OL | Organic Letters

pubs.acs.org/OrgLett Letter

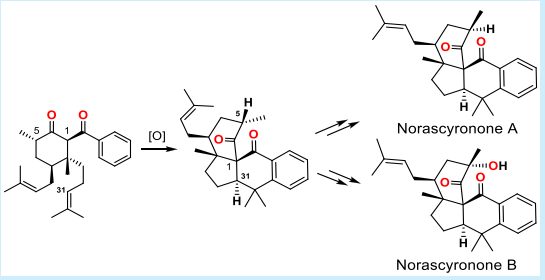
# Protecting-Group-Free Total Syntheses of (±)-Norascyronones A and B

Tingting Cao,[‖] Lei Zhu,[‖] Yu Lan,* Jun Huang,* and Zhen Yang*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00212 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** Protecting-group-free total syntheses of natural products norascyronone A and norascyronone B were accomplished in eight steps from the commercially available starting material 1-bromo-4-methoxy-2-methylbenzene. The key step was a Mn/Cu-mediated oxidative cascade annulation reaction that formed the tetracyclic core of the target molecules bearing vicinal bridge-head all-carbon quaternary chiral centers. Our investigation indicated that the C5 stereogenic center of norascyronone C plays a critical role in the proposed biomimetic oxidative reaction for B-ring formation.






Norascyronones A (**2**) and B (**3**) (Figure 1) were recently isolated from *Hypericum ascyron*. Both compounds

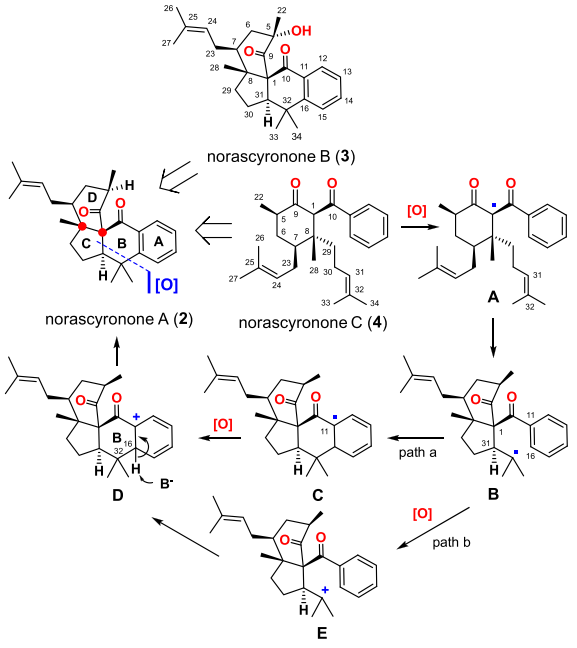



**Figure 1.** Proposed synthetic transformations.

contain a congested 6/6/5/6 polycyclic core bearing five stereogenic centers, two of which are all-carbon quaternary carbons (C1 and C8).[1] Their absolute configurations have been determined from X-ray diffraction data for **2** and experimental and calculated electronic circular dichroism spectra of **3**. Biologically, both compounds show cytotoxicities against the SK-BR-3 cell line ($IC_{50}$ values of 4.3 and 7.8 $\mu$M, respectively).[1]

In the biosynthetic pathway proposed when these compounds were isolated,[1] **2** and **3** are postulated to be derived from norascyronone C (**4**) via an oxidative 1,3-dicarbonyl radical-initiated cascade cyclization through intermediates **A**–**D** (Figure 1). Compound **4** undergoes an oxidative 5-*exo*-*trig* radical cyclization to afford radical **B** through intermediate **A**. Further cyclization of **B** at C16 of the phenyl ring yields resonance-stabilized radical **C** (path a), which undergoes further oxidation to carbonium ion **D** and then aromatization via proton loss to give **2**. From a chemistry perspective, intermediate **B**, bearing a stable tertiary radical, might also undergo further oxidation to form stabilized carbocation **E**, as proposed by George and Lee,[2] which might trigger an intramolecular Friedel–Crafts reaction to form carbonium ion **D**, followed by aromatization to give **2**.

