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Synthesis of enantiopure (αMe)Dip and other α-methylated β-branched amino acid derivatives

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Abstract—This report describes the synthesis of the two enantiomerically pure α-methylated β-branched phenylalanine derivatives, (*S*)- and (*R*)-α-methyl-β,β-diphenylalanine—(αMe)Dip—starting from the chiral building blocks (*R*)- and (*S*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserine methyl esters, respectively. The key step involves a double alkylation with a Grignard reagent on an ester group. The use of the same protocol for the preparation of other α-methylated β-branched serine derivatives is also described.

1. Introduction

In the last few years the synthesis of quaternary α-amino acids has received a great deal of attention,[1,2] particularly α-methylated α-amino acids since they are capable of stabilising certain conformations when they are incorporated into peptides.[3–5] In this context, several authors have focused their interest on the special case of α-methylated α-amino acids with a β-branched side chain.[6,7] For example, α-methyl-β,β-diphenylalanine—(αMe)Dip—has been the subject of several theoretical calculations and these indicate a marked preference for folded conformations.[8] This predicted behaviour has been demonstrated experimentally by incorporation of this unit into peptides.[9] However, (αMe)Dip has only been synthesised on two occasions. The *R*-isomer was obtained by asymmetric synthesis from highly stereoselective enolate trapping of lithium (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisobornyl-2-cyano-3,3-diphenylpropanoate combined with the appropriate rearrangement process.[10] More recently, both isomers of (αMe)Dip were obtained by HPLC resolution of a racemic precursor, followed by the convenient transformation of each enantiomerically pure compound.[11] Taking into account the importance of the α-methylated β-branched α-amino acids (*S*)- and (*R*)-**1**, as well as our experience in the synthesis of quaternary α-amino acids from the chiral building blocks *N*-Boc-*N*,*O*-isopropylidene-α-methylserinals (*S*)- and (*R*)-**2**,[12–15] we wanted in the first instance to develop a new and straightforward synthesis of both enantiomers of (αMe)Dip (Fig. 1).

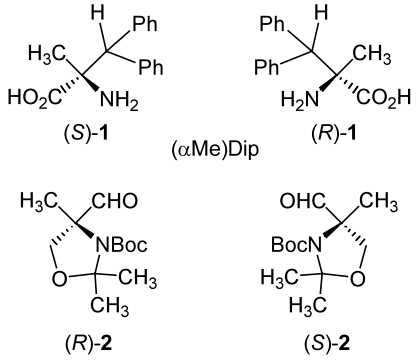

Figure 1. (*S*)- and (*R*)-α-Methyl-β,β-diphenylalanines and chiral building blocks (*R*)- and (*S*)-**2**.

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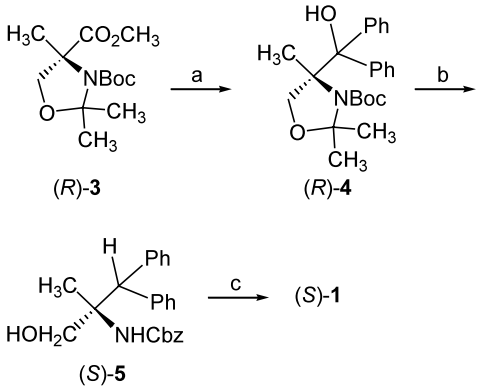
2. Results and discussion

2.1. Synthesis of (αMe)Dip

Our synthesis started from the methyl ester derivative (*R*)-**3**, a precursor of the chiral building block (*R*)-**2**, and the key step was the double alkylation with phenylmagnesium bromide to give the alcohol (*R*)-**4** in good yield (Scheme 1). Single crystals of (*R*)-**4** were obtained in order to confirm its structure by X-ray diffraction (Fig. 2).[†]



Scheme 1. *Reagents and conditions*: (a) PhMgBr, THF, 35°C, 12 h, 87%; (b) (i) $Pd(OH)_2$, 5 atms H_2, HCOOH, 60°C, 36 h; (ii) NaOH, H_2O/MeOH (1:1), reflux, 12 h; (iii) CbzCl, $Na_2CO_3{\cdot}10H_2O$, H_2O/THF (1:5), rt, 12 h, 80%; (c) (i) Jones reagent, acetone, 0°C, 3 h, rt, 3 h; (ii) Pd/C, H_2, MeOH, rt, 24 h, 85%.

