OL | Organic Letters

pubs.acs.org/OrgLett Letter

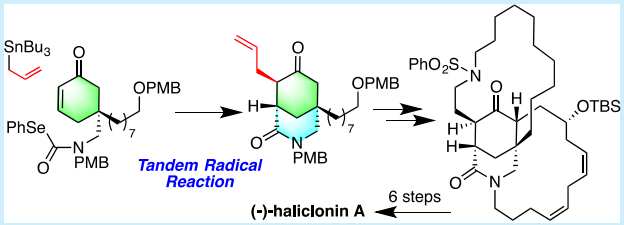
Formal Synthesis of (−)-Haliclonin A: Stereoselective Construction of an Azabicyclo[3.3.1]nonane Ring System by a Tandem Radical Reaction

Keita Komine, Yasuhiro Urayama, Taku Hosaka, Yuki Yamashita, Hayato Fukuda, Susumi Hatakeyama, and Jun Ishihara*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01627 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A formal synthesis of (−)-haliclonin A, isolated from the marine sponge *Haliclona* sp. in Korea, is described. The key feature of the synthesis includes the highly stereoselective tandem radical reaction to construct the azabicyclo[3.3.1]nonane core and the enantioselective formation of an all-carbon quaternary center via the Pd-mediated deracemization.



The marine sponge genus *Haliclona* is known to produce numerous biologically active natural products such as depsipeptides and miscellaneous alkaloids.[1] In 2009, Oh and Shin et al. reported the isolation of (−)-haliclonin A (**1**), a macrocyclic diamide, from *Haliclona* sp. in Korea (Figure 1).[2] This natural product exhibits moderate antibacterial activity with a minimum inhibitory concentration (MIC) value of 6.25 μg/mL against *Bacillus subtilis*, and cytotoxicity against the K562 leukemia cell line with a half maximal inhibitory concentration (IC_{50}) of 15.9 μg/mL. Haliclonin A possesses a fascinating azabicyclo[3.3.1]nonane core with two bridges that form 15- and 17-membered rings containing an *E*-alkene and a (*Z*,*Z*)-skipped diene. The significant biological properties and structural challenges have made haliclonin A an attractive target for synthesis.[3,4] The first total synthesis of (−)-haliclonin A has been accomplished by Huang's group in 2016 employing an organocatalytic asymmetric conjugate addition and a Pd-promoted cyclization to construct the highly functionalized bicyclic core.[3] Another effort toward the synthesis of **1** has recently been reported by Fukuyama and

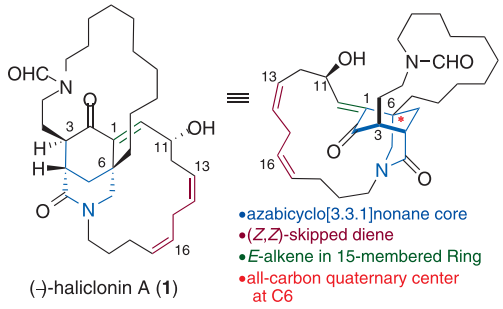
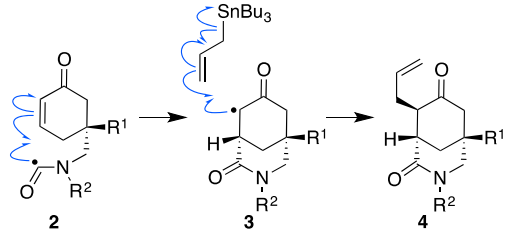


Figure 1. Structure of (−)-haliclonin A (**1**).

