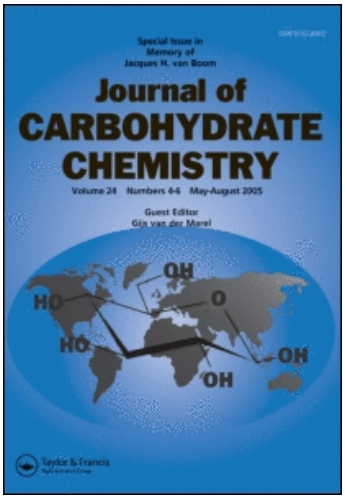

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ON THE WAY TO LIPOSIDOMYCINS, NEW NUCLEOSIDE ANTIBIOTICS. ACCESS TO THE HOMOCHIRAL DIAZEPANONE CORE

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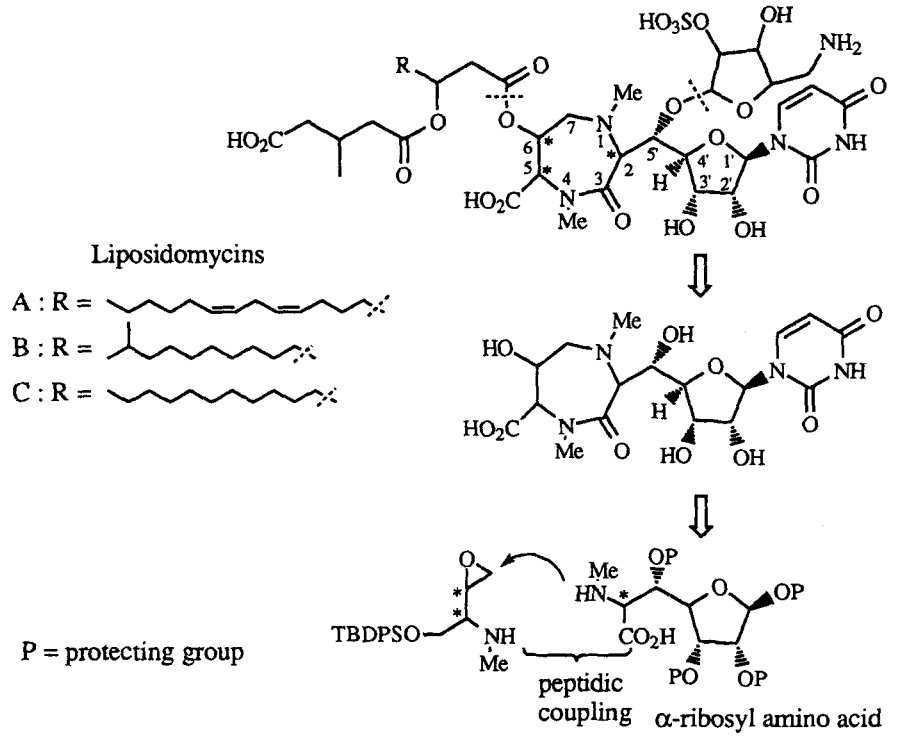
ABSTRACT

Access to the homochiral diazepanone core of liposidomycins has been carried out through the regiospecific nucleophilic opening of an enantiomerically pure α-amino-β,γ-epoxy-acid precursor, by an L-amino acid derivative, on one hand and cyclisation by a peptidic coupling reaction, on the other hand.

INTRODUCTION

The ribosyl-diazepanone moiety is a common component in liposidomycins, a new class of nucleoside antibiotics, isolated from the culture filtrate and mycelia of *Streptomyces griseosporeus*,[1] which strongly inhibit bacterial peptidoglycan synthesis.[2] At least twelve active components were obtained and the structures of the three major constituents, namely liposidomycins A, B and C were previously described and partially elucidated[3] (Scheme 1). These compounds contain 5'-substituted uridine, 5-amino-5-deoxyribose-2-sulfate and 1,4-diazepan-2-one moieties and differ essentially in the structure of the lipid side-chain. However, the absolute and relative configurations at C_2, C_5 and C_6 are still unknown.

