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Synthesis of (2*S*,3*R*)-3-Amino-2-Hydroxydecanoic Acid and (3*R*,4*R*)-3-Amino-4-Hydroxyazepane from D-Isoascorbic Acid.[1]

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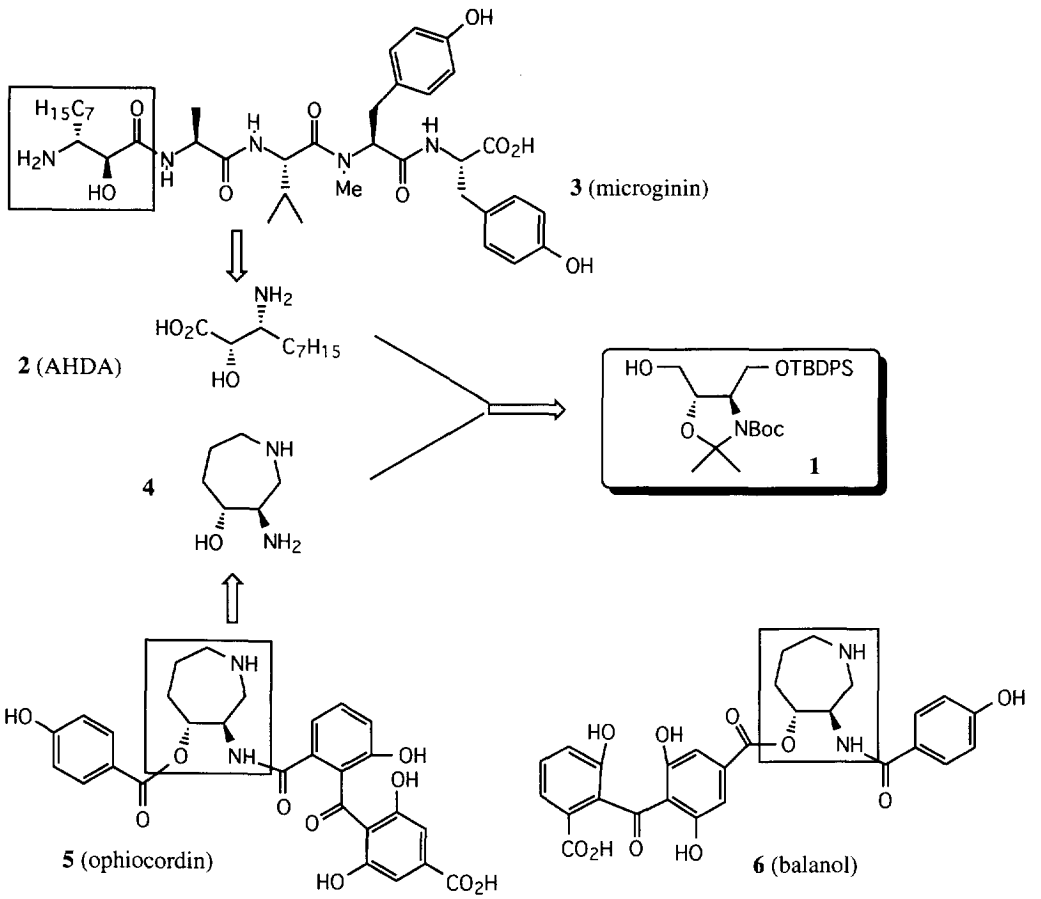
Abstract : Taking advantage of the high functionality of an enantiopure protected *syn*-2*R*-amino-1,3,4-triol derivative, easily available on a multigram scale from D-isoascorbic acid, several biologically active compounds have been synthesized such as the (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA), the *N*-terminal moiety of microginin, and the (3*R*,4*R*)-3-amino-4-hydroxyazepane, the ophiocordin and balanol core structure. Copyright © 1996 Elsevier Science Ltd

Over the past fifty years, many unusual aminoacids have been isolated from natural sources. Among them, 3-hydroxy-2-aminoacids and 2-hydroxy-3-aminoacids represent an important class of these compounds. The latter are important precusors of β-lactam antibiotics,[2] and both are constituents of biologically active peptides such as polyoxines,[2] tatumine,[3] edeine,[4] bestatin,[5] amastatin,[6] microginin[7]. 3-Phenylisoserine is encountered in the side chain of the taxol.[8] Furthermore these hydroxy-aminoacids are of considerable interest in the synthesis of protease inhibitors. Due to the biological importance of these hydroxyaminoacids, various methods have been developed for their stereoselective synthesis,[9] however, alternative methods for their preparation in enantiopure form are still relevant.

Recently, we have reported the enantiospecific synthesis of the conveniently protected *syn*-2*R*-amino-1,3,4-triol derivative **1** on a multigram scale from D-isoascorbic acid, and its transformation into (2*R*,3*R*)-D-*threo*-sphingosine.[10] Now, we would like to demonstrate that this highly functionalized enantiopure chiral building block is a good precursor of other biologically important compounds (Scheme 1), such as :

- (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **2** (AHDA) the *N*-terminal moiety of microginin **3**, a linear pentapeptide isolated from the fresh water blue-green alga *Microcystis aeruginosa*,[7] which acts as an angiotensin-converting enzyme (ACE) inhibitor.[7] The (2*S*,3*R*) absolute stereostructure of **2** has been determined by enantioselective asymmetric dihydroxylation.[11]

