How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 9666–9671
International Edition: doi.org/10.1002/anie.202016343
German Edition: doi.org/10.1002/ange.202016343

Natural Products

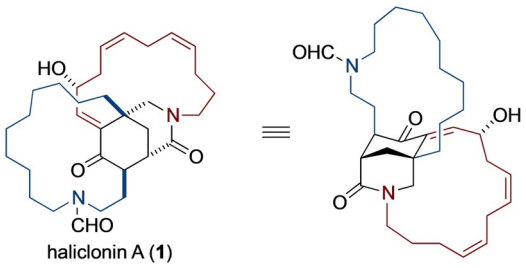
Total Synthesis of Haliclonin A

*Yuan Jin, Kensuke Orihara, Fumiki Kawagishi, Tatsuya Toma, Tohru Fukuyama, and Satoshi Yokoshima**

Abstract: *The total synthesis of haliclonin A was accomplished. Starting from 3,5-dimethoxybenzoic acid, a functionalized cyclohexanone fused to a 17-membered ring was prepared through a Birch reduction/alkylation sequence, ring-closing metathesis, intramolecular cyclopropanation, and stereoselective 1,4-addition of an organocopper reagent to an enone moiety. Reductive C–N bond formation via an N,O-acetal forged the 3-azabicyclo[3.3.1]nonane core. The allyl alcohol moiety was constructed by a sequence involving stereoselective α-selenylation of an aldehyde via an enamine, syn-elimination of a selenoxide, and allylation of the aldehyde with an allylboronate. Formation of the 15-membered ring containing a skipped diene was achieved by ring-closing metathesis, and final transformations led to the synthesis of haliclonin A.*

Introduction

A variety of natural products that contain a nitrogen-containing polycyclic core fused to macrocyclic rings, have been isolated from sponges.[1] These characteristic structures of the natural products have attracted the attention of chemists and spurred the proposal of elegant biosynthetic pathways that can explain the relationship between each structure.[2] Haliclonin A (**1**), one of the natural products, was isolated from *Haliclona sp.* in 2009 (Figure 1).[3] The core structure is a 3-azabicyclo[3.3.1]nonan-2,7-dione that is fused to 17- and 15-membered rings. The 17-membered ring has a formamide moiety and shares a quaternary carbon with the bicyclic core. The 15-membered ring contains a skipped diene and an allyl alcohol moiety. Huang and co-workers reported the first total synthesis of haliclonin A in 2016.[4] The synthesis featured an asymmetric conjugate addition of nitromethane to construct the quaternary carbon, a palladium-mediated carbonyl-enone coupling to form the 3-azabicyclo-[3.3.1]nonane core, and an alkyne metathesis to form the 15-membered ring. Recently, Ishihara and co-workers reported a formal synthesis of haliclonin A that features a tandem radical reaction of a selenocarbamate to form the 3-azabicyclo[3.3.1]nonane core and to install a carbon unit for the 17-membered ring.[5] We also reported our synthetic studies toward haliclonin A in 2018.[6] In that report, we succeeded in constructing the 3-azabicyclo[3.3.1]nonane core via an unexpected 1,5-hydride shift. However, there were challenges in forming the 15-membered ring. After continuous efforts, we completed the synthesis of haliclonin A not via the 1,5-hydride shift to form the 3-azabicyclo[3.3.1]nonane core and with successfully constructing the allyl alcohol moiety, as well as the skipped diene, in the 15-membered ring. Herein we disclose our total synthesis of haliclonin A.



haliclonin A (**1**)

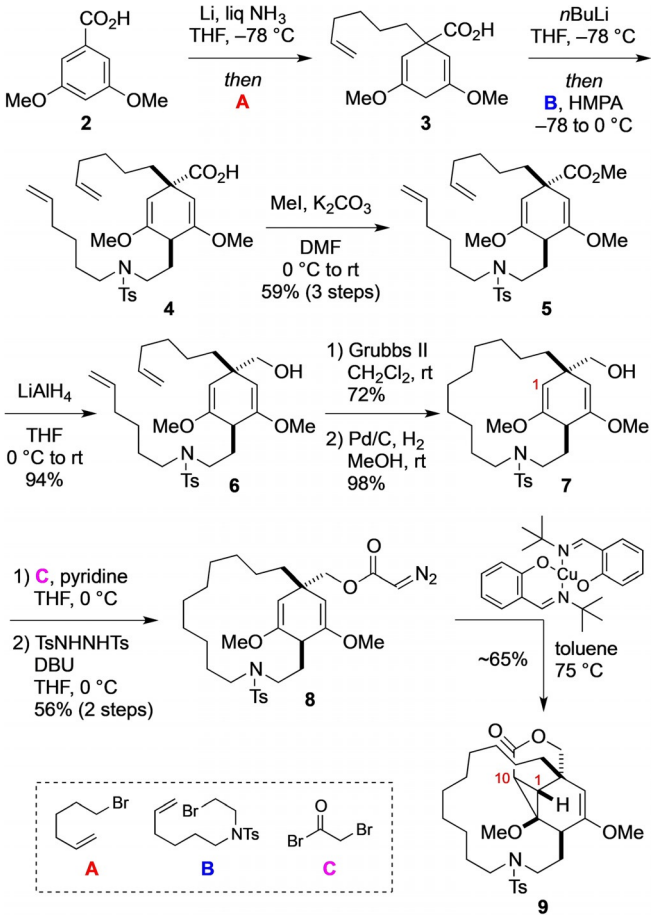
Figure 1. Structure of haliclonin A.

