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Reductive Cyanation : A Key Step For A Short Synthesis Of (-)-(2*S*,3*S*)-3-Hydroxyproline

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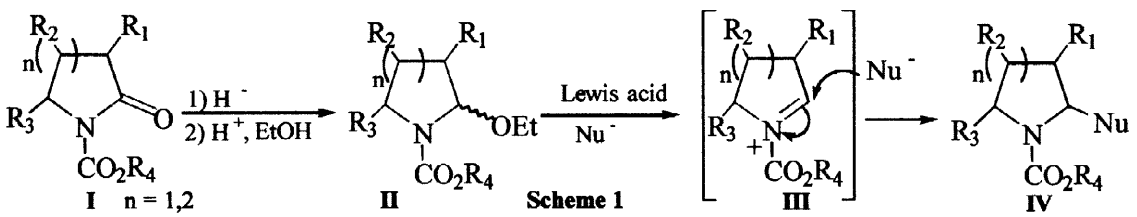
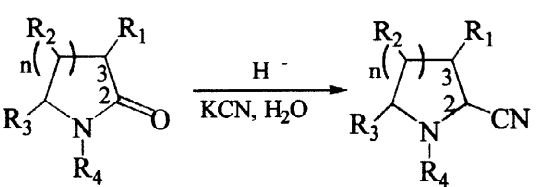
Abstract : A short stereoselective synthesis of (-)-(2*S*,3*S*)-3-hydroxyproline has been realized from L-malic acid as the source of chirality. The key step was the reductive cyanation of the intermediate **1a**, in high stereoselectivity and yield.

Reactions involving acyliminium intermediates are important tools for the functionalization of lactames and derivatives such as **I** (scheme 1)[1].



I n = 1,2 **II** **Scheme 1** **III** **IV**

The reaction generates the nitrogen stabilized cation **III** which readily reacts with different nucleophiles to lead to the functionalized product **IV** in 3 steps from **I**. As the reaction is regio and stereoselective, it was applied to the synthesis of various natural products such as alkaloids. The use of TMSCN as nucleophile provided efficient routes to α-aminoacids[1d-g]. Alternatively, the direct reductive cyanation[2] of cyclic amides such as **1**, in one step, has been less used (scheme 2).



1 n = 1,2 **Scheme 2** **2**

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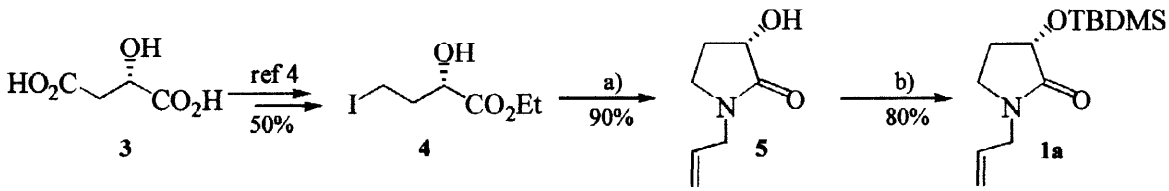
To our knowledge, only two examples of the reductive cyanation applied on 6-membered rings (n = 2), have been described[2e-f] and only one stereoselective study[2d] involves a 5-membered ring (n = 1) with an excellent diastereoselectivity in the former case but a rather low selectivity in the latter.

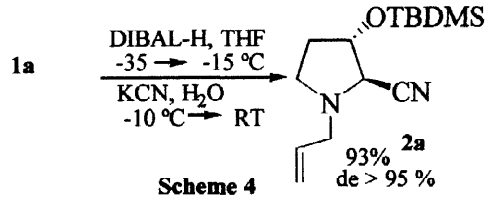
In connection with our work on cyclic peptides syntheses, we thought using the reductive cyanation reaction for the synthesis of (-)-(2*S*,3*S*)-3-hydroxyproline, a uncommon β-hydroxy-α-aminoacid found in collagen hydrolysates[3a] and in biologically active peptides such as mucronin D[3b-c] or the antibiotic telomycin[3d]. As the syntheses described so far in the literature[3e, 1c] are long and tedious, the selective reductive cyanation as the key step would shorten the preparation of (-)-(2*S*,3*S*)-3-hydroxyproline, and thus improve the efficiency of the synthesis. Based on the previous works of Rapoport[2f] and Heathcock[2e] on 6-membered rings, we thought that the reaction applied in the case of a 5-membered ring could be diastereoselective if a bulky group were introduced at C-3 to control the diastereoselectivity at C-2. We thus prepared the cylic key intermediate **1a** (scheme 3).



