Tetrahedron Vol. 46, No. 8, pp. 2807-2816, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

STEREOCONTROLLED SYNTHESIS OF N,O-DIMETHYL-γ-AMINO-β-HYDROXY ACIDS : ANALOGUES OF THE (R)-MeIle-Ψ(CHOMe)-Gly[1] RESIDUE OF THE CYTOTOXIC MARINE PSEUDOPEPTIDE DOLASTATIN 10

I. Maugras, J. Poncet and P. Jouin*

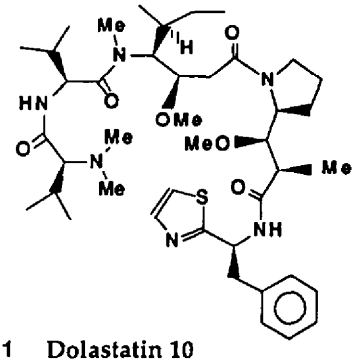
CCIPE, rue de la Cardonille, 34094 MONTPELLIER CEDEX 2, FRANCE

(*Received in Belgium* 12 *February* 1990)

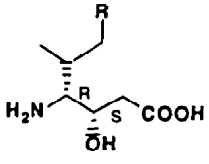
Abstract. The stereocontrolled synthesis of the N,O-dimethylated-γ-amino-β-hydroxy acid (R)-MeVal-Ψ(CHOMe)-Gly (**3b**) is reported; the key step is the formation of the nonmethylated allylic precursor with the *anti* configuration **20** by reduction of the keto analogue **16**.

Introduction.

Marine invertebrates are sources of pseudopeptidic structures with potent antineoplastic activities.[2] Many features of these compounds are unusual such as the thiazole ring junctions in patellamides, ulithiacyclamides,[2d] dolastatin 3,[2a] or the C-terminus found in the acyclic dolastatin 10 (1).[2b] In addition, the nonproteinogenic γ-amino-β-hydroxy acids (S)-D-*allo*-Ile-Ψ(CHOH)-Gly (**2a**) and (S)-D-Val-Ψ(CHOH)-Gly (**2b**) have been found in didemnins[3] and the methylated analog (R)-MeIle-Ψ(CHOMe)-Gly (**3a**) in dolastatin 10.[2b]

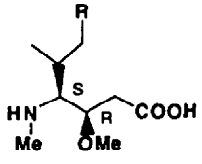


1 Dolastatin 10



2a R = Me
(S)-D-*allo*-Ile-Ψ(CHOH)-Gly

2b R = H
(S)-D-Val-Ψ(CHOH)-Gly



3a R = Me
(R)-MeIle-Ψ(CHOMe)-Gly

3b R = H
(R)-MeVal-Ψ(CHOMe)-Gly

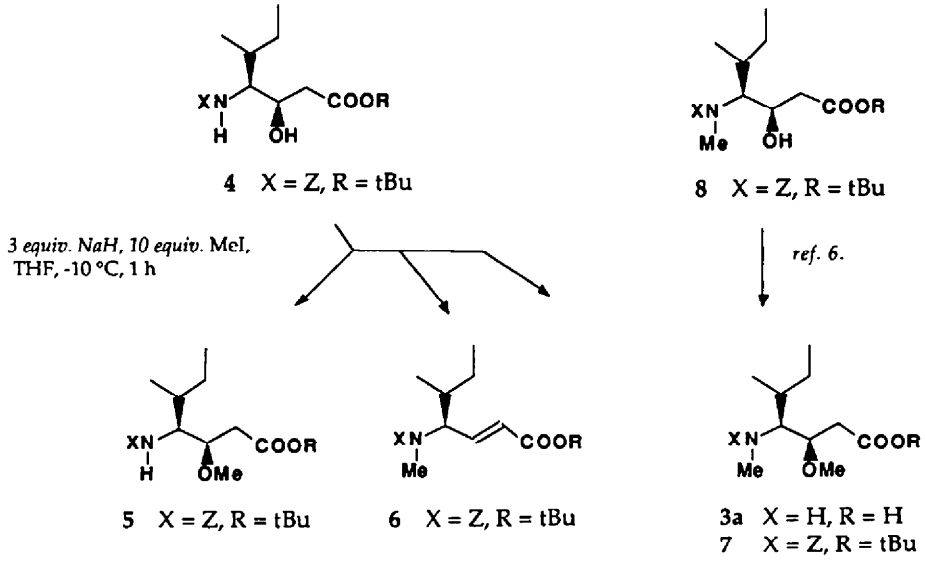
Although stereoselective synthesis of both *syn* and *anti* stereoisomers of γ-amino-β-hydroxy acids is now well documented,[4,5] a stereocontrolled access to the N,O-dimethylated derivative **3a** with the requisite *anti* configuration is still lacking. Recently, in the first publication on the total synthesis of dolastatin 10 (**1**), compound **3a** was obtained by separation of a mixture of diastereomers.[6] The enantioselective synthesis of the corresponding *syn* isomer has been reported but with a low overall chemical yield.[7] We report herein a convenient synthesis of (R)-MeVal-Ψ(CHOMe)-Gly (**3b**), the valine analog of **3a**.

