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A Stereoselective Synthesis of 3(R)-Hydroxy-2(S)-ornithine

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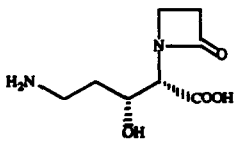
Abstract: (2S,3R) *Threo*-3-hydroxy-ornithine has been synthesized efficiently using a highly stereoselective iodocyclocarbamation of the chiral Z-olefin 7 prepared from D-serine.

β-Hydroxy-α-aminoacids are an important class of compounds, due to their presence in nature as primary metabolites themselves (threonine, serine, 4-hydroxyproline) and as components of more complex natural compounds (e.g. cyclic peptides[1], MeBmt in cyclosporins[2], 3-hydroxyhomotyrosine in echinocandin D[3]). Moreover, they have been used as intermediates in the synthesis of important natural products[4] like β-lactams and aminopolyols[5].

In this context proclavaminic acid 1 has recently been recognised as the biosynthetic precursor of clavulanic acid 2, a potent inhibitor of many bacterial β-lactamases[6].



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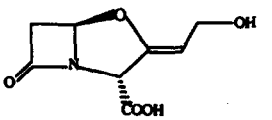

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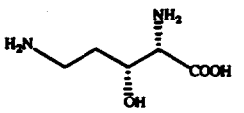

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The chemical structure of proclavaminic acid is strictly related to the *threo*-3-hydroxy L-ornithine 3 which can be considered a suitable synthetic precursor.

As start of a project directed towards the synthesis of natural and unnatural β-hydroxy-α-aminoacids, we focused our attention to the synthesis of the above mentioned non-proteinogenic aminoacids.

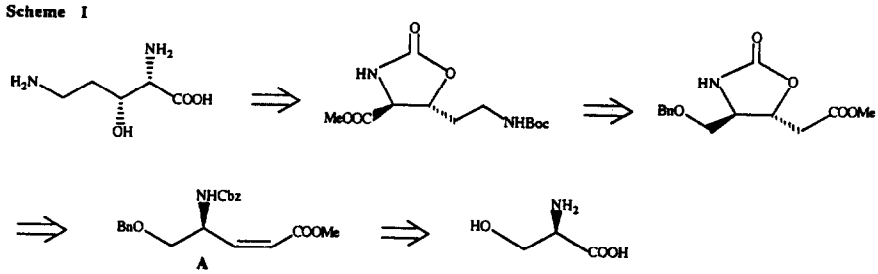
Synthesis of *threo*- and *erythro*-β-hydroxy-L-ornithine has been previously reported by Wakamya *et al.*[7], although in racemic form; more recently, in connection with studies on the biosynthesis of clavulanic acid, two different approaches have been proposed. The first[8] is based on a [3+2] cycloaddition of a suitable nitrone with the protected L-vinylglycine to give the (2S,3R) and (2S,3S) 3-hydroxy-ornithines. The second[9] involves an aldol reaction of the suitable 3-azidopropionaldehyde or 3-(benzyloxycarbonyl-amino)-propionaldehyde with a Schiff's base of glycine ester to give a diastereomeric mixture of *threo*- and *erythro*-amino alcohols in 72:28 and 50:50 ratio respectively. These have been converted into (2S,3R)

and (2S,3S) 3-hydroxy-ornithines as protected forms.

Here we report our approach to the synthesis of (2S,3R) *threo*-3-hydroxy-ornithine in the perspective of a synthesis of proclavaminic acid.

The retrosynthetic pathway is shown in Scheme I. The key step is the introduction of the hydroxy function, with the desired configuration, into the electron poor protected N-allyl-amine A, employing a highly stereoselective cyclocarbamation[10] mediated by iodine.

