Organic LETTERS

Letter

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

pubs.acs.org/OrgLett

Model Reactions for the Enantioselective Synthesis of γ-Rubromycin: Stereospecific Intramolecular Photoredox Cyclization of an *ortho*-Quinone Ether to a Spiroacetal

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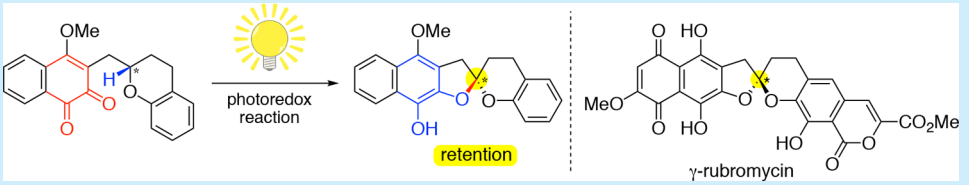
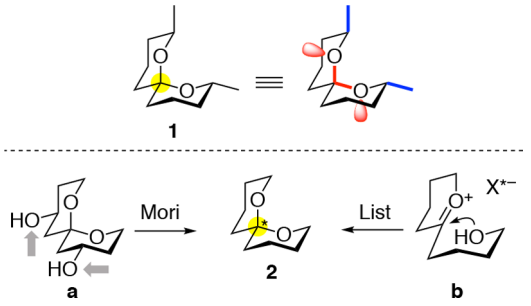
Supporting Information



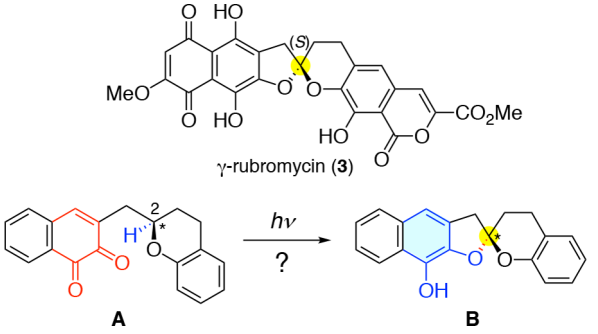
ABSTRACT: A model study for the enantioselective total synthesis of γ-rubromycin has revealed a promising approach for constructing the chiral, nonracemic bicyclic spiroacetal via the stereospecific photoredox reaction of 1,2-naphthoquinone ether.

Bicyclic spiroacetals constitute one of the key structural motifs in various bioactive natural products, and their stereocontrolled construction has been attracting considerable attention from synthetic chemists.[1] As represented by the structure of **1**, a bee pheromone, most natural products correspond to the thermodynamically preferred isomer in view of steric and stereoelectronic effects, where synthetic routes may be rationally designed (see Scheme 1).[2]

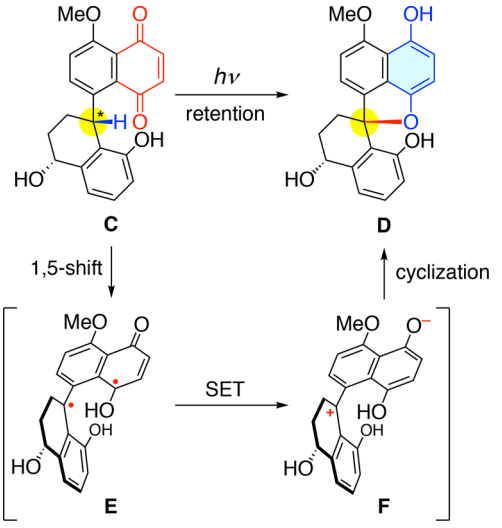
Scheme 1. Bicyclic Spiroacetals



Scheme 2. γ-Rubromycin and Photoredox Approach



Scheme 3. Stereospecific Photoredox Reaction (Previous Work)



On the other hand, an intriguing stereochemical challenge arises, when only a single stereogenicity is present at the spiroacetal center, such as in olean (**2**). An ingenious access is represented by the Mori synthesis of **2**. The strategic use of extra stereogenic centers (see **a** in Scheme 1) enabled the requisite stereocontrol and were eventually removed.[3] Although an interesting methodology for the construction of spiroacetals such as **2** has recently emerged via enantioselective acetalization (**b** in Scheme 1),[4] there are still needs for developing optional approaches.[5]

