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Enantiospecific and Diastereoselective Synthesis of 4,4-Disubstituted-3-amino-2-azetidinones, Starting from D-Serine

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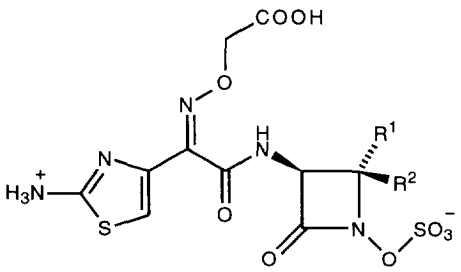
Abstract: A strategy for the preparation of 4,4-disubstituted-3-amino-2-azetidinones, which are useful intermediates for the synthesis of analogues of monosulfactam Tigemonam, was developed. It employs D-serine as chiral starting material and involves, as key steps, the diastereoselective addition of organometal compounds to ketones **9** and the stereospecific cyclization of tertiary alcohols **7** to the β-lactams **6**.

Monocyclic β-lactams characterized by a sulfate moiety at N-1 were first reported in 1982 by Gordon[1] and called monosulfactams. Although they showed high intrinsic antibacterial activity, their practical utilization was initially hampered by chemical and β-lactamase instability of the derivatives monosubstituted at C-4. The introduction of a second substituent at C-4, however, led to compounds stable to both chemical and enzymatic hydrolysis, although still maintaining good antibacterial activity. A member of this class, Tigemonam **1** is currently under clinical evaluation as a potent, orally-active, antibiotic.[2]



1 $R^1, R^2 = Me$
2 $R^1 = Et, R^2 = Me$
3 $R^1 = Me, R^2 = Et$
4 $R^1 = CH_2OCONH_2, R^2 = Me$
5 $R^1 = Me, R^2 = CH_2OCONH_2$

In the course of our research program in the field of monocyclic β-lactam antibiotics,[3] we decided to synthesize analogues of Tigemonam where one of the two diastereotopic methyl groups bonded at C-4 would be replaced by an ethyl group (see **2**,**3**) or by the carbamoyloxymethyl group typical of the important monobactamic antibiotic Carumonam[4] (see **4**,**5**). In order to achieve this goal we chose to explore a new general strategy for the synthesis of 3-amino-2-azetidinones bearing two different substituents at C-4. This approach, depicted in Scheme 1, utilizes D-serine as chiral building block, and was hoped to furnish enantiomerically and

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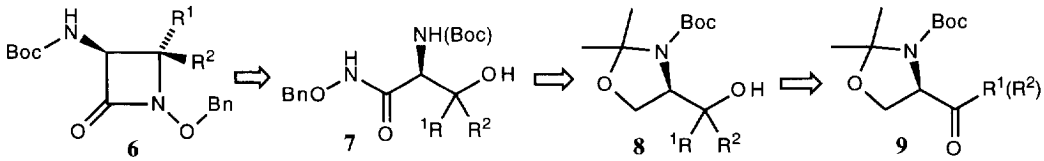
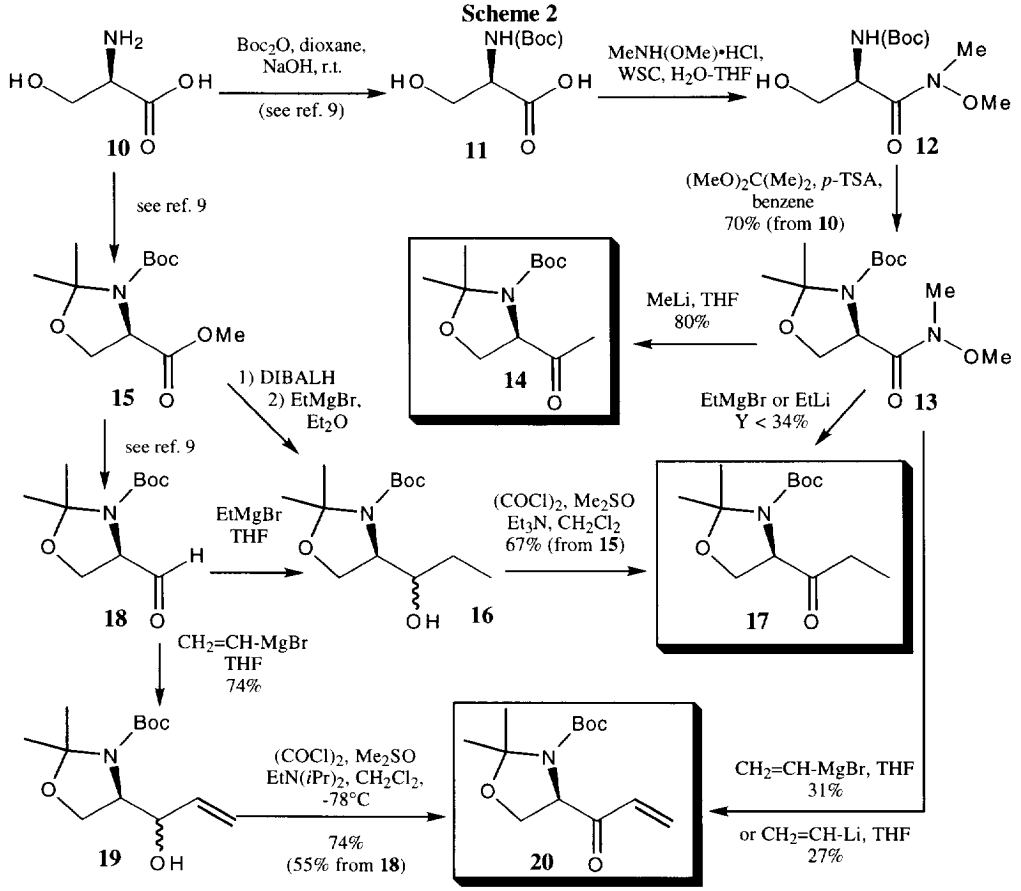
Scheme 1



diastereomerically pure products. The key step is the diastereoselective nucleophilic addition of organometal compounds to ketones of general formula **9**. The resulting protected aminodiols **8** can be then oxidized, converted into the corresponding hydroxamates **7**, and finally cyclized[5,2a,b] to the β-lactams **6.**

The first problem was the choice of the appropriate protecting groups for ketones **9**. Some of these ketones were already reported in the literature.[6-8] However, we reasoned that the protecting groups employed in these papers, were not ideally suited for monosulfactam synthesis. Thus, we decided to explore the enantiospecific preparation of previously unreported ketones **14**, **17**, and **20** (Scheme 2), where the amino and the hydroxy group deriving from serine are fully blocked as the N-*tert*-butoxycarbonyl-N,O-isopropylidene derivative.[9] The vinyl ketone **20** was chosen, since the vinyl group, thanks to the

Scheme 2



ozonolysis/reduction protocol, can be considered synthetically equivalent to a CH_2OH group.

D-Serine **10** was converted in three steps into Weinreb's hydroxamate[10] **13**, whose condensation with methyllithium proceeded smoothly to give the expected methyl ketone **14**. On the contrary, surprisingly, condensation of **13** with ethylmagnesium bromide, ethyllithium, vinylmagnesium bromide, or vinyllithium afforded the desired ketones **17** and **20** in only poor yields. In the case of **17**, this problem was overcome by employing the known,[9] easily available ester **15**. It was transformed "one pot"[11] into the diastereoisomeric mixture of alcohols **16**, which were in turn oxidized to **17** under Swern conditions. **20** was prepared by the same strategy, but in this case we obtained better yields by isolating the intermediate known aldehyde **18**. It is interesting to note that oxidation of the mixture of diols **19** by the usual Swern conditions did not lead to the expected **20**, but, instead, to a monochlorinated ketone. This problem was overcome by employing the modified conditions recently developed by us.[12]

We next examined the addition of organometal compounds to these ketones, in order to obtain both diastereoisomers of tertiary alcohols **21** and **22** (see the Table). Addition of ethyl magnesium bromide to methyl ketone **14** proceeded with excellent diastereoselectivity, giving raise to the *anti*-Felkin diastereoisomer **21a** as major product (entry 1). This result was confirmed by the addition of Me-MgCl to ethyl ketone **17** (entry 11), which also gave the *anti*-Felkin adduct with high asymmetric induction. Obviously, since the order of introduction of the two alkyl groups was in this case reversed, **21b** was in this case obtained. The latter isomer could be also prepared, although with lower yield and diastereoselection, by addition of ethyl-lithium to methyl ketone **14** (entries 2,3).

