Chem. Listy *116*, 204–214 (2022) Review

TOTAL SYNTHESIS OF NATURAL PRODUCTS: CASE STUDIES IN THE EVALUATION OF NEW SYNTHETIC METHODS, STRUCTURAL ELUCIDATION AND DRUG DISCOVERY

LUKÁŠ RÝČEK

Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 9, 128 40 Prague 2
rycekl@natur.cuni.cz

Keywords: natural products and derivatives, total synthesis, biological activity

https://doi.org/10.54779/chl20220204

Table of Content

1. Introduction – total synthesis

Total synthesis is a privileged discipline in organic chemistry, which can be considered a mirror, reflecting the progress in the field. A lot has been written about it by more erudite people[1,2]. However, on this occasion, it is difficult not to look back or to point out at least a few milestones which have inevitably influenced this field. As the first step, one can consider the synthesis of urea by Wöhler in 1828, which had a crucial impact not only on organic chemistry but also on science in general and, in fact, affected our perception of life as such[3]. Another great milestone was Robinson synthesis of tropinone[4], which was far ahead of its time. Despite not being the first one, Robinson synthesis is a lesson about effectivity, and the attributes attached to it (one step, one-pot, multicomponent or biomimetic) can be easily found in the titles of scientific publications even today. And that was in 1917. Next, Woodward accomplishments must be mentioned, represented, for instance, by the syntheses of strychnine[5] or by the controversial synthesis of quinine[6] in 1946, which evoked an intense discussion on whether it had actually ever been performed (the definite answer was provided by Robert Williams – a student of Woodward – only at the beginning of the 21st century)[7], and last but not least, the one and only completed synthesis of vitamin B (ref.[8]). The fascinating fact is that all of these achievements were accomplished before the availability of analytical and purification tools, which are nowadays essential to every organic chemist, namely nuclear magnetic resonance (NMR) and chromatography. It was the lack of the analytical tools that was one of the major motivations for the synthesis of natural products, which served as a reliable tool for the confirmation of their structure. In this context, it is noteworthy to mention the Gates synthesis of morphine, which was a conclusion of a 120-year-long quest for the determination of the structure of this alkaloid[9].

The second half of the 20th century witnessed a shift in the complexity of targeted molecules and in the significance of total synthesis. The revolutionary discovery of NMR allowed a relatively easy structural analysis, and total synthesis did not primarily serve the purpose to answer questions related to structural problems. However, its new role probably meant an even greater challenge. Hand in hand with the development of novel chemical methodologies, it aimed to explore the limits of what we can achieve in the laboratory. This exciting period is mainly linked to the names of E. J. Corey, who established the

Dr. Lukáš Rýček, M.Sc. conducted his bachelor's studies at Masaryk University, Brno, Czech Republic and master's studies at Vrije Universiteit, Amsterdam, Holland. In 2015 he obtained a doctoral degree from Vienna University of Technology in Austria and between years 2015 and 2017 he worked as a postdoctoral fellow in the group of prof. Tomas Hudlicky at Brock University in Canada. After his return to the home country he worked for a year as a development chemist in Zentiva, k.s. and later as a postdoc in the group of prof. Martin Kotora at the Department of Organic Chemistry, Faculty of Science, Charles University in Prague. In 2020 he established his research group at the same department. His research interest includes development of new catalysts and chemistry of natural products.

* Author was awarded the Alfter Bader Prize for Organic Chemistry in 2020.

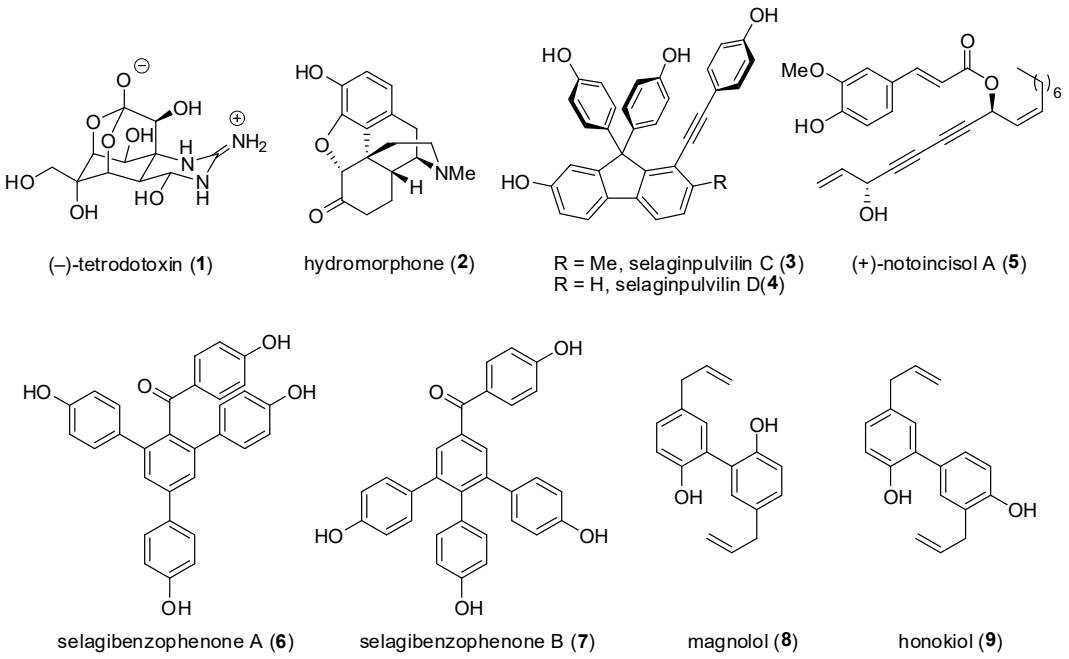
logical concept termed retrosynthetic analysis[10], and K. C. Nicolaou, who, with his syntheses of molecules, like brevetoxin[11], taxol[12] or vancomycin[13], convinced the synthetic community that nothing is impossible, at least when it comes to organic synthesis.

What is the purpose of total synthesis today, at the beginning of the 21st century? Is it still worth our attention or is it an anachronism that no longer has a place in modern science? This review aims to convince the reader that the first choice is the right one and that total synthesis remains a privileged discipline. The effort and the resources that need to be invested to be capable of preparing almost any molecule in the lab are often beyond the limits of acceptability. The driving force has shifted from the target to the means, and aspects such as creativity and mainly effectivity become pivotal. Utilizing the novel chemical reaction as a key step in the total synthesis of natural products is perhaps the most effective way to convince the community that the reaction is useful. On the other hand, during total synthesis, one is often forced to develop a novel transformation for the construction of certain structural motifs, and total synthesis therefore serves as a platform or inspiration for the development of new reactions. It is also important to state that, even in times of advanced NMR analysis, incorrect assignments of the structure of newly discovered natural products are not rare[14]. In most cases, the misassignment relates to stereochemical aspects of the molecules, but it is not always the case. Here, the total synthesis seems indispensable. Last but not least, total synthesis plays an important role in the development of new remedies. The importance of this aspect is underlined by the fact that about 10% of FDA approved drugs are natural product and about one third are compounds derived from them[15]. Particularly in the latter case, total synthesis is often the only means of accessing them.