Scheme I

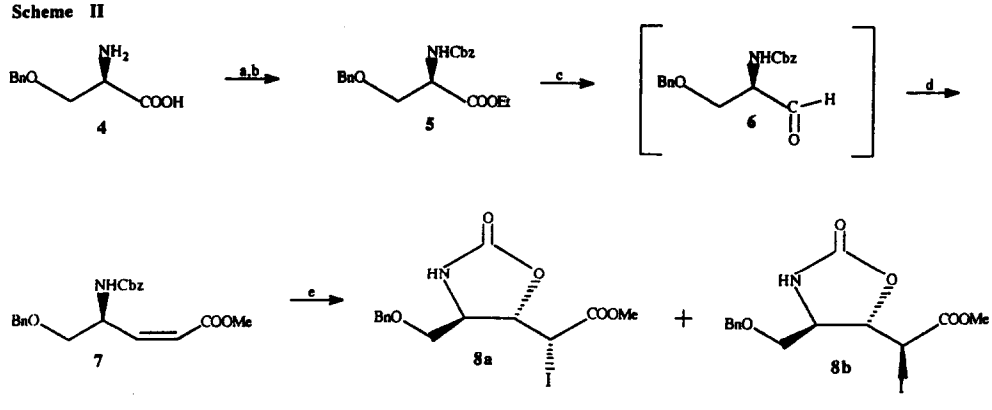


Cbz= -COOCH$_2$Ph Bn= -CH$_2$Ph

In the event, commercially available[11] O-benzyl-D-serine **4** was used as starting material and it was easily converted, in high yield (>90%), into the O-benzyl N-benzyloxycarbonyl-D-serine ethyl ester **5** by reaction with Cbz_2O followed by esterification, according to the Kim's procedure[12]. The ethyl ester was then treated at -78°C with DIBAL-H to give the corresponding α-amino aldehyde **6**, which was immediately converted into the Z-olefin **7** (65% yield from **5**) employing a slightly modified Still's procedure[13] (Scheme II). Pure **7** was then submitted to the iodocyclocarbamation reaction with an excess of iodine in dry acetonitrile[10g]. Under these conditions, reaction takes place to give a mixture of the two *trans*-oxazolidin-2-ones **8a** and **8b** in a ratio of 15:1 (60% yield). The *trans*-orientation in both oxazolidin-2-ones **8a** and **8b** was supported by the value of the coupling constant $J_{4\text{-}5}$ [14]; therefore the two compounds are epimeric at the carbon bearing the iodine.

On the other hand, when the intermediate **7** was reacted according to Guindon *et al.*,[10h] we observed that 2 equivalents of silver triflates were sufficient to enable the reaction in acetonitrile within 2 h and with higher yield (80%), but with a lower **8a/8b** ratio (11:1).[15]

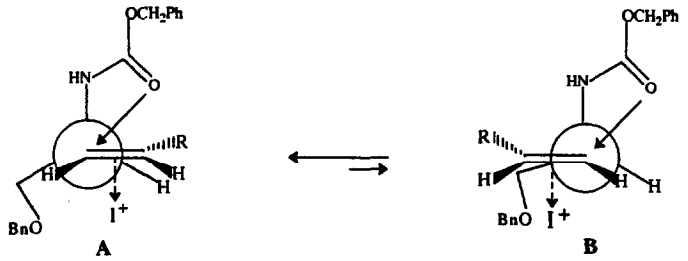
Scheme II



Bn= -CH$_2$Ph Cbz= -COOCH$_2$Ph

a)Cbz_2O,NaOH 1N,dioxane b)EtOCOCl,NMM,DMAP,CH_2Cl_2 0°C c)DIBAL-H,toluene,-78°C d)$(CF_3CH_2O)_2POCH_2COOMe$, 18-crown-6,$(TMS)_2NK$,THF, -78° C e) I_2(3 eq.),CH_3CN or I_2(3 eq.),AgOTf(2 eq.),$NaHCO_3$(2 eq.),CH_3CN

The stereochemical outcome arises from reaction of the Z-olefin through a transition state in which the allylic 1,3-strain[16] can be minimized; conformer B suffers from interaction between CH_2OBn and the R group, whereas A is essentially strain free.

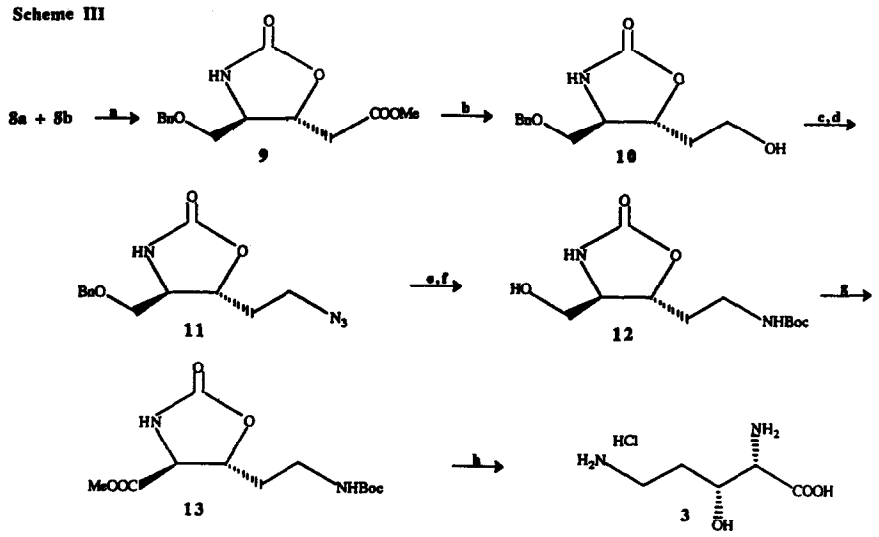


R= -COOMe

Anyway in the following step of our synthetic pathway the iodine atom has to be removed to convert the stereogenic center bearing the iodine into the methylene group. The reaction of deiodination was performed directly on the diastereomeric mixture to give in good yield (83%) the oxazolidin-2-one **9**. The oxazolidin-2-one ring can be considered as a suitable protecting group of the 1,2-amino alcohol function, therefore it was kept through the synthesis and removed only in the last step.