Scheme 1. Tandem Radical Reaction



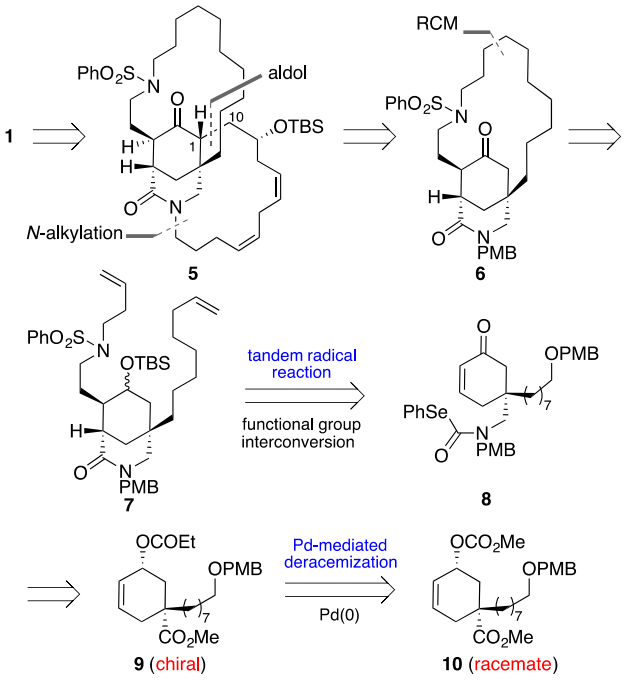
Yokoshima et al., which was based on a creative strategy via an intramolecular cyclopropanation and a conjugate addition of an organocopper reagent.[4c] In this context, we are interested in a tandem radical strategy for the construction of the formidable highly condensed core. Herein, we report the formal synthesis of (−)-haliclonin A (**1**) by a highly stereoselective tandem radical reaction.

Our radical strategy is shown in Scheme 1. Carbon-centered radical reactions enable the chemoselective formation of sterically hindered carbon−carbon bonds in the presence of various susceptible functional groups.[5,6] It was envisaged that, once nucleophilic carbamoyl radical **2** is generated,[7] it would be captured by an electron-poor enone to form cyclized intermediate **3** containing an electrophilic radical. The radical would in turn undergo the second C−C bond formation by the

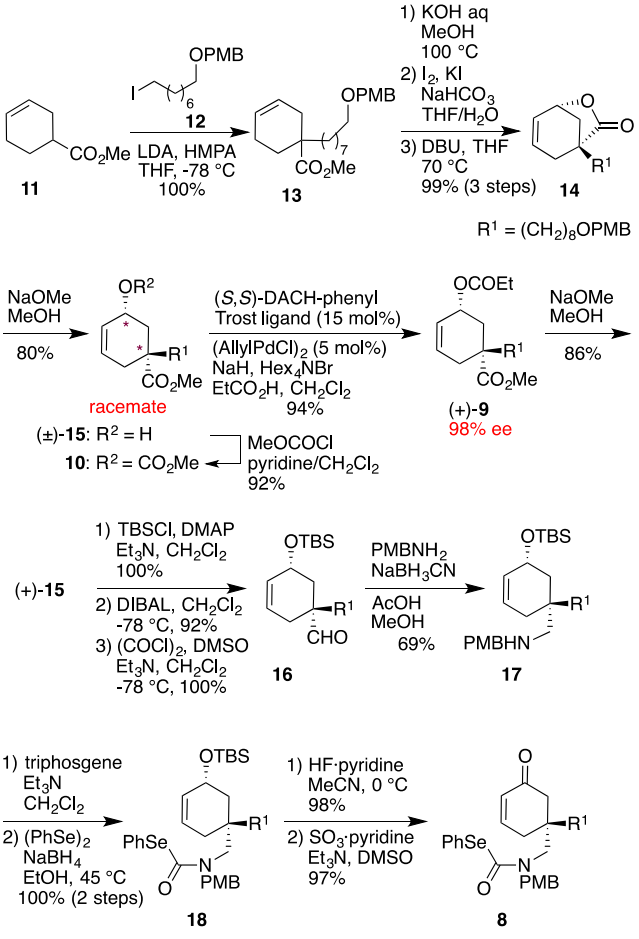
Received: May 13, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01627
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Synthetic Plan

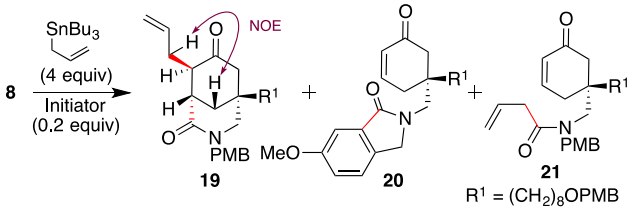


Scheme 3. Synthesis of 8



convex face attack of nucleophilic allylstannane to produce a suitably functionalized azabicyclo[3.3.1]nonane core **4**.

