New asymmetric syntheses of β-hydroxy α-amino acids and analogues. Components of biologically active cyclopeptides

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*Abstract : MeBmt and analogues components of cyclosporine **2** were prepared by nucleophilic regioselective opening of chiral epoxyacids by methylamine. An efficient asymmetric hydrogenation-electrophilic amination sequence of β-ketoesters allowed the production of anti β-hydroxy-α-amino acids present in cyclopeptides (luzopeptine, vancomycin). An ideal kinetic dynamic resolution of α-acylamido-β-ketoester using ruthenium catalysts has been used for the production of L and D-threonine. This sequence was used for the preparation of (2S, 3R)-methyl-2-amino-3-(3'-chloro-4'-hydroxyphenyl) propionate precursor of a key component of vancomycin **1** .*

I- Introduction

β-Hydroxylated amino acids are biologically of major importance both as natural products and as chiral intermediates. They are also components of various cyclopeptides such as vancomycin **1** (antibiotic)(1) and Cyclosporine **2**. Cyclosporine (CsA) is a selective immunosuppressive drug which is used clinically to suppress the rejection of transplanted human organs (2). Seven of the amino acids which constitute its skeleton are N-methylated. Structure activity relationships have demonstrated that an unusual amino-acid, the (4R)-4-(E)-2-butenyl)-4,N-dimethyl-L-threonine (MeBmt) (3) was essential for the biological activity of CsA.
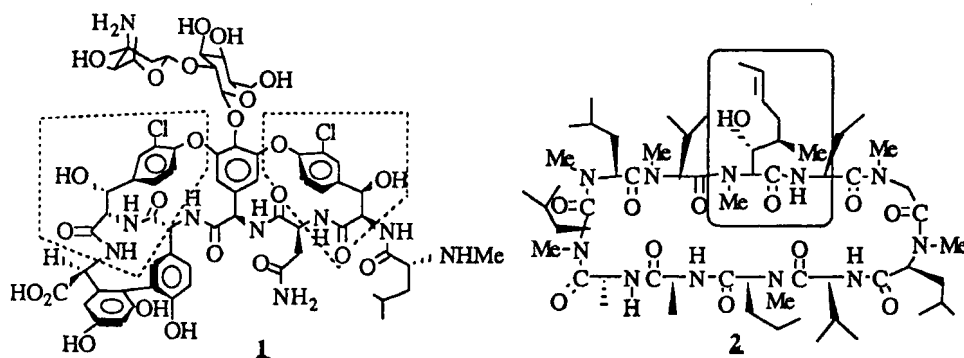

Since the first 24 steps synthesis reported by Wenger (4), about fifteen syntheses (5) of this important target molecule and analogues such as MeBma have been performed. There is some interest from a synthetic view point in the development of asymmetric synthesis of both syn and anti β-hydroxy α-aminoacids. In this context we considered three different strategies for the synthesis of optically pure β-hydroxylated amino acids : (i) Nucleophilic amination, (ii) Electrophilic amination of ester enolates, (iii) Asymmetric hydrogenation of α-acetamido-ß-ketoesters.

## II- Nucleophilic amination. Synthesis of Mebmt and analogues

Nucleophilic opening of epoxy acids by heteronucleophiles such as amines is a method of choice for controlling asymmetric centers (6). We have developed this technology for the synthesis of allothreonine which was obtained in a few steps from crotyl alcohol (7). This approach was used as shown in scheme 1 for the synthesis of MeBma. Nucleophilic attack of the epoxi acid by methylamine furnished **4** in enantiopure form and with 24% overall yield from **3** (8).

Scheme 1   *Synthesis of Mebma*
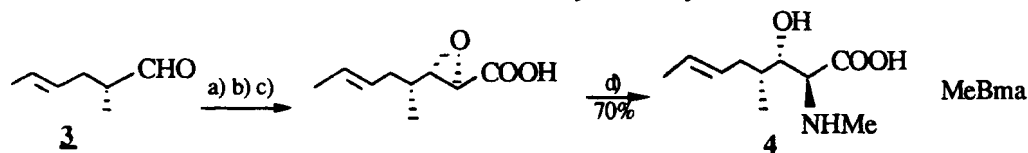
a) i) 1.2 equiv.$(CH_3O)_2PCH_2CO_2Me$, 1.1 equiv BuLi, DME, 20°C, ii) 3 equiv DibalH Et_2O, -78°C. 60% yield ; b) 2.5 equiv tBuOOH, 5% Ti(OiPr)$_4$, 7.5% L(+)DET CH_2Cl_2, -20°C. 81% yield ; c) 6 equiv PDC, DMF, 20°C. 70% yield ; d) i) MeNH$_2$, H$_2$O, 90°C ; ii) HCl 6N, iii) propylene oxide, EtOH, 90°C.