Treatment of **9** with $LiAlH_4$ at 0°C allowed the reduction of the ester function to give pure **10** without any effect on the other protecting groups. The hydroxy group was easily converted in the azido group through the corresponding *p*-chlorobenzene sulfonate, affording **11** in 80% yield. Catalytic hydrogenolysis at the same time reduced the azido group to $-NH_2$ and removed the benzylic protecting group; the free amino alcohol was isolated as the N-Boc derivative **12** (70% yield from **11**) by treatment with Boc_2O. Finally, the primary alcohol was oxidized with the Jones' reagent and converted into the fully protected *threo*-3-hydroxy-L-ornithine **13** by treatment with an ethereal solution of diazomethane.

Scheme III



a)nBu_3SnH,AIBN,benzene,reflux b)$LiAlH_4$ 1M in THF,0°C c)$pClC_6H_4SO_2Cl$,Et_3N,DMF d)NaN_3,DMF,85°C e)H_2,10%Pd/C,EtOH f)Boc_2O,Et_3N,DMF g)Jones' reagent h)CH_2N_2 i)HCL 6N,reflux;NH_4OH to ph6.5,EtOH

The target product **3** was obtained as the monochloridrate by acid hydrolysis of **13**, which showed analytical data in agreement with that reported in literature[8a].

In conclusion, a stereospecific synthesis of *threo*-3-hydroxy-L-ornithine was achieved using a highly stereoselective iodocyclocarbamation on an electron-poor allyl amine. Following the results above

reported, further studies are in progress direct to the synthesis of proclavaminic acid together with other synthetic applications.

EXPERIMENTAL

Melting points were determined in open capillaries using a Buchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5DX FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were run on a Varian XL-300 spectrometer at 300 and 75 MHz respectively, in $CDCl_3$, unless otherwise reported. Chemical shifts (δ scale) are relative to TMS as internal reference, unless otherwise reported. The non-trivial assignment of chemical shifts were confirmed by decoupling experiments for the proton signals and by HETCOR measurements for the carbon resonance. Diastereomeric ratios for **8a** and **8b** were measured on a Waters HPLC apparatus (Column: SiO_2; eluent, 1% IPA in CH_2Cl_2). Optical rotations were determined on a Perkin Elmer 243 polarimeter at 21°C. All solvents were dried[17] prior to use. Thin layer chromatography was performed on Merck silica gel 60 F_{254} glass plates.

O-Benzyl-N-(benzyloxycarbonyl)-D-serine ethyl ester (5)

To a solution of O-benzyl-D-serine **4** (3.9 g, 20 mmol) and 1 N, NaOH (20 ml, 20 mmol) in dioxane (40 ml) at 0°C a solution of Cbz_2O (5.72 g, 20 mmol) in dioxane (40 ml) was added dropwise. The mixture was stirred at room temperature for 60 min and dioxane was evaporated under vacuum. The aqueous solution was diluted with water (25 ml), acidified with 1N HCl to pH 2 and extracted with EtOAc (3 × 100 ml). The combined extracts were washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. Hexane was added to the residue to give the crystalline product which was isolated by suction: yield 6.45 g (98%). M.p. 98-99 °C; $[\alpha]_D$ = -17.0° (c = 0.35 EtOH) (Lit[18] for the L isomer: m.p. 98-100°C; $[\alpha]_D$ = +17.1° (EtOH).

To the O-benzyl-N-benzyloxycarbonyl-D-serine (6.0 g, 18.22 mmol) dissolved in CH_2Cl_2 (70 ml), N-methyl morpholine (2.3 ml, 20.95 mmol) and ethyl chloroformate (1.56 ml, 20.04 mmol) were added at 0°C. After15 min of stirring at 0°C, DMAP (244 mg, 2 mmol) was added and the mixture stirred at the same temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 (100 ml) and washed with satd. NH_4Cl (100 ml), H_2O, satd. $NaHCO_3$ (100 ml) and satd. NaCl.