- (3*R*,4*R*)-3-amino-4-hydroxyazepane **4**, the ophiocordin and balanol core structure. Ophiocordin **5**, which has been isolated from the fungus *Cordyceps ophioglossoides*,[12] is an antibiotic exhibiting antifungal activity.[12] Balanol **6**, initially isolated from *Verticillium balanoids*[13] and more recently from species of *Fusarium mesismoides*,[14] shows remarkable inhibitory properties towards proteine kinase C.[13,14,15a] Due to its chemical structure, its biological activity as well as its low availability from natural sources, the development of synthetic routes to balanol is of considerable interest. Apart from the synthesis of (±)-*trans*-3-amino-4-hydroxyazepane,[16] its enantioselective synthesis has been performed from aminoacids such as D-serine[15b,c] or (2*S*,3*R*)-3-hydroxylysine[17] as well as from an acyclic chiral epoxy-alcohol obtained *via* Sharpless asymmetric epoxidation.[18] Recently, to a precursor for the synthesis of non-natural analogues of balanol has been reported from D-quinic acid.[19]



Scheme 1

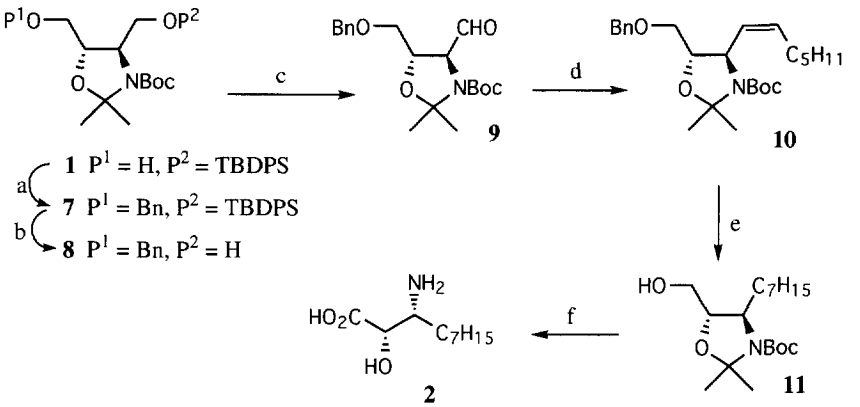
Our proposed strategy to reach the target molecules (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **2** (AHDA) and (3*R*,4*R*)-3-amino-4-hydroxyazepane **4**, from the homochiral *syn*-2*R*-amino-1,3,4-triol synthon **1**[20] is described in the following schemes 2 and 3. It required the introduction of the carbon chain either at C-1' or C-1" of **1** to give **2** and **4**, respectively.

Synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid 2 (AHDA)

The synthesis of AHDA is outlined in scheme 2 and has been carried out from the enantiopure synthon **1** in 34% overall yield. Protection of the free hydroxyl group of **1** as its *O*-benzyl derivative by benzyl chloride in the presence of silver oxide easily occurred (87% yield); then the deprotection of the *tert*-butyldiphenylsilylether (*n*Bu4NF, THF, 89%) generated the free primary alcohol function on the C-1' side of the molecule. Introduction of the alkyl chain required initial oxidation of the alcohol into aldehyde using Swern conditions followed by Wittig reaction with the ylide obtained from *n*-hexyltriphenylphosphonium bromide in the presence of *n*-butyllithium at -78°C. The resulting alkene **10** was obtained in 64% yield and the stereochemistry of the double bond was revealed to be exclusively *Z*. Subsequent deprotection of the benzyl

ether together with saturation of the alkene moiety cleanly occurred in a single step upon hydrogenation in the presence of palladium on charcoal to give **11** in 94 % yield. Finally, the conversion of **11** into the target (2*S*,3*R*)AHDA **2** was readily achieved in 3 steps (73 % overall yield) : Swern oxidation of the primary alcohol to aldehyde, with further oxidation to carboxylic acid in the presence of sodium chlorite and sulfamic acid, acid hydrolysis of the remaining protective groups and purification on Dowex® (50x8) resin .

To our knowledge, this represents the first enantiospecific synthesis of AHDA.The specific rotation, melting point, ^1H and ^{13}C NMR spectra were fully in agreement with the literature data which showed that the natural aminoacid of microginin was indeed AHDA with the *syn* relative stereochemistry.[11a]

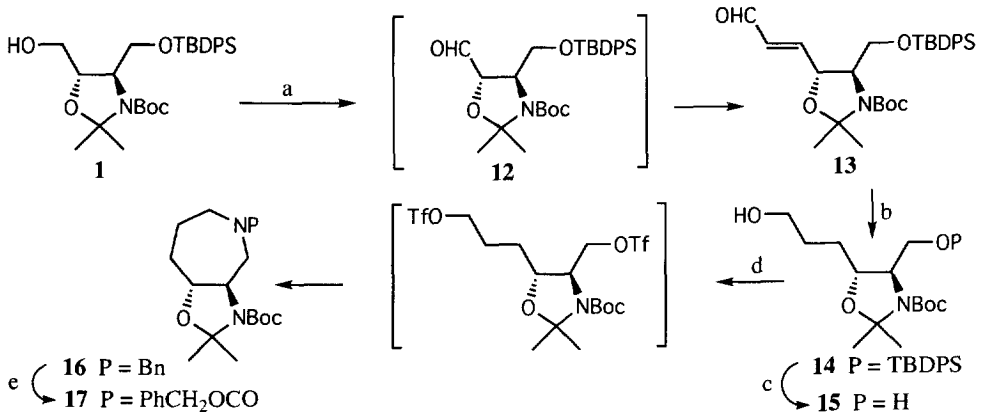


a) $PhCH_2Cl$, Ag_2O, DMF, 24h, 20°C, 87%. b) nBu_4NF, THF, 20°C, 89%. c) $(COCl)_2$, DMSO Et_3N, CH_2Cl_2. d) $C_6H_{13}PPh_3Br$, nBuLi, THF, -78°C, 64%. e) H_2, Pd/C 10%, EtOH, 94%.
f) *i* : $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; *ii* : $NaClO_2$, NH_2SO_3H, dioxane, H_2O, 0°C;
iii : TFA, H_2O, 20°C, then Dowex, 73% from **11**.

