Regio- and Stereoselective Opening of Oxiranes through Neighbouring Group Participation: Stereocontrolled Synthesis of Enantiopure Hydroxylated Oxazolidin-2-ones

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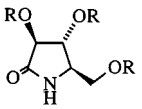
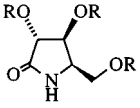
The regio- and stereo-selective ring opening of (*S*)-pyroglutaminol derived epoxides provides an effective route to protected *syn,syn*-aminodiol units. The procedure involves the chemoselective aminolysis or alcoholysis of (3*R*,4*R*,5*R*)-*N*-(*tert*-butoxycarbonyl)-3,4-epoxy-5-[(1-ethoxy)ethoxymethyl]pyrrolidin-2-one (**10**), followed by the formation in quantitative yield of oxazolidinone intermediates, through the mediation of neighbouring *N*-Boc groups. The practical synthetic interest of this route is illustrated by the example of (3*R*,4*S*,5*R*)-3,4-diacetoxy-5-(acetoxymethyl)pyrrolidin-2-one which should serve as useful building block in further syntheses.

Introduction

The trihydroxylated pyrrolidin-2-ones **1** and **3** as well as their enantiomers, and suitably protected derivatives such as the triacetates **2**[1] and **4**, could be useful intermediates in the synthesis of various interesting compounds. They could led to the corresponding pyrrolidines which are known as azasugars and gave rise to intensive studies related to their activities as glycosidase inhibitors.[1–4] The pyrrolidinones **1** and ***ent*-3** could also constitute chiral templates in the synthesis of more complex pyrrolizidine alkaloids such as alexine, australine, and 3-epi-analogues.[5] Furthermore, **3** could be a precursor of (−)-anisomycin, a well-known antifungic anbitiotic,[6] and ***ent*-3** derivatives could led to the aziridine core of antitumour azinomycins A and B.[7]

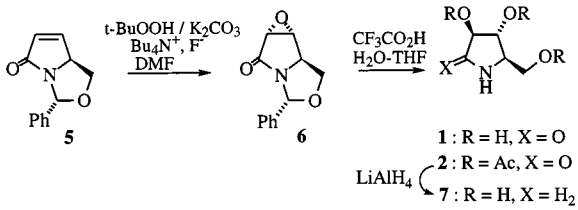


1 : R = H
2 : R = Ac



3 : R = H
4 : R = Ac

Starting from the versatile α,β-unsaturated lactam **5** derived from (*S*)-pyroglutaminol, we already prepared **1** and its triacetate **2** through the epoxide **6** and the reduction of **2** afforded 1,4-dideoxy-1,4-imino-D-arabinitol **7** as well (Scheme 1).[1]



Scheme 1. Synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol **7** from γ-lactam **5**

In this acidic epoxide-ring opening with attack α to the carbonyl, the high regioselectivity was the same as that observed with various other reagents such as $LiAlH_4$,[8] Me_2CuLi, aluminum amalgam[9] and SmI_2.[10]

We planned to synthesize also **3** or **4** by reversing the opening regioselectivity of the same epoxide **6**, owing to its accessibility in high yield.[11]

Results and Discussion

For this purpose, we envisaged to follow a route involving, as the key step, the mediation of the *tert*-butoxycarbonyl protecting group in the ring opening of an acyclic epoxy derivative **A**, leading to an oxazolidinone **B** (Scheme 2).[12]

After quantitative and chemoselective hydrolysis of the oxazolidine **6** into **8** under controlled acidic conditions which kept intact the oxirane (CF_3CO_2 H, THF/H_2O 1:1, 30°C), the *N*-Boc-3,4-epoxypyrrolidin-2-one **10** was easily prepared from **8** by classical protections. The primary alcohol function was protected as acetal with ethyl vinyl ether (93%) and *tert*-butoxycarbonyl was selected as the *N*-protecting group (88%). Indeed, the *N*-protection as carbamate is known to enhance the reactivity of pyrrolidin-2-ones

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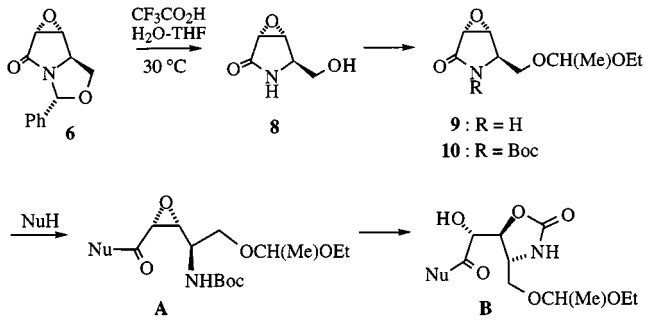
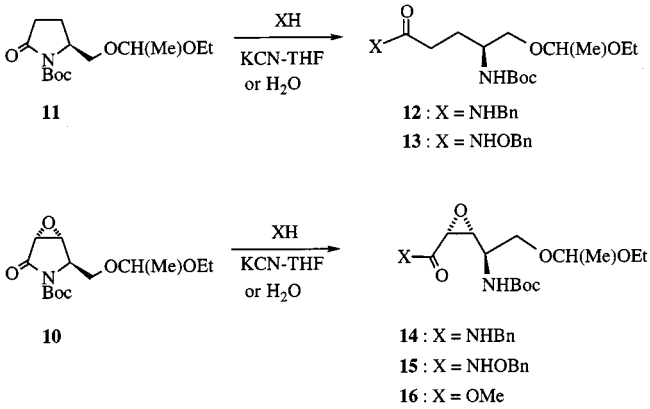


