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Synthesis of (3*S* , 4*S*)-4-Hydroxy-2, 3, 4, 5-Tetrahydropyridazine-3-Carboxylic Acid, Component of Luzopeptin A.

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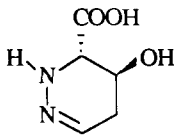
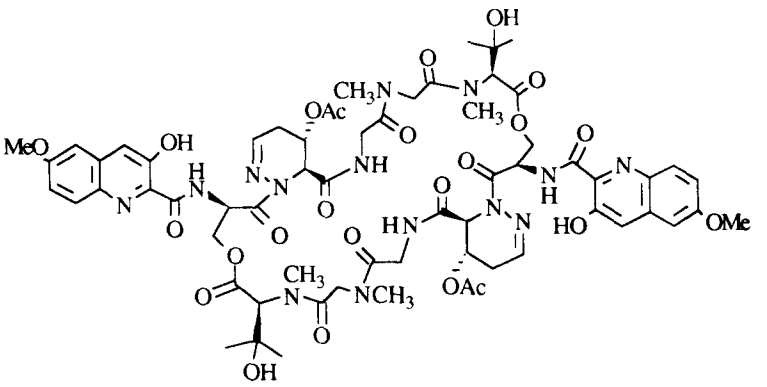
Abstract : The enantioselective synthesis of (3*S*, 4*S*)-4-hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid **1** is described. The two stereogenic centers in *anti* relationship are obtained by sequential enantio and chemoselective hydrogenation of β-ketoester in presence of chiral ruthenium catalyst and diastereoselective amination of β-hydroxyester with di *t*-butylazodicarboxylate.

(3*S*, 4*S*)-4-Hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid **1** is an unusual amino acid constituent of Luzopeptin A **2**. The antibiotic antitumor agent luzopeptin A is a bis-inetercalator of DNA and was isolated from *Actinomadura luzonensis*.[1]



1



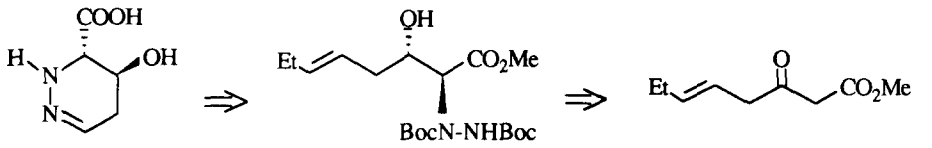
2

Luzopeptin A **2** is a dimeric cyclic depsipeptide constituted by six amino acids[2] : four are known and the two others are a new quinoline and the exotic cyclic amino acid **1**. The tetrahydropyridazine ring system is a rare structure in natural products : it has been found in the cirratiomycin antbiotics under its 3-carboxylic acid form,[3] and its synthesis has been recently reported.[4] To our knowledge, only one enantioselective synthesis of (3*S*, 4*S*)-4-hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid **1** has been described starting from malonaldehyde dimethyl acetal via Sharpless epoxidation and subsequent ring opening at C_2 of an epoxyacid with hydrazine.[5]

In connection with our continued work on the asymmetric synthesis of α-amino β-hydroxy acids by sequential catalytic hydrogenation and electrophilic or nucleophilic amination, we report here an efficient and enantioselective synthesis of this unusual amino acid. The key step was the introduction of the hydrazine moiety to a carbon unit and the creation of the two stereogenic centers having an *anti* relationship. This could

be accomplished by the diastereoselective electrophilic amination of a β-hydroxyester with di *t*-butylazodicarboxylate (DBAD).[6]

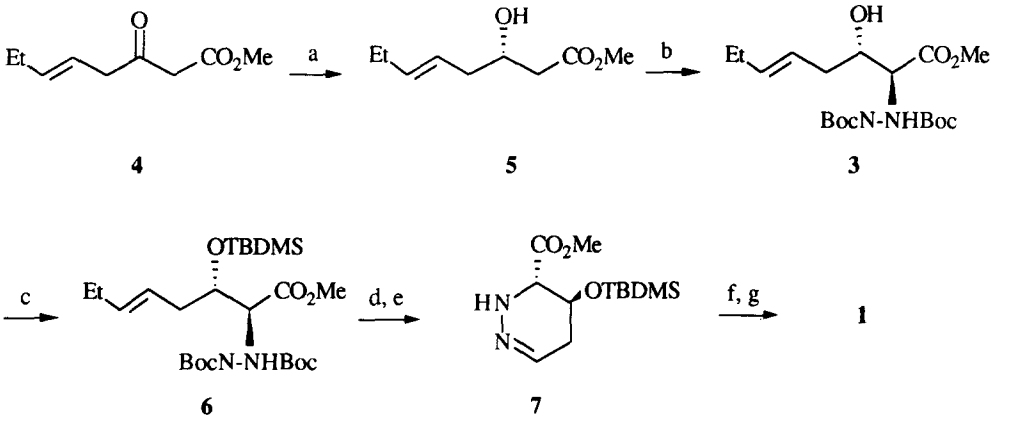
Scheme I



1 **3** **4**

In the α-hydrazino β-hydroxyester **3**, a double bond at C5 was introduced, as a masked aldehyde necessary for the hydrazone formation. As illustrated in Scheme I, **3** was derived from β-ketoester **4** using the following reactional sequence : enantioselective hydrogenation catalyzed by chiral complexes of ruthenium[7] and diastereoselective electrophilic amination.[6]