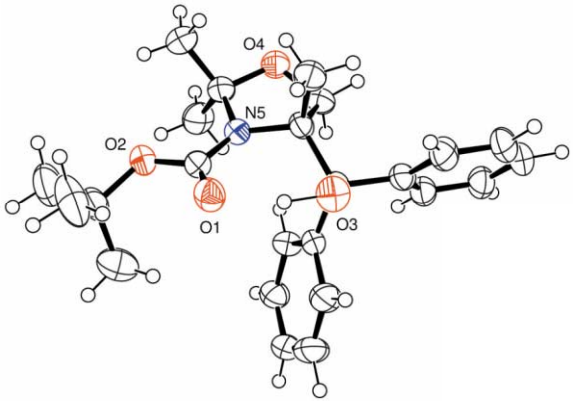


Figure 2. ORTEP diagram of compound (*R*)-**4**.

[†] Crystal data: $C_{24}H_{31}NO_4$, $M_w = 397.50$, colourless prism, $T = 293$ K, monoclinic, space group $C2$, $Z = 4$, $a = 20.0527(4)$, $b = 6.3789(2)$, $c = 18.6631(4)$ Å, $\beta = 111.042(2)°$, $V = 2228.10(10)$ Å^3, $D_{calcd} = 1.185$ g cm^{-3}, $F(000) = 856$, $\lambda = 0.71073$ Å (Mo, Kα), $\mu = 0.080$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 2.18–26.73°, 9391 collected reflections, 4402 unique, full-matrix least-squares (SHELXL97[a]), $R_1 = 0.0469$, $wR_2 = 0.1216$, ($R_1 = 0.0617$, $wR_2 = 0.1299$ all data), goodness of fit = 1.300, residual electron density between 0.314 and −0.190 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 Center, 12 Union Road, Cambridge, UK on quoting the depository number 195672. (a) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.

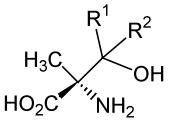
Catalytic dehydroxylation of (*R*)-**4** followed by hydrolysis in basic medium gave the corresponding amino alcohol, the amine group of which was protected with CbzCl to give compound (*S*)-**5**. Oxidation of the alcohol to the carboxylic acid, using Jones' reagent, and subsequent hydrogenolysis in the presence of Pd/C as a catalyst in order to deprotect the Cbz carbamate group, gave the required (αMe)Dip of *S*-configuration in 85% yield [overall yield of 59% from starting material (*R*)-**3**]. The (αMe)Dip of *R*-configuration was obtained in a similar way but starting from chiral building block (*S*)-**3** (Scheme 1).

2.2. Synthesis of α-methylated β-branched serine derivatives (αMe)Dps and (αMe)Dms

Another aspect of our research programme is focused on other valuable unnatural quaternary α-amino acids; the β-branched serine derivatives. In this respect, and in order to increase the number of available α-methylserine derivatives[14–17] (Fig. 3), we recently reported the synthesis of all stereoisomers of α-methylated β-phenylserine—new 'chimeras' that are a combination of α-methylated phenylalanine and serine—in their enantiomerically pure forms.[14] We wish to report herein the synthesis of suitably protected α-methylated β,β-diphenylserine—(αMe)Dps—(*S*)-**7**.

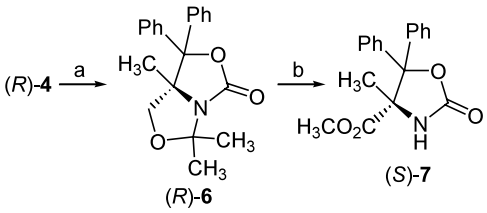
The starting material for this synthesis was *N*-Boc protected *N*,*O*-acetal compound (*R*)-**4** and this approach utilises the propensity of the *N*-Boc protecting group to react intramolecularly with nucleophiles.[18]

Treatment of (*R*)-**4** with sodium hydride in DMF, as a solvent, led to nucleophilic attack of the alkoxide anion on the carbamate to give compound (*R*)-**6** (Scheme 2). Cleavage of the *N*,*O*-acetal in acidic medium, followed by Jones' oxidation and addition of diazomethane, afforded the requisite α-methylated β-branched amino acid, in which the amine and hydroxyl groups are protected as the oxazolidine ring and the carboxylic acid group as the methyl ester (Scheme 2). In a similar way, but starting from (*S*)-**4** [prepared from (*S*)-**3**], the enantiomer (*R*)-**7** was obtained. The structure of



R^1	R^2	Amino Acid	Ref.
H	Ph	(αMe)Phs	14
H	CH_3	(αMe)Thr	16
Ph	Ph	(αMe)Dps	--
CH_3	CH_3	(αMe)Dms	17

Figure 3. Unnatural quaternary α-methylated β-branched serine derivatives.