Scheme 2. General route to hydroxylated oxazolidinones



Scheme 3. γ-lactam ring opening of **10** and **11** with hetero-nucleophiles

towards hetero-nucleophilic attacks at C-2 with cleavage of the lactam ring.[13] This ring cleavage could be carried out in anhydrous conditions, in the presence of a catalytic amount of potassium cyanide. As in the cases of aminolysis and transesterification of esters,[14] the cyanide salt promotes the reaction through the formation of a cyanoketone intermediate.[15] Although sonication could accelerate the process, the reaction remained slow. As noted in previous work,[16] the presence of water speeded-up the nucleophilic attack of benzylamine at C-2. We took advantage of this observation to compare the two sets of experimental conditions, and we started with the less functionalized model **11** (Scheme 3). The main results are summarized in Table 1. These two methods preserved the epoxide ring of **10**. The speeding-up by the benzylamine/H_2O system was verified with both compounds **10** and **11** (entries 2 and 5) and the rate of aminolysis with *O*-benzylhydroxylamine[17] was appreciably increased by the addition of sodium carbonate to the reaction mixture (entries 7 and 8).

The 2,3-epoxy-4-(*tert*-butoxycarbonylamino)pentanamides **14** and **15**, as well as methyl 2,3-epoxypentanoate **16** underwent a completely regio- and stereo-selective 5-*exo* ring closure with formation of oxazolidinones **17**−**19**, in quantitative yield, when adsorbed on silica gel (Scheme 4). It is worthy of note that the primary alcohol functions were not deprotected under these mild conditions. A very slow conversion of **14**−**16** into **17**−**19**, respectively, occurred also in the absence of silica gel. No 6-*endo* cyclization leading to oxazinones was observed. High similar regio- and stereoselectivities have been reported for iodocyclocarbamations.[18] Opposite regioselectivity, however, have also been described in halonium-initiated cyclization of allylic *N*-Boc amino derivatives[19−21] and thermolysis of cyclic sulfates.[22] In the ^{1}H-NMR spectra of **17**−**19**, the values of coupling constants between the protons 4-H and 5-H (4−5 Hz) are characteristic of a *trans* relationship.[23] The *N*-Boc group participation to oxirane opening could proceed with loss of either isobutene (path a) or *tert*-butyl alcohol (path b). The analogy with oxazolidinone formation from β-*N*-Boc aminotosylates being in favour of the path a (Scheme 4).[24]

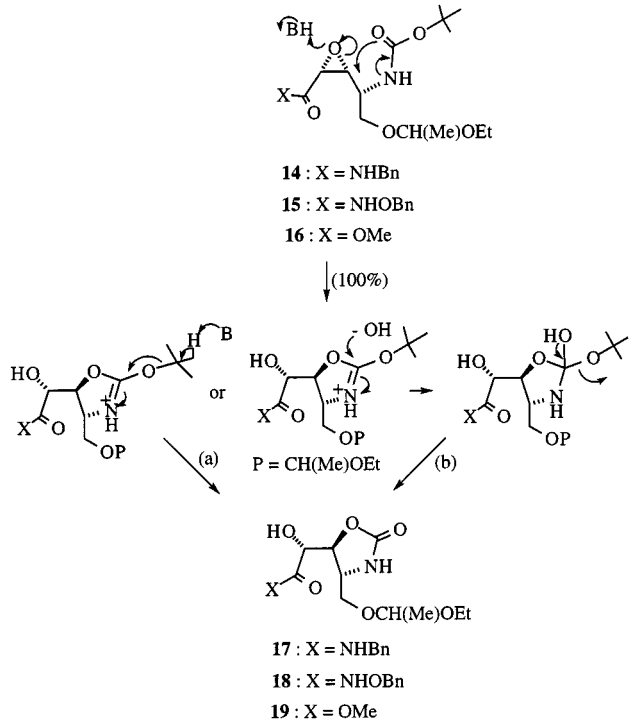
Oxazolidin-2-ones are known to be cleaved by alkaline or acidic hydrolysis[18] and the oxazolidinones rings of **17**−**19** could be considered as protecting groups of *syn*-amino alcohol functions. Thus, potential precursors of highly functionalized aminodiol cores with *syn,syn* definite configurations[22] became accessible by the stereocontrolled way described here. In particular, the regio- and stereo-selective cyclocarbamation of the epoxymethyl ester **16** into **19** allowed a straightforward synthesis of the desired triacetate **4**, as outlined in the Scheme 5.

Under acidic conditions, all the functional groups of **19** were hydrolysed in one pot by refluxing in 6 N HCl leading to a compound which was used without any purification (a minor probably lactonic by-product was not removed at this stage). The crude hydrolysis product was treated with a mixture pyridine−triethylamine (92:8 v/v) and then with acetic anhydride in excess under conventional conditions to afford the triacetoxypyrrolidinone **4**, isolated in 55% yield from **19**.