Among various oxidative transformations of enolized carbonyl moieties mediated by metal ions (such as Mn(III), Cu(II), Fe(III), and Ce(IV)),[3] Mn(III)-based oxidative radical cyclizations of carbonyl compounds with unactivated olefins[4] have attracted much interest because they allow unconventional and efficient access to a range of molecules[5] that cannot be easily synthesized using other methods.

As part of our continuing interest in the development of diastereoselective syntheses of complex natural products bearing vicinal bridged all-carbon quaternary chiral centers,[6] we were intrigued by the possibility of constructing the

**Received:** January 17, 2020



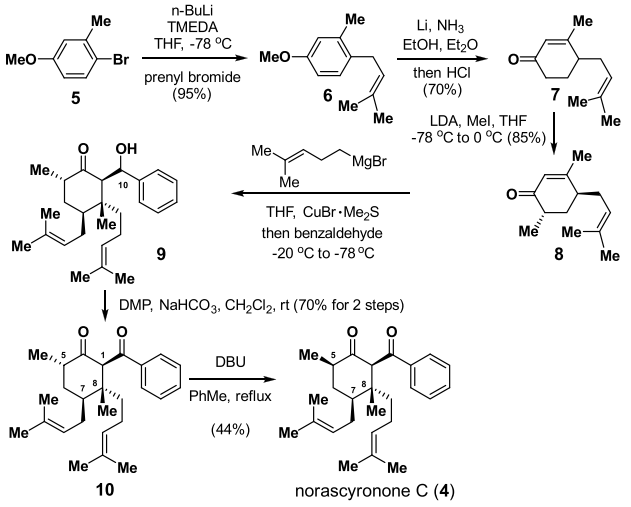

https://dx.doi.org/10.1021/acs.orglett.0c00212
Org. Lett. XXXX, XXX, XXX−XXX

tetracyclic cores of **2** and **3** through the proposed biomimetic pathway, taking into account that the diastereoselective formation of the vicinal all-carbon quaternary chiral centers at C1 and C8 might be difficult owing to their steric effect.[7]

Inspired by the application of a Mn(III)-mediated oxidative radical cyclization in the total syntheses of yezo'otogirins A and C by the groups of George[2b] and Lee,[5i] we decided to use this oxidative radical reaction as a key step for the formation of the tetracyclic cores of **2** and **3**. Herein, we report the development of a protecting-group-free approach to the diastereoselective total syntheses of **2** and **3**, including the serendipitous finding that the stereochemistry of C5 plays a critical role in the proposed oxidative cyclization owing to its steric effect in the aromatization step for B-ring formation. The developed chemistry allowed us to achieve the total syntheses of **2** and **3** for the first time.

Our syntheses of **2** and **3** began with the diastereoselective preparation of key intermediate **4** in a protecting-group-free manner (Scheme 1). Accordingly, the exposure of commercially available aryl bromide **5** to *n*-BuLi in the presence of tetramethylethylenediamine (TMEDA)[8] in THF at −78 °C afforded an aryllithium species, which was then reacted with prenyl bromide to give **6** in 95% yield. To install the enone motif in **7**, compound **6** was subjected to a Birch reduction (Li in $NH_3$ at −78 °C),[9] and the resultant methyl vinyl ether was then hydrolyzed with HCl to afford **7** in 70% yield. Methylation of enone **7**, by treating with lithium diisopropylamine (LDA) followed by methyl iodide, gave compound **8** as a single diastereomer in 85% yield.[2b,5i]