Results and discussion

General comments

The most obvious approach toward the N,O-dimethylated derivatives **3a** and **3b** is methylation of the corresponding N-protected γ-amino-β-hydroxy acid **4** (Scheme 1). Unfortunately this direct methylation following the procedure described by Cheung and Benoiton[8] for the preparation of N-methylated amino acids gave poor yields of the expected N,O-dimethylated compound **7** together with a complex mixture from which the following compounds were identified : the O-methylated ester **5**, the N-methylated dehydro ester **6**, and other N-deprotected derivatives. Modifications of the original procedure, e. g. solvent composition, were unsuccessful.

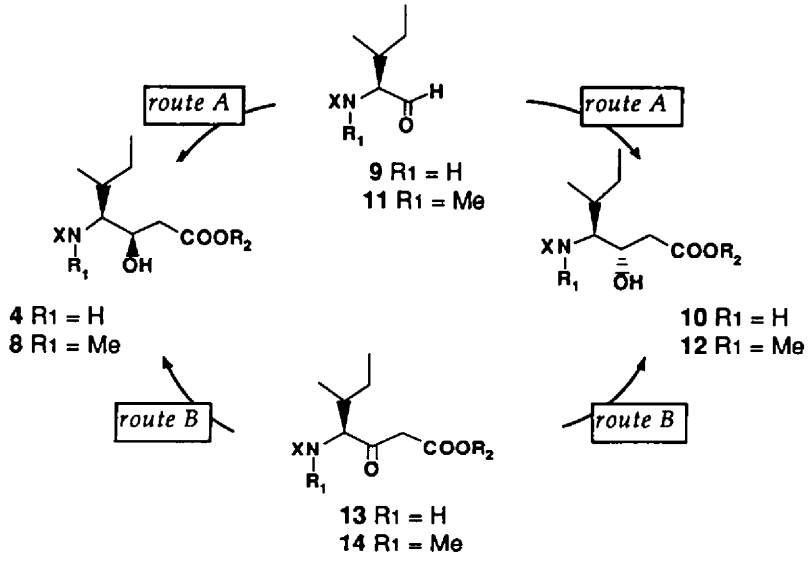
Scheme 1. *Methylation of γ-amino-β-hydroxy acids.*



