OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Progress toward the Enantioselective Synthesis of Curcusones A−D via a Divinylcyclopropane Rearrangement Strategy

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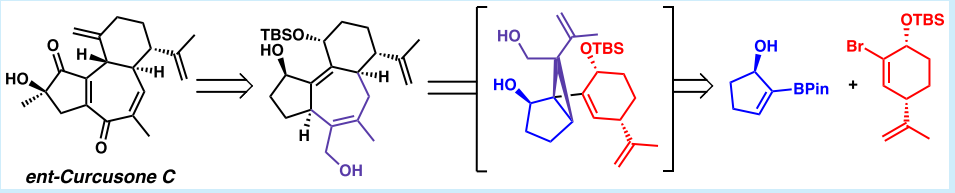
Supporting Information



ABSTRACT: We report our iterative efforts toward the divergent total syntheses of curcusones A−D via Suzuki coupling, intramolecular cyclopropanation, and a key divinylcyclopropane rearrangement. Progress of our synthesis was repeatedly challenged by the highly substrate-dependent cyclopropanation step, which we could ultimately overcome by judicious choice of substituents on the six-membered ring fragment.

The curcusone family comprises various synthetically challenging and biologically active rhamnofolane diterpenoid natural products, several of which have known bioactivity.[1] Among them, curcusone C (**3**, Figure 1) demonstrates the most potent and varied anticancer properties, including antiproliferative activity against human hepatoma, ovarian carcinoma, and promyeolycytic leukemia.[2] Despite these enticing biological features, **3** and all of its structural relatives have yet to surrender to any total synthesis campaigns. It is worthwhile to note that the Dai lab recently reported a synthesis of racemic oxo-bridged **5** and **6** over 21 steps, but found that the putative natural product structures had been incorrectly assigned by NMR.[3,4] We do not anticipate these issues with **3**, as its structure has been unambiguously determined by X-ray crystallography.[2] Herein, we report our early synthetic forays into the enantioselective construction of curcusones A−D via Suzuki coupling and sequential divinylcyclopropane rearrangement.

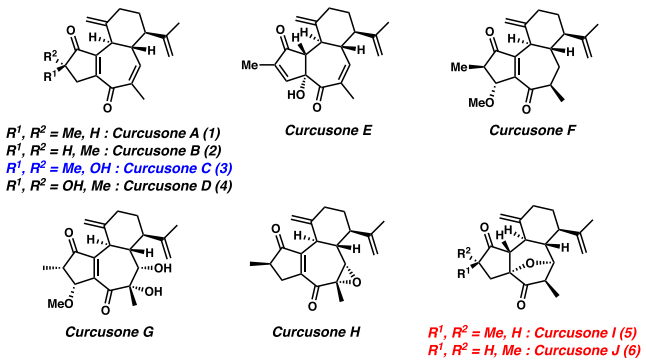
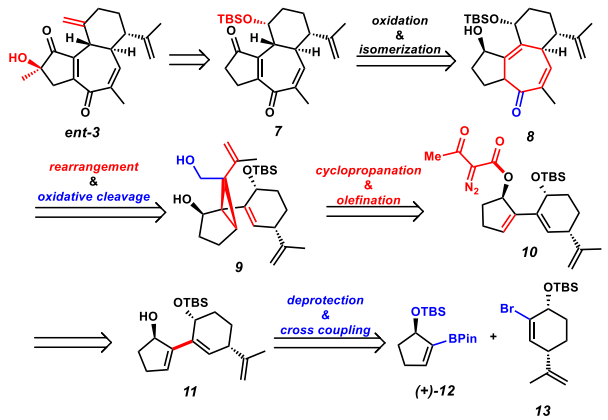


Figure 1. Proposed structures of curcusones A−J.

