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Syntheses of the *syn* and *anti* α-Amino-β-Hydroxy Acids of Vancomycin : (2*S*, 3*R*) and (2*R*, 3*R*) *p*-Chloro-3-hydroxytyrosines.

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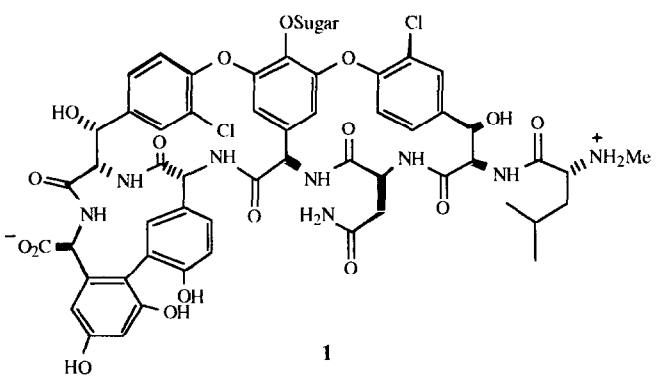
***Abstract** : Syntheses of (2S, 3R) and (2R, 3R) methyl p-chloro-3-hydroxytyrosinates 2 and 3 respectively, have been achieved from 3-chloro-4-hydroxybenzoic acid. These approaches relied on the asymmetric hydrogenation of highly functionalized carbonyl derivatives using chiral ruthenium complexes.* Copyright © 1996 Elsevier Science Ltd

β-Hydroxylated α-amino acids are biological compounds of major importance. They are components of various cyclic peptides possessing a wide range of biological activity such as antibiotic and immunosuppressive properties. By virtue of their extremely complex structural arrangement coupled with their impressive biological potential, the synthesis of cyclic peptides represent a challenge for organic chemists.



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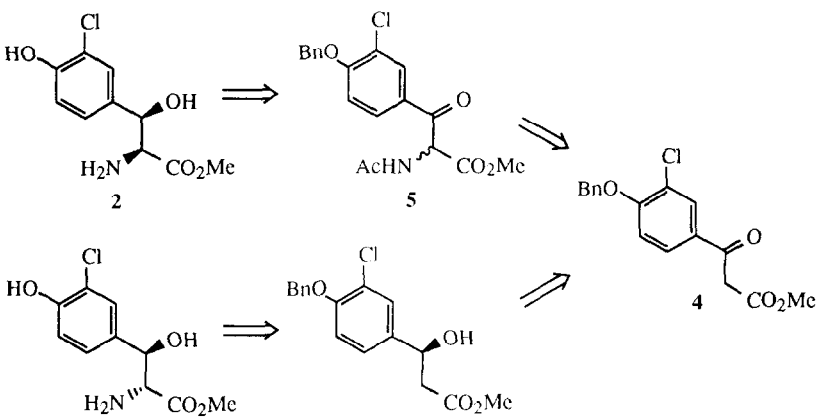
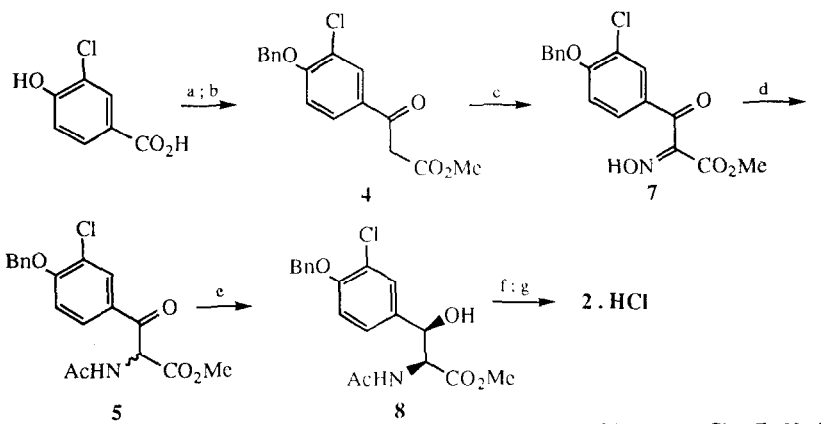
Vancomycin **1** was isolated in 1956 from *Streptomyces orientalis* and is the widely used antibiotic in the treatment of methicillin resistant *Staphylococcus aureus*.[1] This representative member of a large family of glycopeptides antibiotics, is characterized by a tricyclic heptapeptide backbone. There have been no reported total syntheses of vancomycin, however Evans[2] and Yamamura[3] groups reported bicyclic hexa and heptapeptides models. Two β-hydroxyaryl α-amino acids are present in vancomycine and are symmetrically linked to the central *p*-hydroxyphenylglycine. These two amino acids are the *syn* (2*S*, 3*R*) and *anti* (2*R*, 3*R*) diastereomers of the same *p*-chloro-3-hydroxytyrosine. These exotic α-amino β-hydroxy acids have been described by Evans[4] and Rao[5] groups. A variety of approaches have been developped for the synthesis of β-

hydroxy α-amino acids : we and others reported several methods based on nucleophilic opening of epoxides,[6] on electrophilic amination[7] or on asymmetric hydrogenation of N-protected α-amino β-ketoesters.[8]

Herein, we report the syntheses of both α-amino β-hydroxy esters *syn* (2*S*, 3*R*) **2** and *anti* (2*R*, 3*R*) **3** starting from the same β-ketoester **4**. The key steps of our approaches are the kinetic dynamic resolution[8] of the α-acetamido β-ketoester **5** and the chiral hydrogenation of **4** followed by the electrophilic amination[9] of the β-hydroxyester **6** to obtain respectively **2** and **3**.



