*)-2,3-dihydroxy-*N*-methoxy-2,*N*-dimethylpropionamides, respectively, which were obtained by Sharpless asymmetric dihydroxylation (AD) of the olefin *N*-methoxy-2,*N*-dimethylacrylamide with AD-mix α or β as chiral catalytic ligands.

1. Introduction

In recent years, several research groups have focused on various β-amino acid containing oligomers, since such systems are viewed as very promising tools in medicinal chemistry.[1] In particular, β-peptides are of great importance because, in addition to their biological stability,[2–5] they are capable of adopting stable helical, turn and sheet conformations in solution. On the basis of these properties β-peptides have been used to mimic natural peptides and proteins.[6] As in α-peptides, which are composed of α-amino acids, the conformational properties of β-peptides, which are composed of β-amino acids that form amide bonds, depend on the main chain torsional angles (ω, ϕ, θ and ψ) of the β-amino acid units, as depicted in Figure 1.[7]

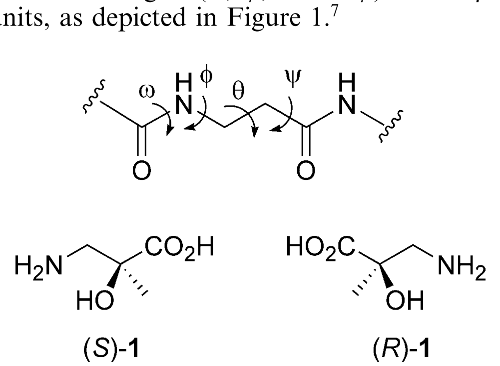

Figure 1.

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In this sense, substituted β-amino acids are of great interest, particularly 2-substituted β-amino acids since the presence of an alkyl substituent at the 2-position favours a gauche conformation about the θ torsion angle, defined by the C2–C3 bond.[8] Such a conformation is required in β-peptides for the adoption of folded conformations.

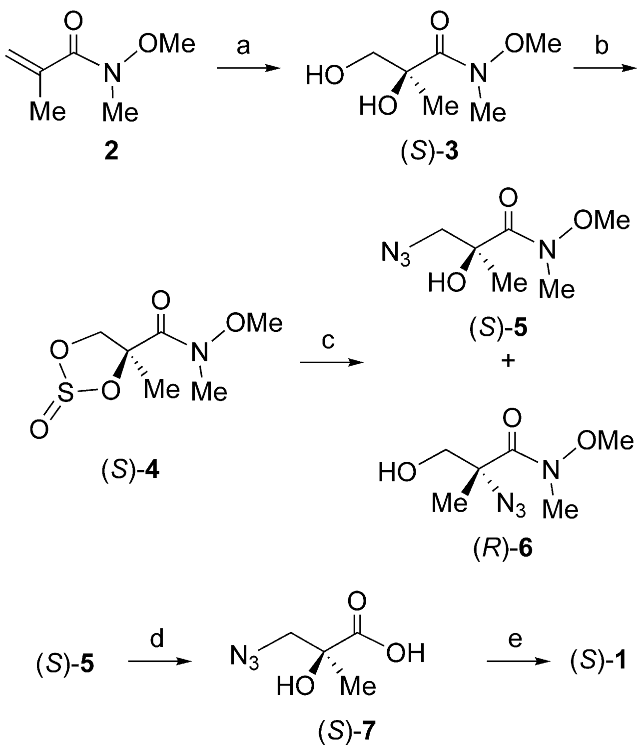
In connection with a research project directed towards the synthesis of hydroxylated amino acids, we herein report the syntheses of both enantiomers of 2-methyl isoserine, (*S*)- and (*R*)-**1** (Fig. 1). This enantiomerically pure β-amino acid has only been synthesised on two previous occasions. The (*R*)-enantiomer[9] was found to have a specific rotation of −11.2. The (*S*)-enantiomer[10] was found to have a specific rotation of −11.3 and, moreover, was incorporated into peptides. In order to expand the scope of research in this area and to clarify this apparent contradiction, we synthesised both enantiomers of 2-methyl isoserine through two different synthetic routes.

2. Results and discussion

2.1. Synthesis of 2-methyl isoserine via sulfites

The best method to obtain enantiomerically pure 2-methyl isoserine is the Sharpless asymmetric aminohydroxylation (AA)[11–15] of 2-methyl-2-propenoic acid derivatives. However, in a recent study we demonstrated that these reactions give good yields and regioselectivities but with poor enantioselectivities.[15]

Considering these previous results, and taking into account the excellent results obtained in the Sharpless asymmetric dihydroxylation (AD)[16–18] with olefin **2** on using AD-mix α or β,[15,19] we decided to use the diols (*S*)-**3** and (*R*)-**3** as starting materials in our synthetic routes. We followed the protocol used in the synthetic method for 2-methyl serine[15] but applied the modification recently described in the literature.[20] Thus, diol (*S*)-**3** was transformed into its 2,3-cyclic sulfite (*S*)-**4** using thionyl chloride. Furthermore, the ring-opening reaction of this sulfite with sodium azide at 70 °C in DMF gave a mixture of the azido alcohols (*S*)-**5** and (*R*)-**6** with a regioselectivity of 4:1 in favour of the β-azido α-alcohol (*S*)-**5** (Scheme 1).



