Communication

A Flexible Approach to the γ-Amino-β-hydroxy Acid Moiety of Hapalosin†

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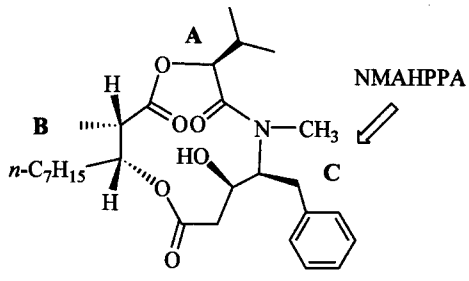
A flexible approach to ethyl (3*R*,4*S*)-*N*-Boc-4-amino-3-hydroxy-5-phenylpentanoate (*N*-Boc-AHPPA-OEt), the γ-amino-β-hydroxy acid moiety of hapalosin is described. The synthetic method features a ring-opening ethanolysis of an activated *N*-Boc-lactam, which is obtained via a diastereoselective reductive-alkylation of (*R*)-malimide derivative. The flexibility of the method resides in the introduction of the alkyl side chain by Grignard reagent addition.

Keywords (*R*)-malic acid, hapalosin, *anti*-AHPPA, asymmetric synthesis, reductive alkylation

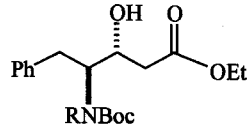
(3*R*, 4*S*)-*N*-Methyl-4-amino-3-hydroxy-5-phenylpentanoic acid (NMAHPPA) is a key component found in hapalosin (**1**), a novel cyclodepsipeptide isolated from the blue-green algae *Hapalosiphon welwitschii*.[1] This natural product was shown to be quite active in reversing multidrug resistance caused by over expression of the *P*-glycoprotein. The important bioactivity of hapalosin has stemmed the total synthesis of this molecule[2,3] and its analogues.[3d,3e,3g,3i,4] Parallelly, NMAHPPA, the γ-amino-β-hydroxy acid moiety (**C**) of hapalosin, also become the target of several synthetic effort.[2,3,5] In addition, protected (3*R*,4*S*)-AHPPA (**2b**) (AHPPA: ethyl *N*-Boc-4-amino-3-hydroxy-5-phenylpentanoate)[3e-3g,6] and its synthetic equivalent[3a] have been used as key intermediates in the total synthesis of both hapalosin[3e,3g,3i,3j] and non-*N*-methyl hapalosin (Scheme 1).[3a,3d,3g]

The synthesis of non-*N*-methyl hapalosin helped to attribute the MDR-reversing activity to the major *s-cis* rotamer of hapalosin.[3d,4] However, in all but one[5e] of the known syntheses of both protected (3*R*,4*S*)-NMAHPPA (**2a**) and protected (3*R*,4*S*)-AHPPA (**2b**), the benzyl group was presented as an integral part of the starting materials such as (*R*)-phenylalanine. Such approach does not allow for an easy variation of the side chain (benzyl group), thus limits the structure-bioactivity relationship studies in this issue, while it has been shown that side chain modification may improve the MDR-reversing activity

Scheme 1



Hapalosin (**1**)



(3*R*,4*S*)-NMAHPPA (**2a**) R = Me
(3*R*,4*S*)-AHPPA (**2b**) R = H

of hapalosin.[4] Moreover, all the known syntheses of protected NMAHPPA (**2a**) and AHPPA (**2b**) were achieved via acyclic intermediates, which gave, in some cases,[6a,6b,6e] modest stereoselectivity in establishing 3,4-*anti* stereochemistry.

In a program aiming at the total synthesis of hapalosin and its analogues, a highly stereoselective and flexible synthesis of protected AHPPA (**2b**) is highly desirable. We wish to communicate herein a highly stereoselective and flexible approach to *N*-Boc-(3*R*,4*S*)-AHPPA-OEt (**2b**) which features an highly *trans* stereochemical control via a cyclic intermediate (**D**) generated in a flexible fashion from malimide derivative (*R*)-**4** (Scheme 2).

Since our first demonstration on the use of (*S*)-*N*,*O*-dibenzyl malimide (*S*)-**5** as a valuable intermediate in the asymmetric synthesis of nitrogen containing bioactive compounds,[7] this compound is becoming a suitable molecule