The organic layer was dried over Na_2SO_4 and evaporated. The residue was subjected to silica gel chromatography eluting with CH_2Cl_2 to give pure **5** (6.06 g, 93%; overall yield 91%).
$[\alpha]_D$ = -7.1° (c = 0.6 $CHCl_3$). Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92 %. Found: C, 67.40; H, 6.60; N, 3.87 %. IR ν_{max}/cm^{-1}: 3410, 2934, 2869, 1720, 1710, 1499, 1450, 1335, 1185.
^1H NMR δ: 7.40-7.20 (10H, m, 2 × Ph), 5.67 (1H, d, J = 8.5 Hz, -NH), 5.12 (2H, s, -COOCH_2Ph), 4.54, 4.46 (1H each, d, J = 12 Hz, -CH_2OCH_2Ph), 4.49 (1H, dt, J = 8.5 and 2 ×3.0 Hz, -C*HN), 4.20 (2H, q, J = 7.0 Hz, -COOC$H_2$$CH_3$), 3.89 (1H, dd, J = 9.5 and 3.0 Hz, -OC$H_A$$H_B$), 3.70 (1H, dd, J = 9.5 and 3.0 Hz, -OC$H_A$$H_B$), 1.24 (3H, t, J = 7.0 Hz, -COOCH_2CH_3). ^{13}C NMR δ: 170.23 (s, COOC$H_2$$CH_3$), 155.97 (s, -NHCO), 137.43, 136.24 (s each, Ph), 128.47, 128.37, 127.78, 127.55 (2 ×d each, Ph), 128.10, 128.01 (d each, Ph), 73.23 (t, -OCH_2Ph), 69.79 (t, -OCH_2), 66.95 (t, -COOCH_2Ph), 61.61 (t, -OC$H_2$$CH_3$), 54.42 (d, -C*HN), 14.08 (q, -COOCH_2CH_3).

Methyl (Z,4R)-4-[(benzyloxycarbonyl)amino]-5-benzyloxy-2-pentenoate (7)

To a solution of **5** (1.785 g, 5 mmol) in toluene (10 ml) at -78°C a solution of DIBAL-H (1.4 M in toluene, 8 ml) was added over 20 min with stirring under N_2. The resulting solution was stirred at -78°C for 2 h then dry methanol (2 ml) was added cautiously, followed by a solution of Rochelle salt (37 ml, 1M in H_20). The solution was stirred for 2 h at room temperature until two clear layers were formed. The toluene layer was separated and aqueous layer was washed with Et_2O. The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under vacuum at a temperature ≤35°C to afford the crude aldehyde **7** as a viscous yellowish oil.

To a solution containing 18-crown-6 (6.62 g, 25 mmol) and bis(2,2,2-trifluoroethyl) (methoxy-

carbonylmethyl) phosphonate (1 ml, 5 mmol) in THF (90 ml) at -65°C a solution of $KN(TMS)_2$ (10 ml, 0.5 M in THF) was added over 15 min while stirring under N_2. The mixture was stirred for 20 min at the same temperature, cooled to -78°C and a solution of the crude aldehyde in THF (10 ml) was added dropwise. The solution was stirred at -78°C for 1 h, whereupon a satd. solution of NH_4Cl (20 ml) was added cautiously. The mixture was diluted with Et_2O (100 ml) and separated. The organic layer was washed again with satd. NH_4Cl, satd. NaCl, H_2O, and dried over Na_2SO_4. The solution was filtered and concentrated under vacuum. The residue was purified by flash chromatography eluting with hexane/EtOAc (4:1) to give pure **7** (1.2 g, 65% yield).
$[\alpha]_D$ = -16.2° (c = 1.75 $CHCl_3$). Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79 %. Found: C, 68.11; H, 6.44; N, 3.70 %. IR ν_{max}/cm^{-1}: 3320, 2926, 1737, 1714, 1458, 1384, 1266. ^1H NMR δ: 7.40-7.20 (10H, m, 2 × Ph), 6.22 (1H, dd, J = 11.5 and 8.0 Hz, -CH=CHCO), 5.84 (1H, d, J = 11.5 Hz, =CHCOO), 5.55 (1H, br d, J = 7.0 Hz, -NH), 5.45 (1H, m, ΣJ = 24.0 Hz, -C*HN), 5.10, 5.07 (1H each, d, J = 12.0 Hz, -COOCH$_2$Ph), 4.52, 4.48 (1H each, d, J = 12.0 Hz, -CH$_2$OCH$_2$Ph), 3.71 (3H, br s, -COOCH$_3$), 3.70 (1H, dd, J = 10.0 and 3.5 Hz, -OCH$_A$H$_B$), 3.64 (1H, dd, J = 10.0 and 3.5 Hz, -OCH$_A$H$_B$). ^{13}C NMR δ: 166.01 (s, COOCH$_3$), 155.90 (s, -NHCO), 148.27 (d, -CH=), 137.63, 136.37 (s each, 2 × Ph) 128.47, 128.40, 127.80, 127.69 (2 ×d each, 2 × Ph), 128.08, 128.04 (d each, 2 × Ph), 120.43 (d, =CHCO), 73.21 (t, -CH$_2$OCH$_2$Ph), 71.85 (t, -OCH$_2$), 66.78 (t, -COOCH$_2$Ph), 51.42 (q, -COOCH$_3$), 49.61 (d, -C*HN).