Scheme II



4 **5** **3**

6 **7**

(a) H_2, MeOH, 0.3% Ru (S)-Biphemp Br_2, 6 bars, 80°C, 30 min.(100%; ee>99%). (b) (i) MeZnBr (ii) LDA (iii) DBAD. (53%, de>98%). (c) TBDMSOTf, 2,6-lutidine. (85%). (d) (i) O_3 (ii) Me_2S. (e) TFA, CH_2Cl_2 then H_2O, MeOH. (50% from **6**) (f) nBu_4NF. (g) K_2CO_3, MeOH, H_2O. (90% from **7**).

(*E*)-Methyl-3-oxooct-5-enoate **4** was easily accessible from (*E*)-hex-3-enoic acid[8] or from (*E*)-hex-3-enoic acid chloride.[9] **4** was hydrogenated to β-hydroxyester **5** with use of the ruthenium catalyst : Ru (*S*)-Biphemp Br_2, prepared as described earlier.[7] This reaction was quantitative and highly enantio and chemoselective. Only one enantiomer was seen by ^1H NMR in presence of chiral Europium salt : (+)-Eu(tfc)$_3$. The absolute configuration of the hydroxylated center was correlated with (3*S*)-methyl-3-hydroxyoctanoate by simultaneous hydrogenation of the double bond and the ketone.[10] Using our procedure for the electrophilic amination of the ester enolate of **5**, DBAD was added in presence of methylzinc bromide

which favored an excellent diastereoselectivity. The desired (2*S*, 3*S*)-2-hydrazino-3-hydroxyester **3** was only detected. X-ray analysis confirmed the *anti* position of the hydrazino and hydroxyl groups. The hydroxyl function of **3** was then protected with a *t*-butyldimethylsilyl group before the ozonolysis of the double bond. The N, N, O-protected α-hydrazino β-hydroxyester **6** was converted to 2, 3, 4, 5-tetrahydropyridazine 7 without purification of the intermediates. The ozonolysis was conducted under reductive conditions in presence of triphenylphosphine and dimethylsulfide, to give the corresponding aldehyde and the acidic treatment produced in one pot, the cyclic product **7** via the cleavage of the *t*-butyloxycarbamates and the intramolecular hydrazone formation. ^1H analysis of **7** showed a coupling constant for the protons on C_2 and C3 of 7.9 Hz. This value confirmed a *trans* relationship for these two protons. Furthermore, to achieve the synthesis of **1,** the silyl ether was deprotected with tetra *n*-butylammonium fluoride and the ester saponified with potassium carbonate in aqueous methanol at 0°C. The product was purified by chromatography through an exchange resin column to remove the salts and was isolated as a white solid. IR, ^1H and ^{13}C NMR data of (3*S*, 4*S*)-4-hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid **1** were identical with those reported in the literature except the specific rotation which was in our hands : +59 (c 0.6, MeOH).[11]

This synthetic route provides an efficient and general method for obtaining both enantiomers of *trans* -3-carboxy-4-hydroxy-2, 3, 4, 5 tetrahydropyridazine (overall yield 20% from the β-ketoester **4**). As a final structural correlation and extension of the methodology described above, (3*R*, 4*R*) 4-hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid was synthetized.[12] The synthesis proceeded in a similar manner from the β-ketoester **4** using Ru (*R*)-Binap Br_2 as catalyst in the hydrogenation step.

This work illustrates the synthetic potential of sequential catalytic hydrogenation and electrophilic amination.

Experimental section

Infrared spectra (IR) were taken using a Bruker 45 FTIR instrument. NMR spectra were recorded on a Bruker AC200 spectrometer using $CDCl_3$ as a solvent. ^1H spectra were run at 200MHz and ^{13}C spectra at 50.3MHz. Elemental analyses were performed by the Service Régional de Microanalyses de l'Université Pierre et Marie Curie. Column chromatographic separations were carried out over Merck silica gel 60 (0.040-0.063 mm); analytical thin layer chromatography (TLC) experiments were performed on Merk silica gel TLC plates F254.