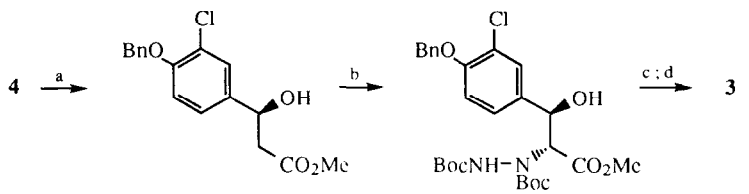
For the planned synthesis of these β-hydroxylated α-amino acids, the β-ketoester **4** was prepared from the commercially avalaible *m*-chloro-*p*-hydroxybenzoic acid by a simple sequence of reactions.The phenol and the carboxylic acid functionnalities were benzylated and the resulting carboxylic ester was saponified. The homologation of two carbons was performed by addition of the magnesium salt of monomethylmalonate on the corresponding acid chloride.[10] The β-ketoester **4** was obtained in a 55 % yield.



(a)-NaH, $PhCH_2Br$, DMF; NaOH 2N, MeOH.(85%). (b)-$SOCl_2$; $KO_2CCH_2CO_2Me$, $MgCl_2$, Et_3N, CH_3CN. (65%). (c)-BuONO, HCl 30%, Et_2O. (75%). (d)-Zn, AcOH, Ac_2O. (88%). (e)-H_2, 140 bars, $RuBr_2$[(*R*)-MeOBiphep] 1,2%, CH_2Cl_2, 80°C. (100%; de=95%; ee=80%). (f)-H_2, Pd/C, MeOH. (g)-HCl 1M, 60°C; $SOCl_2$, MeOH, 40°C.(30% from **8**).

The β-ketoester **4** was first transformed to the oxime **7** by treatment with *n*-butyl nitrite in the presence of HCl 30% in ether. The oxime **7** was reduced with zinc in acetic acid in the presence of acetic anhydride affording the desired α-acetamido-β-ketoester **5**. Our next concern was to generate the *syn* β-hydroxy α-amino acid from the key intermediate **5**. The asymmetric hydrogenation was carried out using chiral ruthenium catalyst : $RuBr_2$[(*R*)-MeOBiphep]. The chiral complex was prepared *in situ* from commercially available Ru(Cod)(2-methylallyl)$_2$.[11] The kinetic dynamic resolution was highly diastereoselective (de>95%) to afford the *syn* α-acetamido-β-hydroxyester **8**. A poor enantioselectivity was observed at room temperature and low pressure. However, **8** was obtained quantitatively in 80% enantiomeric excess at 140 bars and 80°C. Enantiomerically pure (2*S*, 3*R*) **8** was isolated after two recristallisations in ethanol. Hydrogenolysis of the benzyl ether under standard conditions, acid hydrolysis of both acetamido and ester functions and esterification with thionyl chloride in methanol produced the hydrochloride of (2*S*, 3*R*) methyl *p*-chloro-3-hydroxytyrosinate **2**.[12]

The second synthesis using sequential asymmetric hydrogenation and electrophilic amination, is directed toward the *anti* diastereomer **3**.



(a)-H_2, 6 bars, $RuBr_2$[(*R*)-Binap] 1%, CH_2Cl_2, 27°C. (100%; ee=95%). (b)-MeZnBr, 1 eq., 0°C; LDA, 2 eq., -78°C; DBAD, 2 eq., -78°C, NH_4Cl, H_2O. (65%; de>98%). (c)-H_2, Pd/C, MeOH. (d)-CF_3CO_2H, CH_2Cl_2; H_2, Raney Ni, MeOH, ultrasound.(70% from **9**).

4 was hydrogenated enantioselectively in the presence of $RuBr_2$[(*R*)-Binap]. The reaction was performed at room temperature and low pressure and (3*S*) **6** was obtained quantitatively with 95% e.e. The zinc enolate of **6** was then aminated with *t*-butylazodicarboxylate. The electrophilic amination was highly diastereoselective providing the α-hydrazino β-hydroxy ester **9** as the only detectable *anti* diastereomer. The stereoselectivity of this electrophilic amination was anticipated from our preceding study.[9] The bulky di *t*-butyl azodicarboxylate approaches the chelated zinc enolate trans to the aryl group. After hydrogenolysis of the benzyl ether, the hydrazine function was deprotected and the N-N bond was cleaved by H_2 in the presence of Raney Ni under ultrasound.[13] (2*R*, 3*R*) Methyl *p*-chloro-3-hydroxytyrosinate **3**[14] was isolated in 70% overall yield for the three reaction steps.

In conclusion, we have achieved a versatile method for the preparation of *syn* and *anti* β-hydroxy α-amino acids present in vancomycin from a common intermediate. This route offers the possibility to produce easily all the stereomers and analogues.

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12 - (2*S*, 3*R*) **2.HCl** : ^{1}H NMR (200 MHz, CD_3OD) δ(ppm) : 7.43 (s, 1H); 7.19 (d, J=8.5 Hz, 1H); 6.94 (d, J=8.5 Hz, 1H); 5.12 (broad s, 1H); 4.09 (broad s, 1H); 3.78 (s, 3H). $[\alpha]_D^{20}$= +5 (c=0.3, EtOH).

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14 - (2*R*, 3*R*) **3** : ^{1}H NMR (200 MHz, DMSO-d6) δ(ppm) : 7.25 (d, J=1.9 Hz, 1H); 7.05 (dd, J=1.9; 8.3 Hz, 1H); 6.88 (d, J=8.3 Hz, 1H); 4.5 (d, J=6.7 Hz, 1H); 3.57 (s, 3H); 3.37 (d, J=6.7 Hz, 2H). $[\alpha]_D^{20}$= -25 (c=1, EtOH).

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