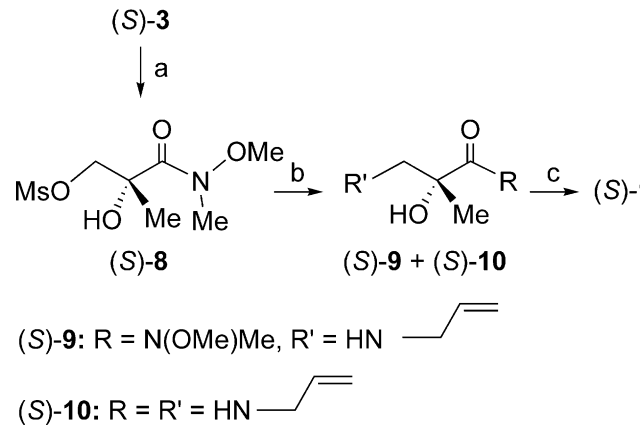
Scheme 1. Reagents and conditions: (a) AD-mix beta, $MeSO_2NH_2$, tBuOH/H_2O (1:1), 0 °C, 12 h, 81%, ee = 93%; (b) $SOCl_2$, CCl_4, reflux, 4 h, 90%; (c) NaN_3, DMF, 70 °C, 48 h, column chromatography, 69% of (*S*)-**5**; (d) LiOH·H_2O, MeOH/H_2O (3:1), 2 h, rt, then conc. HCl to pH = 1; (e) H_2, Pd-C, EtOH, rt, 24 h, 96%.

The mixture of azido alcohols was separated by column chromatography and β-azido-α-alcohol (*S*)-**5** subjected to hydrolysis in a basic medium to give the corresponding carboxylic acid derivative (*S*)-**7** after neutralisation. Subsequent hydrogenation of this compound using EtOH as solvent and Pd/C as catalyst provided the required 2-methyl isoserine (*S*)-**1** in 96% yield and with a specific rotation of +2.8 (five steps, 48% from olefin **2**, 93% ee) (Scheme 1).

The other enantiomer of 2-methyl isoserine, (*R*)-**1**, was obtained using the same strategy as described above starting from olefin **2** but using AD-mix α instead of AD-mix β as the chiral catalytic ligand. In this case the specific rotation of the product was the same but opposite in sign.

2.2. Synthesis of 2-methyl isoserine via mesylates

In an attempt to increase the yield of the β-amino acid (*S*)-**1** from the diol (*S*)-**3**, we developed a second synthetic route, which involved the regioselective introduction of the mesylate group at the primary alcohol using methanesulfonyl chloride (MsCl) in the presence of a basic medium containing diisopropylethylamine (DIEA). This reaction gave excellent results and (*S*)-**8** was obtained in good yield. Unfortunately, the subsequent nucleophilic substitution on this compound with sodium azide proved to be unsuccessful (Scheme 2).



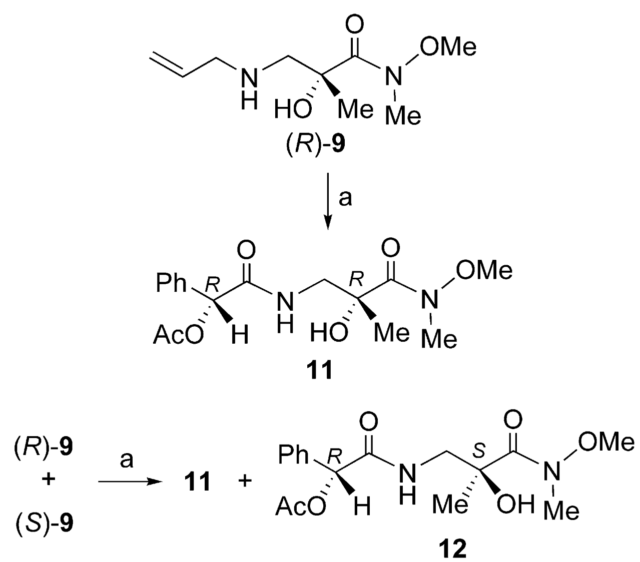
Scheme 2. Reagents and conditions: (a) MsCl, CH_2Cl_2, DIEA, rt, 2 h, 97%; (b) allylamine, reflux, 6 h, 93%; (c) (i) $Pd(PPh_3)_4$, NDMBA, CH_2Cl_2, 30 °C, 3 h, (ii) 6N HCl (aq.), 60 °C, 8 h, (iii) propylene oxide, EtOH, reflux, 2 h, 85%.

This problem was solved by using an excess of allylamine so it could act as both the nucleophile and the solvent in this substitution reaction. Compound (*S*)-**9** was obtained along with the side product (*S*)-**10** in a 75/25 ratio. The mixture of the two products was subjected to deallylation in the presence of tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] and *N*,*N'*-dimethylbarbituric acid (NDMBA).[21] The subsequent acid hydrolysis gave the β-amino acid as its hydrochloride salt. This compound was transformed into the free β-amino acid (*S*)-**1** by the action of propylene oxide under reflux in EtOH. The specific rotation was determined to be +2.9 and this value agrees with our previous result (Scheme 2).