Results and Discussion

Our synthesis commenced with Birch reduction of 3,5-dimethoxybenzoic acid (**2**) followed by alkylation with 6-bromo-1-hexene (**A**, Scheme 1).[6] The resultant carboxylic acid **3** was treated with 2.05 equivalents of *n*-butyllithium to generate a dianion, which stereoselectively reacted with alkyl bromide **B** to afford **4** as the sole isomer.[7] After methylation with iodomethane, the resulting methyl ester **5** was reduced with lithium aluminum hydride to afford alcohol **6**. Ring-closing metathesis with the Grubbs second-generation catalyst,[8] followed by hydrogenation, furnished **7**.

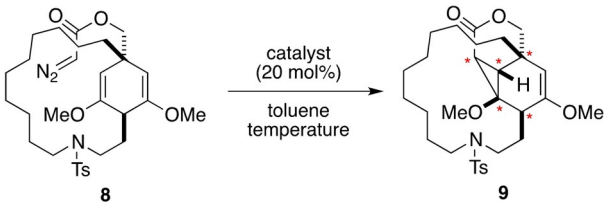
The next task was introduction of a carbon unit on C1. We found that installation of a carbon unit on C1 was problematic after construction of the 3-azabicyclo[3.3.1]nonane core, consistent with a published report.[4a] The problem was partially attributed to the steric hindrance of the quaternary carbon adjacent to C1. To address this issue, we chose to conduct an intramolecular cyclopropanation at this stage to deliver the carbon unit. Alcohol **7** was converted into diazoacetate **8**.[9] Upon treatment with a catalytic amount of copper complex, **8** underwent an intramolecular cyclopropanation to afford tetracyclic lactone **9**,[10] thereby generating the C1–C10 bond.

[*] Y. Jin, Dr. K. Orihara, Dr. T. Toma, Prof. Dr. T. Fukuyama, Prof. Dr. S. Yokoshima
Graduate School of Pharmaceutical Sciences, Nagoya University
Furo-cho, Chikusa-ku, Nagoya, 464-8601 (Japan)
E-mail: yokosima@ps.nagoya-u.ac.jp
Dr. F. Kawagishi
Graduate School of Pharmaceutical Sciences, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033 (Japan)
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202016343.



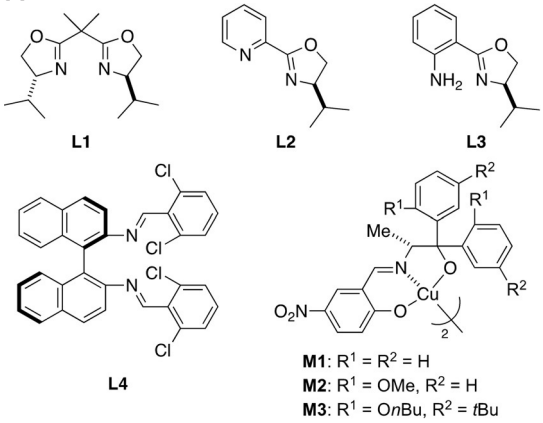
Scheme 1. Synthesis of **9** via Birch reduction, ring closing metathesis, and intramolecular cyclopropanation.

Table 1: Asymmetric cyclopropanation.



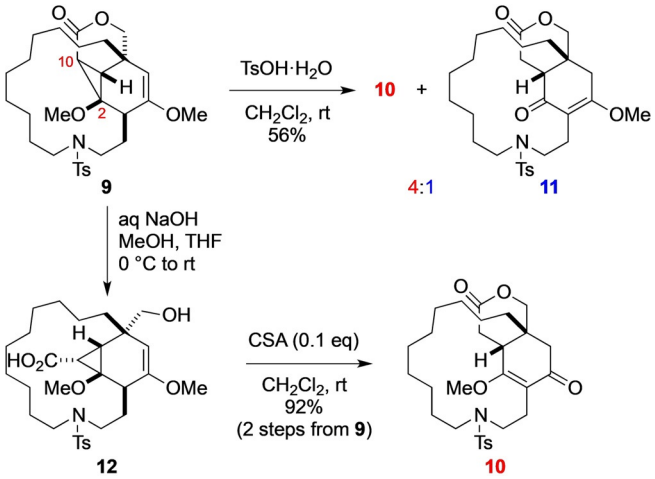
Entry	Catalyst	*T*	Yield [%]	Enantiomer ratio
1	**L1**, Cu(OTf)	rt	6	52:48
2	**L2**, Cu(OTf)	rt	3	48:52
3	**L3**, Cu(OTf)	rt	2	45:55
4[a]	**L4**, Cu(OTf)	rt	27	60:40
5	**M1**	75 °C	34	35:65
6	**M2**	75 °C	32	34:66
7	**M3**	75 °C	45	21:79