We have applied this approach to the synthesis of MeBmt **10** as well (9) as shown in scheme 2. The cis chiral epoxy acid **8** which is sterically hindered at the γ position was synthesized. Evans' procedure is used to fix the desired configuration at C4, and the chiral aldehyde **5** thus obtained is immediately reacted without purification under Still modified Horner-Emmons conditions, to give the cis acrylate, and reduced to lead to the alcohol **6** (55% from **5**). Sharpless' protocol was used to perform the chiral synthesis of **10**. To solve the problem of the low induction encountered, we have prepared the cis allylic alcohol **6** which contains a non bulky alkynyl side chain at the γ position. Sharpless' stoechiometric reaction works in 70% yield and with an acceptable 70% diastereoisomeric excess. The epoxy acid **8** is synthesized using PDC oxidation. So, after regioselective opening of **8** with methylamine,which gave the β-hydroxy α-aminoacid **9** in 60% yield, there remained for us to reduce the alkynyl side-chain. This is performed using Li, NH_3 (70% yield). The synthesis of MeBmt **10** is thus accomplished in a 9% overall yield from **5** (9).

<div align="center">Scheme 2   Synthesis of MeBmt</div>
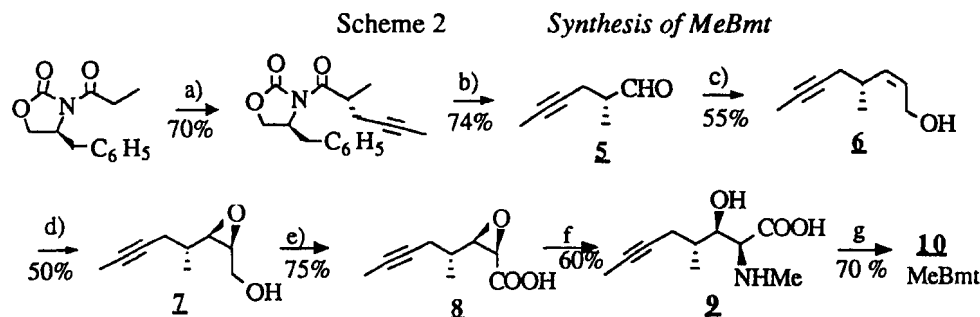
a) i) 1.8 equiv.NaHMDS, 2.2 equiv Br, THF, -78°C, ii) Separation by MPLC ; b) i) 1 equiv LiAlH$_4$, ether, -78°C, ii) DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$, -30°C ; c) i) 1 equiv (CF$_3$CH$_2$O)$_2$P(O)CH$_2$CO$_2$Me, 1 equiv KHMDS, 4 equiv 18-crown-6, THF, -78°C, ii) 3 equiv DibalH, Et$_2$O, -78°C ; d) i) 2.2 equiv tBuOOH, 1.05 equiv Ti(OiPr)$_4$, 1.05 equiv L(+)DET, CH$_2$Cl$_2$, -20°C, ii) Separation by MPLC ; iii) Propylene oxide, EtOH, 90°C ; g) 20 equiv Li, NH$_3$, HCl, 3.5 N.

This synthetic route provides an expeditive and general method for obtaining γ-alkyl branched, anti β-hydroxy α-amino acids such as MeBmt and MeBma and analogues.
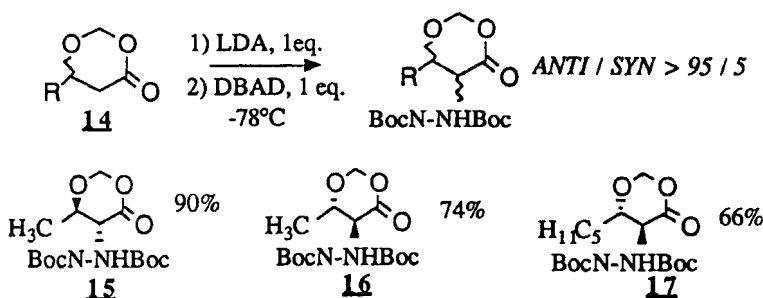
III- Electrophilic Amination

