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Synthesis of Hapalosin and 8-Deoxy-hapalosin

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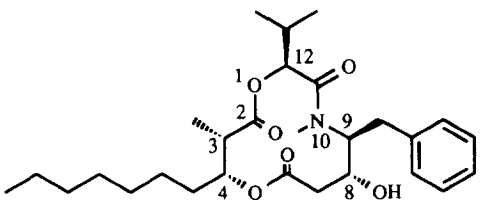
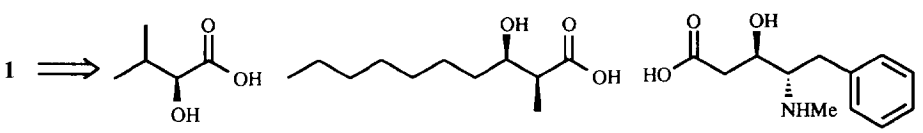
Abstract: Hapalosin, a new MDR reversing agent, and its congener 8-deoxyhapalosin have been synthesized *via* macrolactamization. A new procedure for selective N-methylation of a vicinal amino alcohol is uncovered in the course of this study.

Multidrug resistance (MDR)[1] describes a complex phenotype whose predominant feature is the resistance to a wide range of structurally unrelated cytotoxic compounds, many of which are anticancer agents. Very recently, Moore and co-workers[2] have isolated a new cyclic depsipeptide from a blue-green alga (cyanobacterium, 0.12% yield based on dry weight of alga), named hapalosin (**1**) which showed better MDR-reversing activity than verapamil, especially in promoting [^{3}H] taxol accumulation.



Hapalosin **1**

Intrigued by its bioactivity and interested in the synthesis of macrocyclic natural products,[3] we planned a total synthesis of **1** and its congeners according to the following retrosynthetic analysis (Scheme 1).[4] As (*S*)-(+)-2-hydroxy-3-methylbutanoic acid **2** is readily available from L-valine,[5] the synthetic endeavour is reduced to the synthesis of fragments **3** and **4**.

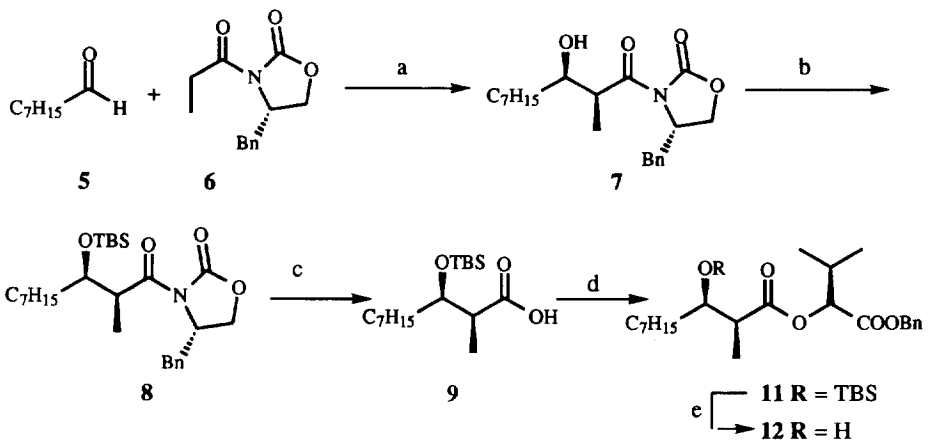


2 **3** **4**

Scheme 1

Diastereoselective aldol condensation has been utilized for the synthesis of β-hydroxy acid (Scheme 2). Reaction of n-octanaldehyde (**5**) and chiral imide (**6**) under Evans' conditions[6] furnished *syn* aldol **7** in excellent yield and diastereoselectivity. Installation of TBS protecting group followed by removal of chiral auxiliary gave then the β-hydroxy acid **9** uneventfully. Esterification of **9** with benzyl (*S*)-(+)-2-hydroxy-3-methylbutanate, obtained in two straightforward steps from L-valine,[5] was carried out under different conditions and was best realized using Yamaguchi's reagent[7] to provide compound **11** in 88% yield.

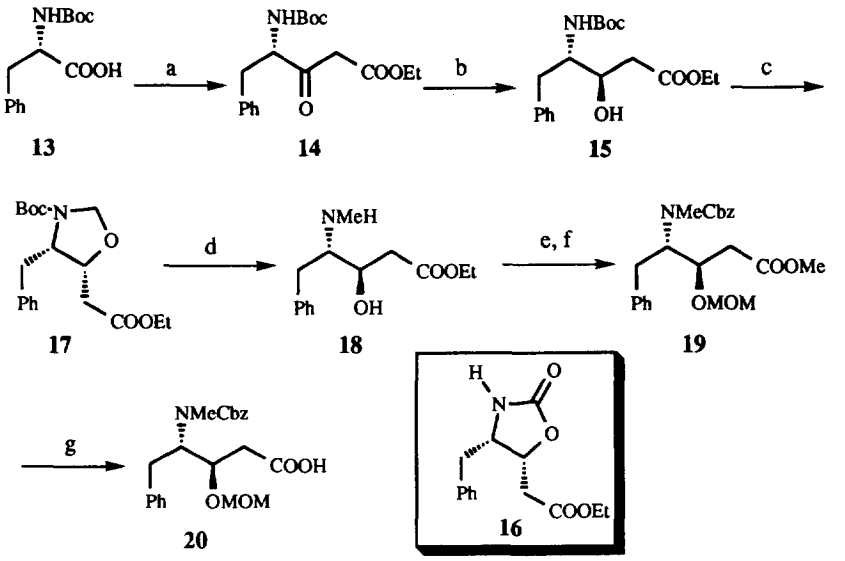
Deprotection of silyl ether proved to be more difficult than expected and among a range of reagent tested, only HF in MeCN was found to be highly efficient in our hands to furnish **12**[8] in 90% yield.