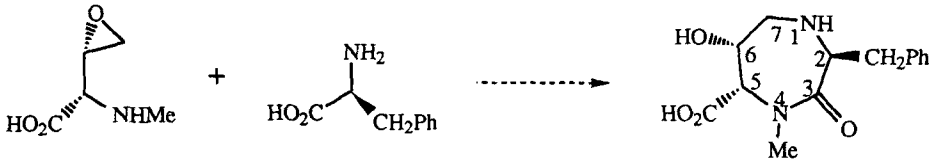


Scheme 1

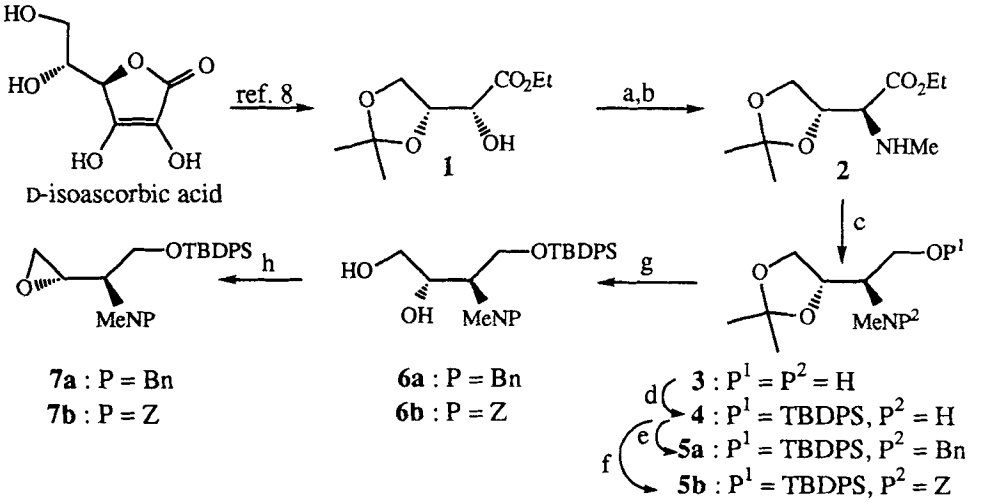
RESULTS AND DISCUSSION

When we began our study, only two syntheses of the 1,4-diazepan-2-one system had been reported[4] and both of them required separation of stereo- or regioisomers; we have been aiming at developing an approach using homochiral precursors. The two proposed key steps (Scheme 1) are: the regiospecific nucleophilic opening of an epoxide by the amino group of an α-ribosyl amino acid and cyclisation by a peptidic coupling reaction.[5] More recently, reports concerning a similar approach, but involving a glycine derivative,[6,7] prompted us to submit our results *in extenso*.

Taking the hypothesis that the biosynthetic route to liposidomycins involves naturally occurring amino acids, we postulated that the absolute configuration at C_2 and C_5 was *S*. For this reason, we chose to study the nucleophilic opening of a β,γ-epoxy-L-*threo*-amino acid derivative by L-phenylalanine (Scheme 2), as a test of the feasibility of our synthetic scheme.



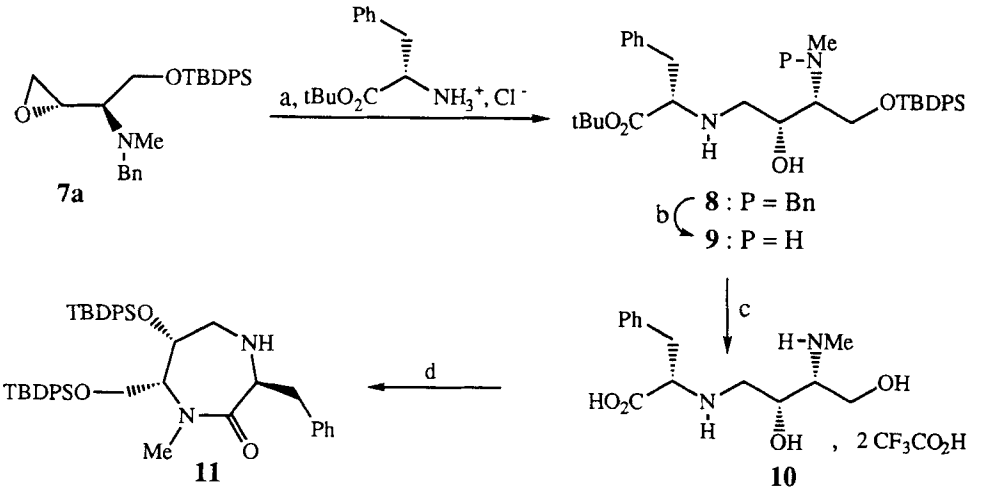
Scheme 2



Scheme 3 : a) Tf_2O, 2,6-lutidine, -78 °C. b) $MeNH_2$, EtOH, 70%. c) $LiAlH_4$, THF, Δ. d) TBDPSCl, DMF, imidazole, 86%. e) BnBr, K_2CO_3, DMF, 88%. f) $PhCH_2OCOCl$, K_2CO_3, DMF, 90%. g) TFA, H_2O, 95%. h) Ph_3P, DIAD, 67% for **7a** and 75% for **7b**.

D-Isoascorbic acid was revealed to be a good precursor of the epoxy amino acid derivative. In fact, due to stability reasons, we first synthesized a C_4 building block in which the carboxylic acid function was reduced to a primary alcohol and the amine function was protected as its *N*-benzyl or *N*-benzyloxycarbonyl derivative (Scheme 3).

Ethyl 3,4-*O*-methylethylidene D-erythronate **1** was obtained according to a known route.[8] Activation of the secondary alcohol by reaction with trifluoromethane sulfonic anhydride in the presence of 2,6-lutidine in CH_2Cl_2 at -78 °C was followed by nucleophilic substitution of the triflate with an excess of methylamine in ethanol at 20 °C. This cleanly afforded the secondary amine **2** in 70% overall yield from **1**. $LiAlH_4$ reduction of the ester function in refluxing THF gave the primary alcohol **3** (quantitative yield) which was then protected as its *O*-TBDPS derivative in 86% yield. The secondary amine was subsequently



Scheme 4: a) tBuOH, NaH, Δ, 75%. b) HCO_2NH_4, MeOH, 10% Pd/C, 84%. c) TFA, H_2O 65%. d) DCC, DMAP, DMAP·HCl, $CHCl_3$, Δ then TBDPSCl, imidazole, DMF, 45 °C.

protected either as its *N*-benzyl (**5a**) or *N*-benzyloxycarbonyl (**5b**) derivative in good yield. Acidic hydrolysis of the acetonide moiety afforded the corresponding diols **6a** and **6b** in 95% and 92% yield, respectively. Epoxide formation cleanly occurred under Mitsunobu conditions to give the expected epoxides **7a** and **7b** in 67% and 75% yield, respectively.