Methyl (4R,5S)-4-(benzyloxy)methyl-2-oxo-5-oxazolidine (R)-1-iodoacetate (8a). Methyl (4R,5S)-4--(benzyloxy)methyl-2-oxo-5-oxazolidine (S)-1-iodoacetate (8b)

Iodocyclocarbamation with I_2/CH_3CN

To a solution of **7** (0.738, 2mmol) in CH_3CN (15 ml), I_2 (3 g, 6 mmol) was added at room temperature. The solution was stirred overnight, then diluted with $CHCl_3$ (40 ml) and extracted with an aqueous solution of $Na_2S_2O_3$ (0.3 M, 2 × 50 ml). The aqueous layers were washed with $CHCl_3$ (2 ×50 ml) and the combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated to dryness under reduced pressure to give the crude mixture of **8a** and **8b** in a ratio of 15:1. The residue was purified by flash chromatography eluting with hexane/EtOAc (1:1) to give **8a** (456 mg) and **8b** (30 mg, overall yield 60%).

Iodocyclocarbamation with I_2/AgOTf in CH_3CN

To a solution of **7** (2.06 g, 5.57 mmol), $NaHCO_3$ (0.94 g, 11.15 mmol) and AgOTf (2.87 g, 11.15 mmol) in CH_3CN (30 ml) I_2 (4.25 g, 16.7 mmol) was added at room temperature. The reaction was stirred for 2 h, then diluted with $CHCl_3$ (50 ml) and extracted with an aqueous solution of $Na_2S_2O_3$ (0.3 M, 2 × 50 ml). Standard work-up gave the two oxazolidin-2-ones **8a** and **8b** in 11:1 ratio and 80% overall yield.
8a: mp: 112-3°C (EtOAc/hexane). $[\alpha]_D$ = +13.6° (c = 0.6 $CHCl_3$). IR. ν_{max}/cm^{-1}: 3279, 2930, 2860, 1770, 1737, 1458, 1376, 1204, 1031. Anal. Calcd. for $C_{14}H_{16}NO_5I$: C, 41.50; H, 3.98; N, 3.46 %. Found: C, 41.22; H, 3.70; N, 3.33 %. ^1H NMR (CD_3COCD_3) δ: 7.40-7.25 (5H, m, Ph), 5.96 (1H, br s, -NH), 4.60 (1H, d, J = 6.5 Hz, -C*HI), 4.56 (2H, s, -OCH$_2$Ph), 4.53 (1H, dd, J = 6.5 and 4.5 Hz, -C*HO), 3.96 (1H, m, ΣJ = 15.0 Hz, -C*HN), 3.75 (3H, s, -COOCH$_3$), 3.59 (1H, dd, J = 9.5 and 4.0 Hz, -OCH$_A$H$_B$), 3.50 (1H, dd, J = 9.5 and 6.5 Hz, -OCH$_A$H$_B$). ^{13}C NMR δ: 168.93 (s, COOCH$_3$), 157.51 (s, -NHCO), 137.19 (s, Ph), 128.58, 127.76 (2 ×d each, Ph), 128.05 (d, Ph), 77.94 (d, -C*HO), 71.90 (t, -OCH$_2$Ph), 71.69 (t, -CH$_2$O), 55.91 (d, -C*HN), 53.03 (q, -COOCH$_3$), 19.56 (d, -C*H-I).
8b: $[\alpha]_D$ = +17.9° (c = 0.5 $CHCl_3$). Anal. Calcd. for $C_{14}H_{16}NO_5I$: C, 41.50; H, 3.98; N, 3.46 %. Found: C, 41.76; H, 4.05; N, 3.60 %. I.R. ν_{max}/cm^{-1}: 3275, 2926, 2860, 1769, 1745, 1458, 1302, 1261, 1177.
^1H NMR (CD_3COCD_3) δ: 7.40-7.25 (5H, m, Ph), 5.84 (1H, br s, -NH), 4.57 (2H, s, -OCH$_2$Ph), 4.53 (1H, d, J = 7.0 Hz, -C*HI), 4.42 (1H, dd, J 7.0 and 4.5 Hz, -C*H-O), 3.92 (1H, m, ΣJ = 13.5 Hz, -C*H-N), 3.77 (3H, s, -COOCH$_3$), 3.73 (1H, dd, J = 10.0 and 4.0 Hz, -OCH$_A$H$_B$), 3.65 (1H, dd, J = 10.0 and 5.0

Hz, -OCH$_A$H$_B$). ^{13}C NMR δ: 169.05 (s, COOCH$_3$), 157.60 (s, -NHCO), 135.27 (s, Ph), 128.56, 127.73 (2 ×d each, Ph), 128.03 (d, Ph), 77.74 (d, -C*H-O), 73.57 (t, -OCH$_2$Ph), 71.51 (t, -CH$_2$O), 56.91 (d, -C*HN), 53.30 (q, -COOCH$_3$), 21.41 (d, -C*HI).

