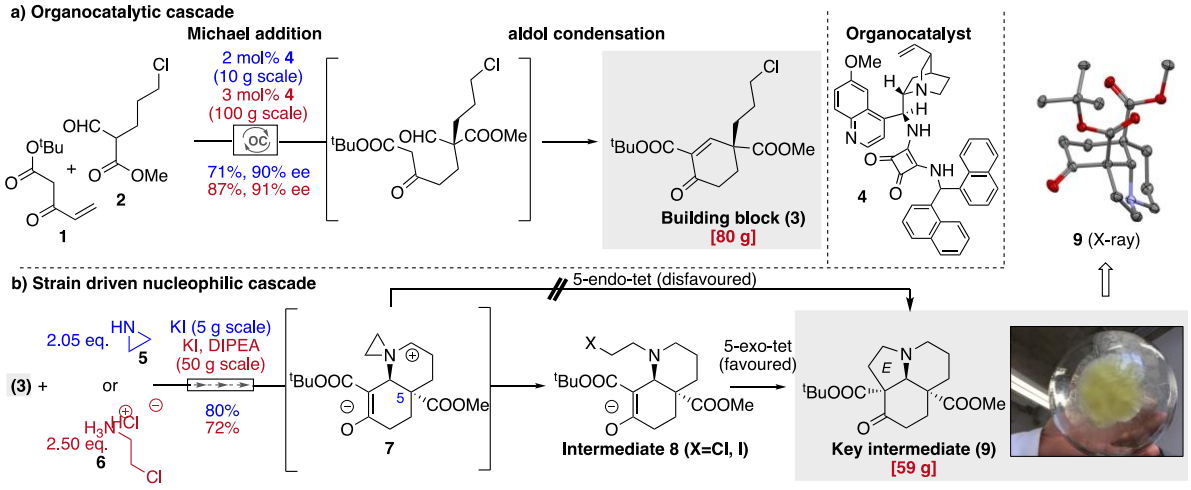
Synthesis of indole terpenoids using cascade reactions
Final Research Report

Our research program has focused on the synthesis of indole alkaloids via cascade reactions. The family of the monoterpene indole alkaloids (MIA) is one of the largest groups of natural alkaloids. The biosyntheses of these compounds are based on a common motif: these MIAs are derived from tryptophan and secologanin and are assembled via cascade reactions (the reaction chain of condensations, rearrangements, etc.).
Our research program has had two pillars, which aimed to synthesize MIAs:
a) the total synthesis of aspidosperman alkaloids
b) the synthesis of the curan skeleton and assembling strychnos alkaloids
Our synthesis planning was based on the bioinspired approaches, which means that we tried to use the basic principles of the biosynthesis of such kind (e.g. chemical economy, rapid generation of molecular complexity, modularity).