The latter method provided the best results in terms of yield and, although the number of steps was greater than in the route via sulfites, this method made available the free amino acid in the easiest and quickest fashion. In fact, we obtained both enantiomers of the 2-methyl isoserine, (*S*)-**1** and (*R*)-**1**, starting from the Sharpless AD reaction on olefin **2** in six steps with a 62% overall yield and 93% ee.

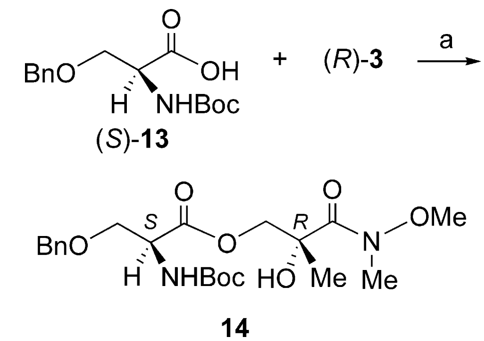
2.3. Determination of the enantiomeric purity and absolute configuration

The enantiomeric purity of 2-methyl isoserine derivatives was determined by the transformation of β-allylamino α-alcohol (*R*)-**9**, after separation of (*R*)-**10** by column chromatography, into a diastereomeric derivative, which had two stereogenic centres. Firstly, the allyl group of (*R*)-**9** was removed as described above and the corresponding β-amino α-alcohol reacted with (*R*)-2-acetylmandelic acid chloride, in CH_2Cl_2 acting as the solvent and triethylamine (TEA) as the base, to give compound **11** in good yield (Scheme 3). Unfortunately, single crystals of this compound could not be obtained for the determination of its absolute configuration. However, in order to ensure that β-amino acids (*S*)-**1** and (*R*)-**1** were almost enantiomerically pure, we determined the cross-contamination by conversion of a mixture of (*R*)-**9** and (*S*)-**9** in a ratio 60/40 to their chiral amide derivatives **11** and **12**, respectively, via coupling with (*R*)-acetylmandelic acid chloride under the same conditions (Scheme 3). Analysis of the ^{1}H NMR spectrum of this mixture and comparison with the spectra of **11** and **12** showed that the enantiomeric purity of (*R*)-**9** and (*S*)-**9** was greater than 93%, since only one isomer was detected. Thus, the enantiomeric purity of the starting diols (*S*)-**3** or (*R*)-**3** was completely retained during the reaction sequences to obtain the final products.



Scheme 3. Reagents and conditions: (a) (i) $Pd(PPh_3)_4$, NDMBA, CH_2Cl_2, 30 °C, 3 h, (ii) (*R*)-acetylmandelic acid chloride, TEA, CH_2Cl_2, rt, 10 h, 88%.

The absolute configuration of 2-methyl isoserines (*S*)-**1** and (*R*)-**1** was unambiguously determined via the transformation of diol (*R*)-**3** into a chiral derivative that had two stereogenic centres. One of these centres was created in the AD reaction and the second one originated from a chiral compound of known stereochemistry; (*S*)-*O*-benzyl-*N*-Boc-serine (*S*)-**13**. Therefore, coupling[22] of the primary alcohol group of diol (*R*)-**3** with the carboxylic acid group of (*S*)-**13** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP), using CH_2Cl_2 as solvent, gave the chiral derivative **14** in good yield (Scheme 4). Fortunately, we were able to obtain single crystals of this oily compound by slow evaporation at low temperature (−40 °C approximately) of a solution in hexane and CH_2Cl_2. The absolute configurations of the stereogenic centres of compound **14** were found to be (*S*)- for the serine moiety and (*R*)- for the diol moiety. This situation is shown in the ORTEP diagram obtained from the X-ray analysis of these monocrystals (Fig. 2).[†]



Scheme 4. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, rt, 6 h, 85%.

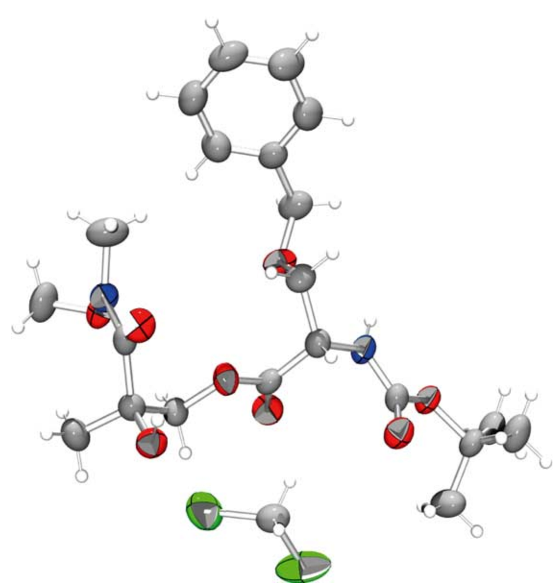


Figure 2. ORTEP diagram of compound **14**.