We considered a second synthetic route for the preparation of hydroxylated aminoacids. The electrophilic amination of ß-hydroxy ester enolates. We have developed few years ago an efficient synthesis of L- threonine and D- threonine from (R)-hydroxybutanoate (10). The generality of this approach requires the preparation of optically pure β–hydroxy esters. In this context we have reported (11) as shown in scheme 3 a general and new synthesis of chiral biphosphines Ru(allyl)2 complexes **12**. Our synthetic general method allows the production of ruthenium complexes from a wide variety of diphosphines including diphosphines having chirality at the phosphorus atom such as Dipamp (12). This synthesis uses the very accessible and stable CODRu(2-methylallyl)$_2$ complex **11** as starting material (Scheme 3). The complexes **12** are suitable for the preparation of chiral P*PRuX$_2$ **13** bearing a whole set of chiral diphosphines. More recently we have prepared directly these catalysts **13** *in situ* from (COD)Ru(2-methylallyl)$_2$ **11** by adding in acetone at room temperature 1 to 1.3 equiv. of the appropriate chiral ligand in the presence of HBr (13).

<div align="center">Scheme 3   Synthesis of chiral ruthenium (II) (2-methylallyl)$_2$ and chiral RuX$_2$</div>
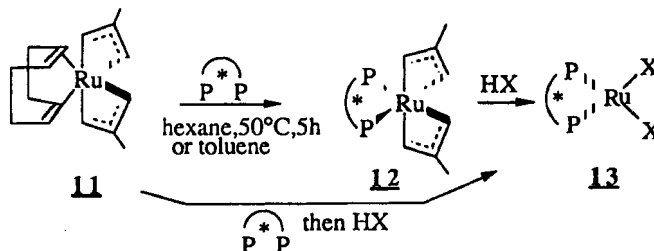

P*P = DIOP, CHIRAPHOS, PROPHOS, BPPM, DIPAMP, CBD, NORPHOS,DEGUPHOS, BINAP, BIPHEMP etc.

These catalysts are very efficient for the production of optically pure (>99%) β-hydroxy esters from the corresponding β-ketoesters (15) which are converted, with formaldehyde, into the corresponding dioxanones **14**. The electrophilic amination of these derivatives proceeded smoothly with di-ter-azodicarboxylate and furnished the *anti* diastereoisomers **15, 16, 17** in good to excellent yields as shown in scheme 4.

Scheme 4   *Electrophilic Amination of Dioxanones*

$ANTI / SYN > 95 / 5$

We also found (Scheme 5) that the zinc enolate **19** sequentially prepared by the reaction of the β-hydroxyester **18** with methylzinc bromide followed by lithium diisopropylamide ; the electrophilic amination proceeded with moderate yield (50%) giving **20** with complete *anti* stereoselectivity (15).
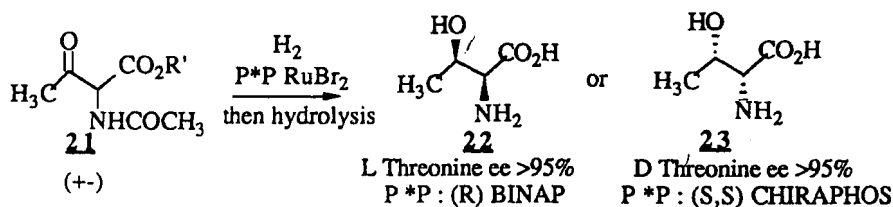
Scheme 5
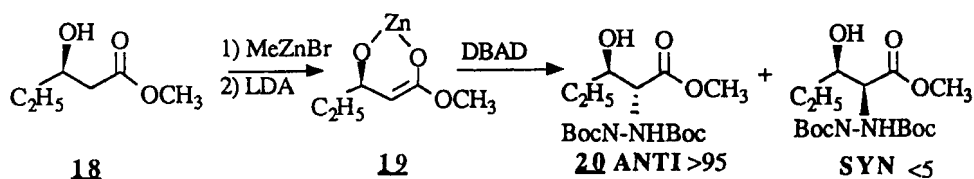
This reaction is efficient for the synthesis of any optically pure anti α-hydrazino-β-hydroxyacids (15), for which, to our knowledge, no efficient method was available so far.

