BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS
FACULTY OF CHEMICAL AND BIOENGINEERING
OLÁH GYÖRGY DOCTORAL SCHOOL

SYNTHESIS OF GALANTHAMINE DERIVATIVES

Theses of the PhD dissertation

Written by: Herke Klára
Supervisor: Prof. Hazai László
Consultant: Prof. Szántay Csaba

Budapest University of Technology and Economics
Department of Organic Chemistry and Technology

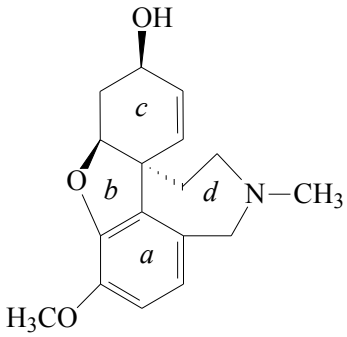
Sponsor: Richter Gedeon Ltd.

2011

1. Introduction

It has been known for a long time that several plants in nature have healing effects. Mankind used this option based on their experiences in the beginning, and then, as chemistry developed, began to isolate the active ingredients deliberately, and subsequently to synthesize them.

In my Ph.D. dissertation I describe the results that were achieved during the elaboration of the total synthesis of **(-)-galantamin (1)**, which is known as a natural substance.



(-)-1

2. Literary background

Galanthamine, which belongs to the *Amaryllidaceae* alkaloids, has been used in clinical practice for 40 years in the case of myasthenia gravis and other neurological diseases, such as infantile paralysis (poliomyelitis) as an anti-curare agent and as a parasympathomimetic drug[I]. Even more important is its role in the treatment of *Alzheimer*'s disease. In Austria, England and the United States the third phase of clinical trials are in progress.

Galanthamine is commercially available in several countries as its hydrobromide salt, under the brand names Nivalin, Razadyne and Reminyl[II].

Galanthamine is a selective acetylcholine esterase inhibitor. It has a dual effect based on the inhibition of acetylcholine esterase and the modulation of the nicotinic receptors in the brain.

[I] Pharmindex Kompendium 1995/96, Medimedia Információs Kft.

[II] Maelicke, A.; Samochocki, M.; Jostock, R.; Fehrenbacher, A.; Ludwig, J.; Albuquerque, E. X.; Zerlin, M.: *Biol. Psychiatry*, **2001**, *49*, 279-288

The decreased level of acetylcholine plays a major role in the development of *Alzheimer*'s disease, and therefore the release of acetylcholine induced by the molecule's modulation of the nicotinic receptors may slow the progression of the disease. In additon, galanthamine has a positive effect on the activities of everyday life and behavioral disorders.

A review was published about galanthamine in 2006, which deals with the various methods for the total synthesis of the molecule, its derivatives and its pharmacology in detail[III]. Most of the known syntheses applied the method of biomimetic intramolecular phenolic oxidative coupling – in which the quaternary carbon atom is formed - as the key step for the preparation of galanthamine[IV]. In the course of some recently published syntheses the construction of the azepine ring took place after the intramolecular *Heck*-reaction, which yielded the tricyclic compound containing the benzofuran skeleton[V]. Other methods are also found in the literature, some of which involve a photochemical reaction, or the *Grewe* cyclisation, which was applied previously by our research group[VI].

To the present day papers are continuously published about galanthamine, which also shows the importance of the molecule. 185 papers were published on the topic in 2010, out of which 61 have a synthetic focus. *Alzheimer*'s disease receives remarkable attention in both chemical and especially biological-medical research.

Our research group led by professor Csaba Szántay (member of the Hungarian Academy of Sciences) operating at the Budapest University of Technology and Economics, the Departement of Organic Chemistry and Technology, has been dealing with the preparation of various alkaloids and their derivatives for several decades.

[III] Marco-Contelles, J.; Carreiras, M.; Rodríguez, C.; Villaroya, M.; Garcia, A. G.: *Chem Rev.,* **2006**, *106* (1), 116-133.

