A Novel, Facile and Diastereoselective Synthesis of (3*S*, 4*S*) and (3*R*, 4*S*)-*N*-Me-AHPPA

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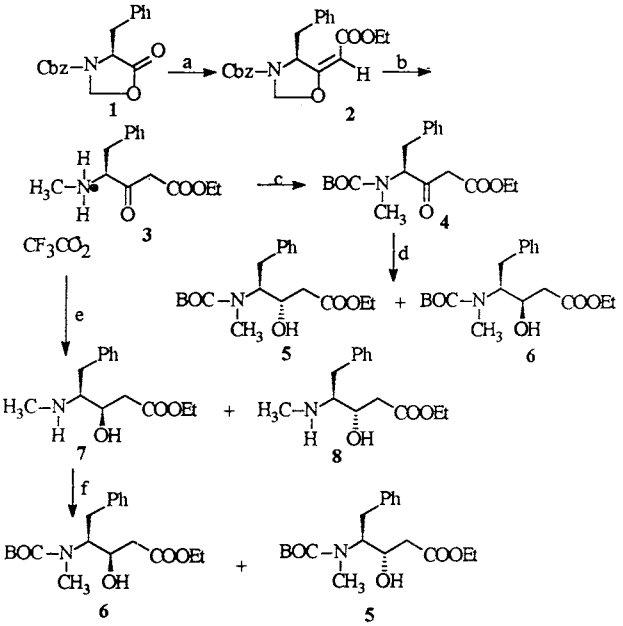
Diastereoselective syntheses of (3*S*,4*S*) and (3*R*,4*S*)-*N*-methyl-AHPPA are achieved via a novel Wittig reaction of an oxazolidinone followed by reduction.

N-Methyl-4-amino-3-hydroxy-5-phenyl pentanoic acid (N-Me-AHPPA) is a non proteinogenic amino acid, a key component of the cyclic depsipeptide hapalosin,[1] which shows promising multidrug resistance reversing activity. In view of this bioactivity, a variety of approches have been developed for the semi and total synthesis of hapalosin.[2-4] Particularly, in most of the cases, *N*-Me-AHPPA was prepared by the treatment of *N*-protected - AHPPA with a strong base followed by methyl iodide. However, this method suffers due to competitive reactions such as ß-elimination resulting in the formation of α,β-unsaturated acid derivatives and pyrrolidinone ring formation. Other problems involved with this method are *O*-methylation and *N*-deprotection, resulting in a complex mixture of products. In view of our interest in the synthesis of hapalosin analogues, we report here an entirely novel, short and efficient syntheses of both (3*S*,4*S*) and (3*R*,4*S*) isomers of *N*-Me-AHPPA from a common intermediate involving two new reactions viz., a) a Wittig reaction of an oxazolidinone (1→2) b) reduction of the corresponding α,β-unsaturated ester (2→5,6) (Scheme 1).

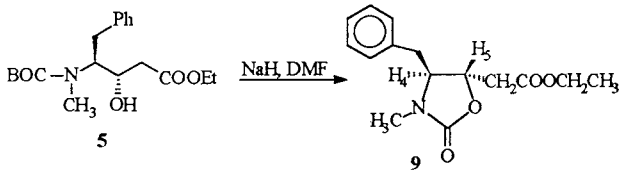
N-Cbz-Oxazolidinone[5] **1** obtained from *N*-Cbz-phenylalanine by reaction with paraformaldehyde in presence of catalytic pTSA was subjected to a Wittig reaction with ethoxycarbonylmethylenetriphenylphosphorane to give the α,β-unsaturated ester[6] **2** in excellent yields. Since there was no enhancement of the signal in the NOE experiment between the olefinic proton and the methine proton in the ring, the olefin geometry was assumed to be '*E*'. Pd/C catalysed hydrogenolysis of **2** in presence of trifluoroacetic acid in methanol afforded the trifluoroacetate of *N*-Me-γ-amino-β-ketoester **3**. Treatment of **3** with BOC_2O and Et_3N in methanol gave the *N*-BOC-*N*-Me-γ-amino-β-ketoester **4**. Sodium borohydride reduction of **4** in methanol at 0°C furnished an easily separable mixture of **5** and **6**[6] in a ratio of 9:1 in 94% combined yield.