Scheme 2

Synthesis of (3*R*,4*R*)-3-amino-4-hydroxyazepane 16

The synthesis of **16** , precursor of both ophiocordin and the balanol core, from the *syn*-2*R*-amino-1,2,3-triol **1** is described in the scheme 3 and required only 4 steps to be performed with a good overall yield (43%). Swern oxidation of the free primary alcohol function into aldehyde at C-1" side of the molecule was followed by *in situ* condensation with the formylmethylene triphenylphosphorane to afford the expected α,β-ethylenic aldehyde **13** in 91 % overall yield (E configuration exclusively). Hydrogenation of the double bond together with reduction of aldehyde into primary alcohol was carried out by using hydrogen in the presence of Raney nickel to give the saturated alcohol **14** in quantitative yield. Deprotection of *tert*-butyldiphenylsilyl ether (nBu4NF, THF) led to the diol **15** in 83% yield. In order to carry out the ring closure into the hexahydroazepine **16**, the two primary hydroxyl groups of **15** were activated as their triflate derivative, and subsequent treatment with benzylamine gave the desired product **16** (57 % overall yield from **15**). The structure of **16** was unambiguously established by conversion to *N*-benzyloxycarbonyl hexahydroazepine **17** described by Nicolaou et.al.[15] Comparison of the physical and spectroscopic data of **17** with those described by Nicolaou were in good agreement.



a) $(COCl)_2$, DMSO, NEt_3,CH_2Cl_2, 1h30 then Ph_3P=CHCHO, 24h, 91%. b) H_2, Ni, EtOH, 100%
c) nBu_4NF, THF, 20h, 20°C, 83%. d) $(CF_3SO_2)_2O$, CH_2Cl_2, 2,6-lutidine then $PhCH_2NH_2$, 20h, 20°C, 57%. e) *i* : H_2, Pd/C 10%, EtOH, 24h; *ii* : $PhCH_2OCOCl$, CH_2Cl_2, Et_3N, 0°C, 1h, 58% from **16**

Scheme 3

In conclusion, we have demonstrated the synthetic utility of the enantiopure conveniently protected *syn*-2*R*-amino-1,3,4-triol derivative **1**, easily available in a multigram scale from D-isoascorbic acid, by the enantiospecific synthesis of (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA, 34% overall yield from **1**), and the (3*R*,4*R*)-3-amino-4-hydroxyazepane (43% overall yield from **1**). It is worthy of note that the strategy developed in the synthesis of AHDA involving introduction of the alkyl chain by Wittig reaction allows the obtention of various α-hydroxy-β-aminoacids according to the nature of the ylide used. Further utilization of this building block in the synthesis of other biologically active compounds will be reported in due course.

EXPERIMENTAL SECTION

Prior to use, tetrahydrofuran (THF) and diethylether (Et_2O) were distilled from sodium-benzophenone and dichloromethane (CH_2Cl_2) from P_2O_5. CH_2Cl_2 and ethyl acetate (EtOAc) were filtered on K_2CO_3 prior to use. ^1H NMR (250 MHz) and ^{13}C NMR (62,9 MHz) spectra were recorded in C_6D_6 at 65°C (unless otherwise indicated) on a Bruker AM 250. Chemical shifts are reported in δ (ppm)[20] and coupling constants are given in Hertz. High Resolution Mass Spectra were recorded in Service de Spectrométrie de Masse, Université Pierre et Marie Curie. Specific rotations were measured on a Perkin Elmer 241C polarimeter with sodium (589 nm) lamp at 20°C. All reactions were carried out under argon atmosphere, and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (1.2 mm) on glass. Chromatography was performed with Merck Kieselgel 60 (200-500 μm) or 60H (5-40 μm). Spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

(4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-2,2-dimethyl-1,3-oxazolidine 7. To a stirred solution of **1** (2 g ; 4.11 mmol) in dimethyl formamide (29 mL) was dropwise added , at 20°C, benzylbromide (3.92 mL ; 32.95 mmol) then silver oxide (3.82 g ; 16.47 mmol). After stirring for 24 h in darkness and filtration through a celite pad, another addition of both benzyl bromide and silver

oxide (same quantities) allowed completion of the reaction within 24h. The reaction mixture was poured into water (50 mL), then extracted with cyclohexane (3x100 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 95/5 ; Rf 0.3) afforded 2.1 g (87 %) of **7**. $[\alpha]_D$ -12 (c 1.10, CH_2Cl_2). ^1H NMR (C_6D_6, 70°C) δ : 8.50-7.70 ; 7.30-7.00 (15H, 2m, Ph), 4.68 (1H, dd, H-5, $J_{4,5} = J_{5,1"a} = J_{5,1"b} = 5$ Hz), 4.40 (2H, m, CH_2Ph), 4.10-4.00 (3H, m, H-4, H-1'), 3.58 (2H, m, H-1"), 1.73, 1.64 (6H, 2s, CMe_2), 1.35 (9H, s, O*t*Bu), 1.15 (9H, s, Si*t*Bu). Anal. Calcd for $C_{35}H_{47}NO_5Si$: C, 71.27 ; H, 8.03 ; N, 2.37 ; Found : C, 71.82 ; H, 7.98 ; N, 2.29.