Reagents and Conditions: a) Bu_2BOTf, Et_3N, 74%; b) TBSOTf, 2,6-lutidine, 97%; c) LiOH, H_2O_2, 97%; d) 2,4,6-trichlorobenzoyl chloride, (*S*)-(+)-Benzyl 2-hydroxy-3-methylbutanate **10**, Et_3N, 88%; e) HF-MeCN, 90%

Scheme 2

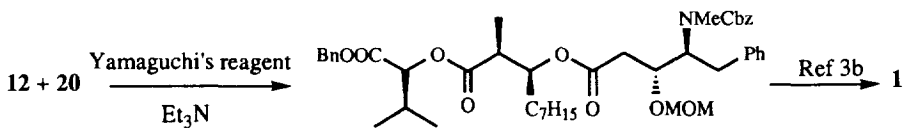
Synthesis of suitably protected β-hydroxy-γ-amino acid **20** was accomplished as shown in Scheme 3. Treatment of N-Boc Phe (**13**) in THF with carbonyl diimidazole (CDI) gave the corresponding imidazolide which was reacted directly with ethyl lithium acetate to provide β-ketone ester **14** in 92% yield.[9] Reduction of **14** with $NaBH_4$ in ethanol[10] at -78°C gave amino alcohol (*de* 80%) from which the diastereomerically pure *anti* product **15** could be isolated in 63% yield by a simple recrystallization (ether-heptane). The diastereoselectivity of this reduction resulted from the chelation controlled process and the stereochemistry was confirmed by converting **15** into the corresponding oxazolidinone **16**. Decoupling experiment and NOEDIFF spectra indicated a *cis* relationship between two substituents of **16**, indicative of (3*R*, 4*S*) stereochemistry. Selective N-methylation of β-hydroxy-γ-amino ester of type **15** was reported to be troublesome[11] probably due to the competitive β-elimination and pyrrolidinone ring forming process. After several unsuccessful trials, we devised a new method taking advantage of the proximity of amino alcohol functions. Thus, reaction of **15** with aqueous formaldehyde in the presence of a catalytic amounts of pTsOH gave smoothly the corresponding oxazolidine **17** which was reduced with $NaBH_3CN$-TFA to afford selectively the N-methylated compound **18** in 81% yield. This two-step procedure is reminiscent of that developed by Freidinger *et. al.*[12] for the preparation of Fmoc protected N-alkyl amino acid. It is worthy noting that classic one-step reductive amination conditions failed to give the desired product even under recently modified conditions[13]. Benzoxycarbamate formation[14] followed by protection of secondary hydroxyl group as MOM ether[15] gave compound **19** uneventfully. Finally, the ethyl ester function was hydrolyzed in refluxing methanol to provide the appropriately protected acid **20** in 90% yield.



Reagents and Conditions: a) CDI, then lithium salt of ethyl acetate, 92%; b) $NaBH_4$, EtOH, -78°C, 63%; c) HCHO, pTsOH, Toluene, Dean-Stark, 75%; d) CH_2Cl_2-TFA, $NaBH_3CN$, 81%; e) CbzOSu, $NaHCO_3$, Acetone-H_2O, f) MOMBr, iPr_2NEt, 86%, g) K_2CO_3, MeOH, reflux, 90%

Scheme 3

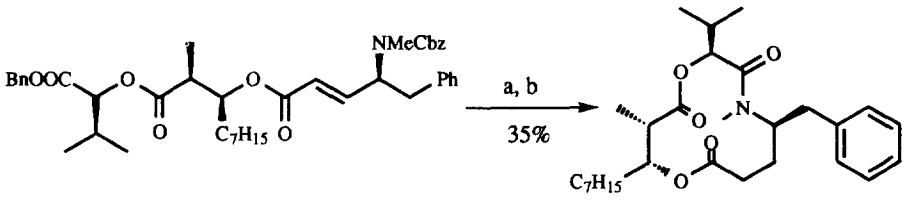
Esterification of **20** with alcohol **12** under Yamaguchi's conditions afforded triester **21** which has been converted into natural hapalosin by Ghosh et.al[4b] *via* a two step sequence.



21

Scheme 4

For structure-activity-relationship (SAR) studies, we were interested in the synthesis of 8-deoxy hapalosin **23** (Scheme 5). Triester **22** was prepared *via* coupling of **12** with an appropriate γ-amino-α,β-unsaturated acid. Removal of benzyl ester, benzoxycarbamate and 1,4-reduction of α,β-unsaturated ester was realized by hydrogenolysis ($Pd(OH)_2$/C, EtOAc-MeOH) in a one-pot fashion to afford the seco-imino acid which was cyclized[16] [diphenylphosphoryl azide (DPPA), $^iPr_2EtN$, 0°C to room temperature] to give the desired 8-deoxy hapalosin in 35% overall yield. From the chemical shift of the two methyls of the isopropyl group (δ = 0.48, 0.65 ppm in 8-deoxyhapalosin *vs* 0.23, 0.55 ppm in hapalosin), it became clear that the conformation of **23** may be significantly different from that of **1**. Further studies on the conformational properties and bioactivities of compound **23** are in progress.



22 **23**

Reagents and Conditions: a) $Pd(OH)_2/C$, EtOAc-MeOH; b) DPPA, iPr_2NEt, CH_2Cl_2, 0°C to rt

Scheme 5

In conclusion, we have described an efficient synthesis of hapalosin and 8-deoxy hapalosin; the synthesis is flexible and amenable to other analogues for SAR studies. A new selective N-methylation procedure has been developed and should be useful in the protection of other vicinal amino alcohols.

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