SYNTHESIS OF A PERHYDROINDOLIC ANALOG OF KAINIC ACID

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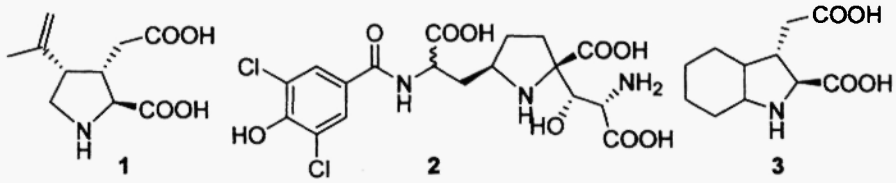
Abstract : Synthesis of perhydroindolyl-2-carboxy-3-acetic acid, a strained analog of kainic acid, is described. This compound was obtained in 7 steps by the use of the Barco procedure from nitrocyclohexene.

Introduction

In the recent years there has been a growing interest in the L-glutamate receptors in the central nervous system. This neurotransmitter plays a role of utmost importance in many physiological processes such as neuronal plasticity, memory and learning (1) but an excessive L-glutamate release can result in neuronal cell death by excitotocity.

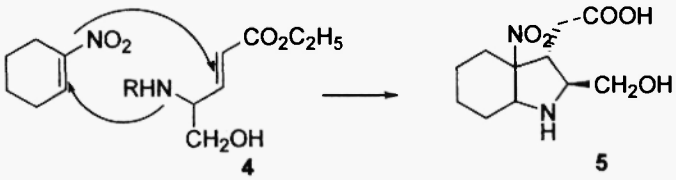
Among the different sub-types of receptors of L-glutamate (AMPA, kainic acid, MNDA, metabotropic) (2) kainic acid **1** is an agonist of kainic acid receptor and kaitocephalin **2** (3) is an antagonist but the selectivity is low and these compounds have affinity in particular for the AMPA receptor.



With the aim to obtain a selective affinity for the kainic acid receptor, we had projected to synthesize the analog **3** of kainic acid.

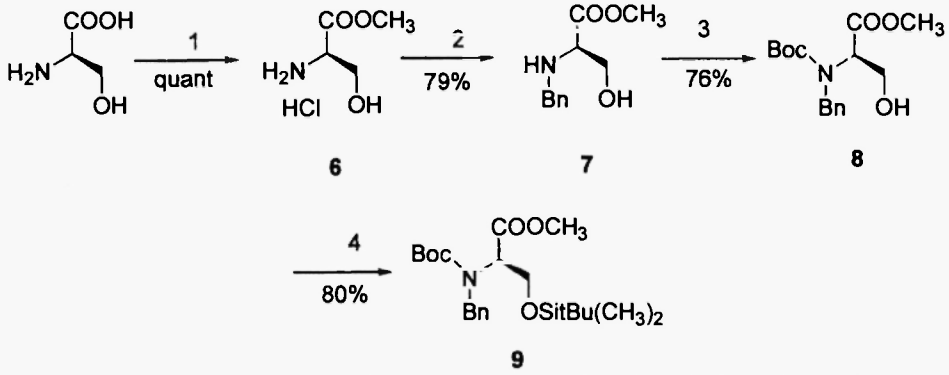
Result and discussion :

The precursor **5** of **4** is obtained by the use of Barco's process (4) with two Michael reactions with 1-nitro-cyclohexene and the amino-alcohol-ester **4**. Some chemical modifications of **5** give **3**.



-Synthesis of the amino-alcohol-ester 4

The ester **4** was obtained from serine in seven steps.

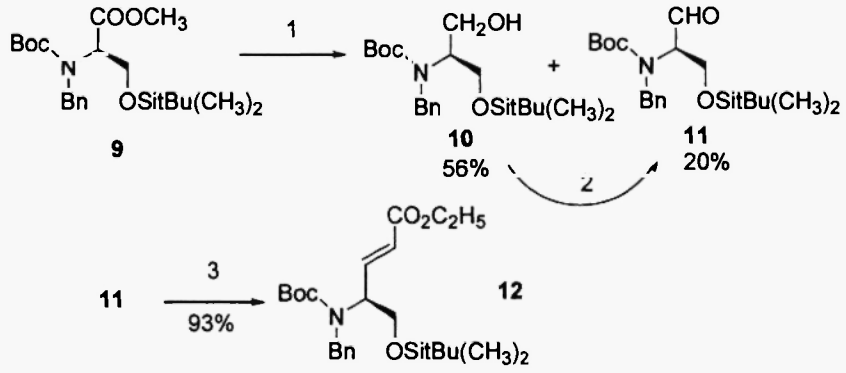


Scheme 1 – 1- CH_3OH, CH_3COCl, 0°C, then reflux for 3h. 2- a- Et_3N, C_6H_5CHO –b- $NaBH_4$. 3- $(Boc)_2O$, Et_3N, THF. 4- TBDMSiCl, Et_3N, DMAP, CH_2Cl_2.

D-serine gave the ester **6** as hydrochloride quantitatively. After reductive alkylation (PhCHO-$NaBH_4$) the secondary amine **7** was transformed in the carbamate **8** and then alcohol function was protected as silyl ether **9**.