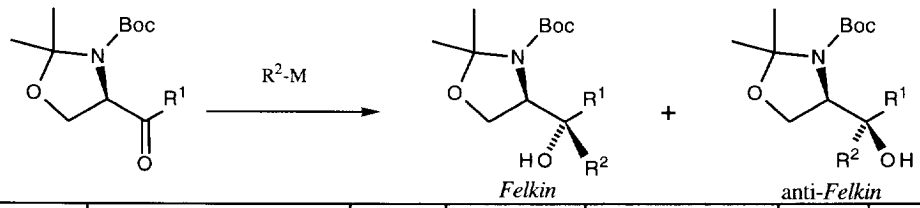
On the contrary, the addition of vinyl magnesium bromide to **14** proceeded with unsatisfactory stereoselection (entries 5,7). In this case, the most efficient methodology involved addition of vinyl-lithium, which gave Felkin adduct **22b** in good yield and with acceptable induction (entry 10). On the other hand, the epimer **22a** was best prepared by addition of a methyl-cerium derivative[13] to vinyl ketone **20** (entry 12). Also in this case the Felkin adduct was prevailing. On the contrary, the reaction with MeLi afforded only a very poor yield of the expected product. Thus, all four compounds **21a,b** and **22a,b** could be efficiently synthesized.

The result of Et-MgBr and Me-MgCl addition to **14** and **17** can be rationalized by a cyclic chelated transition state[14] (Scheme 3), involving the α-nitrogen. The propension of magnesium ion for α-chelation, in addition reactions to α-alkoxy-aldehydes and ketones[14] as well as to protected α-aminoaldehydes, is well known.[15] Moreover, some cases of chelation-controlled additions to the related aldehyde **18** have been reported.[15a,f-h,j] On the other hand, the results obtained with organo-lithium and methylcerium reagent can be explained by taking into account the Felkin model, where the nitrogen plays the role of "large" group.[16,17]

The striking difference in behaviour between Me-MgCl or Et-MgBr and vinyl magnesium bromide is more difficult to explain. However it should be noted that, while addition of vinyl Grignard reagents to monoprotected α-aminoaldehyde (where there is still a hydrogen bonded to nitrogen) affords usually the adducts predicted by an α-chelation control,[15d,e,h] addition to aldehyde **18**[15f,17] or to other N,N-diprotected α-aminoaldehydes[18] is known to afford as main products the isomers predicted by the Felkin model. Although good chelation control in addition to aldehyde **18** was realized by using vinylzinc,[15f] in our case the yield with this organometal reagent was rather poor.

The tertiary alcohols **21a,b** were then converted (Scheme 4) into β-lactams **26a,b**, which are key intermediates for the preparation of Tigemonam analogues **2** and **3**. A critical step in this sequence was the oxidation of diols **23a,b** to the corresponding carboxylic acids **24a,b**. Many known methods[19] for carrying

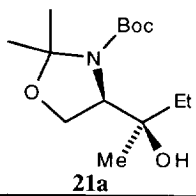
Table. Addition of organometal compounds to ketones **14**, **17**, and **20**.



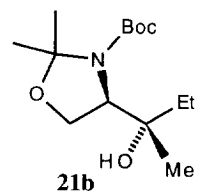
Felkin anti-*Felkin*

Entry	Ketone	Reagent	Major Product	Solvent	Temp.	Yield[a]	diast. ratio Felkin : *anti*-Felkin
1	**14**	Et-MgBr	**21a**	THF	-78°C → -20°C	76%	10 : 90[b]
2	**14**	Et-Li	**21b**	THF	-78°C → -10°C	38%	77 : 23[b]
3	**14**	Et-Li	**21b**	Et_2O	-78°C → -25°C	33%	74 : 26[b]
4	**14**	Et-MgBr / $CeCl_3$	**21a**	THF	-78°C → -10°C	48%	40 : 60[b]
5	**14**	CH_2=CH-MgBr	**22a**	THF	-78°C → -40°C	55%	40 : 60[c]
6	**14**	CH_2=CH-MgBr	**22b**	Et_2O	-78°C → -40°C	58%	57 : 43[c]
7	**14**	CH_2=CH-MgBr	**22b**	THF-HMPT	-78°C → r.t.	9%	51 : 49[c]
8	**14**	CH_2=CH-MgBr / $CeCl_3$	**22b**	THF	-78°C	68%	66 : 34[c]
9	**14**	CH_2=CH-MgBr / $CeCl_3$	**22a**	Et_2O	-78°C	64%	36 : 64[c]
10	**14**	CH_2=CH-Li	**22b**	Et_2O	-78°C	89%	80 : 20[c]
11	**17**	Me-MgCl	**21b**	THF	-78°C → -10°C	90%	6 : 94[b]
12	**20**	Me-MgCl / $CeCl_3$	**22a**	THF	-78°C → 0°C	65%	88 : 12[c]

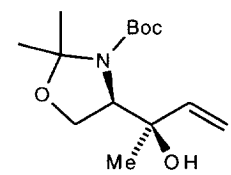
[a] Isolated yield of the diastereomeric mixture. [b] Determined by chromatographic separation and weighing of the two isomers. [c] Determined by ^1H n.m.r.



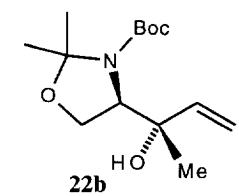
21a



21b



22a

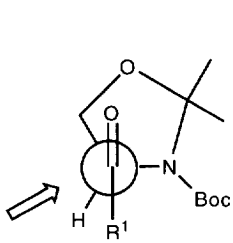


22b

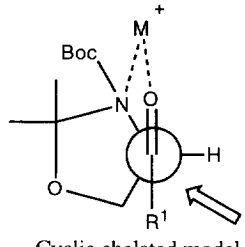
out this transformation were found to be inefficient. We finally found that best results could be obtained by Jones oxidation under very carefully controlled conditions (see the experimental section). Cyclization of the hydroxamates **25a,b** to the azetidinones **26a,b** were then performed *via* activation of the tertiary alcohol as sulfate. This method, developed by Squibb chemists,[2a] was designed in order to avoid rearrangement reactions.[2b]

Scheme 5 shows the conversion of allylic tertiary alcohols **22a,b** into the potential intermediates for the synthesis of tigemonam-carumonam hybrids **4** and **5**. Ozonolysis-reduction furnished the diols **27**, which were regioselectively converted into the urethanes **28**.[20] Deblocking of the *iso* propylidene group gave diols **29**. Also in this case oxidation to the carboxylic acids **30** was troublesome. Although **30a,b** could be obtained by Jones oxidation, the yields were unsatisfactory (< 40%). After various efforts we found that

Scheme 3



Felkin model



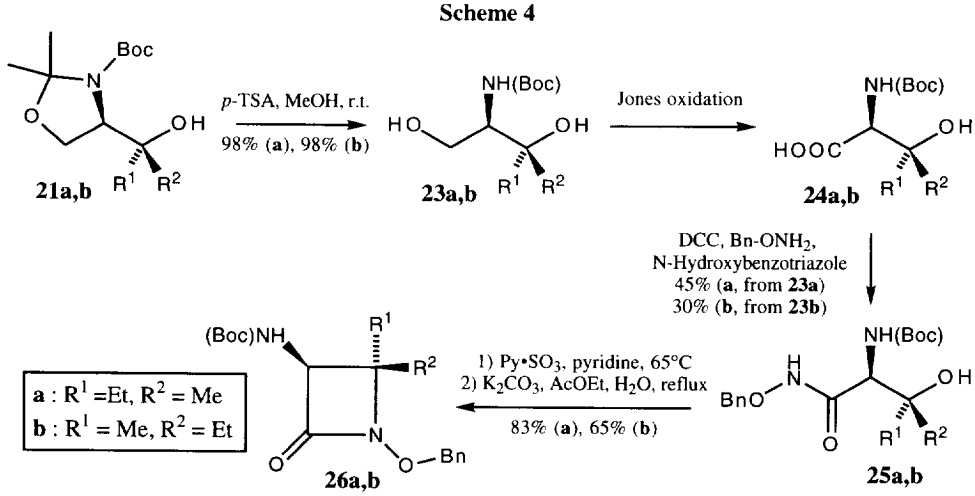
Cyclic chelated model
(leading to *anti*-Felkin products)