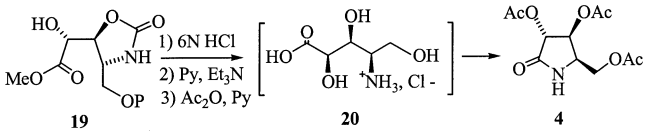
Table 1. γ-Lactam ring opening of **10** and **11** with hetero-nucleophiles

Entry	Substrate	Nucleophile (equiv.)	Experimental conditions	Product (Yield%)
1	**11**	$BnNH_2$ (6.0)	THF, KCN (15 mol-%) room temp., 20 h	**12** (82)
2	″	$BnNH_2$ (3.6)	H_2O (5 equiv) room temp., 2.5 h	**12** (85)
3	″	$BnONH_2$ (1.8)	THF, KCN (20 mol-%)[a] room temp., 15 h	**13** (87)
4	″	$BnONH_2$ (3.0)	H_2O (5 equiv)[b] room temp., 48 h	**13** (81)
5	**10**	$BnNH_2$ (3.6)	H_2O (5 equiv), room temp., 0.5 h	**14** (80)
6	″	$BnONH_2$ (1.4)	THF, KCN (25 mol-%) room temp., 44 h	**15** (74)
7	″	$BnONH_2$ (3.0)	H_2O (5 equiv), room temp., 64 h	**15** (70)
8	″	$BnONH_2$ (3.0)	H_2O (5 equiv),[b] room temp., 16 h	**15** (87)
9	″	CH_3OH (6.7)	THF, KCN (13 mol-%) room temp., 5 h	**16** (94)

[a] With intermittent sonication. − [b] Na_2CO_3 (1.4 equiv.) was added.



Scheme 4. Oxirane opening with oxazolidinone formation



Scheme 5. Synthesis of triacetate **4**

Conclusion

The regio- and stereo-selective ring opening of the epoxide **10** with the assistance of the vicinal *N*-*tert*-butoxycarbonylamino group provided an entry to precursors of *syn,syn*-3-amino-1,2-diol units. The synthetic interest of this access was illustrated by the preparation of (3*R*,4*S*,5*R*)-3,4-diacetoxy-5-(acetoxymethyl)pyrrolidine-2-one **4**, and other applications to the synthesis of bioactive compounds are under investigation.

Experimental Section

General Remarks: Melting points were determined on a microscope Leitz apparatus and are uncorrected. Optical rotations were measured on a Perkin−Elmer 241; the concentrations in $CHCl_3$ solution were given in g/100 mL. − IR spectra ($\tilde{\nu}$ in cm^{-1}, $CHCl_3$) were recorded on a Nicolet 205 (FT). − ^{1}H-NMR spectra were obtained ($CDCl_3$, Me_4Si: δ = 0, unless otherwise indicated) from Bruker AM300; coupling constants *J* values are given in Hz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively). ^{13}C-NMR spectra were recorded on AC250 (62.5 MHz) or AM300 (75.0 MHz). − Mass spectra were 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 (TLC) on silica gel (Merck HF 254 + 366). − Usual workup means that the organic layer was dried with magnesium sulfate, filtered, and evaporated under vacuum.

(3*R*,4*R*,5*R*)-3,4-Epoxy-5-[(1-ethoxy)ethoxymethyl]pyrrolidin-2-one (9): To a solution of bicyclic epoxide **6** (2.80 g, 12.9 mmol) in a mixture THF/H_2O (1:1, 25 mL) stirred at room temp. under argon, was added CF_3CO_2H (2.0 mL). The mixture was stirred at +30°C for 5 h. Toluene was added and the solvents, excess reagents and benzaldehyde were evaporated under reduced pressure. The crude product was crystallized in MeOH/Et_2O and the white crystals were washed with Et_2O, to give the deprotected epoxide **8** (1.67 g, 100%): Mp: 140−141°C. MS (IC, isobutane, *m*/*z*): 259 [2 M + H]$^+$, 130 [M + H]$^+$ (100%). − ^{1}H NMR (D_2O, δ HOD = 4.80): 4.11 (d, 1 H, *J* = 3, OCH), 3.90 (dd, 1 H, $J \approx J' \approx 5$, 5-H), 3.75 (broad d, 1 H, OCH), 3.70 (2dd, 2 H, OCH_2).

The epoxide **8** (1.60 g, 12.4 mmol) was powdered before the addition of EtOAc (72 mL) and the mixture was stirred under argon atmosphere at 70°C for 1 h and then cooled at +40°C. Ethyl vinyl ether (1.46 mL, 15.3 mmol) and trichloroacetic acid (82 mg, 0.5 mmol) were added and the mixture was stirred at 40°C for 8 h, the same amounts of reagents were added and the mixture was stirred until completion of the reaction (17 h). Solid $NaHCO_3$ was added and the solution was filtered. The solvent was evaporated under reduced pressure to give the compound **9**, pure enough to the next step (2.31 g, 93%). An analytical sample could be obtained by a rapid filtration on silica gel (eluent: Et_2O) as a colourless oil. − IR: $\tilde{\nu}$ = 1725. − MS (CI, isobutane, *m*/*z*): 403 [2 M + H]$^+$ (100%), 389, 284, 228, 202 [M + H]$^+$, 156. − ^{1}H NMR (300 MHz): δ = 5.95 (broad s, 1 H, NH) 4.72 (q, 1 H, OCHO), 3.93 (1 H) and 3.58 (1 H) (3-H, 4-H), 3.89 (m, 1 H, 5-H), 3.6 and 3.5 (2m, 4 H, 2 × OCH_2), 1.32 (d, 3 H, $CHCH_3$), 1.21 (t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHz): (CO not visible), δ = 99.92 (OCHO), 64.68, 64.62 (OCH_2), 61.40 (OCH_2), 55.4, 55.0 and 51.8 (C-3, C-4, C-5), 19.56 ($CHCH_3$), 15.26 (CH_2CH_3). − $C_9H_{15}NO_4$ (201.22): calcd. C 53.72, H 7.51, N 6.96; found C 53.42, H 7.37, N 6.77.

