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Diastereoselective Synthesis of (2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline, a Common Constituent of Several Antifungal Cyclopeptides

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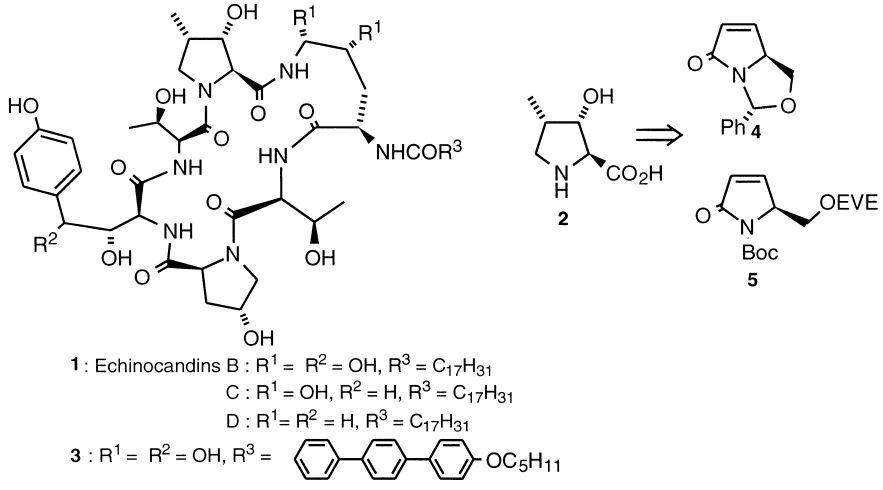
Abstract—(2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline **2** was synthesized from unsaturated γ-lactams **4** and **5** derived from (*S*)-pyroglutaminol. Starting from **5**, haplophilic effect in the hydrogenation of a 4-*exo*-methylenic intermediate improved the diastereoselectivity of the synthesis, which was achieved in 19% yield.

Introduction

Echinocandins **1**, isolated from *Aspergillus*, as well as some related cyclohexapeptides (pneumocandins A, sporiofungin A, mulundocandins), are constituted by five α-amino-β-hydroxy acids including (2*S*,3*S*,4*S*)-3-hydroxy-4-methylproline **2** (HMP), by ornithine or its 4,5-dihydroxy derivative, and by an acid with a lipophilic long chain (R^3).[1,2] They are inhibitors of 1,3-β-D-glucan synthase and exhibit interesting specific fungicidal activities against *Candida albicans* and *Pneumocystis carinii*.[2,3] Numerous antifungal semi-synthetic analogues of these lipopeptides retain HMP as an aminoacid unit, particularly those containing a modified polyaromatic side chain like LY303366 **3** and its derivatives.[4]

Two syntheses of **2**,[5,6] and a synthesis of its methyl ester hydrochloride,[7] have already been described before this study. As part of our program on the synthesis of bioactive products from easily available (*S*)-pyroglutamic acid or



Scheme 1.

Keywords: 3-hydroxy-4-methylproline; antifungals; (*S*)-pyroglutaminol; nitrone [3+2] cycloaddition; Cope elimination; stereoselective hydrogenation.
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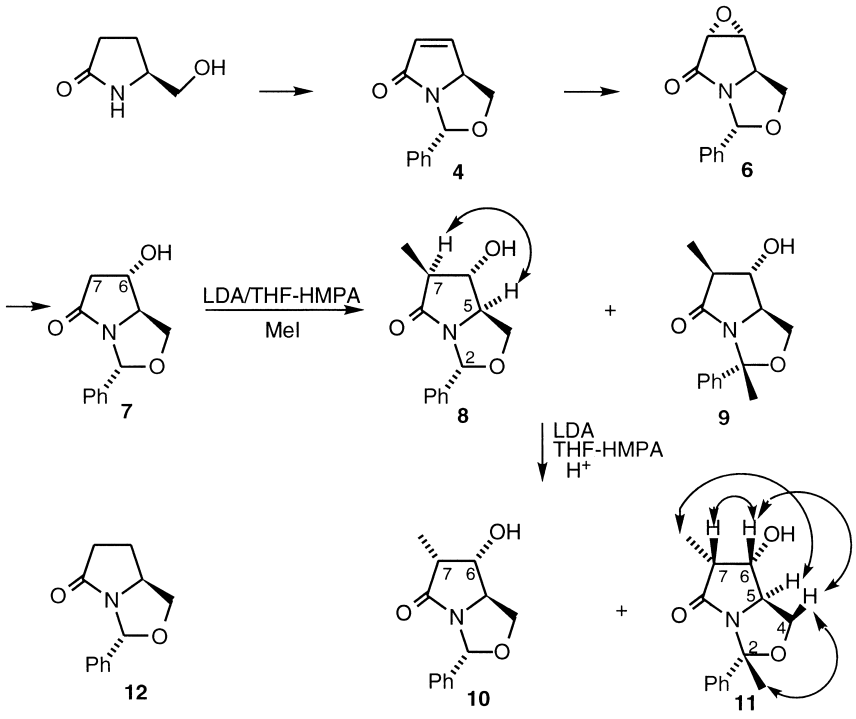


Scheme 2.

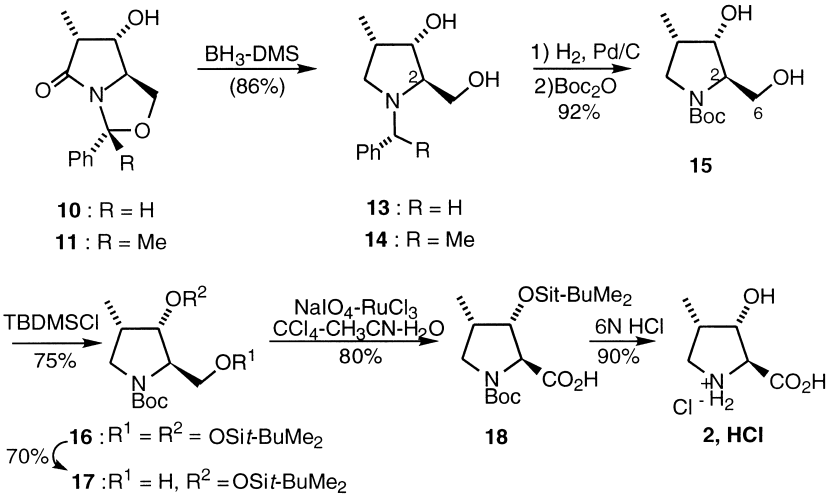
(*S*)-pyroglutaminol,[8] several synthetic ways towards HMP, starting from the γ-lactams **4** or **5**, were studied and our main results are presented here (Scheme 1).[9]

Results and Discussion

Sequential introduction of hydroxy and methyl groups

The first route involved sequential introduction of the hydroxy and methyl groups on the bicyclic unsaturated lactam **4** (Scheme 2). The γ-lactam **4** was easily prepared from (*S*)-pyroglutaminol,[10] and its interest in the synthesis of various enantiopure compounds was widely demonstrated.[11] Indeed, the rigid backbone of **4** induced a high diastereoselectivity in several addition reactions on the convex side of the molecule.[11–13] Particularly, the epoxidation of **4**[8e] was shown to be diastereospecific under the conditions developed by Herdeis et al., and the epoxide **6** could be isolated in 87% yield.[14] Furthermore, an efficient and regiospecific cleavage of this oxirane with SmI_2 was carried out in our laboratory, leading to the (6*S*)-6-hydroxy derivative **7** in 95% yield.[8g] The alcohol **7** therefore was deprotonated and methylated at C-7 (Scheme 2). Obviously, α-alkylation of dianions from β-hydroxy esters,[15] lactones,[16] and lactams[17] are known to occur with high *trans* diastereoselectivity, and the lithium enolate of the resulting methylated product **8** was anticipated to be reprotonated with the same stereoselectivity to afford the desired *cis*-6,7-disubstituted derivative **10**. Thus, the dianion obtained from **7** (LDA–THF–HMPA, −78°C) was alkylated with methyl iodide in excess (6 equiv.), giving rise to *trans* derivative **8** (68%) as a single diastereomer.[9] In ^{1}H NMR, the observation of a nOe between the protons H-7 and H-5 allowed to confirm the C-7 configuration. The yield of this alkylation could be improved to 80% by using a large excess of reagents (4 equiv. LDA, 4 equiv. HMPA, 10 equiv. MeI), at the same temperature. However, an inseparable mixture of **8** and dimethyl compound **9** was obtained under these conditions. In the ^{1}H NMR spectrum of **9**, the additional methyl group gave rise to a singlet at 1.92 ppm indicating a quaternary bearing carbon. A deprotonation at the benzylic position of *N*-benzylpyrrolidin-2-ones has been observed already[18] and the formation of **9** could be explained by the loss of the proton at C-2. In our case, noteworthy is the fact that only one diastereomer of the dialkylated product was detected and its configuration at C-2 (2*R*) was supported by NOESY data of the *cis* derivative **11** (see below). Since the *N*,*O*-protecting oxazolidine will be removed, the lack of regiocontrol in this methylation step was not a real drawback.

To complete the synthesis of **2**, the configuration of the centre C-7 of **8** has to be inverted. The treatment of **8** with LDA–THF–HMPA, followed by quenching at −78°C with pivaloic acid, afforded, in 73% yield, a separable mixture (ca. 1:1) of **8** and *cis* diastereomer **10**. Thus, the epimerisation of **8** took place only in modest yield. Albeit retro-aldolisation could not be excluded in this reaction, the initial configuration at C-6 (6*S*) was retained. On the basis of a deprotonation–protonation sequence, this result could be explained by a competition between the *trans* orientation induced by the vicinal alkoxide and an *exo*-protonation on the less hindered convex face of the molecule, but this result remains surprising owing to previous data. Studies of alkylations of a series of bicyclic γ-lactams showed that the diastereofacial selectivities are governed by electronic or steric control depending upon the type and the position of substituents.[19] In the particular case of electrophilic additions to the lithium enolate of the related bicyclic



Scheme 3.