good yields could be achieved by using stoichiometric TEMPO$^+$ Cl$^-$ for the oxidation to the aldehyde,[21,22] followed by *in situ* treatment with $NaClO_2$.[23] The use of catalytic TEMPO together with NaClO under phase-transfer conditions[24] gave considerably lower yields. After conversion into O-benzyl hydroxamates **31a,b**, cyclization to the β-lactam was attempted with the previously employed methodology, involving hydroxyl activation *via* sulfate formation. In this case, however, we could not obtain the desired azetidinones **32**. We feel that in this case the presence of the carbamoyl group, which can also react with SO_3•pyridine complex may prevent the desired reaction. Thus we returned to the classical Mitsunobu conditions (DEAD, PPh_3),[5] which afforded **32a** in moderate yield. Interestingly we did not detect any other β-lactamic by-products, indicating that in this case, the rearrangement observed by Slusarchyk *et al.* during Tigemonam synthesis did not take place. Moreover, the cyclization was completely stereospecific. Also starting from the epimer **31b** the outcome was similar. However in this case better yields were achieved with the system CCl_4-PPh_3.[5]

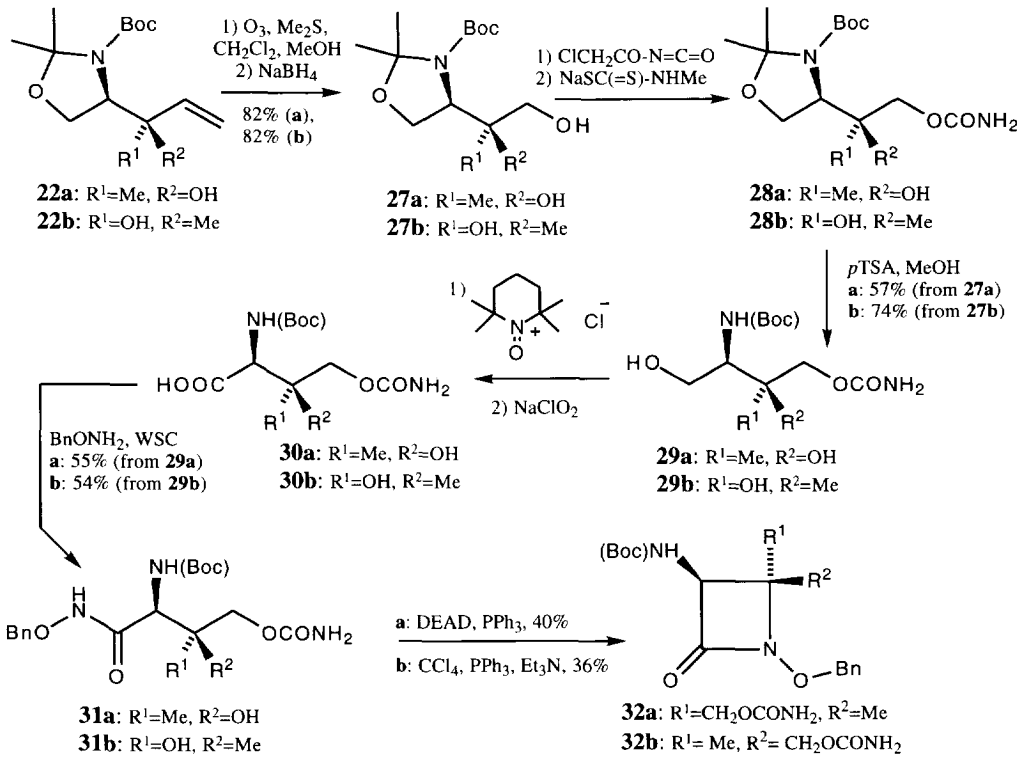
The relative configuration of **32a,b** was established by NOE difference experiments (see the Experimental section), which showed, in **32b**, a 14% NOE enhancement of the hydrogen bonded to C-3 on irradiation of the C-4 bonded methyl. The relative configuration of all their precursors **22a,b** and **27a,b**-**31a,b** was deduced on the reasonable assumption that cyclization of **31** to **32** proceeds with inversion of configuration.[25] Finally **22a,b** and **21a,b** were mutually correlated by hydrogenation of the formers.

In conclusion, we have developed a new entry into the class of 3-amino-2-azetidinones bearing two different substituents at C-4. We believe that this strategy can be easily extended to other derivatives of this family. Compounds **26a,b** and **32a,b** could be transformed, by following a route similar to that described for Tigemonam **1**,[2] into analogues **2**-**5**. These transformations, as well as the exploitation of the biological activity of these analogues are in progress.

Scheme 4



Scheme 5



EXPERIMENTAL

N.m.r. spectra were recorded on a Varian Gemini 200 spectrometer. Tetramethylsilane was used as internal standard for spectra in $CDCl_3$, and d-6 DMSO. In ^{13}C n.m.r. the assignment was aided by DEPT experiments. I.r. spectra were recorded on a Perkin-Elmer 881 instrument as $CHCl_3$ solutions. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Organic extracts were dried over Na_2SO_4 and filtered before removal of solvent under reduced pressure. All reactions employing dry solvents were run under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried over K/benzophenone; toluene, CH_2Cl_2, dimethylformamide (DMF), acetone, and acetonitrile were doubly dried over 4 Å molecular sieves.[26] Dry diethyl ether and dry methanol were purchased from Fluka. Chromatographies were carried out on 220-400 mesh silica gel. Thin layer chromatographies were carried out on 0.25 mm silica gel F 254 plates (Merck). Spots were detected by spraying with an aqueous 35% HBr solution, followed by heating, immersion in a solution of 0.3 g ninhydrin, 100 ml *n* BuOH and 3 ml AcOH, and finally heating. PE = petroleum ether 40-60°C.

(*R*) Methyl N-methyl-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanohydroxamate 12. A solution of D-serine (15.81g, 150.4 mmol) in 1N NaOH (300 ml), was treated, at 0°C, with a solution of di-*tert*-butyl dicarbonate (41.5 ml, 180.5 mmol) in dioxane (140 ml).[9] The mixture was stirred at 0°C for 30 min. at r.t. for 3 days. During this time, the pH was, when necessary, adjusted to 9 by additions of 1N NaOH. The mixture was concentrated to about half volume, cooled to 0°C, and carefully treated with 1M H_2SO_4 (≈150 ml) until pH ≈ 2-3. Saturation with solid NaCl, and extraction with AcOEt (6 x 150 ml) gave, after

evaporation, crude **11** as a thick oil (31.8 g). It was taken up in THF (140 ml), and treated with a solution of N-methyl-O-methyl hydroxylamine hydrochloride (97%)(17.40 g, 173 mmol) in H_2O (140 ml). The pH was brought to 4.5 by addition of 1N NaOH. While cooling in an ice bath, and maintaining the pH at 4.5 by addition of 1N NaOH, a solution of N-(3-dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride (WSC) (34.6 g, 180 mmol) in H_2O (350 ml) was slowly added during 45 min. After stirring for 3.5 h at r.t. tthe solution was saturated with NaCl, and extracted with AcOEt (4 x 250 ml), and with AcOEt / MeOH 9:1 (3 x 100 ml). The reunited organic extracts gave, upon evaporation, a crude solid (33.3 g), which was crystallized from AcOEt / PE to give pure **12** as a white solid (26.83 g). The mother liquors where chromatographed (AcOEt / PE 8:2 → 100:0) to give further 0.80 g of **12**. Yield= 27.63 g, 74%. P.f.: 118.5°-119.5°C. R_f: 0.41 (AcOEt). Found: C, 48.6; H, 8.4; N, 11.2%. Calculated for $C_{10}H_{20}N_2O_5$: C, 48.37; H, 8.12; N, 11.28%. $[\alpha]_D$= -1.4° (c 2.6, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): 5.59 [1 H, broad s, N*H*]; 4.86-4.72 [1 H, m, mc = 4.79, C*H*-NH]; 3.75 [2 H, d, CH_2OH, J= 4.8 Hz.]; 3.72 [3 H, s, OCH_3]; 3.17 [3 H, s, N-CH_3]; 1.38 [9 H, s, $(CH_3)_3C$]. I.r. ($CHCl_3$): ν_{max}: 3430, 1700, 1655, 1480, 1390, 1370, 1160 cm^{-1}.