Table 1. Tandem Radical Reaction of 8



entry	concn (M)	condition	yield (%) 19	20	21
1[a]	0.1	AIBN, PhH, reflux, 7 h	21	9	11
2[b]	0.02	AIBN, PhH, reflux, 7 h	19	13	
3[c,d]	0.02	V-40, PhH, 110 °C, 7 h	55	18	
4	0.02	V-40, PhCl, 110 °C, 7 h	60	26	
5[d]	0.02	V-40, PhH, 130 °C, 2 h	67	8	
6	0.02	V-40, PhCl, 130 °C, 2 h	73	13	
7[d]	0.02	V-40, PhCl, 150 °C, 2 h	63	15	

[a]Recovery of **8**; 47%. [b]Recovery of **8**; 61%. [c]Recovery of **8**; 19%. [d]Reaction was conducted in a sealed tube.

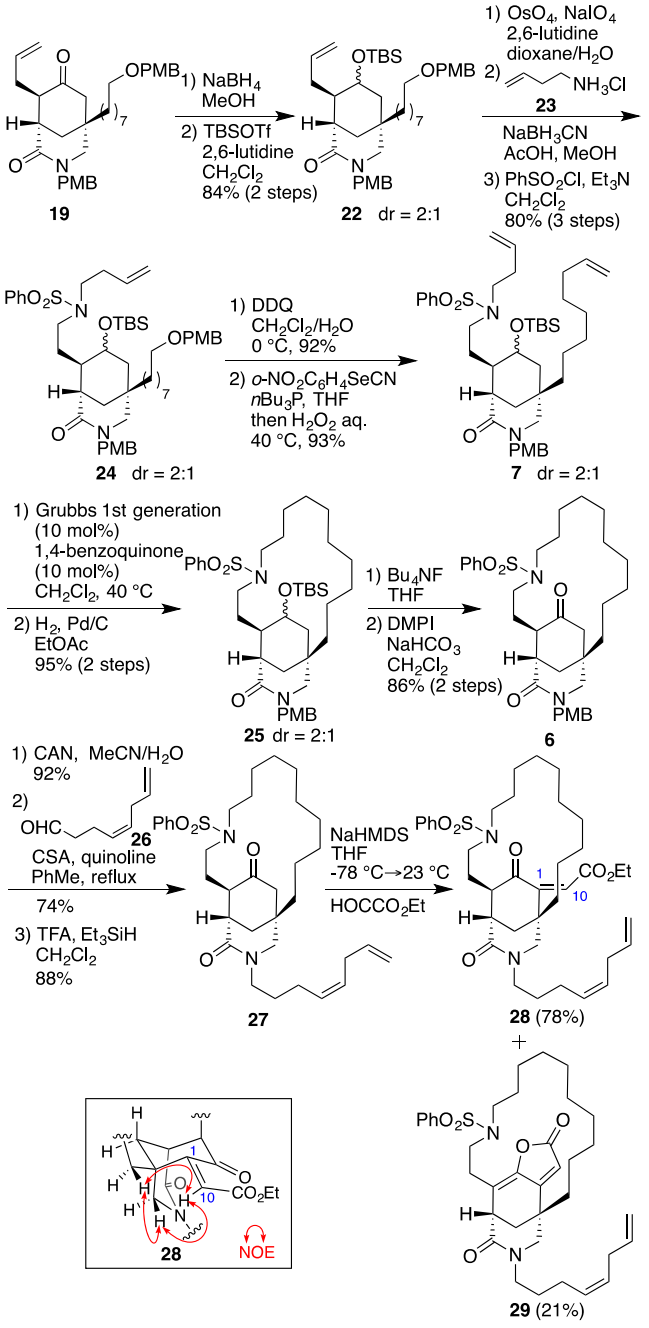
This radical strategy allowed us to analyze the synthesis of **1** as illustrated in Scheme 2. For the synthesis of haliclonin A (**1**), we selected Huang's intermediate **5**[3] as a precursor, which would be accessible from **6** via a *N*-alkylation and an aldol reaction between C1 and C10 positions. We assumed that **6** would be derived from **7** by ring-closing metathesis (RCM) followed by hydrogenation of the resulting alkene. Then, given the key tandem radical cyclization−allylation reaction[8,9] to secure the azabicyclo[3.3.1]nonane ring system, selenocarbamate **8** would be considered as a precursor of **7** via an additional functional group interconversion. The radical precursor would be accessible from cyclohexene **9** bearing an all-carbon quaternary stereogenic center. To synthesize enantiomerically pure **9**, we envisioned an approach from racemic compound **10** via the Pd-mediated deracemization, which we have recently developed.[10]