Although many examples of nucleophilic opening of an epoxide by amines have been described,[9] relatively few involve the opening by an α-amino acid.[10] The nucleophilic opening of the epoxide **7a**[11] by reaction with *tert*-butyl L-phenylalaninate hydrochloride could be efficiently achieved (Scheme 4) in the presence of sodium *tert*-butoxide in *tert*-butyl alcohol at 100 °C for 24 hours. The expected product **8**[12] was obtained in this way in 75% yield.[13] Hydrogenolysis of the *N*-benzyl moiety cleanly occurred in methanol in the presence of an excess of ammonium formate and Pd/C (10%) and afforded **9** in 84% yield.[14] Both silyl ether and *tert*-butyl ester deprotections were then effected by acid hydrolysis (TFA, H_2O, 65% crude yield). A sample of the resulting salt **10** was successfully cyclized in the presence of an excess of DCC, DMAP, DMAP·HCl in refluxing chloroform.[15] In order to decrease the polarity of the product and facilitate chromatographic purification, the crude mixture was persilylated (TBDPSCl excess, imidazole, DMF) to afford the diazepanone **11** in moderate yield.[16]

The 1,4-diazepan-2-one structure was unequivocally established[12] by mass spectroscopy and 2D NMR experiments [COSY ^1H-^1H, COSY ^1H-^{13}C, and long range ^1H-^{13}C correlation (PFG-HMBC)[17]].

CONCLUSION

We have shown here that the diazepanone core of liposidomycins can be obtained according to the synthetic route we proposed, namely: the regiospecific nucleophilic opening of an epoxide by the amino group of an α-ribosyl amino acid and cyclisation by a peptidic coupling reaction. Our current efforts are directed towards obtaining the ribosyl-diazepanone present in the liposidomycins structure.

EXPERIMENTAL

^{1}H NMR (250 MHz) and ^{13}C NMR (63 MHz) spectra were recorded in $CDCl_3$ (unless otherwise indicated). 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) or mercury (365 nm) lamps. All reactions were carried out under a nitrogen atmosphere using dried solvents and were monitored by thin-layer chromatography with Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60H (5-40 μm). Spectroscopic (^{1}H and ^{13}C NMR, MS) and/or analytical data were obtained using chromatographically homogeneous samples.

Ethyl (2*S*, 3*S*)-2-*N*-Methylamino-3,4-*O*-methylethylidene-3,4-dihydroxybutanoate (2). To a solution of the hydroxy ester **1** (4.6 g, 22.5 mmol) in CH_2Cl_2 (63 mL), at -78°C, were successively added 2,6-lutidine (3.67 mL, 1.4 eq) and trifluoromethanesulfonic anhydride (5.33 mL, 1.4 eq). After 30 min, thin-layer chromatographic analysis (EtOAc:cyclohexane 6:4) of the reaction mixture revealed the absence of starting material (*Rf* 0.26) and the presence of the expected triflate (*Rf* 0.82). Methylamine (11.2 mL, 4 eq) was then added and the mixture was stirred at 20 °C for 12 h. Concentration *in vacuo* and purification by flash chromatography (EtOAc: cyclohexane:Et_3N 6:4:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.34) afforded 3.4 g (70%) of the amino ester **2**: $[\alpha]_D$ -40 (*c* 1.00, CH_2Cl_2); ^{1}H NMR δ 1.28 (t, 3H, J = 7 Hz, OEt), 1.41, 1.33 (2s, 6H, CMe_2), 2.42(s, 3H, NHMe), 3.18 (d, 1H, $J_{2,3}$ = 6 Hz, H-2), 3.92 (dd, 1H, $J_{4,4'}$ = -8 Hz, $J_{4,3}$ = 7 Hz, H-4), 4.01 (dd, 1H, $J_{4',4}$ = -8, $J_{4',3}$ = 7 Hz, H-4'), 4.22 (q, 2H, J = 7Hz, *O*Et), 4.28 (m, 1H, H-3); ^{13}C NMR δ 14.3 (OEt), 25.2, 26.4 (CMe_2), 34.8 (NMe), 61.1 (OEt), 65.1 (C-2), 66.5 (C-4), 75.9 (C-3), 109.7 (CMe_2), 172.0 (C-1); IR (neat) : 3400-3300, 1740 cm^{-1}.

Anal. Calcd for $C_{10}H_{19}O_4N$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.31; H, 8.82; N, 6.45.

(2*S*,3*R*)-3-*N*-Methylamino-1,2-*O*-methylethylidene-butan-1,2,4-triol (3). To a suspension of lithium aluminium hydride (854 mg, 1.44 eq) in THF (15.8 mL), at 0 °C, was dropwise added a solution of the amino ester **2** (3.39 g, 15.6 mmol) in THF (10.5 mL). After 1.5 h stirring at 20 °C and 1.5 h at 65 °C, the mixture was cooled to 0 °C. Careful additions of water (854 µL), of a 15% aqueous solution of NaOH (854 µL) and finally of water (2.6 mL) led to the formation of a white precipitate which was filtered off and successively rinsed with ether and boiling chloroform. The organic extracts were then dried (Na_2SO_4) and concentrated *in vacuo* to afford 2.68 g (98%) of the crude alcohol **3** which was used in the next step without further purification. A sample was purified by flash chromatography (EtOAc:cyclohexane:Et_3N 7:3:0.01; pre-saturation of the column with 1% Et_3N). ^1H NMR δ 1.32,1.39 (2s, 6H, CMe_2), 2.42 (s, 3H, NHMe), 2.50 (ddd, 1H, $J_{3,2}$ = 7.5 Hz, $J_{3,4}$ = 3 Hz, $J_{3,4'}$ = 4 Hz, H-3), 3.33 (dd, 1H, $J_{4,4'}$ = -11.5 Hz, $J_{4,3}$ = 3 Hz, H-4), 3.68 (dd, 1H, $J_{4',4}$ = -11.5 Hz, $J_{4',3}$ = 4 Hz, H-4'), 3.73 (dd, 1H, $J_{1,1'}$ = -8 Hz, $J_{1,2}$ = 6 Hz, H-2), 4.04 (dd, 1H, $J_{1',1}$ = -8 Hz, $J_{1',2}$ = 6 Hz, H-1'), 4.15 (ddd, 1H, $J_{2,3}$ = 7.5 Hz, $J_{2,1}$ = $J_{2,1'}$ = 6 Hz, H-2).