Scheme 2. *Reagents and conditions*: (a) NaH, DMF, rt, 6 h, 99%; (b) (i) 4N HCl/THF (1:1), rt, 4 h; (ii) Jones reagent, acetone, 3 h, 0°C and another 3 h, rt; (iii) CH_2N_2, MeOH, 0°C, 30 min, 85%.

bicyclic compound (*R*)-**6** was confirmed by X-ray analysis (Fig. 4).‡

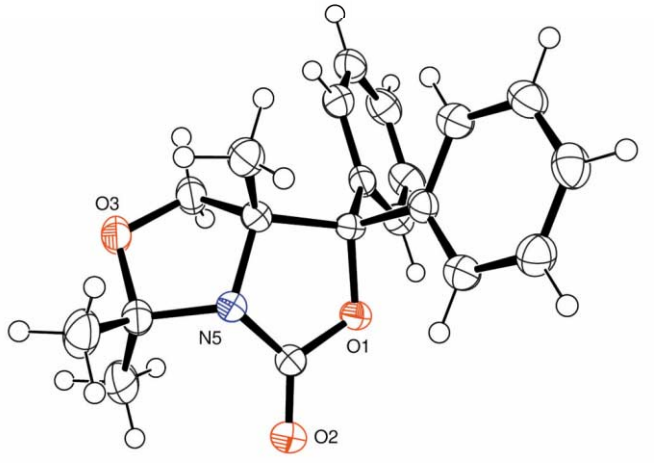
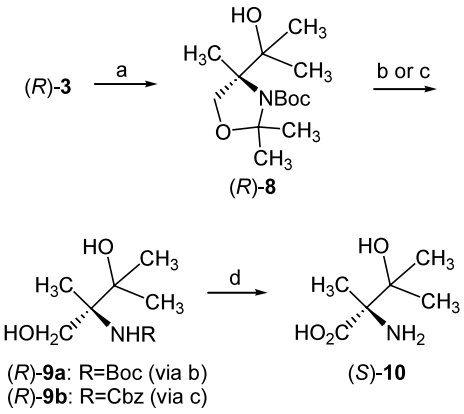


Figure 4. ORTEP diagram of compound (*R*)-**6**.

Moreover, using the same protocol as described above for the synthesis of (αMe)Dip, we obtained the α-methylated β,β-dimethylserine—(αMe)Dms—(*S*)-**10**. The only previous synthesis of the *R*-enantiomer of this amino acid was reported by Schöllkopf.[17] The double alkylation of the chiral building block (*R*)-**3** gave the tertiary alcohol (*R*)-**8**, which was treated with $Sc(TfO)_3$ in H_2O/acetonitrile to drive the cleavage of *N*,*O*-acetal exclusively. This route gave compound (*R*)-**9a** (Scheme 3).

‡ Crystal data: $C_{20}H_{21}NO_3$, $M_w = 323.38$, colourless prism of 0.38×0.2×0.15 mm, $T = 173$ K, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 8.3083(3)$, $b = 7.3248(3)$, $c = 28.0136(11)$ Å, $\beta = 101.5410(17)°$, $V = 1670.34(11)$ Å^3, $D_{calcd} = 1.286$ g cm^{-3}, $F(000) = 688$, $\lambda = 0.71073$ Å (Mo, Kα), $\mu = 0.086$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 3.48–27.89°, 12353 collected reflections, 3967 unique, full-matrix least-squares (SHELXL97[a]), $R_1 = 0.0510$, $wR_2 = 0.1113$, ($R_1 = 0.0962$, $wR_2 = 0.1312$ all data), goodness of fit = 1.024, residual electron density between 0.222 and −0.204 e Å^{-3}. Hydrogen atoms fitted at theoretical positions. Further details on the crystal structure are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository number 195673. (a) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.



Scheme 3. *Reagents and conditions*: (a) MeMgBr, THF, rt, 12 h, 91%; (b) $Sc(TfO)_3$, H_2O/acetonitrile, rt, 36 h, 82%; (c) (i) 6N HCl/THF (1:1), rt, 2 h; (ii) CbzCl, $Na_2CO_3 \cdot 10H_2O$, H_2O/THF (1:5), rt, 15 h, 74%; (d) (i) Jones reagent, acetone, 3 h, 0°C and another 3 h, rt; (ii) Pd/C, H_2, MeOH, rt, 24 h, 64%.