[IV] (a) Czollner, L.; Frantsits, W.; Küenburg, B.; Hedenig, U.; Fröhlich, J.; Jordis, U.: *Tetrahedron Letters*, **1998**, *39*, (15), 2087-2088. (b) Kodama, S.; Hamashima, Y.; Nishide, K.; Node, M.: *Angew. Chem. Int. Ed.*, **2004,** *43* (20), 2659-2661. (c) Node, M.; Kodama, S.; Hamashima, Y.; Katoh, T.; Nishide, K.; Kajim
oto, T.: *Chem. Pharm. Bull.*, **2006**, *54* (12), 1662-1679

[V] (a) Trost, B. M.; Tang, W.; Toste, F. D.: *J. Am. Chem. Soc.*, **2005**, *127* (42), 14785-14803. (b) Guillou, C.; Beunard, J.—L.; Gras, E.; Thal, C.: *Angew. Chem.*, **2001**, *113* (24), 4881-4882.

[VI] (a) Holton, R. A.; Sibi, M. P.; Murphy, W. S.: *J. Am. Chem. Soc.*, **1988**, *110* (1), 314-316. (b) Sanchez, I. H.; Soria, J. J.; Lopez, F. J.; Larraza, M. I.; Flores, H. J.: *J. Org. Chem.*, **1984**, *49* (1), 157–163. (c) Lukács, A.; Szabó, L.; Hazai, L.; Ifj. Szántay, Cs.; Mák, M.; Gorka Á.: *Tetrahedron*, **2001**, *57*, 5843-5850.

I participated in one of the research topics preceding and supporting the total synthesis of galanthamine; my task was the preparation of one of the intermediates.

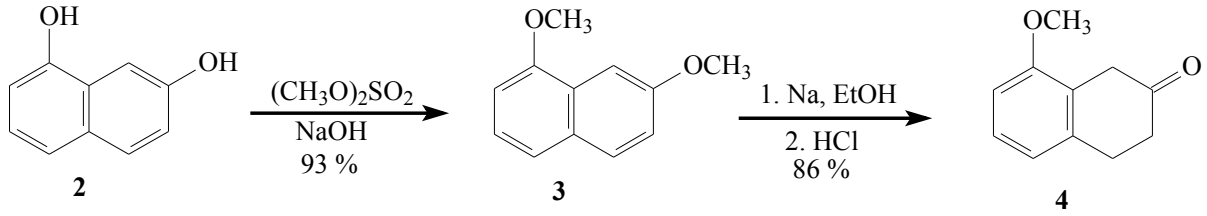
3. Experimental methods

In the course of my synthetic work I applied the preparative and separation methods of organic chemistry. I used thin layer chromatography with silica gel and aluminum oxide TLC plates for monitoring the reactions. For the isolation and purification of the products crystallization, distillation and preparative thin layer chromatography as well as column chromatography were used. The structures of the prepared compounds were identified by spectroscopic methods (IR, ^{1}H and ^{13}C-NMR, MS).

4. Summary of the results

4.1. Construction of the tetracycle typical of *Amaryllidaceae* alkaloids containing the galanthamine skeleton

In the research group the synthesis leading to galanthamine was previously studied on a model compound which contained no methoxy group. I performed the preparation of the intermediate containing one methoxy group based on the previously developed model synthesis and the existing analogies. To do this, we chose the commercially available 1,7-dihydroxy-naphtalene **(2)**, which was methylated in the first step according to a method found in the literature, and thus we obtained 1,7-dimethoxy-naphtalene **(3).** Compound **3** was then reduced in the *Birch*-reaction, this way yielding 8-methoxy-2-tetralone **(4)** which is equivalent to the initial compound of the model synthsesis.

