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Differential Oxidation of Endocyclic Enecarbamates. Synthesis of Cyclic β-Hydroxy-α-Amino Acids.

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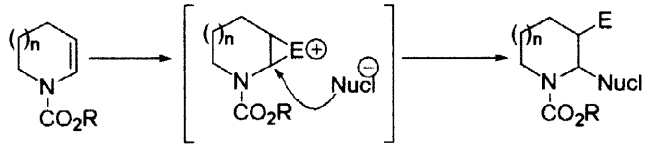
Abstract:. The differential oxidation of five and six-membered endocyclic enecarbamates was investigated employing *m*-CPBA, DMD, as well as enantioselective protocols such as the Kochi-Jacobsen-Katsuki's epoxidation and the Sharpless dihydroxylation. By this strategy the syntheses of β-hydroxyprolines and β-hydroxypipecolic acids were accomplished. X-Ray crystallographic analysis of the *trans*-β-hydroxypipecolic acid was instrumental to solve structural assignment conflicts.

There have been considerable efforts in recent years directed towards the synthesis of cyclic amino acid analogues motivated by their importance in physiological and pathological processes.[2] Additionally, incorporation of extra functional groups into native α-amino acid structures is a desired feature since it normally affects the biological function of these systems. For example, hydroxyprolines are critical for the stability of protocollagen triple helix, and some ring substituted prolines have been employed as conformational restrictive elements for the study of bioactive polypeptides.[3]

In the last few years we have been using endocyclic enecarbamates as frameworks suitable for the construction of a number of nitrogen containing heterocycles.[4] It was also realized from the outset of our studies that electrophilic additions to endocyclic enecarbamates could provide useful intermediates for the synthesis of a number of nitrogen-containing natural products (Scheme 1).



Scheme 1

Due to our interest in the synthesis of conformationally constrained α-amino acids we envisioned endocyclic enecarbamates as starting materials for the construction of 3-hydroxyprolines and 3-hydroxypipecolic acids (homoprolines). These are, in a structural sense, examples of serine and threonine surrogates. Besides their biological utility, they have been used as key intermediates in chemical synthesis.[5]

The basic strategy set forward to the synthesis of the β-hydroxyprolines/homoprolines was based on a differential oxidation of five and/or six membered endocyclic enecarbamates with a number of common oxidizing agent such as *m*-CPBA and DMD (dimethyldioxirane), or by enantioselective oxidation protocols such as the Sharpless dihydroxylation and the Kochi-Jacobsen-Katsuki's epoxidation (chiral (salen)$Mn^{III}Cl$). Herein we present our initial results related to the synthesis of 5 and 6-membered β-hydroxy amino acids.

Oxidation of endocyclic enecarbamates **1** and **2** with *m*-CPBA in MeOH proceeded cleanly to afford the β-hydroxy-α-methoxy pyrrolidines **3** (cis:trans; 1:2) in 80-90% yield and β-hydroxy-α-methoxy-piperidines **4** (cis:trans; 1:1.5) in 90 % yield (Table 1, entries 1 and 2). These results are in sharp contrast with recent results

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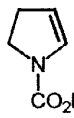
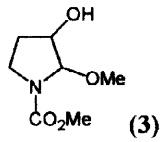
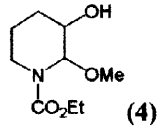
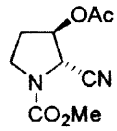
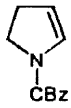
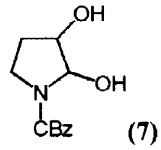
reported by Burgess and coworkers who obtained complex mixtures by reacting enecarbamates **1** and **2** with peracids.[6] Oxidation of enecarbamates **1** with dimethyldioxirane in MeOH provided the corresponding hydroxypyrrolidines **3** in 66-70% yield (Table 1, entry 3).