γ-lactam **12**, the selectivity depends also upon the electrophile.[10a,20] An *endo*-selectivity was observed in the electrophilic addition of methyl iodide or proton, the nitrogen lone pair directing the addition of these small electrophiles.[20b] The nitrogen configurations in **8** and **12** were postulated to be the same. Thus, a more selective *endo* kinetic protonation of the lithium enolate from **8** to the *cis* derivative **10**, favoured by several factors, could be expected. The mixture (**8**+**9**) in the same conditions led to the mixture (**10**+**11**, 44%) by partial epimerisation at C-7 (recovered **8**+**9**: 32%). The compound **11** gave NOESY cross peaks between H-5 and CH_3-7, H-7 and H-6 and between H-4 (*endo*) and H-6 as well as CH_3-2, supporting the configurations 2*R*, 6*S*, 7*R* (Scheme 2).

A synthesis of HMP **2** was achieved from the mixture (**10**+**11**) without separation as depicted in Scheme 3.[9] Reduction with BH_3-DMS led to the *N*-benzyl pyrrolidines **13** and **14** in 86% yield and a X-ray analysis of **14** confirmed the previous deductions from the NOESY data of its precursor **11**.[21]

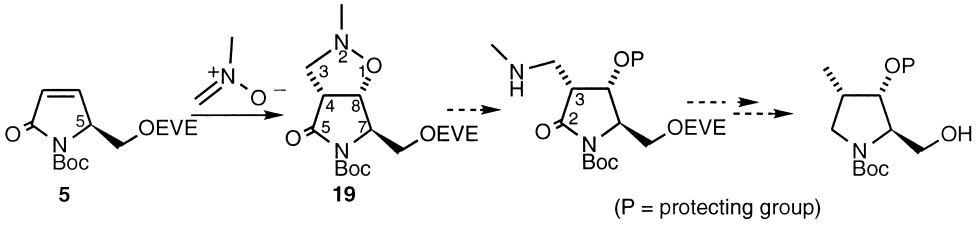
Hydrogenolysis of the mixture (**13**+**14**) and *N*-protection with $(Boc)_2O$ furnished the *N*-Boc pyrrolidine **15** (92%). The corresponding disilylated derivative **16** (75%) was selectively deprotected into the primary alcohol **17** (70%) which was oxidised under Sharpless conditions into **18** (80%).[22] HMP **2** hydrochloride was then obtained in 90% yield after acid hydrolysis with 6N HCl.

The steps leading from **15** to **18** were not optimised since the lack of stereoselectivity in the deprotonation–protonation sequence led us to research another route.

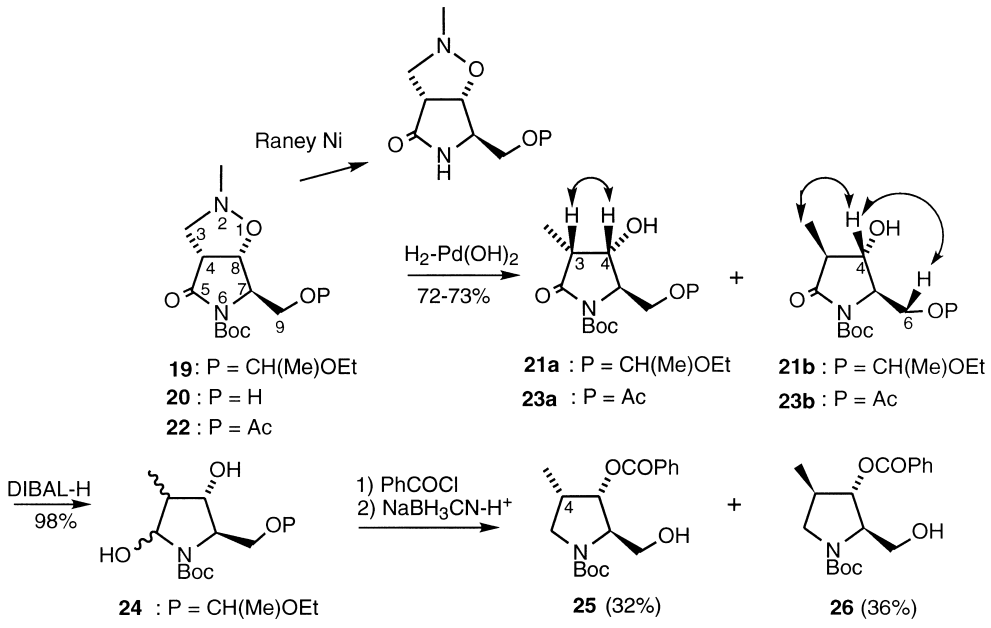
Cycloadduct of *N*-methylnitrone as an intermediate

It was anticipated that the hydroxy group of HMP **2** and additional carbon of its methyl group could be both introduced through 1,3-dipolar cycloaddition of methylnitrone to the α,β-unsaturated γ-lactam **5**, which is conveniently *N*-protected for final steps.[12] A 3-(*N*-methyl)aminomethyl derivative was expected to be formed by hydrogenolysis of the N–O bond, allowing a subsequent conversion into a methyl group after suitable protection of the vicinal hydroxy group (Scheme 4).[23]

The regio- and stereo-selective [3+2] cycloaddition of *N*-methylnitrone to the unsaturated pyrrolidinone **5** was performed by heating in toluene at 110°C. During our preliminary work,[12] the *N*-methylnitrone was prepared as described,[24] except that benzene was replaced by toluene. The cycloadducts were isolated in this case in 59% yield (54% of **19** and 5% of the regioisomer), owing to competitive conjugate addition (15%) of *N*-methylhydroxylamine present in the reaction medium. The preparation of *N*-methylnitrone with an excess of paraformaldehyde with regard to *N*-methylhydroxylamine hydrochloride, and the use of a slight excess of nitrone in the cycloaddition (1.33 equiv., heating for 2 h) improved the yield of **19**, which was isolated (70%) together with the regioisomer (9%), whereas the 1,4-addition product of *N*-methylhydroxylamine was not detected. Unlike observed under other



Scheme 4.

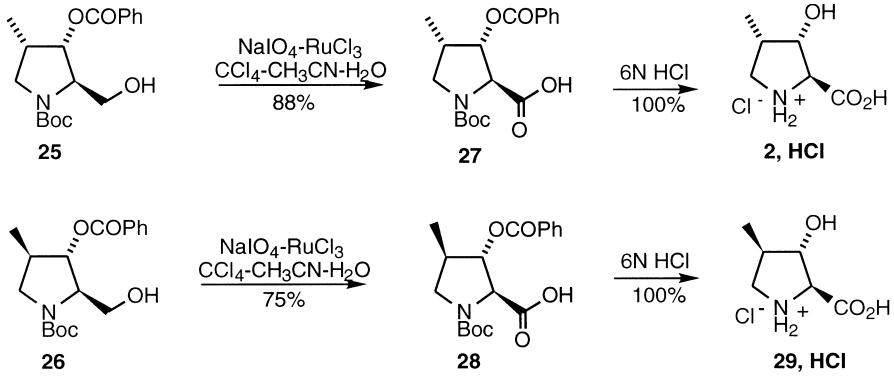


Scheme 5.

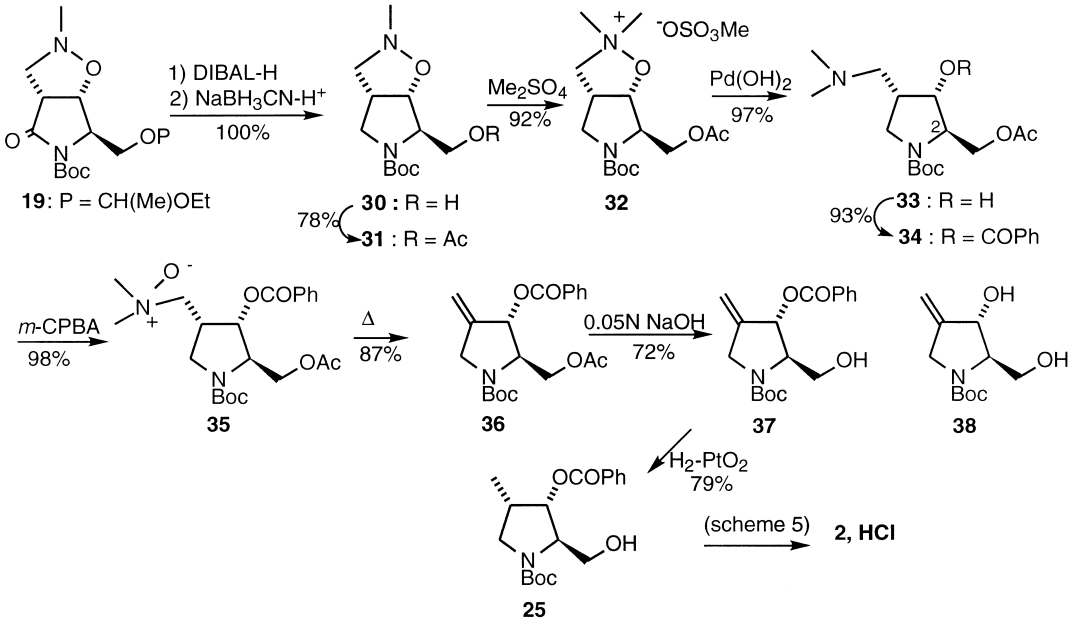
conditions,[13] the stereogenic centre of **5** (C-5) was unaffected in this reaction. Thus, the enantiopurity of the compound **19** was established after deprotection into the primary alcohol **20** and preparation of the corresponding Mosher's esters. Several reagents were tested to cleave isoxazolidine N–O bond. $Mo(CO)_6$[25] was inefficient and the use of $TiCl_3$[26] led only to the primary alcohol deprotection. In the major product obtained by the treatment of **19** with Raney nickel, the *N*-protective group was removed, probably through the complexation of the two carbonyls (Scheme 5).