(*R*) Methyl N-methyl-[3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-oxazolidin]carbohydroxamate 13. A suspension of **12** (27.5 g, 111 mmol) in dry benzene (600 ml) was treated with 2,2-dimethoxypropane (40.9 ml, 332 mmol) and *p*-toluensulfonic acid hydrate (845 mg, 4.44 mmol). The mixture was refluxed for 30 min., and then the MeOH-benzene azeotrope was slowly distilled during 1h (≈ 200 ml). Other 15 ml of 2,2-dimethoxypropane were added and the slow distillation was continued for 3 h more. After cooling, the solution was poured into ice-water and neutralized with 5% aqueous $NaHCO_3$. Extraction with Et_2O, followed by washing of the organic extracts with saturated brine gave crude **13** (34 g), which was chromatogtraphed through 350 g of silica gel (AcOEt / PE 2:8 → 100:0) to give pure **13** as a white solid (30.23, 94%). P. f.= 65.7°-67.5°. Found: C, 54.25; H, 8.4; N, 9.6%. calculated for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72%. $[\alpha]_D$= +37.1° (c 2.36, $CHCl_3$). ^1H n.m.r. (DMSO, 120°C):[27] δ 4.76 [1 H, dd, C*H*-N, J= 7.4 and 3.5 Hz.]; 4.20 [1 H, dd, OC*H*H, J= 9.1 and 7.4 Hz.]; 3.82 [1 H, dd, OC*H*H, J= 9.1 and 3.5 Hz.]; 3.70 [3 H, s, CH_3ON]; 3.15 [3 H, s, CH_3-N]; 1.58 and 1.49 [2 x 3 H, 2s, CH_3-C-CH_3]; 1.41 [9 H, s, $(CH_3)_3C$]. I.r. ($CHCl_3$): ν_{max}: 1679, 1450, 1379 cm^{-1}.

(*R*) 4-Acetyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-oxazolidine 14. A solution of **13** (15.19 g, 52.7 mmol) in dry THF (150 ml) was cooled to -78°C, and slowly treated with a 1.6 M solution of MeLi in Et_2O (65.6 ml, 105 mmol). After stirring at -65°C for 1h, the reaction was quenched by addition of saturated aqueous NH_4Cl (100 ml). After warming to r.t., and diluting with H_2O, the mixture was extracted with Et_2O to give, after chromatography (Pe / AcOEt 9:1 → 0:100), pure **14** as an oil (9.26 g, 72%). R_f: 0.71 (PE / AcOEt 3:7); 0.32 (PE / Et_2O 6:4). Found: C, 58.9; H, 8.5; N, 5.55%. Calculated for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76%. $[\alpha]_D$= + 55.7° (c 2.34, $CHCl_3$). ^1H n.m.r. (d-6 DMSO, 120°C):[27] δ 4.40 [1 H, dd, C*H*-N, J= 3.4 and 7.5 Hz.]; 4.15 [1 H, dd, C*H*HO, J= 9.3 and 7.5 Hz.]; 3.91 [1 H, dd, C*H*HO, J= 9.3 and 3.4 Hz.]; 2.13 [3 H, s, CH_3-C=O]; 1.59 and 1.48 [2s, 2 x 3H, CH_3-C-CH_3]; 1.42 [9 H, s, $(CH_3)_3C$].

(*R*) 3-(*tert*-Butoxycarbonyl)-2,2-dimethyl-4-propanoyloxazolidine 17. A solution of ester **15**[9] (14.82 g, 57.15 mmol) in dry toluene (200 ml) was cooled to -78°C, and slowly treated with a 1M solution of diisobutylaluminium hydride in toluene (60 ml, 60 mmol). After stirring for 30 min. at this temperature, the mixture was treated with a 3M solution of EtMgBr in Et_2O (57.15 ml, 171.45 mmol). The temperature was allowed to rise to r.t. during 2h. After further stirring for 3h, the reaction was cooled to 0°C, and carefully quenched with saturated aqueous NH_4Cl (200 ml). The resulting mixture was transferred to an Erlenmayer flask, diluted with Et_2O (100 ml), treated with saturated aqueous Rochelle salt (Na,K tartrate) (250 ml), and stirred overnight. The phases were separated (and the aqueous one reextracted twice with Et_2O). The reunited organic extracts gave a crude product, which was purified by chromatography (PE / AcOEt 8:2 → 4:6) to give the pure diastereomeric mixture of **16** (11.44 g, 44.1 mmol, 77%)(R_f: 0.32, PE / AcOEt 7:3). A 2.93M solution of $(COCl)_2$ in CH_2Cl_2 (37.6 ml, 110 mmol) was diluted with 150 ml of dry CH_2Cl_2, cooled

to -78°C, and treated with a solution of dimethyl sulfoxide (12.52 ml, 176 mmol) in CH_2Cl_2 (25 ml). After 15 min., a solution of the above obtained **16** in CH_2Cl_2 (30 ml) was added. After 15 min., triethylamine (36.9 ml, 265 mmol) was added, and the temperature allowed to rise to -20°C during 1h. Quenching with saturated aqueous NH_4Cl (250 ml), extraction with Et_2O, and usual treatment, gave a crude product which, upon chromatography (PE / AcOEt 9:1 → 8:2) afforded pure **17** as an oil (9.85 g, 67% from **15**). R*f*: 0.56 (PE / AcOEt 7:3); 0.56 (PE / Et_2O / CH_2Cl_2 40 : 40: 20). Found: C, 60.9; H, 9.2; N, 5.35%. Calculated for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44%. $[\alpha]_D$= + 62.6° (c 1.77, $CHCl_3$). ^1H n.m.r. (d-6 DMSO, 120°C)[27]: δ 4.46 [1 H, dd, C*H*-N, J= 3.3 and 7.6 Hz.]; 4.15 [1 H, dd, C*H*H-O, J= 7.6 and 9.2 Hz.]; 3.87 [1 H, dd, C*H*H-O, J= 3.3 Hz. and 9.2 Hz.]; 2.65-2.38 [2 H, m, CH_2-CH_3]; 1.58 and 1.47 [2 x 3H, 2 s, $(CH_3)_2C$]; 1.40 [9 H, s, $(CH_3)_3C$]; 1.00 [3 H, t, CH_3CH_2, J= 7.3 Hz.].

***(R)* 3-(*tert*-butoxycarbonyl)-2,2-dimethyl-4-propenoyloxazolidine 20.** A solution of aldehyde **18**[9] (3.09g, 13.48 mmol) in dry THF (60 ml) was cooled to -78°C, and treated with 1M vinylmagnesium bromide in THF (27 ml, 27 mmol). The temperature was allowed to rise to -50°C during 2h. After quenching with saturated aqueous NH_4Cl, and extraction with Et_2O, the crude product was purified by chromatography (PE / AcOEt 75:25 → 7:3) to give the pure inseparable mixture of alcohols **19** (2.57 g, 9.99 mmol, 74%)(R_f: 0.46, PE / AcOEt 7:3). A 2.3 M solution of $(COCl)_2$ (10.87 ml, 25 mmol) was diluted with dry CH_2Cl_2 (50 ml), and treated, at -78°C, with a solution of dimethyl sulfoxide (2.84 ml, 40 mmol) in CH_2Cl_2 (10 ml). After 10 min., a solution of the above obtained alcohols **19** in CH_2Cl_2 (10 ml) was added. After 10 min., $EtN(iPr)_2$ (13.94 ml, 80 mmol) was added, and the mixture stirred at -78°C for 1h. The temperature was allowed to rise to -45°C during 30 min. and the reaction quenched with 5% aqueous NaH_2PO_4, and extracted with Et_2O. The crude product was purified by chromatography (PE / AcOEt 85 : 15) to give pure **20** as an oil (1.89 g, 74%, 55% from **18**).R*f*: 0.42 (PE / AcOEt 8:2), 0.42 (PE / Et_2O / CH_2Cl_2 6:2:2). Found: C, 61.0; H, 8.4; N, 5.4%. Calculated for $C_{13}H_{21}O_4N$: C, 61.16; H, 8.29; N, 5.49%. $[\alpha]_D$= + 54.1° (c 1.21, $CHCl_3$). ^1H n.m.r. (d-6 DMSO, 110°C)[27]: δ 6.56 [1 H, dd, C*H*=CH_2, J= 10.6 and 17.5 Hz.]; 6.27 [1 H, dd, CH=C*H*H, J= 1.4 and 17.5 Hz.]; 5.92 [1 H, dd, CH=C*H*H, J= 1.4 and 10.6 Hz.]; 4.78 [1 H, dd, C*H*-N, J= 3.4 and 7.6 Hz.]; 4.21 [1 H, dd, C*H*H-O, J= 7.6 and 9.3 Hz.]; 3.83 [1 H, dd, C*H*H-O, J= 3.4 and 9.3 Hz.]; 1.58 and 1.49 [2 x 3H, 2 s, $(CH_3)_2C$]; 1.38 [9 H, s, $(CH_3)_3C$].