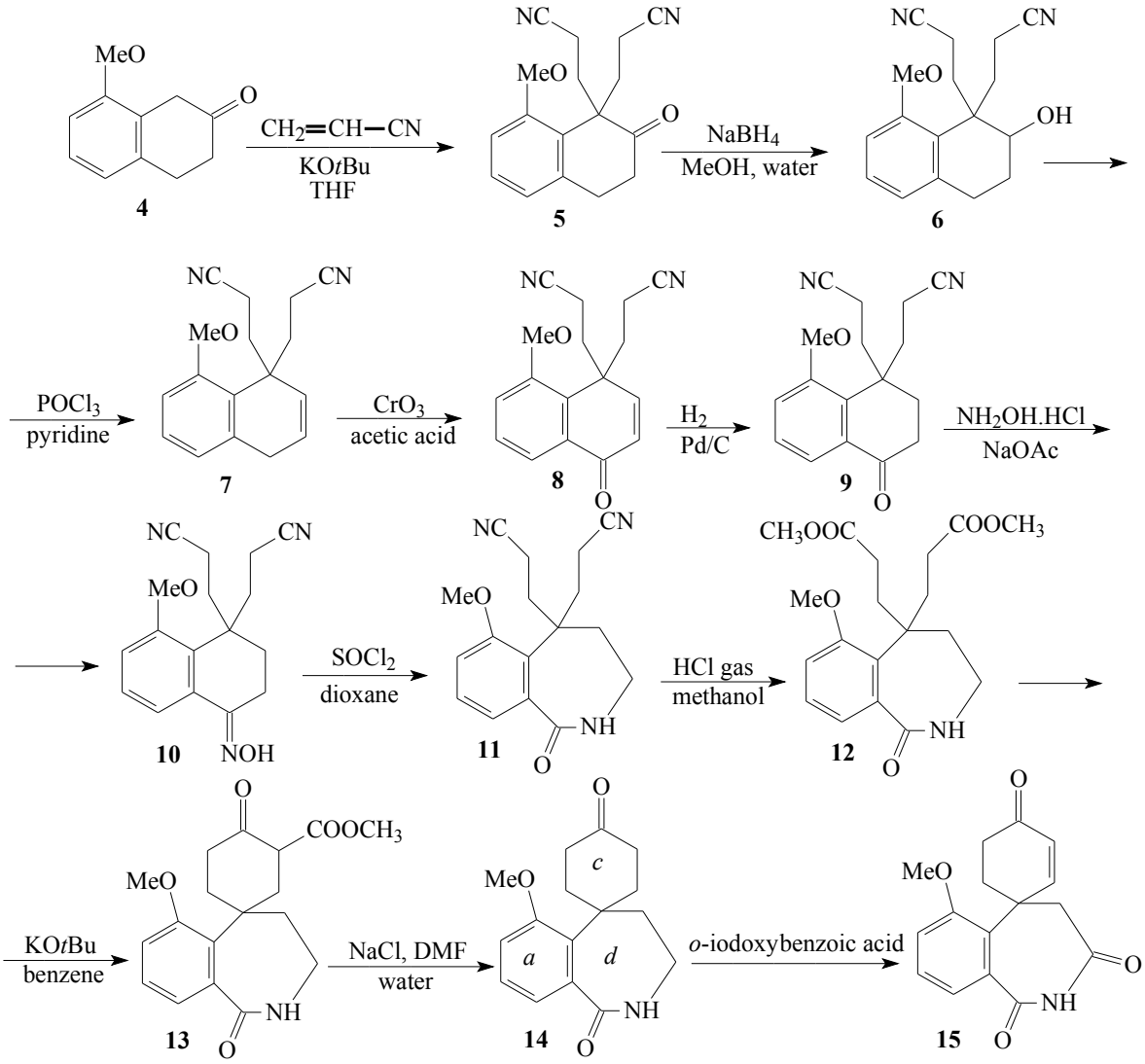


2 **3** **4**

The reduction of ketone **5** obtained from tetralone **4** by cyanoethylation resulted in alcohol **6**, the dehydratation of which has led to the unsaturated compound **7**. The catalytic