(3*S*) Methyl-3-hydroxyoct-5(*E*)-enoate (5). Methyl-3-oxooct-5(*E*)-enoate (1g, 5.8 mmol) was diluted under argon in degassed methanol (1 ml). This solution was canulated into a 10 ml Schlenk tube containing the (S)-BiphempRuBr$_2$ complex (0.3 mol %). The reaction mixture was immediately placed in an autoclave which was purged 3 times with hydrogen and pressured under 6 bars (87 psi). The autoclave was heated to 80°C and magnetic stirring was started as soon as the required temperature was reached. Stirring was stopped after 30 min and the autoclave was cooled to RT. The brownish solution obtained was concentrated under vacuum and the residue was distilled (135°C, 2 mm Hg) to give **5** (1g, 100%).$[\alpha]_D$ = +18 (1, $CHCl_3$); IR ν_{max} : 3467, 2958, 1724, 1622, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.46 (dt, J = 15.3, 6.2 Hz, 1H), 5.28 (dt, J = 15.3,

6.2 Hz, 1H), 3.95 (m, 1H), 3.57 (s, 3H), 3.15 (broad s, 1H), 2.40 (dd, J = 16.3, 3 Hz, 1H), 2.28 (dd, J = 16.3, 9 Hz, 1H), 2.10 (m, 2H), 1.9 (qd, J = 7.4, 6.2 Hz, 2H), 0.87 (t, J = 7.4 Hz, 3H); Anal Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found : C, 62.85; H, 9.31.

(2*S*, 3*S*) 2-(N,N-di *t*-butyloxycarbonyl)hydrazino-3-hydroxyoct-5(*E*)-enoate (3). To **5** (0.35 g, 2 mmol) in dry THF (2.5 ml) at 0°C, was added dropwise a solution of MeZnBr (2.1 mmol) in dry THF (2 ml) prepared from $ZnBr_2$ (0.473 g, 2.1 mmol) and MeLi (1.7 ml, 2.1 mmol, 1.2 M sol in Et_2O). After stirring for 1h, the mixture was cooled at -78°C and a solution of lithiumdiisopropylamide (4.4 mmol) in THF (4ml) was added dropwise. After further 1h at -78°C, a solution of DBAD (0.92g, 4mmol) in THF (1 ml) was added dropwise, the reaction mixture was stirred 10 min, hydrolysed at -78°C with a saturated aqueous solution of NH_4Cl (2 ml), warmed at RT, extracted into Et_2O, dried and evaporated. The crude product was purified by flash chromatography eluting with cyclohexane/AcOEt (4:1) to give **3** (0.43 g, 53%). $[\alpha]_D$ = -27.5 (1.3, EtOH); IR ν_{max} : 3370, 3194, 2978, 1727, 1710, 1533 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.6 (broad s, 1H), 5.5 (m, 2H), 4.85 (m, 1H), 4.12 (ddt, J = 6.5 Hz, 1H), 3.75 (s, 3H), 3.5 (broad s, 1H), 2.35 (m, 1H), 2 (qd, J = 6.9, 7.4 Hz, 1H), 1.46 (s, 9H), 1.45 (s, 9H), 0.95 (t, J = 7.4 Hz, 3H); Anal Calcd for $C_{19}H_{34}N_2O_7$: C, 56.70; H, 8.51; N, 6.95. Found : C, 56.67; H, 8.67; N, 6.99.

(2*S*, 3*S*) 2-(N,N-di *t*-butyloxycarbonyl)hydrazino-3-(O-*t*-butyldimethylsilyl)hydroxyoct-5(*E*)-enoate (6). *t* -Butyldimethylsilyltriflate (0.2 ml, 1.15 mmol) was added dropwise in 15 min at -78°C to a solution of **3** (0.31g, 0.77 mmol) in CH_2Cl_2 (1.5 ml) containing 2,6-lutidine (0.19 ml, 1.55 mmol). The solution was stirred 1h at -78°C, MeOH (1 ml) was added and the mixture was warmed to RT. The solvents were removed in vacuo and the residue was purified by chromatography eluting with cyclohexane/AcOEt (4:1) in presence of 1% of Et_3N, to give a colorlesss oil **6** (0.247g, 85%). $[\alpha]_D$ = +20.7 (1, $CHCl_3$); IR ν_{max} : 3392, 3019, 2972, 1740, 1709, 1523, 1214, 755 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.4 (broad s, 1H), 5.48 (dt, J = 15, 5.8 Hz, 1H), 5.32 48 (dt, J = 15, 6.5 Hz, 1H), 4.7 (broad s, 1H), 4.07 (m, 1H), 3.61 (s, 3H), 2.5 (m, 1H), 1.96 (m, 1H), 1.4 (s, 9H), 1.36 (s, 9H), 0.9 (t, J = 7.4 Hz, 3H), 0.77 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H); Anal Calcd for $C_{25}H_{48}N_2O_7Si$: C, 58.11; H, 9.36; N, 5.42. Found : C, 58.09; H, 9.41; N, 5.46.

