[A0038]

4,5-Disubstituted Pyrrolidin-2-ones starting from D-Xylose

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Introduction

Several non-proteinogenic amino acids containing the pyrrolidine ring show high affinity towards NMDA (N-methyl-D-aspartic acid) and glutamate receptors. Thus, they can be employed in order to establish the mechanisms involved in transmission of nerve impulse. Moreover, they can be used for treatmentment of CNS diseases. Among them, 2-carboxy-3-pyrrolidinacetic acid (CPAA), **1**, and the diastereomeric 2-carboxy-4-(2-methoxyphenyl)-3-pyrrolidineacetic acids **2** and **3** are significant examples. [1-11]
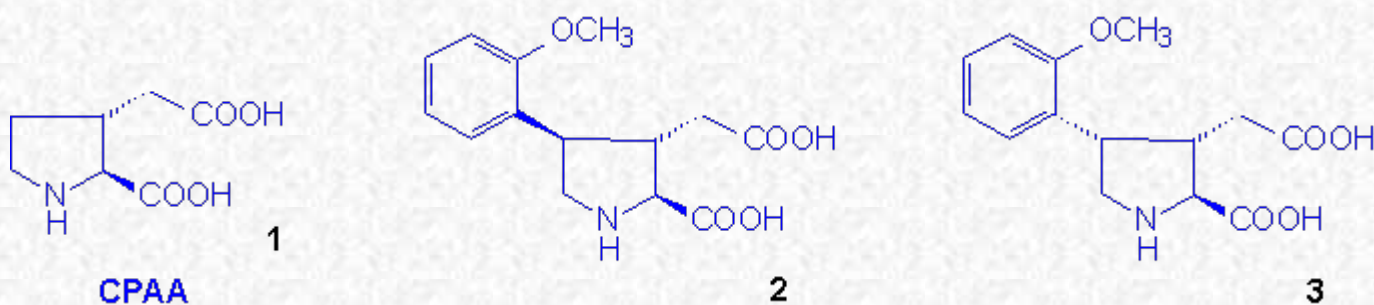
In particular, compound **1** is highly effective towards NMDA receptors, whereas **3** shows activity higher than kainic acid.