**Scheme 1. Diastereoselective Synthesis of Diketones 4 and 10**

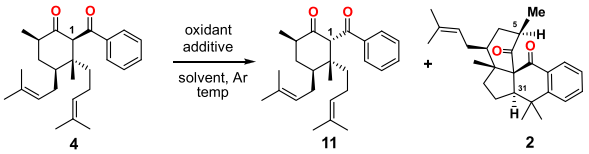



To achieve the diastereoselective synthesis of diketone **10**, we adopted a domino Michael/aldol condensation reaction strategy developed by Shibasaki,[10] George,[2b] and Lee.[5i] Accordingly, Cu-catalyzed conjugate addition of (4-methylpent-3-en-1-yl)magnesium bromide to enone **8** at −20 °C for 20 min, an *in situ* trapping of the resulting magnesium enolate by benzaldehyde at −78 °C, afforded hydroxy ketone **9** as a pair of diastereomers at the newly generated C10 chiral center. Further oxidation of the hydroxyl group at C10 via Dess−Martin oxidation gave diketone **10** as a single diastereomer in 70% yield over two steps. The stereochemistry of substituents at C1, C5, C7, and C8 on the cyclohexanone ring of **10** was assigned based on the 2D $^1$H NMR spectrum (see SI for details).

To prepare key intermediate **4**, a toluene solution of **10** was treated with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) at reflux for 48 h, affording **4** as the more thermally stable product in 44% yield. The stereochemistry of **10** was assigned unambiguously by 2D NMR analysis (see SI for details).

With diketone **4** in hand, our investigation then concentrated on the proposed biomimetic cyclization of diketone **4** for the formation of the tetracyclic core in **2** and **3**. Initially, we used $Mn(OAc)_3/Cu(OAc)_2$ as oxidant[3a] to perform the proposed biomimetic oxidative annulation of diketone **4**[4] in EtOH as solvent. Unfortunately, only a trace amount of desired product **2** was observed after conducting the reaction at 80 °C for 48 h, with the majority of starting material diketone **4** decomposed under these conditions (Table 1, entry 1). To evaluate the solvent effect on the annulation outcome, the above reaction was conducted in various solvents, including acetic acid,[11] 2,2,2-trifluoroethanol,[12] and DMF.[2b,13] However, no desired product **2** was obtained, and significant amounts of starting material decomposition were observed (entries 2−4). Furthermore, replacing $Mn(OAc)_3/CuOAc_2$ with $Mn(OAc)_3$

**Table 1. Profile of the Oxidative Cascade Reaction of Diketone 4**




| entry | oxidant | equiv | solvent | temp (°C) | time (h) | yield (%)[a] 4 | 11 | 2 |
|---|---|---|---|---|---|---|---|---|
| 1 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | $(Mn^{III}/Cu^{II}$ = 2/1) | EtOH[b] | 80 | 48 | 30 | | trace |
| 2 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | $(Mn^{III}/Cu^{II}$ = 2/1) | AcOH[b] | 80 | 16 | 25 | 10 | |
| 3 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | $(Mn^{III}/Cu^{II}$ = 2/1) | $CF_3CH_2OH$[c] | 80 | 16 | | | |
| 4 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | $(Mn^{III}/Cu^{II}$ = 2/1) | DMF[c] | 130 | 16 | | | |
| 5 | $Mn(OAc)_3{\cdot}2H_2O$ | (2) | AcOH[b] | 80 | 16 | 34 | 8 | |
| 6 | $Mn(OAc)_3{\cdot}2H_2O$; $Yb(OTf)_3{\cdot}H_2O$ | $(Mn^{III}/Yb^{III}$ = 2.2/1) | $CF_3CH_2OH$[c] | 80 | 16 | | | |
| 7 | CAN | (2) | MeCN[c] | 70 | 12 | | | |
| 8 | $FeCl_3$ | (2) | MeCN[c] | 70 | 12 | | | |

[a]Isolated yield. [b]Starting material partially decomposed. [c]Starting material decomposed.



https://dx.doi.org/10.1021/acs.orglett.0c00212
Org. Lett. XXXX, XXX, XXX−XXX

or $Mn(OAc)_3/Yb(OTf)_3$[14] (entries 5 and 6) or using other oxidants, such as CAN[15] and $FeCl_3$,[16] failed to afford the desired product **2** (entries 7 and 8). The observed extensive decomposition of diketone **4** led us to speculate that the initial oxidative step might occur but that the generated radical did not undergo the proposed cascade reaction to afford the tetracyclic ring in product **2**.

