論文の内容の要旨

論文題目：Total Synthesis of 4-Hydroxyzinowol and Synthetic Study of Talatisamine
(4-ヒドロキシジノウォールの全合成とタラチサミンの合成研究)

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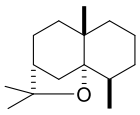
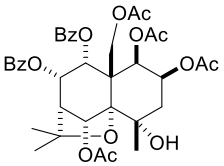
1. Total synthesis of 4-hydroxyzinowol



dihydro-β-agarofuran skeleton (**1**)

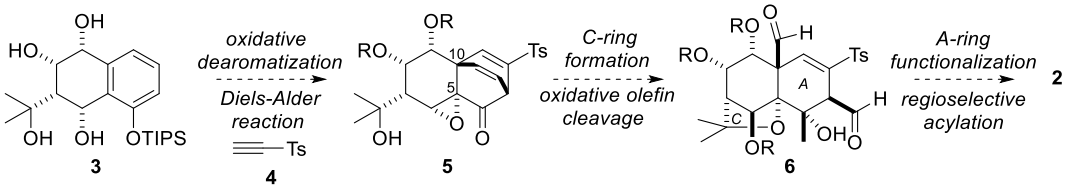


4-hydroxyzinowol (**2**)

Dihydro-β-agarofuran sesquiterpenoid is a large class of natural products possessing the common tricyclic skeleton (**1**). Nearly 500 compounds of this class have been identified to date, and most of them have the high oxidation state.[1] Despite of the apparent structural similarity, dihydro-β-agarofurans exhibit diverse biological activities such as cytotoxic, antifeedant, anti-HIV activities. Among those, P-gp inhibitory activity was quite interesting. P-gp is a molecular pump which excretes small molecules such as drugs out of cells. P-gp is known to involve in the acquired resistance of cancer cells to chemotherapies. Such acquired resistance could be reversed by inhibiting P-gp, thus P-gp inhibitor is a promising drug candidate for cancer chemotherapy. 4-Hydroxyzinowol (**2**), which was isolated in 2005,[2] showed potent P-gp inhibitory activity against cancer cells *in vitro*. In addition to the fascinating biological activity, **2** has nine contiguous stereocenters including three contiguous stereocenters, eight oxygen functionalities, and six acyl groups on the dihydro-β-agarofuran skeleton, thus posing the formidable synthetic challenge. The first part of the present dissertation discloses the total synthesis of **2**.

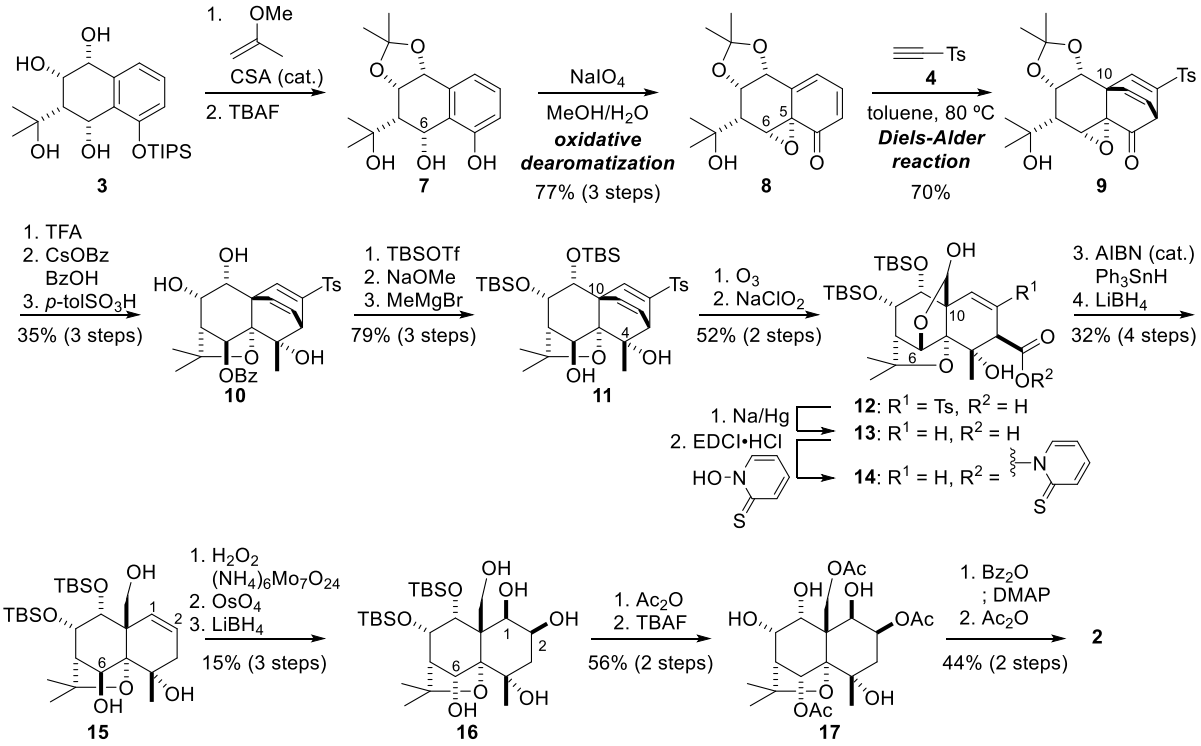
Synthetic plan of **2** is shown in Scheme 1. Our laboratory has already reported the asymmetric synthesis of tetraol **3**.[3] Starting from **3**, Construction of the contiguous tetrasubstituted carbons at angular positions (C5 and C10) would be achieved by oxidative dearomatization of the phenol and following Diels-Alder reaction with ethynyl-*p*-tolyl sulfone **4**. After C-ring (5-membered ether) formation, chemoselective oxidative olefin cleavage would be realized to afford the tricyclic skeleton **6** by exploiting the difference of the electron density between two olefins of **5**. Finally, A-ring functionalization and ensuing regioselective introduction of acyl groups would afford 4-hydroxyzinowol (**2**).