Received: May 14, 2018

DOI: 10.1021/acs.orglett.8b01475
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Preparation of 1,2-Naphthoquinone 9

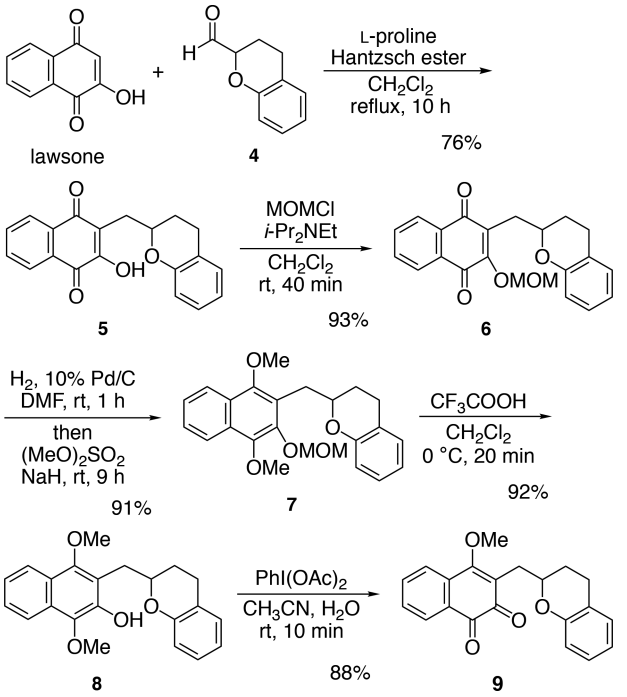
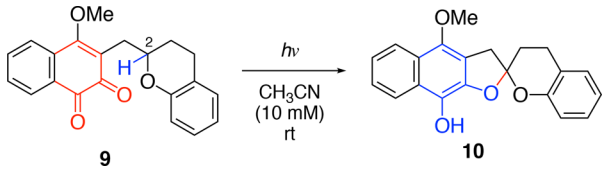
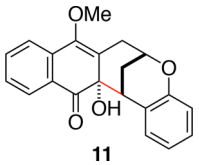


Table 1. Photoredox Reaction of γ-Rubromycin Model 9



entry	light source	time	**10** [%]	**11** [%]
1[a]	fluorescent light (32 W)	156 h	55	trace
2[b]	Xe lamp (300 W)	20 min	71	12

[a]Recovery = 9%. [b]Recovery = 8%.

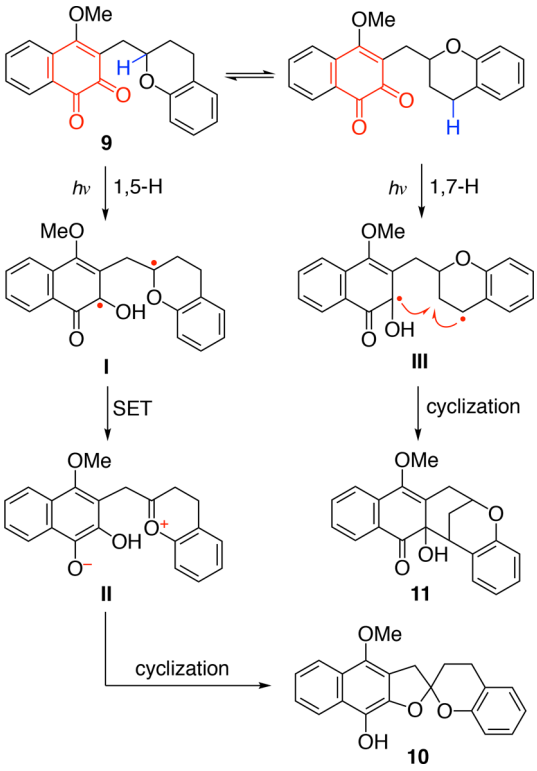


We became intrigued by this challenge in the context of the synthetic project toward γ-rubromycin (**3**),[6−9] an antibiotic having a spiroacetal center as the sole stereogenicity (Scheme 2). The absolute configuration of **3** was assigned as (*S*) by quantum chemical CD calculation;[6b] however, it has never been verified by chemical synthesis.