(3*R*,4*R*,5*R*)-1-*tert*-Butoxycarbonyl-3,4-epoxy-5-[(1-ethoxy)ethoxymethyl]pyrrolidin-2-one (10): Triethylamine (1.52 mL, 10.9 mmol) and a solution of di-*tert*-butyldicarbonate (4.75 g, 21.8 mmol) in dry CH_2Cl_2 (33 mL) were successively added under argon at room temp. to a stirred solution of epoxide **9** (2.19 g, 10.9 mmol) in dry CH_2Cl_2 (55 mL). DMAP (1.33 g, 10.9 mmol) was added and the mixture was stirred at room temp. for 0.5 h. The solvent was evaporated at room temp. under reduced pressure and the residue was chromatographied on silica gel (eluent: heptane/Et_2O, 1:1) to afford the compound **10** as a colourless oil (2.90 g, 88%): $[\alpha]_D^{28} = -52$ (*c* = 1.04). − IR: $\tilde{\nu}$ = 1792, 1757, 1715. MS (CI, *m*/*z*): 302 [M + H]$^+$, 288, 260, 246, 232, 202, 188, 164, 146, 130, 73. HRMS (CI): calcd for $C_{14}H_{24}NO_6$ [M + H]$^+$: 302.1604; found: 302.1617. − ^{1}H NMR (300 MHz): δ = 4.73, 4.68 (2m, 1 H, OCHO), 4.35 (m, 1 H, 5-H), 3.90−3.65 (OCH_2), 3.83 and 3.66 (3-H, 4-H), 3.58−3.45 (OCH_2), 1.51 (s, 9 H, *t*Bu), 1.29, 1.27 (2d, 3 H, $J \approx 5.5$, $CHCH_3$), 1.19 (t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 169.07, 168.95 (C-2), 149.93 (NCO_2), 99.85, 99.52 (OCHO), 83.58 (qC, *t*Bu), 62.0, 61.93 (OCH_2), 61.63, 61.27 (OCH_2), 57.97, 57.82 (C-5), 52.37 (C-3, C-4), 27.99 (CH_3, *t*Bu), 19.57, 19.39 ($CHCH_3$), 15.23, 14.24 (CH_2CH_3). − $C_{14}H_{23}NO_6$ (301.33): calcd. C 55.80, H 7.69, N 4.65; found C 55.61, H 7.73, N 4.86.

(4*S*)-1-*N*-Benzyl-4-(*N*-*tert*-butoxycarbonyl)amino-5-[(1-ethoxy)ethoxy]pentanamide (12): − *Method A:* To a solution of *N*-Boc pyrrolidinone **11**[25] (120.5 mg, 0.42 mmol) in THF (1.68 mL) were added benzylamine (270 mg, 2.52 mmol) and KCN (4.1 mg,

0.063 mmol) and the mixture was submitted to intermittent sonication at room temp. for 20 h. The solvent was removed under reduced pressure and the product was purified by preparative TLC (eluent: heptane/EtOAc, 6:4) to afford the *N*-benzylamide **12** as white crystals (135.6 mg, 82%).

Method B: To the *N*-Boc pyrrolidinone **11** (115.0 mg, 0.40 mmol) were successivly added H_2O (36 μL, 2.0 mmol) and benzylamine (157 μL, 1.44 mmol) and the mixture was vigorously stirred under argon at room temp. for 2.5 h. After dilution with dichloromethane and drying with magnesium sulfate, the solution was filtered and evaporated to dryness. The product was purified by preparative TLC as above to afford **12** as white crystals (134.3 mg, 85%): Mp: 79−81°C. − IR: $\tilde{\nu}$ = 3684, 3622, 3443, 3017, 1702, 1664, 1514, 1424. − ^{1}H NMR (300 MHz): δ = 7.25 (m, H−Ar), 6.84 (m, 1 H, NH), 5.06, 4.94 (2 broad d, 1 H, $NHCO_2$), 4.63 (m, 1 H, OCHO), 4.44, 4.37 (2 dd, 2 H, J_{AB} = 14.8, J' = 5.5, CH_2Ph), 3.68 (m, 1 H, 4-H), 3.65−3.40 (4 H, 2 × OCH_2), 2.27 (m, 2 H, 2-H_2), 1.86 (m, 2 H, 3-H_2), 1.40 (s, 9 H, *t*Bu), 1.27 (d, 3 H, *J* = 5.5, CHCH_3), 1.18 (splitted t, 3 H, *J* = 6.5, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 172.77 (C-1), 156.41 (NCO_2), 138.54 (qC, Ar), 128.60, 127.79, 127.31 (CH, Ar), 100.14, 99.75 (OCHO), 79.45 (qC, *t*Bu), 67.62, 67.19 (OCH_2), 61.48, 61.08 (OCH_2), 50.00 (C-4), 43.62 (CH_2Ph), 33.29 (C-2), 28.98 (C-3), 28.40 (CH_3, *t*Bu), 19.81, 19.69 (CHCH_3), 15.30 (CH_2CH_3). − $C_{21}H_{34}N_2O_5$ (394.50): calcd. C 63.93, H 8.69, N 7.10; found C 63.62, H 8.58, N 7.07. To clarify the NMR analysis, the primary alcohol function of **12** was deprotected as described below:

(4*S*)-*N*-Benzyl-4-(*N*-*tert*-butoxycarbonyl)amino-5-hydroxypentanamide: To a solution of **12** (71.0 mg, 0.18 mmol) in THF (0.54 mL) was added 0.1 N HCl (0.40 mL) and the mixture was stirred at room temp. for 1.5 h. Aqueous solution of $NaHCO_3$ was added after dilution with EtOAc and the alcohol was extracted 3 times with EtOAc and obtained, after usual workup, as white crystals (58.2 mg, 100%): Mp: 106−108°C. $[\alpha]_D^{28}$ = −19 (*c* = 1.50). − IR: $\tilde{\nu}$ = 3440, 3320, 3016, 1702, 1665, 1503. − ^{1}H NMR (300 MHz): δ = 7.29 (m, 5 H, H−Ar), 6.83 (NH), 5.25 (m, 1 H, $NHCO_2$), 4.39 (2 H, CH_2Ph), 3.56 (m, 4 H, 4-H, 5-H_2, OH), 2.27 (m, 2 H, 2-H_2), 1.88, 1.80 (2m, 2 H, 3-H_2). − ^{13}C NMR (75.0 MHz): δ = 173.24 (C-1), 156.63 (NCO_2), 138.27 (qC, Ar), 128.72, 127.82, 127.49 (CH, Ar), 79.66 (qC, *t*Bu), 64.68 (C-5), 52.25 (C-4), 43.74 (CH_2Ph), 32.93 (C-2), 28.46 (CH_3, *t*Bu), 27.35 (C-3). − $C_{17}H_{26}N_2O_4$ (322.39): calcd. C 63.33, H 8.13, N 8.69; found C 63.26, H 8.15, N 8.49.

(4*S*)-*N*-Benzyloxy-4-(*N*-*tert*-butoxycarbonyl)amino-5-[(1-ethoxy)-ethoxy]pentanamide (13). − Method A: To a solution of *N*-Boc pyrrolidinone **11** (129.0 mg, 0.45 mmol) in anhydrous THF (1.0 mL) were added *O*-benzylhydroxylamine (100 mg, 0.81 mmol) in THF (0.8 mL) and KCN (5.9 mg, 0.09 mmol) and the mixture was submitted to intermittent sonication at room temp. for 15 h. The solvent was removed under reduced pressure and the product was purified by preparative TLC (eluent: heptane/EtOAc, 6:4) to afford the compound **13** as white crystals (160.5 mg, 87%).

Method B: To the *N*-Boc pyrrolidinone **11** (86 mg, 0.3 mmol) were successively added H_2O (27 μL, 1.5 mmol), *O*-benzylhydroxylamine (112 mg, 0.91 mmol), and Na_2CO_3 (45 mg, 0.42 mmol). The mixture was vigorously stirred for 48 h, diluted with CH_2Cl_2 and dried with magnesium sulfate. The product was purified as above to give **13** as white crystals (99 mg, 81%): Mp: 75−77°C. − IR: $\tilde{\nu}$ = 3448, 2997, 1702, 1669 (sh), 1516. − MS (*m*/*z*): 310 [M^+ − Boc], 308, 265, 91 (100%). − ^{1}H NMR (300 MHz): δ = 9.8 (ONH), 7.40, 7.35 (2m, 5 H, H−Ar), 5.13 (0.5 H, NH), 5.00, 4.89 (2d + m, 2.5 H, CH_2Ph + 0.5 × NH), 4.64 (m, 1 H, OCHO), 3.70−3.55 (5 H, 4-H + 2 × OCH_2), 2.15 (m, 1 H, 2-H), 2.06 (m, 1 H, 2-H), 1.82 (m, 2 H, 3-H_2), 1.40 (s, 9 H, *t*Bu), 1.27 (2d, 3 H, CHCH_3), 1.19 (2t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 170.75 (C-1), 156.81 (NCO_2), 135.87 (qC, Ar), 129.07, 128.57 (CH, Ar), 100.29, 99.83 (OCHO), 79.85 (qC, *t*Bu), 77.99 (CH_2Ph), 67.97, 67.51 (OCH_2), 61.72, 61.11 (OCH_2), 49.51 (C-4), 30.40 (C-2), 29.70 (C-3), 28.41 (CH_3, *t*Bu), 19.81 (CHCH_3), 15.34 (CH_2CH_3). − $C_{21}H_{34}N_2O_6$ (410.50): calcd. C 61.44, H 8.35, N 6.82; found C 61.44, H 8.24, N 6.76. The primary alcohol function of **13** was deprotected as described below:

(4*S*)-*N*-Benzyloxy-4-(*N*-*tert*-butoxycarbonyl)amino-5-hydroxypentanamide: To a solution of **13** (28.7 mg, 0.07 mmol) in THF (0.21 mL) was added 0.1 N HCl (0.15 mL). The mixture was stirred at room temp. until completion of the reaction (2 h) and then diluted with EtOAc. Aqueous $NaHCO_3$ solution was added and the product was extracted 3 times with EtOAc. After usual workup, the alcohol was crystallized in Et_2O and obtained as white crystals (22.5 mg, 95%): Mp: 81−83°C. $[\alpha]_D^{26}$ = −26 (*c* = 0.99). − IR: $\tilde{\nu}$ = 3442, 3035, 1695, 1609, 1509. MS (*m*/*z*): 307, 238, 201, 174, 91 (100%), 84, 77. − ^{1}H NMR (300 MHz): δ = 9.9 (broad s, 1 H, ONH), 7.36 (m, 5 H, H−Ar), 5.20 (d, 1 H, *J* = 8, $NHCO_2$), 4.90 (m, 2 H, CH_2Ph), 3.50 (3 H, 4-H, 5-H_2), 2.12 (m, 2 H, 2-H_2), 1.80, 1.71 (2m, 2 H, 3-H_2), 1.39 (s, 9 H, CH_3, *t*Bu). − ^{13}C NMR (75.0 MHz): 171.16 (C-1), 156.96 (NCO_2), 135.58 (qC, Ar), 129.15, 128.60 (CH, Ar), 79.93 (qC, *t*Bu), 78.09 (CH_2Ph), 64.76 (C-5), 51.79 (C-4), 30.02 (C-2), 28.44 (CH_3, *t*Bu), 28.01 (C-3). − $C_{17}H_{26}N_2O_5$ (338.39): calcd. C 60.34, H 7.74, N 8.28; found C 59.99, H 7.62, N 8.08.