[†] Crystal data: (a) $C_{22}H_{34}Cl_2N_2O_8$, $M_w = 525.41$, colourless prism of 0.5×0.25×0.25 mm, $T = 223$ K, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 8.3816(2)$ Å, $b = 11.1599(3)$ Å, $c = 28.3281(9)$ Å, $V = 2649.75(13)$ Å^3, $d_{calc} = 1.317$ g cm^{-3}, $F(000) = 1112$, $\lambda = 0.71073$ Å (Mo, Kα), $\mu = 0.291$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 1.44–28.03°, 15,369 collected reflections, 5978 unique, full-matrix least-squares (SHELXL97),[23] $R_1 = 0.0667$, $wR_2 = 0.1217$, ($R_1 = 0.1587$, $wR_2 = 0.1988$ all data), goodness of fit = 1.044, residual electron density between 0.259 and −0.222 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK on quoting the depository number 215525.

3. Conclusions

The work described herein involved the synthesis of the two enantiomerically pure 3-amino-2-hydroxy-2-methylpropionic acids—(*S*)- and (*R*)-2-methyl isoserines—starting from the chiral diols (*S*)- and (*R*)-2,3-dihydroxy-*N*-methoxy-2,*N*-dimethylpropionamides, respectively. These two starting materials were obtained by Sharpless asymmetric dihydroxylation (AD) on olefin *N*-methoxy-2,*N*-dimethylacrylamide with AD-mix α or β as chiral catalytic ligands. The synthesis of these 2-substituted β-amino acids was achieved by two different synthetic routes and the absolute configurations were unambiguously determined by X-ray analysis of a chiral derivative.

4. Experimental

4.1. General procedures

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in 1.0 and 0.5 dm cells of 1.0 and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values.

4.2. (*S*)-2,3-Dihydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*S*)-3

A round-bottomed flask was charged with *tert*-butyl alcohol (80 mL), water (80 mL), AD-mix-β (21.7 g) and methanesulfonamide (1.50 g). The mixture was stirred at 25 °C until both phases were clear, and then cooled to 0 °C, whereupon the inorganic salts partially precipitated. Olefin **2** (2.00 g, 15.5 mmol) was added and the heterogeneous slurry stirred vigorously at 0 °C for 24 h. The reaction was quenched at 0 °C by the addition of sodium sulfite (23.20 g) and then stirred for 1 h. The reaction mixture was extracted with ethyl acetate (3 × 30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 3:7) to give compound (*S*)-**3** as a colourless oil (2.05 g, 12.5 mmol); yield: 81%. $[\alpha]_D^{25}$ −4.6 (*c* 1.80, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 3H, CH_3), 3.31 (s, 3H, NCH_3), 3.63 (d, 1H, $J = 11.4$ Hz, CH_2OH), 3.76 (s, 3H, $NOCH_3$), 3.93 (d, 1H, $J = 11.4$ Hz, CH_2OH); ^{13}C NMR ($CDCl_3$): δ 21.8 (CH_3), 34.0 (NCH_3), 61.4 ($NOCH_3$), 68.0 (CH_2OH), 76.2 [*C*OH(CH_3)], 174.8 (CON); ESI$^+$ (m/z) = 164. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.01; H, 8.02; N, 8.56.

4.3. (*R*)-2,3-Dihydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*R*)-3

As described for enantiomer (*S*)-**3** but using AD-mix-α, compound (*R*)-**3** (2.00 g, 81%) was obtained from olefin **2** (1.95 g, 15.10 mmol). $[\alpha]_D^{25}$ +4.7 (*c* 1.80, MeOH). Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.05; H, 8.03; N, 8.56.

4.4. (*S*)-4-Methyl-2-oxo-2λ^4-[1,3,2]dioxathiolane-4-carboxylic acid *N*-methoxy-*N*-methylamide (*S*)-4

Diol (*S*)-**3** (1.33 g, 8.16 mmol) was dissolved in CCl_4 (30 mL) after which $SOCl_2$ (1.46 g, 12.27 mmol) was added. The resulting solution was heated under reflux for 4 h. The solvent and excess $SOCl_2$ were evaporated and the crude product purified by column chromatography (hexane/ethyl acetate, 7:3) to give the corresponding sulfite (*S*)-**4** as a colourless liquid (1.52 g, 7.27 mmol); yield: 90%. $[\alpha]_D^{25}$ +37.9 (*c* 1.05, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.64, 1.86 (2s, 3H, CH_3), 3.18–3.23 (m, 3H, NCH_3), 3.75 (s, 3H, $NOCH_3$), 4.27 (d, 0.5H, $J = 9.0$ Hz, CH_2O), 4.44 (d, 0.5H, $J = 9.0$ Hz, CH_2O), 5.23 (m, 1H, CH_2O); ^{13}C NMR ($CDCl_3$): δ 22.2, 22.7 (CH_3), 33.4 (NCH_3), 61.4 ($NOCH_3$), 74.1, 74.4 (CH_2O), 88.0, 89.3 [*C*O(CH_3)], 169.0 (CON); ESI$^+$ (m/z) = 210. Anal. Calcd for $C_6H_{11}NO_5S$: C, 34.44; H, 5.30; N, 6.69; S, 15.33. Found: C, 34.37; H, 5.53; N, 6.65; S, 15.23. Duplication of some signals was observed in the ^{1}H and ^{13}C NMR spectra, indicating the existence of two conformers in solution.

