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Stereospecific total synthesis of (−)-8-*epi*-hyperaspine

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Abstract—Condensation of protected δ-hydroxy-β-amino ester **7** with a β-keto ester provides vinylogous urethane **8**, which is cyclized under the action of *t*-BuOK followed by decarboxylation to afford enone **12**. Hydrogenation of **12** or its *N*,*O*-diprotected derivative **13** gives 2,6-*cis*-disubstituted piperdines. Using these intermediates, (−)-8-*epi*-hyperaspine is synthesized.

Hyperaspine is a new member of ladybird alkaloids, which was isolated from *Hyperaspia campestris*, a number of an as yet uninvestigated tribe.[1] This compound possesses a 3-oxoquinolizidine skeleton, which was not discovered among over 50 known ladybird alkaloids. By using 2D NMR and MS methods, Braekman and his co-workers established its structure as shown in Figure 1. However, its absolute configuration was not determined. Obviously, this molecule can be constructed using piperidine **A** as the key intermediate. During the investigation on the synthesis from enantiopure β-amino acid derivatives,[2] we have developed an efficient method to assemble 4-hydroxy-2,6-disubstituted piperdines diastereoselectively.[2i] It was our hope to apply this methodology to the synthesis of hyperaspine. The studies thus undertook are reported here.

As outlined in Scheme 1, our synthesis started from (*S*)-3-hydroxybutanoic acid ethyl ester, which was prepared from ethyl acetate using baker's yeast mediated reduction in light petroleum.[3] Treatment of this β-hydroxyl ester with benzyl 2,2,2-trichloroacetimidate under acid condition afforded the benzyl ether **4**.[4] After the ester moiety of **4** was reduced with diisobutylaluminium hydride to give the crude aldehyde, Wittig reaction was carried out to provide α,β-unsaturated ester **5** in 90% yield. Subjected the ester **5** to a diastereoselective Michael addition with lithium (*S*)-*N*-benzyl-α-methylbenzylamide according to Davis's procedure provided β-amino ester **6** in 85% yield.[5] Only one isomer was determined by ^{1}H NMR, which indicated that the diastereoselectivity of this step was over 98%. Next, hydrogenolysis with Pearlman's catalyst was employed to remove all the benzyl protecting groups and the resultant hydroxyamine was treated with *t*-butyl dimethylsilyl chloride to give **7** in 77% yield for two steps.

With the β-amino ester **7** in hand, we planned to condense it with a β-keto ester and then carry out an intramolecular Dieckmann reaction to obtain the cyclization product using the procedures as described before.[2i] However, we found that the previous reaction

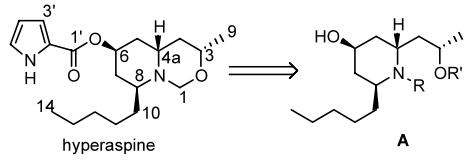
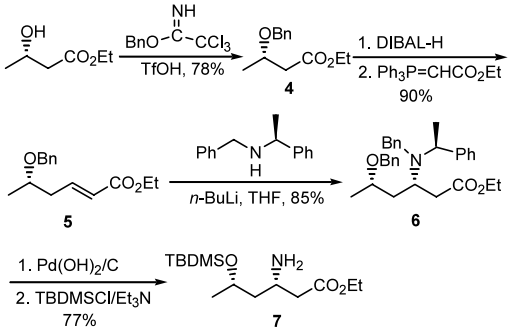


Figure 1. Structure of hyperaspine and its retrosynthetic analysis.



Scheme 1.

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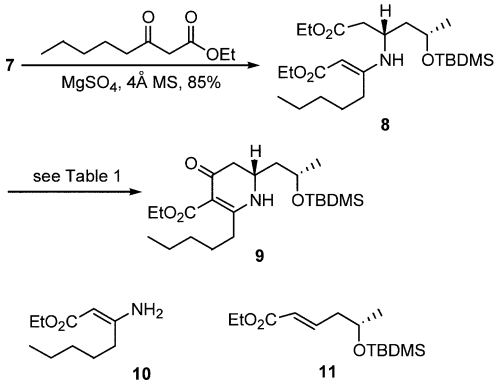
conditions[2i] for these two steps were not suitable for the present substrate. Because the TBDMS protecting group could not survive at acid-catalyzed azeotropic removal of water condition,[2i] we decided to condense **7** with 3-oxooctanoic acid ethyl ester under solvent-free condition with the assistance of $MgSO_4$ and 4 Å MS.[2d] This mild condition allowed us to obtain the vinylogous urethane **8** in 85% yield. The cyclization step of **8** was found to be a difficult task and several methods were thus investigated (Scheme 2). The results are summarized in Table 1.