Our synthesis began with the preparation of enone **8** with high enantiopurity (Scheme 3). Commercially available methyl cyclohex-3-ene-1-carboxylate (**11**) was alkylated with the known alkyl iodide **12**[11] to deliver **13** in quantitative yield. Compound **13** was converted to lactone **14** by a three-step sequence involving saponification, iodolactonization, and elimination in 99% yield. Methanolysis and carbonation afforded racemic carbonate **10** in 74% yield, which was then subjected to a Pd-mediated deracemization.[10] Thus, racemic compound **10** was reacted with sodium propionate using 5 mol % allylpalladium(II) chloride dimer and 15 mol % (*S*,*S*)-DACH-phenyl Trost ligand in CH_2Cl_2 at ambient temperature to provide **9** in 94% yield with excellent enantioselectivity (98% ee)[12] as a sole product. After methanolysis of **9**, the resulting (+)-**15** was converted to aldehyde **16** via silylation, DIBAL reduction, and Swern oxidation in good yield. Reductive amination of **16** with 4-methoxybenzylamine furnished **17** in 69% yield. Treatment of **17** with triphosgene, followed by addition of phenylselenide,[14] afforded selenocarbamate **18** in excellent yield. Compound **18** was then converted to enone **8** by desilylation and Parikh−Doering oxidation.

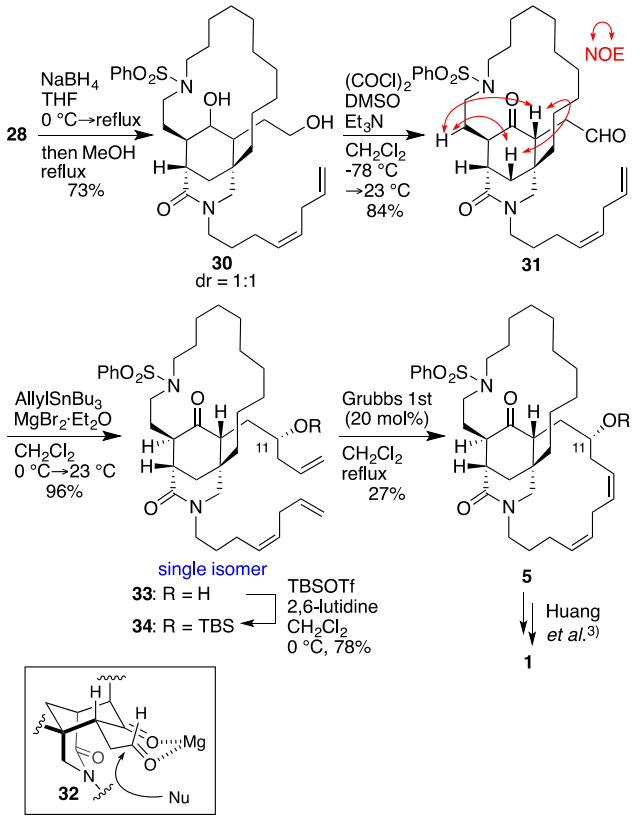
With the required **8** in hand, we then focused on the tandem radical reaction with allyltributylstannane (Table 1). When enone **8** was heated under reflux in benzene in the presence of

https://dx.doi.org/10.1021/acs.orglett.0c01627
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Synthesis of 28



Scheme 5. Formal Synthesis of (−)-Haliclonin A (1)



2,2′-azodiisobutyronitrile (AIBN), the desired **19** was obtained in 21% yield, along with isoindolinone **20**[13] (9% yield) and butenamide **21** (11% yield) (entry 1). It is clear that products **20** and **21** were generated by the capture of the resulting carbamoyl radical with the phenyl ring and allylstannane. To prevent the formation of undesired **20** and **21**, we next examined the reaction at lower reactant concentration and higher temperatures. When the reaction was performed at 0.02 M concentration of **8**, the production of **21** was totally suppressed, but the yield of **19** was not improved (entry 2). On the other hand, when the reaction was carried out at 0.02 M concentration using 1,1′-azobis(cyclohexane-1-carbonitrile) (V-40) as an initiator at higher temperatures,[15] the yield of **19** was dramatically improved (entries 3−7). To our delight, it was found that the reaction of **8** in chlorobenzene at 130 °C furnished **19** in 73% yield (entry 6). However, the reaction at 150 °C decreased the yield to 63% (entry 7).