(2*R*,3*R*,4*R*)-*N*-Benzyl-4-(*N*-*tert*-butoxycarbonyl)amino-2,3-epoxy-5-[(1-ethoxy)ethoxy]pentanamide (14): To *N*-*tert*-butoxycarbonyl-3,4-epoxypyrrolidinone **10** (95.0 mg, 0.32 mmol) were successively added under argon H_2O (30 μL, 1.66 mmol) and $BnNH_2$ (126 μL, 1.15 mmol). The mixture was stirred at room temp. for 0.5 h. After dilution with dichloromethane and drying with magnesium sulfate, the product was purified by preparative TLC (eluent: heptane/EtOAc, 1:1) to afford the compound **14** as a colourless oil (103 mg, 80%): − IR: $\tilde{\nu}$ = 3423, 2984, 1707, 1680, 1527, 1501. − MS (CI, isobutane, *m*/*z*): 409 [M + H]$^+$, (100%), 363, 337, 307, 281. − ^{1}H NMR (300 MHz): δ = 7.35, 7.30 (5 H, H−Ar), 6.60 (m, 1 H, X part of ABX, BnN*H*), 5.16, 5.05 (2 broad d, 1 H, $NHCO_2$), 4.72 (q, 1 H, *J* = 6, OCHO), 4.60 (dd, 1 H, *J* = 15, *J'* = 6.5) and 4.38 (dd, 1 H, *J* = 15, *J'* = 5) CH_2Ph, 3.85−3.47 (m, 6 H, 2 × OCH_2, 2-H, 3-H), 3.32 (m, 1 H, 4-H), 1.45 (s, 9 H, *t*Bu), 1.31 (d, 3 H, CHCH_3), 1.19 (2t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 166.25 (C-1), 155.04 (NCO_2), 137.68 (qC, Ar), 128.84, 128.24, 127.74 (CH, Ar), 100.27, 99.96 (OCHO), 80.3 (qC, *t*Bu), 65.30, 64.99 (OCH_2), 61.81, 61.41 (OCH_2), 55.74, 55.49, 55.37, 48.93 (C-2, C-3, C-4), 43.50 (CH_2Ph), 28.42 (CH_3, *t*Bu), 19.73 (CHCH_3), 15.32 (CH_2CH_3). − $C_{21}H_{33}N_2O_6$ (M + H)$^+$ calcd 409.2339; found 409.2327 (MS).

(2*R*,3*R*,4*R*)-*N*-Benzyloxy-4-(*N*-*tert*-butoxycarbonyl)amino-2,3-epoxy-5-[(1-ethoxy)ethoxy]pentanamide (15). − Method A: A solution of *O*-benzylhydroxylamine (246.0 mg, 2.0 mmol) in THF (10.0 mL) was added to the epoxypyrrolidinone **10** (420 mg, 1.4 mmol) and the mixture was stirred under argon at room temp. After the addition of KCN (23 mg, 0.35 mmol) and additional stirring for 18 h, the mixture was submitted to intermittent sonication until completion of the reaction (26 h). The solvent was evaporated and the residue was readily purified by preparative TLC (eluent: heptane/EtOAc, 7:3) to give the compound **15** as a colourless oil (440 mg, 74%).

Method B: To the epoxypyrrolidinone **10** (394 mg, 1.31 mmol) were successively added under argon H_2O (120 μL, 6.67 mmol) and *O*-benzylhydroxylamine (486 mg, 3.95 mmol) and Na_2CO_3 (194 mg, 1.83 mmol) and the mixture was stirred at room temp. for 16 h. Excess of reagent was evaporated under vacuum. A solution of the residue in CH_2Cl_2 was dried with magnesium sulfate and the product, obtained after filtration and evaporation to dryness, was purified by a rapid chromatography on silica gel to afford the compound **15** as a colourless oil (484 mg, 87%): − IR: ṽ = 3384, 1760, 1692, 1395. − MS (CI, isobutane, *m*/*z*): 425 $[M + H]^+$, 379 (100%), 353, 323, 297, 279, 217, 191, 172, 147, 107. − ^{1}H NMR (300 MHz): δ = 7.43, 7.36 (H−Ar), 5.33, 5.15 (1 H, NH), 5.00 (2 H, C*H*$_2$Ph), 4.68 (m, 1 H, OCHO), 3.8−3.15 (2-H, 3-H, 4-H, 2 × OCH_2), 1.43 (s, 9 H, *t*Bu), 1.30 (2d, 3 H, CHC*H*$_3$), 1.21 (2t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHZ): δ = 135.7 (qC, Ar), 129.23, 128.68 (CH, Ar), 100.53, 100.10 (OCHO), 80.7 (qC, *t*Bu), 78.42 (*C*H$_2$Ph), 65.25, 64.83 (OCH_2), 62.0, 61.55 (OCH_2), 57.38, 54.5, 48.76 (C-2, C-3, C-4), 28.41 (CH_3, *t*Bu), 19.79 (CH*C*H$_3$), 15.32 (CH_2CH_3). − $C_{21}H_{33}N_2O_7$ $(M + H)^+$ calcd 425.2287; found 425.2276 (MS).