***(4R,2'R)* 4-(2-Hydroxy-2-butyl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine 21a.** A solution of **14** (8.368 g, 34.39 mmol) in dry THF (160 ml) was cooled to -78°C, and treated slowly with a 3 M solution of EtMgBr in Et_2O (30 ml, 90.0 mmol). The temperature was allowed to rise to -20°C during 3h. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with Et_2O. The organic phase was washed with saturated brine, and chromatographed (PE / Et_2O 9:1 → 1:1) to give pure **21a** as an oil (6.36 g, 68%). This chromatography gave also 732 mg of a 55:45 (n.m.r.) inseparable mixture of **21b** and unreacted **14** . R_f: 0.45 (PE / Et_2O / CH_2Cl_2 50:25:25); 0.45 (PE / Et_2O 6:4). Found: C, 61.82; H, 10.17; N, 5.32%. Calculated for $C_{14}H_{27}NO_4$: C, 61.51; H, 9.96; N, 5.12%. $[\alpha]_D$= +33.8° (c 1.16, $CHCl_3$). ^1H n.m.r. (d-6 DMSO, 120°C):[27] 4.32 [1 H, broad s, C*H*-N]; 3.93 [2 H, s, CH_2O]; 1.55 [3 H, s, (CH_3)-C-CH_3]; 1.47 [12 H, s, $(CH_3)_3C$ and CH_3-C-CH_3]; 1.50-1.35 [2 H, m, CH_2-CH_3]; 1.05 [3 H, s, CH_3-C-Et]; 0.89 [3 H, t, CH_3-CH_2, J= 7.4 Hz.].

***(4R,2'S)* 4-(2-Hydroxy-2-butyl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine 21b.** A solution of ethyl ketone **17** (4.733 g, 18.39 mmol) in dry THF (100 ml) was cooled to -78°C, and treated with 3M CH_3MgCl in THF (18.4 ml, 55.2 mmol). After 15 min. the temperature was allowed to rise slowly to 0°C during 3h. The mixture was quenched with saturated aqueous NH_4Cl, extracted with Et_2O and purified by chromatography (PE / AcOEt 9:1 → 8:2) to give pure **21b** as an oil (4.29 g, 85%). R_f: 0.37 (PE / Et_2O / CH_2Cl_2 50:25:25); 0.32 (PE / Et_2O 6:4). $[\alpha]_D$= + 24.6 (c 1.77, $CHCl_3$). ^1H n.m.r. (d-6 DMSO, 100°C):[27] δ 4.20-4.07 (1 H, m, C*H*-N]; 3.94-3.80 [2 H, m, CH_2O]; 1.53 [3 H, s, CH_3-C-CH_3]; 1.44 [12 H, s, $(CH_3)_3C$ and CH_3-C-CH_3]; 1.48-1.35 [2 H, m, CH_2CH_3]; 1.01 [3 H, s, CH_3-C]; 0.86 [3 H, t, CH_3-CH_2, J= 7.4 Hz.].

(4R,2'R) **4-(2-Hydroxybut-3-en-2-yl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine 22a**. A suspension of anhydrous $CeCl_3$ [previously dried as described in ref. 13 starting from $CeCl_3 \cdot 6H_2O$ (3.64 g, 10.3 mmol)] in dry THF (40 ml) was cooled to 0°C, and treated with a 3M THF solution of Me-MgCl (3.4 ml, 10.2 mmol). After 1 h, the mixture was cooled to -78°C, and treated with a solution of **20** (874 mg, 3.423 mmol) in THF (5 ml). The temperature was allowed to rise to 0°C during 2h, and the reaction was quenched with saturated aqueous NH_4Cl, and filtered through a celite cake, washing the residue with AcOEt. The phases were separated and the aqueous one rextracted twice with AcOEt. The reunited organic extracts afforded, after silica gel chromatography (PE / AcOEt 85:15), the pure inseparable mixture of **22a** and **22b** (603 mg, 65%). The diastereomeric ratio of 88:12 was determined by ^1H n.m.r., *via* integration of the CH_3-C singlets. R_f: 0.42 (PE / AcOEt 8:2), 0.33 (PE / Et_2O / CH_2Cl_2 6:2:2). Found: C, 62.1; H, 9.1; N, 5.0%. Calculated for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16%. ^1H n.m.r. (d-6 DMSO, 110°C):[27] 5.95 [1 H, dd, C*H*=CH_2, J= 10.7 and 17.3 Hz.]; 5.24 [1 H, dd, CH=C*H*H, J= 2.0 and 17.3 Hz.]; 5.01 [1 H, dd, CH=C*H*H, J= 2.0 and 10.7 Hz.]; 4.63 [1 H, broad s, O*H*]; 4.00-3.80 [3 H, m, CH_2O and C*H*-N]; 1.53 and 1.43 [2 x 3H, 2s, $(CH_3)_2C$]; 1.45 [9 H, s, $(CH_3)_3C$]; 1.19 [3 H, s, CH_3-C].

(4R,2'R) **4-(2-Hydroxybut-3-en-2-yl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidine 22b.** A solution of **14** (1.091 g, 4.48 mol) in dry Et_2O (20 ml) was cooled to -78°C, and treated with a 1.2 M solution of vinyllithium[28] in Et_2O (15 ml, 18.0 mmol). After stirring for 1h at the same temperature, the reaction was quenched with saturated NH_4Cl, and extracted with AcOEt. Chromatography as for **22a** gave a 80:20 mixture of unseparable **22b** and **22a** (determined by ^1H n.m.r.)(1.09 g, 89%). ^1H n.m.r. (d-6 DMSO, 110°C):[27] 5.93 [1 H, dd, C*H*=CH_2, J= 10.7 and 17.2 Hz.]; 5.21 [1 H, dd, CH=C*H*H, J= 2.0 and 17.2 Hz.]; 4.99 [1 H, dd, CH=C*H*H, J= 2.0 and 10.7 Hz.]; 4.63 [1 H, broad s, O*H*]; 4.00-3.80 [3 H, m, CH_2O and C*H*-N]; 1.53 [3 H, s, CH_3-C-CH_3]; 1.45 [12 H, s, CH_3-C-CH_3 and $(CH_3)_3C$]; 1.15 [3 H, s, CH_3-C].

(2R,3R) **2-[(*tert*-Butoxycarbonyl)amino]-3-methyl-1,3-pentanediol 23a**. A solution of **21a** (5.81 g, 21.25 mmol) in dry MeOH (180 ml) was treated with *p*-toluenesulfonic acid hydrate (404 mg, 2.12 mmol). The solution was stirred for 30 min. at r.t., quenched with saturated aqueous $NaHCO_3$, and concentrated at reduced pressure in order to remove most methanol. The concentrated mixture was diluted with saturated brine and extracted with AcOEt. The organic extracts were washed with saturated brine, evaporated to dryness, and chromatographed to give pure **23a** as a white solid (4.85 g, 98%). R_f: 0.45 (PE / AcOEt 3:7). Found: C, 56.9; H, 9.9; N, 6.2%. Calculated for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00%. P.f.= 108°-111°C. $[\alpha]_D$= -25.7° (c 1.25, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 5.48 [1 H, d, N*H*, J= 8.7 Hz.]; 3.99 and 3.82 [2 H, AB part of an ABX system, CH_2OH, J_{AB}= 11.4; J_{AX} and J_{BX}= 3.3 and 2.8 Hz.]; 3.60-3.40 [1 H, m, C*H*-N]; 2.50 [2 H, broad s, O*H*]; 1.70-1.40 [2 H, m, CH_2-CH_3]; 1.46 [9 H, s, $(CH_3)_3C$]; 1.28 [3 H, s, CH_3-C-Et]; 0.90 [3 H, t, CH_3-CH_2, J= 7.5 Hz.]. I.r. ($CHCl_3$): δ 3680, 3335, 1655, 1455, 1368, 1164, 1060 cm^{-1}.