After attempting several strategically related routes, our final retrosynthesis proposed that a late-stage α-functionalization of enone **7** would permit a divergent approach to the enantiomeric series of curcusones A−D (Scheme 1). As

Scheme 1. Retrosynthetic Analysis of *ent*-Curcusone C (*ent*-3)



such, we envisioned performing an α-functionalization, oxidation, and olefination of silyl ether **7** (highlighted in red). The ene-dione moiety of **7** may be derived from ketoalcohol **8** by means of alcohol oxidation and acid- or base-promoted olefin migration. The central seven-membered ring present in **8** could be assembled by a stereospecific divinylcyclopropane rearrangement and subsequent oxidative

Received: October 27, 2019

DOI: 10.1021/acs.orglett.9b03829
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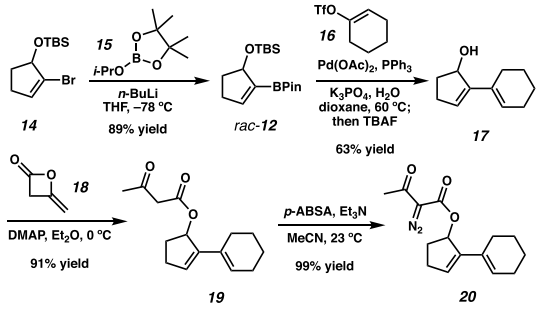
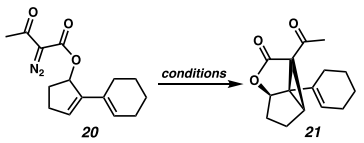
cleavage of hydroxymethylated cyclopropane **9**. We predicted that the cyclopropane moiety in **9** might be installed via intramolecular π-bond-cyclopropanation of a metallocarbenoid derived from diazo ketoester **10** followed by methylenation and reductive lactone opening. The diazo oxobutanoyl functionality in **10** (highlighted in red) could be incorporated by acylation and diazo transfer of alcohol **11**. Bicycle **11** may be accessed by a Suzuki cross-coupling of monocyclic fragments (+)-**12** and **13**.

In order to validate our synthetic approach, we focused on developing a suitable model system with which we could investigate the crucial divinylcyclopropane rearrangement. To this end, we were able to join coupling partners *rac*-**12** and **16**[5] via Suzuki coupling to expediently provide **17** (Scheme 2). Upon assembling the model bicycle, we turned our attention toward constructing the cyclopropane functionality. Thus, esterification of **17** with diketene (**18**) afforded ketoester **19**, which was subjected to α-diazo transfer to furnish cyclopropanation precursor **20** in excellent yield.[6]

Scheme 2. Model Studies for the Crucial Rearrangement



With model precursor **20** in hand, we attempted the key cyclopropanation step. Both rhodium and copper catalysts were employed to effect this transformation (Figure 2). Although dirhodium catalysts (entries 1–4) either offered no reactivity or resulted in decomposition, $Cu(TBSal)_2$ (entry 5) gratifyingly furnished desired annulated product **21** in moderate yield and with only minor levels of decomposition.



Entry	Catalyst	Solvent	Temperature	Result
1	$Rh_2(OAc)_2$	CH_2Cl_2	23 °C	no reaction
2	$Rh_2(OAc)_2$	CH_2Cl_2	reflux	decomposition
3	$Rh_2(esp)_2$	CH_2Cl_2	23 °C	decomposition
4	$Rh_2(cap)_4$	CH_2Cl_2	reflux	decomposition
5	$Cu(TBSal)_2$	PhMe	reflux	65% yield

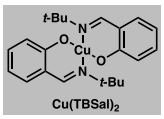
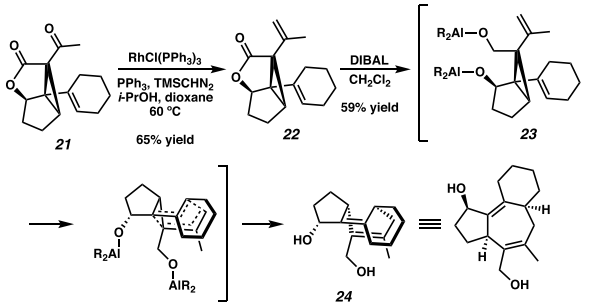


Figure 2. Optimization screen for the cyclopropanation step.

