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An enantioselective, stereodivergent synthesis of threonine analogs

Giuliano delle Monache,[a] Maria Cristina Di Giovanni,[b] Domenico Misiti [b,*] and Giovanni Zappia [b]

[a] Centro Chimica dei Recettori del CNR, Università Cattolica S. Cuore, Largo F. Vito 1, 00168 Roma, Italy
[b] Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università 'La Sapienza', P. le A. Moro 5, 00185 Roma, Italy

Abstract: An enantioselective and stereodivergent methodology for the synthesis of the four isomers of β-hydroxy norvaline is presented starting from the common oxazolidin-2-one intermediate **1**, *via* an iterative formation of the oxazolidin-2-one ring to achieve the stereochemical control of the stereogenic centers. The flexibility of the present approach, for the synthesis of several threonine analogs, lies in the ready displacement of the sulfonate group in **2** with the Grignard reagents in the presence of CuI. © 1997 Elsevier Science Ltd. All rights reserved.

Introduction

β-Hydroxy-α-amino acids are an important class of compounds, due to their presence in nature as primary metabolites themselves (e.g. serine, threonine), and as components of biologically active natural compounds such as peptides[1] (e.g. Echinocandin D, Teicoplanin, MeBmt in Cyclosporins, Vancomycin, etc), polyoxins and toxic peptides. Moreover, these compounds have shown particular activity as enzyme inhibitors. For instance, the diastereomeric mixture of 3-hydroxy norvaline, a simple analog of threonine, has been studied[2] as an inhibitor of herpes simplex virus type 1 (HSV-1). In particular, it inhibits markedly the synthesis of all glycoproteins, present in the viral envelope and the DNA replication, due to the inhibition of HSV-1 thymidine kinase and DNA polymerase, respectively. Notably, these are also the enzymatic targets of 'acyclovir'. The role of 3-hydroxy norvaline as a glycosylation inhibitor has also been studied in HIV (LAV/HTLV-II)-infected cells.[3]

Stereoselective syntheses of this class of compounds have been based mainly on aldol condensations between a chiral glycine derivative with the appropriate aldehyde.[4] In these methods the preparation of different (*syn*, *anti* L- and D-)-β-hydroxy-α-amino acids involves the use of various chiral auxiliaries to control the stereoselectivity of the aldol reactions. Moreover, each target compound requires its own aldehyde as starting material.

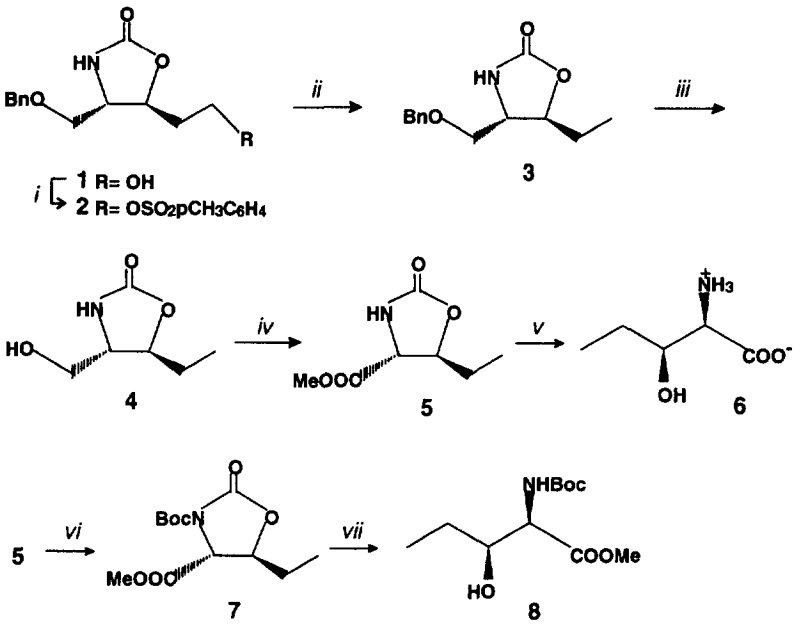
However, when the biological response of a series of compounds has to be evaluated, a synthetic approach leading to the maximum stereochemical variations and substitution patterns is desirable. Furthermore, a synthetic scheme which makes use of parallel, repetitive transformations from a single precursor, should be preferred.

As part of our ongoing program for the synthesis of biologically relevant β-hydroxy-α-amino acids,[5] by the use of homochiral 4,5-disubstituted oxazolidin-2-ones as chiral intermediates,[5,6] we wish to report our results directed towards the development of such a flexible approach to the synthesis of some analogs of threonine.

Results and discussion

Our first aim was to develop a simple methodology for the control of the absolute and relative stereochemistry of the two stereogenic centers. The stereodivergent synthesis of the four isomers of β-hydroxy norvaline was selected as a model for establishing the methodology.

* Corresponding author.



Scheme 1. *Reagents and conditions*: (*i*) TosCl, Et_3N, CH_2Cl_2, O°C (90%); (*ii*) Super Hydride®, THF, r.t. (95%); (*iii*) H_2, 10% Pd/C, EtOH abs., (97%); (*iv*) 1) Jones' reagent; 2) CH_2N_2 (73%); (*v*) 6 N HCl (71%); (*vi*) Boc_2O, Et_3N, DMAP cat., THF (89%); (*vii*) Cs_2CO_3 cat., MeOH (78%).

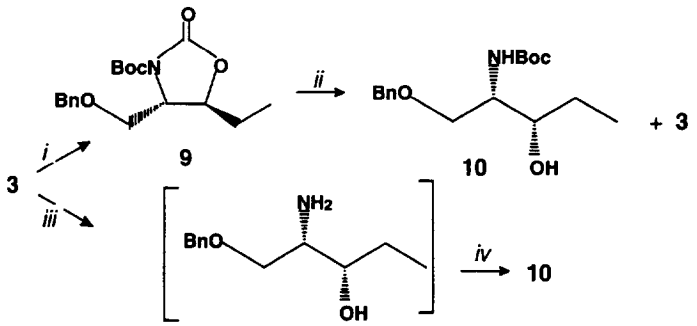
In this way the hydroxy *trans*-oxazolidin-2-one **1** was the starting material of choice. The above compound **1**[7] was readily available[5b] in multigram quantities by stereoselective iodocyclocarbamation of methyl (*Z*,4*S*)-5-benzyloxy-4-((benzyloxycarbonyl)-amino)-2-pentanoate, followed by removal of the iodine, under radical conditions, and reduction of the ester function.

The synthetic strategy in Scheme 1 allows the conversion of **1** into the *syn* 3-hydroxy D-norvaline **6**. The *p*-toluensulfonate **2**, by treatment with lithium triethylborohydride,[8] Super-Hydride®, gave the 4,5-disubstituted oxazolidin-2-one **3** in 86% yield from **1**. Subsequently, hydrogenolysis over 10% Pd/C quantitatively removed the benzyl protecting group, to give the hydroxy derivative **4**, which was in turn oxidized under Jones' conditions.[9] The acid then obtained was isolated as the methyl ester **5** in 70% yield from **3**. Comparable yields were achieved when two step oxidations were performed (TEMPO, NaClO/NaBr[10] and 1M $KMnO_4$/5% NaH_2PO_4,[11] 64% yield), or when the oxidation was run with $RuCl_3/NaIO_4$[12] in $CH_3CN/CCl_4/H_2O$ (61%). However, the Jones' oxidation was adopted for its simplicity, safety and the low cost of reagents.

(2*R*,3*S*)-3-Hydroxy norvaline **6**,[13] formally D-β-hydroxy-norvaline, was obtained by acid hydrolysis of **5**. On the other hand, the same β-hydroxy-α-amino acid was obtained in protected form by treatment with Boc_2O in the presence of catalytic DMAP to give **7** in 89% yield and subsequent ring opening with Cs_2CO_3.[14] Clean ring opening took place in 3 h and in 78% yield to give **8** (70% yield based on **5**). The enantiomeric excess of **8** was 91%, obtained by integrating the relevant peaks in ^1H NMR spectrum[15] in the presence of 0.33 equiv. of Eu(hfc)$_3$. It must be underlined that the protected amino acid **8** can be an useful intermediate in peptide chemistry.