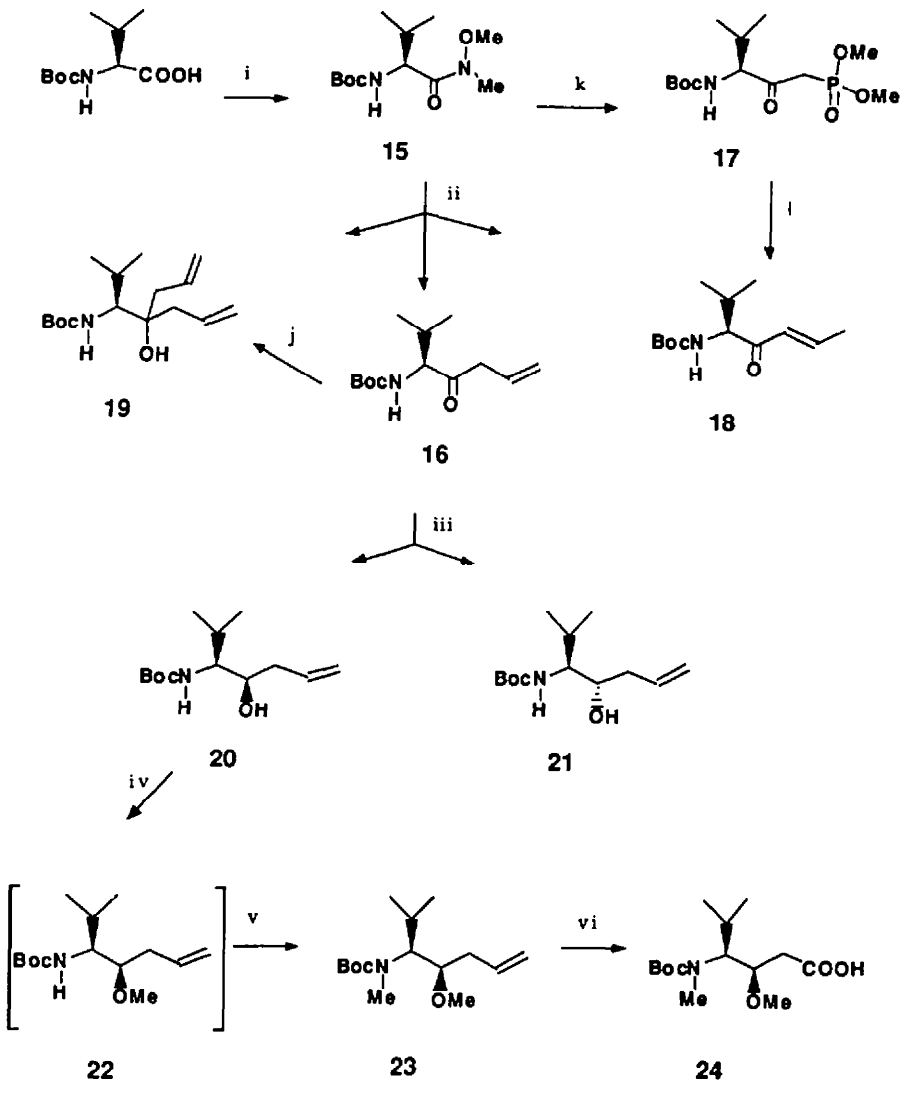
Attempts to O-methylate the N-methylated derivative **8** under basic conditions were disappointing. Better yields were obtained wiht diazomethane under acidic conditions.[6] Nevertheless, this did not provide an efficient solution for a stereoselective synthesis of the intermediate N-methylated γ-amino-β-hydroxy acid.

Access to the N-protected γ-amino-β-hydroxy acids was provided by two general routes : the first involved an aldol condensation of the corresponding N-protected amino aldehyde **9** with a metallated acetic acid derivative, which yielded a mixture of the *anti* and *syn* diastereomers **4** and **10** (Route A in Scheme 2)[9]. The second involved the reduction of the β-keto ester **13** which proved to be highly stereoselective and gave the *anti* isomer **4** (Route B in Scheme 2).[5] Aldol condensation of the N-Z, N-methylated isoleucine aldehyde **11** only produced a 33% yield of the *anti* isomer **8** together with the *syn* isomer **12**.[6] We also found that reduction of N-Z, N-Me γ-amino β-keto ester **14** did not induce the stereoselectivity observed for the non-N-methylated compound **13**. The N-Z, N-Me isoleucine was prepared following Benoiton's procedure. The preparation of the β-keto ester **14** was achieved, in 80% yield, following a previously described procedure.[4d] Sodium borohydride reduction of the keto group provided a diastereomeric mixture of alcohols **8** and **12**.[10] The required *anti* isomer **8** could not be purified by column chromatography.

Scheme 2. *Preparation of γ-amino-β-hydroxy acids.*



Scheme 3. Synthesis of (R)-Boc-MeVal-Ψ(CHOMe)-Gly



i - Me(MeO)NH, HCl, TEA, BOP, CH_2Cl_2, 92%; ii - CH_2=$CHCH_2MgBr$, Et_2O, 96%; iii - $NaBH_4$, MeOH, 73%; iv - NaH (2.2 equiv.), MeI, 2 h, 90%; v - NaH (3 equiv.), MeI, 86% from **20**; vi - $NaIO_4$, RuO_2, $CCl_4/CH_3CN/H_2O$, 70%; j - CH_2=$CHCH_2MgBr$, Et_2O, 96%; k- $LiCH_2P(O)(OMe)_2$, THF, - 45 °C, 68%; l - CH_3CHO, NaH, THF, 70%.