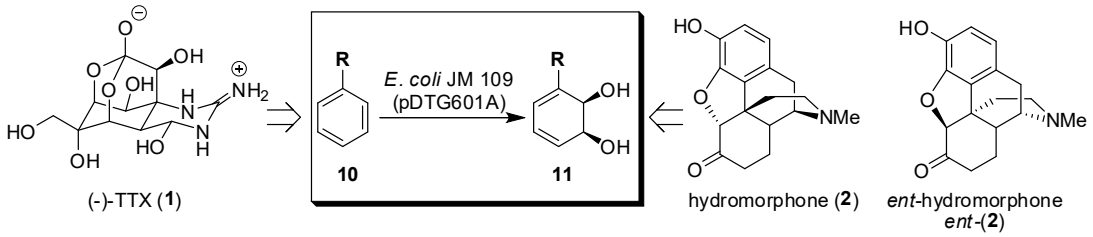
The following review deals with aspects discussed above in the context of our work. First, our strategy within the synthesis of natural products (–)-tetrodotoxin (TTX, **1**), morphinanes hydromorphone (**2**) and *ent*-hydromorphone (*ent*-**2**) and natural selaginpulvilines C (**3**) and D (**4**) is outlined. Modern synthetic transformations are utilized for an effective synthesis of these compounds. In the second part, the synthesis of the natural product notoincisol A (**5**) is discussed, and the absolute configuration of the natural compound is confirmed. Furthermore, the synthesis of the natural products selagibenzophenones A (**6**) and B (**7**) is described, which allowed us to determine that one of the natural products was incorrectly assigned. In the last part of the review, the synthesis of magnolol (**8**) and honokiol (**9**) derivatives and their biological profiling is discussed (Scheme 1).

2. Total synthesis and method development – (–)-tetrodotoxin, hydromorphone and selaginpulvilins C and D

Enzymatic *cis*-dihydroxylation (ED) of aromatic compounds is a useful transformation during which the achiral building blocks are converted into optically active products, utilizing genetically modified bacteria. The high enantioselectivity and the relatively high tolerance for many



Scheme 1. **Natural product relevant to this review**



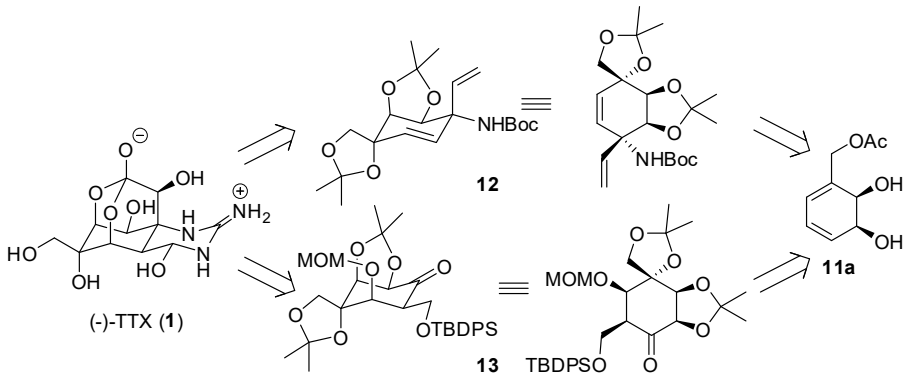
Scheme 2. **Enzymatic dihydroxylation of aromatics as a key step in synthesis of tetrodotoxin, hydromorphone and *ent*-hydromorphone**

functional groups (some of which serve as handles for further transformation) make this method attractive. The products have been used in many total syntheses, but the potential of this reaction does not seem to be exhausted[16]. Our targets were (–)-TTX (**1**) and hydromorphone (**2**). In the latter, our aim was to demonstrate that using enzymatic dihydroxylation and properly selecting a set of stereospecific operations can result in the synthesis of both enantiomers of this analgesic. (Scheme 2).

Tetrodotoxin (TTX, **1**) is a fascinating marine toxin with a long history, which is being produced by symbiotic bacteria living in some pufferfish[17]. The dish called *fugu*, prepared from this fish, is a delicacy of traditional Japanese cuisine, and its consumption combines a gastronomical with a high-adrenalin experience. The incorrect preparation of the fish can result in the consumer's poisoning and even death, and therefore the consumer must fully rely on the skills of the chef. The poisoning is caused by TTX, which acts as a blocker of sodium channels and restrains the spread of neuronal excitation. Subsequently, some of the vital functions fail, for instance, muscle functioning and breathing, and the intoxicated person eventually dies of suffocation. The specific feature of the TTX structure is the presence of oxoadamantyl and guanidine units, which, however, do not represent a great synthetic challenge. The true problem is the construction of the central six-membered ring where all of the carbons contain a stereogenic centre with an all-*cis* relative configuration.

The chemistry of TTX represented many challenges for chemists. The first of them was the elucidation of its complex structure. This problem was eventually solved by several chemists, including R. B. Woodword, in 1964. The next challenge was total synthesis. The first researcher to tackle this challenge was Kishi, in 1972 (ref.[18]). The key steps of the synthesis were the Diels-Alder reaction for the construction of the central cyclohexane ring and the Beckmann rearrangement for the introduction of the amino moiety into C8a in the early stage of the synthesis. The following sequence of precisely chosen regioselective and stereospecific operations, including epoxidations and nucleophilic substitutions, led to the formation of (±)-TTX in, remarkably, 32 steps. The next three decades witnessed a number of unfinished attempts, and only in 2003, Isobe revealed first synthesis of the optically pure (–)-TTX, commencing from a sugar as a chiorn[19]. The synthesis was 72 steps long, and the key for the construction of the central cyclohexane ring relied on intramolecular Mukaiyama aldol condensation. In the same year, DuBois described a significantly shorter synthesis of (–)-TTX, with 33 steps overall[20]. The two strategic operations, namely the central ring construction and the introduction of the amine, relied on a rhodium-catalysed intramolecular insertion of carbene and nitrene, respectively. One year later, Isobe described a shortened version of his previous synthesis in which (–)-TTX was prepared in 39 steps and the lengthy preparation of the cyclohexene ring from the first synthesis was shortened, relying on the Diels-Alder reaction[21]. In the context of this article, the two syntheses developed by Sato in 2005 (ref.[22]) and 2008 (ref.[23]) play an important role. Within the first one, (±)-TTX was prepared in 33 steps from *myo*-inositol, which represented the central core and was converted into the all-carbon containing intermediate in a series of C_1 homologation reactions. The second, 34 steps long synthesis of (–)-TTX commenced from D-glucose, which was converted into a highly-substituted central ring in a series of operations, using the Henry reaction as a key transformation. In 2017, Fukuyama described a 31-step-long synthesis of optically pure (–)-TTX starting from *p*-benzoquinone, representing the central ring of TTX, which was gradually decorated by various stereospecific transformations, including dihydroxylation, the Ichikawa rearrangement, or [3+2]-dipolar cycloaddition[24]. In 2020, Fukuyama and Yokoshima reported a 22-step-long synthesis of (–)-TTX, beginning however from an advanced starting material[25]. This strategy was based on a stereospecific Diels-Alder reaction and on a Curtius rearrangement for the construction of the central ring and introduction of the amine into the C8a position, respectively. For completeness, it is necessary to mention Ciufoini[26] and Alonoso[27] formal syntheses of (±)-TTX, which were achieved in 30 and 26 steps, respectively. A more detailed description of the syntheses is beyond the scope of this article, and the reader should refer to a review in which the history, biology and synthesis of this fascinating natural product is discussed in detail[17].