Methyl (4R,5R)-4-(benzyloxy)methyl-2-oxo-5-oxazolidineacetate (9)

To a solution containing **8a** and **8b** (1.215 g, 3mmol) and AIBN (492 mg, 3mmol) in dry benzene, tributyltinhydride (1.59 ml, 6 mmol) was added dropwise at room temperature. The solution was held at reflux for 4 h and then concentrated under vacuum. The residue was diluted with CH$_3$CN (50 ml) and washed with hexane (2 ×25 ml). The acetonitrile layer was concentrated under vacuum and the residue was purified by flash chromatography with hexane/EtOAc (2:3) as eluent to give **9** (545 mg, 89%).
Mp: 49-50°C (Et$_2$O/hexane); [α]$_D$ = +31.6° (c = 1.14 CHCl$_3$). Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02 %. Found: C, 60.41; H, 6.07; N, 5.10 %. IR (KBr) ν_{max}/cm^{-1}: 3360, 2930, 1778, 1737, 1383, 1375, 1244, 1121. ^{1}H NMR δ: 7.40-7.25 (5H, m, Ph), 5.67 (1H, br s, -NH), 4.66 (1H, dt, J = 7.0 and 2 ×5.0 Hz, -C*HO), 4.54 (2H, s, -OCH$_2$Ph), 3.76 (1H, dt, J = 7.0 and 2 ×5.0 Hz, -C*HN), 3.70 (3H, s, -COOCH$_3$), 3.56 (1H, dd, J = 9.5 and 5.0 Hz, -OCH$_A$H$_B$), 3.50 (1H, dd, J = 9.5 and 7.0 Hz, -OCH$_A$H$_B$), 2.85 (1H, dd, J = 16.5 and 5.0 Hz, -CH$_C$H$_D$CO), 2.63 (1H, dd, J = 16.5 and 7.0 Hz,-CH$_C$H$_D$CO). ^{13}C NMR δ: 168.68 (s, -COOCH$_3$), 158.04 (s, -NHCO), 137.22 (s, Ph), 128.56, 127.76 (2 ×d each, Ph), 128.05 (d, Ph), 74.89 (d, -C*HO), 73.62 (t, -OCH$_2$Ph), 71.57 (t, -CH$_2$O), 56.95 (d, -C*HN), 52.05 (q, -COOCH$_3$), 38.96 (t, -CH$_2$).

(4R,5R)-4-(Benzyloxy)methyl-5-(2-hydroxyethyl)-2-oxo-oxazolidine (10)

To a solution of **9** (698 mg, 2.5 mmol) in THF (20 ml) at -25°C (CO_2/CCl_4 bath) a solution of LiAlH$_4$ (1 M in THF, 5 ml) was added dropwise over 30 min with stirring under nitrogen. The reaction mixture was maintained at 0°C until complete conversion of substrate (2 h). The excess of hydride was destroyed with EtOAc (5 ml) followed by addition of a satd. solution of Rochelle salt (20 ml). The mixture was stirred for 1 hr, then extracted with EtOAc (3 ×50 ml), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (CHCl$_3$/MeOH 9:1) to give **10** (507 mg, 81%).
M.p. 71-2°C (EtOAc/hexane); [α]$_D$ = +22.8° (c = 1.8 CHCl$_3$); Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57 %. Found: C, 61.96; H, 7.01; N, 5.37 %. I.R. (KBr) ν_{max}/cm^{-1}: 3312, 3213, 2960, 1712, 1458, 1376. ^{1}H NMR δ: 7.40-7.25 (5H, m, Ph), 6.03 (1H, br s, -NH), 4.53 (2H, s, -OCH$_2$Ph), 4.48 (1H, dt, J = 8.0 and 2 ×5.0 Hz, -C*HO), 3.78 (2H, br t, J = 6.0 Hz, -CH$_2$OH), 3.75 (1H, br q, J = 3 ×5.0 Hz, -C*HN), 3.49 (2H, d, J = 6.0 Hz, -OCH$_2$), 2.34 (1H, br s, -OH), 1.99 (1H, m, ΣJ = 29.0 Hz, -OCH$_A$H$_B$-), 1.89 (1H, m, ΣJ = 34.0 Hz, -OCH$_A$H$_B$). ^{13}C NMR δ: 158.81 (s, -NHCO), 137.16 (s, Ph), 128.54, 127.76 (2 ×d each, Ph), 128.05 (d, Ph), 77.34 (d, -C*HO), 73.59 (t, -OCH$_2$Ph), 71.62 (t, -CH$_2$O), 58.36 (t, -CH$_2$OH), 57.17 (d, -C*HN), 37.30 (t, -CH$_2$).