The above sequence of reactions nicely evidenced the potential of the 4,5-disubstitued *trans*-oxazolidin-2-one **1** in our approach.

We then focused our attention on the synthesis of (2*R*,3*R*)-3-hydroxy norvaline **14**, formally D-*allo*-β-hydroxy-norvaline, which requires essentially an inversion of configuration at C-3. To achieve this objective our synthetic strategy involved the opening of the *trans*-oxazolidin-2-one ring in **3**



Scheme 2. *Reagents and conditions*: (*i*) Boc_2O, Et_3N, DMAP cat., THF (93%); (*ii*) Cs_2CO_3 cat., MeOH (74%, **10**+**3**); (*iii*) aqueous $Ba(OH)_2$, EtOH, reflux; (*iv*) Boc_2O, THF (71% from **3**).

followed by conversion into the *cis*-isomer. Therefore, **3** was treated with Boc_2O/DMAP and then with Cs_2CO_3/MeOH (Scheme 2).

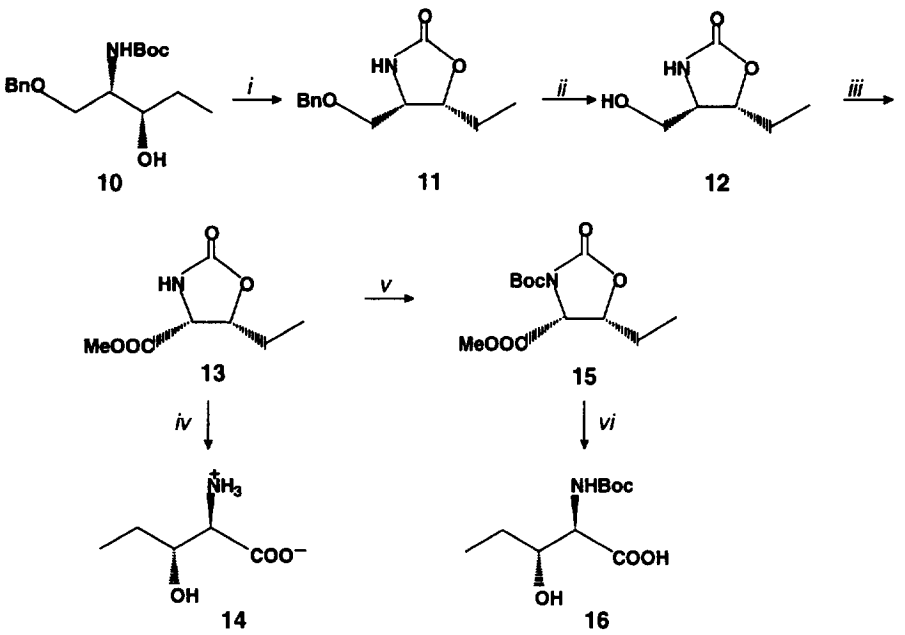
In contrast with the literature report[14] and our above results, the reaction of **9** with Cs_2CO_3/MeOH gave, only after 16 h, a mixture of **10** and **3** in a moderate regioselectivity (60:40). The lack in regioselectivity[16] for this reaction has been already observed by us[5d] for other 4,5-disubstituted N-Boc oxazolidin-2-ones. To overcome this shortcoming, compound **3** was directly treated under alkaline conditions with satd. aq. $Ba(OH)_2$–EtOH under reflux for 16 h, to achieve the ring opening, followed by reprotection of the amine function, to give the N-Boc derivative **10** in 71% from **3**.

Compound **10** was then converted into the *cis* oxazolidin-2-one **11** following the procedure reported by Ohfune,[17] which involves mesylation of the hydroxy function, conversion of the Boc protecting group into the trimethylsilyl-carbamate and finally treatment with a solution of TBAF in THF.

Since the desired *cis*-**11** was obtained in low (41%) and variable yields, we searched for an alternative method, to obtain it directly. Our studies culminated with the use of the solid complex Ph_3P/Cl_2, a reagent used to convert alcohols into chlorides,[18] in hot $CHCl_3$ to give, after chromatographic separation, the required *cis*-**11** in 68% yield. The reaction takes place[19] very likely by activation of the hydroxy group followed by internal carbamate displacement which occurs faster than the substitution reaction.

Compound **11** was converted into the target *anti*-β-hydroxy-α-amino acid by a pathway parallel to that which gave the *syn* stereoisomer **8** from **3** (Scheme 1). As summarised in Scheme 3 compound **11** gave **14**[13] in 51% overall yield, and its protected form **16** in 45% yield. The above shown *cis*-oxazolidin-2-ones are characterized by a coupling constant $J_{H4,H5}$ (*ca.* 7–8.5 Hz)[20] higher than that of the *trans*-stereoisomers (*ca.* 5 Hz).[5,6,20] The values of the coupling constants may be modified by different substituents and are not easily determined when the C-4 and C-5 are substituted by methylene or methyl groups unless decoupling experiments are performed.

In Table 1 the coupling constant $J_{H4,H5}$ and other spectral features of some *trans*/*cis* pairs of oxazolidinones are compared. Notably, for all the *cis* derivatives the signals for H-4 and H-5 appear at lower field than those of the *trans* stereoisomers. A similar behaviour, induced by a γ-effect is shown in the ^{13}C NMR spectra by the C-4 and C-5 substituents, the difference in chemical shift depending on the nature of the substituent. Therefore a simple comparison of the ^{1}H and/or ^{13}C NMR spectra of *trans* and *cis* stereoisomers allows their identification. Table 1 also shows that the methylene signal of the ethyl group at C-5 appears at very different values in the *trans* and *cis* compounds and is independent of the C-4 substitution. The CH_2 chemical shift (*ca.* δ_C28 ppm for the *trans* and *ca.* 23 ppm for the *cis*-stereoisomer) may thus be diagnostic when only one of the stereoisomers is available.



Scheme 3. *Reagents and conditions*: (*i*) $Ph_3P{\bullet}Cl_2$, $CHCl_3$, 45°C (68%); (*ii*) H_2, 10% Pd/C, EtOH abs. (96%); *iii*) 1) Jones' reagent; 2) CH_2N_2 (70%); (*iv*) 6 N HCl (79%); (*v*) Boc_2O, Et_3N, DMAP cat., THF (93%); (*vi*) Cs_2CO_3 cat., MeOH (75%).

Table 1. Selected ^1H- and ^{13}C NMR data for *trans/cis* pairs of oxazolidin-2-ones[a]

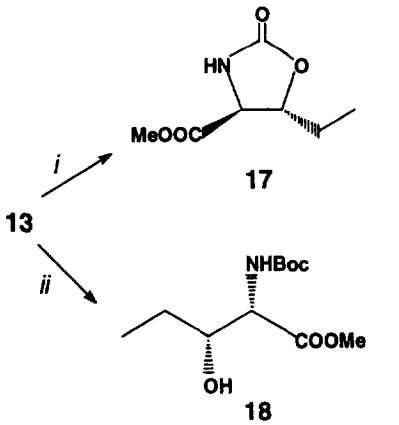
	3	11	4	12	5	13	7	15
J_{H_4,H_5}	5.5	7	5	7.5	5	8.5	4.5	8.5
δ_{H_4}	3.65	3.91	3.60	3.84	4.01	4.44	4.39	4.73
δ_{H_5}	4.20	4.52	4.32	4.57	4.47	4.69	4.30	4.53
$\delta_{C\text{-}4subst.}$	71.87	68.50	63.63	61.08	170.58	169.75	169.13	167.96
$\delta_{C\text{-}5subst.}$	27.80	22.23	27.75	22.29	28.09	23.95	28.25	23.77

[a] *J*: Hz; δ: ppm.