(3*S*, 4*S*) Methyl-4-(O-*t*-butyldimethylsilyl)hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylate (7). A solution of **6** (0.18 g, 0.35 mmol) in CH_2Cl_2 (4 ml) at -78°C was treated with O_3 during 1h, until the blue coloration persisted. A stream of argon was then flushed through the solution before the addition of a solution of PPh_3 (0.096 g, 0.36 mmol) in dimethylsulfide (3 ml). The mixture was warmed at 40°C and stirred during 16 h. The solvents were evaporated in vacuo and the residue dissolved in CH_2Cl_2 (3 ml). The solution was cooled at 0°C and trifluoroacetic acid (3 ml) was added dropwise. The mixture was refluxed 10 min until the gas evolution stopped. The trifluoroacetic acid and CH_2Cl_2 were removed under reduced pressure. The residue was dissolved at 0°C in H_2O/MeOH (4:1) (7 ml), titrated to pH = 1.5 and stirred until no more starting material was detectable in TLC (15 min). The mixture was extracted with CH_2Cl_2. The aqueous layers were titrated to pH = 9 with NH_4OH and extracted with CH_2Cl_2. The organic layers were combined, washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtrated and evaporated in vacuo. The residue was purified by medium pressure chromatography eluting with AcOEt/cyclohexane (1:1) to give **7** as

an oil (0.135 g, 50%). $[\alpha]_D$ = +111 (1.5, $CHCl_3$); IR ν_{max} : 3365, 2954, 2929, 1746, 1632, 1259, 1117, 837 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.7 (broad s, 1H), 5.73 (broad s, 1H), 4.25 (ddd, J = 7.9, 7, 6.4 Hz, 1H), 3.75 (s, 3H), 3.50 (d, J = 7.9 Hz, 1H), 2.48 (ddd, J = 18.4, 6.4, 2.9 Hz, 1H), 2.12 (ddd, J = 18.4, 7, 1.6 Hz, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H)); Anal Calcd for $C_{12}H_{27}N_2O_3Si$: C,52.91; H,8.88; N,10.28. Found : C,53.48; H,8.88; N,10.11.

(3*S* 4*S*) 4-Hydroxy-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (1). Tetrabutylammonium fluoride (0.2 ml, 1M sol in THF) was added dropwise at 0°C to a solution of **7** (0.05 g, 0.18 mmol) in THF (1 ml). The solution was stirred 30 min at 0°C. The solvent was evaporated in vacuo and the residue filtered through a short column of silica eluting with Et_2O/MeOH (9:3) in presence of 1% of Et_3N. The crude product was treated with a solution of potassium carbonate (0.026 g, 0.19 mmol) in MeOH/H_2O (4:1) (1.25 ml) at 0°C. The mixture was stirred 1h at 0°C and concentrated under vacuum. The residue was chromatographied through a weak acid exchange column (Amberlite CG 50, 100-200 mesh) to give **1** (0.02 g, 90%) as a white solid. $[\alpha]_D$ = +59 (0.6, MeOH); IR ν_{max} : 3350, 2980, 2928, 1680, 1635, 1593, 1200, 1185, 1130 cm^{-1}; ^1H NMR (200 MHz, D_2O) δ 6.54 (broad s, 1H), 4.12 (ddd, J = 5.5, 5.5, 4.4 Hz, 1H), 3.29 (dd, J = 5.5, 1.7 Hz, 1H), 2.23 (ddd, J = 19.5, 5.5, 2 Hz, 1H), 1.95 (broad d, J = 19.5 Hz, 1H).

Acknowledgement:

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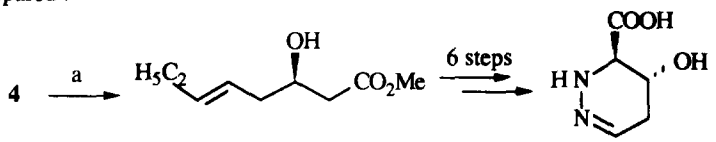
11 - $[\alpha]_D$: -57.5 reported was incorrect.[5] We thank Dr P. Hughes for private communication which confirmed the specific rotation for **1** : $[\alpha]_D$: +57.5 (c : 5.3, MeOH).

12 - The enantiomer of 1 : (3*R*, 4*R*)-4-hydroxy-2, 3, 4, 5-tetrahydropyridazine-3-carboxylic acid was prepared :



(a) H_2, MeOH, 0.3% Ru (*R*)-Binap Br_2, 6 bars, 80°C, 30 min. (100%; ee>99%).

^1H and ^{13}C NMR were identical with those obtained for **1**. $[\alpha]_D$: -61 (c : 1.1, MeOH).

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