(4R,5R)-4-(Benzyloxy)methyl-5-(2-azidoethyl)-2-oxo-oxazolidine (11)

To a solution of **10** (502 mg, 2 mmol) and Et$_3$N (0.84 ml, 6 mmol) in CHCl$_3$ (6 ml) at 0°C p-chlorobenzenesulfonil chloride (844 mg, 4 mmol) was added in one portion. The solution was stirred at room temperature overnight, diluted with CHCl$_3$ (20 ml) and washed with 1N HCl (15 ml), 5% NaHCO$_3$ (20 ml) and satd. NaCl. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The residue was dissolved in dry DMF (5 ml) and NaN$_3$ (650 mg, 10 mmol) was added. The mixture was stirred overnight at 85°C, cooled to room temperature, diluted with AcOEt (20 ml) and filtered through a pad of celite. The organic solution was washed with 10% NaHCO$_3$ (15 ml), satd. NaCl (15 ml), H_2O and dried over Na_2SO_4. The organic solution was filtered, concentrated under reduced pressure and purified by flash chromatography (hexane/AcOEt 1:1) to give **11** as an oil (420 mg, 80 % yield).
[α]$_D$ = +69.4° (c = 0.93 CHCl$_3$). Anal. Calcd. for $C_{13}H_{16}N_4O_3$: C, 56.51; H, 5.84; N, 20.28 %. Found: C, 56.33; H, 5.91; N, 20.08 %. IR ν_{max}/cm^{-1}: 3395, 2920, 2099, 1753, 1458, 1253, 1105. ^{1}H NMR δ: 7.40-7.25

(5H, m, Ph), 6.72 (1H, br s, -NHCO), 4.52 (2H, s, -OCH$_2$Ph), 4.39 (1H, dt, J = 9.0 and 2 ×5.0 Hz, -C*HO), 3.62 (1H, q, J = 3 ×5.5 Hz, -C*HN), 3.46 (1H, dd, J = 10 and 7.0 Hz, -CH$_A$H$_B$N$_3$), 3.44 (2H, d, J = 5.5 Hz, -OCH$_2$), 3.42 (1H, dd, J = 10.0 and 6.0 Hz, -CH$_A$H$_B$N$_3$), 1.97 (1H, ddt, J = 14.0, 9.0 and 2 × 6.0 Hz,-CH$_C$H$_D$-), 1.86 (1H, ddt, J = 14.0, 2 × 7.0 and 5.0 Hz, -CH$_C$H$_D$-). ^{13}C NMR δ: 158.86 (s, -NHCO), 137.16 (s, Ph), 128.34, 127.52 (2 ×d each, Ph), 127.76 (d, Ph), 76.59 (d, -C*HO), 73.30 (t, -OCH$_2$Ph), 71.01 (t, -CH$_2$O), 56.93 (d, -C*HN), 46.89 (t, -CH$_2$N$_3$), 34.02 (t, -CH$_2$CH$_2$).

(4R,5R)-4-(Hydroxymethyl)-5-[2-(*tert*-butyloxyocarbonylamino)ethyl]-2-oxo-oxazolidine (12)

Compound **11** (414 mg, 1.5 mmol) was dissolved in absolute ethanol (15 ml) and hydrogenated over 10% Pd/C at 56 psi for 15 h. The mixture was filtered over celite and concentrated under reduced pressure. To the oily residue in DMF (5 ml), Et$_3$N (0.23 ml, 1.65 mmol) and di-*tert*-butyl dicarbonate (654 mg, 3 mmol) were added. The solution was stirred at room temperature for 18 h, then poured into crushed ice and water (20 ml) and extracted with EtOAc (3 ×20 ml). The organic layers were dried over Na$_2$SO$_4$, filtered, concentrated under vacuum and purified by silica gel chromatography with CHCl$_3$/MeOH (85:15) as eluent to give **12** (260 mg, 70%) as a colourless oil.
[α]$_D$ = +58.5° (c = 2.38 MeOH). Anal. Calcd. for C$_{11}$H$_{20}$N$_2$O$_5$: C, 50.76; H, 7.75; N, 10.76 %. Found: C, 50.93; H, 7.67; N, 10.59 %. IR ν_{max}/cm^{-1}: 3476, 3377, 2962, 1712, 1688, 1458, 1378. ^{1}H NMR δ: 6.80 (1H, br s, -NHCO), 5.17 (1H, t, J = 6.0 Hz, -NHBoc), 4.47 (1H, q, J = 6.5, -C*HO), 3.65 (1H, dt, J = 2 ×9.0 and 6.5 Hz, -C*HN), 3.59 (2H, d, J = 9.0 Hz, -CH$_2$OH), 3.26 (2H, m, ΣJ = 19.0 Hz, -CH$_2$NH), 1.92 (2H, q, J = 6.5 Hz, -CH$_2$), 1.44 (9H, s, 3 × CH$_3$). ^{13}C NMR δ: 159.78 (s, -NHCO), 156.35 (s, -NHCOC), 79.62 (d, -C*HO), 77.34 (s, -C(CH$_3$)$_3$), 63.21 (t, -CH$_2$OH), 59.23 (d, -C*HN), 36.59 (t, -CH$_2$N), 35.13 (t, -CH$_2$-) 28.38 (q, C(CH$_3$)$_3$).