Analysis of this overall disappointing picture prompted us to reexamine the stereocontrolled synthesis and methylation conditions of the allylic derivative **20**, a suitable precursor of (R)-Boc-MeVal-Ψ(CHOMe)-Gly **24** as recently shown by Kano *et al.*.[7]

The improved allylic approach.

We have previously described the preparation and reduction of α-amino ketones derived from N-protected α-amino acids for stereoselective preparation of the corresponding α-amino alcohols with the *anti* configuration.[5a] Careful addition of the N,O-dimethyl-hydroxamate Boc-Val-N(Me)OMe (**15**) to the allyl Grignard reagent in diethyl ether gave ketone **16** in 91% yield.[5a, 11] For reproducible results, reaction conditions have to be scrupulously respected to avoid formation of two main by-products corresponding either to the double addition of the allyl Grignard reagent to **15** or to an isomerisation of the double bond into conjugation with the keto group. Under controlled conditions described in the experimental section, only 4% yield of alcohol **19** and less than 3% of ketone **18** were obtained (^{1}H NMR analysis). These by-products were identified by comparison with authentic samples obtained by alternative pathways. The tertiary alcohol **19** was obtained by Grignard alkylation of the ketone **16**. The conjugated ketone **18** was prepared by Wittig condensation of the lithium salt of dimethyl methylphosphonate with dimethyl hydroxamate **15** according to reference 5a. The Horner-Emmons condensation of acetaldehyde with **17** gave ketone **18** in 70% yield.

The unpurified ketone **16** was subjected to sodium borohydride reduction to give a mixture of both *anti* and *syn* alcohols **20** and **21** in a 97 : 3 ratio, together with 4% of alcohol **19**. After chromatography on silica gel, pure *anti* isomer **20** was obtained in 68% yield, (calculated from N,O-dimethyl-hydroxamate **15**).

Methylation of the N-Boc amino alcohol **20** was achieved by first adding two equivalents of sodium hydride and an excess of methyl iodide. Then, after one hour, three more equivalents of sodium hydride were added to effect the second methylation giving 86% yield of **23**. We noticed that O-methylation occurred first. The mono-methylated derivative **22** could be isolated in 90% yield. This one pot two-step procedure gave the best results.

Sharpless RuO_2-$NaIO_4$ oxidation of the allylic group of **23** gave 70% yield of the protected form **24** of (R)-MeVal-Ψ(CHOMe)-Gly (**3b**).[12]

Experimental

Melting points were determined on a Buchi melting-point apparatus. NMR data were obtained at 360 MHz on a Bruker WM-360 instrument; chemical shifts (ppm) were reported relative

to internal tetramethylsilane. Specific optical rotations were measured on a Schmidt and Haensch Polartronic D apparatus at ±1°. FAB mass measurements were supplied by Prof. J. L. Aubagnac, USTL, Montpellier. Column chromatographies were performed using silica gel (70-200 µm, Amicon). Analytic TLC were performed on silica gel F254 aluminium sheets (0.2 mm thick; Merck). Amino acid derivatives were purchased from Bachem or Novabiochem.

Boc-Val-N(Me)OMe (15).

The BOP method.[13] Boc-Val (6.52 g, 30 mmol) was dissolved in CH_2Cl_2 (100 mL). To this stirred solution the following were added successively: N,O-dimethylhydroxylamine hydrochloride (3.32 g, 33 mmol), triethylamine (12.47 mL, 90 mmol) and BOP (13.2 g, 30 mmol). After 1.5 h, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed successively with 5% $KHSO_4$, 5% $NaHCO_3$, and saturated brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give pure **15** as a colorless paste after flash column chromatography (ethyl acetate / hexane, 30:70) (7.21 g, 92%).

The DCC method.[14] Boc-Val (10.86 g, 50 mmol) was dissolved in CH_2Cl_2 (200 mL). To this stirred solution maintained at 0 °C, the following were added successively: N,O-dimethylhydroxylamine hydrochloride (5.85 g, 60 mmol), DIEA (10.21 mL, 60 mmol), DMAP (0.15 g, 0.6 mmol) and DCC portionwise (12.32 g, 50 mmol). After stirring 1 h at O °C, then 3 h at room temperature, the DCU was filtrated and washed with CH_2Cl_2 (100 mL). The same treatment as described above for the organic solution was followed by DCU precipitation in ether followed by flash chromatography to give pure **15** as a colorless paste (11.22 g, 86%).