(4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine 8.

To a stirred solution of **7** (2.1 g ; 3.56 mmol) in THF (94 mL) was dropwise added, at 0°C, *n*-tetrabutylammonium fluoride (3.9 mL ; 3.92 mmol ; 1M in THF). After stirring for 24 h at 20°C, water (30 mL) was added ; after extraction with CH_2Cl_2 (3x40 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/EtOAc 7/3 ; Rf 0.4) afforded 1.1g (89 %) of **8**. $[\alpha]_D$ -9 (c 1.03, CH_2Cl_2). ^1H NMR δ : 7.40-7.00 (5H, m, Ph), 4.34 (2H, m, CH_2Ph), 4.05 (1H, X from ABX, H-5, $J_{4,5} = 6.8$, $J_{5,1"a} = J_{5,1"b} = 5.3$ Hz), 3.90 (1H, m, H-4), 3.75 (2H, m, H-1'), 3.52-3.40 (2H, AB from ABX, H-1", $J_{1"a,1"b} = 10.5$ Hz), 1.6, 1.48 (6H, 2s, CMe_2), 1.36 (9H, s, O*t*Bu). ^{13}C NMR δ : 153.5 ($N\underline{C}O_2$), 138.8, 128.5, 127.8, 127.7 (Ar), 94.9 ($\underline{C}Me_2$), 80.3 ($O\underline{C}Me_3$), 77.0 (C-5), 73.6 ($Ar\underline{C}H_2$), 71.7 (C-1"), 64.1 (C-1'), 62.8 (C-4), 28.4 ($\underline{Me}_3C$), 28.0, 26.8 ($\underline{Me}_2C$).

(4*S*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-formyl-2,2-dimethyl-1,3-oxazolidine 9. To a stirred solution of oxalyl chloride (222 µL ; 2.52 mmol) in CH_2Cl_2 (2 mL) at -78°C was slowly added DMSO (366 µL ; 5.16 mmol). The resulting complex was stirred for 15 min at -78°C prior to the addition of alcohol **8** (605 mg ; 1.72 mmol) in CH_2Cl_2 (10 mL). After 45 min at -65°C, Et_3N (1.4 mL ; 10.33 mol) was added and 1.5 h later Et_2O (50 mL) was added at - 65°C into the reaction mixture. The salt (Et_3NHCl) was removed by filtration through celite, and the filtrate was concentrated *in vacuo* to give **9** (colorless oil) which was used without further purification in the next step. A sample was purified by flash chromatography (cyclohexane/EtOAc 8/2 ; Rf 0.4). $[\alpha]_D$ -20 (c 1.00, CH_2Cl_2). ^1H NMR δ : 9.39 (1H, *br* s, CHO), 7.22-7.07 (5H, m, Ph), 4.31 (2H, m, CH_2Ar), 4.19 (1H, m,H-4), 4.04 (1H, dt, H-5, $J_{4,5} = 7.4$ Hz, $J_{5,1"a} = J_{5,1"b} = 4.5$ Hz), 3.49-3.35 (2H, AB, H-1", $J_{1"a,1"b} = 10.5$ Hz), 1.65, 1.53 (6H, 2s, CMe_2), 1.34 (9H, s, O*t*Bu). ^{13}C NMR (C_6D_6, 65°C) δ : 196.7 (C-1'), 151.5 ($N\underline{C}O_2$), 138.5, 128.5, 128.2, 127.9 (Ph), 95.6 (C-2), 80.8 ($\underline{C}Me_3$), 74.7 (C-5), 73.7 ($\underline{C}H_2Ph$), 70.3 (C-1"), 67.3 (C-4), 28.2 ($\underline{Me}_3C$), 26.8 , 25.8 ($\underline{Me}_2C$).

(4*R*,5*S*)-5-Benzyloxymethyl-3-*N*-*tert*-butoxycarbonyl-4-[(Z)-1-heptenyl]-2,2-dimethyl-1,3-oxazolidine 10.

To a suspension of the *n*-hexyltriphenylphosphonium bromide (2.2 g ; 5.16 mmol) in THF (21 mL) at -78°C, was dropwise added *n*-butyllithium (1.4 M in hexane, 3.56 mL, 4.99 mmol) ; red coloration progressively appeared . After 4 h stirring, a solution of the crude aldehyde **9** in THF (17 mL) was added. The temperature was then raised to 20°C for 15 h to achieved the Wittig reaction. The reaction mixture was then concentrated *in vacuo* and poured into water (20 mL) and extracted with CH_2Cl_2 (3x30 mL). The organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (cyclohexane/EtOAc 95/5 ; Rf 0.3) to give 461 mg (64 %) of **10**. $[\alpha]_D$ +77 (c 1.39, CH_2Cl_2). ^1H NMR δ : 7.30-7.10 (5H, m, Ph), 5.50-5.25 (2H, m, H-1',2'), 4,69 (1H, dd, H-4, $J_{4,1'} = 8.9$ Hz, $J_{4,5} = 6.5$ Hz), 4.40 (2H,