Inspection of the 3D structure of **4** (Figure 2) showed that the methyl group at C5 might have a profound steric effect on the outcome of the tetracyclic ring formation in product **2**. To better understand this domino reaction, we performed density functional theory (DFT) calculations to determine whether different relative conformations at C5 adjusted this domino oxidative radical cyclization.

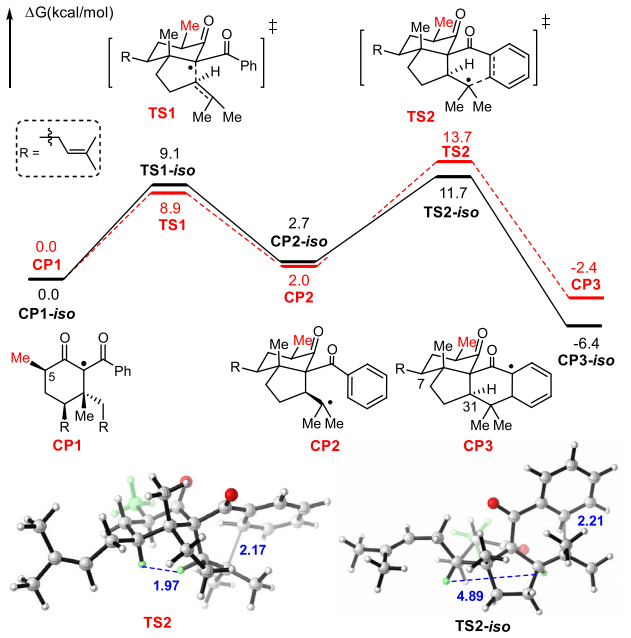


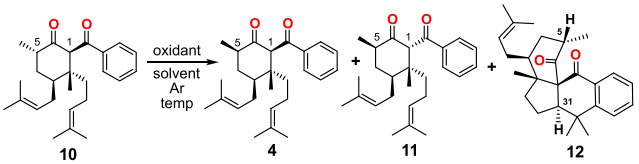

**Figure 2.** Free energy profiles of the radical cyclization. Red line represents the reaction of the 1,3-dicarbonyl radical obtained from norascyronone **C**. Black line represents the reaction of the 1,3-dicarbonyl radical obtained from **10**.

As shown in Figure 2, 1,3-dicarbonyl radical **CP1** could be obtained from norascyronone **C** through initiation by the oxidant. Subsequent radical addition to the C−C double bond via five-membered transition state **TS1** afforded tertiary carbon radical **CP2** reversibly. Starting from **CP2**, an electrophilic radical addition to the phenyl moiety via transition state **TS2** generates intermediate **CP3**, with subsequent oxidation/aromatization leading to desired compound **2**[17] (see note in reference). The calculated results showed that the electrophilic radical addition was the rate-determining step, with an energy barrier of 13.7 kcal/mol. This indicated that the process of initiation of the 1,3-dicarbonyl radical was endergonic, which would increase the overall activation energy of the annulation reaction. Meanwhile, we also conducted calculations for 1,3-dicarbonyl radical **CP1**-*iso* from diastereoisomer **10** (black line). The inverse chirality at C5 resulted in a larger conformational adjustment of the transition state (**TS2**-*iso*) in the electrophilic radical addition step. Structure analysis indicated the methylene at C1 presented as an axial bond in **TS2**, resulting in strong intramolecular strain (shortest H(C7)−H(C31) distance of 1.97 Å), while the analogous strain was absent in **TS2**-*iso* due to the methylene being equatorial. This conformational adjustment led to a 2.0 kcal/mol decrease in the energy barrier for **TS2**-*iso*. The generated tetracyclic core intermediate **CP3**-*iso* was also more stable than **CP3**, suggesting that diastereoisomer **10** would exhibit enhanced reactivity in this oxidative radical cyclization.

To explore this synthetic feasibility, diketone **10** was treated with $Mn(OAc)_3/Cu(OAc)_2$ in AcOH at 80 °C for 16 h. To our delight, desired annulated product **12** was obtained in 40% yield as a single diastereoisomer (Table 2, entry 1). In this reaction, compounds **4** and **11** were also formed in 22% and 13% yields, respectively, which were derived from the epimerization of **10** at the corresponding C1 and C5 chiral centers.