Nevertheless, all attempts to oxidize the primary alcohol (Jones' reagent, Swern, Dess–Martin) were unsuccessful. Therefore, (*R*)-**8** was treated in an acid medium to get the cleavage of *N*,*O*-acetal and the *N*-Boc group, giving the corresponding aminodiol. This aminodiol was protected with CbzCl to give compound (*R*)-**9b**, which was selectively oxidized at the primary alcohol using Jones' reagent. The resulting product was hydrogenated in the presence of Pd/C as a catalyst and MeOH as a solvent to give (αMe)Dms (*S*)-**10** (Scheme 3). The other enantiomer of (αMe)Dms [(*R*)-**10**] was obtained in the same way, but starting from the chiral building block (*S*)-**3**.

3. Conclusions

In summary, we have developed a versatile route to synthesize both enantiomers of (αMe)Dip [(*S*)- and (*R*)-**1**] from the *N*-Boc-*N*,*O*-isopropylidene-α-methylserine methyl esters (*R*)- and (*S*)-**3**, respectively. These syntheses were achieved by double alkylation of the methyl ester group of the aforementioned chiral building blocks with a Grignard reagent. Moreover, following the same protocol, we have synthesised both enantiomers of other α-methylated β-branched serine derivatives such as a suitably protected (αMe)Dps [(*S*)- and (*R*)-**7**] and (αMe)Dms [(*S*)- and (*R*)-**10**]. These β-branched quaternary α-amino acids are of great interest for incorporation into peptides.

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). ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O with

TMS as the external standard using a coaxial microtube (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. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 1000 spectrophotometer.

4.1.1. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-(hydroxydiphenylmethyl)-2,2,4-trimethyloxazolidine, (*R*)-4. To a precooled solution of (*R*)-**3** (0.50 g, 1.83 mmol) in THF (15 mL) at 0°C was added dropwise a 3 M solution of phenylmagnesium bromide (4.3 mL, 12.8 mmol) in THF. The cooling bath was removed and the mixture warmed to 35°C for 12 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography (hexane:ethyl acetate, 9.5:0.5) to give (*R*)-**4** as a white solid (0.63 g, 1.59 mmol); yield: 87%. Mp: 96°C. $[\alpha]_D^{25}=+54.1$ (*c* 1.10, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.11 (s, 3H, CH_3), 1.37 [s, 9H, $(CH_3)_3C$], 1.48 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.64 (d, 1H, $J=9.6$ Hz, CH_2O), 4.69 (d, 1H, $J=9.6$ Hz, CH_2O), 7.25 (m, 5H, Ph), 7.48 (m, 2H, Ph), 7.64 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.7, 25.6, 26.4 ($3CH_3$), 28.1 [$(CH_3)_3C$], 71.4 [$C(CH_3)NH$], 73.6 (CH_2O), 81.4, 82.0 [$(CH_3)_3C$, $C(OH)Ph_2$], 95.5 [$C(CH_3)_2$], 126.6, 126.9, 127.0, 127.6, 127.8, 128.4, 144.5, 145.9 (Ph), 154.1 (OCON); MS (EI) (m/z) = 56, 100, 167, 331; ESI$^+$ (m/z) = 398. Anal. calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.71; H, 7.93; N, 3.63%.

4.1.2. (*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(hydroxydiphenylmethyl)-2,2,4-trimethyloxazolidine, (*S*)-4. As described for enantiomer (*R*)-**4**, compound (*S*)-**4** (0.61 g, 87%) was obtained from compound (*S*)-**3** (0.48 g, 1.76 mmol). $[\alpha]_D^{25}=-54.3$ (*c* 1.20, MeOH). Anal. calcd for $C_{24}H_{31}NO_4$: C, 72.52; H, 7.86; N, 3.52. Found: C, 72.69; H, 7.95; N, 3.65%.