(2*R*,3*S*)- 1-*tert*-Butyldiphenylsilyloxy- 2-*N*-methylamino- 3,4-*O*-methylethylidene-butan-3,4-diol (4). To a solution of the amino alcohol **3** (2.63 g, 15 mmol) in DMF (91.5 mL) were added imidazole (2.24 g, 2.2 eq) and *tert*-butyldiphenylsilylchloride (4.3 mL, 1.1 eq). The resulting mixture was stirred for 48 h at 20 °C and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane:EtOAc:Et_3N 1:1:0.01; pre-saturation of the column with 1% Et_3N, *Rf* 0.31) gave 5.35 g (86%) of the silyl ether **4** as a white solid: mp 56 °C; $[\alpha]_D$ -9 (*c* 0.94, CH_2Cl_2); ^1H NMR δ 1.04 (s, 9H, CMe_3), 1.33, 1.36 (2s, 6H, CMe_2), 2.34 (s, 3H, NHMe), 2.55 (m, 1H, H-2), 3.57 (dd, 1H, $J_{1,1'}$ = -10.5 Hz, $J_{1,2}$ = 6 Hz, H-1), 3.64 (dd, 1H, $J_{1',1}$ = -10.5 Hz, $J_{1',2}$ = 4.5 Hz, H-1'), 3.78 (dd, 1H, $J_{4,4'}$ = -7.5 Hz, $J_{4,3}$ = 7.5 Hz, H-4), 4.01 (dd, 1H, $J_{4',4}$ = -7.5 Hz, $J_{4',3}$ = 6 Hz, H-4'), 4.11 (ddd, 1H, $J_{3,4}$ = 7.5 Hz, $J_{3,2}$ = 7 Hz, $J_{3,4'}$ = 6 Hz, H-3), 7.39, 7.62 (2m, 10H, Ph); ^{13}C NMR δ 19.1 (CMe_3), 25.4 (CMe_2), 26.8 (CMe_3), 34.7 (NMe), 62.9 (C-1), 63.5 (C-2), 67.1 (C-4), 77.3 (C-3), 108.4 (CMe_2), 127.7, 129.7, 133.1, 135.5 (Ph).

Anal. Calcd for $C_{24}H_{35}O_3NSi$: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.59; H, 8.56; N, 3.53.

(2*R*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzylamino-3,4-*O*-methylethylidene-butan-3,4-diol (5a). To a solution of the amine **4** (550 mg, 1.3 mmol) in DMF (6.5 mL) were successively added potassium carbonate (276 mg, 1.5 eq) and benzyl bromide (217 µL, 1.37 eq) after cooling to 0 °C. The mixture was then stirred at 20 °C for 12 h. After having discarded the excess of potassium carbonate by

filtration, the filtrate was concentrated *in vacuo*. To the resulting residue, ether was added and the insoluble potassium chloride was filtered off. The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography of the residue (cyclohexane:EtOAc:Et_3N 9:1:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.38) afforded 590 mg (88%) of the benzylated amine **5a**: $[\alpha]_D$ -4 (*c* 1.00, CH_2Cl_2), $[\alpha]_{365}$ -14 (*c*1.00, CH_2Cl_2); ^1H NMR δ 1.04 (s, 9H, CMe_3), 1.35, 1.36 (2s, 6H, CMe_2), 2.36 (s, 3H, NMe), 2.79 (ddd, 1H, $J_{2,3}$ = 6.5 Hz, $J_{2,1}$ = 6 Hz, $J_{2,1'}$ = 5.5 Hz, H-2), 3.72 (dd, 1H, $J_{1,1'}$ = -10.5 Hz, $J_{1,2}$ = 6 Hz, H-1), 3.76 (m,1H, H-4), 3.83 (dd, 1H, $J_{1',1}$ = -10.5 Hz, $J_{1',2}$ = 5.5 Hz, H-1'), 3.68, 3.93 (AB, 2H, $J_{A,B}$ = -13.5 Hz, CH_2Ph), 3.97 (dd, 1H, $J_{4',4}$ = -8 Hz, $J_{4',3}$ = 6 Hz, H-4'), 4.33 (ddd, 1H, $J_{3,4}$ = 8 Hz, $J_{3,2}$ = 6.5 Hz, $J_{3,4'}$ = 6 Hz, H-3), 7.26, 7.40, 7.65 (3m, 15H, Ph); ^{13}C NMR δ 19.1 (CMe_3), 25.6 (CMe_2), 26.6, 26.9 (CMe_3), 38.8 (NMe), 60.2, 62.5 (C-1, NCH_2Ph), 64.6 (C-2), 67.5 (C-4), 76.0 (C-3), 108.4 (CMe_2), 126.6, 127.7, 128.1, 128.7, 129.7, 133.2, 135.6, 140.4 (Ph).

Anal. Calcd for $C_{31}H_{41}O_3NSi$: C, 73.91; H, 8.20; N, 2.78. Found: C, 73.96; H, 8.29; N, 2.77.