Total Synthesis of Aspidosperman Alkaloids

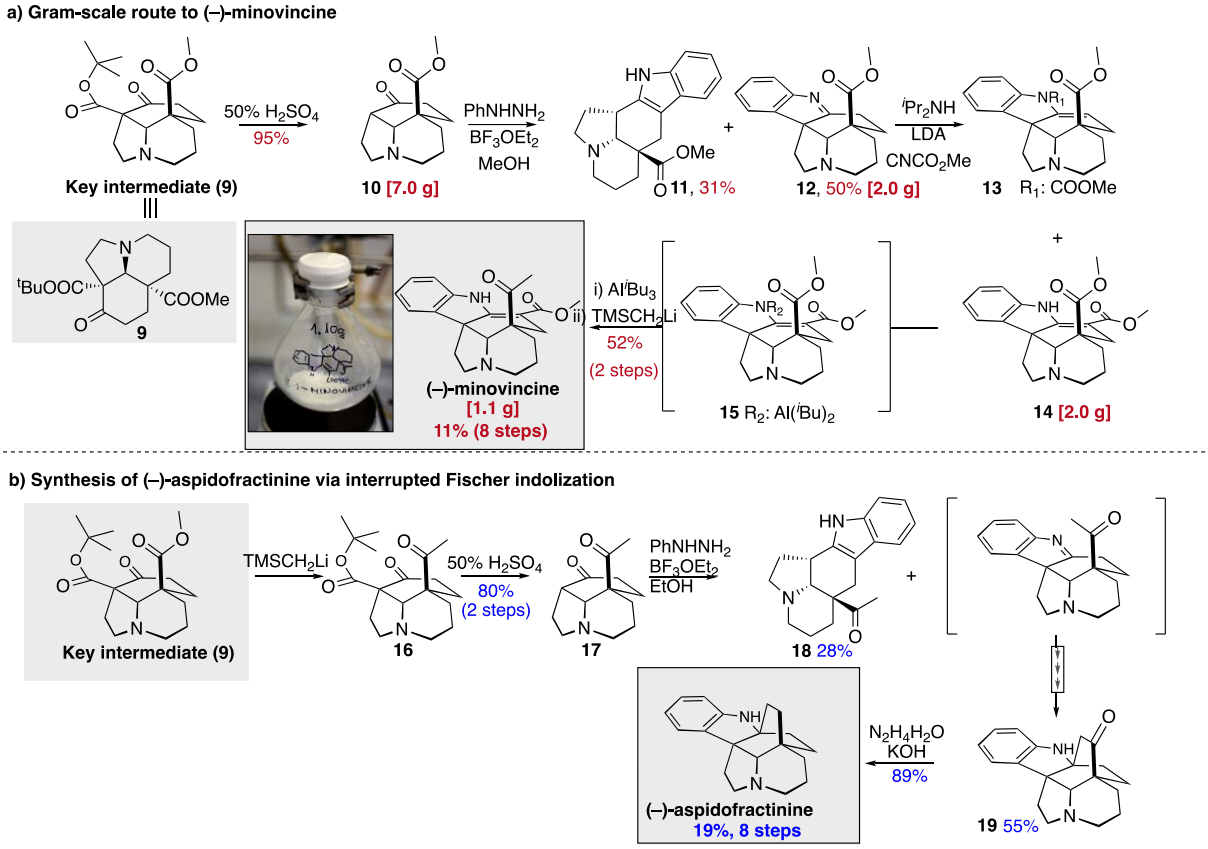
Our approach to synthesize Aspidosperma alkaloids was based on an organocascade reaction to assemble the quaternary carbon stereocentre containing key intermediate (**3**). This method also proved to be amenable for scale up, ultimately allowing access to 80 g of enone **3**. With a robust approach to **3** in hand, we focused on the synthesis of a tricyclic terpene-like building block via a nucleophilic cascade process. We have chosen aziridine (**5**) as a strained, nucleophilic reagent, which seemed an ideal C2N synthon. The envisioned aza-Michael-S_N2 or S_N2-aza-Michael annulation was successful and diastereoselective. Pleasingly, the absolute configuration of **9** tricyclic intermediate was the desired for the natural aspidosperman alkaloids (the configuration was determined by X-ray crystallography). Next, as a less harmful and hazardous synthetic precursor of aziridine (**5**), 2-chloroethylamine (**6**) was also probed. To our delight, the intriguing nucleophilic cascade proceeded also well with **6** amine in the presence of DIPEA, which allowed us to conduct the process in a batch of 80 g with a 72% yield.



To furnish the pentacyclic aspidosperma skeleton, the selective deprotection of tBu-ester and the spontaneous decarboxylation of the resulting β-oxo carboxylic acid was followed by a Fischer indolisation step. With the aspidospermane-type indolenine **12** in our hands, the