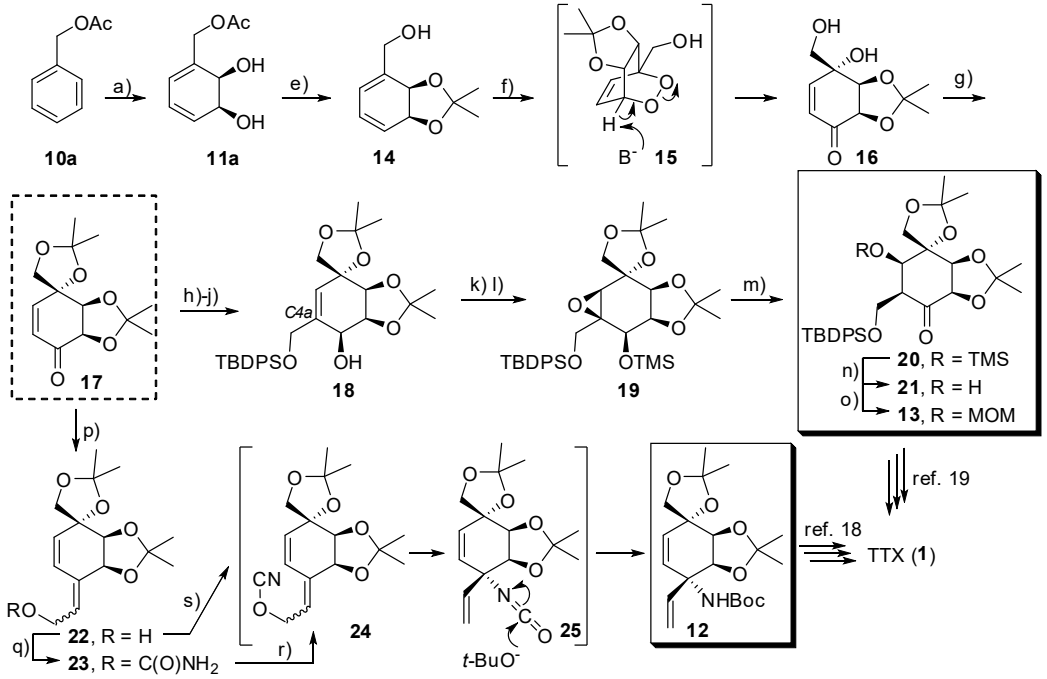
Our strategy was based on the utilization of ED in the preparation of the known advanced intermediates for the synthesis of TTX. Namely, we aimed to prepare Fukuyama intermediate **12** and Sato intermediate **13**. Our motivation was to shorten the synthesis of these intermediates,



Scheme 3. **Strategy for the formal synthesis of tetrodotoxin (5)**

which would impact the overall length of the synthesis of TTX[28] (Scheme 3).

The synthesis of both intermediates relied on the synthesis of the common intermediate enone **17**, which subsequently diverged into the synthesis of **12** and **13** (Scheme 4). The synthesis commenced by ED of benzyl acetate (**10a**). The resulting diendiol **11a** was protected as acetal in one operation, and the acetate was hydrolyzed to afford alcohol **14**. The elegant sequence consisting of a [4+2] cycloaddition with a singlet oxygen and an *in situ* base-initiated Korblum-DeLaMare rearrangement of endoperoxide **15** resulted in diol **16**, which was once again protected as acetal to yield the key enone **17**.



a) *E. coli* JM 109 (pDTG$_{601}$A), 10-15 g.L^{-1}; b) *p*-TsOH·H_2O, 2,2-DMP, 25 °C; then K_2CO_3, MeOH, 25 °C; f) O_2, TPP, hν, CH_2Cl_2; Et_3N, 25 °C, 68% (2 steps from **52**); g) *p*-TsOH·H_2O, 2,2-DMP, 25 °C, 80%; h) Br_2, CH_2Cl_2, 0 °C; Et_3N, 0 °C, 68%; i) $Pd(OAc)_2$, $Bu_3SnCH_2OTBDPS$, 1,4-dioxane, 90 °C, 64%; j) DIBAL, toluene, -78 to 0 °C, 94%; k) *m*-CPBA, $CHCl_3$, reflux; l) TMSCl, imidazole, CH_2Cl_2, 60% (2 steps); m) $TiCl_4$, CH_2Cl_2, -78 °C, 52 %; n) BF_3·Et_2O, CH_2Cl_2, 0 °C, 93%; o) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 25 °C, 79%; p) BuLi, $Ph_3P^+CH_2CH_2OH$ Br$^-$, THF, -30 °C to 25 °C, 64% (*E*/*Z*=8:1); q) $Cl_3CC(O)NCO$, CH_2Cl_2, 25 °C; Et_3N, MeOH, 25 °C, 96%; r) TFAA, i-Pr_2NEt, CH_2Cl_2, -78 °C to 25 °C; LiOt-Bu, -78 to 0 °C, 56%; s) BrCN, DMAP, CH_2Cl_2, 0 °C to 25 °C, 39%

Scheme 4. **Synthesis of advanced intermediates for the formal synthesis of tetrodotoxin (5)**

For the synthesis of Sato intermediate **13**, enone **17** was first converted into alcohol **18**. The hydroxymethyl group was introduced into the position C4a (TTX numbering) by a sequence of bromination and Stille coupling. The reduction of the keto group then provided alcohol **18**, which was further converted into the epoxide **19**. A treatment of this epoxide with Lewis acid resulted in hydride (and TMS group) migration and formation of ketone **20**. The presence of the bulky TMS group was essential for this transformation by forcing the moiety to adopt the equatorial position for the proper alignment of the orbitals and successful migration of the hydride. In the absence of the TMS group, the reaction was not observed. Further manipulation of the protecting groups led to the formation of Sato intermediate **12**. For the synthesis of Fukuyama amine **12**, enone **17** was first subjected to the Wittig olefination to yield alcohol **22** as a mixture of *E/Z* isomers, which was further converted into carbamate **23**. Dehydration of **23** led to the formation of two stereoisomers of cyanate **24**, which spontaneously underwent 1,3-Ichikawa transposition to isocyanate **25**. *In situ* nucleophilic attack of **25** by *t*-butoxide afforded Fukuyama intermediate **13**.

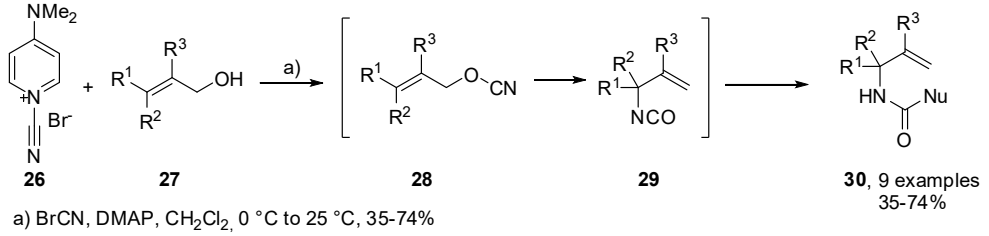
Alternatively, the two-step protocol for the preparation of the allylic amine **12** can be replaced by a one-step protocol. Alcohol **22** reacts with *in situ* prepared cyanoaminopyridine **26** to yield cyanate **28**, which undergoes 1,3-transposition, and upon the attack of the nucleophile provides the desired product. The reaction was general for various allylic alcohols, which provided desired allylic amines in 35–74 % yields (Scheme 5)[29].

In comparison with the originally reported synthesis of the aimed intermediates, our strategy, based on the enzymatic dihydroxylation of arenes, was beneficial. The preparation of Sato intermediate **13** was shortened from 21 to 11 steps, and the synthesis of Fukayama intermediate was shortened from 13 to six steps, starting from iodobenzene. The overall length of the (–)-TTX synthesis is therefore 25 steps via Sato and 21 steps via Fukuyama intermediate. The synthesis was significantly shortened, and the combination of our and Fukuyama strategy represents the shortest synthesis of the natural product.

