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FACULTY OF CHEMICAL AND BIOENGINEERING

Synthesis of aspidosperma and related indole alkaloids, recognition of an unexpected reaction

Thesis of the PhD dissertation

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2009

1. Introduction, our aims

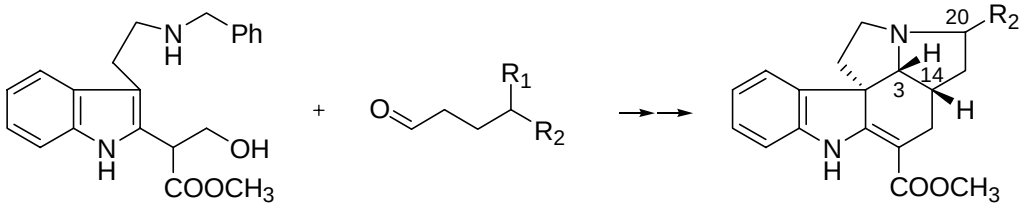
Nowadays the natural organic matters, which contain nitrogen heterocycles, alkaloids and their derivatives occupy considerable place in the modern medical science. As an example, the dimer indole alkaloid, vincristine (brand name: Oncovin) is used in the childhood leukemia with great efficiency, or ethyl apovincaminate (brand name: Cavinton), which has been shown good effect in the cerebrovascular disorders. In the past decades the BME-MTA research group of alkaloid chemistry made a big emphasis lie onto the research of indole alkaloids inside this the synthesis of eburnane and aspidosperma alkaloids and alkaloid-like molecules. Following the supposed biosynthetic route they worked out a synthetic strategy for construction the aspidosperma skeleton.

At the beginning of my PhD studies, following the biosynthetic route we planned to develop a new, simple total synthesis of ibophyllidine alkaloids, as well as first or new synthesis of some alkaloids and analogs. Appreciating the earlier negative experimental results, we modified of the original synthetic strategy and took efforts for the preparation of 15β-hydroxyvincadifformine. We wished to examine the synthesis of 19-hydroxy-20-epipandoline, which one of the representatives of Ψ-aspidosperma alkaloids.[*]

[*] The compounds described in this thesis are racemates, but only one of the antipodes is shown.

2. Synthesis of ibophyllidine alkaloids and related compounds

Following the biosynthetic route, the build-up of the ibophyllidine skeleton was carried out by a new convergent synthetic strategy, through the D-*seco*-Ψ-aspidosperma intermediates. The tryptamine derivative (**1**), which contains a masked acrylate structural unit was chosen for the synthesis. The key step of our synthesis was the reaction of **1** with the appropriately functionalized aldehydes (**2**-**7**). First of all the aldehydes (**2**-**7**) formed enamines with the amino group of **1**, then the water elimination resulted in diene structures, which were instantly reacted with the dienophile enamine, leading to the formation of tetracyclic intermediates, from which the pentacyclic molecules (**9**-**14**) can be made to form easily. (Scheme 1.).