(2R,3S) **2-[(*tert*-Butoxycarbonyl)amino]-3-methyl-1,3-pentanediol 23b**. It was prepared from **21b** (4.69 g) in 98% yield, by following the same procedure used for **23a**. R_f: 0.45 (PE / AcOEt 3:7). Found: C, 56.9; H, 9.8; N, 5.95%. Calculated for $C_{11}H_{23}NO_4$: C, 56.63; H, 9.94; N, 6.00. $[\alpha]_D$= -22.8° (c 1.66, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 5.44 [1 H, d, N*H*, J= 8.2 Hz.]; 4.00 and 3.79 [2 H, AB part of an ABX system, CH_2OH, J_{AB}= 11.3 Hz. J_{AX} and J_{BX}= 3.3 and 3.2 Hz.]; 3.60-3.45 [1 H, m, C*H*-N]; 1.80-1.50 [2 H, m, CH_2-CH_3]; 1.46 [9 H, s, $(CH_3)_3C$]; 1.18 [3 H, s, CH_3-C]; 0.95 [3 H, t, CH_3-CH_2, J=7.5 Hz.].

(2S,3R) **Benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-3-methyl-1,3-pentanohydroxamate 25a.** A solution of **23a** (3.38 g, 14.68 mmol) in dry acetone (100 ml) was cooled to -15°C, and treated with 390 drops (from a Pasteur pipette) of Jones reagent (prepared from 10g CrO_3, 8.6 ml of 96% H_2SO_4, 14 ml of H_2O, and brought up to 40 ml).[29] After stirring at the same temperature for 2h and 45 min. (an excess of Cr (VI) was still present, as evidenced by the green-orange colour), the reaction was quenched with 5% $(NH_4)H_2PO_4$. After saturation with NaCl, the aqueous phase was extracted with CH_2Cl_2 / MeOH 9:1. The

organic extracts were washed with saturated brine containing some 10% Na_2SO_3 solution. Evaporation and chromatography (AcOEt / PE / AcOH 48.5:48.5:3) gave slightly impure **24a** (R_f: 0.24, PE / AcOEt / AcOH 49:49:2)(2.213 g). It was taken up in dry THF (25 ml), treated with N-hydroxybenzotriazole (1.476 g, 10.92 mmol), and cooled to -15°C. A solution of dicyclohexylcarbodiimide (2.253 g, 10.92 mmol) in THF (18 ml) was slowly added. After stirring for 1.5 h at 0°C, a solution of O-benzylhydroxylamine (prepared from 1.869 g of its hydrochloride, 11.71 mmol, by dissolving it in H_2O, treating with 1N NaOH to pH 10, extracting with Et_2O, washing the organic extract with saturated NaCl, and evaporating to dryness), in THF (22 ml) was introduced. After stirring for 1h at 0°C, the suspension was concentrated under vacuum, diluted with AcOEt, and filtered to remove most dicyclohexylurea. The filtrate was washed with saturated NaCl acidified to pH 1 by HCl. Evaporation to dryness and chromatography (PE / Et_2O 1:1 → 3:7) gave pure **25a** as a white foam (2.411 g, 47%). R_f: 0.41 (PE / AcOEt / MeOH 63 : 27 : 10). Found: C, 61.15; H, 7.9; N, 8.05%. Calculated for $C_{18}H_{28}N_2O_5$: C, 61.34; H, 8.01; N, 7.95%. $[\alpha]_D$= -38.9° (c 1.38, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 9.00 [1 H, s, N*H*-O]; 7.45-7.32 [5 H, m, aromatics]; 5.54 [1 H, d, N*H*Boc, J= 9.0 Hz.]; 4.91 [2 H, s, CH_2Ph]; 3.90 [1 H, s, O*H*]; 3.68 [1 H, d, C*H*-NH, J= 9.0 Hz.]; 1.58-1.34 [2 H, m, CH_2CH$_3$]; 1.43 [9 H, s, (CH_3)$_3$C]; 1.21 [3 H, s, CH_3CEt]; 0.84 [3 H, t, CH_3CH$_2$, J= 7.5 Hz.]. I.r. ($CHCl_3$): ν_{max} 3427, 1691, 1485, 1368, 1159 cm^{-1}.

(*2S,3S*) **Benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-hydroxy-3-methyl-1,3-pentanohydroxamate 25b.** It was prepared from **23b** (3.97 g) in 30% overall yield, following the same procedure utilized for **25a** (but this time without chromatographing the intermediate crude acid **24b**. R_f: 0.41 (PE / AcOEt / MeOH 63 : 27 : 10). $[\alpha]_D$= -48° (c= 1.4, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 9.25 [1 H, broad s, N*H*-O]; 7.37 [5 H, s, aromatics]; 5.61 [1 H, d, N*H*(Boc), J= 9.1 Hz.]; 4.90 [2 H, s, CH_2Ph]; 3.71 [1 H, d, C*H*-N, J= 9.1 Hz.]; 1.80 [1 H, broad s, O*H*]; 1.70-1.30 [2 H, m, CH_2-CH$_3$]; 1.43 [9 H, s, (CH_3)$_3$C]; 1.10 [3 H, s, CH_3-C]; 0.96 [3 H, t, CH_3-CH$_2$, J= 7.5 Hz.].

(*3S,4S*) **1-(Benzyloxy)-3-[(*tert*-butoxycarbonyl)amino]-4-ethyl-4-methyl-2-azetidinone 26a.** A solution of **25a** (2.380 g, 6.75 mmol) in dry pyridine (28 ml), containing 100 mg of powdered 4Å molecular sieves, was treated with pyridine•SO_3 complex (2.15 g, 13.51 mmol). The mixture was immediately warmed to 65°C and stirred for 3h at this temperature. A second portion of Py•SO_3 was added (1.50 g) followed by a third one after 1.5 h (1.11 g). After an overall reaction time of 6h, the solution was evaporated to dryness under reduced pressure. It was taken up with CH_3CN and evaporated again for three times. Finally it was taken up with benzene and evaporated to give a crude product which was stripped at 10^{-1} mbar for 15 min. It was taken up in AcOEt (45 ml), and H_2O (12 ml), and treated at 0°C with solid K_2CO_3 (5.784 g, 41.85 mmol). The biphasic system was refluxed under vigorous stirring for 2h. The mixture was cooled, diluted with H_2O, and extracted with AcOEt. The organic extracts were washed with saturated NaCl, evaporated, and chromatographed (PE / Et_2O 7:3 → 1:1) to give pure **26a** (1.879 g, 83%). R_f: 0.62 (PE / Et_2O 4:6), 0.34 (PE / Et_2O 6:4). Found: C, 64.8; H, 7.9; N, 8.2%. Calculated for $C_{18}H_{26}N_2O_5$: C, 64.65; H, 7.84; N, 8.38%. $[\alpha]_D$= + 11.0° (c 2.33, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 7.38 [5 H, s, aromatics]; 4.97 [2 H, s, CH_2Ph]; 5.00-4.90 [1 H, broad m, N*H*]; 4.39 [1 H, d, C*H*-NH, J= 7.4 Hz.]; 1.82-1.58 [2 H, m, CH_2-CH$_3$]; 1.43 [9 H, s, (CH_3)$_3$C]; 1.06 [3 H, s, CH_3C-Et]; 0.98 [3 H, t, CH_3-CH$_2$, J= 7.5 Hz.]. I.r. ($CHCl_3$): ν_{max} 1768, 1710, 1490, 1370, 1160 cm^{-1}.