(2*R*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzyloxycarbonylamino-3,4-*O*-methylethylidene-butan-3,4-diol (5b). To a solution of the amine **4** (230 mg, 0.56 mmol) in DMF (2.7 mL) were successively added potassium carbonate (93 mg, 1.3 eq) and benzylchloroformate (87.5 µL, 1.1 eq) after cooling to 0 °C. After 30 min stirring at 20 °C, further addition of both potassium carbonate (0.6 eq) and benzylchloroformate (0.55 eq) allowed completion of the reaction within 30 min stirring at 20 °C. The mixture was then filtered and washed with DMF and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in chloroform and washed with brine. The organic layer was then dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (cyclohexane:EtOAc 8:2, *Rf* 0.38) afforded 276 mg (90%) of the carbamate **5b**: ^1H NMR δ 1.00 (s, 9H, CMe_3), 1.27, 1.29 (2s, 6H, CMe_2), 2.96 (s, 3H, NMe), 3.49-3.97 (m, 4H, H-1,1',4,4'), 4.13, 4.28 (2m, 2H, H-2,3), 5.10 (m, 2H, OCH_2Ph), 7.35, 7.64 (2m, 15H, Ph).

(2*R*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzylaminobutan-3,4-diol (6a). To the acetonide **5a** (660 mg,1.3 mmol) in water (9.4 mL) at 0°C was dropwise added trifluoroacetic acid (9.4 mL). The mixture was stirred for 2 h and concentrated *in vacuo*. The resulting residue was dissolved in MeOH and silica gel was then added. After concentration *in vacuo*, the crude, absorbed on silica gel, was purified by flash chromatography (EtOAc:cyclohexane:Et_3N 6:4:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.24) to give 625 mg (95%) of the diol **6a**: $[\alpha]_D$ -6 (*c* 1.20, CH_2Cl_2),

$[\alpha]_{365}$ -20 (*c* 1.20, CH_2Cl_2); ^1H NMR δ 1.07 (s, 9H, CMe_3), 2.22 (s, 3H, NMe), 2.84 (ddd, 1H, $J_{2,3}$ = 9 Hz, $J_{2,1'}$ = 6 Hz, $J_{2,1}$ = 5 Hz, H-2), 3.44 (dd, 1H, $J_{4,4'}$ = -11.5 Hz, $J_{4,3}$ = 4 Hz, H-4), 3.60 (ddd, 1H, $J_{3,2}$ = 9 Hz, $J_{3,4}$ = 4 Hz, $J_{3,4'}$ = 3.5 Hz, H-3), 3.74 (dd, 1H, $J_{4',4}$ = -11.5 Hz, $J_{4',3}$ = 3.5 Hz, H-4'), 3.77 (dd, 1H, $J_{1,1'}$ = -11.5 Hz, $J_{1,2}$ = 5 Hz, H-1), 3.58, 3.81 (AB, 2H, $J_{A,B}$ = -13 Hz, CH_2Ph), 3.87 (dd, 1H, $J_{1',1}$ = -11.5 Hz, $J_{1',2}$ = 6 Hz, H-1'), 7.27, 7.44, 7.66 (3m, 15H, Ph); ^{13}C NMR δ 19.0, 26.8 (CMe_3), 37.0 (NMe), 59.5, 60.1 (C-4, NCH_2Ph), 63.9 (C-1), 65.2 (C-2), 68.4 (C-3), 127.1, 127.6, 128.3, 128.7, 129.8, 129.9, 132.7, 135.5, 135.6, 138.8 (Ph); HRMS calcd for $C_{28}H_{37}O_3NSi$: 463.2543. Found: 463.2543.

(2*R*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzyloxycarbonylaminobutan-3,4-diol (6b). To the acetonide **5b** (194 mg, 0.36 mmol), at 20 °C, was added an aqueous solution of acetic acid (5.9 mL, AcOH:H_2O 6:1). After 48 h stirring at 20 °C, the mixture was concentrated *in vacuo* and purified by flash chromatography (EtOAc:cyclohexane 7:3, *Rf* 0.31) to afford 165 mg (92%) of the diol **6b**: $[\alpha]_D$ +8 (*c* 1.03, CH_2Cl_2); ^1H NMR δ 1.02 (s, 9H, CMe_3), 3.00 (s, 3H, NMe), 3.49 (m, 2H, H-4,4'), 3.86 (m, 2H, H-1,1'), 4.03 (m, 2H, H-2,3), 5.13 (m, 2H, OCH_2Ph), 7.34, 7.61 (2m, 15H, Ph); ^{13}C NMR δ 19.1, 26.8 (CMe_3), 33.7 (NMe), 60.1 (C-2), 62.4, 63.9 (C-1,4), 67.5 (OCH_2Ph), 71.7 (C-3), 127.8, 128.1, 128.5, 129.9, 132.9, 135.5, 136.5 (Ph), 158.2 (CO_2CH_2Ph); HRMS calcd for $C_{29}H_{37}O_5NSi$ (M^+-*t*Bu): 450.1737. Found: 450.1733.

