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

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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 21\(^{\text{st}}\) 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 20\(^{\text{th}}\) 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...
logical concept termed retrosynthetic analysis\textsuperscript{10}, and K. C. Nicolaou, who, with his syntheses of molecules, like brevetoxin\textsuperscript{11}, taxol\textsuperscript{12} or vancomycin\textsuperscript{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 21\textsuperscript{st} 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 efectivity 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\textsuperscript{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\textsuperscript{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 (\textit{–}tetrodotoxin (TTX, 1)), morphinanes hydromorphone (2) and \textit{ent}-hydromorphone (\textit{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 – (\textit{–})-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](image-url)
Enzymatic dihydroxylation of aromatics as a key step in synthesis of tetrodotoxin, hydromorphone and ent-hydromorphone

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. 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. The dish called fugu, prepared from this fish, is a delicacy of traditional Japanese cuisine, and its consumption combines a gastronomic 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 stereo- genic 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. Woodward, in 1964. The next challenge was total synthesis. The first researcher to tackle this challenge was Kishi, in 1972 (ref.17). The key steps of the synthesis were the Diels-Alder reaction for the construction of the central cyclohexene ring and the Beckmann rearrangement for the introduction of the amino moiety into C8α 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 chiron. The synthesis was 72 steps long, and the key for the construction of the central cyclohexene ring relied on intramolecular Mukaiyama aldol condensation. In the same year, DuBois described a significantly shorter synthesis of (-)-TTX, with 33 steps overall. 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. In the context of this article, the two syntheses developed by Sato in 2005 (ref.20) and 2008 (ref.21) 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 C1 homologation reactions. The second, 34 steps long synthesis of (-)-TTX commenced from α-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 stereo- specific transformations, including dihydroxylation, the Ichikawa rearrangement, or [3+2]-dipolar cycloaddition44. In 2020, Fukuyama and Yokshima reported a 22-step-long synthesis of (-)-TTX, beginning however from an advanced starting material. 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 C8α position, respectively. For completeness, it is necessary to mention Ciufolini and Alonosó 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.

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,
which would impact the overall length of the synthesis of TTX28 (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 dieniodiol 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.

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).

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 Fukuyama 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.5), 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 morphinanes were described. Noteworthy to mention is for instance Rice syntheses of dihydrocodeine, achieved in 14 steps10. 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-codeine31,32 was synthesized in 15 steps, codeine in 18 steps33, hydrocodeine in 21 steps34 and, last but not least, the first generation of the synthesis of ent-hydromorphine was developed as well35. The synthesis was 12 steps long and served as the starting point for the development of our second generation ent-hydromorphine (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 stereochmical course of the reaction and to extend the synthesis on the enantiomer with the natural configuration36. The synthesis began from dieniodiol 11b, which, by a sequence of known steps, was converted into amine 31 (ref.25). 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 hydroxyl 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 deaomtization, 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

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**Chem. Listy 116, 204–214 (2022) Review**
Selaginulvinils are natural products from Selaginella pulvinata with a rather unusual fluorene motif. The shortest synthesis of the representative of this group is the four-step-long synthesis of selaginulvinil D. The method relies on Suzuki coupling, on a sequence of SAr reactions and on Sonogashira coupling to construct the carbon skeleton of the natural product. This method is however applicable only to Selaginulvinil D. An alternative synthetic strategy relies on a hexaehydro Diels-Alder reaction of tetryne, applied in the synthesis of selaginulvinils C (3) and D (4), with the longest linear sequence of 12 steps. 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. 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. 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 selaginulvinil 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 fluorenone 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 selaginulvinil D (4), ethylene- trimethylsilane 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 fluorenone 44b to the corresponding fluorenoles, the removal of the TMS from both regioisomers provided the same compound, intermediate 45b, also previously described in the synthesis of selaginulvinil D (ref. 43).

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.
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. 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.

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 pulvina 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. 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-
Scheme 8. Total synthesis of notocinisol A and stereoisomers

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 with a broad spectrum of biological activities, as allosteric modulators of GABA\textsubscript{A} receptors and agonists of nuclear transcription factors PPAR\textsubscript{γ}. 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 developing derivatives 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). Twelve new derivatives, 64a-1, were prepared, starting from 4-bromo-2-chlorophenol (63), in a sequence of two regioselective cross-couplings. Among these compounds, derivative 64a showed the most interesting properties at GABA\textsubscript{A}, 1\textbeta}2\gamma 2 (\%\textsubscript{GABA} = 440±60 at 3 \textmu M and 913±286 at 10 \textmu M. For comparison: magnolol \%\textsubscript{GABA} = 338±93 at 3 \textmu M a 702±86 at 10 \textmu M, honokiol \%\textsubscript{GABA} = 162±31 at 3 \textmu M and 594±131 at 10 \textmu M). Moreover, compound 64a displayed a significantly lower activity at α1β1γ2 and did not interact with all other tested receptors (PPAR\textsubscript{γ} and RXR\textsubscript{α}), which makes this compound a selective GABA\textsubscript{A}, α1β2γ2 modulator. In addition to 64a, several other compounds were identified as promising RXR\textsubscript{α} agonists with no activity against GABA\textsubscript{A} receptors (unpublished data).

With selective agents for GABA\textsubscript{A} and RXR\textsubscript{α} receptors, we focused on the development of selective agonists for PPAR\textsubscript{γ}. Our work was based on an X-Ray structure of the PPAR\textsubscript{γ}-magnolol aggregate, which indicated that there are two molecules of 8 bound in the binding pocket in close proximity. Our strategy relied on connecting the two magnolol units with a suitable linker to avoid compromising the desired orientation required for the effective binding. Using molecular docking, compound 73 was proposed, where the linker connects the aliphic 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 acetyl 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 PPAR\textsubscript{γ} receptor than magnolol (9) (Ki = 5.03 nM for 73 compared to 64.42 nM for 9). The compound did not interact with the RXR\textsubscript{α} 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. Both sesquimagnolols, 74 and 75, showed agonistic properties comparable to those of dimer 73, with no activity at the RXR\textsubscript{α} 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.

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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 selaginulvulins 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

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 selaginpulvinol. The review also describes the structural aspects of the compounds. Last but not least, synthesis and pharmaceutical profiling of derivatives of magnolol and honokiol is discussed as well.

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**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 selaginpulvinol. The review also describes the structural aspects of the compounds. Last but not least, synthesis and pharmaceutical profiling of derivatives of magnolol and honokiol is discussed as well.

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