With azabicyclo[3.3.1]nonane core **19** in hand, we next turned our attention to the completion of the synthesis of target molecule (Scheme 4). $NaBH_4$ reduction of **19** and silylation of the resulting alcohol afforded **22** as a 2:1 diastereomeric mixture in 84% yield. Without separation of the stereoisomers, **22** was then converted to **24** in 80% yield by a three-step sequence involving Lemieux−Johnson oxidation,[16] reductive amination with 3-buten-1-amine hydrochloride (**23**), and benzenesulfonylation. Cleavage of the PMB ether of **24** and Nishizawa−Grieco elimination[17] gave terminal alkene **7** in 86% yield. RCM reaction of **7** using Grubbs first generation catalyst (10 mol %) and 1,4-benzoquinone (10 mol %) in boiling CH_2Cl_2 and successive hydrogenation allowed the formation of the 17-membered ring bridge to give **25** in excellent yield. Desilylation of **25** followed by Dess−Martin oxidation afforded ketone **6** in 86% yield, which was then converted to **27** in 59% yield via cleavage of the *N*-PMB with CAN, enamine formation with **26**[18] following Fukuyama's protocol,[19] and silane reduction. At this stage, the subsequent mission was to install the C10−C13 fragment, which proved to be problematic. After considerable experiments, we gratifyingly found that aldol condensation of **27** with ethyl glyoxylate provided **28** and **29** in 78% and 21% yields, respectively, although the major isomer **28** had the *Z*-configuration at the $\Delta^{1,10}$-double bond.

Next, we explored the construction of another 15-membered bridge (Scheme 5). Reduction of **28** with $NaBH_4$ in methanol according to Soai's protocol[20] successfully provided diol **30** as a 1:1 diastereomeric mixture in 73% yield. Swern oxidation of **30** afforded ketoaldehyde **31**[21] in 84% yield. To construct the

https://dx.doi.org/10.1021/acs.orglett.0c01627
Org. Lett. XXXX, XXX, XXX−XXX

11*R* chiral center, we examined stereoselective allylation under various conditions. Eventually, when **31** was treated with allyltributylstannane and magnesium bromide ethyl etherate ($MgBr_2{\cdot}Et_2O$) in CH_2Cl_2 at 0 °C according to Linclau's method,[22] the allylation was found to take place with perfect chemo- and diastereoselectivities to afford **33**[23] in excellent yield. The selective allylation can be rationalized via chelated intermediate **32** where the *re* face attack of the allyl nucleophile is favored by steric reasons. After silylation of **33**, all our efforts for *Z*-selective RCM[24] of **34** using various metathesis catalysts were totally fruitless, giving only unreacted **34**. However, the RCM reaction in the presence of classic Grubbs first generation catalyst in boiling CH_2Cl_2 afforded the desired *Z*-product **5** in 27% yield.[25] Compound **5**, thus obtained, exhibited spectral properties identical in all respects to those reported by Huang et al.[3] Therefore, the formal synthesis of (−)-haliclonin A (**1**) was achieved.

In conclusion, we have developed a novel approach for the synthesis of (−)-haliclonin A (**1**) in an enantiomerically pure form. The present work illustrates an efficient methodology for the enantio- and diastereoselective construction of highly functionalized azabicyclo[3.3.1]nonane ring systems which relies on Pd-mediated deracemization of cyclohexenyl ester derivatives and the tandem radical cyclization−allylation process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01627.