IV- Dynamic Kinetic Resolution of α-acetamido β-ketoesters

The most direct approach to the construction of hydroxylated α-amino acids would be via the asymmetric hydrogenation of the readily available racemic α-acetamido β-ketoesters **21**. This reduction should in principle provide four stereoisomers with anti and syn stereochemistry. In this respect we have used several transition metal catalysts. With rhodium catalysts, a syn selection is seen but with moderate enantioselectivity, up to 40 % ee (16). Interestingly, the use of chiral Ru^{II} complexes with (S,S)-Chiraphos and (R)-Binap allowed selective production of one stereoisomer **23** or **22** respectively among the four possible isomers (16,17).

**Scheme 6**   *Practical Synthesis of L and D- Threonine*

So we have established optimal conditions for the asymmetric hydrogenation of this racemic substrate with an ideal dynamic kinetic resolution (Scheme 6). This represents a practical synthesis of optically pure L and D-threonine in three steps from methyl acetoacetate (17,18).

V- Synthetic applications

Luzopeptine A is a dimeric cyclic peptide. This compound is a bis intercalator of DNA and this is thought to play a role in its activity. The six unique constituants of luzopeptine are four known amino acids; among them there is an interesting new exotic amino acid 3(S)-carboxy-4(S)-hydroxy-2,3,4,5-tetrahydropyridazine **29**. We applied our sequential method hydrogenation-electrophilic amination for the synthesis of this exotic aminoacid (Scheme 7). The chemoselective and enantioselective reduction of **24** proceeded smoothly with ruthenium Biphemp catalyst. The desired ß-hydroxyester **25** was obtained

in almost optically pure form. This ß-hydroxyester was aminated with DBAD, leading to the ß-hydroxy-α-hydrazino ester **26** with an excellent diastereoselectivity above 95%. After a selective protection of the alcohol, the double bond was converted into the desired aldehyde by a two steps hydroxylation-oxidative cleavage reaction. After quantitative deprotection of the hydrazine, cyclisation and subsequent deprotection 3(S)-carboxy-4(S)-hydroxy-2,3,4,5-tetrahydropyridazine **28** was obtained with an overall yield of 54% as its methyl ester in an enantiomeric pure form. In a last step, classical saponification afforded the desired free acid **29** (19).

Scheme 7   *Synthesis of 3-5S)-carboxy-4- (S) hydroxy-2,3,4,(tetrahydropyridazine)*
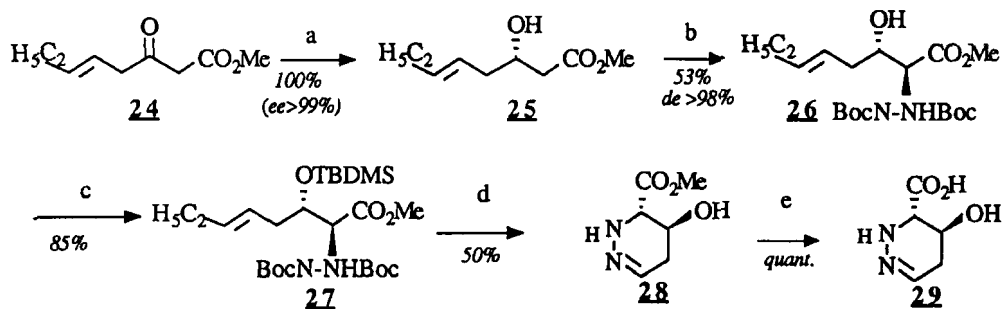
a)H_2, MeOH 0.3% Ru(S-Biphemp)Br_2 6 bars, 80°C, 30 min.   b)i) MeZnBr, 1 eq.   ii) LDA, 2 eq.   iii) DBAD, 2 eq.
c) 2,6-lutidineTBDMSOTf ;d) i)O_3,CH_2Cl_2 ii) Me_2S, PPh_3 iii)TFA, CH_2Cl_2puis H_2O, MeOH   iv nBu_4NF ;e)KOH

Having in hands the technologies for the synthesis of both syn and anti β-hydroxy-α-amino acids, we achieved the syntheses of the two components present in vancomycin **1**. In our approach, the synthesis of (2R, 3R)-methyl-2-amino-3-hydroxy 3-(3'-chloro-4'-hydroxyphenyl) propionate was made by sequential asymmetric hydrogenation-electrophilic amination of methyl-3-oxo(3-(3'-chloro-4'-hydroxyphenyl) propionate in 50% overall yield and 95% ee. The second β-hydroxy-α-amino acid (syn) having the (2S, 3R) configuration was prepared by the expeditious dynamic kinetic resolution of racemic α-acetamido-β-ketoesters using chiral ruthenium (II) catalysts (20).

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