Scheme 1. Synthetic Plan of **2**



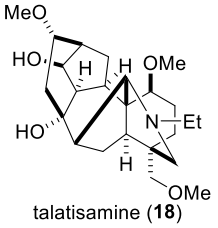
First, phenol **7** was obtained in 2 steps from tetraol **3** (Scheme 2). Oxidative dearomatization of **7** with $NaIO_4$ cleanly yielded diene **8** in high yield. The following Diels-Alder reaction of **8** and **5** proceeded smoothly under the heating conditions to afford the adduct **9** in completely regio- and stereoselective manner. The C-ring of tetracyclic compound **10** was then constructed from **9** in 3 steps via acid-mediated ether ring formation. After protecting group manipulation, introduction of the methyl group at C4 underwent with high diastereoselectivity to give **11**, constructing the third tetrasubstituted carbons. As expected, ozonolysis of diene **11** proceeded chemoselectively. At the same time, one of the aldehydes at the angular position spontaneously formed the hemiacetal under the reaction conditions. Taking advantage of the different reactivity of the aldehyde and the hemiacetal, the oxidation with $NaClO_2$ was performed to give carboxylic acid **12** with the hemiacetal intact. Reductive removal of the tosyl group, Barton decarboxylation, and the reduction of the hemiacetal afforded the tricyclic dihydro-β-agarofuran skeleton **15**. Inversion of the stereochemistry at C6-position and dihydroxylation of the C1-C2 olefin installed the remained three stereocenters to afford **16**. At this point, Fully functionalized tricyclic skeleton of **2** was successfully constructed. Finally, four acetyl groups and two benzoyl groups were introduced in a regioselective manner over 4 steps to afford 4-hydroxyzinowol (**2**).[4]

Scheme 2. Total synthesis of 4-hydroxyzinowol (**2**).



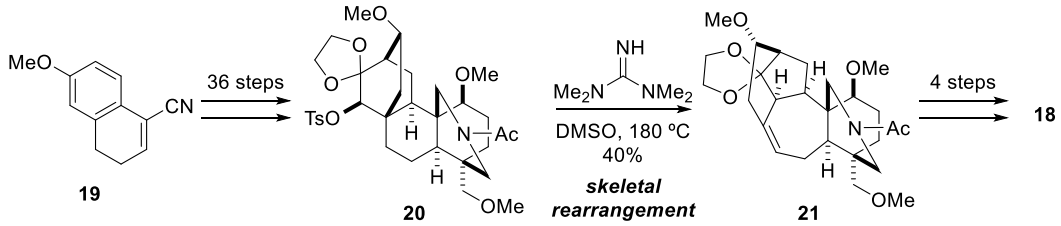
2. Synthetic study of talatisamine

Talatisamine (**18**), a member of C_{19}-diterpene alkaloids, is a potent and selective K^+ channel inhibitor and exhibits antiarrhythmic effect.[5] The fused hexacyclic skeleton of **18** contains twelve contiguous stereocenters including three tetrasubstituted carbons. The total synthesis of this synthetically challenging natural product was achieved in


talatisamine (**18**)