[a] Instead of toluene, dichloromethane was used as a solvent.



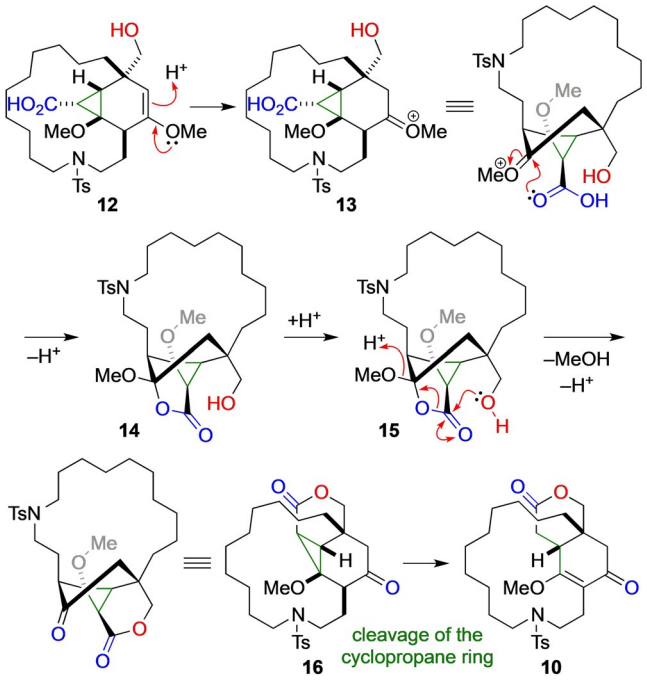
Compound **8**, the substrate for the cyclopropanation, is symmetric, and therefore cyclopropanation employing chiral catalysts would afford enantioenriched cyclopropane **9**.[11] We screened catalysts for asymmetric cyclopropanation (Table 1). Reactions with the oxazoline ligands **L1–3** gave almost racemic products in low yields (entries 1–3).[12] Reactions with the binaphthyl ligand **L4** slightly induced enantioselectivity (entry 4).[13] Employing **M1–3** as a catalyst improved the enantioselectivity, and a reaction of **8** in the presence of **M3** produced **9** in 45% yield with an enantiomer ratio of 21:79.[14] These results showed the possibility of the asymmetric synthesis, and development of novel ligands or catalysts will lead to high yield and enantioselectivity; however, we decided to proceed our synthesis in racemic form.[15]

Attempted acidic treatment of **9** produced an inseparable mixture of **10** and **11** (Scheme 2). Acidic hydrolysis of the enol ether and the subsequent cleavage of the cyclopropane ring between C2 and C10 would produce **10**, whereas cleavage of the cyclopropane ring prior to the hydrolysis of the enol ether would produce **11**. To control the reaction sequence, we attempted to open the lactone ring to reduce the ring strain of the cyclopropane. Thus, **9** was treated with sodium hydroxide to give carboxylic acid **12**, which was treated with 10-camphorsulfonic acid (CSA) in dichloromethane, resulting in selective formation of **10** in 92% yield over 2 steps.[16]



Scheme 2. Hydrolysis of the enol ether and cleavage of the cyclopropane ring.

One of the factors affecting the selective transformation of **9** into **10** was the decrease in the ring strain of the cyclopropane by the lactone opening.[17] More importantly, the carboxy group in **12** worked as both an acid and a nucleophile. The proximity of the carboxy group would promote protonation of the enol ether moiety in **12**, and the



Scheme 3. Proposed mechanism for the selective formation of **10**.

resultant oxocarbenium ion would be attacked by the carboxy group (Scheme 3). Indeed, upon standing in $CDCl_3$ at room temperature, carboxylic acid **12** was slowly converted into lactone **14** even without external acid. By adding an acid, the lactone formation occurred more smoothly, and the primary hydroxy group in **15** subsequently attacked the lactone intramolecularly to liberate a ketone moiety with elimination of methanol. The resultant lactone **16**, which restored the strained ring system, underwent cleavage of the cyclopropane ring to give **10**. Intermediates **14** and **16** could be isolated and be converted into compound **10** in 85% and 92% yields, respectively. The reaction sequence shown in Scheme 3 could also be detected by a reaction conducted in a NMR tube (Figure 2).

