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Preparation of *syn*-δ-Hydroxy-β-amino Esters via an Intramolecular Hydrogen Bond Directed Diastereoselective Hydrogenation. Total Synthesis of (3*S*,4a*S*,6*R*,8*S*)-Hyperaspine

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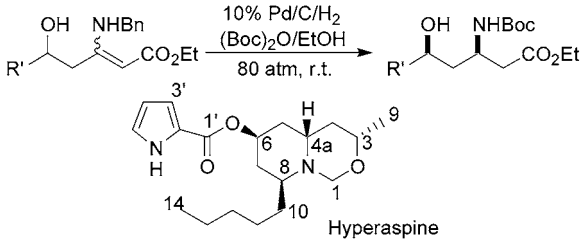
ABSTRACT



Hydrogenation of δ-hydroxy-β-ketoester-derived enamines 8 produces *syn*-δ-hydroxy-β-amino esters 9 diastereoselectively, which may be directed by the formation of an intramolecular hydrogen bond between the δ-hydroxyl and β-amino groups. By using this method and a Dieckmann reaction as the key steps, (3*S*,4a*S*,6*R*,8*S*)-hyperaspine, a new type of ladybird alkaloid, is synthesized.

The δ-hydroxy-β-amino ester moiety exists in many biologically important molecules such as scytonemin A,[1] the potent gastroprotective agent AI-77B1;[3] and the antibacterial natural products negamycin[4] and sperabillin A−D.[5] To synthesize these molecules, several concise protocols for preparing the δ-hydroxy-β-aminoester units have been developed.[2,6] However, most of them are long or use not so readily available starting materials.

In the course of our investigations into the total synthesis of hyperaspine, we became interested in developing a good method for preparing *syn*-δ-hydroxy-β-amino esters because our proposed strategy would make use of such a compound as a starting material.

Hyperaspine is a new type of ladybird alkaloid that was isolated by Braekman and co-workers from *Hyperaspis campestris*.[7] We envisioned accessing the natural product from the bicyclic ketone **1**, which would be prepared from

(1) Helms, G. L.; Moore, R. E.; Niemczura, W. P.; Patterson, G. M. L.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298.

(2) Ensch, C.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 233 and references therein.

(3) Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. *Agric. Biol. Chem.* **1982**, *46*, 1823.

(4) Hamada, M.; Takeuchi, T.; Kondo, S.; Ikeda, Y.; Naganawa, H.; Maeda, K.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 170.

(5) Katayama, N.; Nozaki, Y.; Tsubotani, S.; Kondo, M.; Harada, S.; Ono, H. *J. Antibiot.* **1992**, *45*, 10.

(6) (a) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465. (b) Hashiguchi, S.; Kawada, A.; Natsugari, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2435. (c) Chakraborty, T. K.; Hussain, A. K.; Joshi, S. P. *Chem. Lett.* **1992**, 2385. (d) Broady, S. D.; Rexhausen, J. E.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1991**, 708. (e) Ward, R. A.; Procter, G. *Tetrahedron Lett.* **1992**, *33*, 3359. (f) Masters, J. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 4547. (g) Jain, R. P.; Williams, R. M. *J. Org. Chem.* **2002**, *67*, 6361. (h) Shimizu, M.; Morita, A.; Fujisawa, T. *Chem. Lett.* **1998**, 467. (i) Schmidt, U.; Stäbler, F.; Lieberknecht, A. *Synthesis* **1992**, 482. (j) Maycock, C. D.; Barros, M. T.; Santos, A.; Godinho, L. S. *Tetrahedron Lett.* **1992**, *33*, 4633. (k) Socha, D.; Jurczak, M.; Chemielewski, M. *Tetrahedron Lett.* **1995**, *36*, 135. (m) Davies, S. G.; Ichihara, O. *Tetrahrdeon: Asymmetry* **1996**, *7*, 1919. (n) Davies, S. G.; Ichihara, O. *Tetrahedron Lett.* **1999**, *40*, 9313.

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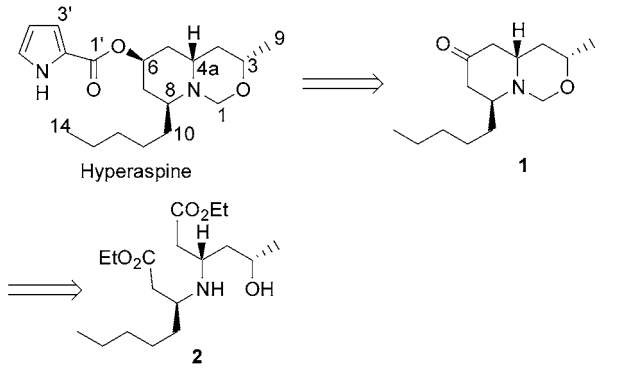


Figure 1. Retrosynthetic analysis of hyperaspine.