Methyl (2*R*,3*R*,4*R*)-4-(*N*-*tert*-Butoxycarbonyl)amino-2,3-epoxy-5-[(1-ethoxy)ethoxy]pentanoate (16): To a solution of (3*R*,4*R*,5*R*)-1-*tert*-butoxycarbonyl-3,4-epoxy-5-(1-[ethoxy)ethoxymethyl]-pyrrolidin-2-one **10** (485.5 mg, 1.61 mmol) in anhydrous THF (2.7 mL) were successively added a mixture THF/MeOH (9:1, 2.7 mL) and KCN (13.5 mg, 0.21 mmol). The reaction mixture was stirred at room temp. for 5 h and the solvents were removed under reduced pressure. The residue was purified by preparative TLC (eluent: heptane/EtOAc, 7:3) and the methyl ester was obtained as a colourless oil (504 mg, 94%). − IR: ṽ = 3450, 2930, 1751, 1712, 1503, 1450. − MS (CI, isobutane, *m*/*z*): 334 $[M + H]^+$, 288, 232, 206, 188 (100%). − ^{1}H NMR (300 MHz): δ = 5.30, 5.11 (2 broad d, 1 H, NH), 4.72 (m, 1 H, OCHO), 3.95−3.20 (7 H, 2 × OCH_2, 2-H, 3-H, 4-H), 3.84 (s, 3 H, OCH_3), 1.42 (s, 9 H, *t*Bu), 1.32 (2d, 3 H, *J* = 5.5, CHC*H*$_3$), 1.21−1.22 (2d, 3 H, *J* = 7, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 168.38 (OCO), 155.06 (NCO), 79.7 (qC, *t*Bu), 65.69, 65.10 (OCH_2), 62.12, 61.45 (OCH_2), 56.64, 53.16, 52.67, 47.90 (OCH_3, C-2, C-3, C-4), 28.38 (CH_3, *t*Bu), 19.93, 19.78 (CH*C*H$_3$), 15.31 (CH_2CH_3). − $C_{15}H_{28}NO_7$ $(M + H)^+$ calcd 334.1865; found 334.1847 (MS).

Oxazolidin-2-one 17 [(4*R*,5*S*,1′*R*)-5-[*N*-benzylamido-(1′-hydroxy)-methyl]-4-[(1-ethoxy)ethoxymethyl]oxazolidin-2-one]: To a solution of epoxyamide **14** (212 mg, 0.52 mmol) in MeOH (2 mL) was added silica gel (230−400 mesh, 416 mg). The solvents were evaporated and the mixture was allowed to stand at room temperature for 4 days. After addition of CH_2Cl_2/MeOH 85:15 (6 mL), silica gel was removed by filtration and was washed by CH_2Cl_2/MeOH (85:15). Elimination of the solvents under vacuum afforded the compound **17** as white crystals (183 mg, 100%). − Mp: 98−100°C. $[\alpha]_D^{26}$ = +85 (*c* = 1.97). − IR: ṽ = 3466, 3409, 1762, 1673, 1525. − MS (FAB, thioglycerol, *m*/*z*): 375 $[M + Na]^+$, 353 $[M + H]^+$, 307, 281 (100%), 263, 106. − ^{1}H NMR (300 MHz): δ = 7.46, 7.27 (5 H, Ar−H), 6.4 (broad s, 1 H, X part of ABX, BnN*H*), 5.15 (broad s, 1 H, OCONH), 4.69 (masked q, 1 H, OCHO), 4.62 (dd, 1 H, $J_{4,5}$ = 4.3, $J_{5,1'}$ = 4, 5-H), 4.47, 4.36 (2dd, 2 H, J_{AB} = 14.5, $J_{AX} \approx J_{BX} \approx$ 5.5, PhC*H*$_2$), 4.15 (d, 1 H, *J* = 4, 1′-H), 4.05 (m, 1 H, 4-H), 3.70−3.36 (4m, 4 H, 2 × OCH_2), 1.27 (d, 3 H, *J* = 7, CHC*H*$_3$), 1.18 (t, 3 H, *J* = 7, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 170.5 (NCO), 159.52 (NCO), 137.8 (qC, Ar), 127.75, 127.72, 127.54 (CH, Ar), 100.11 (OCHO), 79.56 (C-5), 72.42 (C-1′), 66.42, 66.24 (OCH_2), 61.77, 61.62 (OCH_2), 54.04 (C-4), 43.24 (Ph*C*H$_2$), 19.77 (CH*C*H$_3$), 15.31 (CH_2CH_3). − $C_{17}H_{24}N_2O_6$ (352.38): calcd. C 57.94, H 6.87, N 7.95; found C 58.08, H 6.91, N 7.83.