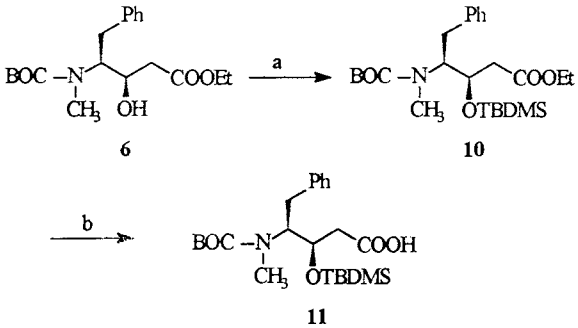
Reagents and conditions : a) Ph_3P=CH-CO_2Et, $PhCH_3$, Δ, 3 h, 96%; b) 10% Pd/C, H_2, MeOH, CF_3CO_2H, RT, 2 h. 98%; c) BOC_2O, Et_3N, MeOH, RT, 8 h. 92%; d) $NaBH_4$, MeOH, 0 °C-RT, 1 h.; e) $NaBH_4$, Et_3N, MeOH, -10 °C, 2 h. 88%; f) 1.1 eq. BOC_2O, DMAP, $CHCl_3$, RT, 6 h.

Scheme 1.

As expected, the major isomer **5** was found to be *syn*[7] from ^1H NMR data of the corresponding oxazolidinone **9**, obtained by the treatment of **5** with NaH in DMF (J = 4.5 Hz for ring protons H-4 and H-5), (Scheme 2), which may be explained by the Felkin - Anh model (Figure 1).[8] This was further confirmed by converting the minor *anti* isomer **6** into the known compound **11**[6] {oil; $[\alpha]_D^{25}$ = -42.9 (c=1, $CHCl_3$);



Scheme 2.



Reagents and conditions : a) TBDMSCl, imid, DMF, RT, 10 h, 95%; b) 2N NaOH, THF, RT, 4 h. 92%.

Scheme 3.

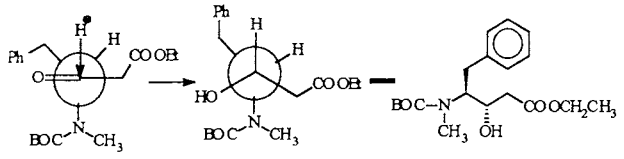


Figure 1.

lit.[3] $[\alpha]_D^{25}$ = -41.2 (c=1, $CHCl_3$)} and comparing specific rotations, spectral data with those of reported values which were in good agreement (Scheme 3).

To achieve other isomer viz., (3*R*,4*S*)-N-Me-AHPPA, **3** was directly treated with $NaBH_4$ in methanol at -10 °C to give an inseparable mixture of **7** and **8** in good yield. Upon treating the mixture of **7** and **8** with di-*tert*-butyl dicarbonate an easily separable mixture of **6** and **5** in a ratio of 4:1 in 94% combined yield was obtained (Scheme-1). The *anti* selectivity is due to chelation control[7] and may be explained by Cram model (Figure 2).[6]

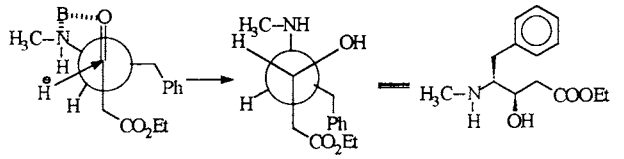


Figure 2.

All the compounds obtained were fully characterized by spectral data. Important characteristic signals of **5** ^{1}H NMR δ 2.80 (s, 3H, NCH_3), 1.30 (t, 3H, *J* = 6, 4 Hz, CH_3), 4.20 (q, 2H, *J* = 6.4 Hz, CH_2), clearly indicating the N-methyl group and ethyl ester. The spectroscopic data and optical rotations are well in accordance to those of reported values.

In summary, we report an entirely novel, straightforward and practical methodology for synthesis of (3*S*,4*S*) and (3*R*,4*S*)-N-methyl-AHPPA, key components of the potential MDR active hapalosin. The present methodology enables the synthesis of analogous series of N-methyl-γ-amino-β-hydroxy acids, which are present in several bioactive molecules with ease and hence offers a practical alternative to the earlier methodologies. Further work is in progress and will be reported in due course.