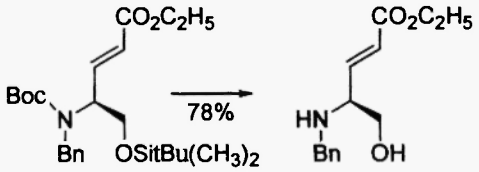
To obtain aldehyde function, ester **9** was reduced in alcohol by the use of lithium aluminium hydride at -50°C and then oxidized in aldehyde by the Swern reaction. During the reduction step a few quantity of aldehyde **11** was isolated.

The aldehyde **11** was not purified and directly reacted with (carboethoxymethylene) triphenylphosphorane to give **12** (trans isomer) in a good yield.



Scheme 2 – 1- $LiAlH_4$, THF. 2- Et_3N, DMSO, $(COCl)_2$. 3- $(C_6H_5)_3PCHCO_2C_2H_5$, CH_2Cl_2.

The aldehyde obtained during the reduction step gave **12** to increase yield. Thus **12** was obtained with a good yield (93% from **9**). At last, the protective group was cleaved with trifluoroacetic acid to give **4**.



12 **4**

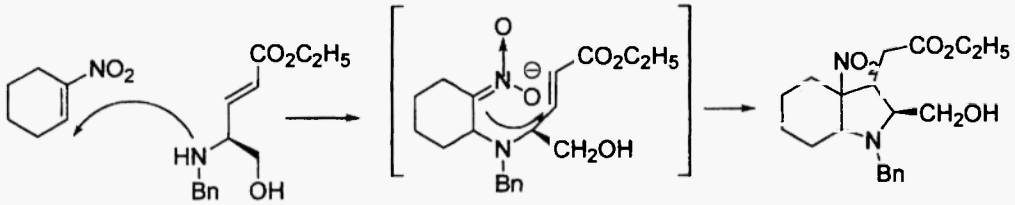
Scheme 3 – CF_3CO_2H, CH_2Cl_2

The global yield of the synthesis of **4** from serine in 7 steps was 24%.

-Condensation of 4 with 1-nitrocyclohexane.

Nitrocyclohexene and **4** were stirred for seven days at room temperature. After this time, **13** was obtained with a 65% yield. All modifications of these conditions (time, temperature, solvent....) lead to low yields.

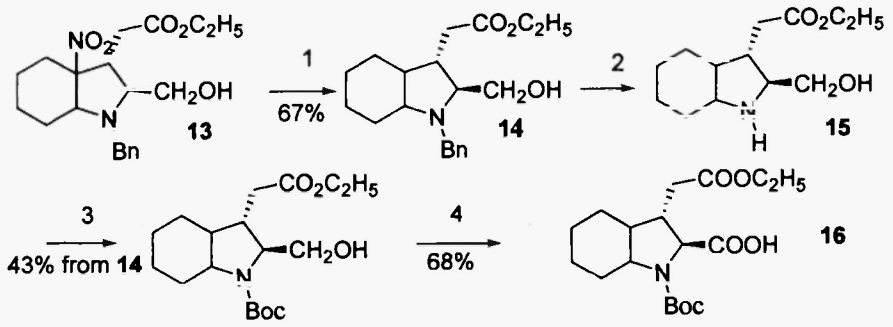
This reaction is a double-Michael addition:



The nitro group was eliminated by reflux into toluene with tributyltin hydride in the presence of catalytic quantity of AIBN to give **14**.

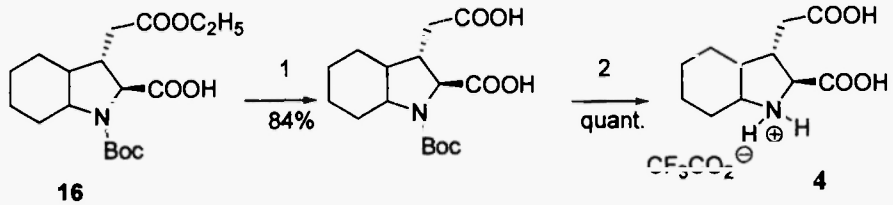
Debenzylation succeeded with Pd-C 5% in alcohol under hydrogen pressure (25 bars) on the condition that one or two drops of 10% hydrochloric acid be added. In the absence of acid no reaction took place.

It's known that in case of amino-alcohol the amino group must be protected with *tert*-butoxycarbamate function during the oxidation of the alcohol function into acid (4,5); then, after debenzylation and protection of amine with *tert*-butoxycarbonyl group, the oxidation with PDC gave acid **16**.



Scheme 4 – 1-Bu_3SnH, AIBN, toluene, reflux. 2- H_2 25 bars, Pd.C, C_2H_5OH, HCl 10% 2 drops. 3- $(Boc)_2O$, Et_3N, THF. 4- PDC, CH_2Cl_2.

This acid-ester **16** was hydrolysed by LiOH and deprotected with trifluoroacetic acid.



Scheme 4- 1-LiOH, H_2O, THF. 2- CF_3CO_2H, CH_2Cl_2.

Conclusion

The compound **4** was obtained with a global yield of 11% from nitrocyclohexene. Now, we synthesize other compounds by this strategy and we have to test these ones with different L-glutamate sub-type receptors

Aknowledgements
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References

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(6) Analytical data **4**: yellow oil, ^{1}H-NMR ($CDCl_3$, 200MHz) δ (ppm) : 1.05-2.45 (m, 9H, H-3a and $(CH_2)_4$), 2.45-3.00 (m, 3H, H-3, CH_2CO_2), 3.80-4.50 (m, 2H, H-2 and H-7a), 10.16 and 12.01 (2s, 4H, 2 COOH, 2NH). MS (EI): 228 ($M^{+\cdot}$).

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