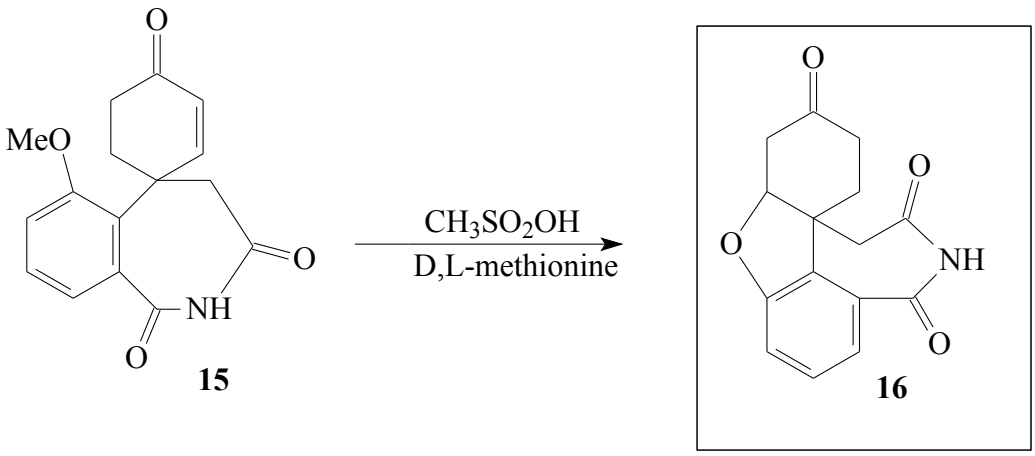
hydrogenation of ketone **8** obtained by the allylic oxidation of **7** yielded the saturated ketone **9**. The *Beckmann* rearrangement of oxime **10** prepared from ketone **9** resulted in the required benzo[*c*]azepinone **(11)**.

Then the diester **12** obtained in the *Pinner*-reaction of dinitrile **11** was converted to ketoester **13** by *Dieckmann* condensation. Demethoxycarbonylation of ketoester **13** resulted in the expected tricycle **14**, which already contained the *adc* ring system. We formed a double bond in the *c* cyclohexane ring of tricycle **14** by the method according to *Nicolau*[VII]. Compound **15**, having a methoxy group and the previously introduced double bond, was suitable for the formation of the fourth ring.



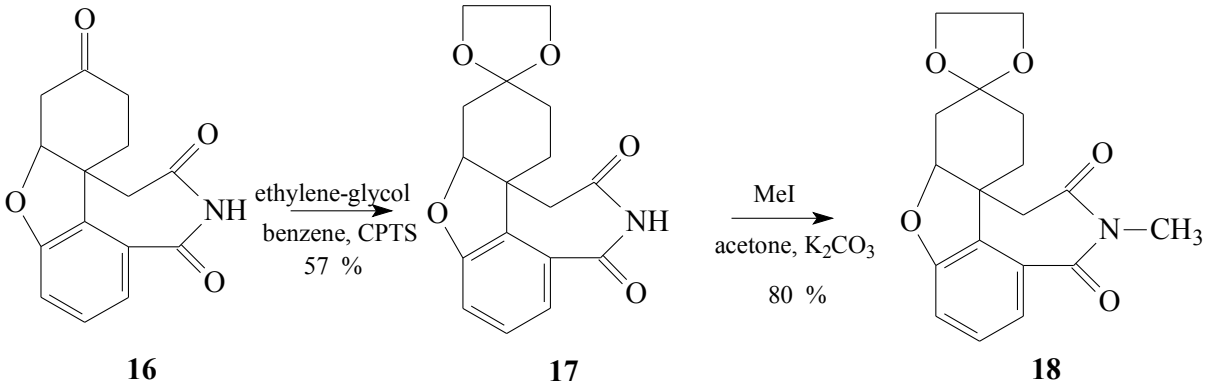
[VII] (a) Nicolau, K. C.; Zhong, Y.-L.; Baran, P. S.; *J. Am. Chem. Soc.*, **2000**, *122*, 7596-7597 (b) Nicolau, K. C.; Baran, P. S.; Zhong, Y.-L.: *J. Am. Chem. Soc.*, **2001**, *123*, 3183-3185 (c) Nicolau, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L.: *J. Am. Chem. Soc.*, **2002**, *124*, 2245

Several attempts were made in the research group to close the fourth ring. Finally, the preparation of the expected compound **16** was carried out in the presence of D,L-methionine in methansulfonic acid. The formation of the tetracycle proved the correctness of the synthesis strategy.