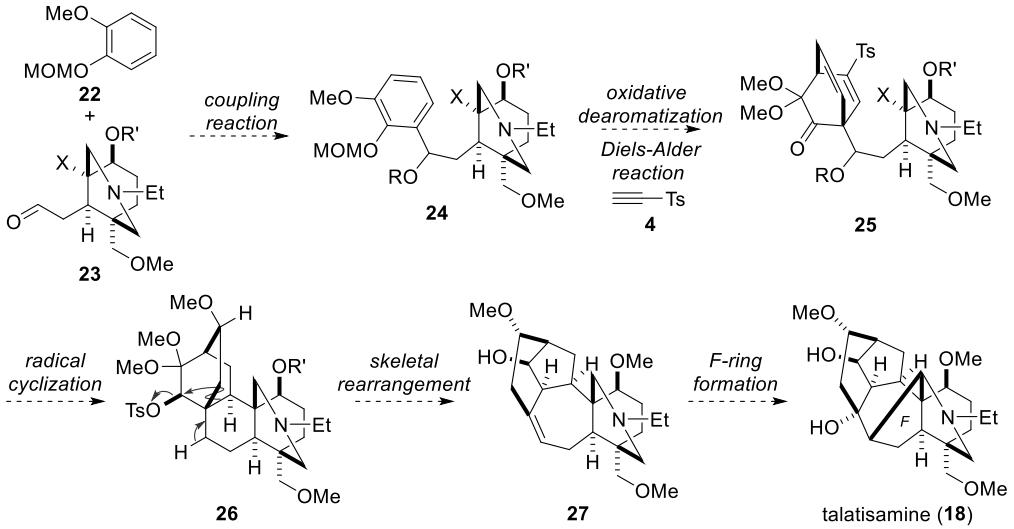
1970s using the bioinspired skeletal rearrangement as a key step (Scheme 3).[6]

Scheme 3. Wiesner's total synthesis of talatisamine (**18**)



Although the synthesis was elegantly achieved in 1970s, the synthesis requires 41 steps. Furthermore, there remains to be improved concerning the yield of the fascinating key rearrangement. Thus the author set **20** or its derivative as a key intermediate, and determined to establish the more efficient synthetic route toward the key intermediate by combining the strategies developed in our laboratory: the oxidative dearomatization and the Diels-Alder reaction sequence, and the bridgehead radical cyclization. The synthetic plan is shown in Scheme 4. Coupling of aromatic compound **22** and aldehyde **23** would give alcohol **24**. The oxidative dearomatization and the following Diels-Alder reaction with **4** would afford bicyclo[2.2.2]octane **25**. Connection of the bicyclo[2.2.2]octane moiety and the azabicyclo[3.3.1]nonane moiety would be achieved by the bridgehead radical cyclization to afford the key intermediate **26**. Talatisamine (**18**) would be synthesized from **26** through **27** via the key skeletal rearrangement and the final F-ring cyclization.