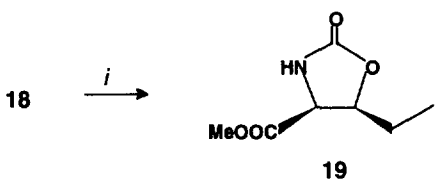
***trans* 3, 4** R = Bn X = H_2 ***cis* 11, 12** R = Bn X = H_2

***trans* 5, 7** R = Me X = O ***cis* 13, 15** R = Me X = O

Although in principle, the L-isomers of **8** and **16** can be prepared by the above protocol starting from the (4*R*,5*R*) isomer of **1**,[5a] readily available from L-serine,[21] we studied the possibility of exploiting some of the above intermediates to obtain the (2*S*,3*R*)- and (2*S*,3*S*)-isomers. Thus, since the *trans*-oxazolidin-2-one is more stable than the *cis*-isomer,[22] the methyl ester **13** was treated under alkaline conditions with 0.6 N ethanolic KOH at reflux. Under these conditions, both hydrolysis and C-4 epimerization took place, and the *trans*-oxazolidin-2-one **17** was isolated in 80% yield after



Scheme 4. *Reagents and conditions*: (*i*) 1) Ethanolic 0.6 N KOH, reflux, 1 h; 2) CH_2N_2 (80%); (*ii*) 1) ethanolic 0.6 N KOH, reflux, 1 h, then aqueous 2 N KOH; 2) Boc_2O, 1 N NaOH, dioxane (63%).



Scheme 5. *Reagents and conditions*: (*i*) $SOCl_2$, r.t. (38%).

esterification with CH_2N_2. On the other hand, when the mixture from the epimerization reaction was directly treated with aqueous 2 N KOH under reflux for 7 h followed by Boc_20, the (2*S*,3*R*)-amino acid L-norvaline was obtained as the N-Boc methyl ester **18** in 63% yield from **13** (Scheme 4).The e.e. (92%) of **18** was determined by the same method as for the compound **8**.

In summary, three of the four stereoisomers of 3-hydroxy norvaline can be prepared by the synthetic pathways shown above, starting from a common precursor. In order to obtain the remaining (2*S*,3*S*)-isomer, the inversion of configuration at C-3 in compound **18** was studied. The best result was obtained by treatment of **18** with neat $SOCl_2$[23] at room temperature for 24 h, which gave the *cis*-oxazolidin-2-one **19** in only 38% yield (Scheme 5). The last compound is the enantiomer of **13** and may be formally converted into the L-*allo*-β-hydroxy-norvaline according to the same reactions of Scheme 3.

Finally, with the aim of extending the synthetic possibility offered by the 4,5-disubstituted oxazolidin-2-one **1**, we have investigated the functionalization of C-5 using the sulfonate **2** as an electrophilic threoninol synthon. The results of the reactions of **2** with several Grignard reagents in the presence of CuI[24] (1.5 eq.) are reported in Table 2.

An excess (3.5 eq.) of organometallic reagent was required to obtain the products within a reasonable time (18 h). The displacements proceeded in reasonable chemical yields (62–85%) with alkyl- and aryl-Grignard reagents. The use of Li_2CuCl_4[25] to catalyse the above cross-coupling reaction has been briefly considered, but the yields were lower than those obtained with CuI.

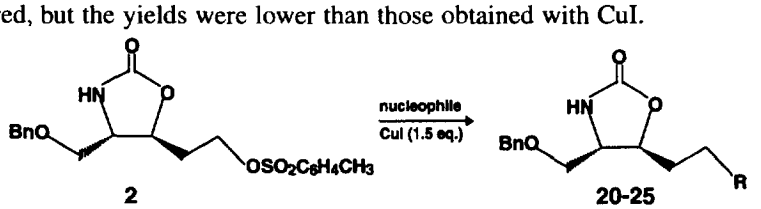


Table 2. Threonine analogues-modification in the C-5 side chain

Compound	R	Nucleophile	Isolated Yield (%)
20	Me	MeMgBr/CuI	73
21	Ph	PhMgBr/CuI	78
		$PhMgBr/Li_2CuCl_4$	60
22	Allyl	AllylMgBr/CuI	62
		$AllylMgBr/Li_2CuCl_4$	39
23	Cyclohexyl	$C_6H_{11}MgBr/CuI$	85
24	Ethyl	C_2H_5MgBr/CuI	78
25	Propyl	C_3H_7MgBr/CuI	72

In conclusion, we have reported a flexible, stereodivergent methodology to the synthesis of *syn* and *anti* 3-hydroxy L- and D-norvaline, from the readily available 4,5-disubstituted oxazolidin-2-one **1**. The reported approach presents as 'leitmotiv' the iterative formation of the oxazolidin-2-one ring both to protect the amino-alcohol function and to achieve the stereochemical control of the stereogenic centers. The present approach can be easily extended to the synthesis of a large number of threonine analogs by modification of the C-5 side chain, which was performed by easy nucleophilic displacement with Grignard reagents of the sulfonate group in **2**. Further studies are in progress in our laboratory on the use of homochiral 4,5-disubstituted oxazolidin-2-ones as chiral intermediates.

Experimental

Melting points were determinated in open capillaries using a Buchi apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5DX FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were run on a Varian Gemini 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. The proton chemical-shifts in ^{1}H NMR spectra were assigned by HETCOR correlations with carbon signals, but the multiplicities were not determined. Optical rotations were determined on a Perkin Elmer 243 polarimeter at 21°C (concentration g/100 ml). All solvents were dried prior to use.[26] Thin layer chromatography was performed on Merck silica gel 60 F_{254} glass plates.

*(4S,5S)-4-(Benzyloxy)methyl-5-(2-*p*-toluensulfonyloxyethyl)-2-oxo-oxazolidine* **2**

To a well stirred solution of **1** (2.372 g, 9.45 mmol) and Et_3N (3.96 ml, 28.32 mmol) in dry CH_2Cl_2 (26 ml) at 0°C *p*-toluensulfonyl chloride (3.24 g, 17 mmol) was added in one portion. The solution was stirred for 4 h at room temperature, diluted with CH_2Cl_2 (150 ml) and washed with 1 N HCl (2×100 ml), 5% aqueous $NaHCO_3$ (2×100 ml) and brine (2×100 ml). The organic layer was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by silica gel chromatography with EtOAc/*n*-hexane (1:1) as eluent to give **2** (3.58 g, 90%) as a white solid. M.p.=84–85°C; $[\alpha]_D$=−20.1 (c=2.9, $CHCl_3$). IR (KBr) ν: 3289, 1746, 1724, 1362, 1175, 1096, 993, 907 cm^{-1}. ^{1}H NMR δ: 7.77, 7.34 (d, *J*=8.0 Hz, 2H each, $CH_3C_6H_4$), 7.40–7.25 (m, 5H, C_6H_5), 5.60 (s, 1H, NH), 4.53 (s, 2H, $C_6H_5CH_2O$), 4.36 (dt, *J*=7.5 and 2×5.5 Hz, 1H, CHO), 4.18 (dt, *J*=10.0 and 2×5.0 Hz, 1H, $CH_AH_BOC_6H_4$), 4.12 (ddd, *J*=10.0, 7.0 and 6.0 Hz, 1H, $CH_AH_BC_6H_4$), 3.64 (brq, *J*=5.5 Hz, 1H, CHN), 3.46 (dd, *J*=9.0 and 5.0 Hz, 1H, OCH_CH_D), 3.43 (dd, *J*=9.0 and 7.5 Hz, 1H, OCH_CH_D), 2.45 (s, CH_3, 3H), 2.06 (brq, *J*=6.0 Hz, 2H, CH_2); ^{13}C NMR δ: 158.03 (s, NHCO), 145.15, 132.56, 130.01, 127.91 (s, s, 2×d, 2×d, $CH_3C_6H_4$), 137.15, 128.63, 128.13, 127.81 (s, 2×d, d, 2×d, C_6H_5), 75.33 (d, CHO), 73.63 (t, $C_6H_5CH_2O$), 71.27 (t, CH_2O), 65.88 (t, CH_2OSO_2), 57.06 (d, CHN), 34.40 (t,

CH_2), 21.65 (q, CH_3). Anal. Calcd. for $C_{20}H_{23}NO_6S$: C=59.24, H=5.72, N=3.46; Found: C=59.35, H=5.64, N=3.36.