Initially, sodium ethoxide mediated Dieckmann reaction in refluxing ethanol was attempted.[2i] We found that at this condition the reaction worked but gave the desired product **9** in less than 20% yield (entry 1). Considerable amount of enamine **10** was isolated, which implied that the β-elimination of **8** to form **10** and **11** occurred at the present condition. The similar result was observed when the reaction was taken place in refluxing *t*-BuOH under the action of *t*-BuOK (entry 4). In order to depress the β-elimination we decided to run this reaction at lower temperature. Accordingly, LDA or NaH was employed as the base to carry out the reaction at 0°C or room temperature. In these two cases no reaction occurred (entries 2 and 3). However, when the base was switched to *t*-BuOK the reaction worked in THF at 0°C to give **9** in good yield (entry 5). After optimization of experimental conditions, the yield was further improved to 79% by adding **8** in one portion to a refluxing solution of 2.5 equiv. of *t*-BuOK in THF and quickly quenching the reaction (in 2 min) after the addition (entry 6). By this mean, the β-elimination of **8** was minimized.



Scheme 2.

Table 1. Intramolecular Dieckmann reaction of **8**

Entry	Reaction condition	Isolated yield of **8** (%)
1	NaOEt/EtOH, rt–reflux	<20
2	LDA/THF, −78°C to 0°C	–[a]
3	NaH/THF, 0°C to rt	–[a]
4	KOBu-*t*/*t*-BuOH, reflux	<20
5	KOBu-*t*/THF, 0°C	67
6	KOBu-*t*/THF, reflux	79

[a] The starting material was recovered.

Treatment of **9** with aqueous NaOH in refluxing ethanol provided the decarboxylation and desilylation product **12**. After the free hydroxyl group of **12** was reprotected with TBDMSCl, its amine group was protected with $(Boc)_2O$ mediated with *n*-BuLi to afford **13** in 90% yield. We expected that the installation of this Boc group would help us to get a *trans*-2,6-dialkylpiperidine in hydrogenation step because direct hydrogenation of **12** would give a *cis*-2,6-dialkylpiperidine through the conformation **B** (Fig. 2) as demonstrated before.[2i] The similar selectivity change has been observed by Comins and his co-workers during the synthesis of indolizidine alkaloids.[6] The strong $A^{(1,3)}$ strain between the alkyl substituent at C-2 and *N*-protecting group was used to explain the selectivity as indicated in conformation **C** of Figure 2, which forced C-2 substituent into an axial orientation thereby resulting in attack from the C-2 substituent face.[6] One could logically think if the hydrogenation of **13** occurred in a similar manner the desired *trans*-2,6-dialkylpiperidine would be obtained. Thus, hydrogenation of **13** over 10% Pd/C in MeOH was carried out and a single diastereoisomer **14**[7] was obtained in 95% yield. After cleavage of all the protecting groups of **14** with trifluoroacetic acid in methylene chloride, reprotection was carried out with 37% formaldehyde to provide a bicyclic product **15**.[8] The stereochemistry of **14** was easily determined by the NOE correlation as indicated in Scheme 3. After careful analysis, we disappointingly found that **14** was a *cis* but not *trans*-2,6-dialkylpiperidine. This conclusion was further confirmed by following two evidences: (1) the presence of Bohlman bands in the FTIR spectrum of **15** strongly supported that **15** exists in a *trans* fused ring conformation as indicated in Scheme 3;[9] (2) Pd/C-catalyzed hydrogenation of **12** followed by treatment with formaldehyde and Dess–Martin oxidation to oxidate the resultant hydroxyl group in hydrogenation step also produced **15**.

Although the reason for selectivity in hydrogenation of **13** was not clear, a possible explanation was proposed based on a conformation of **13** as demonstrated in Figure 3. Through this conformation stereoelectronically preferred axial attack took place to give a kinetically favored chairlike transition state and finally provide *cis*-2,6-dialkylpiperidine **14**.[10]

In order to change the stereoselectivity, reduction of **13** with sodium borohydride or sodium cyanoborohydride, and hydrogenation of **13** with other catalysts such as Pt/C were attempted. However, in all cases only *cis*-2,6-dialkylpiperidine was determined, which allowed us to