AB, CH_2Ph, J_{AB} = 11 Hz), 3.94 (1H, X from ABX, H-5), 3.55, 3.48 (2H, AB from ABX, H-1", J_{AB} = 11 Hz, $J_{H1"a,5}$ = 5 Hz, $J_{H1"b,5}$ = 4.5 Hz), 2.25-2.00 (2H, m, H-3'), 1.75,1.63 (6H, 2s, Me_2C), 1.40-1.20 (15H, m, O*t*Bu, H-4', 5', 6'), 0.87 (3H, t, H-7', $J_{6',7'}$ = 6.6 Hz). ^{13}C NMR δ : 152.9 ($N\underline{C}O_2$), 138.9, 128.5, 127.8, 127.7 (Ar), 132.3, 130.3 (C-1',2'), 94.8 (C-2), 80.5 (C-5), 79.3 ($O\underline{C}Me_3$), 73.7 ($Ar\underline{C}H_2$), 70.4 (C-1"), 57.1 (C-4), 32.0, 29.7, 27.8, 22.8 (C-3'-6'), 28.6 ($\underline{Me}_3C$), 27.6, 26.7 ($\underline{Me}_2C$), 14.1 (C-7'). Anal. Calcd for $C_{25}H_{39}NO_4$: C, 71.91 ; H, 9.41 ; N, 3.35 ; Found : C, 71.96 ; H, 9.30 ; N, 3.43.

(4*R*,5*S*)-3-*N*-*tert* -Butoxycarbonyl-4-heptyl-5-hydroxymethyl-2,2-dimethyl-1,3-oxazolidine 11.
A solution of **10** (256 mg ; 0.61 mmol) in EtOH (9 mL) was stirred for 3 h under hydrogen atmosphere in presence of palladium on charcoal 10 % (12 mg). After filtration through celite and concentration *in vacuo*, flash chromatography of the residue (cyclohexane/AcOEt 7/3 ; Rf 0.5) afforded 189 mg (94 %) of **11**. m.p. 42-44°C. $[\alpha]_D$ -19 (c 1.24, CH_3OH). ^1H NMR δ : 3.85 (1H, ddd, H-5, $J_{4,5}$ = 4.5 Hz, $J_{5,1"a}$ = 5.3 Hz, $J_{5,1"b}$ = 5 Hz), 3.74 (1H, m, H-4), 3.52, 3.46 (2H, part AB, H-1", J_{A-B} = 11 Hz), 1.80 (1H, m, H-1'a), 1.70-1.10 (26H, m, H-1'b, 2', 6', CMe_2, O*t*Bu), 0.85 (3H, t, H-7', $J_{6',7'}$ = 6.9 Hz). ^{13}C NMR δ : 152.1 ($N\underline{C}O_2$), 94.5 (C-2), 81.1 (C-5), 79.4 ($O\underline{C}Me_3$), 64.4 (C-1"), 59.4 (C-4), 33.5, 32.1, 29.9, 29.5, 25.9, 22.9 (C1'-6'), 28.6 ($OC\underline{Me}_3$), 28.4, 27.6 ($C\underline{Me}_2$), 14.1 (C-7'). Anal. Calcd for $C_{18}H_{35}NO_4$: C, 65.62 ; H, 10.71 ; N, 4.25 ; Found : C, 65.66 ; H, 10.61 ; N, 4.30.

(2*S*,3*R*)-3-Amino-4-hydroxydecanoic acid 2. To a stirred solution of oxalyl chloride (43 µL, 0.5 mmol) in CH_2Cl_2 (2 mL), at -78°C was slowly added DMSO (70 µL, 0.99 mmol). The resulting complex was stirred for 15 min at -78°C prior to the addition of alcohol **11** (109 mg, 0.33 mmol) in CH_2Cl_2 (3 mL). After 45 min at -65°C, Et_3N (276 µL, 1.99 mmol) was added, followed 1.5 h later by the addition of Et_2O (20 mL) at -65°C. The salt (Et_3NHCl) was removed by filtration through a celite pad, and the filtrate was concentrated *in vacuo* to give the crude aldehyde which was used without further purification in the next step.

To a solution of the aldehyde in a mixture water-dioxane (1/3, 19 mL) cooled at 0°C were successively added sodium chlorite (120 mg, 1.32 mmol) and sulfamic acid (64 mg, 0.66 mmol). After stirring for one hour, the reaction mixture was poured into brine (10 mL) and extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were dried, filtered and concentrated *in vacuo* to give a yellow oil. Then, a solution of TFA/H_2O (1/1, 10 mL) was added and after stirring for 12 h, the mixture was concentrated *in vacuo* ; the residue was then stirred with an aqueous solution of HCl (5 mL, 1N). After concentration *in vacuo* ; purification by ion- exchange chromatography (Dowex 50x8-100, H_2O-NH_4OH : 99/1 then H_2O/MeOH : 65/45) furnished 49 mg (73 %) of **2**. m.p. 233-235°C, lit. 219-220°C[11a]. $[\alpha]_D$ +5 (c 0.70, HCl, 1N), litt. +5.4 (c 0.59, HCl 1N).[11a] ^1H NMR (D_2O) δ : 4.14 (1H, d, H-2, $J_{2,3}$ = 3.8 Hz), 3.54-3.45 (1H, m, H-3), 1.86-1.34 (12H, m, H-4-9), 0.92 (3H, t, H-10, $J_{9,10}$ = 6.8 Hz). ^{13}C NMR (125 MHz; DMSO d_6) δ : 173.5 (C-1), 69.8 (C-2), 53.0 (C-3), 31.4, 29.1, 28.7, 25.4, 22.3 (C-4-9), 14.2 (C-10).