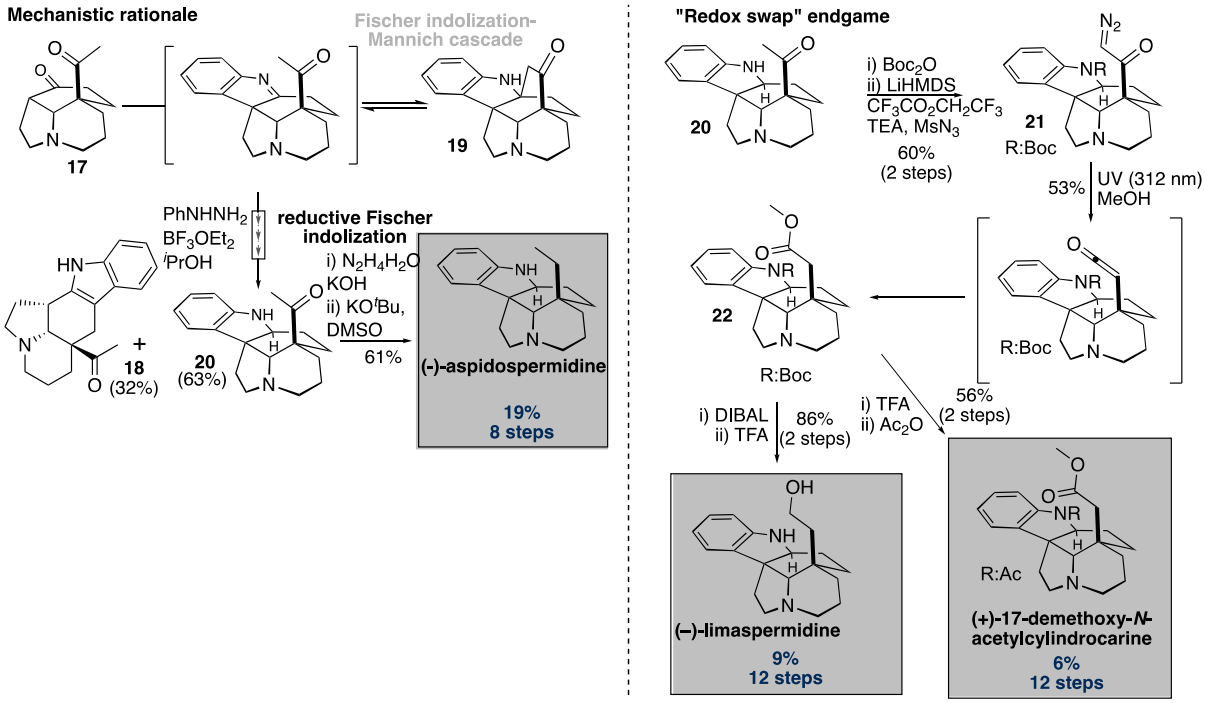
methoxycarbonyl group was introduced into C-3 position of the indolenine using the Mander reagent. The C-5 acetyl group was formed from the ester group using $TMSCH_2Li$ and TRIBAL, which was a temporal protecting group on the indole N-atom and sterically shield on C-3 methoxycarbonyl moiety. Gratifyingly, (–)-minovincine could be obtained on a 1.10 gram scale with 52% yield. Overall, the gram-scale synthesis of (–)-minovincine was accomplished in an overall yield of 15% by an eight-step sequence.

Then, we implemented the synthesis of aspidofractinene, which is a cage-like molecule, via an interrupted Fischer indolization. To access the planned transformation, we redesigned the tricyclic intermediate and the methyl ester was transformed to acetyl group using $TMSCH_2Li$. To our delight, the Fischer indole-Mannich cascade reaction occurred smoothly to afford the corresponding oxo-aspidofractinine **19** in a 55% yield. As the final step of the synthetic route, the substrate **19** was exposed to hydrazine to furnish (–)-aspidofractinine in 89% yield.



We also planned to expand our target pool to a subset of the *Aspidosperma* alkaloids featuring oxidized side chains at C-5 position. After carefully analyzing the products of the Mannich-Fischer indolization process, we were able to modify this process to a Fischer indolization-reduction cascade in the presence of a Lewis acid. We rationalized that this chemoselective reduction of the imine moiety is analogous with a Meerwein-Ponndorf-Verley type reduction, in which the hydride source was the alcohol solvent. In light of this, we employed isopropanol as a solvent to amplify the effectiveness of the reductive transformation. Gratifyingly, these modifications gave the desired 20-oxoaspidospermidine as the major product (63% yield). With the key intermediate (**20**) in our hand, we proceeded to perform the requisite redox modifications. Firstly, (–)-aspidospermidine was synthesized using a modified Kishner-Wolff reduction process (8 steps, overall yield 19%).

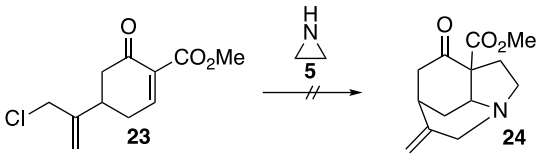
As a next step, the formation of the C-21 oxidized sidechain was probed via a formal "redox swap", the Wolff-rearrangement. First, we synthesized the desired diazo compound (**21**) after the protection of the **20** key intermediate. To our delight, the subsequent redox swap proceeded smoothly through photochemical Wolff rearrangement that afforded ester **22**. This ester was then reduced with DIBAL, followed by the removal of the Boc group to afford (–)-limaspermidine (12 steps, overall yield 9%). Furthermore, the synthesis of (+)-17-demethoxy-N-acetylcylindrocarine was then achieved through a two-step deprotection/acylation sequence to finish our synthetic endeavour (12 steps, overall yield 6%).