Results and discussion

We devised that D-Xylose **9** could be a useful starting material for a new synthetic approach to these amino acids in the enantiomerically pure form.[12] The synthesis we planned proceeds according the reported retrosynthetic scheme, through the formation of the chiral pyrrolidin-2-one **5** which, by removal of the carbonyl group carried out according literature methods, can be eventually converted into the pyrrolidine ring.
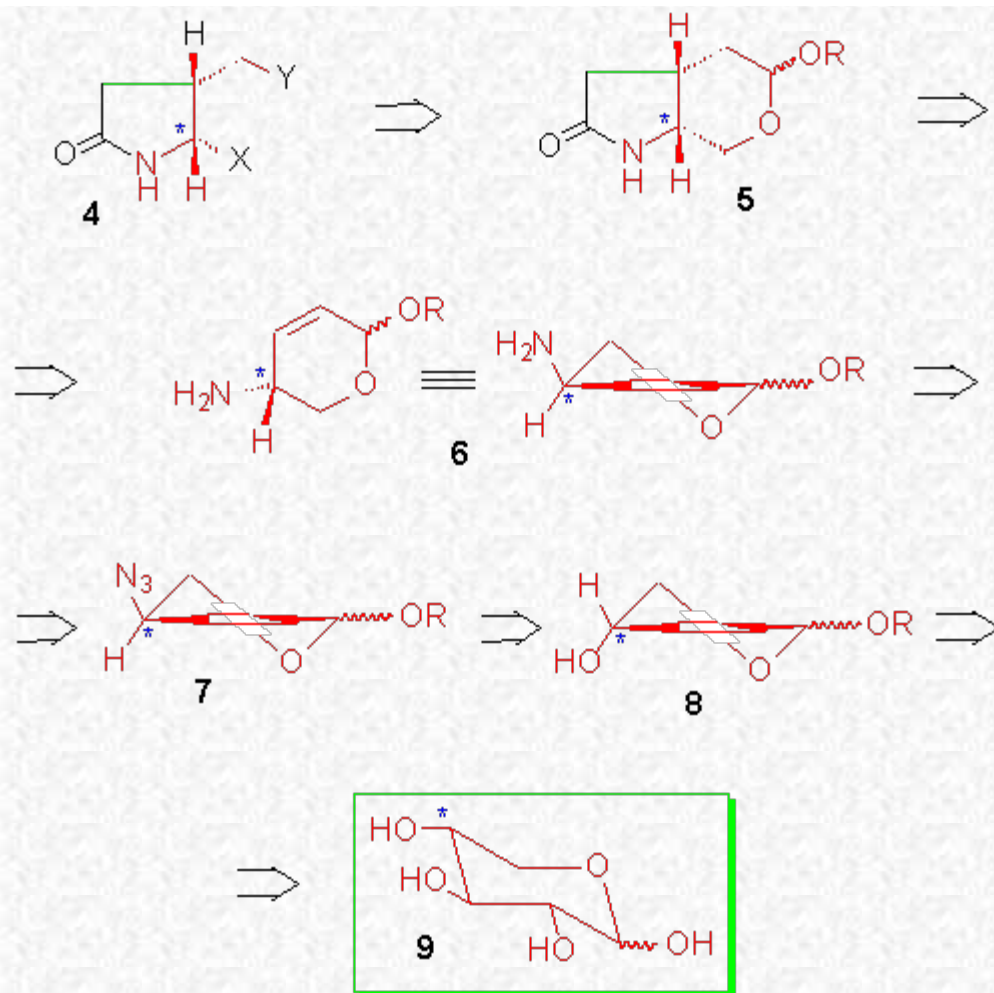
A further challenge relies on the concavity of compound **5**. In fact, alkylation at the a-position with respect to the carbonyl results to be stereoselective, leading to the *exo*-alkylated derivative.

Thus, starting from di-*O*-acetyl-D-xylal, **10**, the anomeric 2-pentenopyranosides **11** and **12** were prepared by using a modified Ferrier reaction. [13-14]
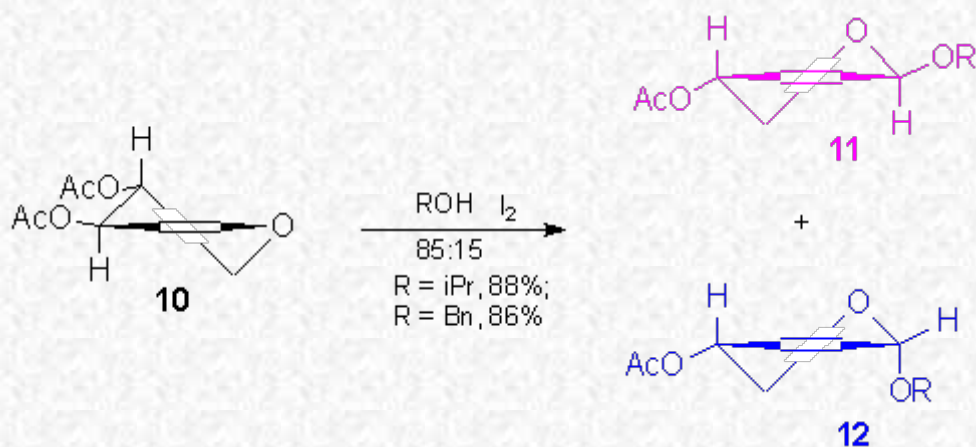

The anomeric mixture was separated by flash chromatography and the configuration of products was assigned of by ^{1}H NMR. The major anomer, **11**,was then converted into the azidoderivative **14** and subsequently into the corresponding amine, **15**.[15]