To address this issue, we devised the idea of the "photoredox approach", i.e., photoinduced conversion of 1,2-naphthoquinone ether **A** into spiroacetal **B**, which is an intramolecular redox reaction, in that the C2 position of chromane **A** becomes oxidized, while the quinone moiety is reduced to the hydroquinone level in **B**. Our hope was that the C−H oxidation would proceed in a stereoretentive manner.

This idea stems from our recent finding, a stereospecific photoredox reaction of 1,4-naphthoquinone **C** that was exploited in the asymmetric synthesis of spiroxin C (Scheme 3):[10,11] Upon photoirradiation of **C**, intramolecular C−H abstraction generates biradical **E**, which undergoes single electron transfer (SET) to zwitterion **F** and following oxycyclization gives **D**. Most importantly, this sequence proceeds in a stereospecific manner with retention of configuration, which could be attributed to the biaryl-like

Scheme 5. 1,5-Hydrogen Abstraction vs 1,7-Hydrogen Abstraction



Scheme 6. Resolution of 7 and Preparation of (−)-9

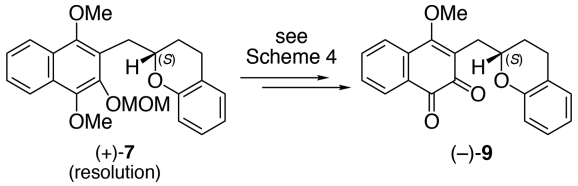
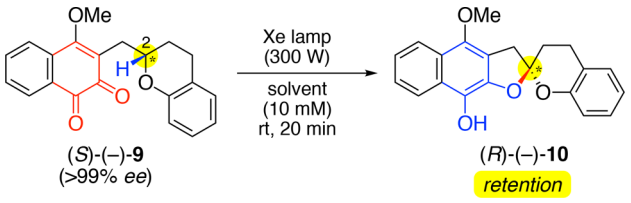


Table 2. Enantiospecific Photoredox Reaction (Solvent Effect)[21]



entry	solvent	yield [%]	enantiomeric excess, ee [%]
1	CH_3CN	69	53
2	toluene	10	12
3	THF	33	13
4	acetone	34	42
5	CH_2Cl_2	46	31
6	MeOH	64	77
7	EtOH	51	61
8	*i*-PrOH	44	45

DOI: 10.1021/acs.orglett.8b01475
Org. Lett. XXXX, XXX, XXX−XXX

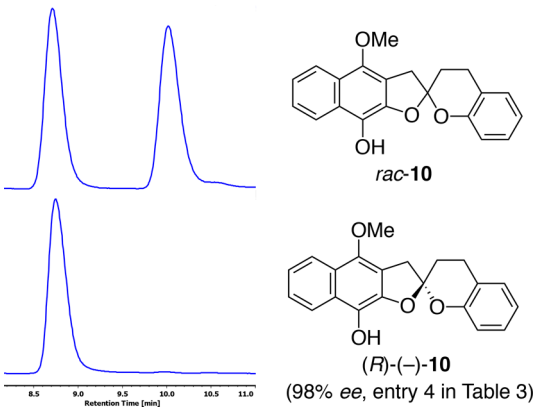


Figure 1. HPLC analysis of *rac*-**10** and (*R*)-(−)-**10**.

Table 3. Temperature Effect in the Enantiomeric Excess (ee) of (*R*)-(−)-10[21]

entry	solvent	temperature [°C]	time [h]	yield [%]	enantiomeric excess, ee [%]
1	MeOH	0	1	65	82
2	MeOH	−40	2	70	87
3	MeOH	−78	3	34	98
4	MeOH, CH_3CN (v/v = 3/1)	−78	3	68	98

scaffold in **E** and **F**: The stereodeteriorating internal C−C bond rotation is slower relative to the sequence, **E** → **F** → **D**.

We wondered if such a stereospecific reaction scenario would apply for the conversion of **A** → **B** (vide supra, Scheme 2) and realized that three major challenges needed to be addressed:

(1) Suitability of 1,2-naphthoquinones as substrates of the photoredox reaction.[12]
(2) C−H oxidation at the C2 position of chromane **A**.
(3) Stereospecificity in a conformationally mobile system as **A**.