To improve the yield of **12**, we first profiled the solvent effect on the oxidative annulation outcome (Table 1, entries 2−5), with the best results obtained in EtOH as solvent, affording **12** in 61% yield (entry 2). Under such reaction

**Table 2. Oxidative Cyclization for the Synthesis of 12**




| entry | oxidant | equiv | solvent | temp (°C) | time (h) | yield (%)[a] 4 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|
| 1 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | ($Mn^{III}/Cu^{II}$ = 2/1) | AcOH | 80 | 16 | 22 | 13 | 40 |
| 2 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | ($Mn^{III}/Cu^{II}$ = 2/1) | EtOH | 80 | 32 | | | 61 |
| 3 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | ($Mn^{III}/Cu^{II}$ = 2/1) | MeCN | 80 | 32 | | | |
| 4 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | ($Mn^{III}/Cu^{II}$ = 2/1) | 1,4-dioxane | 80 | 32 | | | 5 |
| 5 | $Mn(OAc)_3{\cdot}2H_2O$; $Cu(OAc)_2{\cdot}H_2O$ | ($Mn^{III}/Cu^{II}$ = 2/1) | DMF | 80 | 32 | | | 27 |
| 6 | $Mn(OAc)_3{\cdot}2H_2O$ | $Mn^{III}$ = 2 | AcOH | 80 | 16 | 25 | 10 | 18 |
| 7 | $Mn(OAc)_3{\cdot}2H_2O$ | $Mn^{III}$ = 2 | AcOH/$Ac_2O$[b] | 80 | 16 | 22 | 18 | 6 |
| 8 | $Mn(OAc)_3{\cdot}2H_2O$ | $Mn^{III}$ = 2 | EtOH | 80 | 16 | | | 4 |
| 9 | $Cu(OAc)_2{\cdot}H_2O$ | $Cu^{II}$ = 2 | AcOH | 80 | 16 | 61 | 14 | |

[a]Starting material partially decomposed. [b]Starting material decomposed.



https://dx.doi.org/10.1021/acs.orglett.0c00212
Org. Lett. XXXX, XXX, XXX−XXX

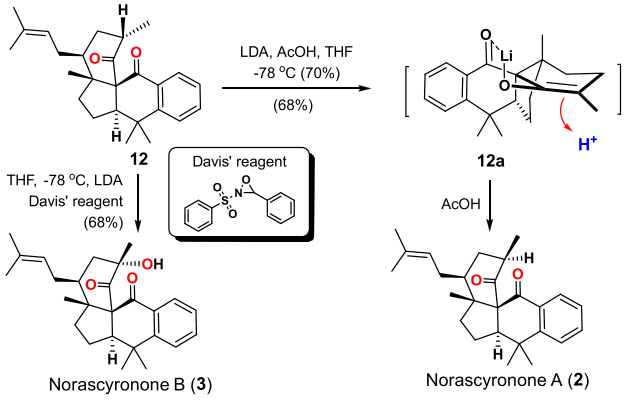
conditions, compounds **4** and **11** were not observed. To demonstrate the synergistic effect of Mn(III) and Cu(II) in this oxidative annulation, we conducted these reactions in the presence of Mn(III) and Cu(II) individually. However, no desired product **12** was observed (Table 2, entries 6–9), indicating that the combination of Mn(III) and Cu(II) was essential for this oxidative annulation reaction.

With streamlined access to diketone **12**, we next investigated the total synthesis of **2** and **3**.

The synthetic feasibility of the direct conversion of product **12** to **2** was explored. We speculated that **12** could be converted into **2** by base-mediated epimerization. In the event, when **2** was treated with DBU in toluene at reflux for 48 h, norascyronone A (**2**) was obtained in 30% yield (with **12** recovered in 67% yield) on a 100 mg scale. We later discovered that **2** could be prepared more effectively by kinetic protonation of enolate **12a** with AcOH at −78 °C, which afforded **2** in 70% yield. The product was confirmed to be norascyronone A (**2**) by comparison of its $^{1}$H NMR and $^{13}$C NMR spectra with those reported in the literature.[4] The high diastereoselectivity was rationalized by the formation of chelation complex **12a**, in which $Li^{+}$ is chelated with the C10 carbonyl group, causing the AcOH to approach from the *Re*-face.

