Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 7, pp. 1527-1530, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00190-5

Stereoselective Synthesis of 2-Aminoethyl Substituted Tricycles with NMDA Receptor Affinity

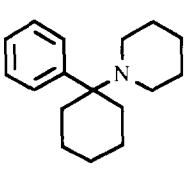
Bernhard Wünsch*, Heike Diekmann and Georg Höfner

Institut für Pharmazie und Lebensmittelchemie der Universität München,
Sophienstr. 10, D-80333 Munich, Germany

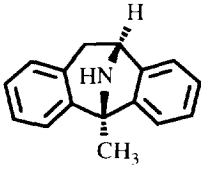
Abstract: In this paper the stereoselective synthesis of the novel noncompetitive NMDA antagonist **15** with a k_i value of 16.1 µM for the phencyclidine binding site is described. Key steps in the preparation of the tricycle **15** are the regio- and stereoselective formation of the acetal **7**, an intramolecular *Heck* reaction (**11** → **12**) and the stereoselective hydrogenation of the double bond of **12** to give **13**.

Five receptor subtypes for the excitatory neurotransmitter glutamic acid have been identified within the central nervous system of mammalians.[1] Among these glutamatergic receptors, the NMDA receptor named after the prototypic agonist *N-m*ethyl-*D-a*spartate has received the most attention because of its possible involvement in a variety of physiological functions such as learning, memory, control of respiration and blood pressure.[2] However an extensive release of glutamate entails an increased influx of calcium ions through the NMDA receptor associated ion channel which contributes to neural death. Thus, excitatory processes following NMDA receptor stimulation play an important role in the pathophysiology of epilepsy, in nerve cell death after ischemic or hypoxic insults, and, furthermore in the development of neurodegenerative disorders, e.g. Alzheimer's and Huntington's diseases.[3,4]

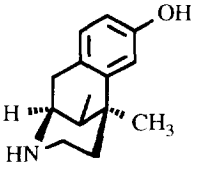
Scheme 1



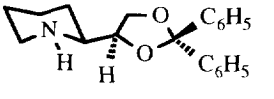
1 Phencyclidine



2 (+)-MK-801



3 (+)-Normetazocine



4 Dexoxadrol

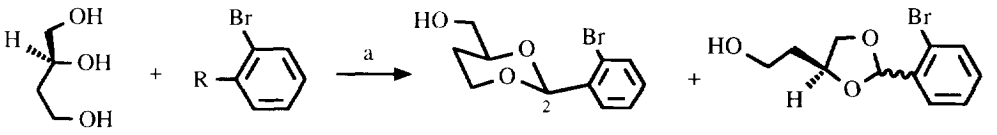
Therefore, compounds blocking the influx of calcium ions into the neuron are of interest because of their anticonvulsant and neuroprotective potential. Such a blockade may be achieved by

occupying the phencyclidine binding site within the ion channel of the NMDA receptor by noncompetitive NMDA antagonists. Typical representatives with high affinity for the phencyclidine binding site of the NMDA receptor are phencyclidine (**1**, k_i = 80 nM[5]), (+)-MK-801 (**2**, k_i = 2.9 nM[6]), the dextrorotatory benzomorphan derivative (+)-normetazocine (**3**, k_i = 30 nM[7]), and the 1,3-dioxolane dexoxadrol (**4**, k_i = 112 nM[5]).[4] The enantiomers of **2**, **3** and **4** exhibit much lower affinity.

With the intention to find novel NMDA antagonists we planned to combine the structural features of two noncompetitive NMDA antagonists - the tricyclic skeleton of (+)-normetazocine (**3**) and the acetal substructure of dexoxadrol (**4**). In this communication we describe the synthesis of the enantiomerically pure tricycle **15** via an intramolecular *Heck* reaction as key step as well as its affinity for the phencyclidine binding site of the NMDA receptor.