(2*R*,3*S*)- 1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzylamino-3,4-epoxy-butane (7a). To a solution of triphenylphosphine (2.32 g, 1.32 eq) in toluene (31 mL) at 0 °C, was dropwise added diisopropyl azodicarboxylate (1.74 mL, 1.32eq). After 15 min stirring at 0 °C, a solution of the diol **6a** (3.1 g, 6.7 mmol) -which was previously twice diluted with toluene (10 mL) and concentrated *in vacuo* in order to avoid any trace of water- in toluene (10 mL) was added and the resulting mixture was stirred at 0 °C for 1 h. After concentration *in vacuo*, the residue was gradually heated to 130 °C under *vacuo* (0.2 mm Hg) for 90 min. An intermediate trap cooled in dry ice was used in order to condense any volatile materials. The crude product was then purified by flash chromatography (cyclohexane:EtOAc:Et_3N 9:1:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.26) to give 2 g (67%) of the expected epoxide **7a**: $[\alpha]_D$ -10 (*c* 1.00, CH_2Cl_2); ^1H NMR δ 1.04 (s, 9H, CMe_3), 2.30 (s, 3H, NMe), 2.41 (ddd, 1H, $J_{2,3}$ = 7.5 Hz, $J_{2,1}$ = 6.5 Hz, $J_{2,1'}$ = 5.5 Hz, H-2), 2.58 (dd, 1H, $J_{4,4'}$ = -5 Hz, $J_{4,3}$ = 2.5 Hz, H-4), 2.74 (dd, 1H, $J_{4',4}$ = -5 Hz, $J_{4',3}$ = 4 Hz, H-4'), 3.13 (ddd, 1H, $J_{3,2}$ = 7.5 Hz, $J_{3,4'}$ = 4 Hz, $J_{3,4}$ = 2.5 Hz, H-3), 3.75 (s, 2H, CH_2Ph), 3.83 (AB from ABX, 2H, $J_{A,B}$ = -10.5 Hz, $J_{A,X}$ = 5.5 Hz, $J_{B,X}$ = 6.5 Hz, H-1',1), 7.28, 7.40, 7.63 (3m, 15H, Ph); ^{13}C NMR δ

19.1, 26.8 (CMe_3), 38.8 (NMe), 44.8 (C-4), 51.6 (C-3), 59.8 (CH_2Ph), 63.3 (C-1), 66.7 (C-2), 126.7, 127.7, 128.1, 128.6, 129.7, 133.3, 135.6, 139.9 (Ph).

Anal. Calcd for $C_{28}H_{35}O_2NSi$: C, 75.46; H, 7.92; N, 3.14. Found: C, 75.41; H, 7.93; N, 3.16.

(2*R*,3*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*-methylbenzyloxycarbonylamino-3,4-epoxy-butane (7b). A solution of the diol **6b** (57 mg, 0.11 mmol) in toluene (1 mL) was twice concentrated *in vacuo* in order to avoid any trace of water. A solution of triphenylphosphine (38 mg, 1.3 eq) in toluene (1 mL) was then added and the mixture was cooled to 0 °C prior to the addition of diisopropyl azodicarboxylate (29 µL, 1.3 eq). After 30 min stirring at 0 °C, the mixture was concentrated *in vacuo* and gradually heated to 130 °C under *vacuum* (0.02 mm Hg) for 2 h. Flash chromatography of the crude product (cyclohexane:EtOAc 8:2, *Rf* 0.27) afforded 41 mg (75%) of the epoxide **7b**: $[\alpha]_D$ -3 (*c* 1.00, CH_2Cl_2); ^1H NMR δ 1.02 (s, 9H, CMe_3), 2.57 (m, 1H, H-4), 2.75 (m, 1H, H-4'), 2.94 (s, 3H, NMe), 3.08-3.17 (m, 1H, H-3), 3.80-3.87 (m, 2H, H-1,1'), 4.06 (m, 1H, H-2), 5.11 (m, 2H, OCH_2Ph), 7.35, 7.61 (2m, 15H, Ph); ^{13}C NMR δ 19.1, 26.7 (CMe_3), 31.7 (NMe), 45.7 (C-4), 50.7 (C-3), 59.2 (C-2), 62.2 (C-1), 67.2 (OCH_2Ph), 127.8, 127.9, 128.4, 129.8, 133.0, 135.5, 136.7 (Ph), 156.6 (CO_2CH_2Ph).

***tert*-Butyl *N*-[(2*R*,3*R*)-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-3-(*N*-methylbenzylamino)butyl]-*S*-phenylalaninate (8).** To a solution of sodium *tert*-butoxide, prepared by the addition of *tert*-butyl alcohol (2 mL) to sodium hydride (41 mg, 1.9 eq), was added *tert*-butyl L-phenylalaninate hydrochloride (463 mg, 2 eq). After stirring for 30 min at 20 °C, a solution of the epoxide **7a** (400 mg, 0.9 mmol) in *tert*-butyl alcohol (2.5 mL) was added and the mixture was then heated to 100 °C for 24 h. After concentration *in vacuo* the residue was added with chloroform and filtered. The filtrate was dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography of the resulting oily residue (toluene: MeOH:Et_3N 98:2:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.32) afforded 450 mg (75%) of the expected product **8**: $[\alpha]_D$ +5 (*c* 1.25, CH_2Cl_2), $[\alpha]_{365}$ +27 (*c* 1.25, CH_2Cl_2); ^1H NMR δ 1.10 (s, 9H, Si*t*Bu), 1.34 (s, 9H, CO_2*t*Bu), 2.28 (s, 3H, NMe), 2.32 (dd, 1H, $J_{1,1'}$ = -12.2 Hz, $J_{1,2}$ = 5.4 Hz, H-1), 2.82-2.85 (m, 3H, H-1', CH_2Ph), 2.94 (X from ABX, 1H, $J_{X,A}$ = 9 Hz, $J_{X,B}$ = 5.4 Hz, H-3), 3.24 (t, 1H, $J_{HPhe,CH2Ph}$ = 7.1 Hz, H-Phe), 3.57 (ddd, 1H, $J_{2,3}$ = 9 Hz, $J_{2,1}$ = 5.4 Hz, $J_{2,1'}$ = 3 Hz, H-2), 3.77 (AB from ABX, 2H, $J_{A,B}$ = -5.4 Hz, $J_{A,X}$ = 9 Hz, $J_{B,X}$ = 5.4 Hz, H-4,4'), 3.69, 3.92 (2d, 2H, J_{NCH2Ph} = -13.2 Hz, NCH_2Ph), 7.11-7.30, 7.40, 7.66 (3m, 20H, Ph); ^{13}C NMR δ 19.1, 26.9 (Si*t*Bu), 28.0 (CO_2*t*Bu), 37.1 (NMe), 39.8 (CH_2Ph), 50.4 (C-1), 59.8, 60.5 (C-4, NCH_2Ph), 63.8, 66.2, 67.3 (C-2,3,Phe), 80.8 (CO_2*t*Bu), 126.3, 127.1, 127.8, 128.1, 128.3, 128.8, 129.4, 129.8, 129.9, 133.1, 135.6, 135.7, 137.9, 139.5 (Ph), 173.7(CO_2*t*Bu).