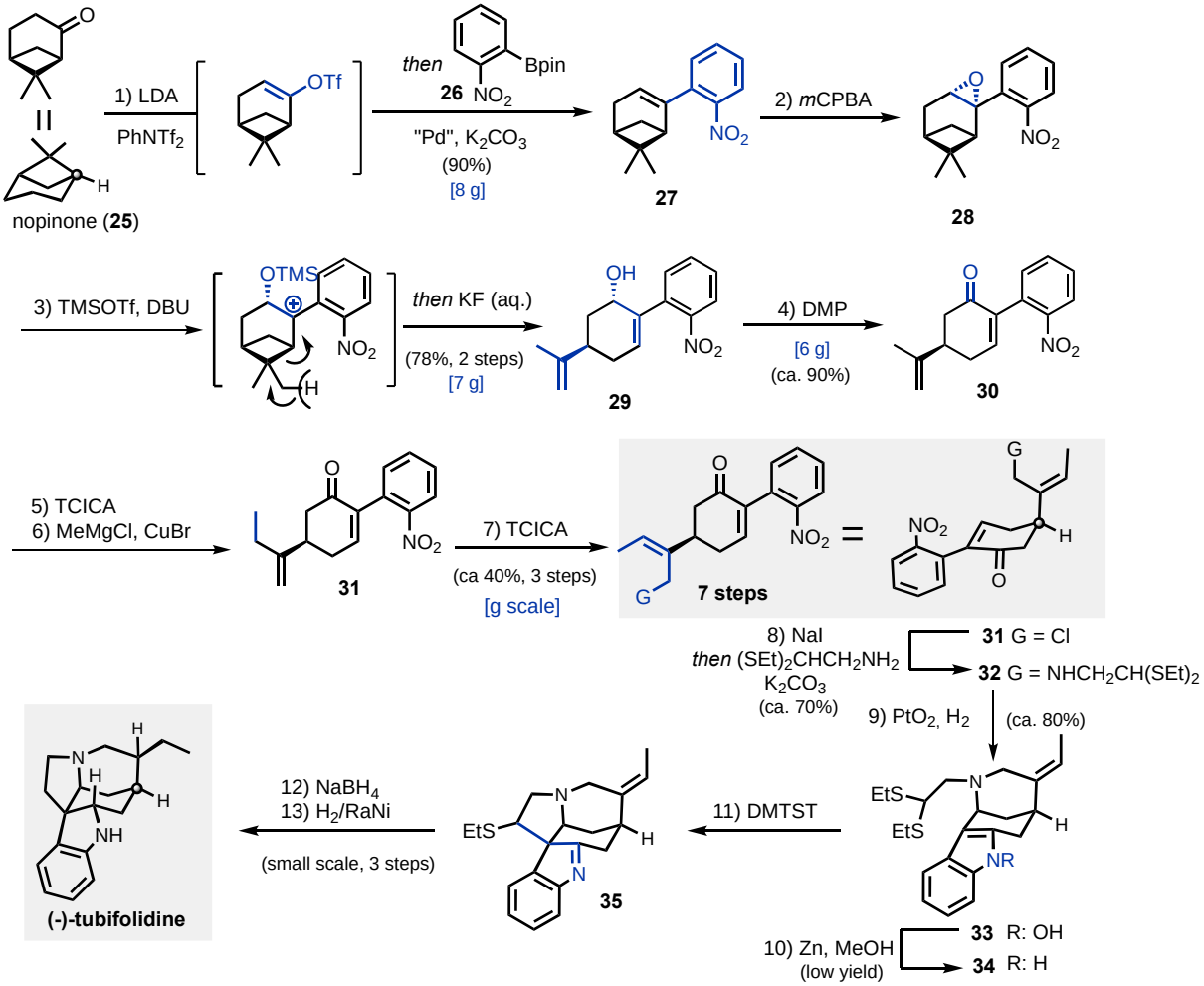
In summary, our aspidosperma research program has been finalized with the total syntheses of 5 natural products (minovincine, aspidofractinine, aspidospermidine, limaspermidine, 17-demethoxy-N-acetylcylindrocarine). Our synthetic routes are bioinspired approaches, which use several economic cascade transformations to rapidly generate molecular complexity. Several important intermediates were synthesized on a multigram scale, which are appropriate starting points for the synthesis of further alkaloids.