4.1.3. (*S*)-(1-Hydroxymethyl-1-methyl-2,2-diphenylethyl)carbamic acid benzyl ester, (*S*)-5. To a solution of compound (*R*)-**4** (0.29 g, 0.73 mmol) in formic acid (15 mL) was added $Pd(OH)_2$ on carbon (1:5 catalyst/substrate by weight). The resulting suspension was stirred with a pressure of 5 atmospheres of H_2 at 60°C for 36 h. The catalyst was removed by filtration and the solvent was evaporated. The mixture was dissolved in H_2O/MeOH (1:1, 20 mL) and NaOH (0.29 g, 7.30 mmol) was added. The suspension was heated under reflux for 12 h. The MeOH was removed, the aqueous layer was extracted with $CHCl_3$/isopropanol (3:1) (4×20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated to give the corresponding amino alcohol. This compound was dissolved in H_2O/THF (1:5, 15 mL) and then $Na_2CO_3{\cdot}10H_2O$ (0.27 g, 0.95 mmol) and $ClCO_2CH_2Ph$ (0.13 mL, 0.88 mmol) were added. The mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (2±15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate, 8:2) to give compound (*S*)-**5** as a white solid (0.22 g, 0.59 mmol); yield: 80%. Mp: 59°C. $[\alpha]_D^{25}=-2.5$ (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.40 (s, 3H, CH_3), 3.62 (d, 1H, $J=12.0$ Hz, CH_2OH), 3.84 (d, 1H, $J=12.0$ Hz, CH_2OH), 4.65 (s, 1H, $CHPh_2$), 4.98 (br s, 1H, NH), 5.02 (d, 1H, $J=12.3$ Hz, OCH_2Ph), 5.12 (d, 1H, $J=12.3$ Hz, OCH_2Ph), 7.27–7.52 (m, 15H, Ph); ^{13}C NMR ($CDCl_3$): δ 21.5 (CH_3), 56.1 (CPh_2), 60.3 [$C(CH_3)NH$], 66.7 (OCH_2Ph), 67.8 (CH_2OH), 126.7, 126.8, 128.0, 128.1, 128.3, 128.4, 128.5, 129.8, 130.0, 136.2, 139.8, 140.0 (Ph), 156.1 ($OCON$); MS (EI) (m/z) = 56, 100, 167, 346; ESI$^+$ (m/z) = 376.2. Anal. calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.91; H, 6.80; N, 3.60%.

4.1.4. (*R*)-(1-Hydroxymethyl-1-methyl-2,2-diphenylethyl)carbamic acid benzyl ester, (*R*)-5. As described for enantiomer (*S*)-**5**, compound (*R*)-**5** (0.23 g, 80%) was obtained from compound (*S*)-**4** (0.30 g, 0.76 mmol). $[\alpha]_D^{25}=+2.7$ (*c* 0.90, MeOH). Anal. calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.60; H, 6.81; N, 3.62%.

4.1.5. (*S*)-2-Amino-2-methyl-3,3-diphenylpropionic acid, (*S*)-1. To a solution of alcohol (*S*)-**5** (0.18 g, 0.48 mmol) in acetone (10 mL) at 0°C was added dropwise a 1.5-fold excess of Jones' reagent over 5 min. The mixture was stirred at 0°C for 3 h and then at room temperature for a further 3 h. The excess Jones' reagent was destroyed with 2-propanol. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil was dissolved in MeOH (15 mL) and palladium on carbon (1:5 catalyst/substrate by weight) was added. The resulting suspension was subjected to hydrogenolysis at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give (*S*)-**1** as a white solid (0.10 g, 0.41 mmol); yield: 85%. Taking into account that this compound is not soluble in H_2O and in order to measure its physical properties, the amino acid was transformed into the corresponding hydrochloride salt. Mp: 271°C. $[\alpha]_D^{25}=-6.8$ (*c* 1.16, HCl_{aq} 1N); [lit.[11] −8.5 (*c* 1.0, HCl_{aq} 1N]. Spectroscopic data were identical to those described in the literature.[11] ES$^-$ (m/z) = 254. Anal. calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 65.97; H, 6.12; N, 4.71%.

4.1.6. (*R*)-2-Amino-2-methyl-3,3-diphenylpropionic acid, (*R*)-1. As described for enantiomer (*S*)-**1**, compound (*R*)-**1** (87 mg, 85%) was obtained from compound (*R*)-**5** (0.15 g, 0.40 mmol). $[\alpha]_D^{25}=+7.0$ (*c* 1.09, HCl_{aq} 1N); [lit.[10] +8.2 (*c* 1.0, 1N HCl_{aq}]. Anal. calcd for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found: C, 66.01; H, 6.15; N, 4.70%.

4.1.7. (*R*)-5,5,7a-Trimethyl-1,1-diphenyldihydrooxazolo[3,4-*c*]oxazol-3-one, (*R*)-6. To a solution of (*R*)-**4** (0.36 g, 0.91 mmol) in DMF (10 mL) at 0°C was added NaH (43 mg, 1.09 mmol). The resulting suspension was stirred at room temperature for 6 h before being quenched at 0°C with H_2O (5 mL). The resulting mixture was concentrated and washed with ethyl acetate (4×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate, 8:2) to give compound (*R*)-**6** as a white solid (0.29 g, 0.90 mmol); yield: 99%. Mp: 114°C. $[\alpha]_D^{25}=-0.8$ (*c* 1.02, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.33 (d, 1H, $J=8.4$ Hz, CH_2O), 3.64 (d, 1H, $J=8.4$ Hz, CH_2O), 7.22–7.40 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$): δ 24.0, 24.7, 28.9 ($3CH_3$), 72.4 (CH_2O), 73.4 [$C(CH_3)NH$], 87.8, 94.9 [$C(CH_3)_2$, $COPh_2$], 125.5, 127.0, 128.0, 128.1, 128.2, 128.4, 139.0, 139.9 (Ph), 155.9 (OCON); MS (EI) (m/z)=42, 83, 105, 182, 323; ESI$^+$ (m/z)=324.2. Anal. calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.41; H, 6.60; N, 4.22%.