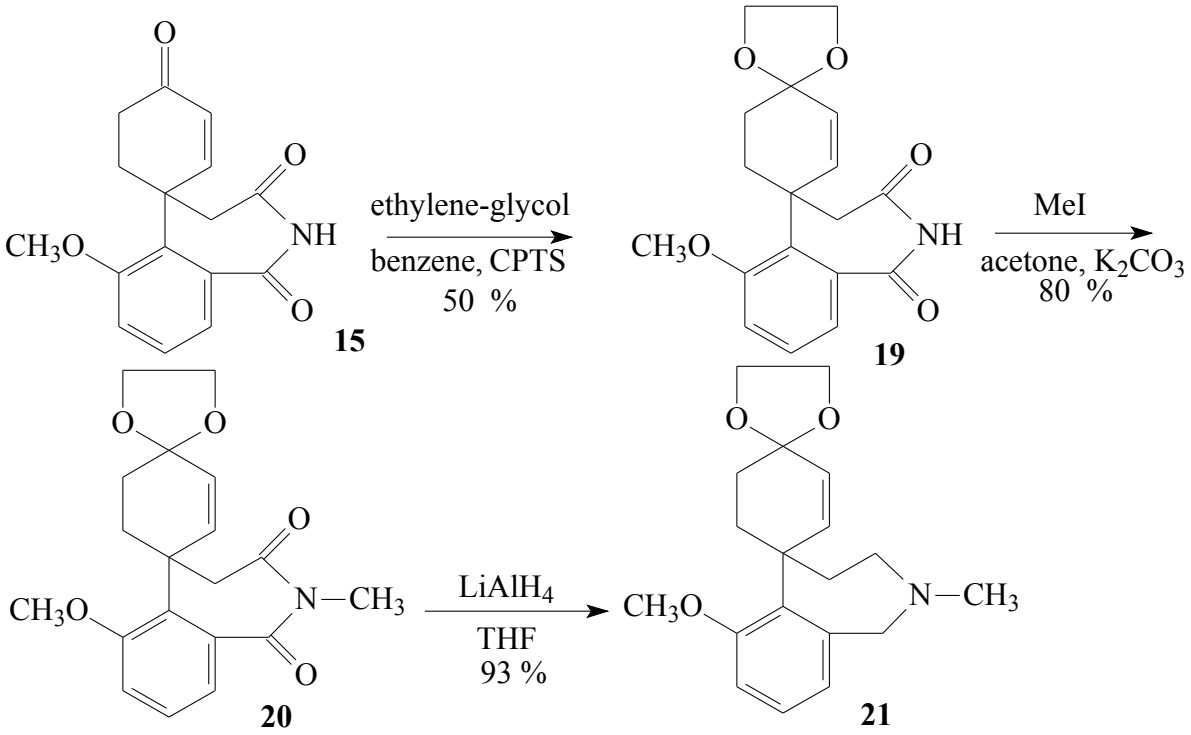


4.2. Preparation of demethoxy-dihydronarwedine

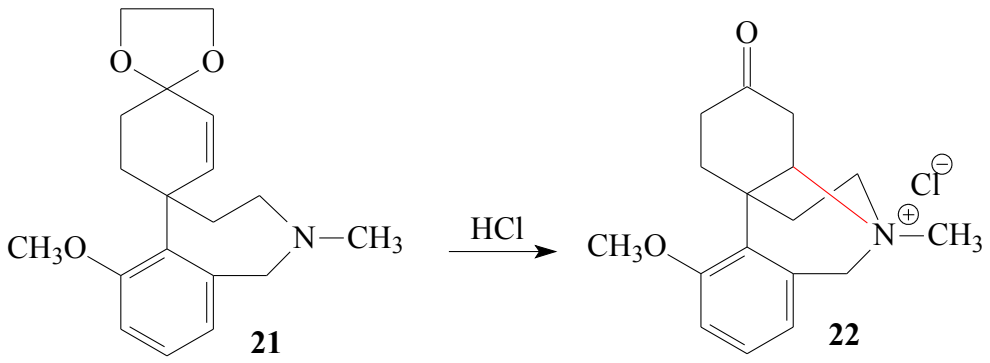
We tried to prepare the targeted demethoxy-dihydronarwedine in two different ways. In the first case, we protected the keto group of tetracycle **16** with a ketal protecting group yielding compound **17**, which was then methylated on the azepinic nitrogen to yield **18**. However, the reduction of the methylated azepinedione with lithium aluminum