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References and Notes

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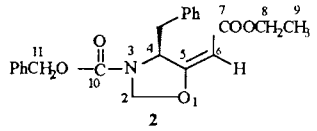
6 Spectroscopic data [^{1}H (200 MHz, $CDCl_3$) ^{13}C(50 MHz, $CDCl_3$) NMR, FABMS] :



2

Compound **2** : Colorless syrup, ^{1}H NMR : δ 1.30 (3H, t, J = 6.4 Hz, $CH_2C\underline{H}_3$), 3.00-3.40 (2H, m, $PhC\underline{H}_2$), 4.20 (2H, q, J = 6.4 Hz, $C\underline{H}_2CH_3$), 4.80-4.90 (1H, m, C<u>H</u>Bn), 5.05 (2H, s, $PhC\underline{H}_2O$), 5.20-5.32 (1H, brs, N-$C\underline{H}_2O$), 5.35 (1H, s, olefin), 5.60 (1H, brs, N-CH_2O), 7.00-7.40 (10H, m, Ar); ^{13}C NMR : δ 14.3(C-9), 38.7 ($\underline{C}H_2Ph$), 59.5 (C-8), 59.8 (C-4), 67.7 (C-11), 91.0 (C-2), 126.7 (Ar), 128.0 (Ar), 128.2 (Ar), 128.3 (Ar), 128.6 (Ar), 129.7 (Ar), 130.5 (Ar), 132.5 (Ar), 136.3 (C-6), 154.2 (C-10), 167.1 (C-5), 171.5 (C-7); FABMS: 382 (M^+ +H). Compound **5** : Colorless syrup, ^{1}H NMR : δ 1.25 (t, 3H, CH_3), 1.45 (s, 9H, $(C\underline{H}_3)_3C$), 2.40-2.55 (m, 2H, $C\underline{H}_2$ ph), 2.70 (s, 3H, N-$C\underline{H}_3$), 2.95-3.10 (m, 2H, $C\underline{H}_2CO_2$), 4.00-4.18 (quartet overlapped with multiplet, 4H, $C\underline{H}_2CH_3$ & C<u>H</u>-NH & C<u>H</u>OH), 7.05-7.35 (m, 10H, Ar), ^{13}C NMR: δ 14.1, 18.2, 30.6, 35.4, 39.4, 58.6, 59.2, 59.9, 79.2, 126.2, 128.2, 129.5, 154.4, 171.4; FABMS : 353 (M^+ +H). Compound **6** : Colorless syrup, ^{1}HNMR : d 1.20 (t, 3H, $C\underline{H}_3$), 1.45 (s, 9H, $(C\underline{H}_3)_3$ C), 2.30-2.45 (m, 2H, $C\underline{H}_2Ph$), 2.75 (s, 3H, N-$C\underline{H}_3$), 3.00-3.20 (m, 2H, $C\underline{H}_2CO_2$), 4.00-4.20 (quartet overlapped with multiplet, 4H, $C\underline{H}_2CH_3$ & C<u>H</u>-NH & C<u>H</u>-OH), 7.10-7.35 (m, 10H, Ar); FABMS : 353 (M^+ +H). Compound **11** : Colorless oil : $[a]_D^{25}$ = -42.9, (c=1, $CHCl_3$); lit.[3] $[a]_D^{25}$ = -41.2, (c=1, $CHCl_3$). ^{1}HNMR : d 0.09 (s, 3H, Si-$C\underline{H}_3$), 0.20 (s, 3H, $C\underline{H}_3$-Si), 0.95 (s, 9H, $(C\underline{H}_3)_3$C-Si), 1.35 (s, 9H, $(C\underline{H}_3)_3$C), 2.35-2.50 (m, 2H, $C\underline{H}_2Ph$), 2.75 (s, 3H, N-$C\underline{H}_3$), 2.90-3.05 (m, 2H, $C\underline{H}_2CO_2$, 4.25-4.40 (m, 2H, C<u>H</u>-NH & C<u>H</u>-OH), 7.10-7.35 (m, 5H, Ph); ^{13}C NMR : d -4.7, -4.6, 14.2, 18.3, 25.6, 30.5, 35.7, 39.9, 56.2, 60.9, 71.1, 76.9, 79.2, 126.3, 128.0, 129.2, 138.7, 155.0, 171.5; FABMS : 324 (M^+ +H).

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