Table 1: Differential Oxidation of Endocyclic Enecarbamates

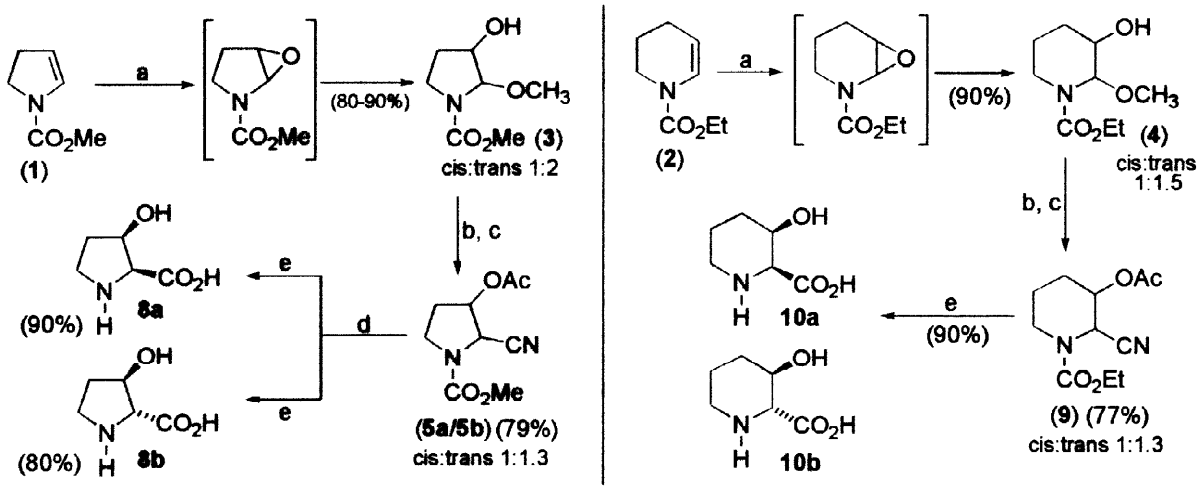
Entry	Enecarbamate	Conditions	Product	Yield	cis:trans (ee)
1	 (1)	*m*-CPBA (1.1 equiv.) MeOH, $NaHCO_3$, CH_2Cl_2 [a]	 (3)	80-90%	1:2 (racemic)
2	 (2)	*m*-CPBA (1.1 equiv.) MeOH, $NaHCO_3$, CH_2Cl_2 [a]	 (4)	90%	1:1.5 (racemic)
3	(1)	DMD/acetone/MeOH [b]	(3)	66-70%	1:1.8 (racemic)
4	(1)	1) DMD, acetone [b] 2) KCN/18-crown 6, CH_2Cl_2 [a]	 (5b) [f]	65%	≥5:95 (racemic)
5	 (6)	$K_3Fe(CN)_6/K_2CO_3$ $K_2OsO_2(OH)_4$ DABCO t-BuOH:H_2O (1:1) [b]	 (7)	90%	1:2 (racemic)
6	(6)	AD-mix-α [c] t-BuOH:H_2O (1:1) [b]	(7)	90%	1:2.7 cis (25%):trans (25%)
7	(6)	(S,S)-(salen)$Mn^{III}Cl$ [d] *m*-CPBA, NMO, CH_2Cl_2 [b,e]	(7)	20% [g]	1:2.4 cis (28%):trans (14%)
8	(6)	(S,S)-(salen)$Mn^{III}Cl$ [d] PhIO, NMO, CH_3CN [b,e]	(7)	70%	1:2 cis (70%):trans (25%)

(a) carried out at room temperature; (b) carried out at 0°C; (c) $(DHQ)_2$-PHAL; $K_3Fe(CN)_6$; K_2CO_3; $K_2OsO_2(OH)_4$ (Aldrich); (d) (S,S)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine (Aldrich) (e) H_2O added at the end of reaction; (f) After acylation of the cyano-alcohol intermediate (Ac_2O, pyr, DMAP, 12h); (g) yield not optimized