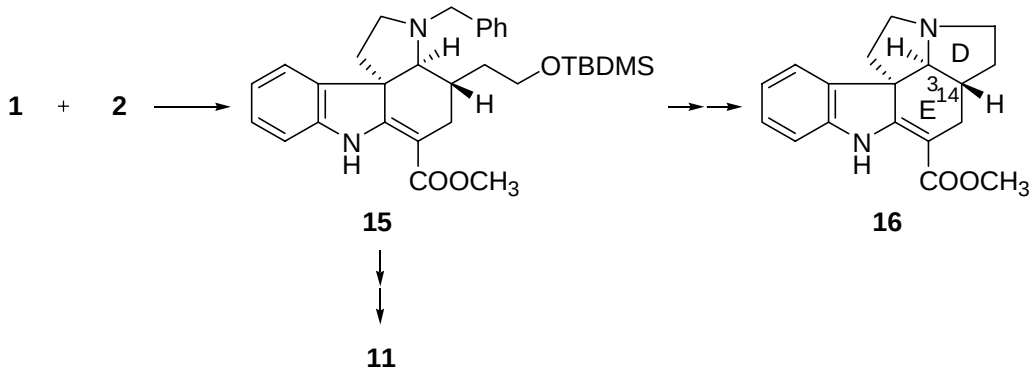
1

2 R_1= OTBDMS R_2= H
3 R_1+R_2= $COOC_2H_5$
4 R_1= OTBDMS R_2= C_2H_5
5 R_1= =O R_2= C_2H_5
6 R_1= Br R_2=CH(OTBDMS)CH_3
7 R_1= OAc R_2= CH_2COOCH_3

9 R_2= α-C_2H_5
10 R_2= β-C_2H_5
11 R_2= H
12 R_2= α-CH(OH)CH_3
13 R_2= β-CH(OH)CH_3
14 R_2= β-CH_2CH_2OH

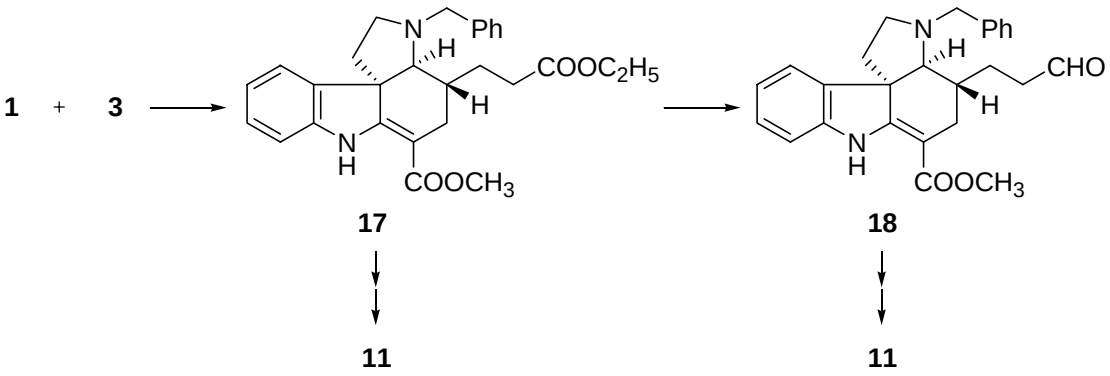
Scheme 1.

At first we accomplished the synthesis of deethylibophyllidine (**11**). We allowed **2** to reacted with the key intermediate (**1**). The reaction resulted in the tetracyclic D-*seco*-Ψ-aspidosperma molecule (**15**), from which the construction of ibophyllidine skeleton's D-ring was formed by intramolecular alkylation in several steps.



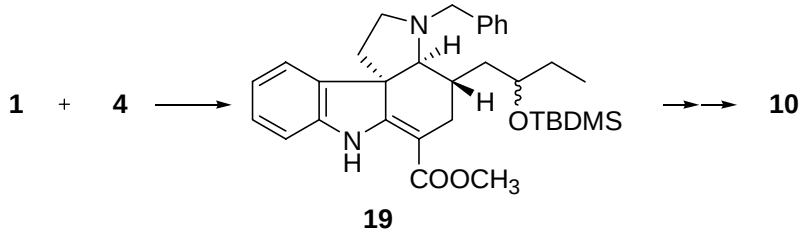
Scheme 2.

We also synthesized the 3-epideethylibophyllidine (**16**) containing trans D/E ring connection. (Scheme 2.). In an other synthetic route the key intermediate (**1**) was reacted with ethyl 4-oxobutanoate (**3**). We gained the D-*seco*-Ψ-aspidosperma compound (**17**), from which, in one hand we obtained **11** after hydrogenolysis, the intramolecular cyclization and reduction steps, in other hand the aldehyde (**18**) was *in situ* debenzylation, ring closure with full epimerization and reduction steps in one operation also led to **11**. (Scheme 3.).