Finally, the isoxazolidine **19** was successfully hydrogenolyzed over Pearlman's catalyst into a complex mixture after 16 h, which, by prolonged time of reaction (50 h), gave rise to 3-methyl derivatives **21a** and **21b** in 72% yield (Scheme 5). The ratio **21a**:**21b** was evaluated as 2:3 by comparison of H-3 signals in ^{1}H NMR. Thus, the cleavage of the N–O bond was followed, under these conditions, by elimination of methylamine and subsequent hydrogenation. Similar results were obtained with the acetate **22** which led to **23a** and **23b** (73%, total yield) in the same ratio 2:3, determined by ^{1}H NMR. A *cis* relationship between the substituents at C-3 and C-4 in **23a** was supported by the strong nOe between H-3 and H-4, while in **23b**, a nOe was observed between the methyl group and H-4 and between H-4 and H-6. The ^{1}H and ^{13}C chemical shifts of the methyl groups and adjacent H-3 are rather different in the diastereomers **a** and **b** and characteristic of the configuration at C-3 centre. In the cases of **21** and **23**, the *cis* diastereomers **a** were the major products of a deprotonation–protonation sequence with a ratio **a**:**b** about 2:1.

For the next steps, a convenient protection of the hydroxy group at C-4 was needed to allow a further selective deprotection of the primary alcohol and its oxidation into a carboxyclic acid. Attempts to prepare the *tert*-butyldimethylsilyl derivative of **23** under the classical conditions (*t*-$BuMe_2SiCl$, Im, DMF)[27] gave only moderate yield (50%). The sensitivity of *N*-Boc-4-hydroxypyrrolidin-2-ones derivatives towards β-elimination could be a drawback in this protection step. For this reason, the lactams **21** were reduced before the protection of the secondary hydroxy group. The straightforward sequence depicted in the Scheme 5 was applied to the mixture **21a**+**21b** obtained from **19**, without separation of the intermediates leading to **25** and **26**.



Scheme 6.



Scheme 7.

Accordingly, partial reduction of **21** with DIBAL-H[28] led to **24** (98% yield) which was directly benzoylated. Subsequent reduction with $NaBH_3CN$ in acetic acid, and concomitant removal of EVE protection afforded the substituted pyrrolidines **25** and **26** (Scheme 5). The diastereomers **25** and **26** were separated by chromatography on silica gel with 32 and 36% overall yield, respectively, for the two steps. These compounds gave poorly resolved ^1H NMR spectra, presumably due to conformational flexibility, but all other data were fully consistent with these structures. The configurations assigned at C-4 were confirmed by the conversion of these alcohols into the amino acids **2** and **29** hydrochlorides (Scheme 6).

This conversion was carried out by Sharpless oxidation of **25** and **26** respectively into **27** (88%) and **28** (75%), followed by quantitative deprotection to **2** and **29** by heating in 6 N HCl. Thus, the synthesis of **2**, **HCl** from **5** could be achieved in ca. 14% yield, despite the lack of selectivity in the formation of the stereocentre bearing the methyl group.

This successful completion of the synthesis of **2** encouraged us to seek conditions improving this stereoselectivity. Thus, it was anticipated that the lactam carbonyl of the cycloadduct **19** could be reduced at an early stage of the synthesis to control the further methylamino group elimination. This step could be followed by a stereoselective hydrogenation of the resulting *exo*-methylene at C-4 controlled by a 'haplophilic' effect[29] (Scheme 7).

Accordingly, **19** was successively reduced by DIBAL-H and $NaBH_3CN$ in acetic acid to afford quantitatively the pyrrolidine **30** (Scheme 7). The primary alcohol was protected as acetate (**31**, 78%). A protection as *tert*-butyldimethylsilyl ether was avoided because this protecting group could be unstable under hydrogenation conditions.[30] The *N*-methylation into **32** (92%) was then carried out with dimethylsulfate, which gave better results than methyl iodide in the following step.[31] Hydrogenolysis of the ammonium salt **32** in the presence of $Pd(OH)_2$ afforded quantitatively the dimethylaminomethyl derivative **33** as its methylsulfate salt, which was converted to the base (97%) and then to the benzoate **34** (93%). The compound **34** was in turn oxidized into its *N*-oxide **35** (*m*-CPBA, 98%) which was submitted to a Cope elimination by heating at 85°C in a diluted mixture of THF and toluene (1:1) to furnish **36** (87%).[32]

It is known that the presence of some neighbouring groups, particularly hydroxy groups can be responsible of the stereoselectivity observed in heterogeneous catalytic hydrogenation. This so-called 'haplophilicity' of hydroxy or hydroxymethyl groups lead to addition of hydrogen from the same face as these polar substituents.[29,33] Thus, a selective reduction of the acetate in **36** was attempted with DIBAL-H to perform a selective deprotection of the primary alcohol, since benzoates can be stable in the presence of this reagent. It gave rise to a mixture, from which **37** was isolated in only 30% yield, together with 50% starting **36**. The primary alcohol of **36** was selectively deprotected to **37** more efficiently by smooth alkaline hydrolysis (0.05N NaOH, MeOH, 72%) which was quenched by dilution before completion, to minimise the formation of diol **38**. Hydrogenation of the methylenic compound **37** in EtOAc, either with 10% Pd/C or PtO_2 as catalyst, led to the 3,4-*cis* derivative **25** as the major product. The last conditions using PtO_2 gave the best result and led to the diastereomer **25**, precursor of HMP **2**, in 79% yield (Scheme 7).

Conclusion

HMP **2** was synthesized from either γ-lactam **4** or **5**, both easily prepared from (*S*)-pyroglutaminol. The diastereoselectivity in the formation of C-4 stereogenic centre of **2** was improved by haplophilic effect in the hydrogenation of

the *exo*-methylenic compound **37**. In this way, the synthesis of **2** hydrochloride was achieved in 19% yield from **5**.

Experimental

Melting points were taken on a Leitz microscope. Optical rotations were measured on a Perkin–Elmer 241; the concentrations in $CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra (ν cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). ^1H NMR spectra were obtained ($CDCl_3$, Me_4Si, δ=0 ppm) from Bruker AC250, AM300 or AM400 (s, d, t, dd and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). ^{13}C NMR spectra (δ ppm relative to the central signal of $CDCl_3$ at 77.14 ppm) were recorded on AC200 (50.0 MHz), AC250 (62.5 MHz) or AM300 (75.0 MHz). Mass spectra and high resolution mass spectra (*m*/*z*) were respectively measured on an AEI MS50 or on a Kratos MS80 spectrometer. Elemental analyses were determined by the Microanalysis Laboratory at ICSN. Flash chromatography was performed on silica gel (SDS 230–400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254+366). Usual workup means that the organic layer was dried with magnesium sulfate, filtered and evaporated under vacuum.

(2*R*,5*R*,6*S*,7*S*)-6-Hydroxy-7-methyl-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0.]octan-8-one 8. To a solution of LDA (5.75 mmol) in THF (5.75 mL), stirred under Ar at −78°C, was added a solution of bicyclic lactam **7** (420 mg, 1.92 mmol) in a mixture THF (4.5 mL) and HMPA (0.83 mL). After being stirred for 1 h at the same temperature and for 1 h at −35°C, the mixture was cooled at −78°C before the addition of CH_3I (0.725 mL, 11.6 mmol). The mixture was stirred at −78°C for 2 h. The reaction was quenched at the same temperature by addition of a saturated aqueous solution of NH_4Cl (4 mL), an aqueous solution of Na_2CO_3 (10% v/w, 4 mL) and the product was extracted with Et_2O. After purification by chromatography on silica gel (eluent: Et_2O–EtOAc 6:4), the compound **8** was obtained as white crystals (304 mg, 68%). Mp: 134–6°C, $[\alpha]_D^{25}$=+181 (*c*=1.02). IR: 3615, 3416, 1709, 1450. MS (EI): 233 ($M^{+\cdot}$), 232 (100%), 218, 203, 186, 156, 148, 105, 91, 77. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.71; H, 6.28; N, 5.92. ^1H NMR (300 MHz): 7.40 (m, 5H, H-Ar), 6.38 (s, 1H, H-2), 4.19 (dd, 1H, *J*=9 Hz, *J*′=6.5 Hz, Ha-4), 3.93 (m, 1H, H-5), 3.90 (masked m, 1H, H-6), 3.82 (dd, 1H, *J*=9 Hz, *J*′=5 Hz, Hb-4), 2.86 (m, 1H, H-7), 2.72 (OH), 1.26 (d, 3H, *J*=7.5 Hz, CH_3-7). ^1H NMR (300 MHz, C_6D_6): 7.47 and 7.10 (2m, 5H, H-Ar), 6.56 (s, 1H, H-2), 3.68 (dd, 1H, $J_{4a,4b}$=8.5 Hz, $J_{4a,5}$=6.6 Hz, Ha-4), 3.36 (m, 1H, H-5), 3.25 (dd, 1H, $J_{4a,4b=}$8.5 Hz, $J_{4b,5}$=5.3 Hz, Hb-4), 3.14 (m, 1H, H-6), 2.37 (m, 1H, H-7), 1.24 (OH), 1.06 (d, 3H, *J*=7 Hz, CH_3-7). (400 MHz, C_6D_6, 40°C): nOe between H-5 and H-7. ^{13}C NMR (75.0 MHz, $CDCl_3$): 177.02 (CO), 137.97 (qC Ar), 128.79, 128.61, 128.18 (CH, Ar), 87.28 (C-2), 80.87 (C-6), 69.86 (C-4), 64.37 (C-5), 48.10 (C-7), 12.33 (CH_3).

The same reaction was carried out with **7** (548 mg, 2.5 mmol) using 4 equiv. LDA, 4 equiv. HMPA and 10 equiv. CH_3I. It led to 485 mg of a mixture of **8** and the dimethyl derivative **9** (ratio about 3:7; ca. 80%) which could not be separated. Data of **9**: MS (EI): 247 ($M^{+\cdot}$), 246. ^1H NMR (300 MHz): 7.46, 7.34 (H-Ar), 4.04 (dd, Ha-4), 3.80 (m, Hb-4, H-6, H-5), 2.76 (m, H-7), 1.92 (s, CH_3-2), 1.27 (d, *J*=7.5 Hz, CH_3-7). ^{13}C NMR (75.0 MHz): 173.28 (CO), 142.22 (qC, Ar), 95.03 (C-2), 80.00 (C-6), 67.81 (C-4), 65.17 (C-5), 49.17 (C-7), 26.02 (CH_3-2), 12.51 (CH_3-7).