hydride was unsuccesful, so we could not continue in this direction.



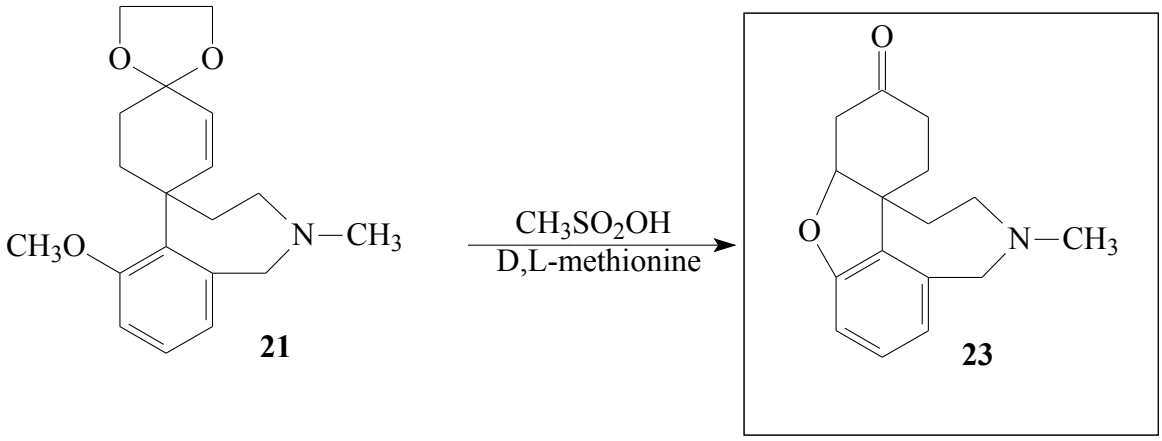
In the other case we started from tricyclic compound **15**. We protected the carbonyl oxygen of ring *c* **(19)**, methylated the azepinic nitrogen **(20)**, and reduced the imide carbonyl groups **(21)**.



While removing the protective ketal group **(21)** with hydrochloric acid the formation of an interesting new crinine derivative **(22)** was detected.