(4S,5S)-4-(Benzyloxy)methyl-5-ethyl-2-oxo-oxazolidine 3

To a well stirred solution of sulfonate **2** (1.458 g, 3.71 mmol) in dry THF (20 ml) was added dropwise a solution of $LiEt_3$ BH (1 M in THF, 13 ml, 13 mmol) under N_2 at 0°C. The solution was stirred at the same temperature for 1 h and at room temperature overnight. After that time the reaction mixture was cooled at 0°C, and an aqueous solution of NaOH (5%, 5 ml) was added. The mixture was stirred for 5 min and extracted with EtOAc (2×100 ml). The organic extracts were washed with brine, dried over Na_2SO_4, concentrated and purified by silica gel chromatography using EtOAc/*n*-hexane (7:3) as eluent to give **3** (0.828 g, 95%). $[\alpha]_D$=+12.12 (c=0.9, $CHCl_3$). IR (neat) ν: 3254, 1750, 1736, 1458, 1368, 1240, 1121 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 5.99 (brs, 1H, NH), 4.54 (s, 2H, $C_6H_5CH_2O$), 4.20 (dt, *J*=7.0 and 2×5.5 Hz, 1H, CHO), 3.65 (q, *J*=3×5.5 Hz, 1H, CHN), 3.45 (d, *J*=5.5 Hz, 2H, OCH_2), 1.77 (dp, *J*=14.0 and 4×7.0 Hz, 1H, $OCH_AH_BCH_3$), 1.69 (ddp, *J*=14.0, 3×7.0 and 5.5, 1H, $OCH_AH_BCH_3$), 1.00 (t, *J*=7.0 Hz, 3H, CH_2CH_3). ^{13}C-NMR δ: 159.02 (s, NHCO), 137.34 (s, C_6H_5), 128.51, 127.67 (d×2 each, C_6H_5), 127.95 (d, C_6H_5), 80.52 (d, CHO), 73.52 (t, $C_6H_5CH_2O$), 71.87 (t, OCH_2), 56.77 (d, CHN), 27.80 (t, CH_2), 8.75 (q, CH_3). Anal. Calcd. for $C_{13}H_{17}NO_3$: C=66.36, H=7.28, N=5.95; Found: C=66.19, H=7.39, N=5.82.

(4S,5S)-4-Hydroxymethyl-5-ethyl-2-oxo-oxazolidine 4

Compound **3** (0.475 g, 2.025 mmmol) was dissolved in abs. EtOH (15 ml) and hydrogenated over 10% Pd/C at 1 atm for 18 h. After that time the solution was filtered over Celite and concentrated under reduced pressure to give **4** (0.287 g, 97%) as a colorless oil, which was used without further purification. $[\alpha]_D$=−31.0 (c=3.6, MeOH). IR (neat) ν: 3336, 1737, 1410, 1255, 1081, 1043 cm^{-1}. ^1H NMR: δ: 6.68 (brs, 1H, NH), 4.32 (brq, *J*=6.0 Hz, 1H, CHO), 3.70 (dd, *J*=11.0 and 2.0 Hz, 1H, OCH_AH_B), 3.60 (dt, *J*=2×5.0 and 2.0 Hz, 1H, CHN), 3.55 (dd, *J*=11.0 and 5.0 Hz, 1H, OCH_AH_B), 1.79, 1.71 (dp, *J*=14.0 and 4×7.0 Hz, 1H each, CH_2), 1.01 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR δ: 160.21 (s, NHCO), 80.25 (d, CHO), 63.63 (t, CH_2OH), 58.96 (d, CHN), 27.75 (t, CH_2), 8.75 (q, CH_3). Anal. Calcd. for $C_6H_{11}NO_3$: C=49.65, H=7.64, N=9.65; Found: C=49.70, H=7.67, N=9.55.

(4R,5S)-4-Carboxymethyl-5-ethyl-2-oxo-oxazolidine 5

The Jones' oxidation[8] was performed. A solution of hydroxy oxazolidin-2-one **4** (0.267 g, 1.86 mmol) in acetone (39 ml) was added dropwise at −5°C to a solution of freshly prepared Jones' reagent (5.88 ml) in acetone (16 ml). The Jones' reagent was a solution of chromic trioxide (2.65 g), conc. H_2SO_4 (2.3 ml) and water (to a total vol. of 10 ml). After 4 h at −5°C, 2-propanol was added dropwise until the medium turned blue, water was added, and extraction with EtOAc (3×100 ml) was performed. The combined organic extracts were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The resulting crude acid was dissolved in EtOAc (10 ml), cooled at 0°C and treated with an ethereal solution of CH_2N_2, followed by stirring for 45 min. at room temperature. Excess of CH_2N_2 was destroyed by addition of a solution of CH_3COOH (5M in CH_2Cl_2, 0.1 ml). After evaporation, the crude mixture was purified by silica gel chromatography using EtOAc/*n*-hexane (3:2) as eluent to give **5** (2.32 g, 73%) as an oil. $[\alpha]_D$=−33.83 (c=0.34, $CHCl_3$). IR (neat) ν: 3295, 1761, 1392, 1220 cm^{-1}. ^1H NMR δ: 6.88 (br s, 1H, NH), 4.47 (dt, *J*=2×6.5 and 5.0 Hz, 1H, CHO), 4.01 (d, *J*=5.0 Hz, 1H, CHN), 3.73 (s, 3H, OCH_3), 1.78 (p, *J*=7.0 Hz, 2H, $CHCH_2CH_3$), 0.98 (t, *J*=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 170.58 (s, $COOCH_3$), 158.68 (s, NHCO), 80.09 (d, CHO), 58.31 (d, CHN), 52.78 (q, OCH_3), 28.09 (t, CH_2), 8.44 (q, CH_3). Anal. Calcd. for $C_7H_{11}NO_4$: C=48.55, H=6.40, N=8.09; Found: C=48.61, H=6.41, N=7.95.

(2R,3S)-3-Hydroxy norvaline 6

A suspension of compound **5** (0.164 g, 0.95 mmol) in 6 N HCl (5 ml) was heated at 90°C overnight. After this time the reaction mixture was concentrated under reduced pressure, dissolved in the minimum

amount of water and filtered through an ion-exchange column (Amberlist IR-120), eluting with H_2O, then with NH_4OH. The fractions containing the amino-acid were concentrated to give **6** (90 mg, 71%). M.p.=228–229°C. $[\alpha]_D$=−8.9 (c=0.71, 1 M HCl). [Lit.[13]: m.p.=232–233°C; $[\alpha]_D$=−9.2 (c=1, 1 M HCl); Lit.[27]: m.p.=232–233°C; $[\alpha]_D$=−9.7 (c=0.87, 1M HCl)].

*(4R,5S)-3-(*tert*-Butoxycarbonyl)-4-(carboxymethyl)-5-ethyl-2-oxo-oxazolidine* ***7***

To a well stirred solution of **5** (0.192 g, 1.11 mmol) in dry THF (20 ml) was added Et_3N (0.22 ml, 1.58 mmol), Boc_2O (0.384 g, 1.76 mmol). After 10 min DMAP (16 mg, 0.13 mmol) was added and the reaction was stirred at room temperature for 16 h. After that time the solution was concentrated under reduced pressure and the residue was diluted with $CHCl_3$ (150 ml), washed with 1 N HCl (2×10 ml), 5% aqueous $NaHCO_3$ (2×10 ml) and brine. The organic solution was dried over Na_2SO_4, filtered, concentrated under reduced pressure and purified by silica gel chromatography with EtOAc/*n*-hexane (1:1) as eluent to give **7** (0.270g, 89%). $[\alpha]_D$=+4.4 (c=0.9, $CHCl_3$). IR (neat) ν: 2978, 1827, 1753, 1728, 1368, 1335, 1212, 1072 cm^{-1}. ^1H NMR δ: 4.39 (d, *J*=4.5 Hz, 1H, CHN), 4.30 (dt, *J*=2×6.5 and 4.5 Hz, 1H, CHO), 3.83 (s, 3H, OCH_3), 1.85 (dp, *J*=10.0 and 4×7.0 Hz, 1H, $CH_AH_BCH_3$), 1.83 (dp, *J*=10.0 and 4×7.0 Hz, 1H, $CH_AH_BCH_3$), 1.51 [s, 9H, $C(CH_3)_3$], 1.06 (t, *J*=7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 169.13 (s, *C*OOCH$_3$), 150.70 (s, N*C*OC), 148.55 [s, N*C*OC(CH$_3$)$_3$], 84.52 [s, *C*(CH$_3$)$_3$], 76.72 (d, CHO), 60.83 (d, CHN), 52.95 (q, OCH_3), 28.25 (t, CH_2), 27.72 [q, C(*C*H$_3$)$_3$], 8.33 (q, CH_3). Anal. Calcd. for $C_{12}H_{19}NO_6$: C=52.74, H=7.01, N=5.13; Found:C=52.61, H=7.18, N=5.10.