(2*R*,5*R*,6*S*,7*R*)-6-Hydroxy-7-methyl-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0.]octan-8-one 10. The compound **8** (40.8 mg, 0.17 mmol) in THF (0.67 mL) and HMPA (93 μL, 0.53 mmol) was added under Ar at −78°C to a solution of LDA (0.52 mmol) in THF (0.45 mL). The mixture was stirred at −78°C for 1 h and at −35°C for 1 h before quenching with excess pivaloic acid. After addition of Na_2CO_3 (10% v/w), extraction with Et_2O and usual workup, the products were separated by preparative TLC (eluent: Et_2O–EtOAc 6:4) to give **8** (14.8 mg, 36%) and **10** (15.2 mg, 37%) as white crystals. **10**: Mp: 144–6°C, $[\alpha]_D^{30}$=+206 (*c*=0.62). IR: 3688, 3608, 3420, 1709, 1603, 1450. MS (EI): 233 ($M^{+\cdot}$), 232 (100%), 216, 203, 186, 176, 156, 148, 105, 91, 77. HRMS: Calcd for $C_{13}H_{15}NO_3$ ($M^{+\cdot}$): 233.1051. Found: 233.1019. ^1H NMR (300 MHz): 7.37 (m, 5H, H-Ar), 6.35 (s, 1H, H-2), 4.38 (dd, 1H, $J_{6,7}$=7.5 Hz, $J_{5,6}$=4.9 Hz, H-6), 4.23 (dd, 1H, $J_{4a,4b}$=8.4 Hz, $J_{4a,5}$= 6.8 Hz, Ha-4), 3.98 (ddd, 1H, $J_{4a,5}\sim J_{4b,5}$=6.8 Hz, $J_{5,6}$=4.9 Hz, H-5), 3.69 (dd, 1H, $J_{4a,4b}$=8.4 Hz, $J_{4b,5}$= 6.9 Hz, Hb-4), 2.80 (m, 1H, H-7), 1.34 (d, 1H, *J*=7.5 Hz, CH_3). ^{13}C NMR (75.0 MHz): 179.97 (CO), 138.11 (qC, Ar), 128.77, 128.61, 125.25 (CH, Ar), 87.51 (C-2), 72.50 (C-6), 69.18 (C-4), 65.15 (C-5), 45.77 (C-7), 10.44 (CH_3).

(2*R*,5*R*,6*S*,7*R*)-6-Hydroxy-2,7-dimethyl-2-phenyl-3-oxa-1-aza-bicyclo[3.3.0.]octan-8-one 11. Epimerisation under the conditions described above of a mixture **8**+**9** (402 mg) afforded a mixture of *cis*-derivatives **10**+**11** (177 mg, 44%), together with the initial mixture **8**+**9** (ca. 3:7, 127 mg, 32%), the two sets of products being separated by chromatography (eluent: Et_2O–EtOAc 6:4). The compounds **10** and **11** were further separated by preparative TLC (eluent: CH_2Cl_2–MeOH 98:2, then Et_2O–heptane–MeOH 14:5:1). Data of **11** (85 mg, 49%). Mp: 161–3°C. $[\alpha]_D^{25}$=+296 (*c*=2.30). IR: 1710. MS (CI, isobutane): 248 [$(M+H)^+$, 100%], 234, 121, 107. HRMS (CI, CH_4): Calcd for $C_{14}H_{18}NO_3$ $(M+H)^+$: 248.1287. Found: 248.1299. ^1H NMR (300 MHz): 7.44 (2H, H-Ar), 7.33 (m, 3H, H-Ar), 4.32 (dd, 1H, $J\sim J'\sim$7 Hz, H-6), 4.06 (dd, 1H, *J*=7 Hz, *J*′=6 Hz, Ha-4), 3.89 (ddd, 1H, H-5), 3.83 (dd, 1H, *J*=7 Hz, *J*′=6 Hz, Hb-4), 2.83 (m, 1H, H-7), 1.92 (s, 3H, CH_3-2), 1.31 (d, 3H, *J*=7 Hz, CH_3-7). ^{13}C NMR (75.0 MHz): 175.60 (CO), 142.44 (qC, Ar), 128.61, 128.54, 128.21, 125.10 (CH, Ar), 94.93 (C-2), 73.19 (C-6), 67.80 (C-4), 65.37 (C-5), 47.52 (C-7), 26.01 (CH_3-2), 10.29 (CH_3-7). nOesy: cross peaks between H-5 and CH_3-7; H-6 and H-7; H-6 and Hb-4; Hb-4 and CH_3-2.

(2*R*,3*S*,4*S*)-1-Benzyl-3-hydroxy-2-hydroxymethyl-4-methyl-pyrrolidine 13, (2*R*,3*S*,4*S*)-1-(1′-phenyl)ethyl-3-hydroxy-2-hydroxymethyl-4-methylpyrrolidine 14 and (2*R*, 3*S*,4*S*)-1-*tert*-butoxycarbonyl-3-hydroxy-2-hydroxymethyl-4-methylpyrrolidine 15. A solution of BH_3-DMS (2 M in THF, 2.1 mL, 4.2 mmol) was added under Ar to a solution

of a mixture **10**+**11** prepared as above (335 mg, ca. 1.38 mmol) in THF (32 mL) stirred at rt under argon. The mixture was heated at 70°C for 2.25 h. After addition of 2N HCl, the THF was evaporated under reduced pressure; 5N HCl was added and the mixture was heated at 70°C for 10 min. After cooling at 0°C, 40% NaOH was added, the cooling bath was removed and the product was extracted with CH_2Cl_2. Usual workup afforded pyrrolidines **13**+**14** (273 mg, ~86%). This product in methanol (16 mL) was hydrogenolyzed with H_2 (ca. 3.5 bars) in the presence of Pd/C 10% (50 mg) for 16 h. The catalyst was filtered on Celite® and washed with MeOH and the solvent was evaporated under vacuum. $(Boc)_2O$ (260 mg, 1.19 mmol) was added to a solution of the residue in MeOH (20 mL) and the mixture was stirred at rt for 2 h, evaporated to dryness and purified by preparative TLC (eluent: CH_2Cl_2–MeOH 92:8) to afford the *N*-Boc pyrrolidine **15** as a colourless oil (252 mg, 92%): $[\alpha]_D^{25}=-38$ (c=1.33). IR: 3608, 3402, 2977, 1669, 1410. MS (CI, isobutane): 232 $(M+H)^+$, 176. HRMS (CI, CH_4): Calcd for $C_{11}H_{22}NO_4$ $(M+H)^+$: 232.1549. Found: 232.1580. ^{1}H NMR (300 MHz, $CDCl_3+D_2O$): 3.99 (d, 1H, $J_{3,4}$=2.8 Hz, H-3), 3.83 (dd, 1H, $J_{2,6a}\sim J_{2,6b}$=6 Hz, H-2), 3.69 (dd, 1H, $J_{6a,6b}$=11 Hz, $J_{6a,2}$=6 Hz, Ha-6), 3.53 (dd, 1H, $J_{6a,6b}$=11 Hz, $J_{6b,2}$=6 Hz, Hb-6), 3.45 (dd, 1H, $J_{5a,5b}\sim J_{5a,4}\sim$9.5 Hz, Ha-5), 3.13 (dd, 1H, $J_{5a,5b}\sim J_{5b,4}\sim$9.5 Hz, Hb-5), 2.27 (m, 1H, H-4), 1.45 (s, 9H, *t*-Bu), 1.05 (d, 1H, J=7 Hz, CH_3-4). ^{13}C NMR (75.0 MHz): 156.68 (NCO_2), 80.23 (qC, *t*-Bu), 74.87 (C-3), 68.41 (C-2), 64.29 (C-6), 51.54 (C-5), 36.15 (C-4), 28.55 (CH_3, *t*-Bu), 11.15 (CH_3-4).

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-2-*tert*-butyldimethylsilyloxymethyl-4-methylpyrrolidine 16. A solution of *t*-BuMe_2SiCl (386 mg, 2.56 mmol) in DMF (0.6 mL) was added under Ar to a solution of diol **15** (185 mg, 0.80 mmol) and imidazole (218 mg, 3.2 mmol) in DMF (0.4 mL). The mixture was stirred at 40°C for 18 h and diluted with Et_2O after cooling. An aqueous solution of $NaHCO_3$ was added and the product was extracted four times with Et_2O. After washing of the organic layers with H_2O, usual workup and purification by preparative TLC (eluent: heptane–Et_2O 95:5), the disilyloxy derivative **16** was obtained as a colourless oil (276 mg, 75%). $[\alpha]_D^{30}=-23$ (c=0.66). IR: 2964, 2931, 2858, 1682, 1410. MS (CI, isobutane): 460 $[(M+H)^+$, 100%]. HRMS (CI, CH_4): Calcd for $C_{23}H_{50}NO_4Si_2$ $(M+H)^+$: 460.3278. Found: 460.3318. ^{1}H NMR (300 MHz, doubled signals): 4.12 (dd, 1H, $J\sim$4 Hz, H-3), 3.8–3.2 (H_2-6, H-2, Ha-5), 3.11, 3.02 (2dd, 1H, $J\sim J'$=10.2 Hz, Hb-5), 2.26 (m, 1H, H-4), 1.45 (s, 9H, *t*-Bu), 1.00, 0.98 (2d, J=6.8 Hz, CH_3-4), 0.89 (s, 18H, 2×Si-*t*-Bu), 0.08, 0.07, 0.05, 0.04 (4s, 12H, 2×Si$(CH_3)_2$. ^{13}C NMR (75.0 MHz): 154.96 (NCO_2), 79.27, 79.0 (qC, O-*t*-Bu), 75.89, 75.46 (C-3), 68.45, 68.17 (C-2), 62.71, 61.99 (OCH_2), 51.80, 51.15 (C-5), 36.39, 35.44 (C-4), 28.64 (CH_3, *t*-Bu), 26.03, 25.88 (CH_3, Si-*t*-Bu), 18.22 (qC, Si-*t*-Bu), 11.69 (CH_3-4), −4.48, −4.74 ($SiCH_3$), −5.28, −5.35 ($SiCH_3$).