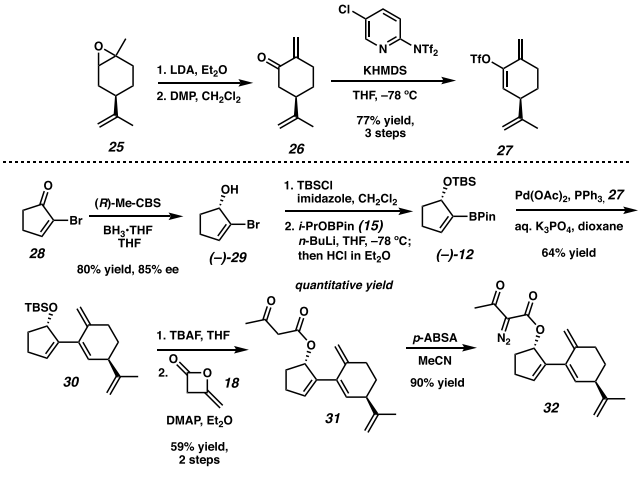
Having successfully forged model cyclopropane **21**, we next aimed to prepare and rearrange the envisioned divinylcyclopropane system. At the outset of our synthetic explorations, we hoped to derive the second necessary vinyl group from the ketone moiety in **21** via silyl enol ether formation. During these studies, we encountered a mechanistically unusual cascade reaction consisting of five successive pericyclic rearrangements.[7] In order to obviate this unexpected pathway, we instead opted to forge the second vinyl group from common intermediate **21** via carbonyl methylenation (Scheme 3). Thus, olefination of the ketone functionality in **21** using Wilkinson's catalyst and $TMSCHN_2$ afforded rearrangement precursor **22**.[8] Gratifyingly, reductive rupture of the butyrolactone ring in **22** resulted in spontaneous rearrangement to provide tricyclic alcohol **24**, presumably via intermediate *bis*-alkoxide **23**. Due to the known conformational restrictions imposed by the cyclopropane moiety, this rearrangement likely proceeds through an *endo*-boat[9] transition state to stereospecifically afford the rearranged product following protodemetalation of the alkoxide.

Scheme 3. Validation of Model Studies



Upon corroborating our synthetic approach via model studies, we attempted to deploy this technology on the actual system. We initially intended to install the *exo*-methylene in the eastern ring of **1**–**4** prior to cross-coupling. To this end, limonene oxide (**25**, Scheme 4) was exposed to eliminative epoxide opening to provide an allylic alcohol, which could be subjected to DMP oxidation[10] to afford enone **26** as well as an undesired hetero-Diels–Alder adduct.[11] Following optimization, we eventually found that **26** could be elaborated to enol triflate **27** in satisfactory yields using KHMDS and Comins reagent.[12] Meanwhile, boronate coupling partner (−)-**12** was assembled from known vinyl bromide **28**[13] via CBS reduction, alcohol protection, and *O*-silylation. Pleasingly, Suzuki coupling of fragments (−)-**12** and **27** delivered requisite bicyclic diene **30**, which upon silyl deprotection, acetoacetylation, and diazo transfer delivered annulation precursor **32** via β-ketoester **31**.

Scheme 4. 1st Generation Synthesis of Diazo 32



DOI: 10.1021/acs.orglett.9b03829
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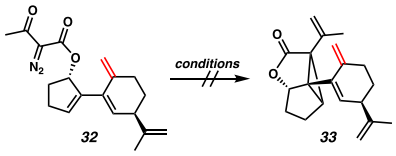
With diazo **32** in hand, we next investigated the critical cyclopropanation step (Figure 3). Unfortunately, all attempts to advance **32** to **33** resulted in decomposition (entries 1−3), a complex mixture of byproducts (entry 4), or simply no reactivity (entry 5). These combined issues necessitated a revision of our synthetic route. Given the amenability of our model substrate (**20**, Figure 2, *vide supra*) toward similar cyclopropanation conditions, we speculated that our inability to execute this transformation on diazo **32** might be due to subtle stereoelectronic influences[14] imparted by the presence of the proximal *exo*-methylene group (Figure 3, highlighted in red). In light of this, we instead chose to install a ketone functionality, which we suspected could be elaborated to the corresponding *exo*-methylene upon olefination.