(4S,5R)-4-(Carboxymethyl)-5-[2-(*tert*-butyloxyocarbonylamino)ethyl]-2-oxo-oxazolidine (13)

To a cooled (0°C) solution of the alcohol **12** (246 mg, 1.05 ml) in acetone (6 ml), Jones' reagent (2.8 M CrO$_3$, 1.20 ml, 3.36 mmol) was added. The reaction mixture was stirred for 2 h at the same temperature. The excess of Jones' reagent was destroyed by addition of isopropyl alcohol (5 ml) followed by stirring for 0.5 hr at room temperature. After evaporation, water (5 ml) and EtOAc (15 ml) were added. The aqueous layer was extracted with EtOAc (4 ×15 ml) and the combined organic layers were washed with brine, dried (Na$_2$SO$_4$) and evaporated to dryness. The resulting crude acid was dissolved in EtOAc (10 ml), cooled at 0°C and a slight excess of an ethereal solution of CH$_2$N$_2$ was added, followed by stirring for 3 h at room temperature. Excess of CH$_2$N$_2$ was destroyed by addition of CH$_3$COOH (3 M in CH$_2$Cl$_2$, 1 ml) followed by stirring for 0.5 hr at room temperature. After evaporation, the crude mixture was purified by silica gel chromatography (hexane/EtOAc 1:1) to give **13** (140 mg, 46%).
[α]$_D$ = +37.9° (c = 2.6 CHCl$_3$). Anal. Calcd. for C$_{12}$H$_{20}$N$_2$O$_6$: C, 49.99; H, 6.99; N, 9.72 %. Found: C, 50.16; H, 6.82; N, 9.63 %. I.R. ν_{max}/cm^{-1}: 3470, 3370, 2950, 1712, 1706, 1660, 1450. ^{1}H NMR δ: 6.89 (1H, br s, -NHCO), 5.13 (1H, brt, J = 6.5 Hz, -NHBoc), 4.68 (1H, dt, J = 8.0 and 2×5,0 Hz, -C*HO), 4.14 (1H, d, J = 5.0 Hz, -C*HN), 3.81 (3H, s, -COOCH$_3$), 3.30 (2H, q, 6.5 Hz, CH$_2$N), 2.06 (1H, m, ΣJ = 35.0 Hz, -CH$_A$CH$_B$), 1.98 (1H, m, ΣJ = 32.0 Hz, -CH$_A$CH$_B$), 1.40 (9H, s, C(CH$_3$)$_3$). ^{13}C NMR δ: 170.23 (s, COOMe), 158.26 (s, -NHCO), 155.99 (s, -COOC), 79.40 (d, -C*HO), 77.10 (s, - C(CH$_3$)$_3$), 58.68 (d, -C*HN), 52.90 (q, -COOCH$_3$), , 36.42 (t, -CH$_2$N), 35.22 (t, -CH$_2$-) 28.19 (q, C(CH$_3$)$_3$).

(3R)-Hydroxy-(2S)-ornithine hydrochloride (3)

To the compound **13** (140 mg, 0.46 mmol), HCl 6N (5 ml) was added and refluxed under stirring for 6 h. The reaction mixture was concentrated under vacuum and the residue was dissolved in the minimum amount of water (0.5 ml). The pH of the solution was adjusted to 6.5 with NH$_4$OH. To this solution ethanol was added, which caused to amino acid to crystallize, affording 59 mg (70 %) of **3**.
Mp: 193°C (Lit[8a]: 195°C). [α]$_D$ = +17.6° (c = 2.08 6 N HCl) (Lit[8a] [α]$_D$ = +17.9° (c = 2.0 6 N HCl). TLC (*n*-BuOH/H$_2$O/AcOH 4:2:1 on cellulose, 0.3% ethanolic ninhydrine spray): R$_f$ 0.33. IR (KBr)

ν_{max}/cm^{-1}: 3350, 2950, 1639, 1616, 1572 1540. ^1H NMR (D_2O/DSS) δ: 4.10 (1H, ddd, J = 8.5, 5.2 and 3.5 Hz, -C*HO), 3.61 (1H, d, J = 5.2 Hz, -C*HN), 3.16, 3.07 (1H each, dd, J = 13.0 and 7.0 Hz, -CH_2N), 1.99 (1H, ddt, J = 16.5, 2×7.0 and 3.5 Hz, -CH_ACH_B), 1.85 (1H, ddt, J = 16.5, 8.5 and 2×7.0 Hz, -CH_ACH_B). ^{13}C NMR (D_2O/dioxane) δ: 174.77 (s, -COOH), 70.45 (d, -C*HO), 62.06 (d, -C*HN), 39.71 (t, -CH_2N), 33.77 (t, -CH_2CH_2-).

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