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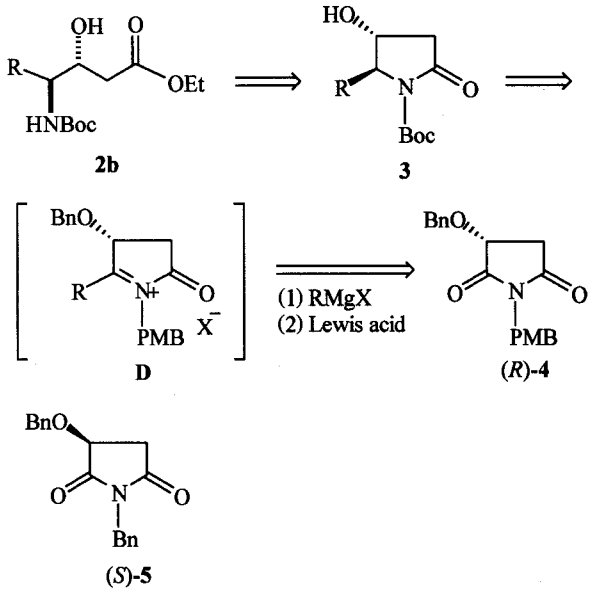
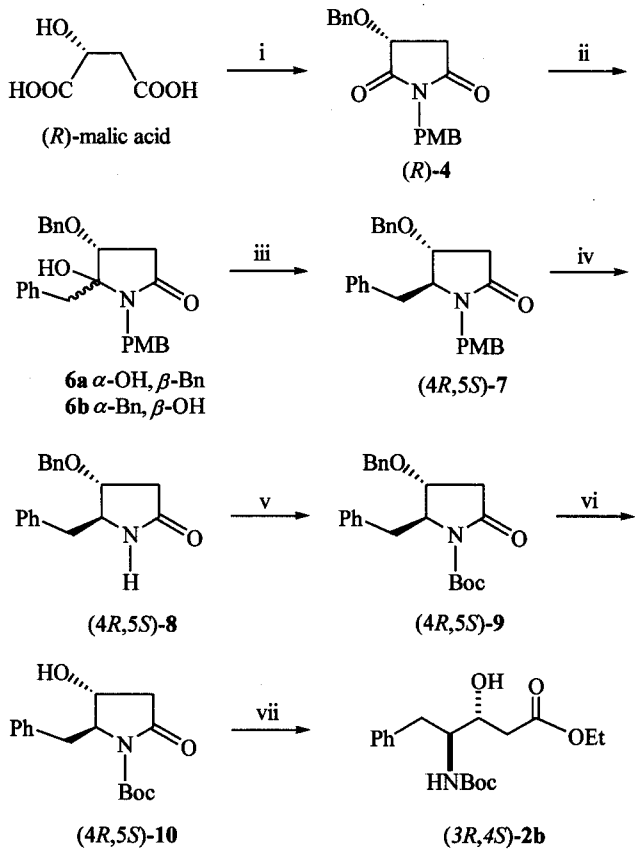
Scheme 2



for testing new synthetic methodologies.[8] In present study, for the synthesis of (3*R*,4*S*)-**2b**, (*R*)-*O*-benzyl-*N*-*p*-methoxybenzyl malimide (**4**) was selected as the key intermediate which would present triple advantages, namely, easy introduction of the side chain via a flexible Grignard reaction; excellent stereochemical control and high stereoselectivity in establishing *trans*-stereochemistry; and easy cleavage of *N*-protective group under oxidative conditions.

The synthesis of *N*-Boc-(3*R*,4*S*)-AHPPA-OEt (**2b**) is outlined in Scheme 3. The requisite (*R*)-**4** {m.p. 68.5—70.0 ℃, $[\alpha]_D^{20}$ 71.7 (*c* 1.1, $CHCl_3$)} was synthesized from (*R*)-malic acid with an overall yield of 74%, following the procedure developed for (*S*)-**4**.[7c] Benzyl magnesium chloride addition (0 ℃, THF) to malimide (*R*)-**4** allowed the introduction of the side chain (benzyl group) presented in hapalosin in high regioselective manner, only the regioisomer resulting from the addition at C-2 carbonyl of **4** was isolated, indicating a regioselectivity higher than 95%. In this reaction, two diastereoisomers **6a/6b** were obtained. These two separable diastereoisomers can be used in the next step as a mixture, since the followed reductive deoxygenation was considered to proceed via the intermediacy of the *N*-acyliminium (**D**)[9] in which the hydridation of the carbon at position **2** is sp^2. Indeed, when the diastereomeric mixture **6a/6b** was subjected to boron trifluoride etherate mediated triethylsilane reduction[7b,10] (−78 ℃, 6 h, then warm up and react for further 4 h), *trans*-**7**[11] {m.p. 70—72 ℃, $[\alpha]_D^{20}$ −41.2 (*c* 1.1, $CHCl_3$)} formed predominately as white crystals. The *trans*/*cis* diastereoselectivity was more than 95:5 according to chromatographic separation. The stereochemistry of the major diastereomer was assigned as *trans* based on the indicative vicinal coupling constant between H-4 and H-5 ($J_{4,5} \approx 0$ Hz).[7,12] This is in agreement with our previous observations and is confirmed later by the transformation of **7** to known **2b**.