Experimental details and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Jun Ishihara − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*; orcid.org/0000-0003-3346-3354; Email: jishi@nagasaki-u.ac.jp

Authors

Keita Komine − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*

Yasuhiro Urayama − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*

Taku Hosaka − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*

Yuki Yamashita − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*

Hayato Fukuda − *Graduate School of Biomedical Sciences, Nagasaki University, Nagasaki 852-8521, Japan*; orcid.org/0000-0003-1636-4469

Susumi Hatakeyama − *Medical Innovation Center, Nagasaki University, Nagasaki 852-8521, Japan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01627

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grants JP16J03966 (K.K.), JP19K15568 (K.K.), JP16H05074 (S.H.), and JP18K05126 (J.I.). This work was the result of using research equipment shared in MEXT project for promoting public utilization of advanced research infrastructure (program for supporting introduction of the new sharing system) Grant JPMXS0422500320.

■ REFERENCES

(1) Zhu, J.; Liu, Y.; Liu, Z.; Wang, H.; Zhang, H. Bioactive nitrogenous secondary metabolites from the marine sponge genus Haliclona. *Mar. Drugs* **2019**, *17*, 682.

(2) Jang, K. H.; Kang, G. W.; Jeon, J. E.; Lim, C.; Lee, H. S.; Sim, C. J.; Oh, K. B.; Shin, J. Haliclonin A, a new macrocyclic diamide from the sponge Haliclona sp. *Org. Lett.* **2009**, *11*, 1713−1716.

(3) Guo, L.-D.; Huang, X.-Z.; Luo, S.-P.; Cao, W.-S.; Ruan, Y.-P.; Ye, J.-L.; Huang, P.-Q. Organocatalytic, Asymmetric Total Synthesis of (−)-Haliclonin A. *Angew. Chem., Int. Ed.* **2016**, *55*, 4064−4068.

(4) (a) Luo, S.-P.; Guo, L.-D.; Gao, L.-H.; Li, S.; Huang, P.-Q. Toward the Total Synthesis of Haliclonin A: Construction of a Tricyclic Substructure. *Chem. - Eur. J.* **2013**, *19*, 87−91. (b) Gao, Y.-J.; Luo, S.-P.; Ye, J.-L.; Huang, P.-Q. An attempted approach to the tricyclic core of haliclonin A: Structural elucidation of the final product by 2D NMR. *Chin. Chem. Lett.* **2017**, *28*, 1176−1181. (c) Orihara, K.; Kawagishi, F.; Yokoshima, S.; Fukuyama, T. Synthetic Studies of Haliclonin A: Construction of the 3-Azabicyclo[3.3.1]-nonane Skeleton with a Bridge that Forms the 17-Membered Ring. *Synlett* **2018**, *29*, 769−772.

(5) For a representative review, see: (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: New York, 1995. For a review on tandem radical reactions, see: (b) Godineau, E.; Landais, Y. Radical and Radical-Ionic Multicomponent Processes. *Chem. - Eur. J.* **2009**, *15*, 3044−3055.

(6) Urabe, D.; Yamaguchi, H.; Inoue, M. Application of α-Alkoxy Bridgehead Radical for Coupling of Oxygenated Carbocycles. *Org. Lett.* **2011**, *13*, 4778−4781.

(7) For representative examples, see: (a) Herzon, S. B.; Myers, A. G. Enantioselective Synthesis of Stephacidin B. *J. Am. Chem. Soc.* **2005**, *127*, 5342−5344. (b) Gill, G. B.; Pattenden, G.; Reynolds, S. J. Cobalt-mediated reactions: inter- and intra-molecular additions of carbamoyl radicals to alkenes in the synthesis of amides and lactams. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369−378. For a review on acyl and carbamoyl radicals, see: (c) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. Chemistry of Acyl Radicals. *Chem. Rev.* **1999**, *99*, 1991−2070.

(8) Mizuno, K.; Ikeda, M.; Toda, S.; Otsuji, Y. Regioselective double vicinal carbon-carbon bond forming reactions of electron-deficient alkenes by use of allylic stannanes and organoiodo compounds. *J. Am. Chem. Soc.* **1988**, *110*, 1288−1290.

(9) (a) Tao, D. J.; Slutskyy, Y.; Overman, L. E. Total Synthesis of (−)-Chromodorolide B. *J. Am. Chem. Soc.* **2016**, *138*, 2186−2189. (b) Brill, Z. G.; Grover, H. K.; Maimone, T. J. Enantioselective synthesis of an ophiobolin sesterterpene via a programmed radical cascade. *Science* **2016**, *352*, 1078−1082. (c) Hashimoto, S.; Katoh, S.; Kato, T.; Urabe, D.; Inoue, M. Total Synthesis of Resiniferatoxin Enabled by Radical-Mediated Three-Component Coupling and 7-endo Cyclization. *J. Am. Chem. Soc.* **2017**, *139*, 16420−16429.