Allylmagnesium Bromide. [15] A dry argon-flushed, three-neck flask containing magnesium turnings (Prolabo) (3.64 g, 150 mmol) was fitted with a dropping funnel and a reflux condenser protected with a dry tube containing silica gel (granulated, self-indicating). Anhydrous diethyl ether was used to cover the magnesium. To the slowly magnetically stirred magnesium-ether mixture, a solution of allylbromide (4.33 mL, 50 mmol) in anhydrous diethyl ether (80 mL) was added dropwise over a period of 16 h. The etheral solution was then filtered under argon. The allyl magnesium bromide was 0.61 N as determined by titration according to Gilman.[16]

(S)-6-Methyl-5-(t-butoxycarbonylamino)-1-heptene-4-one (16). To a 0.61 N solution of allylmagnesium bromide in diethyl ether (90 mL, 54 mmol) in a dry argon-flushed three-neck flask fitted with a dropping funnel were added 35 mL of anhydrous diethyl ether. The Grignard solution was stirred vigorously at - 10 °C. Then a solution of **15** (4.68 g, 18 mmol) in anhydrous ether (55 mL) was rapidly added. The mixture was brought to room temperature and stirred for 5 more minutes. The reaction mixture was hydrolyzed with cold 5% $KHSO_4$ (100 mL). The organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield 4.2 g of a mixture containing compound **16** together with ketone **18** and alcohol **19** in the ratio 94 : 2 : 4, determined by ^1H NMR integration of olefinic protons. This mixture was used without further purification for the following step.

^{1}H NMR (DMSO-d_6) δ 0.79 and 0.84 (d, J = 6.84 Hz, 6H), 1.39 (s, 9H), 1.97-2.14 (m, 1H), 3.24 (d, J = 6.83 Hz, 2H), 3.79-3.87 (m, 1H), 5.07 (d, J = 8.3 Hz, 1H), 5.11 (s, 1H), 5.76-5.9 (m, 1H), 7.13 (d, J = 8.3 Hz, 1H).

(S)-6-Methyl-5-(t-butoxycarbonylamino)-2-heptene-4-one (18). (S)-1-(Dimethoxyphosphoryl)-4-methyl-3-(t-butoxycarbonylamino)pentan-2-one **(17)** was prepared according to ref. 5a in 68% yield from the dimethyl-hydroxamate **15**.
$[\alpha]^{20}_D$ -26° (c 1 MeOH); ^{1}H NMR (DMSO-d_6) δ 0.77 and 0.84 (d, J = 6.8 Hz, 3H), 1.39 (s, 9H), 2.08-2.18 (m, 1H), 3.31 (d, J = 21.5 Hz, 2H), 3.65 (d, J = 11.2 Hz, 6H), 3.89-3.96 (m, 1H), 7.08 (d, J = 8.3 Hz, 1H); FABMS, m/e (relative intensity) 346 (M Na^+, 2%), 324 (M H^+, 34%), 224 (73%), 54 (100%).

To a cold solution (0 °C) of the phosphonate **17** (0.15 g, 0.46 mmol) in THF (2 mL) were added successively acetaldehyde (31 µl, 0.55 mmol) and, over a 1 h period, NaH (80% dispersion in mineral oil, 23 mg, 0.76 mmol). After stirring for 30 min, the mixture was hydrolyzed by cold 5% $KHSO_4$ (50 mL) and extracted with diethyl ether (50 mL). The organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound was purified by column chromatography (ethyl acetate/hexane, 20:80) to give the unsaturated ketone **18** as a colorless oil (79 mg, 70%); $[\alpha]^{20}_D$ +15° (c 1 MeOH); ^{1}H NMR (DMSO-d_6) δ 0.79 (d, J = 6.3 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H), 1.37 (s, 9H), 1.95 (dd, J_1 = 1.9 Hz, J_2 = 6.8 Hz, 3H), 1.94-2.05 (m, 1H), 3.94-4.03 (m, 1H), 6.35 (dd, J_1 = 1.5 Hz, J_2 = 15.6 Hz, 1H), 6.81-6.91 (m, 1H), 6.98 (d, J = 8.8 Hz, 1H); FABMS, m/e (relative intensity) 242 (MH^+, 19%), 142 (70%), 57 (100%).