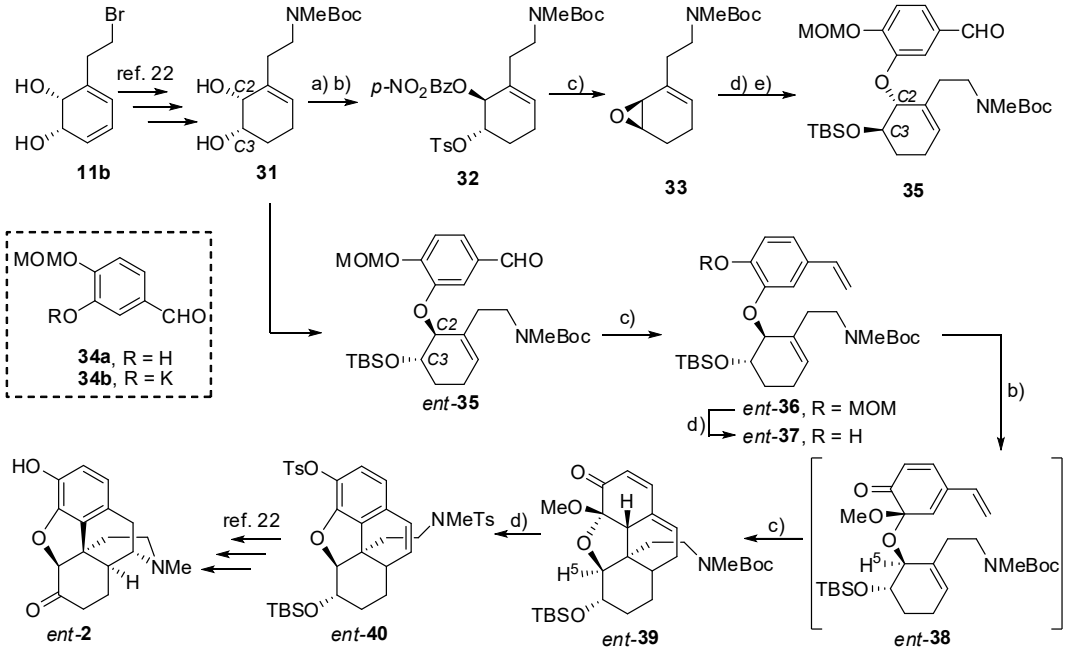
Morphine is the oldest remedy known, and to date it remains in the focus of scientists from many fields. As mentioned in the introduction, the first synthesis was described by Gates in 1952 (ref.[9]), and it is one of the milestones in the total synthesis of natural products. Since that time, more than thirty syntheses of various natural and unnatural morpinanes were described. Noteworthy to mention is for instance Rice syntheses of dihydrocodeine, achieved in 14 steps[30]. The detailed discussion of the syntheses of morphinanes is beyond the scope of the article. However, few syntheses, relevant to our work will be briefly mentioned, namely those that relied on the utilization of enzymatic dihydroxylation of arynes. Using this methodology, *ent*-codeine[31,32] was synthesized in 15 steps, codeine in 18 steps[33], hydrocodone in 21 steps[34] and, last but not least, the first generation of the synthesis of *ent*-hydromorphone was developed as well[35]. The synthesis was 12 steps long and served as the starting point for the development of our second generation *ent*-hydromorphone (*ent*-**2**) synthesis, by employing an oxidative dearomatization/[4+2] cycloaddition of phenol *ent*-**37** to construct the tetracyclic core *ent*-**39**. Our intention was to shed some light on the stereochemical course of the reaction and to extend the synthesis on the enantiomer with the natural configuration[36]. The synthesis began from diendiol **11b**, which, by a sequence of known steps, was converted into amine **31** (ref.[35]). Amine **31** was the last intermediate of the enantiodivergent synthesis of both isomers (Scheme 6). In the case of the unnatural *ent*-**2**, the C3 hydroxy group was selectively protected, and the allylic hydroxy group at C2 was subjected to a Mitsunobu reaction with phenol **34a** to afford ether *ent*-**35**. In another two steps, ether *ent*-**35** was converted into the key phenol *ent*-**37**. Alternatively, the hydroxy group at C2 in amine **31** can be subjected to the Mitsunobu reaction with *p*-nitrobenzoic acid, converting the hydoxyl group at C3 into tosylate **32**. The hydrolysis of the ester group then leads to the formation of epoxide **33**, which is regioselectively opened by phenolate **34b**, providing ether **35**, the enantiomer of previously synthesized *ent*-**35**. The two key enantiomeric intermediates were obtained when using enzymatic dihydroxylation and choosing the appropriate set of stereospecific operations.

For further purposes, only ether *ent*-**37** was used. It was submitted to hypervalent iodine-mediated oxidative dearomatization, and the formed ketal *ent*-**38** underwent *exo* [4+2] cycloaddition, affording the tetracyclic intermediate *ent*-**39**, which was converted into the known intermediate *ent*-(**4**), in two steps, finalizing the formal synthesis.

Within the program involving enzymatic dihydroxylation, we were able to use this transformation in the synthesis of both enantiomers of hydromorphone. In addition, the transformation was utilized in the shortest ever synthesis of marine alkaloid (–)-tetrodotoxin.



Scheme 5. **Direct preparation of allylic cyanates and their *in situ* rearrangement to isocyanates**



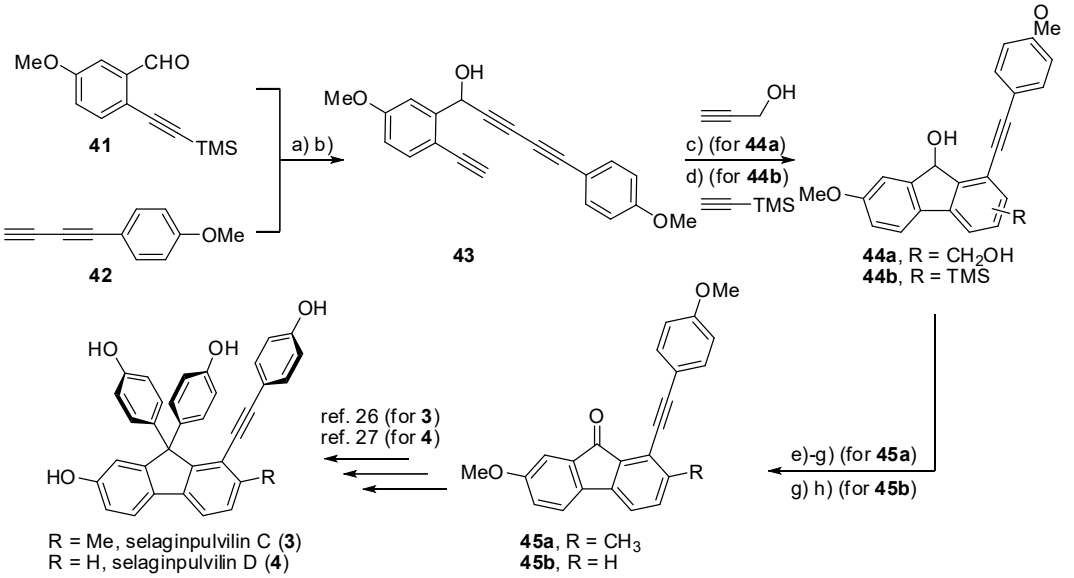
a) *p*-O_2NBzOH, DEAD, PPh_3, 71%; b) TsCl, Et_3N, 73%; c) MeONa, MeOH, THF, 88%; d) **34a**, DME, 18-crown-6, 78%; e) TBSCl, CH_2Cl_2, imidazole, -78 °C to 25 °C, 92% for *ent*-**35**, 85% (brsm) for **35**; f) **34b**, TMAD, PBu_3, 85%; g) CH_3PPh_3Br, BuLi, THF, 78 °C to 0 °C, then reflux, 4 h, 88%; h) $ZnBr_2$, $CH_3(CH_2)_{10}CH_2SH$, CH_2Cl_2, 25 °C, 10 min, 92%; i) DAIB, MeOH, -78 °C to 0 °C; j) PhMe, 80 °C, 20-30% (2 steps); k) TMSI, CH_2Cl_2, then TFA; 2. TsCl, Et_3N, CH_2Cl_2, 41% (2 steps)

Scheme 6. **Formal synthesis of hydromorphone and *ent*-hydromorphone**

Selaginpulvilins are natural products form *Selaginella pulvinata* with a rather unusual fluorene motif[37].