(4*R*,5*R*)-3-*N*-*tert* -Butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-[(E)-2"-formyl-vinyl]-2,2-dimethyl-1,3-oxazolidine 13. To a stirred solution of oxalyl chloride (789 µL, 9.19 mmol) in CH_2Cl_2 (5 mL) at -78°C was slowly added DMSO (1.30 mL, 18.38 mmol). The resulting complex was stirred for 15 min at -78°C prior to the addition of alcohol **1** (3.06 g, 6.13 mmol) in CH_2Cl_2 (38 mL). After 45 min at -65°C, Et_3N (5.11 mL, 36.76 mmol, was added and the temperature was raised to 20°C for 100 min ; then formylmethylene triphenylphosphorane (1.86 g, 6.13 mmol) was added *in situ* to the aldehyde **12** and the reaction mixture was

stirred for 20 h. After addition of Et_2O (100 mL), filtration through a celite pad, washing with Et_2O (3x20 mL), and concentration *in vacuo*, flash chromatography of the residue (cyclohexane/AcOEt : 9/1, Rf 0.3) afforded 2.92 g (91 %) of **13**. $[\alpha]_D$ +7 (c 1.24, CH_2Cl_2). IR (neat) 1700, 1695 cm^{-1}. ^1H NMR δ : 9.30 (1H, d, H-3", $J_{2",3"}$ = 6.8 Hz), 7.75, 7.20 (10H, 2m, Ph), 6.39 (1H, dd, H-1", $J_{1",2"}$ = 15 Hz, $J_{1",5}$ = 4 Hz), 6.25 (1H, dd, H-2", $J_{1",2"}$ = 15 Hz, $J_{2",3"}$ = 6.8 Hz), 4.87 (1H, *br* dd, H-5, $J_{4,5}$ = 5 Hz), 4.13-3.85 (2H, m, H-1'a,1'b, $J_{1'a,1'b}$ = 10 Hz, $J_{1'b,H4}$ = 3 Hz), 3.72 (1H, m, H-4), 1.63, 1.58 (6H, 2s, CMe_2), 1.33 (9H, s, O*t*Bu), 1.12 (9H, s, Si*t*Bu). ^{13}C NMR δ : 191.5 (CHO), 152.6 (C-1"), 151.8 (-N$\underline{C}O_2$), 136.0, 133.6, 130.3, 128.2 (Ar), 132.6 (C-2"), 95.7 (C-2), 80.0 (O$\underline{C}Me_3$), 76.7 (C-5), 63.5 (C-4), 63.0 (C-1'), 28.4 (OC$\underline{Me}_3$), 27.8, 27.0 (C$\underline{Me}_2$), 27.2 ($\underline{Me}_3CSi$), 19.5 ($Me_3\underline{C}Si$).

A sample of the intermediate aldehyde **12** was purified by flash chromatography (cyclohexane/EtOAc 8/2, Rf 0.3). $[\alpha]_D$ -18 (c 1.35, CH_2Cl_2). ^1H NMR δ : 9.5 (1H, *br* s, H-1") 7.75, 7.20 (10H, 2m, Ph), 4.57 (1H, m, H-5), 4.35 (1H, dt, H-4, $J_{4,5}$ = 7.1 Hz, $J_{4,1'a}$ = $J_{4,1'b}$ = 3.6 Hz), 4.06-3.87 (2H, m, H-1'a,1'b, $J_{1'a,1'b}$ = 10 Hz), 1.60, 1.55 (6H, 2s, CMe_2), 1.27 (9H, s, O*t*Bu), 1.12 (9H, s , Si*t*Bu). ^{13}C NMR δ : 200.2 (CHO), 151.6 (N$\underline{C}O_2$), 136.0, 133.9, 130.1, 128.2 (Ar), 96.3 (C-2), 82.2 (C-5), 80.1 (O$\underline{C}Me_3$), 63.4 (C-1'), 59.4 (C-4), 28.3 (OC$\underline{Me}_3$), 27.4, 26.9 (C$\underline{Me}_2$), 27.2 ($\underline{Me}_3CSi$), 19.5 ($Me_3\underline{C}Si$).

(4*R*,5*R*)-3-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldiphenylsilyloxymethyl-5-[3"-hydroxypropyl]-2,2-dimethyl-1,3-oxazolidine (14). A solution of **13** (310 mg, 0.59 mmol) in EtOH (10 mL) was stirred for 20 h under hydrogen in the presence of a catalytic amount of Raney Nickel (70 mg ; P = 3 atm). After filtration through a celite pad and concentration *in vacuo* , 310 mg (99 %) of **14** was obtained. $[\alpha]_D$ -11 (c 1.05, CH_2Cl_2). ^1H NMR δ : 7.75, 7.25 (10H, 2m, Ph), 4.35 (1H, m, H-5), 4.10 (1H, m, H-1'a), 3.95 (1H, m, H-1'b), 3.65 (1H, m, H-4), 3.43 (1H, *br* t, H-3"), 1.80-1.50 (10H, m, H-1", 2",CMe_2), 1.36 (9H, s, O*t*Bu), 1.16 (9H, s, Si*t*Bu). ^{13}C NMR δ : 152.1 (N$\underline{C}O_2$), 136.0, 134.0, 130.1, 128.1 (Ph), 94.5 (C-2), 79.5 (O$\underline{C}Me_3$), 77.8 (C-5), 63.9 (C-4), 66.2 (C-1'), 62.5 (C-3"), 31.7, 29.8 (C-2",1"), 28.5 (OC$\underline{Me}_3$), 27.2 ($\underline{Me}_3CSi$), 28.2, 27.0 (C$\underline{Me}_2$), 19.6 ($Me_3\underline{C}Si$).