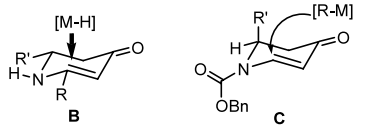
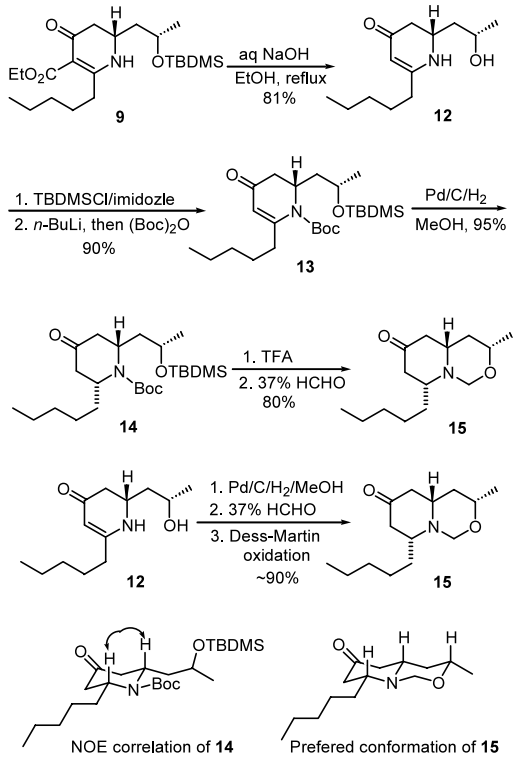


Figure 2. Conformation analysis of 2,3-dihydro-4-pyridones during the addition reactions.



Scheme 3.

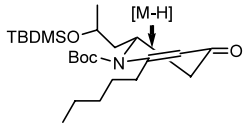
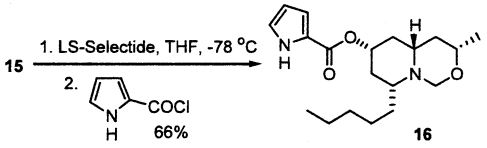


Figure 3. Stereochemical course during the hydrogenation of **13**.

synthesize the 8-*epi*-hyperaspine at this moment. Thus, reduction of **15** with LS-Selectride in THF at −78°C produced an axial alcohol,[11] which was reacted with pyrrole 2-carboxylic acid chloride under the action of triethylamine to give 8-*epi*-hyperaspine **16**[12] in 66% yield (Scheme 4).

In conclusion, we have developed a stereocontrolled route (12 linear steps and 14.8% overall yield) for synthesizing (−)-8-*epi*-hyperaspine, which will be useful for structure–activity relationship studies of hyperaspine. In addition, the chemistry presented here should be of benefit for synthesizing other polysubstituted piperidines.



Scheme 4.

Acknowledgements

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7. Selected data: $[\alpha]_D^{20}$ −2.1 (*c* 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 4.76 (br s, 1H), 4.56 (br s, 1H), 3.90–3.84 (m, 1H), 2.68–2.62 (m, 2H), 2.43 (dt, $J=15.3$, 1.4 Hz, 1H), 2.33 (dd, $J=15.3$, 1.9 Hz, 1H), 1.86–1.78 (m, 1H), 1.61–1.58 (m, 3H), 1.49 (s, 9H), 1.43 (br s, 6H), 1.19 (d, $J=6.0$ Hz, 3H), 0.88–0.86 (m 12H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.2, 154.9, 80.4, 66.1, 52.9, 49.5, 45.7, 43.9, 43.7, 37.2, 31.7, 28.6 (3C), 26.8, 26.0 (3C), 24.0, 22.7, 18.1, 14.1, −4.0, −4.6; ESI-MS *m*/*z* 442 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{47}NNaO_4Si$ 464.3167 $(M+Na)^+$, found 464.3174.
8. Selected data: $[\alpha]_D^{20}$ −5.1 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.86 (d, $J=7.8$ Hz, 1H), 3.60 (d, $J=7.8$ Hz, 1H), 3.60–3.55 (m, 1H), 2.47–2.31 (m, 5H), 1.68–1.47 (m 5H), 1.27–1.20 (m, 9H), 0.91–0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.8, 83.4, 73.0, 60.0, 58.7, 47.7, 46.3, 40.5, 32.5, 32.0, 23.6, 22.4, 21.0, 13.9; MS *m*/*z* 239 (M^+); HRMS calcd for $C_{14}H_{25}NO_2$ 239.1885 (M^+), found 239.1915.
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12. Selected data: $[\alpha]_D^{20}$ −8.0 (*c* 0.35, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.19 (br s, 1H), 7.00–6.98 (m, 1H), 6.96–6.94 (m, 1H), 6.31–6.30 (m, 1H), 5.28–5.27 (m, 1H), 4.83 (d, $J=7.9$ Hz, 1H), 3.60 (d, $J=7.9$ Hz, 1H), 3.57–3.55 (m, 1H), 2.52–2.42 (m, 2H), 2.04–1.22 (m, 17H), 0.90–0.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6, 123.1, 115.2, 115.0, 83.8, 73.7, 68.5, 55.6, 53.0, 40.5, 37.1, 35.7, 32.7, 32.7, 30.1, 24.3, 23.0, 21.6, 14.2; ESI-MS *m*/*z* 335 $(M+H)^+$; HRMS calcd for $C_{19}H_{30}N_2O_3$ 335.2329 $(M+H)^+$, found 335.2332.