In the first step the 2-bromo substituted benzaldehyde **6a** should be condensed with the (S)-configurated butanetriol **5** to give the (1,3-dioxan-4-yl)methanol **7**. In contrast to the regioselective formation of a 1,3-dioxane by reaction of benzaldehyde with the butanetriol **5**[8] the acetalization of 2-bromobenzaldehyde (**6a**) with **5** furnished a 1 : 1 mixture of the regioisomeric acetals **7** and **8** (solvent toluene, 48 h, temperature 20°C or 110°C). However, the regioselectivity was considerably improved by employing the 2-bromobenzaldehyde dimethyl acetal (**6b**) instead of the benzaldehyde **6a**.[9] Thus, a ratio of 91 : 9 (**7** : **8**) was achieved by stirring equimolar amounts of **5** and **6b** in THF at room temperature with 80 % isolated yield of **7** after purification by flash chromatography.[10] Whereas the diastereomer of the six ring acetal **7** with (R)-configuration in position 2 could not be detected, the five ring acetal **8** was obtained as a 1 : 1 mixture of diastereomers.

Scheme 2



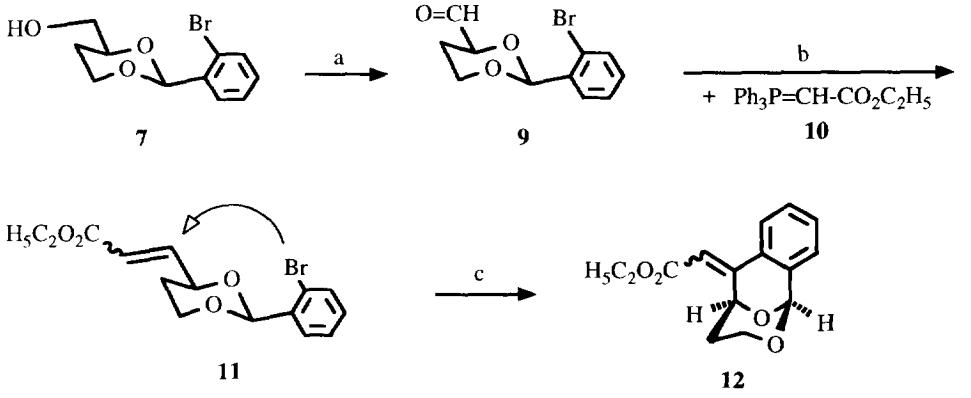
5 **6a**: R = CH=O **7** **8**

6b: R = $CH(OCH_3)_2$

(a) THF, p-toluenesulfonic acid, Mol.-sieve 4 A, 96 h, room temp., yield of **7**: 80 %.

Swern oxidation[11] of the primary alcohol **7** provided the aldehyde **9** which upon treatment with the *Wittig* reagent **10** yielded the α,β-unsaturated ester **11** [(E) : (Z) = 55 : 45]. Attempts to cyclize the α,β-unsaturated ester **11** (mixture of (E) and (Z) isomers) via an aryllithium intermediate (n-butyllithium) or an arylradical (Bu_3SnH) failed. However, the tricycle **12** was obtained on heating the aryl bromide **11** with $(Ph_3P)_4Pd$ in acetonitrile (intramolecular *Heck* reaction).[12] Whereas the transformation at 80°C was incomplete and led to a separable mixture of (E)-**12** and (Z)-**12**, raising the reaction temperature to 140°C resulted in complete transformation with (Z)-**12** as the only product, probably due to Pd catalyzed (E)/(Z)-isomerization.

Scheme 3

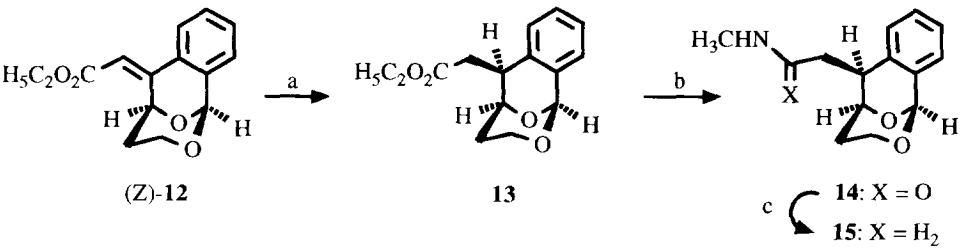


7 9 10 11 12

(a) $(COCl)_2$, DMSO, CH_2Cl_2, NEt_3, -60°C, 87 %.- (b) THF, 12 h, 25°C, 91 % [(E)-**11**: 37 %; (Z)-**11**: 36 %].- (c) $(Ph_3P)_4Pd$, CH_3CN, NEt_3, 48 h, 140°C, sealed tube, 73 %.-

Stereoselective double bond hydrogenation from the "backside" of the tricycle (Z)-**12** (re-re attack) furnished the tricyclic ester **13** with (S)-configuration of the new stereocenter in position 6. Aminolysis of the ester **13** with methylamine afforded the amide **14** which was reduced with $LiAlH_4$ to give the aminoethyl substituted tricycle **15**.