(4*R*,5*R*)-3-*N*-*tert*-Butoxycarbonyl-4-hydroxymethyl-5-[3"-hydroxypropyl]-2,2-dimethyl-1,3-oxazolidine (15). To a stirred solution of **14** (503 mg, 0.995 mmol) in THF (94 mL) was added dropwise at 20°C, *n*-tetrabutylammonium fluoride (1.05 mL, 1.05 mmol, 1M in THF). After stirring for 12 h, water (10 mL) was added ; after extraction with CH_2Cl_2 (3x15 mL) the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (AcOEt, Rf 0.4) gave 229 mg (83 %) of **15**. $[\alpha]_D$ +3 (c 0.80, CH_2Cl_2). ^1H NMR δ : 3.80-3.57 (4H, m, H1',4,5), 3.46-3.36 (2H, m, H-3), 1.70-1.30 (19H, m, H-1",2", CMe_2, O*t*Bu). ^{13}C NMR δ : 152.5 (N$\underline{C}O_2$), 94.4 (C$\underline{Me}_2$), 80.4 (O$\underline{C}Me_3$),77.2 (C-5), 65.6 (C-4), 64.2, 62.3 (C-3",1'), 30.8, 29.4 (C-2",1"), 28.4 C$\underline{Me}_3$), 28.2, 26.6 (C$\underline{Me}_2$). Anal. Calcd. for $C_{14}H_{27}NO_5$: C, 58,11 ; H, 9.40 ; N,4.84 ; Found C, 58.10 ; H, 9.50 ; N, 4.85.

(3*R*,4*R*)-*N*-Benzyl-3,4-[3'-*N*-*tert*-butoxycarbonyl-2',2'-dimethyl-1',3'-oxazolidinyl] azepane 16. To a solution of the diol **15** (42 mg, 0.14 mmol) in CH_2Cl_2 (0.3 mL) were dropwise added successively at -78°C trifluoromethanesulfonic anhydride (54 µL, 0.32 mmol) and 2,6-lutidine (39 µL, 0.33 mmol). After 20 min stirring, CH_2Cl_2 (7 mL) and benzylamine (318 µL, 2.90 mmol) were added . The mixture was slowly warmed to 20°C and stirred for 20 h. The reaction mixture was then concentrated *in vacuo*, and the residue was purified by flash chromatography (cyclohexane/AcOEt 9/1, Rf 0.3) to provide 30 mg (57 %) of **16**. m.p. 208-210°. $[\alpha]_D$ -80 (c 1.04, CH_2Cl_2). ^1H NMR δ : 7.30-7.05 (5H, m, Ph), 4.27 (1H, m, H-4), 3.70-3.35 (4H, m, H-

2a,3,CH_2Ph), 2.50 (1H, m, H-2b), 2.40-2.20 (2H, m, H-7), 2.10-2.00 (1H, m, H-5a), 1.70, 1.56 (6H, 2s, CMe_2), 1.50-1.30 (12H, m, H-5b,6, O*t*Bu). ^{13}C NMR δ : 152.5 ($N\underline{C}O_2$), 140.3, 130, 127 (Ar), 94.5 ($\underline{C}Me_2$), 79.3 ($O\underline{C}Me_3$), 78.1 (C-4), 63.5 ($\underline{C}H_2Ar$), 62.6 (C-3), 59.1, 52.5 (C-2,7), 31.3, 26.2 (C-5,6), 28.5 ($C\underline{Me}_3$), 27.3, 26.1 ($C\underline{Me}_2$). MS (EI, %) 360 M^+ (15), 134 (60), 91 (100). HMRS for $C_{21}H_{32}N_2O_3$ (M^+), calcd.360.24129, found 360.24144.

(3*R*,4*R*)-*N*-Benzyloxycarbonyl-3,4-[3-*N*-*tert*-butoxycarbonyl-2',2'-dimethyl-1',3'-oxazolidinyl] azepane 17. A solution of **16** (43 mg, 0.119 mmol) in EtOH (1 mL) was stirred for 24 h under hydrogen atmosphere in presence of a catalytic amount of palladium on charcoal 10 % (5 mg). After filtration through a celite pad and concentration *in vacuo*, the crude amine was used without purification in the next step.

At 0°C to a solution of the amine in CH_2Cl_2 (400 µL) and NEt_3 (26 µL, 0.19 mmol) was dropwise added benzylchloroformate (22 µL, 0.15 mmol). After stirring for 1 h, the reaction mixture was poured into water (2 mL) and extracted with CH_2Cl_2 (3x2 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane/AcOEt 80/20, Rf 0.3) afforded 28 mg (58 %) of **17**. m.p. 84-86°C, lit, 84-86°C.[15c] $[\alpha]_D$ -117 (c 1.35, $CHCl_3$), lit, -104.6 (c 1.10, $CHCl_3$).[15c] ^1H NMR δ : 7.30-7.00 (5H, m, Ph), 5.15-5.06 (2H, AB, CH_2Ar, J_{AB} = 12.5 Hz), 4.23 (1H, dd, H-2a, $J_{2a,3}$ = 5.6 Hz, $J_{2a,2b}$ = 13 Hz), 3.85-3.35 (4H, m, H-4,3,2b,7a), 2.47 (1H, m, H-7b), 1.91 (1H, m, H-5a), 1.70-1.25 (18H, m, CMe_2, H-5b,6,O*t*Bu). ^{13}C NMR δ : 155.7 ($\underline{C}O_2Bn$), 152.3 ($\underline{C}O_2tBu$),137.8, 128.6, 128.2 (Ph), 94.7 ($\underline{C}Me_2$), 79.8 ($O\underline{C}Me_3$), 78.1 (C-4), 67.2 ($\underline{C}H_2Ph$), 62.3 (C-3), 49.1, 45.5 (C-2,7), 31.3, 24.3 (C-5,6), 28.4 ($C\underline{Me}_3$), 27.2, 26.8 ($C\underline{Me}_2$). Anal. Calcd for $C_{22}H_{32}N_2O_5$: C, 65.32 ; H, 7.97 ; N, 6.93 ; Found : C, 65.33 ; H, 7.99 ; N, 6.85.