Enantioselective epoxidation using (S,S)-(salen)$Mn^{III}Cl$ as catalyst was also examined (Table, entries 7 and 8).[7] Use of *m*-CPBA as terminal oxidant and 4-methylmorpholine *N*-oxide as additive led to diols 7 in only 20% yield (*in situ* opening promoted by H_2O).[8] A very modest enantioselectivity of 28% ee for the *cis*-7 and 14% ee for the *trans*-7 was observed as assayed by chiral HPLC.[9] Higher yields and enantioselectivities were obtained employing iodosylbenzene as terminal oxidant in acetonitrile. In this case a 70% ee was observed for the *cis*-diol 7, whereas a very modest 25% ee was obtained for the *trans*-diol 7. As the α,β-dihydroxy pyrrolidines/piperidines can be considered interesting intermediates at the same level of the α-methoxy-β-

hydroxy analogues, dihydroxylations with OsO_4, as well as the Sharpless catalytic asymmetric dihydroxylation (AD),[10] were also carried out (Table, entries 5 and 6). Yields were very good in both experiments (90%), although AD provided diols 7 with low enantioselectivities (25% ee).

We also sought to apply the differential oxidation of enecarbamates to the synthesis of the amino acids β-hydroxyprolines and β-hydroxypipecolic acids as described in Scheme 2.



Key: a) *m*-CPBA, CH_3OH, $NaHCO_3$, CH_2Cl_2; b) Ac_2O, pyr, 75 °C, 15 h; c) TMSCN, BF_3-OEt_2, CH_2Cl_2; d) chromatographic separation (SiO_2); e) HCl 6M, reflux, 17 h, then ion-exchange chromatography (DOWEX 50X8).

Scheme 2. Synthesis of β-Hydroxyprolines and β-Hydroxypipecolic Acids.

Enecarbamate **1** was oxidized with *m*-CPBA to provide a mixture of *cis* and *trans* α-methoxy-β-hydroxy-pyrrolidines **3**. These were then acylated (Ac_2O) followed by exchange of the α-methoxy group for a cyano group using Wistrand's protocol (TMSCN, $BF_3 \cdot OEt_2$) to give the known α-cyano-β-acetoxy-pyrrolidines **5a/5b**[11] (cis:trans; 1:1.3) in 79% yield for the two steps. The *cis* and *trans* α-cyano-β-acetoxy-pyrrolidines were then separated by column chromatography and hydrolyzed in refluxing HCl 6M to provide the corresponding *cis*-hydroxyproline (**8a**, 90% yield) and the *trans*-hydroxyproline (**8b**, 80% yield) after ion-exchange chromatography.[11,12] Synthesis of the *trans*-β-acetoxy-α-cyano pyrrolidine (**5a**) directly from enecarbamate **1** (Table, entry 4, overall yield of 65%, after acylation) can possibly make the synthesis of *trans*-hydroxyproline (**8b**) more straightforward, although we did not carry out this transformation in this study.

To obtain the hydroxypipecolic acids **10**, the same sequence was applied to the 6-membered endocyclic enecarbamate **2** (Scheme 2, right side). However, contrary to the pyrrolidine series, the cis/trans mixture of α-cyano piperidines **9** could not be properly separated by chromatography. Thus, the mixture α-cyano-β-acetoxy-piperidines **9** was hydrolyzed with HCl 6M to afford a mixture of hydroxypipecolic acids as a fine powder after ion-exchange chromatography. At this point a fortuitous observation made possible the separation of the two stereoisomers: recrystallization of the mixture from EtOH-H_2O afforded only one of the stereoisomers as crystals, whereas the other stereoisomer remained in solution in diastereomeric enriched form.

Structural assignment for the stereoisomeric hydroxypipecolic acids **10a** and **10b** was surprisingly confusing. The ^1H NMR spectroscopic data reported by Gênet[13a] for the "first" synthesis of the *trans*-β-hydroxypipecolic acid (**10b**) were almost identical to those described before by Rapoport[12b] (~0.2 ppm difference), but Rapoport's β-hydroxypipecolic acid is generally assumed as the *cis* stereoisomer **10a**![13a,b] On the other hand, the ^1H NMR data reported by Nozoe[5d] for the *cis*-β-hydroxypipecolic acid **10a** were quite

distinct from those described by Rapoport. In order to solve this apparent conflict we obtained an X-ray of the crystalline β-hydroxypipecolic acid, for which the available spectroscopic data were identical to that prepared by Rapoport and Gênet. X-Ray crystal analysis (Figure 1) confirmed the compound as the *trans*-β-hydroxypipecolic acid (**10b**).[14] Thus, the crystalline compound obtained by us was actually the *trans*-β-hydroxypipecolic acid, and the isomer that remained in solution was mainly the *cis*-β-hydroxypipecolic acid.[5d,15]