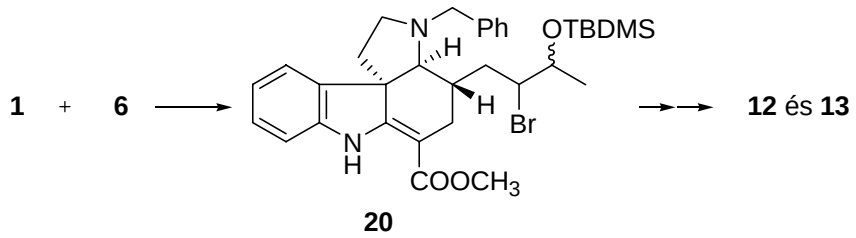
Scheme 3.

Utilizing our experience from the synthesis of deethylibophyllidine (**11**), we developed a convergent biomimetic method for preparation of ibophyllidine (**9**) and its C20-epimer, 20-epiibophyllidine (**10**). The aldehyde (**4**) acting as reaction partner was coupled with the tryptamine derivative (**1**) to lead **19** intermediate containing D-*seco*-Ψ-aspidosperma skeleton, from which the 20-epiibophyllidine (**10**) was obtained in several steps. (Scheme 4.). We synthesized the ibophyllidine (**3**) from **1** and 4-oxohexanal (**5**) with some simple steps. (**1**+**5** →→ **9**).



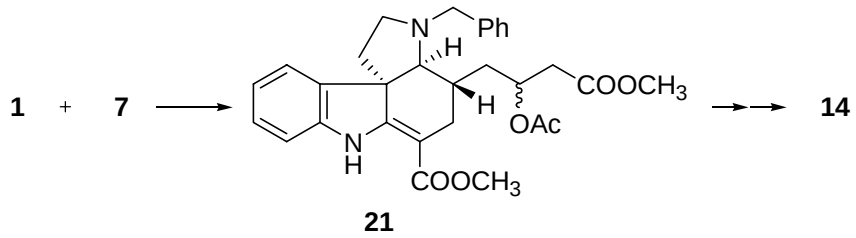
Scheme 4.

The continuation of our work in the biomimetic synthesis of ibophyllidine alkaloids we accomplished the first synthesis of 19-hydroxyibophyllidine (**12**) and 19-hydroxy-20-epiibophyllidine (**13**). The appropriately functionalized aldehyde (**6**) was allowed to react with the secondary amine (**1**) to yield the **20** intermediate. In the following steps of the procedure we formed the D-ring of the pentacyclic skeleton, after that by removing the protective group in the final step, **12** and **13** can be isolated with good yield (Scheme 5.).



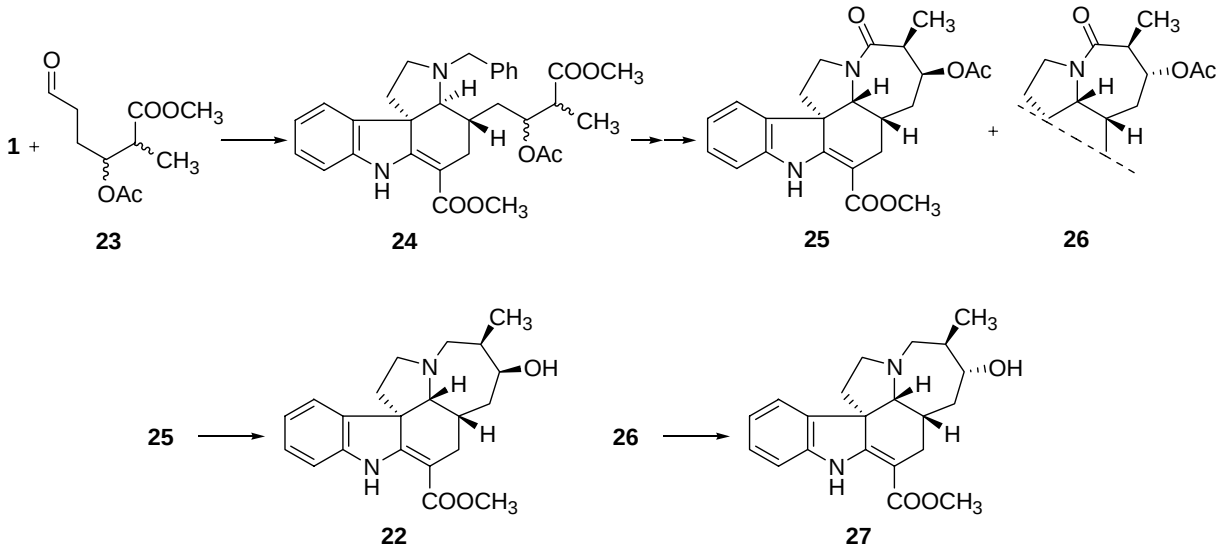
Scheme 5.