the δ-hydroxy-β-amino ester **2** via a Dieckmann reaction and subsequent transformations (Figure 1).[8]

In 1986, Prasad and co-workers reported that the hydrogenation of δ-hydroxyl-β-ketoesters **3** preferentially gave *syn*-1,3-diols **4** with high diastereoselectivity (Figure 2).[9]

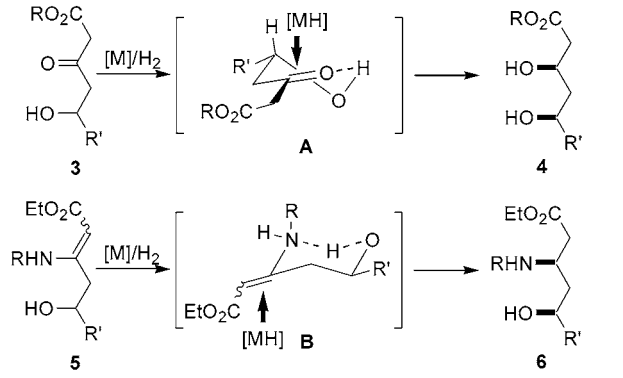


Figure 2. Possible stereochemical courses in the hydrogenation of ketoester **3** and enamine **5**.

Formation of an intramolecular hydrogen bond as indicated in conformer **A** was proposed to explain this stereochemical outcome. Stimulated by this result, we envisaged that if the enamine **5** was hydrogenated, then the *syn*-hydroxylamine **6** would be obtained selectively as a result of similar intramolecular hydrogen bonding between the δ-hydroxyl group and the nitrogen atom as illustrated in conformer **B**.

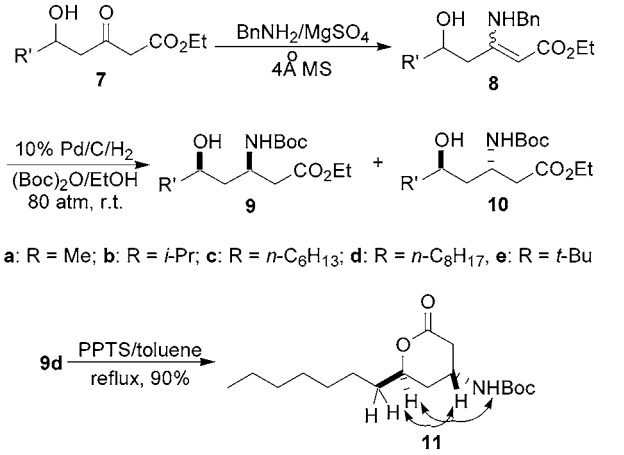
To explore this possibility, we prepared a series of enamines **8**, as inseparable mixtures of *cis* and *trans* isomers, by the condensation of benzylamine with the δ-hydroxy-β-ketoesters **7**, which were readily available from the aldol

(7) Lebrun, B.; Braekman, J.-C.; Daloze, D.; Kalushkov, P.; Pasteels, J. M. *Tetrahedron Lett.* **2001**, *42*, 4621.

(8) For our recent results on the synthesis of enantiopure piperidines using this strategy, see: (a) Ma, D.; Sun, H. *Org. Lett.* **2000**, *2*, 2503. (b) Ma, D.; Sun, H. *J. Org. Chem.* **2000**, *65*, 6009.

(9) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.

Scheme 1



reaction of aldehydes with ethyl acetoacetate.[10] Hydrogenation of **8d** was initially attempted by exposing it to Pd/C and H_2 in ethanol. It was found that hydrogenation and debenzylation occurred under these conditions to give the free δ-hydroxy-β-amino ester as a diastereomeric mixture. Because of the difficulty in separating these two diastereomers, we decided to protect them in situ. Accordingly, the hydrogenation of **8** was carried out in the presence of di-*tert*-butyl dicarbonate, which provided the *syn*-hydroxylamine **9d** and the *anti*-hydroxylamine **10d** in a ratio of 5.3:1 and 61% combined yield. The stereochemistry of the major diastereomer **9d** was established by analyzing the NOE correlations of lactone **11**, which was obtained from **9d** by treatment with PPTS. Of the other enamines that were tested, the δ-methyl-substituted compound **8a** gave poorer *syn*-selectivity (entry 1, Table 1). The best selectivity was

Table 1. Hydrogenation of **8** to **9** and **10**

entry	substrate	yield (%)[a]	**9**/**10** ratio
1	**8a**	79	3.4
2	**8b**	78	5.2
3	**8c**	65	5.7
4	**8d**	61	5.3
5	**8e**	71	7.4