4.5. (*R*)-4-Methyl-2-oxo-2λ^4-[1,3,2]dioxathiolane-4-carboxylic acid *N*-methoxy-*N*-methylamide (*R*)-4

As described for enantiomer (*S*)-**4**, compound (*R*)-**4** (0.61 g, 87%) was obtained from compound (*R*)-**3** (0.48 g, 1.76 mmol). $[\alpha]_D^{25}$ −38.8 (*c* 0.92, MeOH). Anal. Calcd for $C_6H_{11}NO_5S$: C, 34.44; H, 5.30; N, 6.69; S, 15.33. Found: C, 34.33; H, 5.42; N, 6.73; S, 15.21.

4.6. (*S*)-3-Azido-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*S*)-5

To a solution of cyclic sulfite (*S*)-**4** (1.00 g, 4.78 mmol) in DMF (30 mL) was added NaN_3 (1.24 g, 19.11 mmol). The mixture was stirred at 70 °C for 2 d to give a mixture of azido alcohols (*S*)-**5** and (*R*)-**6** in a 4:1 ratio. The solvent was removed and the residue partitioned between H_2O (30 mL) and ethyl acetate (50 mL). The aqueous layer was successively extracted with ethyl acetate (2×20 mL), dried over Na_2SO_4, concentrated and the crude product chromatographed (hexane/ethyl acetate, 7:3) to give the α-azido β-alcohol (*R*)-**6** (0.15 g, 17%) and the β-azido α-alcohol (*S*)-**5** (0.62 g, 3.29 mmol) as colourless liquids; yield: 69%. Overall yield: 86%. Compound (*S*)-**5**: $[\alpha]_D^{25}$ −73.9 (*c* 0.98, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H, CCH_3), 3.27 (s, 3H, NCH_3), 3.40–3.55 (m, 2H, N_3CH_2), 3.69 (s, 3H, $NOCH_3$); ^{13}C NMR ($CDCl_3$): δ 22.8 (CCH_3), 33.5 (NCH_3), 57.5 (N_3CH_2), 60.9 ($NOCH_3$), 75.9 (*C*CH_3), 173.7 (CON); ESI^+ (*m/z*) [M+Na] = 211. Anal. Calcd for $C_6H_{12}N_4O_3$: C, 38.29; H, 6.43; N, 29.77. Found: C, 37.95; H, 6.41; N, 29.71. Compound (*R*)-**6**: $[\alpha]_D^{25}$ +61.6 (*c* 0.96, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.50 (s, 3H, CCH_3), 3.22 (s, 3H, NCH_3), 3.65–3.85 (m, 5H, $NOCH_3$, OCH_2); ^{13}C NMR ($CDCl_3$): 17.6 (CCH_3), 33.2 (NCH_3), 60.9 ($NOCH_3$), 66.6 (*C*CH_3), 68.6 (OCH_2), 171.6 (CON); ESI^+ (*m/z*) [M+Na] = 211. Anal. Calcd for $C_6H_{12}N_4O_3$: C, 38.29; H, 6.43; N, 29.77. Found: C, 37.98; H, 6.42; N, 29.74.

4.7. (*R*)-3-Azido-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*R*)-5

As described for enantiomers (*S*)-**5** and (*R*)-**6**, compounds (*R*)-**5** (0.62 g, 3.29 mmol, 69%) and (*S*)-**6** (0.15 g, 17%) were obtained from compound (*R*)-**4** (1.00 g, 4.78 mmol). Compound (*R*)-**5**: $[\alpha]_D^{25}$ +75.3 (*c* 0.99, MeOH). Anal. Calcd for $C_6H_{12}N_4O_3$: C, 38.29; H, 6.43; N, 29.77. Found: C, 38.05; H, 6.38; N, 29.70. Compound (*S*)-**6**: $[\alpha]_D^{25}$ −60.9 (*c* 1.02, MeOH). Anal. Calcd for $C_6H_{12}N_4O_3$: C, 38.29; H, 6.43; N, 29.77. Found: C, 37.99; H, 6.39; N, 29.82.