The shortest synthesis of the representative of this group is the four-step-long synthesis of selaginpulvilin D. The method relies on Suzuki coupling, on a sequence of S_EAr reactions and on Sonogashira coupling to construct the carbon skeleton of the natural product[38]. This method is however applicable only to Selaginpulvilin D. An alternative synthetic strategy relies on a hexadehydro Diels-Alder reaction of tetrayne, applied in the synthesis of selaginpulvilins C (**3**) and D (**4**), with the longest linear sequence of 12 steps[39]. A similar synthetic strategy was utilized in the synthesis of the same compounds relying on the dehydro Diels-Alder reaction of enyne-alkyne. The compounds are obtained in 9 synthetic steps[40,41]. Within the program involving the development of novel [2+2+2]-cyclotrimerization, we used this transformation for the alternative construction of the fluorene core of these compounds (Scheme 7)[42]. The key substrate **43** was obtained from diyne **42** and aldehyde **41**. Triyne **43** was further subjected to [2+2+2]-cyclotrimerization with the external alkyne **44**. The use of propargyl alcohol was beneficial for the synthesis of selaginpulvilin C. The presence of the polar hydroxy group was crucial for the good course and regioselectivity of the transformation, which preferably provided the desired *ortho* isomer. Oxidation of fluorenol **44a** and reduction of the benzylic alcohol resulted in the intermediate **45b**, which was previously described in the synthesis of **3** (ref.[43]), thereby achieving the formal synthesis. Within the synthesis of selaginpulvilin D (**4**), ethylenetrimethylsilane was used as the external alkyne. The absence of the polar moiety resulted in the formation of two regioisomers, *ortho* and *para*. However, after the oxidation of the fluorenols **44b** to the corresponding florenones, the removal of the TMS from both regioisomers provided the same compound, intermediate **45b**, also previously described in the synthesis of selaginpulvilin D (ref.[44]).

The overall length of both syntheses was 12 steps, and in contrast to the previously described syntheses, our approach offers a modular approach towards both targets, without requiring *de novo* preparation of the key intermediates for the key step. [2+2+2]-cyclotrimerization of the common substrate can be utilized in the synthesis of both natural products.



a) BuLI, THF, -78 °C; b) K_2CO_3, MeOH, 58% (2 steps); c) $RhCl(PPh_3)_3$, DCE, 90 °C, 48% (*ortho:meta* = 9,5:1); d) $RhCl(PPh_3)_3$, DCE, 25 °C, 36% (*ortho:meta* = 6,8:1); e) CBr_4, PPh_3, CH_2Cl_2, 25 °C, 43%; f) Zn, NH_4Cl, H_2O/THF, 25 °C; g) PCC, celite, CH_2Cl_2, 25 °C, 36% after 2 steps for **45a**, 82% for **45b** ; h) TBAF, 70 °C, 78%.

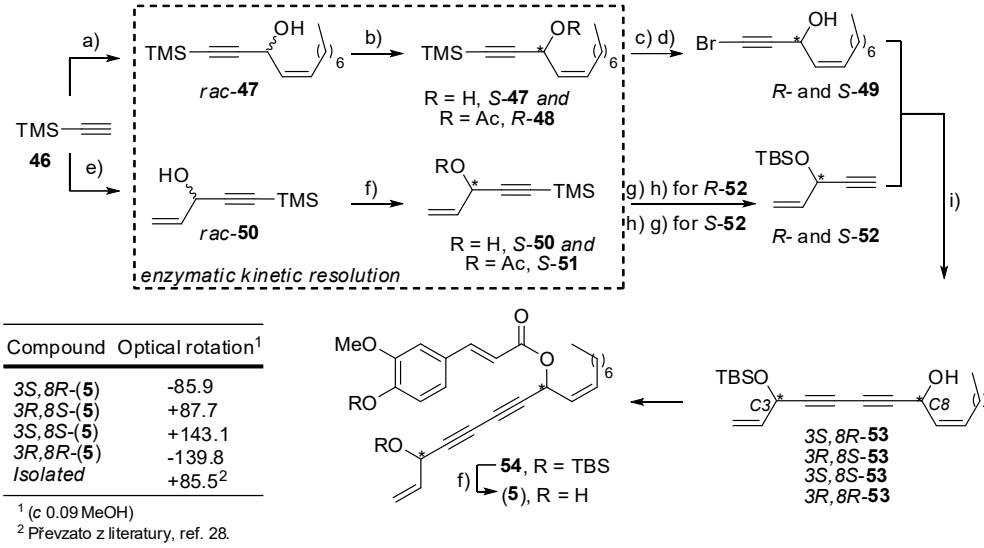
Scheme 7. **[2+2+2]-cyclotrimerization in the formal synthesis of selaginpulvilins C and D**

3. Total synthesis and structural aspects of natural products – notoincisol A and selagibenzophenones A and B

Notoincisol A (**5**), isolated from *Notopterygium incisum* is a natural agonist of PPARγ receptors[45]. To our best knowledge, the natural product had not been synthesized before our work. The goals were to synthesize all stereoisomers of **5** and to confirm the absolute stereochemistry of the natural compound by comparing analytical data of synthetic and isolated compound. We aimed to evaluate the biological effect on $GABA_A$ and PPARγ receptors[46].

The synthetic strategy relied on the preparation of the racemic alcohols *rac*-**47** and *rac*-**50** and on their enzymatic kinetic resolution by lipase PS (Scheme 8), thereby preparing the optically active components of both alcohols, namely alcohols *S*-**47** and *S*-**50** and acetates *R*-**48** and *R*-**51**, which would be further converted into the bromoalkynes *S*- and *R*-**49** and alkynes *S*- and *R*-**52**. The Cadiot-Chodkiewicz reaction of each of the enantiomers of the bromoalkyne **49** with each of the enantiomers of the alkyne **52** would furnish the desired stereoisomers of skeleton **53**. Esterification of the hydroxy group in the position C8 with TBS-protected ferulic acid and subsequent cleavage of TBS groups led to the formation of all the stereoisomers of the natural product **5**. The value of the optical rotation of the isolated compound corresponded to that of the isomer with an absolute configuration of the chiral centres *3R,8S*, and this configuration was therefore ascribed to the naturally occurring notoincisol A (**5**). Only this isomer was capable of activating PPARγ. Docking studies revealed that the change in the absolute configuration at any of the chiral centre inevitably leads to the loss of bonding interactions with the amino acids in the binding pocket. Both diastereomers of the natural products have shown weak allosteric modulatory properties of $GABA_A$ receptor. In addition, the molecules activate the receptor even in the absence of the endogenous ligand GABA. The agonistic effect at these receptors is rather rare, but both molecules displayed only weak modulatory and agonistic effects, and thus their physiological use is rather unlikely.