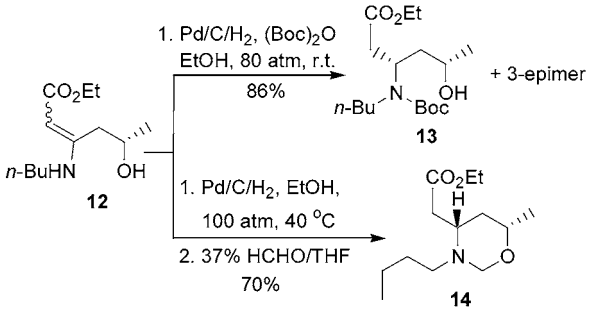
[a] Isolated yield.

observed when the δ-*tert*-butyl-substituted enamine **8e** was used as a substrate (entry 5). For **8b** and **8c**, two substrates possessing similar bulky groups at the δ-position, almost the same ratio of *syn* and *anti* products was obtained (compare entries 2−4). This selectivity pattern gave strong support to the hydrogenation mechanism proposed in Figure 2, where H_2 is delivered to the less hindered face of the alkene in this internally hydrogen-bonded arrangement.

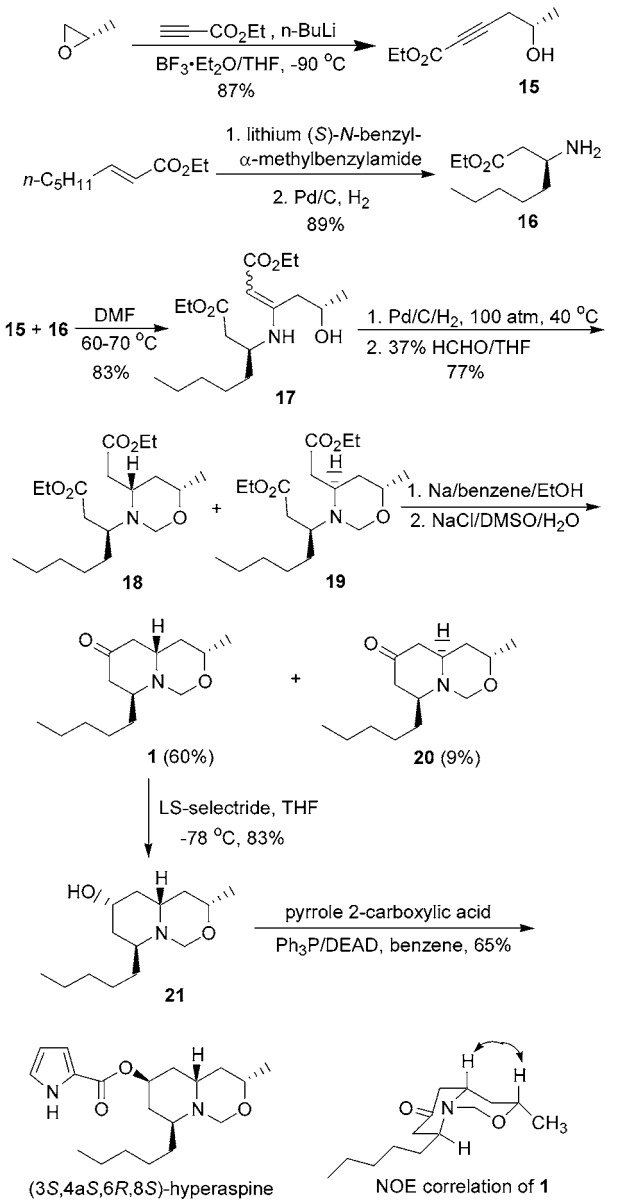
As the *N*-benzyl group of **8** could have been undergoing hydrogenolytic cleavage before the olefin moiety was being

(10) Huckin, S. N.; Weiler, L. *Can. J. Chem.* **1974**, *52*, 2157.

Scheme 2



Scheme 3



reduced, this prompted us to examine the hydrogenation of enamine **12**. Enamine **12** gave *syn*-product **13** and its 3-epimer in a ratio of 6.7:1. This result indicated that there was about a 2-fold increase in *syn*-selectivity compared with the hydrogenation reaction of **8a**, which provided further evidence for our mechanistic hypothesis. Interestingly, when **12** was hydrogenated in the absence of di-*tert*-butyl dicarbonate, 3-oxopiperidine **14** was isolated as a single isomer, after the hydrogenated product was treated with 37% formaldehyde. This result implied that only the *syn*-δ-hydroxy-β-amino ester was being formed during the hydrogenation and that the presence of di-*tert*-butyl dicarbonate was altering the diastereoselectivity. On the basis of the above investigations, a protocol for the first total synthesis of (3*S*,4a*S*,6*R*,8*S*)-hyperaspine was developed.[11] As illustrated in Scheme 3, the synthesis started with the preparation of the two intermediates **15** and **16**.