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-2-hydroxymethyl-4-methylpyrrolidine 17. Disilylderivative **16** (138 mg, 0.3 mmol) in a mixture AcOH–THF–H_2O 13:3:7 (2.0 mL)[34] was stirred at 30°C for 12 h. After dilution with CH_2Cl_2 and addition of Na_2CO_3, the organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. After usual workup, the product was purified by preparative TLC (eluent: heptane–Et_2O: 4:6) to afford the primary alcohol **17** as a colourless oil (72.5 mg, 70%). $[\alpha]_D^{28}=-27$ (c=0.97). IR: 3688, 3389, 2957, 2931, 2858, 1669, 1410, 1370. MS (CI, isobutane): 346 $[(M+H)^+$, 100%], 290, 246. HRMS (CI, CH_4): Calcd for $C_{17}H_{36}NO_4Si$ $(M+H)^+$: 346.2414. Found 346.2436. ^{1}H NMR (300 MHz, C_6D_6): 4.04 (m, 1H, H-2), 3.7–3.6 (3H, H-3, OCH_2), 3.29 (dd, 1H, $J_{5a,5b}$=9.9 Hz, $J_{5a,4}\sim$8 Hz, Ha-5), 3.17 (dd, 1H, $\sim J_{5b,4}\sim J_{5a,5b}$=9.9 Hz, Hb-5), 1.77 (m, 1H, H-4), 1.41 (s, 9H, O-*t*-Bu), 0.88 (s, 9H, Si-*t*-Bu), 0.79 (d, 1H, J=6.7 Hz, CH_3-4), 0.00 (s, 3H, $SiCH_3$), −0.04 (s, 3H, $SiCH_3$). ^{13}C NMR (75.0 MHz): 157.12 (CO), 80.37, 80.28 (qC, O-*t*-Bu), 75.68, 75.12 (C-3), 68.73 (NCH), 65.29, 65.02 (CH_2), 51.83, 51.58 (CH_2), 36.93, 36.34 (C-4), 28.54 (CH_3, *t*-Bu), 18.16 (qC, Si-*t*-Bu), 11.64, 11.16 (CH_3-4), −3.49 ($SiCH_3$), −4.60, −4.72 ($SiCH_3$).

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-*tert*-butyldimethylsilyloxy-4-methyl proline 18 and HMP 2. To a mixture of alcohol **17** (44.2 mg, 0.128 mmol), CCl_4 (0.25 mL), CH_3CN (0.25 mL) and H_2O (0.37 mL) were successively added under stirring $NaIO_4$ (129.5 mg, 0.60 mmol) and $RuCl_3$, $2H_2O$ (3.0 mg). The mixture was vigorously stirred at rt for 0.4 h, diluted with CH_2Cl_2 and H_2O and the aqueous layer was extracted three times with CH_2Cl_2. Et_2O was added to the residue obtained after usual workup and the solution was filtered to afford the carboxylic acid **18** after evaporation to dryness (36.8 mg, 80%). IR: 3396–2450 (broad), 2957, 2931, 2858, 1749, 1676, 1616. The product was dissolved in 6N HCl (1.0 mL) and the mixture was stirred at rt for 0.25 h and then at 118°C for 4 h. After evaporation to dryness, the residue was washed twice with Et_2O, dissolved in H_2O and the solution was filtered and evaporated to dryness under reduced pressure to afford HMP **2** hydrochloride (16.8 mg, 90%). $[\alpha]_D^{25}=+12$ (c=0.32, 5N HCl); literature: $[\alpha]_D=+10$ (c=0.40, 5N HCl).[1] MS (FAB, thioglycerol): 168 (M+23), 146 $[(M+H)^+$, 100%], 131, 105, 100. ^{1}H NMR (300 MHz, D_2O: δ=4.8 ppm): 4.47 (d, 1H, J=3.6 Hz, H-3), 4.16 (s, 1H, H-2), 3.61 (dd, 1H, J=11.5 Hz, J'=7.9 Hz, Ha-5), 3.07 (dd, 1H, $J\sim J'\sim$11.5, Hb-5), 2.28, (m, 1H, H-4), 1.06 (d, 3H, $J\sim$6.8, CH_3). ^{13}C NMR (75.0 MHz, D_2O, dioxane: 67.19 ppm): 170.96 (CO), 75.87 (C-3), 68.45 (C-2), 50.15 (C-5), 37.16 (C-4), 10.03 (CH_3).

(4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-(1-ethoxy)ethoxymethyl-4-hydroxy-3-methylpyrrolidin-2-ones 21. $Pd(OH)_2$ (200 mg) was added to a solution of cycloadduct **19** (760 mg, 2.22 mmol)[12] in EtOAc–MeOH 5:1 (9.2 mL) and the mixture was stirred under H_2 atmosphere at rt for 50 h. The catalyst was filtered on Celite® and washed with MeOH. The crude product obtained by evaporation to dryness was purified by chromatography on silica gel (eluent: CH_2Cl_2–MeOH 95:5) to afford the pyrrolidinones **21** (504 mg, 72%) amorphous. IR: 3613, 3470 (broad), 3014, 2983, 2938, 1783, 1747, 1712, 1476, 1457, 1371, 1313. MS (CI, isobutane): 318 $(M+H)^+$, 262, 218, 216, 190, 172 (100%), 146. HRMS (CI): Calcd for $C_{15}H_{28}NO_6$ $(M+H)^+$: 318.1909. Found: 318.1917. ^{1}H NMR (300 MHz): 4.77–4.62 (OCHO), 4.31 (H-4, dia **a**), 4.12 (H-5),

3.97 (H-5+H-4, dia **b**), 4.0–3.4 (2×OCH_2), 2.92 (H-3, dia **a**), 2.54 (H-3, dia **b**), 1.54 (s, 9H, *t*-Bu), 1.32 (CH_3-3, dia **b**), 1.29 ($OCHCH_3$), 1.20 (OCH_2CH_3, CH_3-3, dia **a**). ^{13}C NMR (75.0 MHz): 175.93, 175.36 (CO), 150.11, 149.94 (NCO_2), 100.38, 99.96, 99.73 (OCHO), 83.28, 83.01 (qC, *t*-Bu), 73.87, 73.58 (C-4, dia **b**), 70.19, 70.10 (C-4, dia **a**), 65.01, 64.89 (C-5), 64.50, 64.02 (OCH_2), 64.02, 63.90 (C-5), 63.27, 62.98 (OCH_2), 61.68, 61.50, 61.15, 61.06 (OCH_2), 46.76 (C-3, dia **b**), 42.96, 42.84 (C-3, dia **a**), 28.09 (CH_3, *t*-Bu), 19.84, 19.64, 19.54 ($OCHCH_3$), 15.29 (CH_3-3, dia **b**), 13.85, 13.76 (OCH_2CH_3), 8.19 (CH_3-3, dia **a**).

(4*R*,7*R*,8*S*)-6-*tert*-Butoxycarbonyl-7-acetoxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane-5-one 22. Acetic anhydride (2.0 mL) was added under Ar to a stirred solution of alcohol **20**[12] (294 mg, 1.08 mmol) in pyridine (5.8 mL) at 0°C. The mixture was stirred at rt for 2.75 h and cooled again at 0°C before the addition of MeOH (2 mL). After being stirred for 0.5 h at rt, the solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2. After being washed with $NaHCO_3$ (5% w/v) the organic layers gave the crude acetate after usual workup. It was purified by chromatography on silica gel (eluent: CH_2Cl_2–MeOH 97:3) to afford **22** as a colourless oil (321 mg, 95%): $[\alpha]_D^{26}=-68$ (*c*=0.73). IR: 2990, 1788, 1742, 1463, 1375. Anal. Calcd for $C_{14}H_{22}N_2O_6$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.45; H, 7.13; N; 9.13. ^{1}H NMR (300 MHz): 4.52 (m+dd, 2H, H-8, Ha-9), 4.35 (m, 1H, H-7), 4.20 (br d, *J*~11 Hz, Hb-9), 3.53 (m, 2H, Ha-3, H-4), 2.74 (masked m, 1H, Hb-3), 2.70 (br s, 3H, NCH_3), 2.07 (s, 3H, $COCH_3$), 1.55 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 173.89 (CO), 170.52 (CO), 149.19 (NCO_2), 84.13 (qC, *t*-Bu), 75.33 (C-8), 63.52 (OCH_2), 62.98 (NCH, C-7), 61.04 (NCH_2, C-3), 52.83 (C-4), 44.95 (N-CH_3), 28.11 (CH_3, *t*-Bu), 20.78 ($COCH_3$).

(4*S*,5*R*)-1-*tert*-Butoxycarbonyl-5-acetoxymethyl-4-hydroxy-3-methylpyrrolidin-2-ones 23. The acetate **22** (201 mg, 0.64 mmol) was hydrogenolyzed as described with **19** to afford, after chromatography on silicagel (eluent: CH_2Cl_2–MeOH 96:4), the compounds **23** as a colourless oil (134 mg, 73%). IR: 3600, 2990, 1786, 1745, 1717 (sh), 1450, 1370, 1310. MS (CI, isobutane): 288 $(M+H)^+$, 232, 188 (100%). Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.34; H, 7.37; N, 4.88. Found: C, 53.99; H, 7.31; N, 4.84. ^{1}H NMR (300 MHz): 4.50 (dd, *J*=11.8 Hz, *J′*=4.6 Hz, Ha-6, dia **b**), 4.36 (Ha-6, dia **a**), 4.34 (Hb-6, dia **b**), 4.28 (m, H-4, dia **a**), 4.23 (Hb-6, dia **a**, H-5, dia **a**), 4.03 (m, H-5, dia **b**), 3.93 (m, H-4, dia **b**), 3.26 (OH), 2.79 (m, H-3, dia **a**), 2.72 (OH), 2.58 (m, H-3, dia **b**), 2.07 (splitted s, 3H, $COCH_3$), 1.53 (s, 9H, *t*-Bu), 1.32 (d, *J*=7 Hz, CH_3-3, dia **b**), 1.22 (d, *J*=7.2 Hz, CH_3-3, dia **a**). NOESY experiments (400 MHz) showed correlations between H-3 and H-4 in **23a**, CH_3-3 and H-4 in **23b**, as well as H-4 and Hb-6 in **23b**. ^{13}C NMR (75.0 MHz): 175.47 (CO), 170.57 (CO), 149.87 (NCO_2), 83.85, 83.70 (qC, *t*-Bu), 72.73 (C-4, **b**), 69.53 (C-4, **a**), 63.84 (C-5, **a**), 63.51 (C-5, **b**), 62.52 (C-6, **a**), 62.37 (C-6, **b**), 46.80 (C-3, **b**), 42.73 (C-3, **a**), 28.02 (CH_3, *t*-Bu), 20.86 ($COCH_3$), 13.85 (CH_3-3, **b**), 8.19 (CH_3-3, **a**).