We next worked on the total synthesis of **3**. Treatment of **12** with LDA (3.0 equiv) at −78 °C gave enolate **12a**, which was then reacted with 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (the Davis reagent; 3.0 equiv) to give desired product **3** in 68% yield as a single diastereomer (Scheme 2). The structure of **3** was confirmed by comparison of its $^{1}$H NMR and $^{13}$C NMR spectra with those reported in the literature.[4]

**Scheme 2. Total Syntheses of Norascyronones A (2) and B (3)**




In summary, protecting-group-free total syntheses of (±)-norascyronones A (**2**) and B (**3**) were achieved for the first time in eight steps, with overall yields of 17% and 16%, respectively, from commercially available aryl bromide **5**. The key step was a Mn(III)/Cu(II)-mediated cascade oxidative cyclization for tetracyclic core formation, in which two new bonds, two new rings, and two new contiguous stereogenic centers were constructed in a single step. Notably, the steric effect of the C5 chiral center on the outcome of the tetracyclic cyclic ring formation was identified.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00212.

Copies of $^{1}$H and $^{13}$C NMR spectra for all new compounds (PDF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

**Yu Lan** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, China;* orcid.org/0000-0002-2328-0020; Email: lanyu@cqu.edu.cn

**Jun Huang** − *State Key Laboratory of Chemical Oncogenomics and Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School and Shenzhen Bay Laboratory, Shenzhen 518055, China*; Email: junhuang@pku.edu.cn

**Zhen Yang** − *State Key Laboratory of Chemical Oncogenomics and Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School and Shenzhen Bay Laboratory, Shenzhen 518055, China; Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education and Beijing National Laboratory for Molecular Science (BNLMS), and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China;* orcid.org/0000-0001-8036-934X; Email: zyang@pku.edu.cn

### Authors

**Tingting Cao** − *State Key Laboratory of Chemical Oncogenomics and Key Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School and Shenzhen Bay Laboratory, Shenzhen 518055, China*

**Lei Zhu** − *School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, China;* orcid.org/0000-0002-7870-8469

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00212

### Author Contributions

‖T.T.C. and L.Z. contributed equally.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was financially supported by the National Science Foundation of China (Grant Nos. 21632002, 21702011, and 21871012), Shenzhen Basic Research Program (Grant Nos. JCYJ20180302150314340 and JCYJ20170818090044432), and the Scientific and Technological Innovation Project supported by Qingdao National Laboratory for Marine Science and Technology (Grant Nos. 2015ASKJ02 and LMDBKF201802).

## ■ REFERENCES

(1) (a) Hu, Y.-L.; Hu, K.; Kong, L.-M.; Xia, F.; Yang, X.-W.; Xu, G. *Org. Lett.* **2019**, *21*, 1007. (b) Yang, X.-W.; Grossman, R. B.; Xu, G. *Chem. Rev.* **2018**, *118*, 3508. (c) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.

(2) (a) Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162. (b) Lam, H. C.; Kuan, K. W.; George, J. H. *Org. Biomol. Chem.* **2014**, *12*, 2519. (c) Cao, J. M.; Thor, W. G.; Yang, S.