4.1.8. (*S*)-5,5,7a-Trimethyl-1,1-diphenyldihydro-oxazolo[3,4-*c*]oxazol-3-one, (*S*)-6. As described for enantiomer (*R*)-**6**, compound (*S*)-**6** (0.26 g, 99%) was obtained from compound (*S*)-**4** (0.32 g, 0.81 mmol). $[\alpha]_D^{25}=+1.1$ (*c* 0.75, MeOH). Anal. calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.42; H, 6.61; N, 4.19%.

4.1.9. (*S*)-4-Methyl-5,5-diphenyloxazolidin-2-one-4-carboxylic acid methyl ester, (*S*)-7. 4N HCl (5 mL) was added to a solution of compound (*R*)-**6** (0.27 g, 0.83 mmol) in THF (5 mL). The solution was stirred at room temperature for 4 h. The reaction mixture was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated to give the corresponding alcohol, which was used without further purification. A 1.5-fold excess of Jones' reagent was added dropwise over 5 min to a solution of this alcohol (0.22 g, 0.77 mmol) in acetone (10 mL) at 0°C. The mixture was stirred at 0°C for 3 h and then at room temperature for a further 3 h. The excess Jones' reagent was destroyed with 2-propanol. The mixture was diluted with H_2O (10 mL) and extracted with ethyl acetate (4×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil was dissolved in MeOH (10 mL), cooled in an ice-bath, and treated with ethereal diazomethane. After 30 min at 0°C the solvent was evaporated and the crude product was purified by column chromatography (hexane:ethyl acetate, 6:4) to give (*S*)-**7** as a colourless oil (0.22 g, 0.71 mmol); yield: 85%. $[\alpha]_D^{25}=-15.2$ (*c* 1.20, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 3H, CH_3), 3.96 (s, 3H, CO_2CH_3), 7.14 (br s, 1H, NH), 7.28–7.45 (m, 8H, Ph), 7.67–7.70 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 24.3 (CH_3), 52.6 (CO_2CH_3), 69.8 [$C(CH_3)NH$], 90.6 ($COPh_2$), 126.2, 127.2, 128.0, 128.1, 128.3, 128.4, 137.2, 139.4 (Ph), 157.6 (OCON), 171.6 (CO_2CH_3). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.27; H, 5.44; N, 4.41%.

4.1.10. (*R*)-4-Methyl-5,5-diphenyloxazolidin-2-one-4-carboxylic acid methyl ester, (*R*)-7. As described for enantiomer (*S*)-**7**, compound (*R*)-**7** (0.19 g, 85%) was obtained from compound (*S*)-**6** (0.23 g, 0.72 mmol). $[\alpha]_D^{25}=+15.7$ (*c* 1.53, MeOH). Anal. calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.29; H, 5.46; N, 4.48%.

4.1.11. (*R*)-*N*-(*tert*-Butoxycarbonyl)-4-(1-hydroxy-1-methylethyl)-2,2,4-trimethyloxazolidine, (*R*)-8. To a precooled solution of (*R*)-**3** (0.22 g, 0.80 mmol) in THF (10 mL) at 0°C was added dropwise a 3 M solution of methylmagnesium bromide (1.34 mL, 4.0 mmol) in THF. The cooling bath was removed and the mixture warmed to room temperature for 12 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (15 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4), concentrated and the crude product was purified by column chromatography (hexane:ethyl acetate, 9.5:0.5) to give (*R*)-**8** as a colourless oil (0.20 g, 0.73 mmol); yield: 91%. $[\alpha]_D^{25}=+4.1$ (*c* 0.66, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.47 (s, 9H, $(CH_3)_3C$), 1.57 (s, 3H, CH_3), 3.58 (d, 1H, $J=9.0$ Hz, CH_2O), 3.71 (d, 1H, $J=9.0$ Hz, CH_2O), 6.20 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$): δ 18.0, 24.8, 25.4, 25.8, 28.0 ($5CH_3$), 28.3 [$(CH_3)_3C$], 70.9 [$C(CH_3)NH$], 72.1 (CH_2O), 72.2 [$COH(CH_3)_2$], 81.1 [$(CH_3)_3C$], 95.2 [$C(CH_3)_2$], 154.1 (OCON); MS (EI) (m/z)=57, 97, 114, 214; ESI$^+$ (m/z)=274.4. Anal. calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.37; H, 10.04; N, 5.23%.