1-*tert*-Butoxycarbonyl-3-benzoyloxy-2-hydroxymethyl-4-methylpyrrolidines 25 and 26. *Reduction of **21** with DIBAL-H:* To a solution of the pyrrolidinones **21** (381 mg, 1.2 mmol) in anhydrous THF (2.9 mL), stirred at −78°C under Ar, was dropwise added DIBAL-H (1 M in hexane, 3.6 mL). The mixture was stirred at −78°C for 30 min. Na_2CO_3 (10% v/v, 14 mL) and saturated aqueous NH_4Cl solution (20 mL) were successively added at the same temperature. After dilution with CH_2Cl_2 the cooling bath was removed and the product was extracted four times with CH_2Cl_2. Usual workup afforded α-hydroxycarbamates **24** (376 mg, 98%) as a colourless oil.

*Benzoylation of **24**:* To a solution of α-hydroxycarbamates **24** (351 mg, 1.1 mmol) in CH_2Cl_2 (5.5 mL) cooled at 0°C were successively added Et_3N (367 μL) and PhCOCl (130 μL). After being stirred for additional 24 h at 40°C, the reaction medium was cooled at 0°C and diluted with CH_2Cl_2 (20 mL). 2 N NaOH (10 mL) was added and the mixture was stirred for 45 min. The aqueous layer was separated and extracted with CH_2Cl_2 (three times). The organic layers were stirred three times for 10 min. with 2N NaOH and afforded after usual workup, a mixture which was directly reduced as below.

$NaBH_3CN$ reduction and primary alcohol deprotection: $NaBH_3CN$ (470 mg, 7.47 mmol) was portionwise added at rt to a stirred solution of the benzoylation crude product in acetic acid (5.5 mL). After complete addition, the mixture was stirred at 30°C for 1.5 h, cooled to 0°C, diluted with CH_2Cl_2 (34 mL) and NaOH was added until pH 7.5. After extraction with CH_2Cl_2 (four times) and usual workup, the crude product was chromatographied on silica gel (eluent: CH_2Cl_2–MeOH 96:4) to give **25** (more polar *cis*, 119 mg, 32%) and **26** (less polar, 133 mg, 36%) as colourless oils. Overall yield 68% for 2 steps.

(2*R*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-benzoyloxy-2-hydroxymethyl-4-methylpyrrolidine 25. $[\alpha]_D^{25}=-30.5$ (*c*=1.34). IR: 3684, 3400 (broad), 2988, 1717, 1687, 1602, 1469, 1462, 1409, 1367. MS (CI, isobutane): 336 $(M+H)^+$, 292, 280, 236 (100%), 123, 114. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.32; H, 7.45; N, 4.13. ^{1}H NMR (300 MHz): 8.05 (d, 2H, H-Ar), 7.60 (dd, 1H, H-Ar), 7.47 (dd, 2H, H-Ar), 5.36, 5.21 (2m, 1H, H-3), 4.10 (m), 3.85 (masked m): H-2, 3.90, 3.75 (OCH_2), 3.66 (m, 1H, Ha-5), 3.26 (m, 1H, Hb-5), 2.60 (m, 1H, H-4), 1.47 (s, 9H, *t*-Bu), 1.10 (d, 3H, *J*=6 Hz, CH_3-4). ^{13}C NMR (75.0 MHz): (CO not visible), 133.36 (CH, Ar), 129.95 (qC, Ar), 129.74, 128.56 (CH, Ar), 80.57 (qC, *t*-Bu), 78.01 (C-3), 66.33 (C-2), 64.66 (OCH_2), 52.35 (C-5), 35.65 (C-4), 28.50 (CH_3, *t*-Bu), 11.48 (CH_3-4).

(2*R*,3*S*,4*R*)-Diastereomer 26. $[\alpha]_D^{24}=-41$ (*c*=1.81). IR: 1718, 1690. MS (CI, isobutane): 336 [$(M+H)^+$, 100%], 292, 280, 236, 123. HRMS ($ClCH_4$): Calcd for $C_{18}H_{26}NO_5$ $(M+H)^+$: 336.1810. Found: 336.1809. ^{1}H NMR (300 MHz): 8.05 (d, 2H, H-Ar), 7.59 (dd, 1H, H-Ar), 7.45 (dd, 2H, H-Ar), 5.01 (m, H-3), 4.01 (m, H-2), 3.9 (Ha-6), 3.83 (Hb-6, Ha-5), 3.07 (m, 1H, Hb-5), 2.42 (m, 1H, H-4), 1.48 (s, 9H, *t*-Bu), 1.13 (d, 3H, *J*=6 Hz, CH_3-4). ^{13}C NMR (75.0 MHz): (CO not visible), 133.46, 129.83 (CH, Ar), 129.63 (qC, Ar), 128.55 (CH, Ar), 80.79 (qC, *t*-Bu), 80.18 (C-3), 65.80 (C-2), 65.14 (OCH_2), 52.32 (C-5), 37.78 (C-4), 28.50 (CH_3, *t*-Bu), 15.51 (CH_3-4).

(2*S*,3*S*,4*S*)-1-*tert*-Butoxycarbonyl-3-benzoyloxy-4-methylpyrrolidine-2-carboxylic acid 27. To a stirred biphasic solution of alcohol **25** (54.0 mg, 0.16 mmol) in a mixture of CCl_4 (0.32 mL), CH_3CN (0.32 mL), H_2O (0.49 mL) were successively added $NaIO_4$ (107.4 mg, 0.50 mmol) and $RuCl_3$, 2 H_2O (1.6 mg). The mixture was vigorously stirred for 50 min. at rt, diluted with CH_2Cl_2 (15 mL) and H_2O (1.5 mL) and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were washed with H_2O (1 mL). After usual workup the crude product was purified by preparative TLC (eluent CH_2Cl_2–MeOH–CH_3CO_2H 92:8:0.05) to afford the carboxylic acid **27** as a white solid (49.6 mg, 88%). $[\alpha]_D^{26}=+19$ (c=2.1, MeOH). IR: 3450 (broad), 3030, 2990, 1716, 1682, 1616, 1417. MS (FAB, thioglycerol +HCl): 350 $(M+H)^+$, 294, 250 (100%), 105. ^{1}H NMR (300 MHz, DMSO-d_6): 7.95 (d, 2H, H-Ar), 7.66 (dd, 1H, H-Ar), 7.53 (dd, 2H, H-Ar), 5.47 (m, 1H, H-3), 4.10, 4.02 (1H, H-2), 3.63 (m, Ha-5, OH), 3.04 (m, 1H, Hb-5), 2.61 (m, 1H, H-4), 1.41, 1.32 (2s, 9H, *t*-Bu), 0.94 (broad d, 3H, CH_3-4). ^{13}C NMR (75.0 MHz, DMSO d_6, δ=39.52 ppm): 165.09 (CO), 153.85 (NCO_2), 133.41 (CH, Ar), 129.67 (qC, Ar), 129.09, 128.82 (CH, Ar), 80.3 (qC, *t*-Bu), 78.19, 77.85 (C-3), 51.06, 50.71 (C-5), 35.39, 34.44 (C-4), 28.24, 28.11 (CH_3, *t*-Bu), 11.54 (CH_3-4).

(2*S*,3*S*,4*R*)-1-*tert*-Butoxycarbonyl-3-benzoyloxy-4-methylpyrrolidine-2-carboxylic acid 28. The less polar alcohol **26** (38.7 mg, 0.115 mmol) was oxidised following the same protocol with $NaIO_4$ (74.5 mg, 0.348 mmol) and $RuCl_3$, 2 H_2O (1.2 mg) for 40 min at rt. The same treatment as before gave rise to the carboxylic acid **28** as a white solid (30.2 mg, 75%). $[\alpha]_D^{26}=+21$ (c=2.15, MeOH). IR: 3350–2600 (broad), 2975, 1719, 1702, 1686, 1630, 1455, 1410, 1375. MS (FAB, thioglycerol+HCl): 350 $(M+H)^+$, 294, 250 (100%), 105. ^{1}H NMR (300 MHz, DMSO-d_6): 7.95 (d, 2H, H-Ar), 7.68 (dd, 1H, H-Ar), 7.55 (dd, 2H, H-Ar), 5.23 (m, 1H, H-3), 4.13, 4.04 (1H, H-2), 3.67 (m, 1H, Ha-5), 3.05 (m, 1H, Hb-5), 2.25 (m, 1H, H-4), 1.44, 1.37 (2s, 9H, *t*-Bu), 1.09 (broad d, 3H, CH_3-4). ^{13}C NMR (62.0 MHz, DMSO-d_6=39.52 ppm): 165.3 (CO), 154.1 (NCO_2), 133.4 (CH, Ar), 129.9 (qC, Ar), 129.15, 128.78 (CH, Ar), 85.0 (qC, *t*-Bu), 78.1, 77.9 (C-3), 66.8 (C-2), 51.8, 51.4 (C-5), 38.09 (C-4), 28.2 (CH_3, *t*-Bu), 17.5 (CH_3-4).