a) CH_2=$CHCH_2NH_2$, THF, RT b) TBDMSCl, Imidazole, DMF, RT

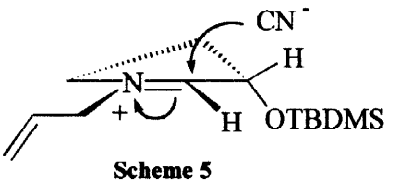
Scheme 3

L-malic acid **3** was used as the source of chirality and was converted into ethyl (2*R*)-2-hydroxy-4-iodobutanoate **4** following a known procedure[4]. Cyclisation using allylamine gave the lactame **5**, the hydroxyl group was then protected as a *t*-butyldimethylsilyl ether, a group known to induce good stereoselectivities in reactions involving acyliminium intermediates[1d]. The key lactame **1a** was thus obtained in 36 % overall yield from L-malic acid. The reductive cyanation of the compound **1a** was then studied (scheme 4). When a nucleophilic hydride such as $LiAlH_4$ was used as the reductive agent[2d], a mixture of the expected compound **2a** and over reduction byproducts was obtained, as already observed[2a-b]. The Lewis acid hydride DIBAL-H[2c] was found to be the most efficient in the reduction of our substrate. When **1a** was treated with DIBAL-H at low temperature for 2.5 h and the mixture reacted with a 4.2M solution of KCN in water, the desired *trans* nitrile **2a** was obtained in 93% isolated yield. The *cis* isomer was not detected by NMR techniques (de>95 %).



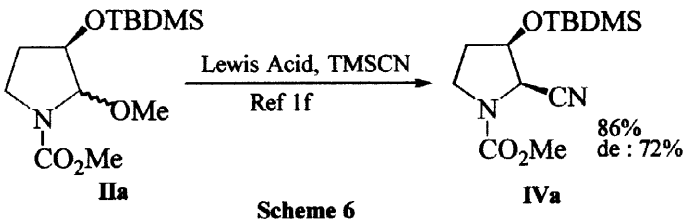
Scheme 4

As an iminium has been postulated to be an intermediate in the reductive cyanation process[2f], our result could therefore be rationalized by an attack of the iminium on its less hindered face (scheme 5).



Scheme 5

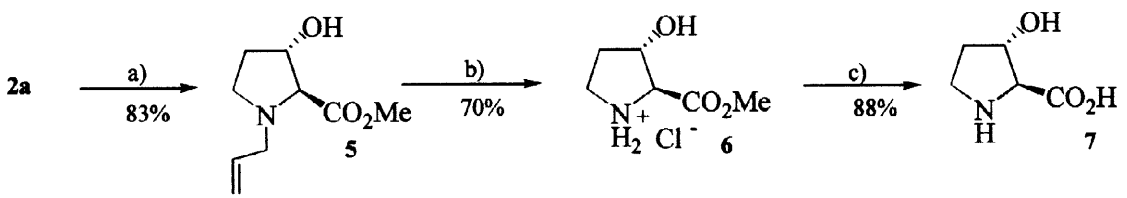
This result is in sharp contrast with the work of Wistrand and coll[1f] (scheme 6). By treatment of the substrate **IIa** with a Lewis acid, the acyliminium was generated and reacted with TMSCN to lead to the *cis* isomer **IVa** in 72% de. This behaviour suggests that the mechanism of the acyliminium substitution proceeds through a pathway different[7] from that of the reductive cyanation process.



IIa **IVa**

Scheme 6

Thus, we have performed an efficient method for the preparation of the *trans* (2*R*,3*S*)-1-allyl-2-cyano-3-*t*-butyldimethylsilyloxypyrrolidine **2a**[8] in excellent diastereoselectivity. Furthermore, this *trans* isomer could not be obtained at a preparative scale by using acyliminium intermediates[1f]. It was then efficiently converted into (-)-(2*S*,3*S*)-3-hydroxyproline (scheme 7).



a) i) HCl, MeOH, -20 °C ii) Amberlyst 15, MeOH, 65 °C b) i) $Pd(dba)_2$, Dppb, mercaptobenzoic acid, THF, RT ii) 1M HCl c) KOH, MeOH, H_2O, RT