We extended our synthetic method for the construction of 18-hydroxy-20-epiibophyllidine (**14**) too. The first total synthesis of **14** was realized an efficient preparation of the D-*seco*-Ψ-aspidosperma molecule (**21**), which was built up from the reaction of the tryptamine deriative (**1**) with the aldehyde (**7**). After debenzylation, full epimerization, intramolecular N-alkylation (Michael addition) and the regioselective ester reduction led to **14** (Sheme 6).



Scheme 6.

3. Rational synthesis of iboxyphylline



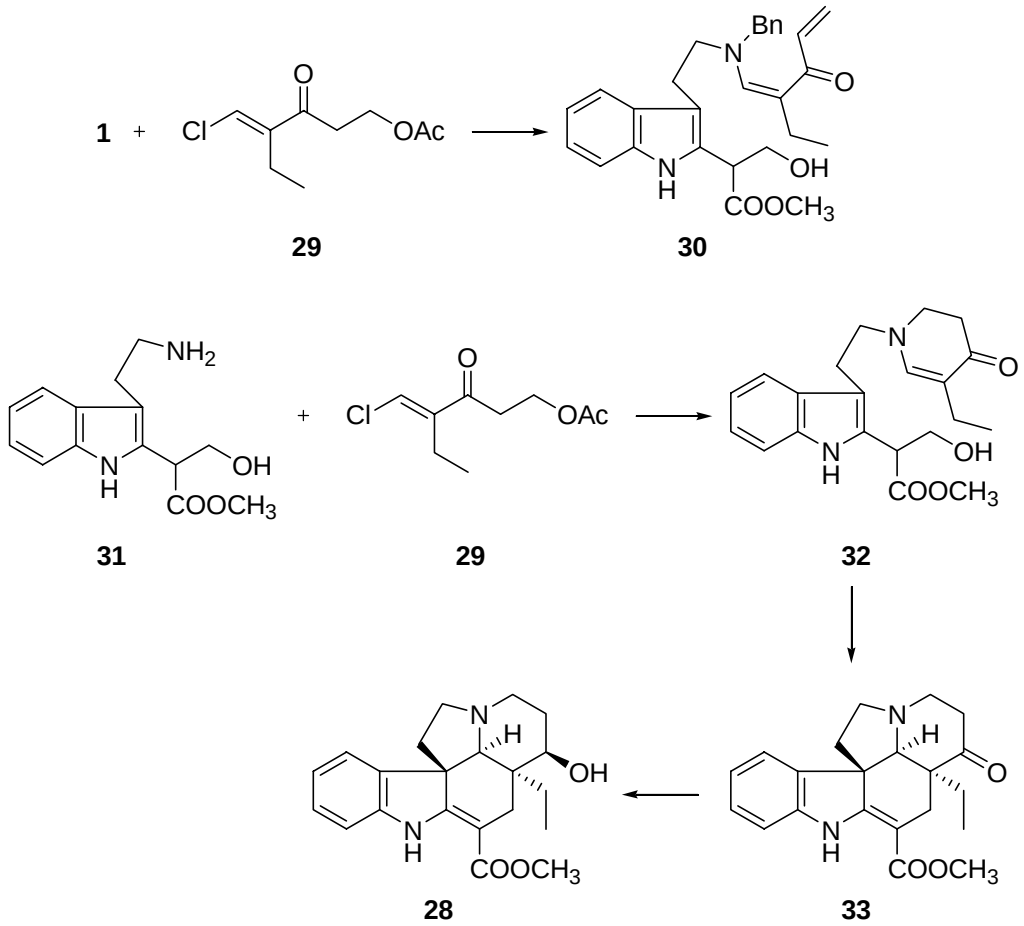
Scheme 7.