4.1.12. (*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(1-hydroxy-1-methylethyl)-2,2,4-trimethyloxazolidine, (*S*)-8. As described for enantiomer (*R*)-**8**, compound (*S*)-**8** (0.19 g, 91%) was obtained from compound (*S*)-**3** (0.21 g, 0.76 mmol). $[\alpha]_D^{25}=-3.9$ (*c* 0.84, MeOH). Anal. calcd for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12. Found: C, 61.32; H, 9.94; N, 5.02%.

4.1.13. (*R*)-(2-Hydroxy-1-hydroxymethyl-1,2-dimethylpropyl)carbamic acid *tert*-butyl ester, (*R*)-9a. A solution of compound (*R*)-**8** (0.1 g, 0.37 mmol) in acetonitrile (3 mL) and H_2O (33 μl, 1.83 mmol) was added to a solution of $Sc(OTf)_3$ (18 mg, 0.04 mmol) in acetonitrile (3 mL) at room temperature. The reaction mixture was stirred for 36 h and quenched with a phosphate buffer (pH 7). The organic materials were extracted with ethyl acetate (2×15 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate, 6:4) to give compound (*R*)-**9a** as a colourless oil (70 mg, 0.30 mmol); yield: 82%. $[\alpha]_D^{25}=$

−3.1 (*c* 1.07, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 6H, $2CH_3$), 1.27 (s, 3H, CH_3), 1.43 [s, 9H, $(CH_3)_3C$], 3.78 (d, 1H, $J=11.7$ Hz, CH_2OH), 3.85 (d, 1H, $J=11.7$ Hz, CH_2OH), 5.41 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 18.7, 25.0, 25.4 ($3CH_3$), 28.3 [$(CH_3)_3C$], 61.1 [$C(CH_3)NH$], 65.9 (CH_2OH), 75.5 [$COH(CH_3)_2$], 79.6 [$(CH_3)_3C$], 156.4 (OCON). Anal. calcd for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. Found: C, 56.54; H, 9.81; N, 6.06%.

4.1.14. (*R*)-(2-Hydroxy-1-hydroxymethyl-1,2-dimethylpropyl)carbamic acid benzyl ester, (*R*)-9b. Aqueous HCl (6N, 5 mL) was added to a solution of compound (*R*)-**8** (0.19 g, 0.70 mmol) in THF (5 mL). The solution was stirred at 25°C for 2 h and the HCl was removed to give the corresponding aminoalcohol. This compound was dissolved in H_2O/THF (1:5, 10 mL) and $Na_2CO_3{\cdot}10H_2O$ (0.50 g, 1.74 mmol) and $ClCO_2CH_2Ph$ (0.14 mL, 0.90 mmol) were added. The mixture was stirred at room temperature for 15 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (2×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (hexane:ethyl acetate, 6:4) to give compound (*R*)-**9b** as a white solid (0.13 g, 0.49 mmol); yield: 74%. Mp: 67°C. $[\alpha]_D^{25}=-5.8$ (*c* 1.34, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.78 (d, 1H, $J=11.7$ Hz, CH_2OH), 3.95 (d, 1H, $J=11.7$ Hz, CH_2OH), 5.02–5.08 (m, 2H, OCH_2Ph), 5.79 (br s, 1H, NH), 7.33–7.36 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 18.5, 24.9, 25.2 ($3CH_3$), 61.2 [$C(CH_3)NH$], 65.8, 66.6 (OCH_2Ph, CH_2OH), 75.7 [$COH(CH_3)_2$], 128.0, 128.1, 128.5, 136.4 (Ph), 156.4 (OCON); ESI$^+$ (m/z) = 268.3. Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.03; H, 7.80; N, 5.30%.

4.1.15. (*S*)-(2-Hydroxy-1-hydroxymethyl-1,2-dimethylpropyl)carbamic acid benzyl ester, (*S*)-9b. As described for enantiomer (*R*)-**9b**, compound (*S*)-**9b** (0.11 g, 74%) was obtained from compound (*S*)-**8** (0.15 g, 0.55 mmol). $[\alpha]_D^{25}=+5.3$ (*c* 0.92, MeOH). Anal. calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.07; H, 7.88; N, 5.30%.