11

IRA 900
azide form

refluxing
benzene
92%

14

LiAlH$_4$

THF
86%

15
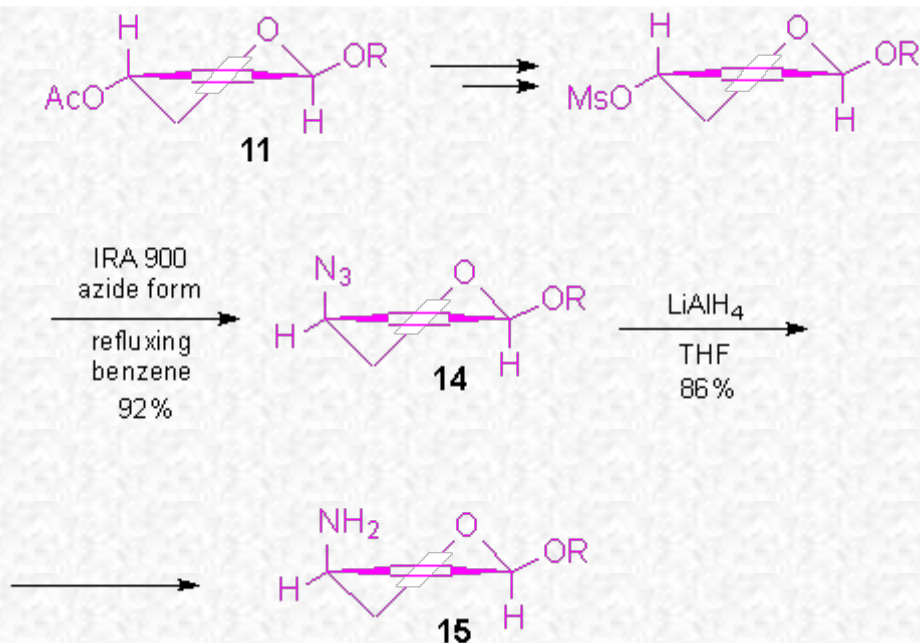
In order to obtain the bicyclic system 18, the amine **15** was acylated with chloroacetyl chloride and then chloroacetamide **16** was converted into iodoacetamide **17**. Eventually, by treating with Bu$_3$SnH, the bicyclic lactam **18** was isolated in moderate yield.