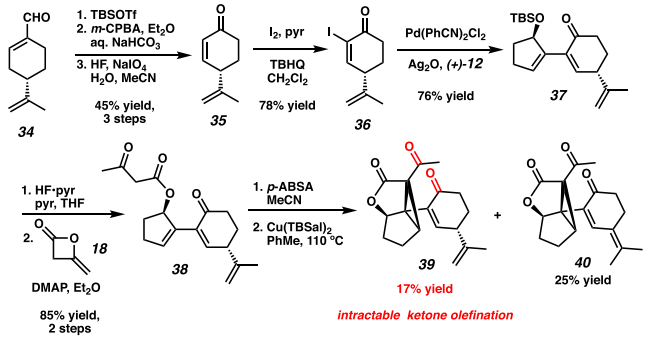
entry	catalyst	solvent	temperature	result
1	$Cu(TBSal)_2$	PhMe	reflux	decomp
2	$Cu(hfacac)_2$	PhMe	45 °C–75 °C	decomp
3	CuOTf	PhMe	45 °C–75 °C	decomp
4	$Rh_2(OAc)_4$	CH_2Cl_2	23 °C	complex mixture
5	$Pd(OAc)_2$	Et_2O	0 °C	no reaction

Figure 3. Unsuccessful cyclopropanation of **32**.

Now targeting the enantiomeric series of curcusones A−D via coupling of enone fragment **36**, we assembled cyclohexenone **35** over three steps from (*S*)-perillaldehyde (**34**, Scheme 5) according to known methods.[15] An ensuing α-iodination of **35** using I_2 and pyridine provided desired iodoenone **36**, which itself could undergo the anticipated Suzuki coupling with boronate (+)-**12**[16] to furnish corresponding bicycle **37** in good yield. Silyl ether **37** could be advanced to β-ketoester **38** without event following deprotection and transacylation. Although the vital base-mediated diazo transfer and cyclopropanation sequence gratifyingly furnished desired enone **39**, significant amounts of unwanted olefin isomer **40** were also observed. Unfortunately, all efforts to perform a subsequent double olefination on the two ketones of **39** failed, prompting us to again reassess our route.

Considering the undesired isomerization pathways facilitated by the presence of the gamma proton in enone **36** (Figure 4, highlighted in red), we finally decided to instead target a 1,2-reduced and protected analogue of enone **36** (i.e., silyl allyl

Scheme 5. Second Generation Route toward *ent*-1−4



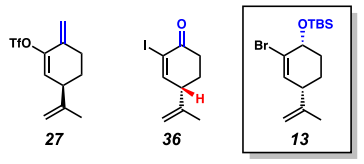
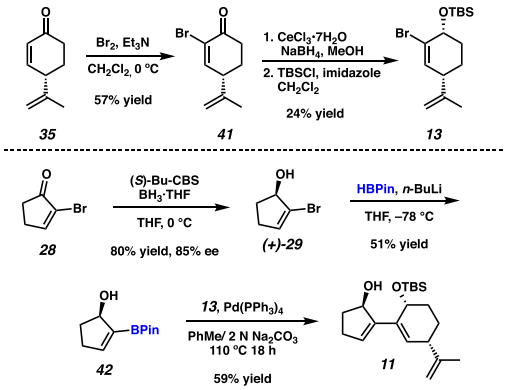


Figure 4. Synthetic evolution of cyclohexene coupling fragments.

ether **13**, Scheme 6). This route commenced with bromination of **35** to afford bromoenone **41**, which could be nonselectively reduced in a 1,2-fashion and *O*-silylated to produce desired *cis* epimer **13** along with the undesired *trans* epimer in roughly equal portions. It is worthwhile to note that the thermodynamically[17] and kinetically[18] favored *trans* epimer was also investigated as a potential synthetic intermediate but was eventually found to be totally uncooperative toward cyclopropanation conditions due to exclusive decomposition. Moving forward, the redundancy of silyl protecting groups in both coupling partners motivated us to attempt deprotecting the boronate fragment prior to cross-coupling. Unfortunately, after an exhaustive screening we found no silyl deprotection conditions that could accommodate the presence of the base- and acid-sensitive boronate functionality. Other protecting groups were also investigated with minimal success.[19] Interestingly, over the course of our efforts we eventually discovered that a cyclopentenol protection strategy could be avoided altogether by performing an unconventional double lithiation/boronate trapping procedure on (+)-**29** with pinacolborane to provide allyl alcohol **42**. With revised boronate **42** and bromide **13** in our possession, we next explored the crucial Suzuki coupling. Gratifyingly, standard coupling conditions afforded bicyclic alcohol **11** in good yield.