Selagibenzophenones A (**6**) and B (**7**) were described as natural products isolated from *Selaginella pulvinata* and *Selaginella tamariscana*, respectively. They differ in the substitution pattern of the central aromatic ring. While in **6**, 4-hydroxyphenyl groups are located in positions 2,4, and 6 (ref.[47]), and compound **7** contains the same groups in positions 3, 4, and 5 (ref.[48,49]) (Scheme 9). Despite this difference, the published NMR spectra share striking similarities, which can be either coincidental or the result of the incorrect assignment of the compounds. For this reason, we synthesized both compounds and compared the spectral characteristics for both synthetic products and the published spectra for the isolated compounds[50]. The choice of the suitable starting material was the key consideration as its substitution pattern is reflected in the substitution of the final product. Isomer **6** was therefore prepared from commercially available 2,4,6-tribromobenzaldehyde (**55**) utilizing Suzuki coupling, addition of lithiated aromatic species to aldehyde **56**, subsequent oxidation and libera-

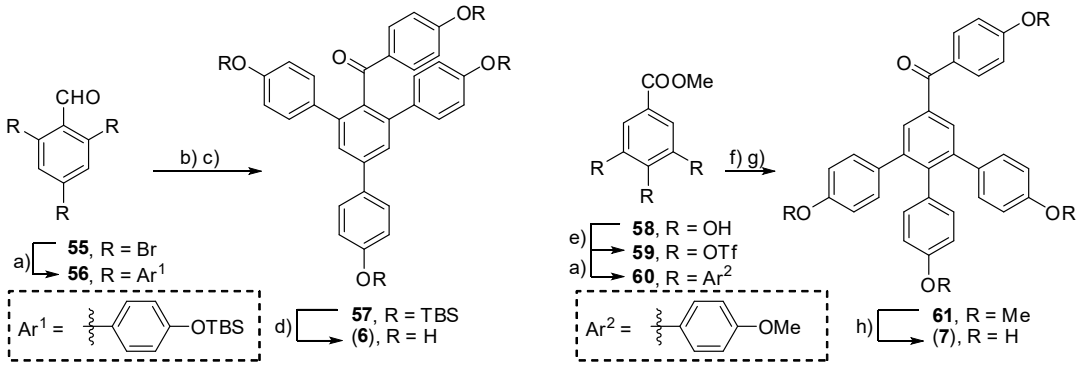


Compound	Optical rotation[1]
3S,8R-(**5**)	-85.9
3R,8S-(**5**)	+87.7
3S,8S-(**5**)	+143.1
3R,8R-(**5**)	-139.8
Isolated	+85.5[2]

[1] (*c* 0.09 MeOH)
[2] Převzato z literatury, ref. 28.

a) BuLi, dec-2-enoen, THF, 0 °C to rt, 4 h; b) Amano lipase PS, MTBE, vinyl acetate, rt, 4 h, 48%, (*ee* > 99%) for *R*-**48**, 45%, (*ee* > 99%) for *S*-**47**; c) K_2CO_3, MeOH, rt, 2 h; d) $AgNO_3$, NBS, acetone, 2 h, rt, 69% for *R*-**49** (2 steps), 62% for *S*-**30** (2 steps) e) BuLi, acrolein, THF, 0 °C to rt, 4 h, 89%; f) Amano lipase PS, MTBE, vinyl acetate, rt, 4 h, 48%, (*ee* > 99%) for *R*-**51**, 33%, (ee > 99%) for *S*-**51**; g) K_2CO_3, MeOH, rt, 2 h; h) TBSCl, imidazole, CH_2Cl_2, 25 °C, 75% for *R*-**52** (2 steps), 73% for *S*-**52** (2 steps); i) $NH_2OH{\cdot}HCl$, $EtNH_2$, CuCl, H_2O/MeOH, 0 °C to rt, 2 h, 64-66%; b) TBS-ferulic acid, EDCI, DMAP c) HF·pyridine, THF, 0-25 °C, 75-83%.

Scheme 8. **Total synthesis of notoincisol A and stereoisomers**



a) $Pd(PPh_3)_4$, K_2CO_3, PhH/H_2O, 90 °C, Ar^1-$B(OH)_2$, 79% for **56**, Ar^2-$B(OH)_2$, 79% for **60**; b) Ar^1-Br, *t*-BuLi, THF, -78 °C; c) PCC, CH_2Cl_2, celite, 25 °C, 57% (2 steps); d) HF·pyridine, 82%; e) Tf_2O, CH_2Cl_2, Et_3N, 0 to 25 °C, 96%; f) DIBAL-H, -78 °C, toluene *then* PCC, CH_2Cl_2, celite, 25 °C, 83%; g) Ar^2-MgBr, THF, 25 °C *then* PCC, CH_2Cl_2, celite, 25 °C, 61%; h) BBr_3, CH_2Cl_2, 25 °C, 36%.

Scheme 9. **Synthesis of selagibenzophenone A and selagibenzophenone B to confirm the structure of natural products**

tion of the phenol groups. The strategy for the synthesis of **7** was similar and commenced from methyl gallate. The hydroxy groups were first converted into triflate **59**, which underwent cross-coupling, with three equivalents of *p*-methoxyphenylboronic acid to yield the trisarylated ester of benzoic acid **60**, which was further reduced to aldehyde and, as compound **6**, subjected to the addition of the Grignard reagent and oxidation to yield ketone **61**. Deprotection of the phenols resulted in the formation of **7**. The synthetic isomers showed significantly different NMR spectra and therefore the coincidental resemblance of the spectra of isolated compounds can be ruled out. The comparison of synthetic and reported spectra led to the conclusions that the structure of the compound described in the litera-

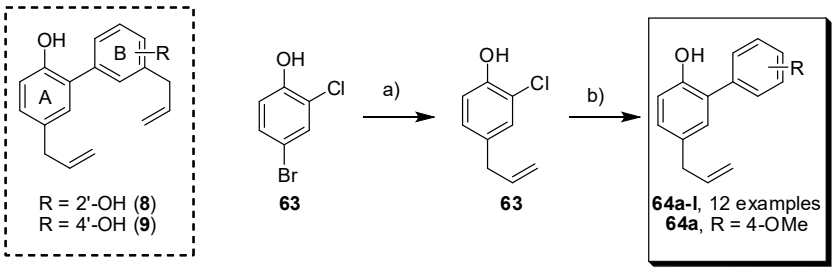
ture as selagibenzophenone B was incorrectly assigned and that in fact the isolated compound was selagibenzophenone A.

4. Total synthesis and development of biologically active compounds

Magnolol (**8**) and honokiol (**9**) are natural products from *Magnolia officinalis*[51] with a broad spectrum of biological activities, as allosteric modulators of $GABA_A$ receptors and agonists of nuclear transcription factors PPARγ. These receptors were in the centre of our attention. The broad spectra of biological effects of compounds is only a seeming advantage. The promiscuity towards pharmaceutical targets can result into side effects, and therefore the development of target (or even subtype) specific agents is desired. Such a strategy was crucial for our project aimed at developingderivatives of **8** and **9**. In the initial phase of the project, we developed simplified derivatives of these compounds, which contained an unchanged aromatic ring A, common to both natural products, and a simplified aromatic ring B, where the original substitution (allyl and hydroxy group) was replaced by one substituent with various chemical properties (Scheme 10)[52]. Twelve new derivatives, **64-a-l**, were prepared, starting from 4-bromo-2-clorophenol (**63**), in a sequence of two regioselective cross-couplings. Among these compounds, derivative **64a** showed the most interesting properties at $GABA_A$ α1β2γ2 ($\%I_{GABA}$ = 440±60 at 3 μM and 913±286 at 10 μM. For comparison: magnolol $\%I_{GABA}$ = 338±93 at 3 μM a 702±86 at 10 μM, honokiol $\%I_{GABA}$ = 162±31 at 3 μM and 594±131 at 10 μM). Moreover, compound **64a** displayed a significantly lower activity at α1β1γ2 and did not interact with all other tested receptors (PPARγ and RXRα), which makes this compound a selective $GABA_A$ α1β2γ2 modulator. In addition to **64a**, several other compounds were identified as promising RXRα agonists with no activity against $GABA_A$ receptors (unpublished data).