(2*S*,3*S*,4*S*)-3-Hydroxy-4-methylproline 2, hydrochloride. The acid **27** (35 mg, 0.10 mmol) in 6N HCl (2 mL) was heated at 80°C for 37 h and the mixture was evaporated to dryness. The residue was washed with small amounts of Et_2O and dissolved in water. After filtration, the solvent was removed under vacuum to provide quantitatively **2**, as hydrochloride salt.

(2*S*,3*S*,4*R*)-3-Hydroxy-4-methylproline 29, hydrochloride. In the same conditions, the acid **28** (23.7 mg, 0.068 mmol) was deprotected to give rise to the aminoacid **29** as its hydrochloride salt (12.3 mg, 100%): $[\alpha]_D^{24}=-4$ (c=0.48, MeOH). MS (FAB, thioglycerol): 147, 146 [$(M+H)^+$, 100%], 131, 100. ^{1}H NMR (300 MHz, D_2O:=4.8 ppm): 4.20 (dd, 1H, $J\sim J'\sim 6$ Hz, H-3), 4.11 (d, 1H, $J\sim 6$ Hz, H-2), 3.64 (dd, 1H, J=12 Hz, J'=7 Hz, Ha-5), 3.13 (dd, 1H, J=12 Hz, J'=9 Hz, Hb-5), 2.34 (m, 1H, H-4), 1.09 (d, J=7 Hz, CH_3-4) ^{13}C NMR (50 MHz, D_2O, dioxane: δ=67.19 ppm): 171.2 (CO), 79.3 (C-3), 65.4 (C-2), 50.4 (C-5), 40.6 (C-4), 14.04 (CH_3-4).

(4*R*,7*R*,8*S*)-6-*tert*-Butoxycarbonyl-7-hydroxymethyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane 30. *A. Reduction of **19** with DIBAL-H:* A solution of DIBAL-H in hexane (1 M, 14.74 mL, 2.4 equiv.) was added dropwise under argon to a stirred solution of **19** (2.11 g, 6.13 mmol) in anhydrous THF at −78°C. The mixture was stirred at −78°C for 35 min. At the same temperature were successively added an aqueous solution of Na_2CO_3 (10% w/v, 60 mL), a saturated aqueous solution of NH_4Cl (85 mL) and dichloromethane (100 mL) and then the cooling bath was removed. CH_2Cl_2 (600 mL) was added and, after being stirred, the layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. After usual workup, the α-hydroxycarbamates were obtained in 100% yield (2.12 g) and directly used in the next step: IR: 1700.

B. Reduction with $NaBH_3CN$: $NaBH_3CN$ (2.33 g, 37.0 mmol) was portionwise added at rt to a stirred solution of dried α-hydroxycarbamates (1.83 g, 5.29 mmol) in acetic acid (26.4 mL). After complete addition, the mixture was stirred at 30°C until completion (c.a. 1.3 h), cooled to 0°C and diluted with CH_2Cl_2 (160 mL). After addition of NaOH until pH 7.5 the mixture was extracted four times with CH_2Cl_2 to afford, after usual workup, the compound **30** (amorphous, 1.365 g, 100%). $[\alpha]_D^{25}=-27$ (c=1.5). IR= 3415, 2990, 1689, 1483, 1463, 1410. MS (EI): 258 ($M^{+\cdot}$), 185 (100%), 184, 157, 128, 127, 115, 112, 98. HRMS: Calcd for $C_{12}H_{22}N_2O_4$ ($M^{+\cdot}$): 258.1580. Found: 258.1569. ^{1}H NMR (300 MHz, very broad signals): 4.0, 3.8–3.4 (OCH_2), 2.7 (3H, NCH_3), 1.47 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 84.59 (weak, C-8), 80.3 (qC, *t*-Bu), 65.25 (NCH), 63.46 (CH_2), 53.04 (CH), 51.74 (NCH_2), 51.12 (NCH_2), 45.04 (NCH_3), 28.50 (CH_3, *t*-Bu).

(4*R*,7*R*,8*S*)-7-Acetoxymethyl-6-*tert*-butoxycarbonyl-2-methyl-1-oxa-2,6-diazabicyclo[3.3.0]octane 31. Acetic anhydride (9.1 mL) was added at 0°C under argon to a solution of the compound **30** (1.34 g, 5.2 mmol, dried by evaporation of toluene), in pyridine (26.0 mL). The mixture was stirred at rt until completion of the reaction (5 h) and cooled to 0°C before addition of methanol (16 mL). After being stirred at rt for 0.5 h, the mixture was concentrated under reduced pressure. After dilution with CH_2Cl_2 (200 mL) and washing with $NaHCO_3$ (5% w/v, 10 mL), the aqueous layer was extracted three times with CH_2Cl_2 (150, 100, 100 mL). After usual workup the organic layers afforded the acetate **32** which was purified by chromatography (eluent: CH_2Cl_2–MeOH 98:2) and obtained as a colourless oil (1.22 g, 78%). $[\alpha]_D^{23}=-41.5$ (c=1.5). IR: 2900, 1743, 1690, 1407. MS (EI): 300 (($M^{+\cdot}$), 184 (100%), 125, 81, 80. Anal. Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05; N, 9.32. Found: C, 55.74; H, 7.98; N, 9.41. ^{1}H NMR (300 MHz, broad signals): 4.66, 4.46 (2m, 1H, H-8), 4.15 (OCH_2), 3.7–2.8 (2×NCH_2), 2.68 (3H, NCH_3), 2.07 (s, 3H, $COCH_3$), 1.46 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz, broad signals): 170.48 (OCO), 153.78 (NCO_2), 84.34 (C-8), 80.06 (qC, *t*-Bu), 65.19, 63.64 (CH_2), 62.19–60.51 (NCH), 51.27 (NCH_2), 44.89 (NCH_3), 28.41 (CH_3, *t*-Bu).

***N,N*-Dimethylisoxazolidinium and methyl sulfate 32.** Dimethyl sulfate (248 μL, 2.62 mmol) was added under argon to a solution of acetate **31** (515 mg, 1.72 mmol) in EtOAc (3.8 mL). The mixture was stirred at rt for 18 h and the solvent and reagent in excess were eliminated under reduced pressure and the white solid was crystallised in MeOH–Et_2O (673 mg, 92%). Mp: 158–160°C. $[\alpha]_D^{28}=-15$ (c=1.50, MeOH). Anal. Calcd for $C_{16}H_{30}N_2O_9S$: C, 45.05; H, 7.09; N, 6.57. Found: C, 44.69; H, 6.94; N, 6.44. ^{1}H NMR (300 MHz, D_2O, HOD δ=4.8 ppm): 5.40, 5.36 (m, 1H, H-8), 4.52 (Ha-3), 4.46 (Ha-9), 4.43 (m, H-7), 4.23 (Hb-9), 3.95 (m, 2H, Hb-3, H-4), 3.75 (masked m, H_2-5), 3.75, 3.68, 3.58 (3s, OCH_3, 2×NCH_3), 2.14 (s, 3H, $COCH_3$), 1.50 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz, D_2O without reference): 173.60 (OCO), 155.26 (NCO_2), 90.15, 89.22 (C-8), 82.84 (qC, *t*-Bu), 71.95 (CH_2, C-3), 63.14, 62.42 (OCH_2), 60.43, 60.13 (NCH), 56.06, 55.37, 54.49 (OCH_3 sulfate, 2×NCH_3), 49.75(C-5), 44.99, 44.22 (C-4), 27.52 (CH_3, *t*-Bu), 20.21 ($COCH_3$).

(2*R*,3*S*,4*S*)-2-Acetoxymethyl-4-(*N,N*-dimethyl)aminomethyl-1-*tert*-butoxycarbonyl-3-hydroxypyrrolidine 33. *N*,*N*-Dimethylisoxazolidinium **32** (653 mg, 1.53 mmol) in MeOH (9.9 mL) was stirred under H_2 atmosphere at rt in the presence of $Pd(OH)_2$ (130 mg) for 25 h. The catalyst was filtered off on Celite® and washed with MeOH. The solution was evaporated to dryness to give the (*N*,*N*-dimethyl)-aminomethyl derivative **33**, as methylsulfate salt (660 mg, 100%). MS (CI, isobutane): 317 [$(M+H)^+$, 100%], 261, 259, 142, 73. HRMS (CI): Calcd for $C_{15}H_{29}N_2O_5$ $(M+H)^+$: 317.2076. Found: 317.2090. ^{1}H NMR (300 MHz): 4.41 (m, 1H, H-3), 4.15 (2m, 2H), 3.95 (m, 1H), 3.75 (s, 3H, OCH_3 sulfate), 3.55 (2 x NCH), 3.25 (m, 1H, NCH), 3.04 (m, 1H, NCH), 2.94 (s, 6H, $N(CH_3)_2$), 2.74 (m, 1H), 1.47 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 170.75 (CO), 154.35 (NCO_2), 80.55 (qC, *t*-Bu), 71.74 (C-3), 65.06 (OCH_2), 62.72 (C-2), 56.34 (OCH_3), 55.11 (NCH_2), 48.04 (NCH_2), 44.49 (NCH_3), 36.88 (C-4), 28.49 (CH_3, *t*-Bu), 20.99 ($COCH_3$). To this salt (608 mg, 1.42 mmol) and CH_2Cl_2 (150 mL) was added an aqueous solution of $NaHCO_3$ (10% w/v, 7 mL). After stirring and separation of the layers, the aqueous layer was extracted three times with CH_2Cl_2. Usual workup afforded the compound **33** (435.5 mg, 97%). $[\alpha]_D^{26}=-40$ (c=0.75). IR: 3400, 3020, 1735, 1685 (broad). ^{1}H NMR (300 MHz): 4.30 (1H), 4.21 (2H), 3.91 (1H), 3.80 (1H): H-3, H_2-6, H-2, 3.40 (m, 1H, NCH), 3.30–3.22 (1H), 2.69 (1H), 2.41 (m, 2H, NCH), 2.27 (s, 6H, $N(CH_3)_2$), 2.05 (s, 3H, $COCH_3$), 1.48 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 170.78 (OCO), 154.54 (NCO_2), 80.14 (qC, *t*-Bu), 75.58, 74.28 (C-3), 63.44 (C-2), 63.12 (OCH_2), 58.75 (NCH_2), 48.76 (NCH_2), 45.81 (NCH_3), 36.80 (C-4), 28.47 (CH_3, *t*-Bu), 20.93 ($COCH_3$).