4.8. (*S*)-3-Amino-2-hydroxy-2-methylpropionic acid (*S*)-1 (via sulfites)

To a solution of compound (*S*)-**5** (0.79 g, 4.20 mmol) in H_2O/MeOH (1:3, 40 mL) was added LiOH·H_2O (0.88 g, 21.1 mmol) with the resulting mixture stirred at 25 °C for 2 h. The *N*,*O*-dimethylhydroxylamine formed in the reaction along with MeOH was removed and the mixture acidified with concd HCl to pH 1–2. The solvent was removed and the residue partitioned between H_2O (10 mL) and ethyl acetate (20 mL). The aqueous layer was successively extracted with ethyl acetate (2×20 mL), dried over Na_2SO_4 and concentrated to give (*S*)-**7** (0.60 g, 4.12 mmol) [^{1}H NMR (CD_3OD): δ 1.40 (s, 3H, CCH_3), 3.37 (d, 1H, $J = 12.3$ Hz, CH_2), 3.49 (d, 1H, $J = 12.3$ Hz, CH_2); ESI^- (*m/z*) = 144. Anal. Calcd for $C_4H_7N_3O_3$: C, 33.11; H, 4.86; N, 28.96. Found: C, 33.22; H, 4.75; N, 29.71]. This compound was dissolved in ethanol (15 mL) after which palladium on carbon (1:5, catalyst/substrate by weight) was added. The resulting suspension was stirred at 25 °C for 24 h. The catalyst was removed by filtration and the solvent evaporated to give (*S*)-**1** (0.48 g, 4.03 mmol); yield: 96%. $[\alpha]_D^{25}$ +2.8 (*c* 1.04, H_2O). Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.25; H, 7.66; N, 11.68.

4.9. (*R*)-3-Amino-2-hydroxy-2-methylpropionic acid (*R*)-1 (via sulfites)

As described for enantiomer (*S*)-**1**, compound (*R*)-**1** (0.40 g, 96%) was obtained from compound (*R*)-**5** (0.66 g, 3.50 mmol). $[\alpha]_D^{25}$ −2.9 (*c* 1.05, MeOH). Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.29; H, 7.65; N, 11.70.

4.10. (*S*)-Methanesulfonic acid 2-hydroxy-2-(methoxymethylcarbamoyl)propyl ester (*S*)-8

A solution of diol (*S*)-**3** (0.52 g, 3.18 mmol) in CH_2Cl_2 (20 mL) was cooled to 0 °C after which MsCl (0.4 mL, 4.77 mmol) and DIEA (0.8 mL, 4.77 mmol) were added dropwise under an argon atmosphere. The mixture was stirred at 25 °C for 2 h and 5% $NaHCO_3$ was added (10 mL). The aqueous layer was extracted with ethyl acetate (3×10 mL) and the combined organic layers washed with brine (10 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 4:6) to give (*S*)-**8** as a white solid (0.75 g, 3.09 mmol); yield: 97%. Mp: 65 °C. $[\alpha]_D^{25}$ −16.5 (*c* 1.00, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.33–1.48 (m, 3H, CH_3), 2.95–3.10 (m, 3H, SO_2CH_3), 3.20–3.36 (m, 3H, NCH_3), 3.68–3.81 (m, 3H, $NOCH_3$), 4.21–4.37 (m, 1H, CH_2), 4.47–4.68 (m, 2H, CH_2+OH); ^{13}C NMR ($CDCl_3$): 21.7 (CH_3), 33.8 (NCH_3), 37.8 (SO_2CH_3), 43.3 (*C*CH_3), 61.2 ($NOCH_3$), 73.9 (CH_2), 172.4 (CON); MS (EI) (*m/z*) = 61, 79, 132, 153; ESI^+ (*m/z*) = 242. Anal. Calcd for $C_7H_{15}NO_6S$: C, 34.85; H, 6.27; N, 5.81; S, 13.29. Found: C, 34.93; H, 6.21; N, 5.72; S, 13.36.

4.11. (*R*)-Methanesulfonic acid 2-hydroxy-2-(methoxymethylcarbamoyl)propyl ester (*R*)-8

As described for enantiomer (*S*)-**8**, compound (*R*)-**8** (1.00 g, 97%) was obtained from diol (*R*)-**3** (0.70 g, 4.29 mmol). $[\alpha]_D^{25}$ +16.8 (*c* 1.01, MeOH). Anal. Calcd for $C_7H_{15}NO_6S$: C, 34.85; H, 6.27; N, 5.81; S, 13.29. Found: C, 34.73; H, 6.23; N, 5.70; S, 13.39.

4.12. (*S*)-3-Allylamino-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*S*)-9 and (*S*)-*N*-allyl-3-allylamino-2-hydroxy-2-methylpropionamide (*S*)-10

Mesylate (*S*)-**8** (0.75 g, 3.09 mmol) was dissolved in neat light-protected allylamine (20 mL) and refluxed for 6 h to give a mixture of the allylaminoalcohols (*S*)-**9** and (*S*)-**10** in a ratio of 65:35. The excess of allylamine was removed and the mixture washed with water (10 mL) and extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4, concentrated and purified by flash column chromatography (CH_2Cl_2/MeOH, 9:1) to give (*S*)-**9** (0.38 g) and (*S*)-**10** (0.20 g) as colourless oils. Overall yield: 93%. Compound (*S*)-**9**: $[\alpha]_D^{25}$ −12.4 (*c* 1.60, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H, CH_3), 2.61 (d, 1H, $J = 11.6$ Hz, CH_2), 3.08 (d, 1H, $J = 11.6$ Hz, CH_2), 3.15–3.27 (m, 5H, NCH_2+NCH_3), 3.69 (s, 3H, $NOCH_3$), 4.98–5.29 (m, 2H,