The vinylogous ester and lactone moieties in **10** were simultaneously reduced with diisobutylaluminum hydride (DIBAL) to give, after acidic hydrolysis, enone **17** (Scheme 4). The hemiacetal moiety in **17** was then converted into cyclic enol ether **18** by treatment with methanesulfonyl chloride and triethylamine. Upon treatment of **18** with vinylmagnesium chloride in the presence of copper(I) iodide, the 1,4-addition of a vinyl group to the enone moiety and protonation of the resultant enolate on workup occurred stereoselectively from the less hindered side, the side opposite to the bridge of the 17-membered ring, to furnish **19** in 61% yield as the sole isomer. The conversion of the hemiacetal moiety in **17** into the cyclic enol ether was essential for the 1,4-addition. Indeed, when **20** or **21** was used as a substrate, the 1,4-addition did not proceed, or provided the corresponding product only in low yield with poor reproducibility. Being flat, the cyclic enol ether might decrease the steric hindrance during the 1,4-addition.

We next constructed the 3-azabicyclo[3.3.1]nonane skeleton (Scheme 5). Ketone **19** was stereoselectively reduced

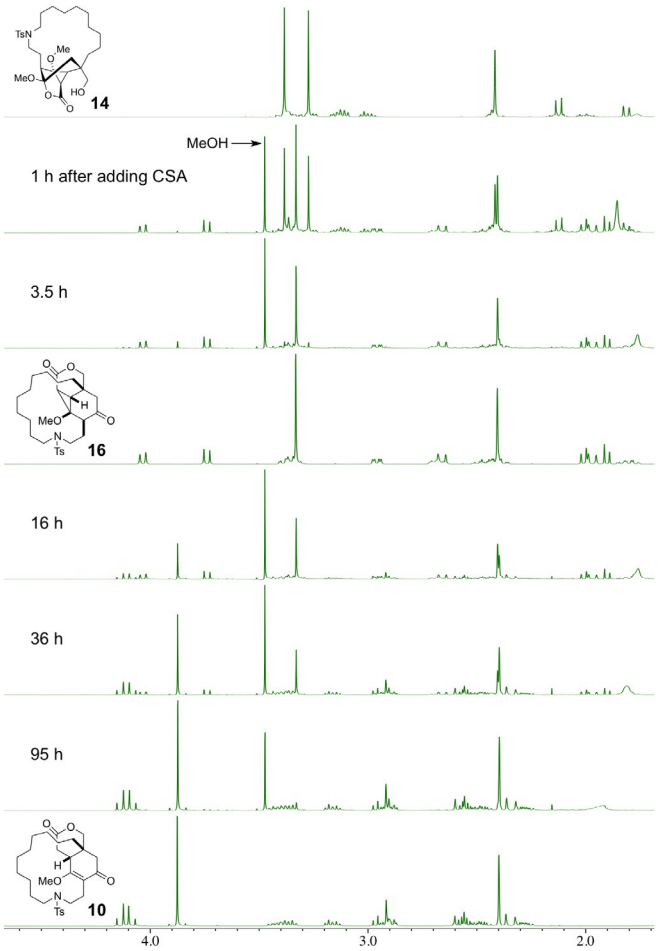
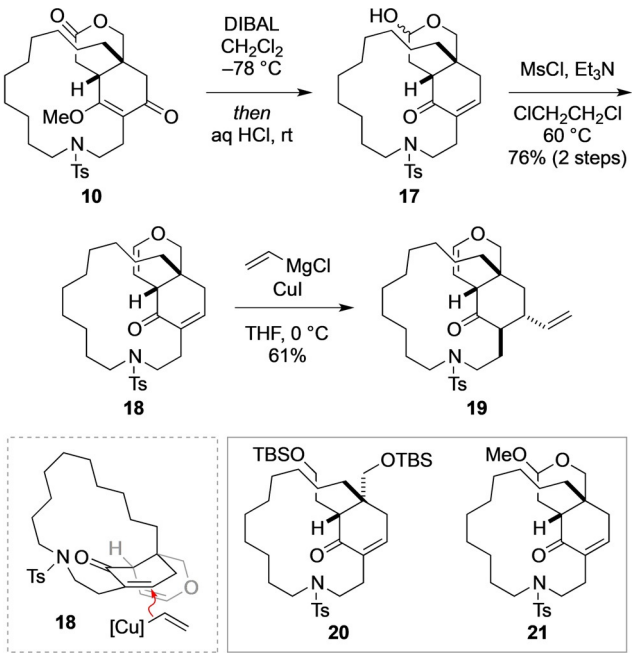
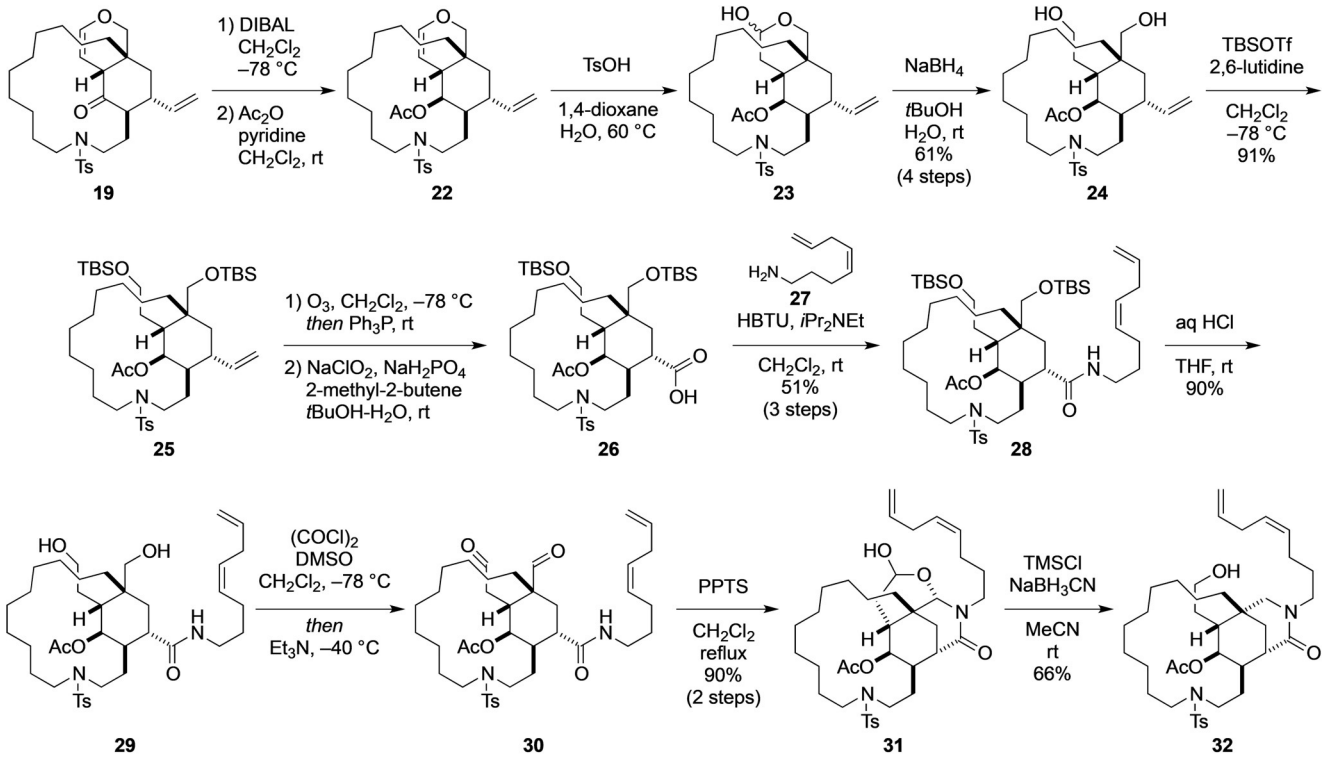