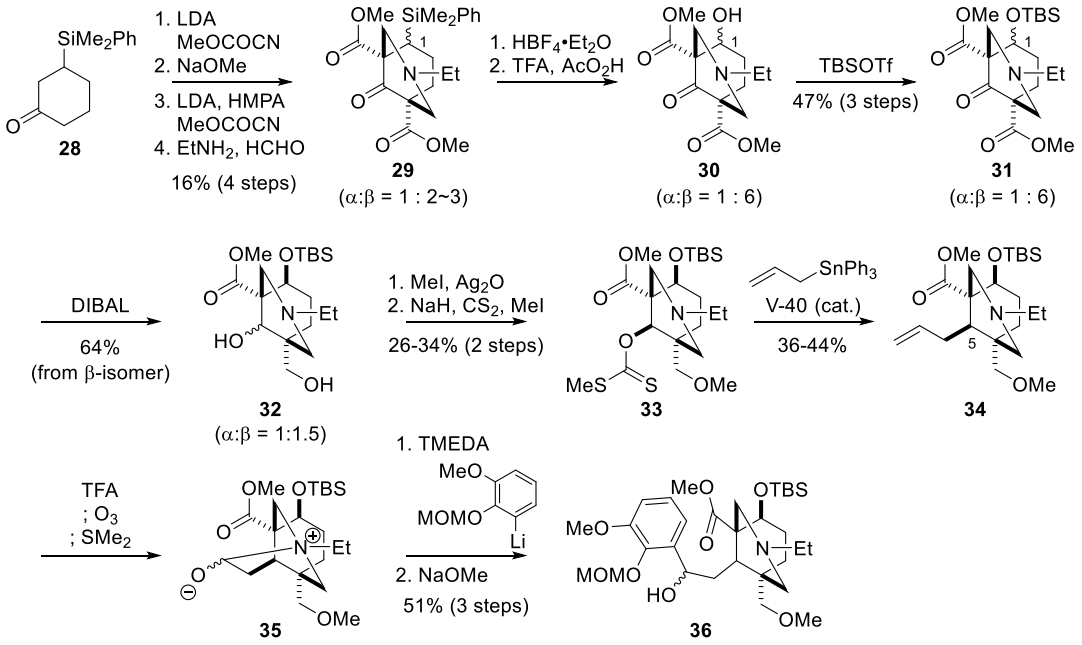
Scheme 4. Synthetic plan of talatisamine (**18**)



The synthesis commenced from the known ketone **28** (Scheme 5). Introduction of the two methoxycarbonyl group followed by the Mannich reaction afforded the bicyclo[3.3.1]nonane skeleton **29** as a mixture of diastereomers. Fleming-Tamao oxidation of silane **29** under the acidic conditions afforded alcohol **30**. The diastereomeric ratio improved under the reaction conditions presumably due to the acid-mediated epimerization of the α-isomer. After TBS protection of alcohol **30**, the ketone and one of the esters of **31** were reduced with DIBAL to afford diol **32**. Then, the primary alcohol was converted to the methyl ether, and the secondary alcohol was converted to the xanthate ester. Keck allylation of **33** proceeded with

high diastereoselectivity to afford the allylated product **34** bearing the desired stereochemistry. Although the ozonolysis of the terminal olefin of **34** proceeded cleanly, zwitterionic species **35** was unexpectedly generated. Addition of the aryl lithium species to **35** went smoothly in the presence of TMEDA to afford the coupling adduct **36**.

Scheme 5. Synthesis of AE-ring fragment and its coupling reaction



3. Summary

In this dissertation, total synthesis of 4-hydroxyzinowol (**2**) and the synthesis of alcohol **36** was presented. The oxidative dearomatization and the Diels-Alder reaction were established as the efficient methods for construction of the angular contiguous tetrasubstituted carbons, which are the ubiquitous structural motifs of dihydro-β-agarofurans. Furthermore, the total synthesis of 4-hydroxyzinowol is the first example of the synthesis of the highly oxygenated and multiply acylated dihydro-β-agarofuran sesquiterpenoid. The strategies developed herein will be a basis for the divergent synthesis of various agarofuran sesquiterpenes and will accelerate the future structure-activity relationship study.

Alcohol **36**, the intermediate for the total synthesis of talatisamine, was successfully synthesized in 14 steps. Future work will be carried out based on the synthetic route developed herein, and also will prove the versatility of the two key reactions developed in our laboratory: the oxidative dearomatization and the following Diels-Alder reaction with ethynyl-*p*-tolyl sulfone, and the bridgehead radical cyclization.

4. References

(1) (a) Spivey, A. C. *et al. Chem. Soc. Rev.* **2002**, *31*, 43. (b) Gao, J.-M. *et al. Nat. Prod. Rep.* **2007**, *24*, 1153. (2) Muños-Martínez, F. *et al. J. Med. Chem.* **2005**, *48*, 4266. (3) Iwatsu, M. *et al. Heterocycles* **2012**, *86*, 181. (4) Todoroki, H. *et al. J. Org. Chem.* **2014**, *79*, 8835. (5) (a) Konpwalowa, R. *et al. Bull. Soc. Chim. Fr.* **1940**, *7*, 95. (b) Song, M.-K. *et al. neuroscience* **2008**, *155*, 469. (6) Wiesner, K. *et al. J. Am. Chem. Soc.* **1974**, *27*, 819.