First, treatment of ethyl propiolate with *n*-BuLi followed by trapping of the anion with commercially available (*S*)-propylene oxide in the presence of boron trifluoride diethyl etherate afforded alkynoic ester **15**.[12] In a parallel procedure, the enantiopure β-amino ester **16** was obtained in 89% yield by the diastereoselective Michael addition of lithium (*S*)-*N*-benzyl-α-methylbenzylamide[13] to (*E*)-2-nonenoic acid ethyl ester and subsequent hydrogenolysis. Next, Michael addition of the β-amino ester **16** to the alkynoic ester **15** was carried out in DMF at 60−70 °C to provide the enamine **17** in 83% yield.[14] According to ^{1}H NMR analysis and Back's report[15] it was found that this enamine was a mixture of *trans* and *cis* isomers in a ratio of 1:1.6; both isomers were inseparable by column chromatography.

Hydrogenation of **17** followed by treatment with 37% formaldehyde provided the cyclic products **18** and **19** in 77% combined yield. These two isomers were inseparable by column chromatography and existed in a ratio of 6.3:1 as determined by ^{1}H NMR spectroscopy. Dieckmann reaction of this mixture was carried out in benzene at room temperature under the action of a catalytic amount of ethanol and 1 equiv of sodium to provide the corresponding β-keto esters, which were subjected to decarboxylation with sodium chloride in DMSO.[16] A separable mixture of **1** (60% yield) and **20** (9% yield) was obtained. NOESY studies confirmed the stereochemistry of **1** by the marked NOE correlation between H-3 and H-4a that was observed. The difference in hydrogenation selectivity between **12** and **17** might result from the influence of the additional ester group in **17**.

Reduction of the bicyclic ketone **1** with LS-selectride[17] in THF at −78 °C produced alcohol **21** in 83% yield as a single isomer. Finally, esterification of **21** with pyrrole 2-carboxylic acid mediated with triphenylphosphine and diethyl azodi-

(11) For synthesis of (−)-8-*epi*-hyperaspine, see: Ma, D.; Zhu, W. *Tetrahedron Lett*. **2003**, *44*, 8609.
(12) Merrer, T. L.; Gravier-Pelletier, C.; Micas-Languin, D.; Mestre, F.; Dureault, A.; Depezay, J.-C. *J. Org. Chem.* **1989**, *54*, 2409.
(13) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.
(14) (a) Pu, X.; Ma, D. *J. Org. Chem.* **2003**, *68*, 4400. (b) Ma, D.; Pu, X.; Wang, J. *Tetrahedron: Asymmetry* **2002**, *13*, 2257.
(15) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566.
(16) Oehlschlager, A. C.; Dodd, D. S. *J. Org. Chem.* **1992**, *57*, 2794.
(17) Bardot, V.; Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.; Remuson, R. *Heterocycles* **1998**, *48*, 507.

carboxylate provided (3*S*,4a*S*,6*R*,8*S*)-hyperaspine[18] in 65% yield. Its analytical data were identical with those reported.[7]

In conclusion, we have described a simple and useful method for preparing *syn*-δ-hydroxy-β-amino esters. The key element was an intramolecular hydrogen bond directed diastereoselective hydrogenation of the δ-hydroxyl-β-ketoester-derived enamines. Using this method we have achieved the first total synthesis of (3*S*,4a*S*,6*R*,8*S*)-hyperaspine in 18% overall yield over nine linear steps. Because the absolute stereochemistry of natural hyperaspine, as well as its biological activities, has not yet been determined owing to the very limited amount from the natural source, our synthetic protocol should be helpful in addressing these issues. Further application for the present strategy to the synthesis of AI-77-B, negamycin, and sperabillin A−D is in progress and will be reported in due course.

(18) Selected data: $[\alpha]^{20}_{D}$ +85.0 (*c* 0.30, CH_3OH); ^1H NMR (CD_2Cl_2, 300 MHz) δ 9.64 (br s, 1H), 6.96 (m, 1H), 6.87 (m, 1H), 6.25 (m, 1H), 5.10 (m, 1H), 4.77 (d, J = 10.8 Hz, 1H), 4.22 (d, J = 10.8 Hz, 1H), 3.61 (m, 1H), 3.38 (m, 1H), 3.16 (m, 1H), 1.86 (m, 1H), 1.67−1.15 (m, 16H), 0.86 (m, 3H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 161.1, 124.0, 123.5, 115.6, 111.0, 81.4, 74.6, 69.5, 56.2, 49.9, 37.3, 37.0, 33.9, 33.1, 33.0, 24.9, 23.4, 22.5, 14.6; IR (KBr) 3313, 1699 cm^{-1}; MS *m*/*z* 334 (M^+); HRMS calcd for $C_{19}H_{30}N_2O_3$ 334.22564 (M^+), found 334.22207.

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Supporting Information Available: Experimental procedures and characterization for compounds **1**, **9a**−**e**, **13**−**15**, and **17**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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