15

74%

16

NaI

acetone
78%

17

Bu$_3$SnH
ABIN

refluxing
benzene
62%

18
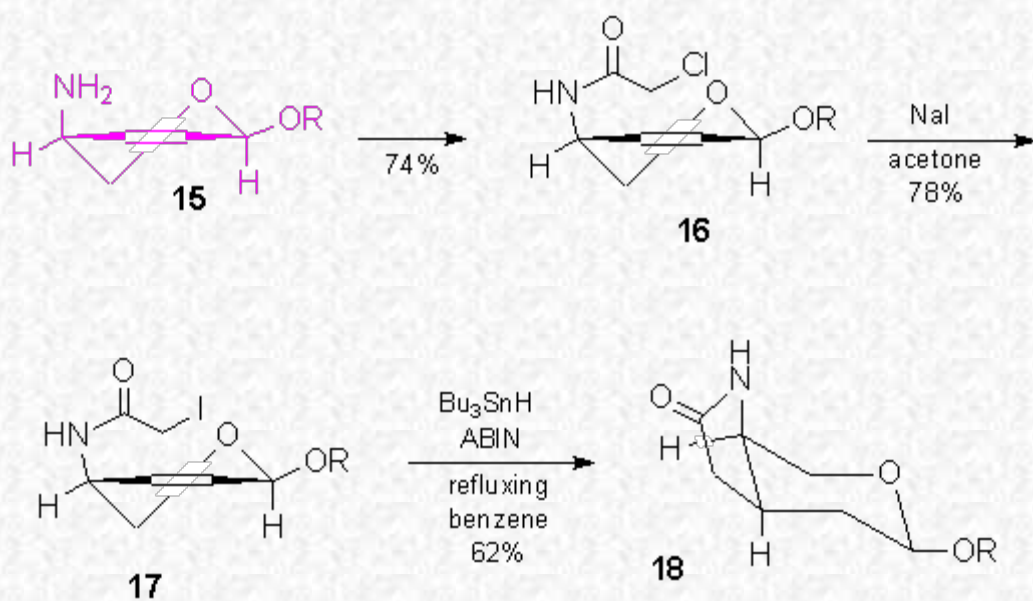
On the contrary, when 4-azido derivative was prepared starting from the minor anomer, **12**, a surprising result was observed. In fact, the corresponding 4-mesyl derivative **19** was prepared, but the nucleophilic substitution, carried out under different conditions (IRA 900 in the azide form in refluxing benzene, NaN$_3$ in DMF at 80 °C, diphenylphosphoryl azide) invariably led to two products, the minor component of the mixture, **20**, arising from a S$_N$2 pathway, as determined on the basis of ^{1}H NMR data.[16] In fact, as it resulted from ^{1}H NMR spectrum and n.O.e. experiments, the major product of the reaction was the 2-azidoderivative **21**, which formed by a S$_N$2' pathway.
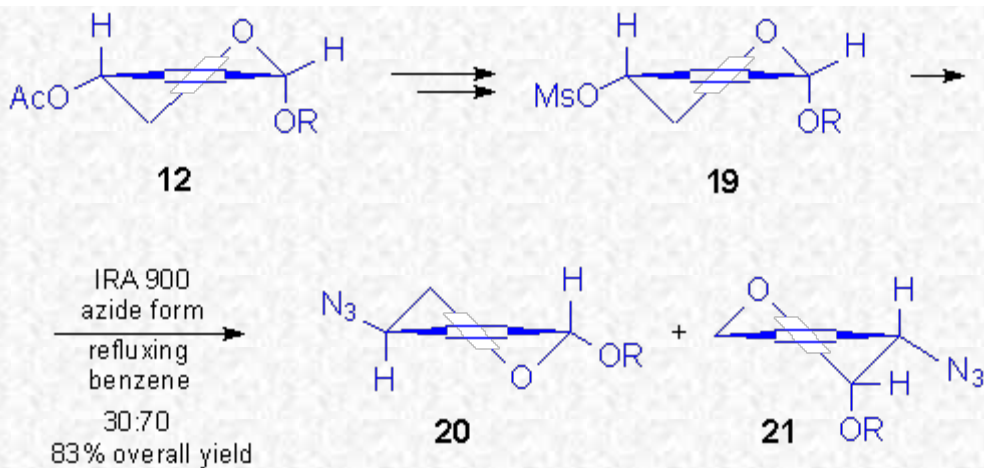
With the aim to check the observed effect, the same reaction sequence was carried out starting from benzyl a-2-pentenopyranoside **22**, and a mixture of azides **24** and **25** was obtained, in 78% overall yield and 30:70 ratio.
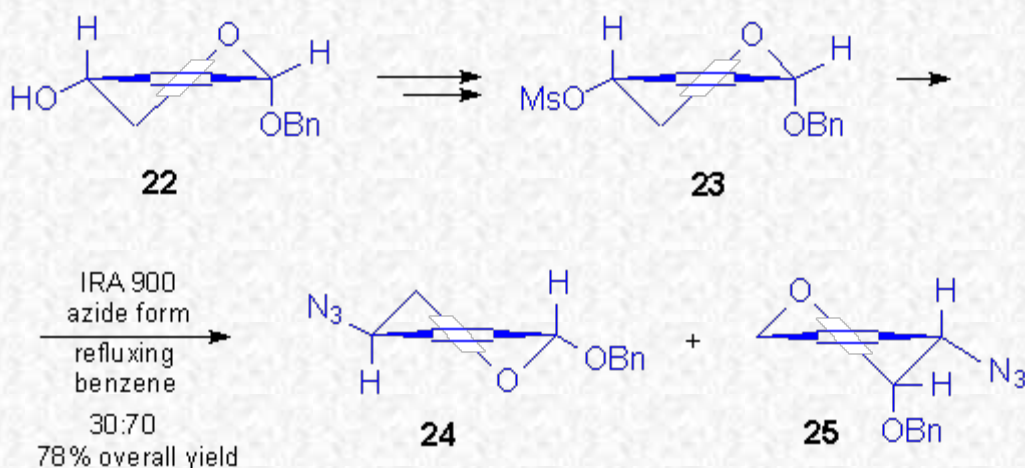