Figure 2. ^{1}H NMR spectra in $CDCl_3$. Conversion of **14** into **10** via intermediate **16** by treatment with 0.1 equivalent of CSA.



Scheme 4. Stereoselective 1,4-addition of a vinyl group.



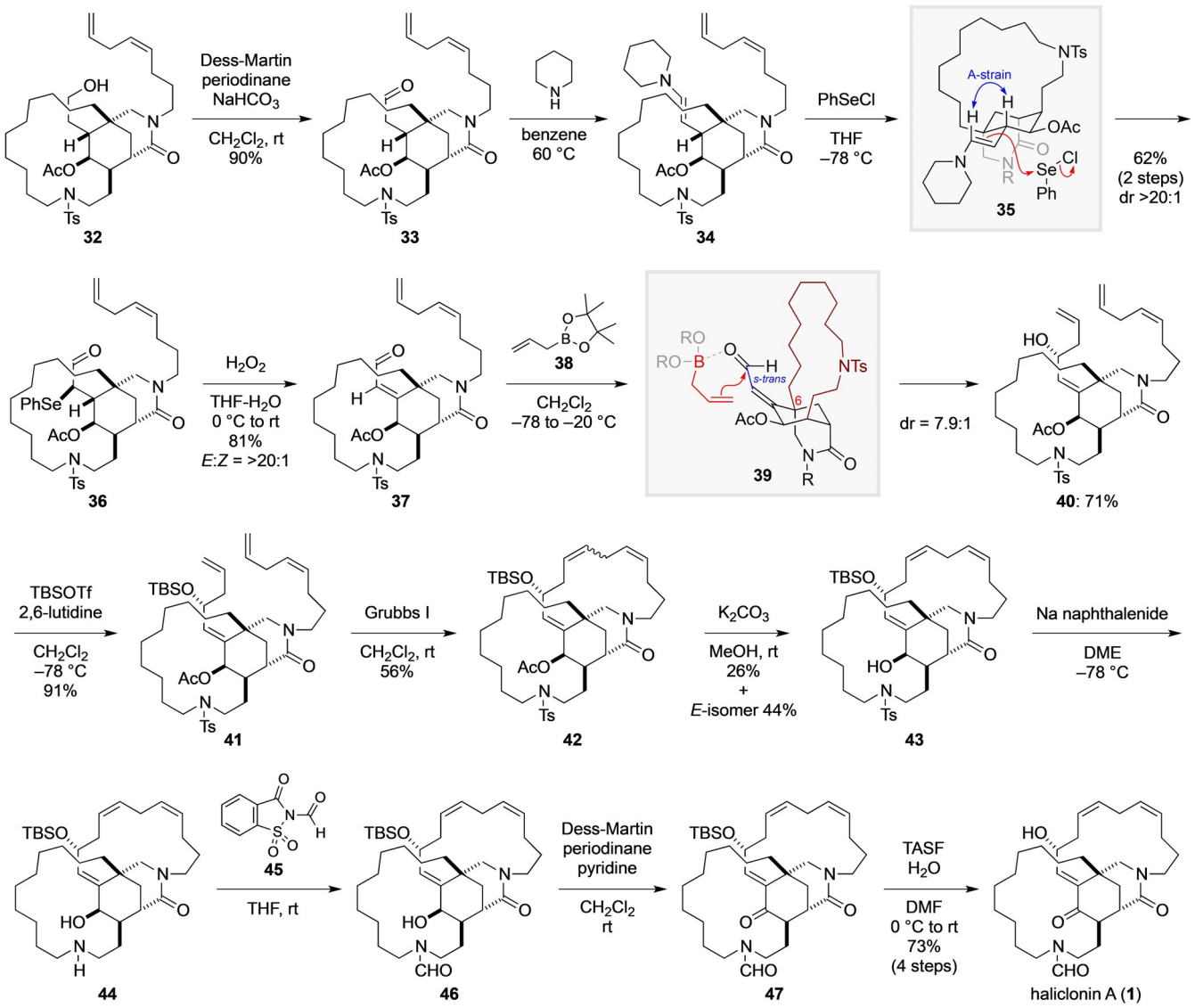
Scheme 5. Construction of the 3-azabicyclo[3.3.1]nonane skeleton.

with DIBAL, and the resultant secondary alcohol was protected with an acetyl group. After acidic hydrolysis of cyclic enol ether **22**, the resultant hemiacetal **23** was reductively cleaved with sodium borohydride to afford diol **24**, and both hydroxy groups were protected with TBS groups. Ozonolysis of the vinyl group in **25** followed by oxidation with sodium chlorite[18] produced carboxylic acid **26**, which was condensed with amine **27**.[19] Removal of the TBS groups under acidic conditions was followed by Swern oxidation to afford dialdehyde **30**.[20] Attempted isolation of the dialdehyde with silica gel resulted in low yield because of its instability. Therefore, the crude mixture was immediately treated with pyridinium *p*-toluenesulfonate (PPTS) in refluxing dichloromethane. Under these conditions, sequential formation of a hemiaminal and a hemiacetal occurred, leading to construction of the 3-azabicyclo[3.3.1]nonane system fused to a cyclic hemiacetal. Product **31** was stable enough to be purified with silica gel and was isolated in 90% yield over 2 steps. Reduction of **31** with sodium cyanoborohydride in the presence of chlorotrimethylsilane as an acid afforded **32**.[21]

The remaining task was construction of the allyl alcohol moiety and the macrocyclic ring containing a skipped diene. Dess–Martin oxidation of alcohol **32** afforded aldehyde **33**,[22] which was converted into enamine **34** by a reaction with piperidine (Scheme 6). The *E* configuration of the enamine was confirmed by ^{1}H NMR, which showed the coupling constant to be 13.7 Hz. Reaction of the enamine with phenylselenyl chloride, followed by oxidation with hydrogen peroxide afforded the desired (*E*)-enal **37**, the configuration of which was confirmed by the NOESY spectrum. The stereochemical outcome of **37** can be explained by considering the following factors: (a) enamine **34** has a conformation in which the allylic strain is minimized; (b) the reaction of the enamine with phenylselenyl chloride occurs from the less-hindered side that is opposite to the quaternary carbon; and (c) *syn*-elimination of the selenoxide occurs. Subsequent allylation of the enal with alylboronic acid pinacol ester occurred via a chair-like transition state **39**, in which the enal assumed the *s*-trans conformation to avoid steric repulsion with the quaternary carbon at C6 and the allylboronate approached from the opposite side of the bridge to give secondary alcohol **40** in 71% yield with a diastereoselectivity of 7.9:1. After protection of the hydroxy group with a TBS group, ring-closing metathesis was conducted with the Grubbs first generation catalyst to afford an *E*,*Z*-mixture of product **42** in 56% yield.[23] The geometrical isomer were separable after removal of the acetyl group. The tosyl group of *Z*-isomer **43** was cleaved with sodium naphthalenide, and a formyl group was installed on the resultant secondary amine **44**. Oxidation of the secondary alcohol moiety in **46** followed by cleavage of the TBS group with TASF afforded haliclonin A (**1**).