Scheme 4



(Z)-**12** **13**

(a) H_2, 1.3 bar, Pd/C, EtOAc, 2 h, 25°C, 87 %.- (b) CH_3NH_2, EtOH, 12 h, 25°C, 83 %.- (c) $LiAlH_4$, THF, 8 h, 25°C, 58 %.

The affinity of the methylamine **15** for the phencyclidine binding site of the NMDA receptor was investigated in competition experiments with tritiated (+)-MK-801 (**2**) as radioligand.[2,13] Thereby, a k_i value of 16.1 µM (± 3.6 µM) was found for the methylamine **15**. Now, we are going to prepare further analogues of **15** and to evaluate their affinity for the phencyclidine binding site of the NMDA receptor.

Acknowledgements: We wish to thank *Prof. Dr. Dr. h.c. F. Eiden* for his generous support. This project is supported by the *Fonds der Chemischen Industrie* and the *Deutsche Forschungsgemeinschaft.*

References and Notes

1) a) Herrling, P. L. *Drug Res.* **1992**, *42*, 202 - 208.- b) Johnson, G. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 9 - 14.

2) Wong, E. H. F.; Kemp, J. A. *Annu. Rev. Pharmakol. Toxikol.* **1991**, *31*, 401 - 425.

3) Yamada, K.; Nabeshima, T. *Drug News Persp.* **1991**, *4*, 524- 529.

4) Lodge, D. in Excitatory Amino Acid Receptors - Design of Agonists and Antagonists (Ed.: Krogsgaard-Larsen, P.; Hansen, J. J.), Ellis Horwood Ltd.: Chichester, **1992**, chapter 9, pp. 201 ff.

5) Thurkauf, A.; Mattson, M. V.; Richardson, S.; Mirsadeghi, S.; Ornstein, P. L.; Harrison, E. A.; Rice, K. C.; Jacobson, A. E.; Monn, J. A. *J. Med. Chem.* **1992**, *35*, 1323 - 1329.

6) Hays, S. J.; Nowak, P. M.; Ortwin, D. F. *J. Med. Chem.* **1993**, *36*, 654 - 670.

7) Carroll, F. I.; Abraham, P.; Parham, K.; Bai, X.; Zhang, X.; Brine, G. A.; Mascarello, S. W.; Martin, B. R.; May, E. L.; Sauss, C.; DiPaolo, L.; Wallace, P.; Walker, J. M.; Bowen, W.D. *J. Med. Chem.* **1992**, *35*, 2812 - 2818.

8) a) Hungerbühler, E.; Seebach, D.; Wasmuth, D. *Angew. Chem.* **1979**,*12*, 1025 - 1026.- b) Tsuri, T.; Kamata, S. *Tetrahedron Lett.* **1985**, *26*, 5195 - 5198- c) Hadvary, P.; Weller, T. *Helv. Chim. Acta* **1986**, *69*, 1862 - 1871.- d) Pawlak, J.; Nakanishi, K. *J. Org. Chem.* **1987**, *52*, 2896 - 2901.- e) Herradon, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191 - 194.

9) The regio- and diastereoselective formation of a six ring acetal by transacetalization of benzaldehyde dimethyl acetal with the triol **5** is reported: a) Isobe, M.; Ishikawa, Y., Bai, D.; Goto, T. *Tetrahedron Lett.* **1985**, *26*, 5203 - 5206.- b) Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 3101 - 3104.- c) Thiam, M.; Slassi, A.; Chastrette, F.; Amouroux, R. *Synth. Commun.* **1992**, *22*, 83 -95.

10) All new compounds gave satisfactory physical and analytical data.

11) a) Swern, D.; Huang, S. L.; Mancuso, A. J. *J. Org. Chem.* **1978**, *43*, 2480 - 2482.- b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651 - 1660.- c) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165 - 185.

12) a) deMeijere, A. *Angew. Chem.* **1994**, *106*, 2473 - 2506.- b) Overman, L. A. *Pure Appl. Chem.* **1994**, *66*, 1423 - 1430.

13) Information sheet "Drug Discovery System: Glutamate Receptor NMDA Subtype, Du Pont NEN".

(*Received in UK* 12 *May* 1995)