Synthesis of Curan Skeleton: Total Synthesis of (-)-Tubifolidine

Strychnos alkaloids are evergreen and widespread synthetic targets within the family of monoterpenoid indole alkaloids due to their complex and synthetically challenging structure and significant pharmacological activities of several of its members. Numerous syntheses of these alkaloids can be found in the literature; however, just few of them are asymmetric, scalable and divergent, which are frequently highlighted goals of modern total synthesis.
We planned our synthetic route to be based on a similar strategy to the one successfully utilized towards aspidosperma type alkaloids; the **24** key tricyclic intermediate was planned to be assembled via a nucleophilic cascade reaction using aziridine (**5**) as C2N synthon. Disappointingly, several attempts to reach this key intermediate had failed; therefore, we decided to redesign our synthetic route to the curan skeleton.



Our scalable synthesis has started from a chiral pool terpene nopinone (**25**), which was transformed into its enol triflate. The activated enol readily reacted in a Suzuki cross-coupling reaction with **26** boronic ester to furnish **27** alkene in one-pot with nearly quantitative yield. Epoxidation of the double bond with mCPBA provided **28** epoxide as a single diastereomer, which was used in the next step without further purification. TMSOTf induced skeletal rearrangement and cleavage of the formed silyl group yielded **29** alcohol. Then, the hydroxyl group was smoothly oxidized with Dess–Martin periodinane into the appropriate **30** ketone. This carvone-like molecule was further transformed utilizing a novel homologation sequence developed by us: 1) ene-type allylic chlorination with trichloroisocyanuric acid; 2) copper mediated C-C bond formation with methyl Grignard reagent. The selectivity of this reaction is remarkable, only the desired S_N reaction occurs, there aren't any products of 1,2- or 1,4-additons detected. Finally, a second ene-type chlorination produced our **31** key intermediate. This intermediate already bears the natural product like terpene carbon core, which highlights the power of the utilized C-C bond forming and cleaving reactions (cross-coupling, rearrangement, homologation). All steps of this skeletal reorganization sequence were optimized and scaled up to gram-scale, respectively.



The next step was an N-alkylation step, which yielded **32** N-alkylated intermediate. Furthermore, a catalytic hydrogenation step enabled the simultaneous formation of the

indole skeleton and the D ring. Interestingly, the reduction was not fully complete, since the obtained compound had a **33** N-hydroxyindole derivative instead of the **34** desired indole compound. To our delight, after vigorous optimization to reduce the N-hydroxyindole moiety, zinc in methanolic solution gave the appropriate result. The next step was a dearomative ring closure, where a thioether activation method was used to form the C ring. The ring closing steps were followed by the two final reduction steps: First, the indoline moiety was reduced by sodium-borohydride and after that the desulfuration and the reduction of the double bond in the side chain was accomplished by using Raney-Ni.
In summary, we designed a chiral pool based curan skeleton synthesis and completed the total synthesis of (-)-tubifolidine. In the future, we will optimize the transformations of hidroxyindole derivatives to accomplish an efficient synthetic route toward tubifolidine.

Presentation of the results

Our results are published in two research articles, which provoked several recognitions in the organic chemistry community.

Articles

- Sz. Varga, P. Angyal, G. Martin, O. Egyed, T. Holczbauer, T. Soós *Angew. Chem. Int. Ed.* **2020**, *59*, 13547-13551.
    - Highlighted in Synfacts 2020, 16, 0757
    - Highlighted on Organic Chemistry Portal (https://www.organic-chemistry.org/Highlights/2021/12April.shtm)
    - Part of Chemistry By Design Total Synthesis web almanac (https://chemistrybydesign.oia.arizona.edu/app/)
    - Video episode on the Simplifying Synthesis youtube chanel (https://youtu.be/YFVin82MsDE)
- G. Martin, P. Angyal, O. Egyed, Sz. Varga, T. Soós *Org. Lett.* **2020**, *22*, 4675-4679.
    - the most read article of the journal in June

Lectures:

- Short communication on European Colloquium on Heterocyclic Chemistry, 2021, Virtual
- Lecture on Heterocyclic and Elemental Organic Chemistry Committee of HAS, 2018
- Lectures on Alkaloid and Flavonoid Chemsitry Committee of HAS 2018, 2021 (2 lectures)
- Lecture on Lecture series in Bruckner Auditorium, Organic and Biomolecular Committee of HAS, 2018

Posters

- 16th Belgian Organic Synthesis Symposium 2018 (2 posters)
- 21st European Symposium on Organic Chemistry, 2019 (poster award)

Furthermore, 1 PhD thesis (Gábor Martin), 3 MSc thesis (Péter Angyal, Bence Sóvári, Bálint Zsigulics), 2 BSc thesis (Péter Angyal, Stefánia Gondár) was completed with the support of this research grant,