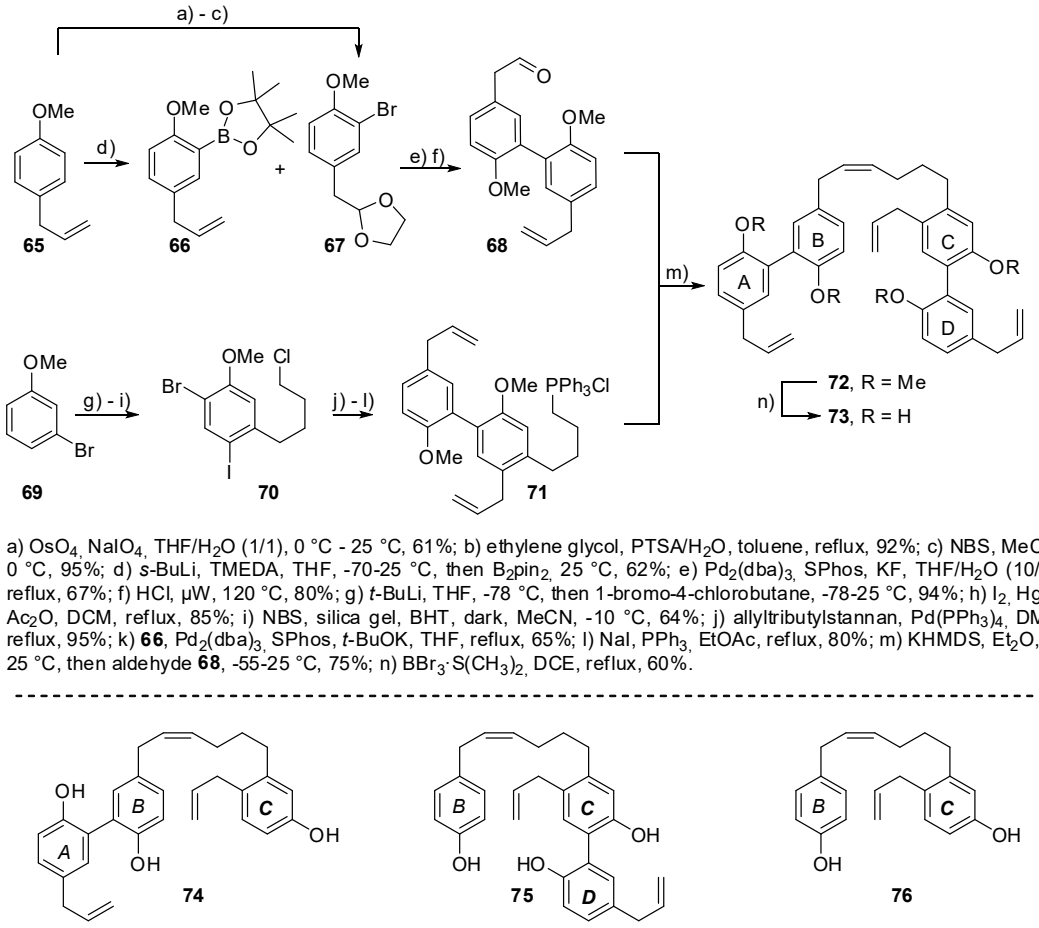
With selective agents for $GABA_A$ and RXRα receptors, we focused on the development of selective agonists for PPARγ. Our work was based on an X-Ray structure of the PPARγ-magnolol aggregate, which indicated that there are two molecules of **8** bound in the binding pocket in close proximity[53]. Our strategy relied on connecting the two magnolol units with a suitable linker to avoid compromising the desired orientation required for the effective binding[54]. Using molecular docking, compound **73** was proposed, where the linker connects the allylic moiety of the magnolol unit with the aromatic ring of the second magnolol molecule (Scheme 11). The convergent synthesis of the dimer **73** commenced from 4-allylanisole (**65**), which was converted into boronic acid **66** and bromide **67**. Cross-coupling of **66** and **67** followed by cleavage of acetal furnished aldehyde **68**. At the same time, 3-bromoanisole (**69**) was in three steps resulted in the anisole **70**, which, upon two regioselective cross-couplings and nucleophilic substitution of chloride by triphenylphosphine, provided the phosphonium salt **71**. Wittig olefination and deprotection of phenols led to the desired dimer **73**. Dimer **73** showed 12× higher affinity to the PPARγ receptor than magnolol (**9**) (*Ki* = 5,03 nM for **73** compared to 64,42 nM for **9**). The compound did not interact with the RXRα receptor.

The structural complexity of the dimer and its relatively difficult synthesis prompted us to develop simplified versions of **73** (ref.[55]). Two sesquimagnolols **74** and **75** missing one of the peripheral aromatic rings (ring D in **74** and ring A in **75**), and truncated dimer **76**, which lacked both peripheral aromatic rings, A and D, were synthesized (Scheme 11). The synthesis was performed similarly to the synthesis of **73** and therefore will not be discussed here, so the reader is encouraged to read the original literature[55]. Both sesquimagnolols, **74** and **75**, showed agonistic properties comparable to those of dimer **73**, with no activity at the RXRα receptor. The antagonistic effect of the truncated dimer **76** was surprising. Docking studies revealed that **76** binds to the binding site of another known antagonist, botulinic acid.



a) PdEn40, dppf, potassium allyltrifluoroborate (**9**), K_2CO_3, 1,4-dioxane/H_2O, 80%; b) arylboronic acid, Pd_2dba_3, SPhos, KF, 1,4-dioxane/H_2O, 34-86%

Scheme 10. **Synthesis of simplified derivatives of magnolol (8) and honokiol (9)**



a) OsO_4, $NaIO_4$, THF/H_2O (1/1), 0 °C - 25 °C, 61%; b) ethylene glycol, PTSA/H_2O, toluene, reflux, 92%; c) NBS, MeCN, 0 °C, 95%; d) *s*-BuLi, TMEDA, THF, -70-25 °C, then B_2pin_2, 25 °C, 62%; e) $Pd_2(dba)_3$, SPhos, KF, THF/H_2O (10/1), reflux, 67%; f) HCl, μW, 120 °C, 80%; g) *t*-BuLi, THF, -78 °C, then 1-bromo-4-chlorobutane, -78-25 °C, 94%; h) I_2, HgO, Ac_2O, DCM, reflux, 85%; i) NBS, silica gel, BHT, dark, MeCN, -10 °C, 64%; j) allyltributylstannan, $Pd(PPh_3)_4$, DMF, reflux, 95%; k) **66**, $Pd_2(dba)_3$, SPhos, *t*-BuOK, THF, reflux, 65%; l) NaI, PPh_3, EtOAc, reflux, 80%; m) KHMDS, Et_2O, 0-25 °C, then aldehyde **68**, -55-25 °C, 75%; n) $BBr_3 \cdot S(CH_3)_2$, DCE, reflux, 60%.

Scheme 11. **Synthesis of the magnolol dimer and the structure of simplified dimers**

5. Conclusions

In our research endeavours, we were able to demonstrate the utility of modern synthetic strategies (enzymatic dihydroxylation and transition metal catalysis) in the synthesis of complex natural products (–)-tetrodotoxin, morphinan hydromorphone and its enantiomer, as well as selaginpulvilins C and D. Our work resulted in new information on structural aspects of notoincisol A, confirming the absolute configuration of the natural product and clarifying the structure of selagibenzophenones A and B. Last but not least, we developed several derivatives of natural products magnolol and honokiol, which displayed better biological properties than the lead structures.