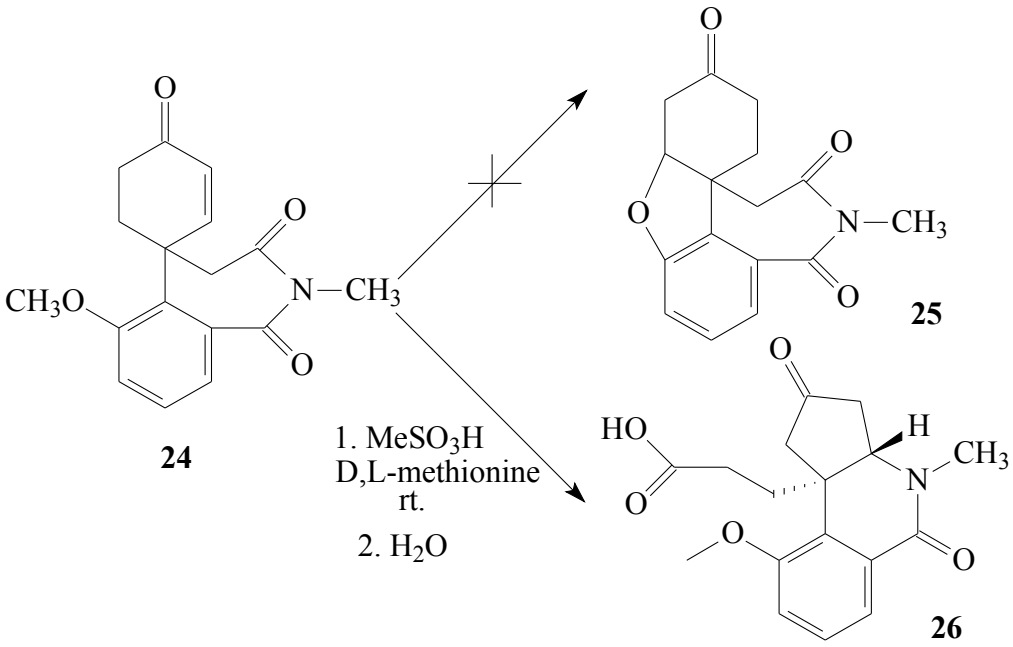


Since during the removal of the ketal protecting group with hydrochloric acid we did not obtain the expected product, we had to modify our synthesis plan, so we carried out the deprotection and the closure of the fourth ring in one step in a methanesulfonic acid medium in the presence of methionine. This way we finally obtained, via ketal **21**, the end product demethoxy-dihydronarwedine **(23)**.



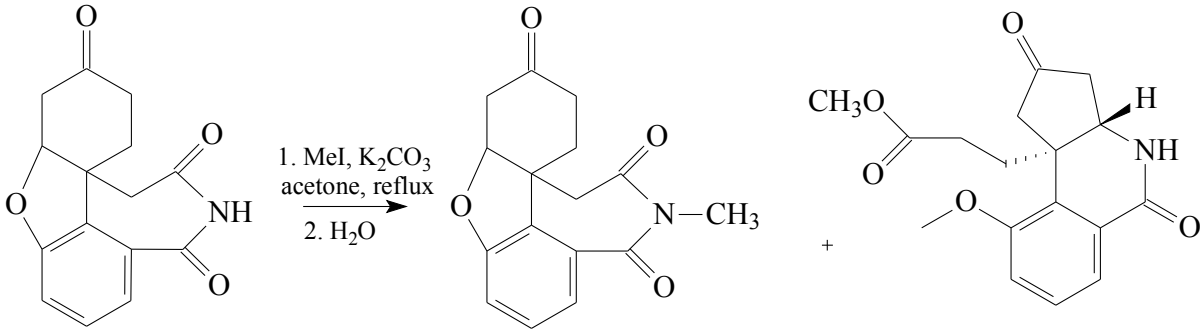
4.3. Preparation of cyclopenta[*c*]isoquinoline derivatives

During our subsequent work we investigated the reactions of tricycle **15** without the formation of the ketal protecting group. Therefore, tricycle **15** was methylated on the nitrogen, and this way we obtained the expected compound **24** as a single product. However, much to our surprise, we did not obtain the expected *N*-methylated tetracycle **25** among the circumstances of the cyclization, but an anomalous tricyclic compound **(26)** was isolated from the reaction mixture, which formed in a ring rearrangement. This compound is not described in the literature, and neither is the ring contraction.



Following this we tried to obtain the expected *N*-methyl-tetracycle by changing the order of the two steps. In this scenario tetracycle **16** was directly methylated under the previously described reaction conditions.

We managed to prepare the expected compound **25**, however, the product of the reaction was not uniform, and we isolated the previously described anomalous ring system **27** in this case, as well.



16 **25** **27**

We presented a hypothetical reaction mechanism for the formation of the cyclopentanoisoquinoline derivatives **26** and **27**.