*Methyl (2R,3S)-2-*tert*-butoxycarbonylamino-3-hydroxy pentanoate* ***8***

To a well stirred solution of **7** (0.150 g, 0.55 mmol) in dry MeOH (8 ml) was added Cs_2CO_3 (0.035 g, 0.11 mmol) in one portion and the solution was stirred at room temperature for 3 h. After that time the solution was neutralized with solid citric acid and concentrated under reduced pressure. The residue was dissolved in EtOAc (50 ml), washed with brine (50 ml), H_2O (50 ml) and dried over Na_2SO_4. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (2:3) as eluent to give **8** (0.107 g, 78%) as a colorless oil. $[\alpha]_D$=+4.9 (c=0.81, EtOH abs.). IR (neat) ν: 3459, 2975, 1720, 1696, 1507, 1368, 1162 cm^{-1}. ^1H NMR δ: 5.72 (br d, *J*=9.0 Hz, 1H, NH), 4.23 (dd, *J*=9.0 and 3.0 Hz, 1H, CHN), 4.19 (d, *J*=6.0 Hz, 1H, OH), 3.98 (dq, *J*=3×6.5 and 3.0 Hz, 1H, CHO), 3.69 (s, 3H, OCH_3), 1.53 (p, *J*=4×7.0 Hz, 2H, CH_2CH_3), 1.42 [s, 9H, $(CH_3)_3$], 0.94 (t, *J*=7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 172.52 (s, *C*OOCH$_3$), 156.67 (s, N*C*OO), 79.41 [s, O*C*(CH$_3$)$_3$], 73.58 (d, CHO), 58.37 (d, CHN), 52.20 (q, OCH_3), 28.43 [q, C(*C*H$_3$)$_3$], 27.67 (t, CH_2), 10.44 (q, CH_3). Anal. Calcd. for $C_{11}H_{21}NO_5$: C=53.43, H=8.56, N=5.66; Found: C=53.38, H=8.49, N=5.55.

*(4S,5S)-3-(*tert*-Butoxycarbonyl)-4-(benzyloxy)methyl-5-ethyl-2-oxo-oxazolidine* ***9***

To a well stirred solution of **3** (0.45 g, 1.91 mmol) in dry THF (26 ml) was added Et_3N (0.39 ml, 2.85 mmol), Boc_2O (0.665 g, 3.05 mmol) and DMAP (0.023 g, 0.20 mmol). The reaction was performed as for the compound **7** and the residue purified by silica gel chromatography with EtOAc/*n*-hexane (3:7) as eluent to give **9** (0.592 g, 93%). $[\alpha]_D$=+13.5 (c=1.6, $CHCl_3$). IR (neat) ν: 2978, 1825, 1743, 1458, 1376, 1123 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5 H, C_6H_5), 4.55 (s, 2H, $C_6H_5CH_2O$), 4.35 (ddd, *J*=7.0, 6.0 and 3.0 Hz, 1H, CHO), 3.94 (dt, *J*=6.0 and 2×3.0 Hz, 1H, CHN), 3.65 (dd, *J*=9.0 and 6.0 Hz, 1H, OCH_AH_B), 3.61 (dd, *J*=9.0 and 3.0 Hz, 1H, OCH_AH_B), 1.76 (dp, *J*=14.0 and 4×7.0 Hz, 1H, $CH_CH_DCH_3$), 1.67 (ddq, *J*=14.0, 3×7.0 and 6.0 Hz, 1H, $CH_CH_DCH_3$), 1.48 [s, 9H, $C(CH_3)_3$], 1.00 (t, *J*=7.0 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 151.85 (s, NCOO), 149.36 [s, *C*OOC(CH$_3$)$_3$], 137.37 (s, C_6H_5), 127.56, 128.49 (d×2 each, C_6H_5), 127.89 (d, C_6H_5), 83.84 [s, O*C*(CH$_3$)$_3$], 77.65 (d, CHO), 73.37 (t, $C_6H_5CH_2O$), 68.54 (t, OCH_2), 58.75 (d, CHN), 27.91 [t and q, CH_2 and OC(*C*H$_3$)$_3$], [in C_6D_6: 27.97 (q, OC(*C*H$_3$)$_3$), 27.88 (t, CH_2)], 8.59 (q, CH_3). Anal. Calcd. for $C_{18}H_{25}NO_5$: C=64.46, H=7.51, N=4.18; Found: C=64.41, H=7.53, N=4.11.

*(2S,3S)-1-Benzyloxy-2-*tert*-butoxycarbonylamino-3-hydroxy pentane* ***10***

A solution of oxazolidin-2-one **3** (1.0 g, 4.25 mmol) in EtOH (300 ml) was added to a satd. solution of $Ba(OH)_2$ (70 ml) and heated at reflux for 10 h. After that time most of the organic solvent was removed under reduced pressure and the resulting aqueous solution was poured on the top of an ion-exchange column (Amberlist IR 120) and eluted with H_2O, followed by 30% NH_4OH. The fractions with the amino-alcohol were concentrated under reduced pressure and the residue dissolved in dry THF (60 ml) followed by the addition of Boc_2O (1.25 g, 5.73 mmol) and Et_3N (0.654 ml, 4.7 mmol). The reaction mixture was stirred overnight at room temperature, concentrated under reduced pressure and purified by silica gel chromatography using EtOAc/*n*-hexane (1:1) as eluent to give **10** (1.31 g, 71%) as a colorless oil. $[\alpha]_D$=+3.21 (c=0.44, MeOH). IR (neat) ν: 418, 1696, 1507, 1458, 1368, 1244, 1171 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 5.21 (d, *J*=7.0 Hz, 1H, NH), 4.55 (d, *J*=12.0 Hz, 1H, $C_6H_5CH_AH_B$), 4.51 (d, *J*=12.0 Hz, 1H, $C_6H_5CH_AH_B$), 3.82 (br dt, *J*=2×7.0 and 2.0 Hz, 1H, CHO), 3.71 (d, *J*=10.0 Hz, 2H, OCH_2), 3.64 (dt, *J*=2×10.0 and 7.0 Hz, 1H, CHN), 3.02 (d, *J*=2.0 Hz, 1H, OH), 1.51 (p, *J*=7.5 Hz, 2H, $CHCH_2CH_3$), 1.44 (s, 9H, $C(CH_3)_3$), 0.95 (t, *J*=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 156.11 (s, NHCO), 137.44 (s, C_6H_5), 127.66, 128.54 (d×2 each, C_6H_5), 127.95 (d, C_6H_5), 79.37 (s, $OC(CH_3)_3$), 74.59 (d, CHO), 73.68 (t, $OCH_2C_6H_5$), 73.23 (t, CH_2O), 52.26 (d, CHN), 28.35 [q, $C(CH_3)_3$], 26.71 (t, CH_2), 10.12 (q, CH_3). Anal. Calcd. for $C_{17}H_{27}NO_4$: C=65.99, H=8.80, N=4.55; Found: C=66.11, H=8.55, N=4.47.