The biomimetic ibophyllidine synthetic strategy was successfully used for the preparation of iboxyphylline (**22**), which contains a seven-membered D-ring. The pentacyclic alkaloid (**22**) could be synthesized by an intramolecular [4+2] cycloaddition reaction, resulted in **24** intermediate, which had been obtained from the tryptamine

derivative (**1**) and the aldehyde (**23**). Debenzylation and full epimerization of **24**, the cyclization reaction furnished a mixture of **25** and **26**. Separation of stereoisomers (**25** and **26**) and subsequent reduction resulted in iboxyphylline (**22**) and its C20-epimer, 20-epiiboxyphylline (**27**) (Scheme 7.).

4. Simple synthesis of 15β-hydroxyvincadifformine

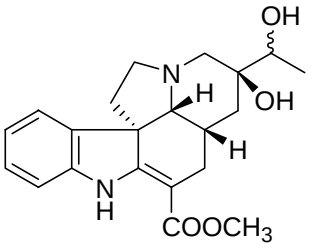
In the earlier years we have already tried to synthesized the 15β-hydroxyvincadifformine (**28**), but we did not obtained the target alkaloid by the applied methods. Analyzing the reaction pathway we set up a hypothesis by which we might obtain the alkaloid (**28**) with aspidosperma skeleton. Under the planned reaction condition, **1** coupled with the aldehyde equivalent (**29**) to lead **30**. In aware of this fact we reacted **29** with a tryptamine derivative containing primer amino-group (**31**) to provide **32**, from which under the cycloaddition condition *via* secodine-type intermediate we could isolate 15-oxovincadifformine (**33**). In the last step of the synthesis, the regio- and stereoselective reduction of **33** supplied **28**. (Scheme 8.).



Scheme 8.

5. Experiments for preparation of 19-hydroxy-20-epipandoline

The interesting biological activities of aspidosperma and Ψ-aspidosperma alkaloids and their synthetically challenging structures make the 19-hydroxy-20-epipandoline (**34**) an attractive target for the synthesis. (Scheme 9.).



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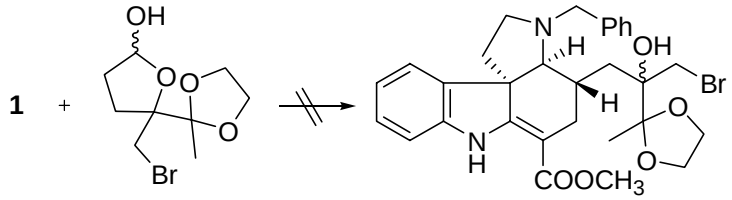
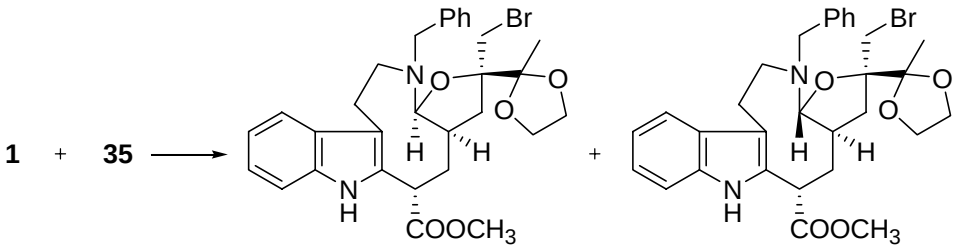
Scheme 9.