5. Theses

1. By prior analogies and experiences we obtained the starting material needed for the preparation of the tetracycle characteristic of the galanthamine type *Amaryllidaceae* alkaloids, the *adc* tricycle, whose succesful cyclization yielded the appropriate tetracycle, thus also proving the correctness of the synthesis strategy[1,4].

2. We achieved our goal: we prepared demethoxy-dihydronarwedine. Besides, we isolated new crinine derivatives, which are not yet described in the literature[2].

3. During our research we isolated two related compounds formed in an anomalous rearrangement, which are two new tricyclic representatives of a different type of ring system not yet described in the literature[3].

6. Publications and presentations

6.1. The PhD dissertation is based on the following publications

1. **Herke, K.,** Hazai,, L., Hudák M. Sz., Ábrahám, J., Sánta Zs., Háda, V., Szántay, Cs. Jr., Szántay, Cs.; Synthesis of the tetracyclic skeleton of the galanthamine-type *Amaryllidaceae* alkaloids. *Arkivoc*, **2009**, *xi*, 235-246. **[IF: 1,253]**

2. **Herke, K.**, Hazai, L., Dubrovay, Zs., Háda, V., Sánta, Zs., Szántay, Cs. Jr., Kalaus, Gy., Szántay, Cs.; Synthesis of demethoxy-lycoraminone. *Heterocycles*, **2011**, *83*, 581-589. **[IF: 1,666]**

3. **Herke, K.**, Hazai, L., Sánta, Zs., Dubrovay, Zs., Háda, V., Szántay, Cs. Jr., Kalaus, Gy., Szántay, Cs.; An unexpected rearrangement on the benzofurobenzazepin skeleton of galanthamine-type alkaloids, *Tetrahedron Letters*, **2010**, *51*, 6932-6934. **[IF: 2,538]**

4. **Herke, K.**, Gorka-Kereskényi, Á., Hazai, L., és Szántay, Cs.; Galantamin és származékai. *Magyar Kémiai Folyóirat*, **2010**, *116* (2), 72-76.

6.2. Presentations and posters

Herke, K., Hazai, L., ifj. Szántay, Cs., Szántay, Cs.: Galantamin-származékok szintézise. MTA Alkaloidkémiai Munkabizottsági Ülés, Balatonfüred, 2008 *ORAL PRESENTATION*

Herke, K., Hazai, L., ifj. Szántay, Cs., Szántay, Cs.: Galantamin-származékok szintézise, II. XXXI. Kémiai Előadó Napok, 2008. Szeged. Presentation summary page 111-114, *ORAL PRESENTATION*

Herke, K., Hazai, L., ifj. Szántay, Cs., Szántay, Cs.: Kulcsintermedierek előállítása a demetoxi-narvedin szintéziséhez. MTA Alkaloidkémiai Munkabizottsági Ülés, Balatonfüred, 2009 *ORAL PRESENTATION*

Herke K., Hazai L., Sánta Zs., Háda V., ifj. Szántay Cs., Szántay Cs.: Kulcsintermedierek előállítása a demetoxi-narvedin szintéziséhez. XXXII. Kémiai Előadói Napok, 2009. Szeged. Presentation summary page 116-117, *ORAL PRESENTATION*

Herke K., Hazai L., Sánta Zs., Háda V., ifj. Szántay Cs., Szántay Cs.: Kísérletek a demetoxi-narvedin előállítására. XV. Nemzetközi Vegyészkonferencia, 2009. Marosvásárhely. Presentation summary page 24, *ORAL PRESENTATION*

Herke K., Hazai L., Szántay Cs.: Experiments for the synthesis of the demethoxynarwedine. Journées de la Section Régionale Centre -Ouest de la Société Chimique de France, 2010. La Rochelle, France. Presentation summary page 45, *ORAL PRESENTATION* (in french)

Herke, K., Hazai, L., ifj. Szántay, Cs., Szántay, Cs.: Galantamin-származékok szintézise, BME, Doktori konferencia, 2009 *POSTER*