(2*R*,3*S*,4*S*)-2-Acetoxymethyl-4-(*N,N*-dimethyl)aminomethyl-3-benzoyloxy-1-*tert*-butoxycarbonylpyrrolidine 34. Triethylamine (190 μL, 1.37 mmol) and benzoyl chloride (159 μL, 1.37 mmol) were successively added to a solution of **33** (379 mg, 1.2 mmol) in dry CH_2Cl_2 (4.85 mL) under stirring at 0°C. The mixture was stirred at rt for 27 h. After dilution with CH_2Cl_2 and addition of Na_2CO_3 (10% w/v, 25 mL) the mixture was stirred at rt for 0.25 h and the aqueous layer was further extracted twice with CH_2Cl_2. After usual workup, the benzoate **34** was purified by chromatography on silica gel (eluent: CH_2Cl_2–MeOH 95:5) and obtained as a colourless oil (469 mg, 93%). $[\alpha]_D^{24}=-22$ (c=2.9). IR: 3030, 1750, 1730, 1700. MS (CI, isobutane): 421 [$(M+H)^+$, 100%], 365, 186, 142, 123. Anal. Calcd for $C_{22}H_{32}N_2O_6$: C, 62.84; H, 7.47; N, 6.66. Found: C, 62.89; H, 7.47; N, 6.62. ^{1}H NMR (300 MHz): 8.02 (d, 2H, J~8 Hz, H-Ar), 7.60 (dd, 1H, H-Ar), 7.47 (dd, 2H, J~J'~8 Hz, H-Ar), 5.43 (m, 1H, H-3), 4.32 (dd, 1H, Ha-6), 4.17 (Hb-6), 4.15, 4.00 (2m, 1H, H-2), 3.74, 3.33 (2m, 2H, NCH_2), 2.75 (m, 1H), 2.58, 2.46 (2m, NCH_2), 2.22 (s, 6H, $N(CH_3)_2$), 2.13 (s, 3H, $COCH_3$), 1.47 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 170.69 ($OCOCH_3$), 165.74 ($COPh$), 155.0 (NCO_2), 133.38 (CH, Ar), 129.88 (qC, Ar), 129.68, 128.57 (CH, Ar), 80.45, 80.14 (qC, *t*-Bu), 77.18, 76.30 (C-3), 63.18 (C-2), 62.78 (OCH_2), 57.27, 56.93 (NCH_2), 49.84, 49.54 (NCH_2), 45.93 ($N(CH_3)_2$), 39.30, 38.47 (C-4), 28.48 (CH_3, *t*-Bu), 20.95 ($COCH_3$).

(2*R*,3*S*,4*R*)-2-Acetoxymethyl-4-(*N,N*-dimethyl,*N*-oxy)-aminomethyl-3-benzoyloxy-1-*tert*-butoxycarbonylpyrrolidine 35. $NaHCO_3$ (298 mg, 3.55 mmol) and mCPBA (230 mg, 1.33 mmol) were successively added to a stirred solution of benzoate **34** (371 mg, 0.88 mmol) in CH_2Cl_2 (17.7 mL) and the mixture was stirred for 5 min before the addition of aqueous Na_2CO_3 (10% w/v, 7 mL). The *N*-oxide was extracted three times with CH_2Cl_2 and the organic layers were washed with 10% Na_2CO_3. Usual workup furnished the *N*-oxide **35** (379 mg, 98%) as a white foam. ^{1}H NMR (250 MHz): 8.00 (d, 2H, H-Ar), 7.61 (dd, 1H, H-Ar), 7.46 (dd, 2H, H-Ar), 5.57 (m, 1H, H-3), 4.4–3.3 (3m, 8H, H-2, OCH_2, 2×NCH_2, H-4), 3.22 (s, 6H, $N(CH_3)_2$), 2.15 (s, 3H, $COCH_3$), 1.46 (s, 9H, *t*-Bu). ^{13}C NMR (62.5 MHz): 170.9 (OCO), 165.6 (OCO), 154.0 (NCO_2), 133.8 (qC, Ar), 129.7 129.2, 128.7 (CH, Ar), 80.9, 80.5 (qC, *t*-Bu), 78.1 (C-3), 68.7 (OCH_2), 62.8 (NCH_3), 62.3 (N^+CH_2), 60.8, 59.8, 59.5, 58.4 (C-2), 50.3, 50.0 (C-5), 36.0, 34.8 (C-4), 28.4 (CH_3, *t*-Bu), 20.9 ($COCH_3$).

(2*R*,3*S*)-2-Acetoxymethyl-3-benzoyloxy-1-*tert*-butoxycarbonyl-4-*exo*-methylenepyrrolidine 36. A solution of *N*-oxide **35** (196 mg, 0.45 mmol) in a mixture THF–toluene 1:1 (70 mL) was heated under inert atmosphere at 85°C for 5 h. After cooling at 30°C, the solvents were evaporated under reduced pressure and the residue was purified by preparative TLC (eluent: heptane–Et_2O 2:8) to afford the compound **36**, amorphous (147 mg, 87%). $[\alpha]_D^{27}=-12.5$ (c=2.36). IR: 3010, 1742, 1717, 1694, 1404. MS (EI): 375 ($M^{+\cdot}$), 302, 260, 246, 215, 152 (100%), 105, 93, 56. MS (FAB): 376 $(M+H)^+$, 320, 276, 260, 198 (100%), 154, 91, 73. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 63.67; H, 6.64; N, 3.73. ^{1}H NMR (300 MHz): 8.02 (d, 2H, H-Ar), 7.59 (dd, 1H, H-Ar), 7.45 (dd, 2H, H-Ar), 5.66 (broad s, 1H, H-3), 5.54 (broad s, 1H, =CHa), 5.36 (1H, =CHb), 4.34, 3.99 (2 broad d, OCH_2), 4.21 (H-2), 2.07 (s, 3H, $COCH_3$), 1.49 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 170.62 (OCO), 165.92 (OCO), 154.00 (NCO_2), 142.91, 141.99 (C-4), 133.35 (qC, Ar), 129.77, 128.49 (CH, Ar), 115.21 (=CH_2), 80.62 (qC, *t*-Bu), 77.58, 76.72 (C-3), 62.72, 62.47 (OCH_2), 62.29, 61.91 (C-2), 49.69, 49.45 (C-5), 28.46 (CH_3, *t*-Bu), 20.81 ($COCH_3$).

(2*R*,3*S*)-3-Benzoyloxy-1-*tert*-butoxycarbonyl-2-hydroxymethyl-4-*exo*-methylenepyrrolidine 37. To a solution of acetate **36** (75.0 mg, 0.2 mmol) in MeOH (1.0 mL) was added 0.05N NaOH (400 μL) and the mixture was stirred at rt for 0.4 h, and diluted with EtOAc (40 mL) and with H_2O (3.0 mL). The aqueous layer was extracted three times with EtOAc. After usual workup, the alcohol **37** was purified by preparative TLC (eluent: CH_2Cl_2–MeOH 96:4) and obtained as a colourless oil (48.0 mg, 72%): $[\alpha]_D^{27}=-39$ (*c*=0.90). IR: 3013, 1716, 1689, 1603, 1477, 1453, 1409. MS (CI, isobutane): 334 $(M+H)^+$, 290, 278, 234 (100%), 123, 114. HRMS: Calcd for $C_{18}H_{24}NO_5$ $(M+H)^+$: 334.1655. Found: 334.1661. ^{1}H NMR (300 MHz): 8.03 (d, 2H, H-Ar), 7.59 (dd, 1H, H-Ar), 7.46 (dd, 2H, H-Ar), 5.60 (m, 1H), 5.48 (broad s, 1H, =CHa), 5.32 (broad s, 1H, =CHb), 4.25 (1H), 4.07, 3.80 (OCH_2), 1.50 (s, 9H, *t*-Bu). ^{13}C NMR (75.0 MHz): 142.31 (C-4), 133.49 (qC, Ar), 129.88, 128.58 (CH, Ar), 114.32 (=CH_2), 80.90 (qC, *t*-Bu), 65.41 (OCH_2), 64.02 (C-2), 50.08 (C-5), 28.55 (CH_3, *t*-Bu). In this reaction, starting acetate **36** (7.5 mg, 10%) was recovered and a more polar compound **38** was isolated in small amount (7 mg, 15%). When the reaction mixture was concentrated under reduced pressure before extraction the yield of diol **38** was significantly improved. Mp: 125°C. $[\alpha]_D^{27}=-59$ (*c*=2.08). IR: 3600, 3406 (broad), 3010, 2992, 2932, 1680, 1478, 1456, 1409, 1369. MS (FAB): 230 $(M+H)^+$, 198, 174 (100%), 156, 154, 147, 130. HRMS: Calcd for $C_{11}H_{20}NO_4$ $(M+H)^+$: 230.1392; Found: 230.1387. ^{1}H NMR (300 MHz): 5.30 (broad s, 1H, =CHa), 5.14 (broad s, 1H, =CHb), 4.30 (1H), 4.15, 3.92 (2 broad d, OCH_2), 3.85–3.60 (3H), 1.47 (s, 9H, *t*-Bu). ^{13}C NMR (50.0 MHz): 146.3 (C-4), 109.8 (=CH_2), 80.8 (qC, *t*-Bu), 74.5 (C-3), 67.5 (C-2), 63.9 (OCH_2), 49.9 (C-5), 28.5 (CH_3, *t*-Bu).

Hydrogenation of 37–25. A solution of **37** (36.6 mg, 0.11 mmol) in EtOAc (3.7 mL) was stirred under H_2 atmosphere in the presence of PtO_2 (4 mg) for 1.5 h. The catalyst was filtered off on Celite® and washed with EtOAc. Evaporation of the solvent under reduced pressure furnished the crude dihydro derivative which was purified by preparative TLC (eluent–CH_2Cl_2–MeOH 96:4) to give **25** (29.0 mg, 79%).

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