Anal. Calcd for $C_{41}H_{54}O_4N_2Si$: C, 73.83; H, 8.16; N, 4.2. Found: C, 73.81; H, 8.34; N, 4.1.

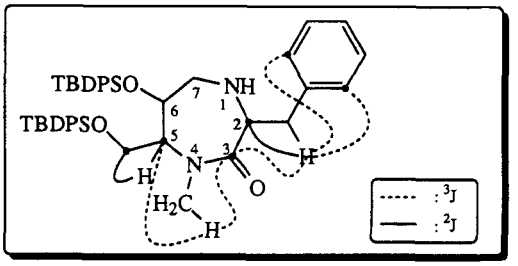
***tert*-Butyl *N*-[(2*R*,3*R*)-4-*tert*-butyldiphenylsilyloxy-2-hydroxy-3-(*N*-methylamino)butyl]-*S*-phenylalaninate (9).** To a solution of the benzylated amine **8** (290 mg, 0.44 mmol) in MeOH (2.9 mL) at 20 °C, were successively added 10% palladium on charcoal (290 mg) and ammonium formate (110 mg, 4 eq). After 3.5 h stirring at 20 °C, the catalyst was removed by filtration through a celite pad and rinsed with chloroform previously filtered on potassium carbonate. Concentration *in vacuo* of the filtrate followed by a flash chromatography (toluene: MeOH:Et_3N 85:15:0.01, pre-saturation of the column with 1% Et_3N, *Rf* 0.30) afforded 211 mg (84%) of **9**: $[\alpha]_D$ -3 (*c* 1.04, pyridine), $[\alpha]_{365}$ -4 (*c* 1.04, pyridine); ^1H NMR δ 1.11 (s, 9H, Si*t*Bu), 1.38 (s, 9H, CO_2*t*Bu), 2.42 (s, 3H, NMe), 2.92 (m, 2H, H-1,3), 3.04 (m, 2H, CH_2Ph), 3.28 (dd, 1H, $J_{1',1}$ = -11.5 Hz, $J_{1',2}$ = 4 Hz, H-1'), 3.66 (t, 1H, $J_{HPhe,CH2Ph}$ = 7 Hz, H-Phe), 3.93 (dd, 1H, $J_{4,4'}$ = -10 Hz, $J_{4,3}$ = 4.5 Hz, H-4), 4.04 (dd, 1H, $J_{4',4}$ = -10 Hz, $J_{4',3}$= 5 Hz, H-4'), 4.19 (dt, 1H, $J_{2,3} = J_{2,1}$ = 5 Hz, $J_{2,1'}$ = 4 Hz, H-2), 7.27, 7.47, 7.85 (3m, 15H, Ph); ^{13}C NMR δ 19.4, 27.0 (Si*t*Bu), 27.9 (CO_2*t*Bu), 35.1 (NMe), 40.0 (CH_2Ph), 51.4 (C-1), 62.9 (C-4), 64.2, 64.3 (C-3,Phe), 70.1 (C-2), 80.5 (CO_2*t*Bu), 126.6, 128.2, 128.4, 129.8, 130.1, 134.0, 136.0, 138.6 (Ph), 174.0 (CO_2*t*Bu).

Anal. Calcd for $C_{34}H_{48}O_4N_2Si$: C, 70.79; H, 8.39; N, 4.86. Found: C, 70.97; H, 8.46; N, 4.69.

***N*-[(2*R*,3*R*)-2,4-dihydroxy-3-(*N*-methylamino)butyl]-*S*-phenylalanine (10).** The ester **9** (210 mg, 0.37 mmol) in a 1:1 (v/v) aqueous solution of trifluoroacetic acid (4 mL) was stirred at 80 °C for 3 h. TLC monitoring of the mixture (toluene:MeOH:Et_3N 85:15:0.01) revealed the disappearance of starting material (*Rf* 0.30) and the formation of the ammonium *bis*-trifluoroacetate salt (*Rf* 0). Concentration *in vacuo* afforded 120 mg (65%) of the crude salt **10**: ^1H NMR (pyridine-*d*5) δ 3.44-3.97 (3m, 5H, H-1,1',3, CH_2Ph), 4.30 (m, 2H, H-4,4'), 4.54 (m, 1H, H-Phe), 4.87 (m, 1H, H-2), 7.02-7.25, 7.52-7.7.63 (2m, 5H, Ph).