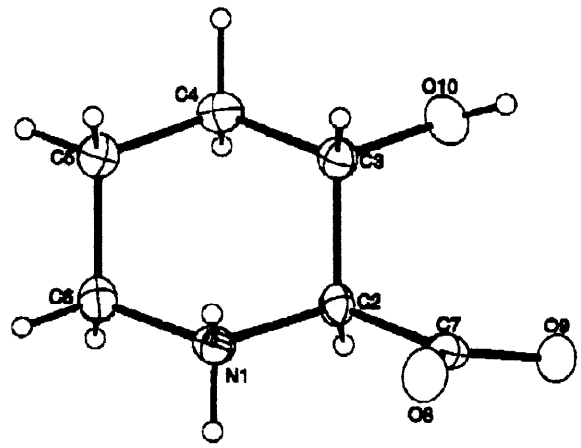


Figure 1. trans 3-hydroxypipecolic acid ORTEP drawing

In summary, endocyclic enecarbamates proved to be useful constructing units for the synthesis of β-hydroxyprolines and β-hydroxypipecolic acids by differential oxidation of their enaminic double bond. The oxidation process can be made enantioselective, which opens up the opportunity to obtain these amino acids in enantiomeric enriched form.

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References and Notes

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8. Epoxidation under Jacobsen's protocol (CH_2Cl_2/NaOCl solution, pH = 10) led mainly to an acyclic α-hydroxy-aldehyde.
9. Enantiomeric excess of diols **7** was evaluated by comparing its chromatogram (Chiralcel-OD, 5,8% isopropanol/hexane; 0.5 mL/min) with that obtained for a diastereomeric (racemic) mixture of the diols (diastereomeric ratio determined by ^{1}H NMR at 60 °C, of diacetates). Retention times for (±)-diols **7**: *cis*-diols (13.58 and 18.98 min.); *trans*-diols (16.30 and 22.50 min.).
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14. What actually happened in this episode was a misfortune. Rapoport prepared both diastereomers of β-hydroxypipecolic acid in enantiopure form (ref. 12b). However, for whatever reason, only the data concerning the *trans* (2R,3R) stereoisomer got included in the experimental section. It seems that since Rapoport's graphical representations were focused on the *cis* stereoisomers (page 1868, ref 12b), some authors mistakenly assumed that the reported data were for the *cis* stereoisomer.
15. Selected spectroscopic data: **RMN ^{1}H** (300 MHz, δ); **5b** (333K, $CDCl_3$): 5.40 (d, J=4.5 Hz, 1H), 4.55 (bs, 1H), 3.78 (s, 3H), 3.76-3.53 (m, 2H), 2.45-2.32 (m, 1H), 2.24-2.07 (m, 1H), 2.06 (s, 3H); **8b** (D_2O): 4.48 (m, 1H), 3.88 (bs, 1H), 3.45-3.25 (m, 2H), 1.88-1.81 (m, 2H); **8a** (D_2O): 4.51 (ddd, J=4.0; 4.0; 1.4 Hz, 1H), 3.95 (d, J=4.0 Hz, 1H), 3.40 (m, 1H), 3.30 (m, 1H), 2.00 (m, 1H), 1.93 (m, 1H); **10b** (D_2O): 3.96 (ddd, J=7.0; 7.0; 3.0 Hz, 1H), 3.41 (d, J=7.0 Hz, 1H), 3.19-3.11 (m, 1H), 2.92-2.85 (m, 1H), 1.85-1.69 (m, 2H), 1.57-1.46 (m, 2H); **RMN ^{13}C** (75 MHz, δ); **8b** (D_2O): 171.19, 73.40, 68.48, 43.72, 31.01; **8a** (D_2O): 170.19, 70.42, 67.09, 43.34, 32.76; **10b** (D_2O): 171.50, 65.40, 61.46, 41.94, 27.68, 17.85; **10a** (D_2O):169.95, 63.40, 60.10, 43.44, 28.71, 15.38.