K.; Zhang, M. X.; Bao, W. L.; Zhu, L. Z.; Yang, W.; Cheng, Y. K.; Lee, C. S. *Org. Lett.* **2019**, *21*, 4896.
(3) (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083. (c) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546. (d) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 4605. (e) Ito, Y.; Konoike, T.; Saegusa, T. *J. Am. Chem. Soc.* **1975**, *97*, 2912. (f) Frazier, R. H., Jr.; Harlow, R. L. *J. Org. Chem.* **1980**, *45*, 5408.
(4) (a) Corey, E. J.; Kang, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 5384. (b) Ernst, A. B.; Fristad, W. E. *Tetrahedron Lett.* **1985**, *26*, 3761. (c) Snider, B. B.; Patricia, J. J.; Kates, S. A. *J. Org. Chem.* **1988**, *53*, 2137. (d) Kates, S. A.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1990**, *55*, 2427. (e) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217. (f) Cole, B. M.; Han, L.; Snider, B. B. *J. Org. Chem.* **1996**, *61*, 7832. (g) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.
(5) Selected examples, see: (a) Mohan, R.; Kates, S. A.; Dombroski, M. A.; Snider, B. B. *Tetrahedron Lett.* **1987**, *28*, 845. (b) Snider, B. B.; Zhang, Q. W.; Dombroski, M. A. *J. Org. Chem.* **1992**, *57*, 4195. (c) Snider, B. B.; Zhang, Q. W. *J. Org. Chem.* **1993**, *58*, 3185. (d) Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975. (e) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (f) Mitasev, B.; Porco, J. A., Jr. *Org. Lett.* **2009**, *11*, 2285. (g) Pepper, H. P.; Tulip, S. J.; Nakano, Y.; George, J. H. *J. Org. Chem.* **2014**, *79*, 2564. (h) Yang, W.; Cao, J. M.; Zhang, M. X.; Lan, R. F.; Zhu, L. Z.; Du, G. G.; He, S. Z.; Lee, C. S. *J. Org. Chem.* **2015**, *80*, 836. (i) He, S. Z.; Yang, W.; Zhu, L. Z.; Du, G. Y.; Lee, C.-S. *Org. Lett.* **2014**, *16*, 496.
(6) (a) Long, R.; Huang, J.; Shao, W. B.; Liu, S.; Lan, Y.; Gong, J. X.; Yang, Z. *Nat. Commun.* **2014**, *5*, 5705. (b) Zheng, N.; Zhang, L.; Gong, J. X.; Yang, Z. *Org. Lett.* **2017**, *19*, 2921. (c) Shao, W.; Huang, J.; Guo, K.; Gong, J. X.; Yang, Z. *Org. Lett.* **2018**, *20*, 1857. (d) Huang, Z.; Huang, J.; Qu, Y.; Zhang, W.; Gong, J. X.; Yang, Z. *Angew. Chem., Int. Ed.* **2018**, *57*, 8744.
(7) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Peterson, E. A.; Overman, L. E. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 11943. (d) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (e) Song, Z. L.; Fan, C. A.; Tu, Y. Q. *Chem. Rev.* **2011**, *111*, 7523.
(8) Gawade, S. A.; Bhunia, S.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 7835.
(9) (a) Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710. (b) Turner, R. B.; Buchardt, O.; Herzog, E.; Morin, R. B.; Riebel, A.; Sanders, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 1766.
(10) (a) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439. (b) Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 14200.
(11) (a) Snider, B. B.; Mohan, R. M.; Kates, S. A. *J. Org. Chem.* **1985**, *50*, 3659. (b) Snider, B. B.; Merritt, J. E.; Dombroski, M. A.; Buckman, B. O. *J. Org. Chem.* **1991**, *56*, 5544.
(12) Chikaoka, S.; Toyao, A.; Ogasawara, M.; Tamura, O.; Ishibashi, H. *J. Org. Chem.* **2003**, *68*, 312.
(13) Snider, B. B.; McCarthy, B. A. *J. Org. Chem.* **1993**, *58*, 6217.
(14) (a) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K. W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658. (b) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579.
(15) (a) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, *26*, 127. (b) Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862.
(16) (a) Booker-Milburn, K. I. *Synlett* **1992**, *1992*, 809. (b) Booker-Milburn, K. I.; Thompson, D. F. *Synlett* **1993**, *1993*, 592.
(17) We also considered the Friedel−Crafts reaction pathway in the formation of the tetracyclic core of **2**. Calculated results indicate the diastereoisomer **10** could also exhibit enhanced reactivity in this oxidative radical cyclization (see Supporting Information for details).


https://dx.doi.org/10.1021/acs.orglett.0c00212
*Org. Lett.* XXXX, XXX, XXX−XXX