Scheme 3



Reagents and conditions: i) Ref. 7c; ii) BnMgCl, THF, 0 ℃, 91%; iii) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 ℃—r.t., 91%; iv) CAN, MeCN-H_2O (3:1), 23 ℃, 79%; v) $(Boc)_2O$, DMAP, NEt_3, CH_2Cl_2, r.t., 91%; vi) HCOOH, 10% Pd/C, MeOH, r.t., 93%; vii) KCN, EtOH, THF, r.t., 87%.

The high *trans* stereoselectivity observed in this transformation might implicate a chelating effect between silicon atom and the C-4 oxygen resulted from a preliminary attack of a fluoride to silicon atom, and which leads to the delivery of hydride from Si atom to sp^2 hybrided C-5 from the same side as the *O*-benzyl group.

Next, the *p*-methoxybenzyl in **7** was cleaved using ceric ammonium nitrate (MeCN-H_2O, 3:1, 25 ℃, 15 min) to furnish amide **8** {$[\alpha]_D^{20}$ −43.4 (*c* 1.2, $CHCl_3$)} in 79% yield. *N*-Re-protection/activation was achieved by treatment of **8** with Boc anhydride under standard conditions [$(Boc)_2O$, K_2CO_3, MeCN], which provided **9** {$[\alpha]_D^{20}$ 14.5 (*c* 1.3, $CHCl_3$)} in 91% yield. Compound **9** was then subjected to catalytic hydrogenolysis (10% Pd-C, HCOOH-MeOH, 1:9, r.t., 20 h) to afford 4-hydroxylactam (**10**) {m.p. 90—92 ℃; $[\alpha]_D^{20}$ 37.9 (*c* 0.9, MeOH)} as white crystals in 93% yield. Finally, the KCN promoting regioselective nucleophilic ring-opening[13] of Boc activated lactam **10** with ethanol-THF (1:1, *V*/*V*) proceeded smoothly to give the desired *N*-Boc-(3*R*,4*S*)-AHPPA-OEt (**2b**) as white crystals {m.p. 142.5—143.5 ℃, lit.[3g] 143—144 ℃; $[\alpha]_D^{20}$ −13.3 (*c* 0.6, MeOH);

$[\alpha]_D^{20}$ + 6.1 (*c* 0.65, $CHCl_3$), lit.[6a] $[\alpha]_D^{20}$ − 14.2 (*c* 1.0, MeOH), lit.[3g] $[\alpha]_D^{20}$ + 3.8 (*c* 1.0, $CHCl_3$)} in 87% yield.

In summary, this synthetic method illustrates a new approach to the key intermediate in the synthesis of hapalosin, which is characterized by: (1) The side chain (benzyl group) presented in the hapalosin is introduced by Grignard reaction so the method is flexible in view of our previous demonstration on the generality of the highly regio and *trans* stereo-selective reductive alkylation based on both **4** and **5**; (2) The formation of C-4 stereogenic center is controlled via a cyclic intermediate which provides advantages such as high stereoselectivity, easy determination of the relative stereochemistry by vicinal coupling constant $J_{4,5}$. Further work is in progress towards the total synthesis of hapalosin.

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Selected data for **2b**: m.p. 142.5—143.5 ℃, lit.[3g] 143—144 ℃; $[\alpha]_D^{25}$ − 13.3 (*c* 0.6, MeOH); $[\alpha]_D^{25}$ + 6.1 (*c* 0.65,

$CHCl_3$), lit.[6a] $[\alpha]_D^{24}$ – 14.2 (*c* 1.0, MeOH), lit.[3g] $[\alpha]_D$ +3.8 (c 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$, 500 MHz) δ: 1.26 (t, J = 7.1 Hz, 3H, CH_3), 1.34 (s, 9H, Bu-*t*), 2.50 (dd, J = 9.1, 16.5 Hz, 1H, CH_2-Ph), 2.58 (d, br, J = 16.5 Hz, 1H, CH_2-Ph), 2.79—2.86 (m, 1H, CH_2CO), 2.94—3.01 (m, 1H, CH_2CO), 3.58 (s, 1H, OH, D_2O exchangeable), 3.82—3.88 (m, 1H, CHN), 3.95—4.05 (m, 1H, CHOH), 4.17 (q, J = 7.1 Hz, 2H, OCH_2Me), 4.55 (brs, 1H, NH), 7.18—7.35 (m, 5H, Ph); IR (KBr) ν: 3353, 1733, 1683 cm^{-1}; MS (ESI) *m/z* (%): 360 ($M + Na^+$, 27), 338 ($M + H^+$, 23), 318 (15), 302 (15), 218 (19), 274 (100).

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