Followed our biomimetic synthetic route, the tryptamine derivative (**1**) reacted with the lactol (**35**) – acting as a masked aldehyde– to do not provide the D-*seco*-Ψ-aspidosperma intrmediate (**36**), it was converted into the unique cyclic carbinolamine ethers (**37** and **38**) in good yield. (Scheme 10.).



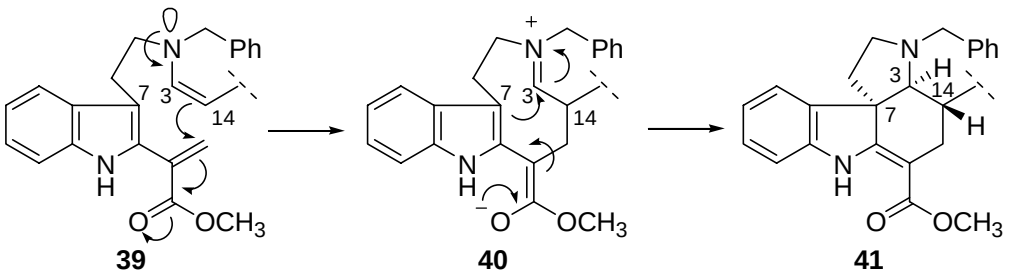
35 **36**



37 **38**

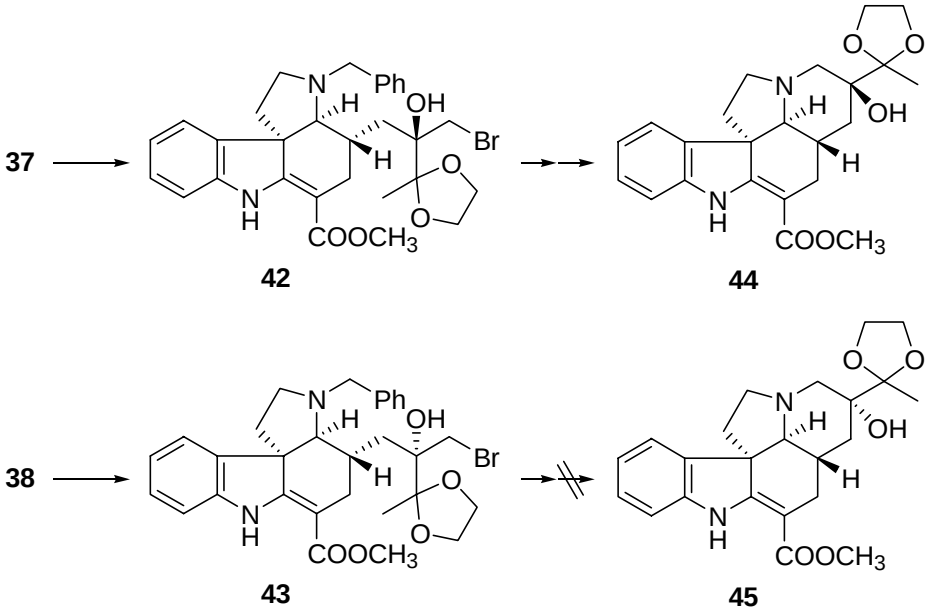
Scheme 10.

In aware of this fact we examined the mechanism of cycloaddition, because the formation of 37 and 38 could not be explained by our previous hypothesis, i. e., a concerted [4+2] intramolecular cycloaddition, which leads to the expected product in one step. Based on our quantum mechanical calculation we found that these intramolecular cyclization follow a step-wise mechanism involving a zwitterionic intermediate to furnish the D-*seco*-Ψ-aspidosperma molecules (**39**→ **40**→ **41**) (Scheme 11.).



Scheme 11.

