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Hydroboration of Enecarbamates and the Synthesis of β-Hydroxypiperidine Alkaloids

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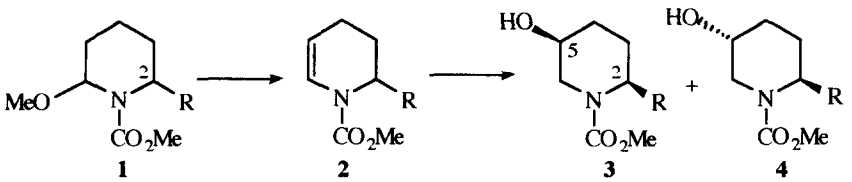
*Abstract: The β-hydroxypiperidine alkaloids **5**, **6** and **8** were diastereoselectively synthesized using hydroboration of enecarbamates **2b-c** as a key step.*

α-Methoxy carbamates **1** are conveniently prepared through anodic methoxylation of carbamates and have proven to be valuable intermediates for the synthesis of 2- and 2,6-substituted piperidine derivatives[1,2,3,5]. Under acidic and thermolytic conditions[4], they furnish the enecarbamates **2** which, although less reactive than enamines, react with several electrophiles. It was shown earlier[4] that hydroboration made possible the introduction of a hydroxyl group into the β position of enecarbamates but, except for the case of a pyrroline derivative, the stereochemistry of the alcohols was not established.

In this communication, we wish to report hydroboration of enecarbamates as a key step for the stereoselective synthesis of both *cis* and *trans* β-hydroxypiperidine derivatives.

The α-methoxy carbamates **1a**[2], **1b** and **1c**[5] were prepared in high yield by anodic oxidation of carbamates in methanol[6]; we found that the corresponding enecarbamates **2a-c** can be obtained efficiently (90-95% yield) by treatment of **1a-c** with p-toluenesulfonic acid (10% w/w) in benzene at room temperature. The hydroboration-oxidation sequence [7] was applied to racemic **2a-b** and to optically pure **2c** (2S,8S) and furnished the diastereomeric alcohols **3a-c** and **4a-c** which could be quantitatively separated by flash chromatography and were fully characterized[8].



1 **2** **3** **4**

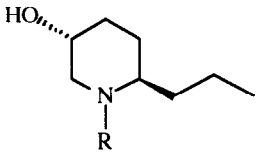
a: R = CH_3 **b**: R = CH_2-CH_2-CH_3 **c**: R = CH_2-CH(OAc)-C_6H_5

The results, summarized in Table I, show that the major product in each case is the 2,5-*trans* isomer resulting from the preferential attack of the borane from the less hindered side of the molecule; at low temperature the selectivity is high. On the other hand, it appears that hydroboration does not proceed to the trialkylborane stage, as it is generally observed with hindered olefins[9].

Table I: Hydroboration of enecarbamates **2a-c**

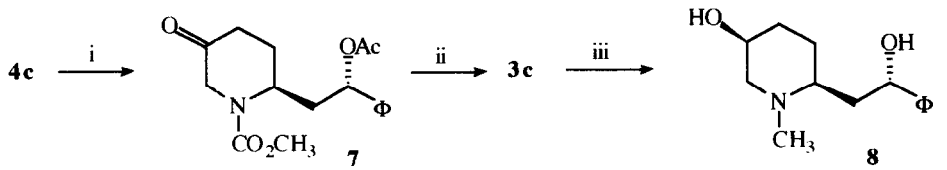
Entry	Enecarbamate	BH_3:SMe_2/ Enecarbamate	Time	Temp.	Global yield (3+4)	Ratio 3/4
1	**2a**	0.3	15 h	20°C	47%	-
2	**2a**	1	15 h	20°C	74%	-
3	**2a**	1	1h	20°C	79%	1: 2
4	**2b**	1	16h	-78°->0°C	71%	1: 6
5	**2c**	1	1h	20°	75%	1: 2

The protective group of **4b** was removed by treatment with TMSI in dichloromethane to furnish racemic pseudoconhydrine **5** (89% yield) or reduced with $LiAlH_4$ (in refluxing THF) to give racemic N-methylpseudoconhydrine **6** (80% yield)[10].



5 R = H
6 R = CH_3

Hydroboration appears therefore as an efficient route for the synthesis of *trans* 5-hydroxypiperidine derivatives **4**. In order to increase the yield in the *cis* compounds **3**, a process of inversion at C-5 in **4** was developed based on the stereoselective reduction ($NaBH_4$) of the ketones resulting from oxidation of the alcohols[11]; the method is illustrated by the synthesis of (-)-5-hydroxysedamine **8**[12] from **4c**.



i: PCC/Aluminium oxide (3 eq.), dichloromethane, reflux 1h. (80% yield); ii: $NaBH_4$, EtOH, 0°C (75%); iii: $LiAlH_4$, THF, reflux 16 h. (80%).

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References and Notes.

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4 Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697-6703.
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6 The anodic methoxylations were carried out in methanol containing Et_4NOTs; a constant potential of 8V was applied between the carbon electrodes.
7 In a typical experiment, 0.32 mL of a 2M THF solution of $BH_3.SMe_2$ (0.64 mmol) were added to a solution of **2a** (100 mg; 0.64 mmol) in dry THF (10 mL) under nitrogen. After one hour, the excess of hydride was decomposed by addition of 5 drops of water and the organoboranes were oxidized by addition of 1 mL of a 3N NaOH solution followed by 1 mL of 30% H_2O_2. After one hour, extractive work-up and flash chromatography (Ethyl acetate/ hexane 2:1) afforded pure **3a** (30 mg) and **4a** (58 mg).
8 All compounds were identified by IR, NMR and mass spectra. ^1H NMR data of representative compounds (250 MHz, $CDCl_3$): **3a**: δ ppm 1.1 (d, J=7 Hz, 3H, CH_3), 1.2-2.3 (m, 5H), 2.6 (dd, J=13 and 10 Hz, 1H, H6ax.), 3.6 (m, 1H, H5), 3.7 (s, 3H, NCO_2CH_3), 4.1 (ddd, J=13, 5 and 1 Hz, 1H, H6eq.), 4.3 (m, 1H, H2); **4a**: δ ppm 1.1 (d, J=7Hz, 3H, CH_3), 1.2-2.2 (m, 5H), 3.1 (dd, J=14 and 2Hz, 1H, H6ax.), 3.7 (s, 3H, NCO_2CH_3), 3.9 (m, 1H, H5), 4.0 (broad d, J=14Hz, 1H, H6eq.), 4.4 (m, 1H, H2); Acetyl **3a:** δ ppm 4.6 (tt, J=10 and 5 Hz, 1H, H5); acetyl **4a:** δ ppm 4.8 (m, 1H, H5).
9 Brown, H.C. *Organic Syntheses via Boranes*, John Wiley & Sons, New York,1975.
10 A stereoselective synthesis of **5** and **6** based on anodic oxidation in AcOH has been described earlier: Shono. T.; Matsumura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. *Chemistry Letters* **1984**, 1101-1104. The convenience and overall yield of this sequence and ours are comparable.
11 We observed that the ketones are obtained in higher yield from the corresponding alcohols rather than by direct oxidation of the intermediate boranes with PCC. As expected, reduction with $NaBH_4$ yielded mainly (de: 85%) the equatorial alcohol.
12 The spectral properties and the rotation of the synthetic compound are identical to those of the alkaloid isolated from *Sedum acre*: Ibebeke-Bomangwa, W.; Hootelé, C. *Tetrahedron* **1987**, *43*, 935-945.

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