(*3S,4R*) **1-(Benzyloxy)-3-[(*tert*-butoxycarbonyl)amino]-4-ethyl-4-methyl-2-azetidinone 26b.** It was prepared from **25b** (1.81 g) in 65% overall yield, by following the same procedure employed for **25a**. R_f: 0.62 (PE / Et_2O 4:6), 0.34 (PE / Et_2O 6:4). Found: C, 64.5; H, 7.8; N, 8.2%. Calculated for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38%. $[\alpha]_D$= + 43.2° (c 1.63, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 7.38 [5 H, s, aromatics]; 5.10 [1 H, d, N*H*, J= 7.0 Hz.]; 4.99 [2 H, s, CH_2Ph]; 4.35 [1 H, d, C*H*-N, J= 3.8 Hz.]; 1.70-1.40 [2 H, m, CH_2-CH$_3$]; 1.43 [9 H, s, (CH_3)$_3$C]; 1.29 [3 H, s, CH_3-C]; 0.92 [3 H, t, CH_3-CH$_2$, J= 7.5 Hz.]. I.r. ($CHCl_3$): ν_{max} 1768, 1712 cm^{-1}.

(*4R,2'S*) and (*4R,2'R*) 4-(1,2-Dihydroxy-2-propyl)-2,2-dimethyl-3-(*tert*-butoxycarbonyl)-oxazolidines 27a and 27b. A solution of the above obtained 88:12 mixture of **22a** and **22b** (2.30g, 9.69 mmol) in dry CH_2Cl_2 (60 ml) and dry MeOH (100 ml) was cooled to -78°C, and ozonized until the grey-blue colour persisted. Dimethyl sulfide (1 ml) was added, followed by solid $NaBH_4$ (1.47g, 39 mmol). The temperature was allowed to rise to 0°C during 2h. A tlc showed the presence of some aldehyde, and so other 700 mg of $NaBH_4$ were added. After stirring for 30 min., the reaction was quenched with saturated aqueous NH_4Cl. Most organic solvents were evaporated, and the residue diluted with H_2O and extracted with Et_2O. The crude product gave, after chromatography (PE / AcOEt 6:4), pure **27a** as a foam (1.68 g, 72%), and pure **27b** (186 mg, 8%). By the same procedure, the 80:20 mixture of **22b** and **22a** gave **27b** as a white solid (66%) and **27a** (16%). R_f: **27a**: 0.35; **27b**: 0.44 (PE / AcOEt 1:1). Found: C, 56.8; H, 9.2; N, 5.0. Calculated for $C_{13}H_{25}NO_5$: C, 56.71; H, 9.15; N, 5.09%. $[\alpha]_D$: **27a**= +28.2° (C 2.3, $CHCl_3$); **27b**: -6.0° (c 2.0, $CHCl_3$). P.f. (**27b**): 69.6°-70.5°C. ^1H n.m.r. (DMSO, 110°C):[27] **27a**: δ 4.08-3.80 [3 H, m, C*H*$_2$O and C*H*-N]; 3.33-3.25 [2 H, m, C*H*$_2$OH]; 1.55 [3 H, s, C*H*$_3$-C-CH$_3$]; 1.47 [12 H, s, C*H*$_3$-C-CH$_3$ and (C*H*$_3$)$_3$C]; 1.04 [3 H, s, C*H*$_3$-C]. **27b**: δ 4.20-3.80 [3 H, m, C*H*$_2$O and C*H*-N]; 3.38-3.15 [2 H, m, C*H*$_2$OH]; 1.54 [3 H, s, C*H*$_3$-C-CH$_3$]; 1.46 [12 H, s, C*H*$_3$-C-CH$_3$ and (C*H*$_3$)$_3$C]; 1.03 [3H, s, C*H*$_3$-C]. I.r. (**27a**)($CHCl_3$): ν_{max} 3400, 1657, 1455, 1368, 1162, 1042 cm^{-1}.

(*2R,3S*) 2-(*tert*-Butoxycarbonylamino)-4-(carbamoyloxy)-3-methyl-1,3-butanediol 29a. A solution of **27a** (2.27 g, 8.24 mmol) in dry CH_2Cl_2/DMF 6:1 (100 ml) was cooled to 0°C, treated with chloroacetyl isocyanate (1 ml, 11.74 mmol), and stirred for 80 min. at the same temperature. The mixture was diluted with H_2O (60 ml) and treated, at 0°C, with sodium N-methyl dithiocarbamate[20] (2 g, 15.48 mmol). After 2h the temperature was raised to r.t., and a second portion of N-methyl dithiocarbamate (1.4 g, 10.8 mmol) was added, followed, after 3 h, by a third one (1 g, 7.74 mmol). After stirring overnight, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic extracts were evaporated to dryness under vacuum (14 mbar first and 10^{-2} mbar for removal of DMF). The crude product was purified by chromatography (PE / AcOEt 1:1 → 3:7) to give **28a** (1.917, 74%, R_f: 0.56, AcOEt) not completely pure at tlc and n.m.r. It was taken up in dry MeOH (70 ml), cooled to 0°C, and treated with a 0.1 M methanolic solution of *p*-toluenesulfonic acid (10 ml, 1 mmol). The mixture was stirred for 2h at r.t., and quenched with saturated aqueous $NaHCO_3$. After evaporation of most MeOH, the residue was diluted with H_2O and saturated brine, adjusted to pH 7, and extracted with AcOEt. Chromatography (AcOEt / PE 9:1 → AcOEt / MeOH 8:2) gave pure **29a** as a white foam (1.310 g, 57%). R_f: 0.54 (AcOEt / AcOH 9:1). Found: C, 47.8; H, 8.1; N, 9.8%. Calculated for $C_{11}H_{22}N_2O_6$: C, 47.47; H, 7.97; N, 10.07%. $[\alpha]_D$: -30.0° (c 1.44, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 5.50 [1 H, d, N*H*, J= 9.1 Hz.]; 5.09 [2 H, broad s, N*H*$_2$]; 4.16 [1 H, d, C*H*H-OCONH$_2$, J= 11.6 Hz.]; 3.99 [1 H, d, C*H*H-OCONH$_2$, J= 11.6 Hz.]; 4.05-3.90 [1 H, m, C*H*-N]; 3.78 [1 H, ddd, C*H*HOH, J= 11.4, 7.0, and 3.6 Hz.]; 3.70-3.55 [1 H, m, mc= 3.63, C*H*H-OH]; 3.18 [1 H, broad s, O*H*]; 1.90 [1 H, broad s, O*H*]; 1.45 [9 H, s, (C*H*$_3$)$_3$C]; 1.30 [3 H, s, C*H*$_3$-C].

(*2R,3R*) 2-(*tert*-Butoxycarbonylamino)-4-(carbamoyloxy)-3-methyl-1,3-butanediol 29b. It was prepared from **27b** in 74% yield, by using the same procedure employed for **29a**. R_f: 0.54 (AcOEt / AcOH 9:1). R_f of **28b**: 0.47 (AcOEt) Found: C, 47.7; H, 8.05; N, 9.85%. Calculated for $C_{11}H_{22}N_2O_6$: C, 47.47; H, 7.97; N, 10.07%. $[\alpha]_D$: -22.6° (c 1.13, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 5.39 [1 H, d, N*H*, J= 9.4 Hz.]; 5.10 [2 H, broad s, N*H*$_2$]; 4.10 [2 H, s, C*H*$_2$-OCONH$_2$]; 4.00-3.60 [3 H, m, C*H*-N and C*H*$_2$OH]; 3.30 [1 H, broad s, O*H*]; 1.87 [1 H, broad s, O*H*]; 1.45 [9 H, s, (C*H*$_3$)$_3$C]; 1.24 [3 H, s, C*H*$_3$-C]. I.r. ($CHCl_3$): ν_{max} 3430, 1715, 1582, 1490, 1370, 1330, 1190, 1160 1075 cm^{-1}.