(4S,5R)-4-(Benzyloxy)methyl-5-ethyl-2-oxo-oxazolidine ***11***

To a well stirred solution of **10** (0.587 g, 1.9 mmol) in $CHCl_3$ (12 ml) was added solid dichlorotriphenylphosphorane[18] (0.646 g, 2.0 mmol) and the mixture was stirred at 45°C for 18 h. The mixture reaction was concentrated under reduced pressure and the residue was purified by silica gel chromatography with EtOAc/*n*-hexane (7:3) as eluent to give **11** (0.304 g, 68%). $[\alpha]_D$=−4.9 (c=0.27, $CHCl_3$). IR (neat) ν: 3254, 2936, 1745, 1458, 1376, 1121 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 6.10 (brs, 1H, NH), 4.53 (d, 1H, *J*=12 Hz, $C_6H_5CH_AH_BO$), 4.51 (1H, ddd, *J*=10.0, 7.0 and 4.0 Hz, CHO), 4.48 (d, 1H, *J*=12.0 Hz, $C_6H_5CH_AH_BO$), 3.91 (dt, 1H, *J*=2×7.0 and 5.0 Hz, CHN), 3.52 (dd, 1H, *J*=9.5 and 5.0 Hz, $OCH_CH_DC^*$), 3.44 (dd, 1H, *J*=9.5 and 7.0 Hz, $OCH_CH_DC^*$), 1.72 (ddq, 1H, *J*=14.0, 10.0 and 3×7.0 Hz, $CH_EH_FCH_3$), 1.61 (ddq, 1H, *J*=14.0, 3×7.0 and 4.0 Hz, $CH_EH_FCH_3$), 1.03 (t, 3H, *J*=7.0 Hz, CH_3). ^{13}C NMR δ=159.44 (s, CONH), 137.26 (s, C_6H_5), 128.40, 127.51 (d×2 each, C_6H_5), 127.83 (d, C_6H_5), 80.32 (d, CHO), 73.49 (t, $C_6H_5CH_2$), 68.50 (t, OCH_2), 54.74 (d, CHN), 22.23 (t, CH_2), 10.52 (q, CH_3). Anal. Calcd. for $C_{13}H_{17}NO_3$: C=66.65, H=6.88, N=5.98; Found: C=66.53, H=6.79, N=5.81.

(4S,5R)-4-Hydroxymethyl-5-ethyl-2-oxo-oxazolidine ***12***

The title compound was obtained from **11** (0.750 g, 3.19 mmol) according to the procedure used for the preparation of **4** (yield: 0.444 g, 96%). $[\alpha]_D$=+36.4 (c=0.29, MeOH). IR (neat) ν: 3377, 1737, 1400, 1253, 1097, 1056 cm^{-1}. ^1H NMR δ: 6.26 (br s, 1H, NH), 4.57 (ddd, *J*=9.5, 7.5 and 4.5 Hz, 1H, CHO), 3.84 (ddd, *J*=7.5, 6.5 and 4.0 Hz, 1H, CHN), 3.73 (dd, *J*=11.5 and 4.0 Hz, 1H, CH_AH_BOH), 3.68 (dd, *J*=11.5 e 6.5 Hz, 1H, CH_AH_BOH); 1.83 (ddq, *J*=14.0, 9.5 and 3×7.5 Hz, 1H, $CH_CH_DCH_3$), 1.67 (ddq, *J*=14.0, 3×7.5 and 4.5 Hz, 1H, $CH_CH_DCH_3$), 1.07 (t, *J*=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 160.23 (s, NHCO), 80.96 (d, CHO), 61.08 (t, CH_2OH), 56.59 (d, CHN), 22.29 (t, CH_2), 10.67 (q, CH_3). Anal. Calcd. for $C_6H_{11}NO_3$: C=49.65, H=7.64, N=9.65; Found: C=49.61, H=7.62, N=9.55.

(4R,5R)-4-Carboxymethyl-5-ethyl-2-oxo-oxazolidine ***13***

According to the procedure used for the preparation of **5**, compound **12** (0.441 g, 3.07 mmol) was converted into **13**. Yield: 0.372 g, 70%. $[\alpha]_D$=+30.6 (c=0.48, $CHCl_3$). IR (neat) ν: 3377, 1737, 1400, 1253, 1097, 1056 cm^{-1}. ^1H NMR δ: 6.50 (br s, 1H, NH), 4.69 (dt, *J*=2×8.5 and 4.5 Hz, 1H, CHO), 4.44 (d, *J*=8.5 Hz, 1H, CHN), 3.80 (s, 3H, OCH_3), 1.69 (ddq, *J*=12.0, 3×7.0 and 4.5 Hz, 1H, $CH_AH_BCH_3$), 1.59 (ddq, *J*=12.0, 8.5 and 3×7.0 Hz, 1H, $CH_AH_BCH_3$), 1.07 (t, *J*=7.0 Hz, 3H,

CH_2CH_3). ^{13}C NMR δ: 159.24 (s, NHCO), 79.62 (d, CHO), 58.08 (d, CHN), 52.50 (q, OCH_3), 23.95 (t, CH_2), 10.05 (q, CH_3). Anal. Calcd. for $C_7H_{11}NO_4$: C=48.55, H=6.40, N=8.09; Found: C=48.50, H=6.38, N=8.10.

(2R,3R)-3-Hydroxy norvaline ***14***

A suspension of compound **13** (0.135 g, 0.78 mmol) in 6 N HCl (4 ml) was heated at 90°C overnight. After that time the reaction mixture was concentrated under reduced pressure, dissolved in the minimum amount of water and filtered through an ion-exchange column (Amberlist IR-120), eluting with H_2O, than with NH_4OH. The fractions containing the amino-acid were concentrated to give **14** (91 mg, 79%). M.p.=222–224°C. $[\alpha]_D$=−24.3 (c=1, 1M HCl). [Lit.[13]: $[\alpha]_D$=−22.3 (c=1, 1M HCl)].

*(4R,5R)-3-(*tert*-Butoxycarbonyl)-4-(carboxymethyl)-5-ethyl-2-oxo-oxazolidine* ***15***

To a well stirred solution of **13** (0.150 g, 0.86 mmol) in dry THF (16 ml) was added Et_3N (0.172 ml, 1.24 mmol), and Boc_2O (0.31 g, 1.38 mmol). After 10 min DMAP (12 mg, 0.1 mmol) was added and the reaction was performed as for the compound **7**, to give **15** (0.218 g, 93%). $[\alpha]_D$=+39.0 (c=0.5, $CHCl_3$). IR (neat) ν: 2975, 1827, 1753, 1728, 1368, 1326, 1220, 1182, 1072 cm^{-1}. ^1H NMR δ: 4.73 (d, *J*=8.5 Hz, 1H, CHN), 4.53 (ddd, *J*=9.0, 8.5 and 4.5 Hz, 1H, CHO), 3.81 (s, 3H, OCH_3), 1.69 (ddq, *J*=12.0, 3×7.5 and 4.0 Hz, 1H, $CH_AH_BCH_3$), 1.59 (ddq, *J*=12.0, 9.0 and 3×7.5 Hz, 1H, $CH_AH_BCH_3$), 1.50 [s, 9H, $C(CH_3)_3$], 1.08 (t, *J*=7.5 Hz, 3H, CH_3). ^{13}C NMR δ: 167.96 (s, COO), 151.07 (s, CON), 148.57 [s, $NCOOC(CH_3)_3$], 84.47 [s, $OC(CH_3)_3$], 75.89 (d, CHO), 60.50 (d, CHN), 52.51 (q, OCH_3), 27.75 [q, $C(CH_3)_3$], 23.77 (t, CH_2), 9.97 (q, CH_3). Anal. Calcd. for $C_{12}H_{19}NO_6$: C=52.74, H=7.01, N=5.13; Found: C=52.84, H=7.09, N=5.11.

*Methyl (2R,3R)-2-*tert*-butoxycarbonylamino-3-hydroxy pentanoate* ***16***

To a well stirred solution of **15** (0.2 g, 0.733 mmol) in dry MeOH (11 ml) was added Cs_2CO_3 (47 mg, 0.148 mmol) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was processed as for the compound **8** to give **16** (0.136 g, 75%). $[\alpha]_D$=+7.1 (c=0.7, EtOH abs.). IR (neat) ν: 3459, 2970, 1720, 1510, 1370, 1162 cm^{-1}. ^1H NMR δ: 5.54 (br d, *J*=8.0 Hz, 1H, NH), 4.39 (dd, *J*=8.0 and 4.5 Hz, 1H, CHN), 3.81 (br dt, *J*=2×7.5 and 4.5 Hz, 1H, CHO), 3.78 (s, 3H, OCH_3), 2.97 (brs, 1H, OH), 1.51 (p, *J*=4×7.5 Hz, 2H, CH_2CH_3), 1.45 [s, 9H, $C(CH_3)_3$], 1.00 (t, *J*=7.5 Hz, 3H, CH_2CH_3). ^{13}C NMR δ: 171.29 (s, COO), 155.91 [s, $COOC(CH_3)_3$], 80.36 [s, $OC(CH_3)_3$], 74.47 (d, CHO), 58.00 (d, CHN), 52.38 (q, OCH_3), 28.23 [q, $C(CH_3)_3$], 26.36 (t, CH_2), 10.47 (q, CH_3). Anal. Calcd. for $C_{11}H_{21}NO_5$: C=53.43, H=8.56, N=5.66; Found: C=53.53, H=8.66, N=5.61.