Conclusion

We have achieved the total synthesis of haliclonin A starting from 3,5-dimethoxybenzoic acid. A Birch reduction/alkylation sequence and ring-closing metathesis were used to construct a cyclohexane ring fused to a 17-membered ring. Intramolecular cyclopropanation formed a C–C bond at



Scheme 6. Completion of the synthesis.

a sterically congested position adjacent to a quaternary carbon. 1,4-addition of an organocopper reagent to an enone moiety introduced a carbon unit, with the stereochemistry completely controlled by a bridge in the 17-membered ring. Reductive C–N bond formation via an *N,O*-acetal constructed the 3-azabicyclo[3.3.1]nonane core. The allyl alcohol moiety was introduced by a sequence involving the stereoselective α-selenylation of an aldehyde via an enamine, *syn*-elimination of a selenoxide, and allylation of the aldehyde with an allylboronate. The stereochemistry of the allylation was also controlled by the bridge fused to the cyclohexane, leading to the stereoselective formation of the allyl alcohol. The 15-membered ring containing a skipped diene was constructed via ring-closing metathesis, and five more steps completed the synthesis.

Acknowledgements

This work was financially supported by JSPS KAKENHI (Grant Number JP17H01523 and JP18H04399) and by the Platform Project for Supporting Drug Discovery and Life Science Research (Basis for Supporting Innovative Drug Discovery and Life Science Research: BINDS) from the Japan Agency for Medical Research and Development (AMED) under Grant Number JP20am0101099.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · macrocycles · marine natural products · metathesis · stereoselective reactions

[1] a) J.-F. Hu, M. T. Hamann, R. Hill, M. Kelly in *The Alkaloids: Chemistry and Biology*, *Vol. 60*, Academic Press, New York, **2003**, pp. 207 – 285; b) B. Delpech in *The Alkaloids: Chemistry and Biology*, *Vol. 73* (Ed.: H.-J. Knölker), Academic Press, New York, **2014**, pp. 223 – 329; c) M. Amat, M. Pérez, R. Ballette, S. Proto, J. Bosch in *The Alkaloids: Chemistry and Biology*, *Vol. 74* (Ed.: H.-J. Knölker), Academic Press, New York, **2015**, pp. 159 – 199; for synthetic studies on related natural products, see: d) B. Cheng, J. Reyes, *Nat. Prod. Rep.* **2020**, *37*, 322 – 337; e) S. Yokoshima, *Chem. Lett.* **2021**, *50*, 96 – 102; f) Z. Meng, A. Fürstner, *J. Am. Chem. Soc.* **2020**, *142*, 11703 – 11708.

[2] a) J. E. Baldwin, R. C. Whitehead, *Tetrahedron Lett.* **1992**, *33*, 2059 – 2062; b) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, R. J. Boughtflower, I. M. Mutton, R. J. Upton, *Angew. Chem. Int. Ed.* **1998**, *37*, 2661 – 2663; *Angew. Chem.* **1998**, *110*, 2806 – 2808; c) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, *Chem. Eur. J.* **1999**, *5*, 3154 – 3161.

[3] K. H. Jang, G. W. Kang, J.-e. Jeon, C. Lim, H.-S. Lee, C. J. Sim, K.-B. Oh, J. Shin, *Org. Lett.* **2009**, *11*, 1713 – 1716.

[4] a) L.-D. Guo, X.-Z. Huang, S.-P. Luo, W.-S. Cao, Y.-P. Ruan, J.-L. Ye, P.-Q. Huang, *Angew. Chem. Int. Ed.* **2016**, *55*, 4064 – 4068; *Angew. Chem.* **2016**, *128*, 4132 – 4136; b) S.-P. Luo, L.-D. Guo, L.-H. Gao, S. Li, P.-Q. Huang, *Chem. Eur. J.* **2013**, *19*, 87 – 91; c) S.-P. Luo, X.-Z. Huang, L.-D. Guo, P.-Q. Huang, *Chin. J. Chem.* **2020**, *38*, 1723 – 1736.