(*2S,3R*) Benzyl 2-(*tert*-Butoxycarbonylamino)-4-(carbamoyloxy)-3-hydroxy-3-methylbutanohydroxamate 31b. A solution of **29b** (1.233 g, 4.43 mmol) in dry CH_2Cl_2 (60 ml) was cooled to -20°C and treated with N-oxo-2,2,6,6-tetramethylpiperidinium chloride (TEMPO$^+$Cl$^-$)[21,22] (1.19 g, 6.2 mmol). The mixture was stirred for 3h between -15°C and -5°C, and a tlc showed the formation of the intermediate

aldehyde, as well as the presence of substrate. At this point 2-methyl-2-butene (5.63 ml, 34.9 mmol), and a solution of $NaClO_2$ (3.205 g, 35.4 mmol) and NaH_2PO_4 (4.096 g, 29.7 mmol) in H_2O (100 ml) were added. After stirring for 1h at 0°C, three portions of $TEMPO^+Cl^-$ (3 x 425 mg) were added every hour. The mixture was finally stirred for 2h at r.t.; quenched with a 5% $Na_2S_2O_5$ solution (20 ml), acidified to pH 1, saturated with NaCl, and extracted with $CHCl_3$ / MeOH 9:1 (5 times) to give, after chromatography (AcOEt → AcOEt / AcOH 85:15) **30b** as a partially impure foam (1.191 g)[R_f: 0.37 (AcOEt / AcOH 90:10)]. It was taken up in dry THF (16 ml), diluted with H_2O (60 ml), and treated with O-benzylhydroxylamine hydrochloride (1.30 g, 8.14 mmol). The pH was adjusted to 4.5 by addition of 1N NaOH. N-[3-(dimethylaminopropyl)]-N'-ethyl carbodiimide hydrochloride (WSC) (1.90 g, 9.91 mmol) was added at 0°C, and the pH adjusted again to 4.5. After stirring for 10 min. at 0°C and 6h at r.t., the pH had raised to 6.5. The mixture was further stirred overnight at r.t. Saturation with solid NaCl, and extraction with AcOEt, gave a crude product, which was chromatographed twice with PE / AcOEt 2:8 → 1:9) to give pure **31b** (968 mg, 55% from **29b**) as a gum. R_f: 0.30 (PE / AcOEt 2:8). $[\alpha]_D$= -8.0° (c 1.5, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 9.93 [1 H, broad s, N*H*-O]; 7.44-7.30 [5 H, m, aromatics]; 5.66 [1 H, d, N*H*-CH, J= 9.5 Hz.]; 5.20 [2 H, broad s, NH_2]; 4.88 [2 H, s, CH_2Ph]; 4.07 [1 H, d, C*H*-NH, J= 9.5 Hz.]; 4.06 [1 H, d, C*H*H-OCONH$_2$, J= 11.4 Hz.]; 3.89 [1 H, d, C*H*H-OCONH$_2$, J= 11.4 Hz.]; 1.43 [9 H, s, $(CH_3)_3$]; 1.16 [3 H, s, CH_3C]. I.r. ($CHCl_3$): ν_{max} 1725, 1695 cm^{-1}.

(2S,3S) **Benzyl 2-(*tert*-Butoxycarbonylamino)-4-(carbamoyloxy)-3-hydroxy-3-methylbutanohydroxamate 31a.** It was prepared from **29a**, via **30a** [R_f: 0.37 (AcOEt / AcOH 90:10)], in 53% overall yield, by employing the same procedure used for **31b**. R_f: 0.30 (PE / AcOEt 2:8). $[\alpha]_D$= -9.0° (c 1.38, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 9.89 [1 H, broad s, N*H*-O]; 7.44-7.30 [5 H, m, aromatics]; 5.72 [1 H, d, N*H*-CH, J= 9.1 Hz.]; 5.15 [2 H, broad s, NH_2]; 4.90 [2 H, s, CH_2Ph]; 4.05 [1 H, d, C*H*-NH, J= 9.1 Hz.]; 3.97 [2 H, s, CH_2OCONH$_2$]; 1.43 [9 H, s, $(CH_3)_3$]; 1.23 [3 H, s, CH_3C].

(3S,4R) **1-(Benzyloxy)-3-[(*tert*-butoxycarbonyl)amino]-4-(carbamoyloxymethyl)-4-methyl-2-azetidinone 32a.** A solution of **31a** (168 mg, 0.423 mmol) in dry THF (10 ml), was treated with a solution of diethyl azodicarboxylate (132 µl, 0.838 mmol) and triphenylphosphine (220 mg, 0.838 mmol) in THF (2 ml). The solution was stirred overnight at r.t., concentrated, and chromatographed twice (PE / AcOEt 6:4 → 45:55) to give pure **32a** as an oil (65 mg, 40%). R_f: 0.29 (AcOEt / PE 1:1). Found: C, 56.75; H, 6.8; N, 10.95. Calculated for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08%. $[\alpha]_D$= -16.2° (c 1.1, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 7.39 [5 H, s, aromatics]; 5.09 [1 H, d, N*H*, J= 7.0 Hz.]; 4.95 [2 H, s, CH_2Ph]; 4.83 [2 H, broad s, NH_2]; 4.67 [1 H, d, C*H*-NH, J= 7.0 Hz.]; 4.30 [1 H, d, C*H*HOCONH$_2$, J= 12.1 Hz.]; 4.08 [1 H, d, C*H*HOCONH$_2$, J= 12.1 Hz.]; 1.43 [9 H, s, $(CH_3)_3$C]; 1.04 [3 H, s, CH_3C]. ^{13}C n.m.r. ($CDCl_3$): δ 163.15 [β lactam *C*=O]; 155.69 and 155.08 [other *C*=O]; 135.12 [quaternary aromatic]; 129.18, 129.10, and 128.62 [other aromatics]; 80.76 [*C*$(CH_3)_3$]; 78.99 [*C*H_2Ph]; 68.38 [CH_3-*C*-N]; 64.71 [*C*H_2OCONH$_2$]; 58.13 [*C*H-NH(Boc)]; 28.18 [C(*C*$H_3)_3$]; 14.70 [*C*H_3C-N]. I.r. ($CHCl_3$): ν_{max} 3540, 3340, 1775, 1730, 1330, 1160 cm^{-1}.

(3S,4S) **1-(Benzyloxy)-3-[(*tert*-butoxycarbonyl)amino]-4-(carbamoyloxymethyl)-4-methyl-2-azetidinone 32b.** A solution of **31b** (468 mg, 1.18 mmol) in dry acetonitrile (12 ml) was treated with CCl_4 (683 µl, 7.08 mmol), triphenylphosphine (619 mg, 2.36 mmol), and triethylamine (378 µl, 2.714 mmol). The mixture was stirred overnight, concentrated, and chromatographed (PE / AcOEt 6:4) to give pure **32b** (161 mg, 36%). R_f: 0.35 (AcOEt / Pe 1:1). Found: C, 56.65; H, 6.75; N, 10.85. Calculated for $C_{18}H_{25}N_3O_6$: C, 56.98; H, 6.64; N, 11.08%. $[\alpha]_D$= + 66.7° (c 1.35, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 7.38 [5 H, s, aromatics]; 5.69 [1 H, d, N*H*, J= 8.4 Hz.]; 4.94 [2 H, s, CH_2Ph]; 5.20-4.90 [2 H, broad m, NH_2]; 4.51 [1 H, d, C*H*-NH, J= 8.4 Hz.]; 4.33 [1 H, d, C*H*HOCONH$_2$, J= 12.1 Hz.]; 3.89 [1 H, d, C*H*HOCONH$_2$, J= 12.1 Hz.]; 1.43 [9 H, s, $(CH_3)_3$C]; 1.20 [3 H, s, CH_3C].

NOE difference experiments on 32a,b.- The sample were prepared (20 mg/ml) using $CDCl_3$ previously dried on 3 Å molecular sieves, and freshly passed through neutral alumina. The tubes were placed

under N_2 and kept for 30 min. in an ultrasound bath, in order to remove O_2. NOEDIF spectra were acquired at 200 MHz. using a delay of 3.9 sec. and 256 transients. A decoupling power so that γH_2= 3-4 Hz. was used. The NOEs were calculated on the basis of the integrals for the "normal" spectrum, and the decoupled one. Irradiation of the methyl group in **32a** gave a NOE < 1% on H-3 (at 45% saturation). On the contrary, the same irradiation in **32b** gave an observed NOE of 7.1% (at 50% saturation), corresponding to an effective NOE of 14.2%. The possible interference due to partial saturation of the C(CH_3) signal, was ruled out by verifying that no NOE was observed on irradiating that signal.

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