The same effect, which was tentatively ascribed to the configuration of the anomeric carbon, was observed when the same reaction was carried out starting from mesyl derivative **26** prepared starting from methyl a-D-2-hexenopyranosides. In fact, an equimolar mixture of azides **27** and **28** was obtained in good yield, whose configuration was assigned by ^{1}H NMR data, and the substitution process was unaffected even on changing both the reaction conditions and the protecting group at 6-OH.
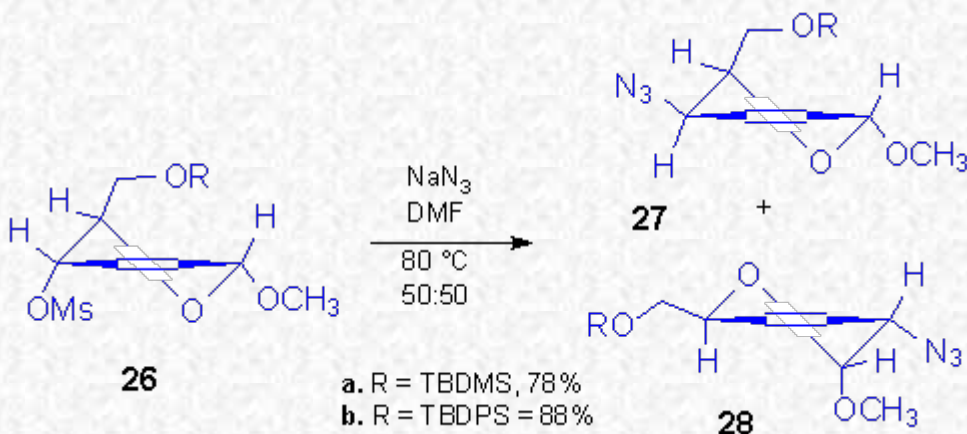

Allo scopo di spiegare il comportamento dell'anomero a nel corso della reazione di sostituzione del gruppo mesile da parte del gruppo azide, si sono calcolate in via preliminare le energie degli stati di transizione della reazione S_N2 e S_N2' per gli anomeri a e b.

Le strutture degli stati di transizione sono state localizzate ed ottimizzate a livello RHF/3-21G* e su tali geometrie e stato condotto un calcolo singolo (single point) a livello B3LYP/3-21G* per tener conto della correlazione elettronica. [17-20]