REFERENCES

1. Nicolaou K. C., Hale C. R. H.: Nat. Sci. Rev. *1*, 233 (2016).
2. Baran P.: J. Am. Chem. Soc. *140*, 4751 (2018).
3. Wöhler F.: Ann. Phys. *88*, 253 (1828).
4. Robinson R.: J. Chem. Soc. Faraday Trans. *111*, 762 (1917).
5. Woodward R. B., Cava M. P., Ollis W. D.: J. Am. Chem. Soc. *76*, 4749 (1954).
6. Woodward R. B., Doering W. E.: J. Am. Chem. Soc. *66*, 849 (1944).
7. Smith A. C., Williams R. M.: Angew. Chem. Int. Ed. *47*, 1736 (2008).
8. Woodward R. B.: Pure Appl. Chem. *33*, 145 (1973).
9. Gates M., Tschudi G.: J. Am. Chem. Soc. *74*, 1262 (1952).
10. Corey E. J., Xue-Min Cheng: *The Logic of Chemical Synthesis*. John Wiley, New York 1989.
11. Nicolaou K. C., Yang Z., Shi G., Gunzner J. L. Agrios K. A., Gärtner P.: Nature *392*, 264 (1998)
12. Nicolaou K. C., Yang Z., Liu J. J.: Nature *367*, 630 (1994).
13. Nicolaou K. V. Mitchell H. J. Nareshkumar F. J., Winssinger N., Hughes R., Bando T.: Angew. Chem Int. Ed. *38*, 240 (1999).
14. Nicolaou K. C., Snyder S. A.: Angew. Chem. Int. Ed.

44, 1012 (2005).
15. Patridge E., Gareiss P., Kinch M. S., Hoyer D.: Drug Discov. Today. *21*, 204 (2016).
16. Bedard K., Hudlicky T., in book: *Strategies and tactics in Organic Synthesis* (Harmata, M., ed.) *v tisku*, 2020.
17. Makarova M., Rycek L., Hajicek J., Baidilov D., Hudlicky T.: Angew. Chem. Int. Ed. *59*, 18338 (2019).
18. Kishi Y., Fukuyama T., Aratani M., Nakatsubo F., Goto T., Inoue S., Tanino H., Sugiura S., Kakoi H.: J. Am. Chem. Soc. *94*, 9219 (1972).
19. Ohyabu N., Nishokawa T., Isobe M.: J. Am. Chem. Soc. *43*, 4782 (2003).
20. Hinman A., DuBois J.: J. Am. Chem. Soc. *125*, 11510 (2003).
21. Nishokawa T., Urabe D., Isobe M.: Angew. Chem. Int. Ed. *43*, 4782 (2004).
22. Sato K., Akai S., Shoji H., Sugita N., Oshawa T., Kogure T., Shoji H., Yoshimura J.: J. Org. Chem. *70*, 7496 (2005).
23. Sato K. and 10 co-authors: J. Org. Chem. *73*, 1234 (2008).
24. Maehara T., Motoyama K., Toma T., Yokoshima S., Fukuyama T.: Angew. Chem. Int. Ed. *56*, 1549 (2017).
25. Murakami K., Toma T., Fukuyama T., Yokoshima S.: Angew. Chem. Int. Ed. *59*, 6253 (2020).
26. Xu S., Ciufolini M. A.: Org. Lett. *17*, 2424 (2015).
27. Cagide-Fagín F., Alonso R.: Eur. J. Org. Chem. *2010*, 6741.
28. Baidilov D., Rycek L., Trant J. F., Froese J., Murphy B., Hudlicky T.: Angew. Chem. Int. Ed. *57*, 10994 (2018).
29. Baidilov D., Makarova M., Rycek L., Hudlicky T.: Synthesis *50*, 4606 (2018).
30. Rice K. C.: J. Org. Chem. *45*, 3135 (1980).
31. Omori A. T., Finn K. J., Leisch H., Carroll R. J., Hudlicky T.: Synlett *2007*, 2859.
32. Endoma-Arias M. A. A., Hudlicky J. R., Simionescu R., Hudlicky T.: Adv. Synth. Catal. *356*, 333 (2014).
33. Leisch H., Omori A. T., Finn K. J., Gilmet J., Bissett T., Ilceski D., Hudlicky T.: Tetrahedron *65*, 9862 (2009).
34. Varghese V., Hudlicky T.: Synlett *24*, 369 (2013).
35. Verghese V., Hudlicky T.: Angew. Chem. Int. Ed. *53*, 4355 (2014).
36. Rycek L., Hayward J. J., Latif M. A., Tanko J., Simionescu R., Hudlicky T.: J. Org. Chem. *81*, 10930 (2016).
37. Liu X., Luo H.-B., Huang Y.-Y., Bao J.-M., Tang G.-H., Chen Y.-Y., Wang J., Yin S. Org. Lett. *16*, 282 (2014).
38. Sowden M. J., Sherburn M. S.: Org. Lett. *19*, 636 (2017).
39. Karmakar R., Lee D.: Org. Lett. *18*, 6105 (2018).
40. Chinta B. S., Baire B.: Org. Biomol. Chem. *16*, 262 (2018).
41. Chinta B. S., Baire B.: Org. Biomol. Chem. *15*, 5908 (2017).
42. Rycek L., Mateus M., Byetlerová N., Kotora M.: Org. Lett. *23*, 4511 (2021).
43. Shankar B., Baire B.: Org. Biomol. Chem. *16*, 262 (2018).
44. Shankar B., Baire B.: Org. Biomol. Chem. *15*, 5908 (2017).
45. Liu X. a 12 spoluatorů: J. Nat. Prod. *77*, 2513 (2014).
46. Rycek L. and 12 co-authors: J. Nat. Prod. *81*, 2419 (2018).
47. Liu X., Tang G.-H., Weng H.-Z., Zhang J.-Z., Xu Y.-K., Yin S.: J. Asian Nat. Prod. Res. *20*, 1123 (2018).
48. Liu R., Zou H., Zou Y.-X., Cheng F., Yu X., Xu P.S., Li X. M., Li D. Xu K.-P., Tan G.-S.: Nat. Prod. Res. *34*, 2709 (2020).
49. Wang C.-G., Yao W.-N., Zhang B., Hua J., Liang D., Wang H.-S.: Bioorg. Med. Chem. Lett. *28*, 2431 (2018).
50. Lapinskaite R., Malatinec Š., Mateus M., Rycek L.: Catalysts *11*, 708 (2021).
51. Lin Y., Li Y., Zeng Y., Tian B., Qu X., Yuan Q., Song Y.: Front. Pharmacol. *12*, 632767 (2021).
52. Rycek L., Puthenkalam R., Schnürch M., Ernst M., Mihivilovic M. D.: Bioorg. Med. Chem. *25*, 400 (2015).
53. Zhang H., Xu X., Chen L., Hu L., Jiang H., Shen X.: PLoS One *6*, e28253 (2011).
54. Dreier D. a 11 spoluautorů: Sci. Rep. *7*, 6022 (2017).
55. Dreier D., Resetar M., Temml V., Rycek L., Kratena N., Schnürch M., Schuster D., Dirsch V. M., Mihovilovic M. D.: Org. Biomol. Chem. *16*, 7019 (2018).

Abstract

This review summarizes our work in the field of synthesis of natural products and their derivatives. Application of modern synthetic method is discussed in the context of the syntheses of both enantiomers of hydromorphone, (–)-tetrodotoxin (a marine toxin), and selaginpulvilins C and D (natural fluorene derivatives). Further, synthesis of notoincisol A, selagibenzophenones A and B is described to clarify the structural aspects of the compounds. Last but not least, synthesis and pharmaceutical profilation of derivatives of magnolol and honokiol is discussed as well.

● Rýček L.: Chem. Listy *116*, 204–214 (2022).
● https://doi.org/10.54779/chl20220204