(10) Komine, K.; Urayama, Y.; Hosaka, T.; Fukuda, H.; Hatakeyama, S.; Ishihara, J. New entry to the enantioselective formation of substituted cyclohexenes bearing an all-carbon quaternary stereogenic center. *Chirality* **2020**, *32*, 273−281.

(11) Bokam, R.; Annam, S. C. V. A. R.; Yalavarthi, N. R.; Gundoju, N.; Ponnapalli, M. G. Bioinspired First Stereoselective Total Synthesis of Spinosulfate B. *ChemistrySelect* **2019**, *4*, 8911−8914.

(12) The enantiomeric ratio was determined by chiral high-performance liquid chromatography (HPLC) analysis of (+)-**15**.

The configuration was determined by modified Mosher's method after conversion of (+)-**15** to the corresponding MTPA esters.
(13) For radical cyclization upon aromatic rings, see: (a) Ly, T.-M.; Quiclet-Sire, B.; Sortais, B.; Zard, S. Z. A convergent approach to indolines and indanes. *Tetrahedron Lett.* **1999**, *40*, 2533−2536. (b) Bennasar, M.-L.; Roca, T.; Ferrando, F. Intramolecular reactions of 2-indolylacyl radicals: cyclisation upon aromatic rings. *Tetrahedron Lett.* **2004**, *45*, 5605−5609. (c) López-Valdez, G.; Olguín-Uribe, S.; Millan-Ortíz, A.; Gamez-Montaño, R.; Miranda, L. D. Convenient access to isoindolinones *via* carbamoyl radical cyclization. Synthesis of cichorine and 4-hydroxyisoindolin-1-one natural products. *Tetrahedron* **2011**, *67*, 2693−2701.
(14) Miyashita, M.; Suzuki, T.; Hoshino, M.; Yoshikoshi, A. The Organoselenium-mediated reduction of α,β-epoxy ketones, α,β-epoxy esters, and their congeners to β-hydroxy carbonyl compounds: Novel methodologies for the synthesis of aldols and their analogues. *Tetrahedron* **1997**, *53*, 12469−12486.
(15) We employed V-40 as a radical initiator in the reactions performed at high temperature (entries 3−7), because the self-accelerating decomposition temperature (SADT) of AIBN is 50 °C, whereas the SADT of V-40 is 80 °C.
(16) Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. Improved Procedure for the Oxidative Cleavage of Olefins by OsO_4−$NaIO_4$. *Org. Lett.* **2004**, *6*, 3217−3219.
(17) Grieco, P. A.; Gilman, S.; Nishizawa, M. Organoselenium chemistry. A facile one-step synthesis of alkyl aryl selenides from alcohols. *J. Org. Chem.* **1976**, *41*, 1485−1486.
(18) See the Supporting Information for the preparation of **26**.
(19) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. Total Synthesis of Ecteinascidin 743. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554.
(20) Soai, K.; Oyamada, H.; Takase, M.; Ookawa, A. Practical Procedure for the Chemoselective Reduction of Esters by Sodium Borohydride. Effect of the Slow Addition of Methanol. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1948−1953.
(21) The stereostructure of **31** was determined by the NOESY spectrum.
(22) Linclau, B.; Cini, E.; Oakes, C. S.; Josse, S.; Light, M.; Ironmonger, V. Stereoarrays with an All-Carbon Quaternary Center: Diastereoselective Desymmetrization of Prochiral Malonaldehydes. *Angew. Chem., Int. Ed.* **2012**, *51*, 1232−1235.
(23) The configuration of **33** was determined by Mosher ester analysis of the corresponding *R*- and *S*-MTPA esters.
(24) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. Stereoselective Access to Z and E Macrocycles by Ruthenium-Catalyzed Z-Selective Ring-Closing Metathesis and Ethenolysis. *J. Am. Chem. Soc.* **2013**, *135*, 94−97.
(25) Two stereoisomers were also generated as an inseparable mixture.

https://dx.doi.org/10.1021/acs.orglett.0c01627
Org. Lett. XXXX, XXX, XXX−XXX