a-S_N2 E = -1284.24246521 u.a. i.f.: -299.86 cm^{-1} a-S_N2' E = -1284.24706417 u.a. i.f.: -281.88 cm^{-1}
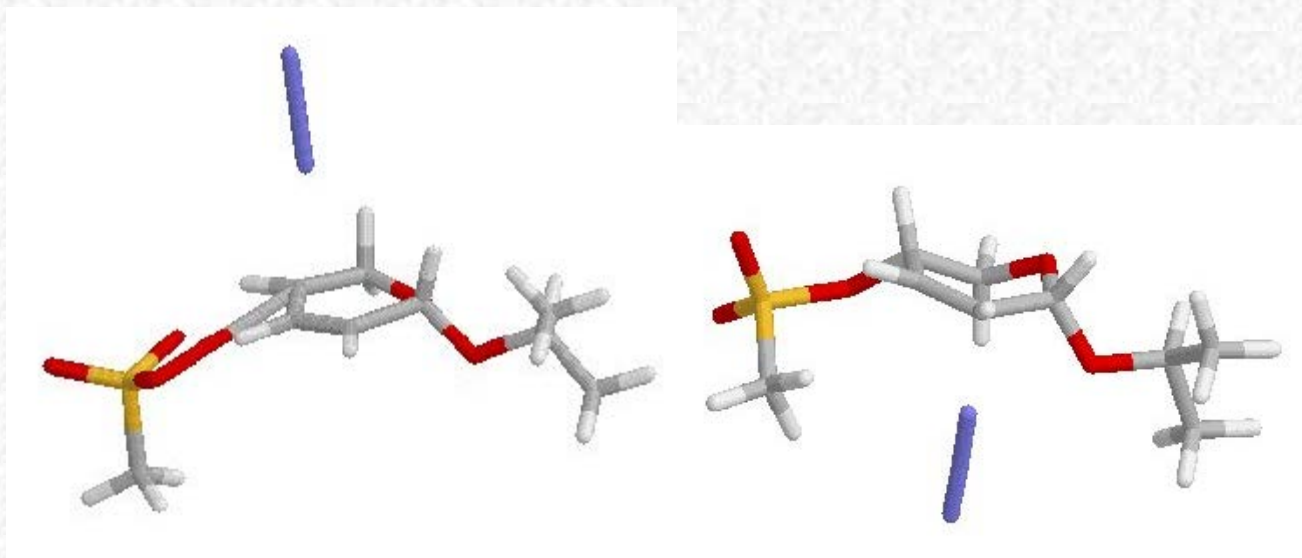
b-S_N2 E = -1284.24759963 u.a. i.f.: -323.57 cm^{-1}; b-S_N2' E = -1284.2679714 u.a. i.f.: -218.0 cm^{-1}
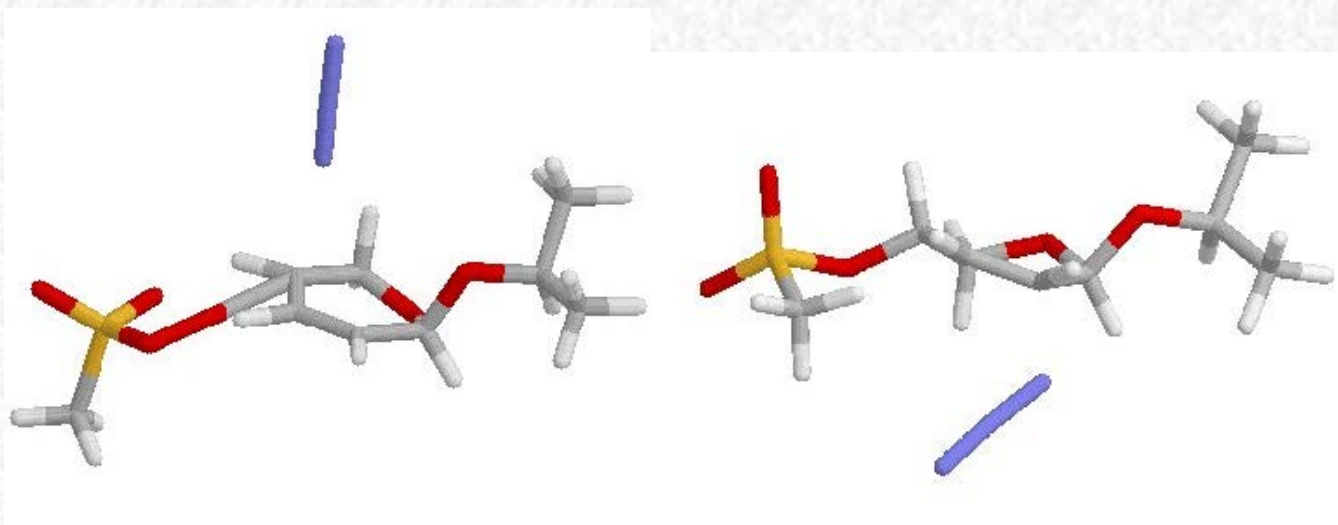
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