4.1.16. (*S*)-2-Amino-3-hydroxy-2,3-dimethylbutyric acid, (*S*)-10. To a solution of alcohol (*R*)-**9b** (90 mg, 0.34 mmol) in acetone (7 mL) at 0°C was added dropwise a 1.5-fold excess of Jones' reagent over 5 min. The mixture was stirred at 0°C for 3 h and then at room temperature for a further 3 h. The excess Jones' reagent was destroyed with 2-propanol. The mixture was diluted with H_2O (7 mL) and extracted with ethyl acetate (4×15 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil was dissolved in MeOH (15 mL) and palladium on carbon (1:5 catalyst/substrate by weight) was added. The resulting suspension was subjected to hydrogenolysis at room temperature for 24 h. The catalyst was removed by filtration and the solvent was evaporated to give (*S*)-**10** as a white solid (32 mg, 0.22 mmol); yield: 64%. $[\alpha]_D^{25}=+6.3$ (*c* 1.2, H_2O); ^{1}H NMR (D_2O): δ 1.42 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 1.62 (s, 3H, CH_3); ^{13}C NMR (D_2O): δ 17.8, 24.4, 24.7 ($3CH_3$), 67.6 [$C(CH_3)NH_2$], 72.2 [$COH(CH_3)_2$], 175.2 (COOH). Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 49.07; H, 9.02; N, 9.46%.

4.1.17. (*R*)-2-Amino-3-hydroxy-2,3-dimethylbutyric acid, (*R*)-10. As described for enantiomer (*S*)-**10**, compound (*R*)-**10** (30 mg, 64%) was obtained from compound (*S*)-**9b** (85 mg, 0.32 mmol). $[\alpha]_D^{25}=-6.0$ (*c* 1.0, H_2O); [lit.[17] +18.3 (*c* 1.1, 5N HCl_{aq} from asymmetric synthesis with e.e. ≈ 70–75%]. Anal. calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 49.10; H, 8.72; N, 9.69%.

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References

1. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599 and references cited therein.
2. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732 and references cited therein.
3. Karle, I. L.; Balaram, P. *Biochemistry* **1990**, *29*, 6747–6756.
4. Marshall, G. In *Intra-Science Chemistry Report*; Kharasch, N., Ed.; Gordon and Breach: New York, 1971; p. 305.
5. Peggion, C.; Formaggio, F.; Crisma, M.; Toniolo, C.; Kaptein, B.; Broxterman, Q. B.; Kamphuis, J. *J. Pept. Sci.* **1999**, *5*, 547–554.
6. Toniolo, C.; Crisma, M.; Bonora, G. M.; Klajc, B.; Lelj, F.; Griamaldi, P.; Rosa, A.; Polinelli, S.; Boesten, W. H. J.; Mejer, E. M.; Schoemaker, H. F.; Kamphuis, J. *Int. J. Pept. Protein Res.* **1991**, *38*, 242–252.
7. Valle, G.; Crisma, M.; Toniolo, C.; Polinelli, S.; Boesten, W. H. J.; Schoemaker, H. F.; Mejer, E. M.; Kamphuis, J. *Int. J. Pept. Protein Res.* **1991**, *37*, 521–527.
8. Gómez-Catalán, J.; Pérez, J. J.; Jiménez, A. I.; Cativiela, C. *J. Pept. Sci.* **1999**, *5*, 251–262.
9. Lapeña, Y.; López, P.; Cativiela, C.; Kaptein, B.; Broxterman, Q. B.; Kamphuis, J.; Mossel, E.; Peggion, C.; Formaggio, F.; Crisma, M.; Toniolo, C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 631–636.
10. Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A. *Tetrahedron* **1994**, *50*, 9837–9846.
11. Royo, S.; López, P.; Jiménez, A. I.; Oliveros, L.; Cativiela, C. *Chirality* **2002**, *14*, 39–46.
12. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *J. Org. Chem.* **1999**, *64*, 8220–8225.

13. Avenoza, A.; Cativiela, C.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4653–4661.
14. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2000**, *11*, 2195–2204.
15. Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Sucunza, D.; Zurbano, M. M. *Tetrahedron: Asymmetry* **2001**, *12*, 949–953.
16. Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240–5244.
17. Schöllkopf, U.; Groth, U.; Hartwig, W. *Liebigs Ann. Chem.* **1981**, *12*, 2407–2418.
18. Agami, C.; Couty, F. *Tetrahedron* **2002**, *58*, 2701–2724.