(4S,5R)-4-Carboxymethyl-5-ethyl-2-oxo-oxazolidine ***17***

A solution of **13** (0.15 mg, 0.87 mmol) in absolute ethanol (5 ml) was treated with a 0.6 N solution of KOH (3 ml) and heated at reflux for 1 h. After that time the solution was concentrated under reduced pressure and partitioned between water and EtOAc. The aqueous layer was acidified with 5% HCl, extracted with EtOAc (2×50 ml), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (10 ml), cooled at 0°C and treated with an ether solution of CH_2N_2, followed by stirring for 30 min at room temperature. Usual work up gave crude ester which was purified by silica gel chromatography using EtOAc/*n*-hexane (3:2) as eluent to give **17** (0.12 g, 80%). $[\alpha]_D$=+32.1 (c=0.5, $CHCl_3$). IR, ^1H and ^{13}C NMR spectra were similar to those described for **5**. Anal. Calc. for $C_7H_{11}NO_4$: C=48.55, H=6.40, N=8.09; Found: C=48.33, H=6.29, N=7.95.

*Methyl (2S,3R)-2-*tert*-butoxycarbonylamino-3-hydroxy pentanoate* ***18***

A solution of *cis*-oxazolidinone **13** (0.2 g, 1.16 mmol) in absolute EtOH (7 ml) was treated with a 0.6 N solution of KOH (4 ml) and heated at reflux for 1 h. After that time a 2 N aqueous solution of KOH (7.81 ml) was added and the solution was refluxed for 7.5 h. The mixture was then cooled to 0°C, acidified to pH=3 with 5% HCl and concentrated under reduced pressure. The crude hydrochloride was

dissolved in 1,4-dioxane (12 ml) and 1 N NaOH (2.72 ml) and treated with a solution of Boc_2O (0.392 g, 1.8 mmol) in 1,4-dioxane (4 ml) at 0°C. The reaction mixture was stirred at room temperature for 3 h then concentrated under reduced pressure to remove the organic solvent, cooled at 0°C and acidified with 1 N HCl. The aqueous solution was extracted with EtOAc (3×25ml). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude acid, was dissolved in EtOAc/MeOH 1:1 (10 ml) and treated with an ether solution of CH_2N_2. After usual work up the crude *syn*-α-amino-β-hydroxy ester was purified by silica gel chromatography with EtOAc/*n*-hexane (2:3) to give **18** (0.181 g, 63%). $[\alpha]_D=-4.6$ (c=0.86, EtOH abs.). IR, ^1H- and ^{13}C NMR spectra were similar to those described for **8**. Anal. Calcd. for $C_{11}H_{21}NO_5$: C=53.43, H=8.56, N=5.66; Found: C=53.53, H=8.55, N=5.61.

(4S,5S)-4-Carboxymethyl-5-ethyl-2-oxo-oxazolidine ***19***

To the N-Boc methyl ester **18** (0.383 g, 1.55 mmol) was added $SOCl_2$ (1 ml) at 0°C and the reaction mixture was stirred at room temperature for 24 h. The mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography with EtOAc/*n*-hexane (3:2) as eluent to give **19** (0.102 g, 38%). $[\alpha]_D=-29.4$ (c=0.1, $CHCl_3$). IR, ^1H and ^{13}C NMR were similar to those reported for **13**. $C_7H_{11}NO_4$: C=48.55, H=6.40, N=8.09; Found: C=48.29, H=6.31, N=8.01.

General procedure for nucleophilic displacement using Grignard reagents/CuI

Compound **2** (2 mmol) and CuI (3 mmol) were added to a flame dried, round-bottom flask which was then flushed with nitrogen and charged with dry THF (20 ml). The suspension was cooled to −78°C (CO_2+acetone) and the Grignard reagent (7 mmol) was added over 10 min. The suspension was stirred at −78°C for 45 min and then for 18 h at room temperature. After this time satd. NH_4Cl (10 ml) was added and the mixture was stirred for 15 min at room temperature. The green solution was then concentrated under reduced pressure and the resulting solution was extracted with EtOAc (3×50 ml), the combined extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography using EtOAc/*n*-hexane (4:6) as eluent.

(4S,5S)-4-(Benzyloxy)methyl-5-propyl-2-oxo-oxazolidine ***20***

M.p. 37–38°C. $[\alpha]_D=-39.8$ (c=0.5, $CHCl_3$). IR (KBr) ν: 3270, 2847, 1738, 1717, 1456, 1250, 1132 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 4.53 (s, 2H, $C_6H_5CH_2O$), 4.25 (dt, *J*=8.0 and 2×5.0 Hz, 1H, CHO), 3.63 (brq, *J*=3×5.5 Hz, 1H, CHN), 3.45 (d, *J*=6.0 Hz, 2H, CH_2O), 1.75 (dddd, *J*=13.0, 10.0, 8.0 and 5.0 Hz, 2H, CH_2), 1.55–1.35 (m, 2H, CH_2), 0.95 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR δ: 159.00 (s, NHCO), 137.28 (s, C_6H_5), 128.52, 127.70 (2×d each, C_6H_5), 127.98 (d, C_6H_5), 79.20 (d, CHO), 73.52 (t, $OCH_2C_6H_5$), 71.78 (t, CH_2O), 57.21 (d, CHN), 36.91 (t, CH_2), 17.88 (d, CH_2), 13.69 (q, CH_3). Anal. Calcd. for $C_{14}H_{19}NO_3$: C=67.45, H=7.68, N=5.62; Found: C=67.35, H=7.71, N=5.55.

(4S,5S)-4-(Benzyloxy)methyl-5-(2-phenyl)ethyl-2-oxo-oxazolidine ***21***

M.p.=63–65°C; $[\alpha]_D=-56.6$ (c=3.6, $CHCl_3$). IR (KBr) ν: 3238, 1743, 1717, 1497, 1454, 1406, 1234, 1125, 1044 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 7.25–7.15 (m, 5H, C_6H_5), 6.12 (brs, 1H, NH), 4.50 (s, 2H, $C_6H_5CH_2O$), 4.26 (dt, *J*=8.5 and 2×4.8 Hz, 1H, CHO), 3.64 (q, *J*=5.5 Hz, 1H, CHN), 3.41 (d, *J*=5.8 Hz, 2H, OCH_2C^*H), 2.82 (ddd, *J*=14.0, 9.0 and 5.0 Hz, 1H, $CH_2CH_AH_BC_6H_5$), 2.71 (ddd, *J*=14.0, 9.0 and 7.0 Hz, 1H, $CH_2CH_AH_BC_6H_5$), 2.07 (ddt, *J*=14.0, 2×9.0 and 5.0 Hz, 1H, CH_CH_D), 1.93 (ddt, *J*=14.0, 9.0, 7.0 and 5.0 Hz, 1H, CH_CH_D). ^{13}C NMR δ: 158.98 (s, NHCO), 140.44 (s, C-1″, C_6H_5), 137.29 (s, C-1′, C_6H_5), 128.51 (d×4, C-3′, C-5′, C-3″, C-5″, C_6H_5), 128.42 (d×2, C-2″, C-6″, C_6H_5), 127.95 (d, C-4′, C_6H_5), 127.69 (d×2, C-2′, C-6′, C_6H_5), 126.18 (d, C-4″, C_6H_5), 78.60 (d, CHO), 73.51 (t, $C_6H_5CH_2O$), 71.58 (t, OCH_2C^*H), 57.21 (d, CHN), 36.60 (t, CH_2), 30.86 (t, $CH_2C_6H_5$). Anal Calcd. for $C_{19}H_{21}NO_3$: C=73.29, H=6.80, N=4.50; Found: C=73.11, H=6.61, N=4.57.