CCH_2), 5.71–5.87 (m, 1H, CHC); ^{13}C NMR ($CDCl_3$): δ 23.6 (CH_3), 34.1 (NCH_3), 52.6 ($CH_2C{=}C$), 56.6 (CH_2), 61.1 ($NOCH_3$), 75.2 (CCH_3), 116.2 ($CH{=}C$), 137.0 ($C{=}CH_2$); 175.5 (CON); ESI$^+$ (m/z) = 202. Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 53.61; H, 8.89, N, 13.81. Compound (*S*)-**10**: $[\alpha]_D^{25}$ −10.2 (*c* 1.19, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 2.40 (d, 1H, $J = 12.3$ Hz, CH_2), 3.19–3.25 (m, 2H, NCH_2), 3.31 (d, 1H, $J = 12.3$ Hz, CH_2), 3.31–3.39 (m, 2H, NCH_2), 5.05–5.20 (m, 4H, $2CCH_2$), 5.72–5.90 (m, 2H, 2CHC); ^{13}C NMR ($CDCl_3$): δ 24.7 (CH_3), 41.8 ($CH_2C{=}C$), 52.5 ($CH_2C{=}C$), 55.9 (CH_2), 74.1 (CCH_3), 116.4 ($CH{=}C$), 117.0 ($CH = C$), 134.4 ($C{=}CH_2$), 136.2 ($C{=}CH_2$); 176.1 (CON); ESI$^+$ (m/z) = 199. Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 61.01; H, 9.13, N, 14.09.

4.13. (*R*)-3-Allylamino-2-hydroxy-*N*-methoxy-2,*N*-dimethylpropionamide (*R*)-9 and (*R*)-*N*-allyl-3-allylamino-2-hydroxy-2-methylpropionamide (*R*)-10

As described for enantiomers (*S*)-**9** and (*S*)-**10**, compounds (*R*)-**9** (0.35 g) and (*R*)-**10** (0.19 g) were obtained from compound (*R*)-**8** (0.70 g, 2.90 mmol). Overall yield: 93%. Compound (*R*)-**9**: $[\alpha]_D^{25}$ +12.2 (*c* 1.60, MeOH). Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 53.32; H, 8.96, N, 13.82. Compound (*R*)-**10**: $[\alpha]_D^{25}$ +10.1 (*c* 1.19, MeOH). Anal. Calcd for $C_{10}H_{18}N_2O_2$: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.91; H, 9.12, N, 14.10.

4.14. (*S*)-3-Amino-2-hydroxy-2-methylpropionic acid (*S*)-1 (via mesylates)

Allylaminoalcohols (*S*)-**9** and (*S*)-**10** (0.11 g, 0.54 mmol) were treated at 30 °C with $Pd(PPh_3)_4$ (0.06 g, 5×10^{-3} mmol) and *N*,*N*-dimethylbarbituric acid (NDMBA, 0.26 g, 1.61 mmol) in dry degassed CH_2Cl_2 (30 mL) with protection from light under an argon atmosphere. The reaction mixture was stirred for 3 h, the solvent evaporated and the crude product treated at 60 °C with 6 M aqueous HCl (2 mL) for 8 h. The mixture was diluted with water (20 mL), washed with ethyl acetate (2×10 mL) and concentrated to give the desired amino acid hydrochloride salt along with *N*,*O*-dimethylhydroxylamine hydrochloride and traces of NDMBA as impurities. Treatment of this mixture with ethanol/propylene oxide gave 0.05 g of (*S*)-**1** as a white solid yield: 85% $[\alpha]_D^{25}$ +2.9 (*c* 1.01, H_2O). Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.24; H, 7.63; N, 11.72.

4.15. (*R*)-3-Amino-2-hydroxy-2-methylpropionic acid (*R*)-1 (via mesylates)

As described for enantiomer (*S*)-**1**, compound (*R*)-**1** (0.046 g, 72%) was obtained from a mixture of compounds (*R*)-**9** and (*R*)-**10** (0.11 g, 0.54 mmol). $[\alpha]_D^{25}$ −2.5 (*c* 1.05, MeOH). Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.10; H, 7.63; N, 11.74.

4.16. (1′*R*,2″*R*)-Acetic acid 1′-[2″-hydroxy-2″-(methoxymethylcarbamoyl)propylcarbamoyl]-1′-(phenyl)methyl ester 11