***(2S,5R,6R)*- 2-Benzyl- 6-*tert*-butyldiphenylsilyloxy- 5-*tert*-butyl diphenylsilyloxymethyl-4-*N*-methylperhydro-1,4-diazepin-3-one (11).** To a solution of dicyclohexylcarbodiimide (60.5 mg, 5eq), DMAP·HCl[15] (46.5 mg, 5 eq) and DMAP (35.8 mg, 5 eq) in refluxing chloroform (3.35 mL, EtOH free), was added during 2 h a solution of ammonium *bis*-trifluoroacetate salt **10** (60 mg, 58 μmol) in chloroform (3.35 mL). The resulting mixture was maintained at 61 °C for another 2 h and concentrated *in vacuo*. The residue was then dissolved in DMF (1 mL) and both *tert*-butyldiphenylsilyl chloride (150 μL, 10 eq) and imidazole (79.8 mg, 20 eq) were added. After stirring at 45 °C for 15 h, ethyl acetate was added to the product mixture which was then hydrolysed by

the addition of a saturated aqueous solution of $NaHCO_3$. After decantation and EtOAc extractions (5x10 mL), the combined extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product absorbed on silica gel was then purified by flash chromatography (cyclohexane:EtOAc:Et_3N 7:3:0.03, *Rf 0.54*) to give the expected perhydro-1,4-diazepin-3-one **11** in 15% yield.[16] ^1H NMR δ 1.03 (*br*.s, 18H, 2*t*Bu), 2.40 (dd, 1H, $J_{7,7'}$ = -15 Hz, $J_{7,6}$ = 9.5 Hz, H-7), 2.96 (s, 3H, NMe), 3.28 (dd, 1H, J_{CH2Ph} = -13.5 Hz, $J_{CHPh,2}$ = 7 Hz, CHPh), 3.38 (dd, 1H, J_{CH2Ph} = -13.5 Hz, $J_{CH'Ph,2}$ = 2 Hz, CH'Ph), 3.43 (dt, 1H, $J_{5,CH'OSi}$ = 6.5 Hz, $J_{5,CH'OSi}$ = 6 Hz, $J_{5,6}$ = 1.5 Hz, H-5), 3.75 (dd, 1H, $J_{7',7}$ = -15 Hz, $J_{7',6}$ = 7.5 Hz, H-7'), 3.93 (dd, 1H, J_{CH2OSi} = -11 Hz, $J_{CHOSi,5}$ = 6.5 Hz, CHOSi), 4.05 (dd and m, 2H, J_{CH2OSi} = -11 Hz, $J_{CH'OSi,5}$ = 6 Hz, CH'OSi, H-6), 4.93 (*br*.dd, 1H, $J_{2,CHPh}$ = 7 Hz, $J_{2,CH'Ph}$ = 2 Hz, H-2), 7.37, 7.59, 7.69 (3m, 25H, Ph); ^{13}C NMR (126 MHz) δ 19.0, 26.6, 26.8 (Si*t*Bu), 31.9 (NMe), 34.1 (CH_2Ph), 48.3 (C-7), 57.1 (C-5), 61.1 (CH_2OSi), 62.7 (C-2), 69.8 (C-6), 127.7, 128.2, 129.6, 130.3, 130.4, 132.1, 134.8, 135.2, 135.4, 135.5 (Ph), 170.3 (C-3); MS (70 eV) : m/z 723 (<1%, $M^{\circ+}$-2H-CH3), 199 (100%, Ph_2SiOH). The long range ^1H-^{13}C correlations observed (^2J and ^3J) are summarized on the following structure :



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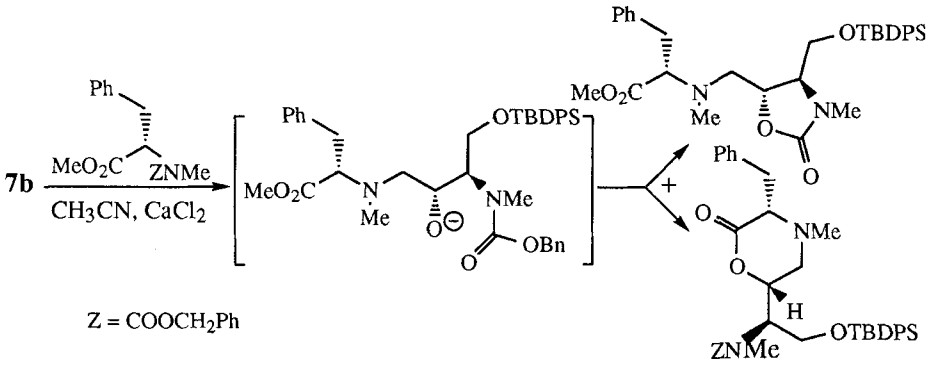
11. In a preliminary study, we observed that during the opening of **7b** by the methyl *N*-methyl-L-phenylalaninate, intramolecular transesterification reactions occurred.



Such reactions were avoided by *N*-benzyl protecting the secondary amine on one hand and by using the *tert*-butyl *N*-methyl phenylalaninate on the other hand.

12. No partial epimerization occurred during this sequence of reactions as confirmed by the absence of diastereoisomeric signals in ^{1}H (250 MHz) and ^{13}C NMR (63 MHz) spectra.

13. **8** could also be obtained in 62% yield in presence of ytterbium triflate at 20 °C in two weeks; see 10b.

14. This transformation can also be performed by hydrogen in presence of Pd/C 10%, but required longer reaction time which led to partial epimerization.

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16. Cyclisation involving a primary amine (RNH_2) instead of a secondary one (RNHMe) should occur in a better yield (71%) according to reference 6.

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