(4S,5S)-4-(Benzyloxy)methyl-5-(4-pentenyl)-2-oxo-oxazolidine ***22***

$[\alpha]_D$=−45.3 (c=1.2 $CHCl_3$). IR (neat) ν: 3274, 2940, 2858, 1741, 1718, 1384, 1250, 1127 cm^{-1}. ^1H NMR δ=7.40–7.25 (m, 5H, C_6H_5), 5.77 (ddt, *J*=17.0, 10.0, 2×7.0 Hz, 1H, C*H*=CH_2), 5.60 (brs, 1H, NH), 5.01 (ddt, *J*=17.0, 2.0 and 2×1.5 Hz, 1H, CH=C$H_A$$H_B$), 4.98 (brdt, *J*=10.0 and 2.0 Hz, 1H, CH=C$H_A$$H_B$), 4.54 (s, 2H, $C_6H_5CH_2O$), 4.25 (dt, *J*=8.0 and 2×5.0 Hz, 1H, CHO), 3.64 (dt, *J*=6.0 and 2×5.0 Hz, 1H, CHN), 3.47 (dd, *J*=10.0 and 5.0 Hz, 1H, OC$H_c$$H_d$C*HN), 3.43 (1H, *J*=10.0 and 6.0 Hz, OC$H_C$$H_D$C*HN), 2.10 (brq, *J*=7.0 Hz, 2H, CH_2CH=), 1.76 (ddt, *J*=15.0, 8.0 and 2×5.0 Hz, 1H, OC*HC$H_E$$H_F$), 1.68 (dq, *J*=15.0 and 3×5.0 Hz, 1H, OC*HC$H_E$$H_F$), 1.56 (dtt, *J*=14.0, 2×7.0 and 2×5.0 Hz, 1H, $CH_2CH_GH_HCH_2$), 1.48 (dtt, *J*=14.0, 2×7.0 and 2×5.0 Hz, 1H, $CH_2CH_gH_hCH_2$). ^{13}C NMR δ: 158.72 (s, NHCO), 137.87 (d, CH=), 137.27 (s, C_6H_5), 128.57, 127.75 (d×2 each, C_6H_5), 128.05 (d, C_6H_5), 115.23 (t, CH=CH_2), 73.61 (t, $C_6H_5CH_2O$), 79.25 (d, CHO), 71.85 (t, OCH_2CHN), 57.23 (d, CHN), 34.24 (t, C*HCH_2), 33.16 (t, CH_2CH=), 23.80 (t, CH_2). Anal. Calcd. for $C_{16}H_{21}NO_3$: C=69.79, H=7.69, N=5.09; Found: C=69.82, H=7.75, N=5.11.

(4S,5S)-4-(Benzyloxy)methyl-5-(2-cyclohexyl)ethyl-2-oxo-oxazolidine ***23***

M.p. 54–55°C. $[\alpha]_D$=−43.45 (c=2.2, $CHCl_3$); IR (KBr) ν: 3236, 2917, 1734, 1716, 1454, 1261, 1119, 1028 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 5.88 (s, 1H, NH), 4.53 (s, 2H, $OCH_2C_6H_5$); 4.22 (dt, *J*=7.5 and 2×5.5 Hz, 1H, CHO), 3.63 (q, *J*=5.7 Hz, 1H, CHN), 3.45 (d, *J*=5.8 Hz, 2H, CH_2O), 1.66, 1.22 (m, 2H each, 2×CH_2), 1.18 (m, 1H, CH), 1.7, 1.2, 0.87 (5H, m, 3H, 2H, cyclohexyl). ^{13}C NMR δ: 159.96 (s, NHCO), 137.34, 128.55, 128.01, 127.72 (s, 2×d, d, 2×d, C_6H_5), 79.78 (d, CHO), 73.59 (t, $OCH_2C_6H_5$), 71.93 (t, CH_2O), 57.23 (d, CHN), 37.32 (d, *C*HCH_2), 33.20, 33.13 (t each, 2×CH_2, cyclohexyl), 32.26, 31.93 (t each, 2×CH_2), 26.54, 26.24 (t each, 3×CH_2, cyclohexyl). Anal. Calcd. for $C_{19}H_{27}NO_3$: C=71.89, H=8.57, N=4.41; Found: C=71.93, H=8.66, N=4.31.

(4S,5S)-4-(Benzyloxy)methyl-5-butyl-2-oxo-oxazolidine ***24***

M.p. 43–44°C. $[\alpha]_D$=−38.9 (c=0.1, $CHCl_3$). IR (KBr) ν: 3261, 2938, 2858, 1739, 1716, 1220, 1027 cm^{-1}. ^1H NMR δ: 7.40–7.25 (5H, m, C_6H_5), 5.39 (1H, s, NH), 4.51 (2H, s, $C_6H_5CH_2O$), 4.29 (dt, *J*=7.5 and 2×5.0 Hz, 1H, CHO), 3.62 (dt, *J*=7.0 and 2×5.0 Hz, 1H, CHN), 3.45–3.40 (m, 2H, OCH_2), 1.71–1.60 (m, 2H, OC*HCH_2), 1.44–1.33 (m, 4H, 2×CH_2), 0.89 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR δ: 158.74 (s, NHCO), 137.10 (s, C_6H_5), 127.71, 128.41 (2×d each, C_6H_5), 127.95 (d, C_6H_5), 78.95 (d, CHO), 73.51 (t, OCH_2), 71.57 (t, $C_6H_5CH_2O$), 57.11 (d, CHN), 36.31 (t, CH_2), 24.11 (t, CH_2), 19.94 (t, CH_2), 13.71 (q, CH_3). Anal. Calcd. for. $C_{15}H_{21}NO_3$: C=68.42, H=8.04, N=5.32; Found: C=68.70, H=8.13, N=5.44.

(4S,5S)-4-(Benzyloxy)methyl-5-pentyl-2-oxo-oxazolidine ***25***

$[\alpha]_D$=−40.5 (c=0.8, $CHCl_3$). IR (KBr) ν: 3274, 2940, 2858, 1741, 1718, 1384, 1250, 1127 cm^{-1}. ^1H NMR δ: 7.40–7.25 (m, 5H, C_6H_5), 5.44 (s, 1H, NH), 4.54 (s, 2H, $C_6H_5CH_2O$), 4.23 (dt, *J*=7.5 and 2×5.0 Hz, 1H, CHO), 3.65 (dt, *J*=7.0 and 2×5.0 Hz, 1H, CHN), 3.47 (dd, *J*=9.0 and 5.0 Hz, 1H, OC$H_A$$H_B$), 3.43 (dd, *J*=9.0 and 7.0 Hz, 1H, OC$H_A$$H_B$), 1.73 (ddt, *J*=14.0, 2×9.0 and 7.5 Hz, 1H, OC*HC$H_C$$H_D$), 1.63 (ddt, *J*=14.0, 10.0 and 2×5.0 Hz, 1H, OC*HC$H_C$$H_D$), 1.46 (m, 1H, $CH_2CH_EH_F$), 1.46–1.33 (m, 3H, $CH_2CH_EH_F$ and CH_2), 1.31 (m, 2H, CH_2CH_3), 0.89 (t, *J*=7.0 Hz, 3H, CH_3). ^{13}C NMR δ: 158.69 (s, NHCO), 137.29 (s, C_6H_5), 127.76, 128.59 (2×d each, C_6H_5), 128.08 (d, C_6H_5), 79.35 (d, CHO), 73.63 (t, OCH_2), 71.98 (t, $C_6H_5CH_2O$), 57.24 (d, CHN), 34.85 (t, CH_2), 31.88 (t, CH_2), 24.20 (t, CH_2), 22.45 (t, CH_2), 13.94 (q, CH_3). Anal. Calcd. for. $C_{16}H_{23}NO_3$: C=69.29, H=8.36, N=5.05; Found: C=69.31, H=8.44, N=5.16.

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