In the next step of the synthesis, the furano ring was opened and the transannular cyclization process of **37** or **38** led to the tetracyclic esters (**42** and **43**). Afterwards the D-ring of the Ψ-aspidosperma skeleton was formed. Unfortunately, only one stereoisomer (**42**) was converted to the pentacyclic alkaloid-like molecule (**44**) with trans D/E ring connection (Scheme 12.).



Scheme 12.

Although the preparation of 19-hydroxy-20-epipandoline (**34**) fell through with our synthetic strategy, but the examination of [4+2] cycloaddition to provide number useful information, which can explain our earlier unsuccessfull cycloaddition reactions.

6. Thesis

A new biomimetic synthetic pathway has been developed to build up molecules with ibophyllidine skeleton. A new convergent synthesis of deethylibophyllidine, ibophyllidine and 20-epiibophyllidine and the first synthesis of 19-hydroxyibophyllidine, 19-hydroxy-20-epiibophyllidine and 18-hydroxy-20-epiibophyllidne have been realized.

The biomimetic ibophyllidine synthetic strategy was successfully used for the preparation of iboxyphylline and its C20-epimer.

Analyzing our previous reaction pathway, 15β-hydroxyvincadifformine was synthesized successfully by changing the substrate.

We tried synthesize one of representatives of Ψ-aspidosperma alkaloids, the 19-hydroxy-20-epipandoline, but we could isolate undesired molecules containing furano ring from the reaction mixture. The mechanism of the cycloaddition reaction was investigated by quantum chemical calculation and it was found to follow a step-wise mechanism involving a zwitter-ionic intrmediate, not a previously supposed concerted [4+2] intramolecular cycloaddition to lead aspidosperma and Ψ-aspidosperma alkaloid and alkaloid-like molecules.

7. Publications:

1. **F. Tóth**, Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai and Cs. Szántay: An efficient convergent synthetic pathway to build up the ibophyllidine skeleton II: Total synthesis of (±)-deethylibophyllidine and (±)-14-epi-deethylibophyllidine
Heterocycles **2006**, *68*, 2301-2317.

2. **F. Tóth**, Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai and Cs. Szántay: An efficient convergent synthetic pathway to build up the ibophyllidine skeleton III: Total synthesis of (±)-ibophyllidine and (±)-20-epiibophyllidine
Heterocycles **2007**, *71*, 865-880.

3. **F. Tóth**, Gy. Kalaus, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai and Cs. Szántay: Efficient convergent synthetic pathway to the ibophyllidine skeleton and synthesis of (±)-19-hydroxy-ibophyllidine and (±)-19-hydroxy-20-epiibophyllidine
Tetrahedron **2006**, *62*, 12011-12016.

4. **F. Tóth**, Gy. Kalaus, V. D. Horváth, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai and Cs. Szántay: Efficient convergent synthetic pathway to the ibophyllidine skeleton IV. First synthesis of (±)-18-hydroxy-20-epiibophyllidine
Tetrahedron **2007**, *63*, 7823-7827.

5. **F. Tóth**, Gy. Kalaus, G. Pipa, I. Greiner, Á. Szőllősy, A. Rill, Á. Gömöry, L. Hazai and Cs. Szántay: An intramolecular [4+2] cycloaddition mediated biomimetic synthesis of (±)-iboxyphylline
Heterocycles **2008**, *75*, 65-76.

6. Gy. Kalaus, **F. Tóth**, I. Greiner, M. Kajtár-Peredy, Á. Gömöry, L. Hazai and Cs. Szántay Cs.: Recognition of an unexpected reaction and its application in building the aspidospermane skeleton. Simple synthesis of 15β-hydroxyvincadifformine
Heterocycles **2006**, *68*, 257-270.

7. **F. Tóth**, J. Oláh, Gy. Kalaus, I. Greiner, Á. Szőllősy, Á. Gömöry, L. Hazai and Cs. Szántay: A new synthetic method for the preparation of pandoline-type alkaloid-like molecules
Tetrahedron **2008**, *64*, 7949-7955.