Scheme 6. Third Generation Assembly of Revised Bicycle 11



As expected, bicycle **11** could be readily advanced to cyclopropanation precursor **10** following esterification and diazo transfer (Scheme 7). We were further pleased to find that exposure of diazo **10** to previously optimized cyclopropanation conditions did indeed afford annulated product **44**, albeit only on small scales (i.e., 20 mg or less) and with substantial portions of an unwanted byproduct.[20,21] With provision of cyclopropane **44**, we next hoped to append the second vinyl tether. After extensive studies, we discovered that methylenation of the ketone in **44** to olefin **45** could be achieved under Kauffmann olefination conditions,[22] thereby finally establishing the essential divinylcyclopropane system.

DOI: 10.1021/acs.orglett.9b03829
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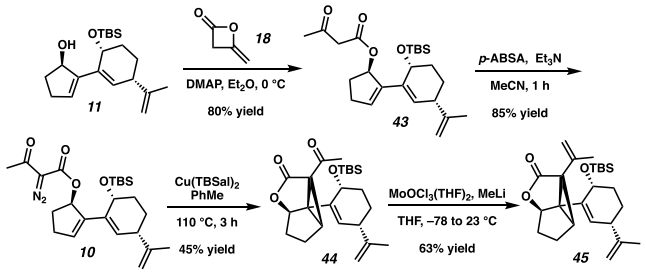
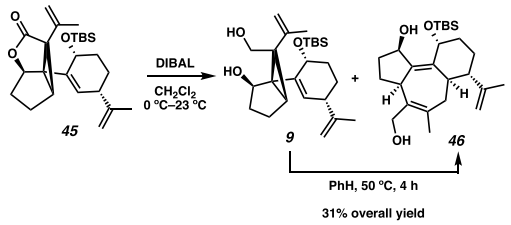
Scheme 7. Third Generation Synthesis of Cyclopropane 45



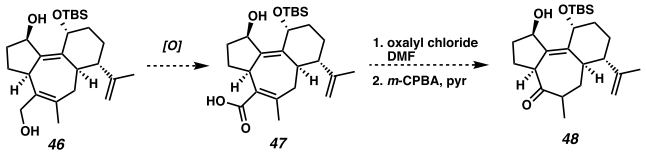
Upon accessing divinylated intermediate **45**, we set out to induce the pivotal rearrangement. To this end, reductive opening of the butyrolactone moiety of **45** provided diol **9** along with minor amounts of desired rearrangement product **46** (Scheme 8). Fortuitously, we found that this crude product mixture smoothly underwent the envisioned divinylcyclopropane rearrangement upon gentle heating to provide tricycle **46**, possessing the carbocyclic skeleton embedded in each of the curcusones.

Scheme 8. Construction of Tricycle 46 by Lactone Opening and Thermal Rearrangement



With the 5−7−6 carbon skeleton finally in hand, we were eager to elaborate diol **46** to ketoalcohol **48** via chemoselective oxidation of the primary alcohol to deliver acid **47** (Scheme 9). We suspected that intermediate **47** may itself undergo the crucial oxidative cleavage upon acid chloride formation and subsequent carboxy-inversion.[23] We were however disappointed to find that all attempts to advance **46** to **47** have thus far led to rapid decomposition, likely due to the exceptional instability of **46** toward oxidative conditions.[24] Eventually, the combined difficulties posed by this substrate instability and by the prohibitively scale-dependent cyclopropanation step motivated us to embark on an entirely new route, which was since found to hinge on an RCM approach to assemble the central seven-membered ring.[25]

Scheme 9. Envisioned Oxidative Cleavage Sequence



In summary, we have presented our introductory synthetic efforts toward the construction of curcusones A−D via a divinylcyclopropane rearrangement disconnection. During our studies, we invoked several unusual reaction procedures, including an uncommon Kauffmann methylenation and a novel one-step borylation of an unprotected α-bromo allyl alcohol. We also notably accessed a late-stage intermediate possessing the 5/7/6 carbocyclic framework of curcusones A−J. Several end-game strategies to complete the first total syntheses of curcusone A−D are currently under careful scrutiny in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03829.

NMR and IR spectra for all unknown compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NSF (CHE-1800511), Amgen, and Caltech for funding this research.

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(4) Revised structures of curcusones I and J were recently proposed, see: Sarotti, A. M. Structural revision of two unusual rhamnofolane diterpenes, curcusones I and J, by means of DFT calculations of NMR shifts and coupling constants. *Org. Biomol. Chem.* **2018**, *16*, 944−950.