[5] K. Komine, Y. Urayama, T. Hosaka, Y. Yamashita, H. Fukuda, S. Hatakeyama, J. Ishihara, *Org. Lett.* **2020**, *22*, 5046 – 5050.

[6] K. Orihara, F. Kawagishi, S. Yokoshima, T. Fukuyama, *Synlett* **2018**, *29*, 769 – 772.

[7] a) N. J. Bennett, M. C. Elliott, N. L. Hewitt, B. M. Kariuki, C. A. Morton, S. A. Raw, S. Tomasi, *Org. Biomol. Chem.* **2012**, *10*, 3859 – 3865; b) E. Koch, A. Studer, *Angew. Chem. Int. Ed.* **2013**, *52*, 4933 – 4936; *Angew. Chem.* **2013**, *125*, 5033 – 5036.

[8] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956.

[9] T. Toma, J. Shimokawa, T. Fukuyama, *Org. Lett.* **2007**, *9*, 3195 – 3197.

[10] E. J. Corey, A. G. Myers, *Tetrahedron Lett.* **1984**, *25*, 3559 – 3562.

[11] For selected reviews on cyclopropanation, see: a) H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977 – 1050; b) M. Honma, H. Takeda, M. Takano, M. Nakada, *Synlett* **2009**, 1695 – 1712; c) P. Tang, Y. Qin, *Synthesis* **2012**, *44*, 2969 – 2984; d) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Synthesis* **2014**, *46*, 979 – 1029; e) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, M. A. McKervey, *Chem. Rev.* **2015**, *115*, 9981 – 10080; f) C. Ebner, E. M. Carreira, *Chem. Rev.* **2017**, *117*, 11651 – 11679.

[12] a) R. Ida, M. Nakada, *Tetrahedron Lett.* **2007**, *48*, 4855 – 4859; b) M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano, M. Nakada, *J. Am. Chem. Soc.* **2003**, *125*, 2860 – 2861; c) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726 – 728; d) J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, *J. Am. Chem. Soc.* **2001**, *123*, 7616 – 7625; e) A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, C. I. Herrerías, G. Legarreta, V. Martínez-Merino, J. A. Mayoral, *J. Mol. Catal. A* **2003**, *196*, 101 – 108.

[13] a) H. Suga, T. Fudo, T. Ibata, *Synlett* **1998**, 933 – 935; b) H. Suga, A. Kakehi, S. Ito, T. Ibata, T. Fudo, Y. Watanabe, Y. Kinoshita, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 189 – 199.

[14] a) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1975**, *16*, 1707 – 1710; b) T. Aratani, Y. Yoneyoshi, T. Nagase, *Tetrahedron Lett.* **1977**, *18*, 2599 – 2602; c) K. Suenobu, M. Itagaki, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 7271 – 7280; d) M. Itagaki, K. Suenobu, *Org. Process Res. Dev.* **2007**, *11*, 509 – 518.

[15] For other trials of asymmetric cyclopropanation, see the Supporting Information.

[16] Impurities, which could not be separated by silica gel column chromatography, were formed in the transformation of **8** into **9**, and therefore, in a large-scale preparation, the yield of compound **10** was calculated to be 61 % as the overall yield in 3 steps from compound **8**. In small-scale reactions, the impurities could be separated by preparative TLC. For details, see the Supporting Information.

[17] DFT calculations suggested that the C2–C10 bond becomes longer by forming the lactone ring. For details, see the Supporting Information. The change in the bond length might be attributed to the fixed conformation of the lactone, in which the C2–C10 bond can interact with the π* orbital of the carbonyl group.

[18] a) B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888 – 890; b) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175 – 1176; c) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825 – 4830; d) B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091 – 2096.

[19] For preparation of amine unit **27**, see the Supporting Information.

[20] The removal of the TBS groups with hydrochloric acid was quenched within 10 minutes. A prolonged reaction time induced formation of a lactone between the amide moiety and the primary alcohol.

[21] a) R. Johansson, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2371 – 2374; b) A. Fürstner, T. Nagano, *J. Am. Chem. Soc.* **2007**, *129*, 1906 – 1907.

[22] a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155 – 4156; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287.

[23] a) P. Schwab, R. H. Grubbs, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100 – 110. Attempted subjection of **41** to the *Z*-selective ring-closing metathesis resulted in no production of **42** and the substrate **41** was recovered. b) B. K. Keitz, K. Endo, P. R. Patel, M. B. Herbert, R. H. Grubbs, *J. Am. Chem. Soc.* **2012**, *134*, 693 – 699; c) V. M. Marx, M. B. Herbert, B. K. Keitz, R. H. Grubbs, *J. Am. Chem. Soc.* **2013**, *135*, 94 – 97.

Manuscript received: December 9, 2020
Revised manuscript received: January 18, 2021
Accepted manuscript online: February 8, 2021
Version of record online: March 11, 2021