Scheme 7

The nitrile **2a** was hydrolyzed[5a] and the hydroxyl group deprotected by using a saturated solution of dry HCl in MeOH at -20 °C. Other procedures (higher temperature, use of aqueous 12N HCl) resulted in the epimerisation of the nitrile to the *cis* isomer. As the reaction led to the primary amide intermediate instead of the expected ester, a two steps procedure was necessary. Treatment of the crude amide with Amberlyst 15 ion-exchange resin, in MeOH at 65 °C[5b], led to the clean conversion of the amide to the methyl ester **5** without any epimerisation. The allyl group was finally removed using Genêt's procedure[6] to afford **6** ($[\alpha]_D^{25}$ = +11 (c = 1.02 MeOH), mp = 170 °C). This deprotection must be carried out at room temperature because of the ester

epimerisation at 50 °C. Note that the compound **2a** did not react under Genêt's conditions. Saponification of **6** led to (-)-(2*S*,3*S*)-3-hydroxyproline **7** which was purified by ion-exchange chromatography (Dowex 50W) and recrystallisation from EtOH, H_2O ($[\alpha]_D^{25}$ = -18.3 (c = 0.9 H_2O), mp = 230-236 °C (decomp.); lit.[3f] $[\alpha]_D^{20}$ = -18.8 (c = 0.14 H_2O), mp = 232 °C).

In conclusion, we have performed an efficient synthesis of (-)-(2*S*,3*S*)-3-hydroxyproline from L-malic acid. We have shown that the reductive cyanation procedure was stereospecific in the case of the 5-membered ring **1a**. This reaction could therefore be a useful tool for enantiospecific syntheses of natural products.

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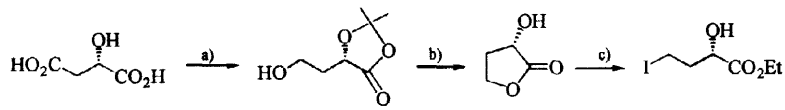
4. Trybulski E.J., Kramss R.H., Mangano R.M., Brabander H.J., Francisco G., *Bioorg. and Med. Chem. Lett.*, **1992**, *2*, 827-832. The synthesis is described as follows :



a) i) $(MeO)_2CMe_2$, ii) BH_3DMS b) CF_3CO_2H c) TMSI, EtOH

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7. For a discussion about the mechanism of the acyliminium substitution, see ref 1d.

8. (2*R*,3*S*)-1-allyl-2-cyano-3-*t*-butyldimethylsilyloxypyrrolidine **2a** : To a solution of (3*S*)-1-allyl-3-*t*-butyldimethylsilyl-oxypyrrolidin-2-one **1a** (2.9g, 11.37 mmol) in THF (11mL), was added a solution of DIBAL-H 1M in hexanes (14.22 mL, 14.22 mmol), at -35°C. The reaction was stirred for 2h30 and the temperature was allowed to increase to -15°C. A solution of KCN (3g, 46.15 mmol) in water (11mL) was then added over 1 min. The reaction was vigorously stirred for 1h and the temperature was allowed to return to RT. The mixture then solidified. It was diluted with ether and water. The solution was extracted with Et_2O, AcOEt; the organic phase was dried ($MgSO_4$), filtered through celite and evaporated to afford 2.8 g (93%) of the pure pyrrolidine (de > 95%). $[\alpha]_D^{25}$ = -7 (c = 1.3 MeOH). ^{1}H-NMR ($CDCl_3$) : 6.00-5.80 (m, 1H); 5.36-5.16 (m, 2H); 4.56 (dt, ^3J = 7.1 Hz, ^3J = 3 Hz, 1H); 3.46 (d, ^3J = 2.5 Hz, 1H); 3.44 (ddt, ^3J = 13.3 Hz, ^3J = 5.7 Hz, ^3J = 1.4 Hz, 1H); 3.11 (dd, ^3J = 13.3 Hz, ^3J = 7.3 Hz, 1H); 2.93-2.68 (m, 2H); 2.33-2.16 (m, 1H); 1.87-1.71 (m, 1H); 0.90 (s, 9H); 0.12 (s, 3H); 0.11 (s 3H). ^{13}C-NMR ($CDCl_3$) : 133.78 (d); 118.37 (t); 117.31 (s); 76.26 (d); 62.03 (d); 55.87 (t); 50.66 (t); 33.98 (t); 25.50 (q); 17.79 (s); -5.075 (q, 2C). IR (NaCl pellets) : 2959; 2931; 2860; 2811; 1644; 1475; 1370; 1250; 1117; 850.