(*R*)-**9** (0.20 g, 0.99 mmol) was treated at 30 °C with $Pd(PPh_3)_4$ (0.11 g, 9×10^{-3} mmol) and *N*,*N*-dimethylbarbituric acid (NDMBA, 0.48 g, 2.95 mmol) in dry degassed CH_2Cl_2 (40 mL) with protection from light under an argon atmosphere. The mixture was stirred for 3 h, the solvent evaporated and the crude product treated with saturated Na_2CO_3 solution (5 mL) and extracted with $CHCl_3$/isopropanol (3:1) (5×20 mL). The solution was dried over Na_2SO_4 and the solvent removed to give the crude amino alcohol. The product was treated at 25 °C with (*R*)-*O*-acetylmandelic acid choride (0.32 g, 1.48 mmol) and TEA (0.15 g, 1.48 mmol) in CH_2Cl_2 (20 mL) for 10 h. The reaction mixture was washed with 5% $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with ethyl acetate (3×20 mL); the combined organic layers were dried over $NaSO_4$, evaporated and purified by column chromatography (hexane/ethyl acetate, 2:8) to give compound **11** as a colourless oil (0.29 g, 0.87 mmol); yield: 88%. $[\alpha]_D^{25}$ +45.0 (*c* 0.92, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.43 (s, 3H, CH_3), 2.19 (s, 3H, $COCH_3$), 3.11–3.38 (m, 4H, NCH_3+CH_2), 3.72 (s, 3H, $NOCH_3$), 3.90–4.10 (m, 1H, CH_2), 4.67 (s, 1H, OH), 5.98 (s, 1H, CH), 6.55 (br s, 1H, NH), 7.28–7.55 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.3 ($COCH_3$), 23.1 (CH_3), 34.0 (NCH_3), 46.1 (CH_2), 61.4 ($NOCH_3$), 74.6 (CCH_3), 76.0 (CH), 127.4, 129.0, 129.3, 135.5 (Ph), 169.0 (NCO), 169.7 ($COCH_3$), 174.1 (CON); ESI$^+$ (m/z) = 339. Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.89; H, 6.51; N, 8.26.

4.17. (1′*R*,2″*S*)-Acetic acid 1′-[2″-hydroxy-2″-(methoxymethylcarbamoyl)propylcarbamoyl]-1′-(phenyl)methyl ester 12

As described for diastereomer **11**, compound **12** (0.15 g, 0.46 mmol, 83%) was obtained from compound (*S*)-**9** (0.11 g, 0.56 mmol). $[\alpha]_D^{25}$ +34.5 (*c* 1.57, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 3H, CH_3), 2.12 (s, 3H, $COCH_3$), 3.07 (s, 3H, NCH_3) 3.19–3.33 (m, 1H, CH_2), 3.61 (s, 3H, $NOCH_3$), 3.98–4.09 (m, 1H, CH_2), 4.71 (s, 1H, OH), 6.00 (s, 1H, CH), 6.72 (br s, 1H, NH), 7.18–7.48 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.2 ($COCH_3$), 22.9 (CH_3), 33.7 (NCH_3), 46.0 (CH_2), 61.2 ($NOCH_3$), 74.5 (CCH_3), 75.7 (CH), 127.3, 127.7, 128.8, 129.1, 135.8 (Ph), 168.6 (NCO), 169.3 ($COCH_3$), 174.1 (CON); Anal. Calcd for $C_{16}H_{22}N_2O_6$: C, 56.80; H, 6.55; N, 8.28. Found: C, 56.87; H, 6.52; N, 8.30.

4.18. (2*S*,2′*R*)-3-Benzyloxy-2-*tert*-butoxycarbonylamino-propionic acid 2′-hydroxy-2′-(methoxymethyl-carbamoyl)propyl ester 14

To a solution of (*R*)-**3** (0.13 g, 0.82 mmol), DCC (0.26 g, 0.90 mmol) and DMAP (9 mg, 0.09 mmol) in CH_2Cl_2 (20 mL) was added a solution of (*S*)-3-benzyloxy-2-*tert*-

butoxycarbonylaminopropionic acid (0.28 g, 0.94 mmol) in CH_2Cl_2 (15 mL). After stirring the mixture at 25 °C for 6 h, the resulting white suspension was filtered to remove *N*,*N*′-dicyclohexylurea. The filtrate was concentrated to give a white slurry, to which Et_2O was added. The resulting suspension was filtered to remove the dicyclohexylurea and the solvent evaporated. The residue was purified by column chromatography (hexane/ethyl acetate, 6:4) to give compound **14** as a colourless oil (0.30 g, 0.70 mmol); yield: 85%. $[\alpha]_D^{25}$ +8.7 (*c* 1.49, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.32–1.45 [m, 12H, $C(CH_3)_3$, CH_3], 3.15 (s, 3H, NCH_3), 3.59 (3H, $NOCH_3$), 3.61–3.71 (m, 1H, CH_2O), 3.80–3.88 (m, 1H, CH_2O), 4.12–4.21 (m, 1H, CH_2O), 4.33–4.57 (m, 5H, $PhCH_2O$, CH_2O, CHN, OH), 5.33–5.42 (m, 1H, NH), 7.20–7.35 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.6 (CH_3), 28.2 [$(CH_3)_3C$], 33.6 (NCH_3), 53.9 (CHN), 61.0 ($NOCH_3$), 69.5 (CH_2O), 70.1 (CH_2O), 73.2 ($PhCH_2O$), 73.7 [$C(OH)CH_3$], 79.9 [$(CH_3)_3C$], 127.3, 127.7, 128.3, 137.5 (Ph), 155.3 (NCO), 170.3, 173.4 (CON, CO_2); ESI^+ $(m/z) = 441$. Anal. Calcd for $C_{21}H_{32}N_2O_8$: C, 57.26; H, 7.32; N, 6.36. Found: C, 58.00; H, 7.36; N, 6.30.

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