(S)-4-(2-Propene)-6-methyl-5-(t-butoxycarbonylamino)-1-heptene-4-ol (19). To a cold solution (0 °C) of the crude ketone **16** (0.24 g) in diethyl ether (5 mL), a solution of allylmagnesium bromide (1.0 M solution in diethyl ether, 3 mL) was added dropwise . After stirring for 3 h at 0 °C and 3 h more at room temperature, the mixture was hydrolyzed by cold 5% $KHSO_4$ (20 mL) and extracted with diethyl ether (20 mL). The organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude compound was purified by column chromatography (ethyl acetate/hexane, 8:92) to give the tertiary alcohol **19** as a white solid (0.15 g, 56%); mp 54-55 °C; $[\alpha]^{20}_D$ +7° (c 1 MeOH); ^{1}H NMR (DMSO-d_6) δ 0.79 and 0.85 (d, J = 6.8 Hz, 6H), 1.39 (s, 9H), 1.99-2.2.9 (m, 5H), 3.25-3.33 (m, 1H), 4.20 (s, 1H), 4.76-5.10 (m, 4H), 5.71-5.87 (m, 2H), 5.95 (d, J = 10.2 Hz, 1H); FABMS, m/e (relative intensity) 284 (MH^+, 17%), 184 (5%), 54 (100%). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 64.16; H, 10.36; N, 4.94. Found: C, 64.46; H, 10.32; N, 4.88.

(4R,5S)-6-Methyl-5-(t-butoxycarbonylamino)-1-heptene-4-ol (20). To a stirred solution of the crude **16** (2.41 g) in methanol (30 mL) was added portionwise 0.38 g (10 mmol) of $NaBH_4$, at -20 °C over a period of 20 min. After 10 mn at 0 °C, diethyl ether was added to the reaction mixture which was hydrolyzed by cold 5% $KHSO_4$ (25 mL). The organic layer was washed with water and satura-

ted brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish 2.26 g of a mixture containing the alcohol of *anti* configuration **20**, the alcohol of *syn* configuration **21** and the alcohol **19** in the ratio 93/3/4, evaluated from ^1H NMR. This mixture was submitted to column chromatography (ethyl acetate/hexane, 15: 85) to furnish a white solid (1.65 g, 68%), which was crystallized (CH_2Cl_2/hexane) to give analytically pure alcohol **20** (1.23 g, 49% yield calculated from the starting hydroxamate **15**) mp 82-84 °C; $[\alpha]^{20}_D$ +17° (c 1 MeOH); ^1H NMR (DMSO-d_6) δ 0.74 and 0.78 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 9H), 1.93-2.10 (m, 2H), 2.15-2.26 (m, 1H), 3.15-3.30 (m, 1H), 4.47 (d, *J* = 6.3 Hz, 1H), 4.96 (s, 1 H), 5.00 (d, *J* = 7.8 Hz, 1H), 5.78-5.92 (m, 1H), 6.35 (d, *J* = 9.8 Hz); FABMS, m/e (relative intensity) 244 (MH^+, 17%), 154 (14%), 54 (100%). Anal. Calcd for $C_{13}H_{25}NO_3$: C, 64.16; H, 10.36; N, 5.76. Found: C, 64.09; H, 10.31; N, 5.82.

(4S,5S)-6-Methyl-5-(t-butoxycarbonylamino)-1-heptene-4-ol (21). ^1H NMR (DMSO-d_6) δ 0.82 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H), 1.38 (s, 9H), 1.66-1.79 (m, 1H), .99-2.13 (m, 1H), 2.98-3.08 (m, 1H), 3.55-3.64 (m, 1H), 4.37 (d, *J* = 7.3 Hz, 1H), 4.93-5.06 (m, 2H), 5.74-5.87 (m, 1H), 5.93 (d, *J* = 9.8 Hz); FABMS, m/e (relative intensity) 244 (MH^+, 3%), 154 (34%), 57 (100%).