REFERENCES

1. This work was presented at the 6th BOSS Meeting, Ghent (Belgium), July 1996.
2. Baks, A.H. *Tetrahedron*, **1996**, *52*, 331-375.
3. Heaney-Kieras, J.; Kurylo-Burowska, Z.; Craig, C.C. *Biochemistry* **1966**, *5*, 2153.
4. Roncari, G.; Kurylo-Burowska, Z. *J. Antibiot.* **1980**, *33*, 359.
5. Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97.
6. Aoyagi, T.; Tobe, H.; Kojima, F.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 636.
7. Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501-504.
8. Dondoni, A.; Perrone, D.; Semola, J. *Synthesis*, **1995**, 181 and referecences cited therein.
9. For examples see: a) Pégorier, L.; Haddad, M.; Larchevêque, M. *Synlett.*, **1996**, 585-586. b) Dell'Uomo, N.; Di Giovanni, M.C.; Misiti, D.; Zappia, G.; Delle Monache, G. *Tetrahedron Asymmetry*, **1996**, *7*, 181-188. c) Warmerdam, G.J.C.; Van Rijn, R.D.; Brussee, J.; Krusa, C.G.; Van der Gen, A. *Tetrahedron Asymmetry*, **1996**, *7*, 1723-1732. d) Pasto, M.; Mayano, A.; Pericas, M.A.; Riera, A. *Tetrahedron Asymmetry*, **1996**, *7*, 243-262.
10. Tuch, A.; Sanière, M.; Le Merrer, Y.; Depezay, J-C. *Tetrahedron Asymmetry*, **1996**, *7*, 897-906.
11. a) Bunnage, M.E.; Burke, A.J.; Davies, S.G.; Goodwin, G.J. *Tetrahedron Asymmetry*, **1995**, *6*, 165-182. b) Matsnura, F.; Hamada, Y.; Shiou, T. *Tetrahedron*, **1994**, *50*, 11303-11314 c) Bunnage, M-E. ; Burke, A.J. ; Davies, S.G. ; Goodwin, C.J. ; *Tetrahedron Asymmetry*, **1995**, *5*, 203-206.

12. a) Muller, A.; Takyar, D.K.; Witt,S .; König, W.A. *Liebigs Ann. Chem.*, **1993**, 651-655 and references cited therein. b) König, W.A.; Sinnwell, V.; Witt, S.; Kneifel, H. *Chem. Ber*, **1980**, *113*, 2221-2226.

13. Kulanthaivel, Y.F.; Hallock, C.; Boros, C.; Hanulton, S.M.; Janzen, W.P.; Ballas, L.M.; Loomis, C.R.; Jiang, J.B.; Katz, B.; Steiner, J.R.; Clardy, J. *J. Am. Chem. Soc.*, **1993**, *115*, 6452-6453.

14. Oshima, S.; Yanagisawa, M.; Katoh, A.; Fujii, T.; Sano,T.; Matsukuma, S.; Fuyumai, T.; Fujui, M.; Watanaba, K.; Yokose, K.; Arisawa, M.; Okuda, T. *J. Antibiotics*, **1994**, *47*, 639.

15. a) Koide, K.; Bunnage, M.E.; Paloma, L.G.; Kanter, J.R.; Taylor, S.S.; Brunton, L.L.; Nicolaou, K.C *Chem. Biol.* **1995**, *2*, 601-608. b) Nicolaou, K.C.; Bunnage, M.E.; Koida, K. *J. Am. Chem. Soc.*, **1994**, *116*, 8402-8403. c) Nicolaou, K.C.; Koide, K.; Bunnage, M.E. *Chem. Eur.*, **1995**, *1*, 454-466.

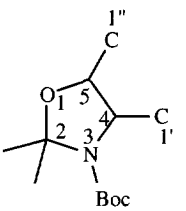
16. a) Hu, H.; Jagdmann Jr., G.E.; Hughes, P.F.; Nichols, J.B. *Tetrahedron Lett.*, **1995**, *21*, 3659-3662. b) Adams, C.P.; Fairway, S.M.; Hardy, C.J.; Hibbs, D.E.; Hursthouse, M.B.; Morley, A.D.; Sharp, B.W.; Vicker, N.; Warner, I. *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2355-2362.

17. a) Hughes, P.F.; Smith, S.H.; Olson, J.T. *J. Org. Chem.*, **1994**, *59*, 5799-5802. b) Lampe, J.W.; Hughes, P.F.; Briggers, C.K.; Smith, S.H.; Hu, H.; *J. Org. Chem.*, **1994**, *59*, 5147-5148.

18. Tanner, D.; Almario, A.; Högberg, T. *Tetrahedron*, **1995**, *51*, 6061-6070.

19. Albertini, E.; Barco, A.; Beretti, S.; De Risi, C.; Pollini, G.P.; Zarinato, V. *Synlett.*, **1996**, 29-30.

20. The numbering system used in this paper corresponds to the current CA index names for substructure 1. For details, see : *Chemical Abstracts Service Index Guide*, American Chemical Society :



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