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DOI: 10.1021/acs.orglett.9b03829
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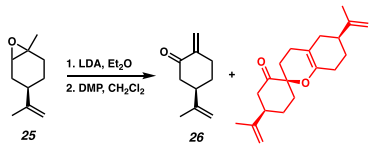
(11) The following hetero-Diels−Alder adduct (highlighted in red) was observed as the major diastereomeric byproduct:



(12) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P. Pyridine-Derived Triflating Reagents: *N*-(2-Pyridyl)-triflimide and *N*-(5-Chloro-2-pyridyl)triflimide. *Org. Synth.* **1997**, *74*, 77−80.
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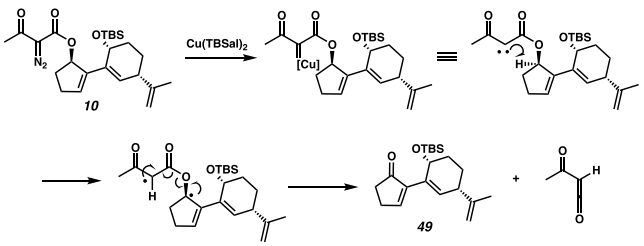
(14) The *exo*-methylene group may pose moderate steric constraints on the system, preventing facile metallocarbenoid formation and subsequent cyclopropanation. It might also electronically deactivate the highly conjugated π system toward cyclopropanation, encouraging an unwanted decomposition pathway.
(15) Siegel, C.; Gordon, P. M.; Razdan, R. K. An Optically Active Terpenic Synthon for Δ9-Cannabinoids: Synthesis of (−)-11-Hydroxy-Δ9-tetrahydrocannabinol (THC) and its 1',1'-Dimethylheptyl Analog. *J. Org. Chem.* **1989**, *54*, 5428−5430.
(16) Coupling partner (+)-**12** was prepared using (*S*)-Me-CBS catalyst.
(17) Reversible Meerwein−Ponndorf−Verley reduction consistently favored the unwanted *trans* isomer, indicating that it is the thermodynamically favored epimer.
(18) All nonasymmetric and irreversible reactions resulted in the *trans* isomer as the predominant diastereomeric product, suggesting that its formation is kinetically favored.
(19) The fragile boronate functionality was incompatible toward most alcohol protection/deprotection strategies. The sole exception to this was found with PMB-based protecting groups, which could be delicately excised under pH-buffered conditions using DDQ.
(20) The sole byproduct of cyclopropanation encountered during our synthetic studies was identified as ketone **49**. A plausible mechanism for its formation involves intramolecular C−H insertion of the carbenoid to afford a β-lactone followed by base-induced lactone opening and fragmentation; see: Xu, X.; Deng, Y.; Yim, D. N.; Zavalij, P. Y.; Doyle, M. P. Enantioselective *cis*-β-lactam synthesis by intramolecular C−H functionalization from enoldiazoacetamides and derivative donor−acceptor cyclopropenes. *Chem. Sci.* **2015**, *6*, 2196−2201. However, we cannot rule out the following radical-based fragmentation pathway:



(21) Similar decomposition pathways were observed during our campaign toward ineleganolide; see: Craig, R. A., II; Roizen, J. L.; Smith, R. C.; Jones, A. C.; Stoltz, B. M. Enantioselective, convergent synthesis of the ineleganolide core by a tandem annulation cascade. *Chem. Sci.* **2017**, *8*, 507−514.
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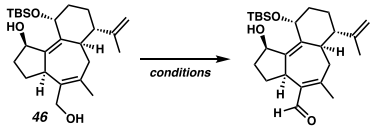
(24) The following oxidizing conditions led to the exclusive decomposition of **46**:



entry	conditions	result
1	DMP	decomp
2	$COCl_2$, DMSO; Et_3N	decomp
3	$[Cu(MeCN)_4]PF_6$, TEMPO, air	decomp
4	Cu(OTf)·PhH, TEMPO, air	decomp
5	MnO_2, CH_2Cl_2	decomp
6	PDC, CH_2Cl_2	decomp

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DOI: 10.1021/acs.orglett.9b03829
Org. Lett. XXXX, XXX, XXX−XXX