(4R,5S)-6-Methyl-4-methoxy-5-(t-butoxycarbonyl-methyl-amino)-1-heptene (23). To a solution of **20** (1.23 g, 5.05 mmol) in THF (20 mL) were successively added, at -5 °C under an inert atmosphere, MeI (5 mL, 80 mmol) and NaH over a 1 h period (80% dispersion in mineral oil, 0.3 g, 10.1 mmol). The mixture was stirred for 1 h at -5 °C and 1 h more at 5 °C prior to adding portionwise an excess of MeI (5 mL) and NaH (0.45 g, 15 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with diethyl ether and hydrolyzed with cold 5% $KHSO_4$. The organic layer was washed with water, aqueous 5% sodium thiosulfate and saturated brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to furnish **23** (1.18 g, 86%) as a colorless oil, after flash chromatography (ethyl acetate/hexane, 5:95); $[\alpha]^{20}_D$ -24° (c 1 MeOH); ^1H NMR (DMSO-d_6) (two conformers in equimolar quantities which where not distinguished) δ 0.82 (d, *J* = 6.8 Hz, 1.5H), 0.83 (d, *J* = 6.8 Hz, 1.5H), 0.91 (d, *J* = 6.3 Hz, 1.5H), 0.92 (d, *J* = 6.8 Hz, 1.5H), 1.37 and 1.38 (s, 9H), 1.94-2.12 (m, 2H), 2.27-2.39 (m, 1H), 2.61 and 2.64 (s, 3H), 3.27 and 3.28 (s, 3H), 3.35-3.47 (m, 1H), 3.66-3.80 (m, 1H), 4.96-5.08 (m, 2H), 5.72-5.86 (m, 1H); FABMS, m/e (relative intensity) 272 (MH^+, 10%), 172 (40%), 54 (100%).

(4R, 5S)-6-Methyl-4-methoxy-5-(t-butoxycarbonylamino)-1-heptene (22): In the process described above, when hydrolysis was performed two hours after addition of the first 2 equiv. NaH, the monomethylated compound **22** was obtained in 82% yield as a colorless oil after flash chromatography (ethyl acetate/hexane, 10:90); $[\alpha]^{20}_D$ -7° (c 1 MeOH); ^1H NMR (DMSO-d_6) δ 0.76 and 0.79 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 9H), 1.80-1.92 (m, 1H), 2.04-2.16 (m, 1H), 2.22-2.34 (m, 1H), 3.07-3.29 (m, 1H), 3.23 (s, 3H), 3.36-3.45 (m, 1H), 4.93-5.08 (m, 2H), 5.72-5.86 (m, 1H), 6.45 (d, *J* = 10.7 Hz, 1H); FABMS, m/e (relative intensity) 258 (MH^+, 7%), 158 (17%), 57 (100%).

(3R,4S)-5-Methyl-3-methoxy-4-(t-butoxycarbonylamino)-hexanoic acid (24). Compound 23

(1.18 g, 4.35 mmol) was dissolved in a ternary biphasic solution of CCl_4 (8.7 mL), CH_3CN (8.7 mL) and water (26 mL). To this vigorously stirred solution were added $NaIO_4$ (9.3 g, 43.5 mmol) and RuO_2 (16 mg, 10 mmol). After 5 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and water (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was removed. The resulting slurry was diluted with diethyl ether and the solution subjected to millipore filtration. The filtrate was extracted with aqueous 5% $NaHCO_3$. The aqueous basic solution was then acidified with 1.0 N HCl and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to furnish the acid **24**, as an oil (1.18 g, 70%); $[\alpha]^{20}_D$ -14° (c 1 MeOH); ^1H NMR (DMSO-d_6) (two conformers in equimolar quantities which could not be distinguished) δ 0.81 (d, *J* = 5.1 Hz, 0.75H), 0.83 (d, *J* = 6.62 Hz, 0.75H), 0.92 (d, *J* = 6.6 Hz, 1.5H), 1.39 (s, 9H), 1.88-2.07 (m, 1H), 2.17-2.33 (m, 1H), 2.37-2.47 (m, 1H), 2.61 and 2.62 (s, 3H), 3.26 and 3.28 (s, 3H), 3.69-3.88 (m, 2H), 12.16 (s, 1H); FABMS, m/e (relative intensity) 312 (MNa^+, 1%), 290 ($M H^+$, 3%) 190 (21%), 54 (100%).

Acknowledgments.