Oxazolidin-2-one 18 [(4*R*,5*S*,1′*R*)-5-[*N*-benzyloxyamido-(1′-hydroxy)methyl]-4-[(1-ethoxy)ethoxymethyl]oxazolidin-2-one]: The epoxide **15** (424 mg, 1.0 mmol) was adsorbed on silica gel as described above to give quantitatively the oxazolidinone **18** as a colourless oil: $[\alpha]_D^{29}$ = +68 (*c* = 2.92). − IR: ṽ = 3674, 3377, 2990, 1760, 1685, 1400. − MS (FAB, thioglycerol, *m*/*z*): 391 $[M + Na]^+$, 369 $[M + H]^+$, 323, 297 (100%). − ^{1}H NMR (300 MHz): δ = 7.39, 7.33 (5 H, H−Ar), 6.26 (1 H, NH), 4.87 (s, 2 H, C*H*$_2$Ph), 4.64 (m, 2 H, OCHO, 5-H), 4.20 (1 H, 1′-H), 3.98 (m, 1 H, 4-H), 3.59 (m, 2 H, OCH_2), 3.44 (m, 2 H, OCH_2), 1.97 (m, 1 H, NH), 1.27 (d, 3 H, CHC*H*$_3$), 1.17 (t, 3 H, CH_2CH_3). − ^{13}C NMR (75.0 MHz): δ = 167.0 (NCO), 158.95 (NCO_2), 134.9 (qC, Ar), 129.49, 128.92, 128.69 (CH−Ar), 100.2 (OCHO), 79.29, 78.60 (C-5, *C*H$_2$Ph), 71.85 (C-1′), 66.2 (OCH_2), 61.69 (OCH_2), 53.93 (C-4), 19.79 (CH*C*H$_3$), 15.34 (CH_2CH_3). − $C_{17}H_{24}N_2O_7$ (368.37): calcd. C 55.43, H 6.56, N 7.61; found: C 55.15, H 6.61, N 7.54.

Oxazolidin-2-one 19: To a solution of methyl ester **16** (500 mg, 1.50 mmol) in MeOH (3.0 mL) was added silica gel (230−400 mesh, 1.45 g) The solvent was evaporated under reduced pressure and the mixture was allowed to stand at room temp. After completion of the conversion (4 days) the product was dissolved in CH_2Cl_2/MeOH (8:2), silica gel was filtered and washed with the same eluent. Evaporation to dryness gave rise to the oxazolidinone **19** as a colourless oil (416 mg, 100%). $[\alpha]_D^{26}$ = +64 (*c* = 2.65). − IR: ṽ = 3530, 3475, 2995, 1769, 1395. MS (CI, isobutane, *m*/*z*): 278 $[M + H]^+$, 232 (100%), 206. − HRMS (CI, CH_4) calcd for $C_{11}H_{20}NO_7$ $(M + H)^+$: 278.1240; found: 278.1228. − ^{1}H NMR (300 MHz): δ = 5.96 (broad d, 1 H, NH), 4.75 (m, 1 H, OCHO), 4.66 (broad d, 1 H, $J_{4,5}$ = 5, 5-H), 4.25 (broad s, 1 H, 1′-H), 4.10 (m, 1 H, 4-H), 3.85 (s, 3 H, OCH_3), 3.65, 3.51 (2m, 4 H, 2 × OCH_2), 1.32 (d, 3 H, *J* = 5.5, CHC*H*$_3$), 1.22 (t, 3 H, *J* = 7, CH_2CH_3). − ^{13}C NMR (300 MHz): δ = 171.37 (CO), 158.51 (NCO), 100.05 (OCHO), 79.29 (C-5), 71.28 (C-1′), 66.30, 66.14 (OCH_2), 61.68, 61.54 (OCH_2), 53.37 (OCH_3), 19.69 (CH*C*H$_3$), 15.34 (CH_2CH_3). $C_{11}H_{19}NO_7$ (277.27): calcd. C 47.65, H 6.90, N 5.05; found C 47.37, H 6.94, N 5.09.

Triacetate 4: To the oxazolidinone **19** (83 mg, 0.3 mmol) was added 6 N HCl (4.5 mL) and the mixture was heated at 118°C for 24 h and evaporated to dryness. To the crude hydrolysis product was added pyridine (2 mL) and triethylamine (175 μL) and the mixture was stirred at 45−50°C for 24 h. The residue obtained after evaporation to dryness, in pyridine (3 mL), was acetylated with Ac_2O in excess (1 mL) at room temp. for 16 h. Excess Ac_2O was eliminated by addition of methanol at 0°C. After being stirred for 0.5 h at room temp., the solvents were evaporated under reduced pressure. The product was purified by preparative TLC (eluent: EtOAc) and crystallisation in Et_2O (45 mg, 55%). Mp: 99−100°C. $[\alpha]_D^{28}$ = +113 (*c* = 0.40). − IR: ṽ = 3425, 1743, 1429, 1371, 1232. − MS (CI, isobutane, *m*/*z*): 274 $[M + H]^+$ (100%), 232, 214, 171, 147, 98, 88. − ^{1}H NMR (300 MHz, C_6D_6): δ = 6.44 (broad s, NH), 5.85 (d, 1 H, *J* = 8, 3-H), 5.40 (dd, 1 H, $J \approx J'$ = 8, 4-H), 3.80 (dd, 1 H, J_{AB} = 12, $J_{5,6a}$ = 3.5, 6-Ha), 3.65 (dd, 1 H, J_{AB} = 12, $J_{5,6b}$ = 3.2, 6-Hb), 1.71 (s, 3 H, $COCH_3$), 1.62 (s, 3 H, $COCH_3$), 1.54 (s, 3 H, $COCH_3$). − ^{13}C NMR (62.5 MHz, C_6D_6): δ = 169.8, 169.7 (CO), 128.5, 128.1, 127.7 (CH, Ar), 73.5 (C−3), 72.4 (C-4), 61.7 (C-6), 51.8 (C-5), 20.2 (CO*C*H$_3$), 19.9 (CO*C*H$_3$). − $C_{11}H_{16}NO_7$ (M + H)$^+$ calcd 274.0927; found 274.0923 (MS).

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