We thank Prof. B. Castro for helpful suggestions. We are grateful to Prof. J. L. Aubagnac for MS measurements and A. Pantaloni for technical assistance in performing the NMR studies.

References.

1- Abbreviations and symbols follow the recommendations of IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9). For instance, designation of the γ-amino-β-hydroxy acids according to the pseudodipeptide nomenclature is more convenient than the systematic name : ((S)-Leu-Ψ(CHOH)-Gly for (3S,4S)-4-amino-3-hydroxy-6-methyl heptanoic acid), and more informative than the esoteric Sta for (S)-Leu-Ψ(CHOH)-Gly), isoSta for (S)-D-*allo*-Ile-Ψ(CHOH)-Gly, Dil[6] for (R)-MeIle-Ψ(CHOMe)-Gly. In addition the following abbreviations are used: BOP: (1H-1,2,3-benzotriazol-1-yloxy)-tris(dimethylamino)-phospho-nium hexafluorophosphate; COMODD: 2,2'-carbonyl-bis-(3,5-dioxo-4-methyl-1,2,4 oxadiazolidine; DCC: N,N-dicyclohexyl-carbodiimide; DIEA: diisopropylethylamine; DMAP: 4-dimethylaminopyridine; TEA: triethylamine; TFA: trifluoroacetic acid.

2- (a) Pettit, G. R.; Kamano, Y.; Fujii, Y.; Herald, C. L.; Inoue, M.; Brown, P.; Gust, D.; Kitahara, K.; Schmidt, J. M.; Doubek, D. L.; Michel, C. *J. Nat. Prod.* **1981**, *44*, 482. (b) Pettit G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883. (c) Rinehart, K. L.; Kishore, V.; Bible, K. C.; Sakai, R.; Sullins, D. W.; Li, K. M. *J. Nat. Prod.* **1988**, *51*, 1. (d) Degnan, B. M., Hawkins, C. J.; Lavin, M. F.; Mc Caffrey, E. J.; Parry, D. L.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1349.

3- (a) Rinehart, Jr., K. L.; Kishore, V.; Nagarajan, S.; Lake, R. J.; Gloer, J. B.; Bozich, F. A.; Li, K.-M.; Maleczka, Jr., R. E.; Todsen, W. L.; Munro, M. H.; Sullins, D. W.; Sakai, R. *J. Am. Chem. Soc.* **1987**, *109*, 6846. (b) Jouin, P.; Poncet, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617.

4- syn configuration : (a) Woo, P. W. *Tetrahedron Lett.* **1985**, *26*, 2973. (b) Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc. Perkin Trans. I* **1987**, 1177. (c) Sakaitani, M.; Ohfune, Y. *Tetrahedron Lett.* **1987**, *28*, 3987. (d) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1988**, *53*, 3865.

5- *anti* configuration : (a) Dufour, M. N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc. Perkin Trans. I* **1986**, 1895. (b) Harris, B. D.; Bhat, K. L.; Joullié, M. *Tetrahedron Lett.* **1987**, *28*, 2837. (c) Maibaum, J.; Rich, D. H. *J. Org. Chem.* **1988**, *53*, 869. (d) Jouin, P.; Poncet, J.; Dufour, M-N.; Maugras, I.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1988**, *29*, 2661.

6- Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463.

7- Kano, S.; Yokomatsu, T.; Shibuya, S. *J. Org. Chem.* **1989**, *54*, 513.

8- Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.

9- Rich, D. H.; Sun, E. T.; Boparai, A. S. *J. Org. Chem.* **1978**, *43*, 3624.

10- This reduction provided a mixture of alcohols in 90% yield. Two pairs of signals attributed to the two different N-Me conformations of both *syn* and *anti* diastereoisomers were present in the ^1H NMR spectrum.

11- Cupps, T. L.; Boutin, R. H.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 3972.

12- Carlsen, P. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

13- Fehrentz, J. A.; Castro, B. *Synthesis*, **1983**, 676.

14- Mendre, C.; Rodriguez, M.; Laur, J.; Aumelas, A.; Martinez, J. *Tetrahedron* **1988**, *44*, 4415.

15- Benkeser, R. A. *Synthesis* **1971**, 347.

16- Gilman, H.; Zoellner, E. A.; Dickey, J. B. *J. Am. Chem. Soc.* **1929**, *51*, 1576.