The third point seemed particularly challenging, as the reaction sites are indirectly connected through a one-carbon tether, providing a system much more dynamic than the biaryl-like structure stated above.

Pleasingly, the model experiments addressing these questions gave us affirmative answers, which will be described in this communication.

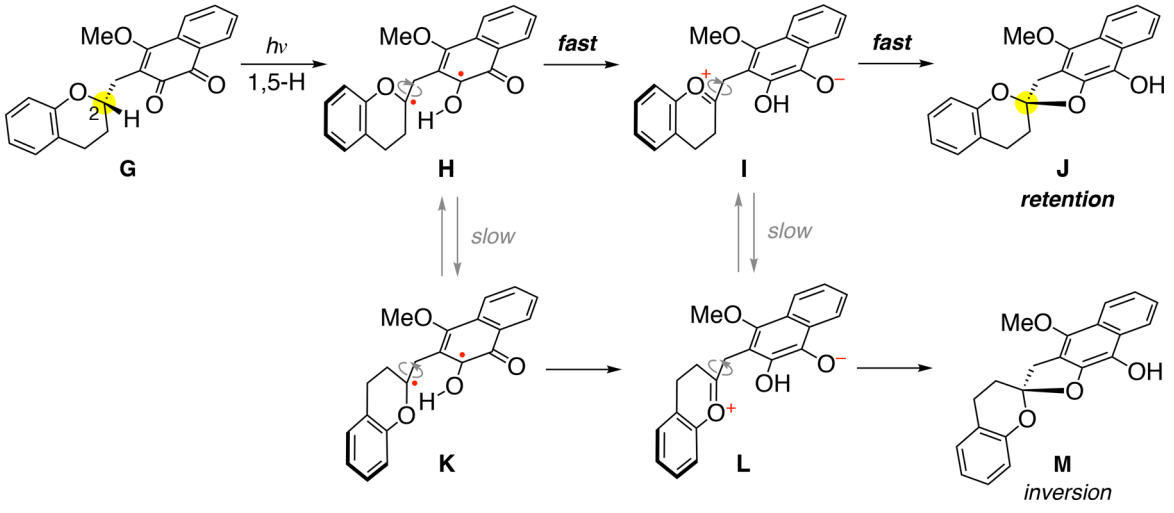
As a model substrate, 1,2-naphthoquinone **9** was prepared (Scheme 4). Lawsone was combined with aldehyde **4**[13] by reductive alkylation[14] to give hydroxynaphthoquinone **5** in 76% yield. Protection of the hydroxy group in **5** by MOM group afforded naphthoquinone **6** in 93% yield. Hydrogenation of **6** to the corresponding hydroquinone followed methylation in a one-pot reaction gave naphthalene **7** in 91% yield. After removal of the MOM group in **7**, the resulting phenol **8** was oxidized to give 1,2-naphthoquinone **9** as an orange solid in 88% yield, ready for examining the photoredox reaction.

Gratifyingly, photoirradiation of 1,2-naphthoquinone **9** indeed provided spiroacetal **10** as the photoredox product (Table 1).[15] Exposure of **9** to normal room light (32 W fluorescent light, CH_3CN, rt) gave spiroacetal **10** in 55% yield, although very long reaction time was required (ca. 1 week, entry 1 in Table 1). However, the reaction time was greatly shortened when a xenon lamp (>380 nm, 300 W) was employed, and the yield was improved to 71% (entry 2 in Table 1).[16] Under these conditions, a small amount of bicyclic compound **11** was coproduced[17] via Norrish−Yang cyclization.[18]

Scheme 5 shows a rationale for the formation of the desired product **10** and the undesired product **11**. Upon light irradiation and excitation of 1,2-naphthoquinone **9**, the productive pathway for **10** is initiated by the intramolecular 1,5-hydrogen abstraction, giving biradical **I**. Subsequent intramolecular SET generates zwitterion **II**, which is trapped by the proximal phenol to give the oxycyclization product **10**. On the other hand, 1,7-hydrogen abstraction gives biradical **III**, which, after Norrish−Yang cyclization, yields side product **11**. This site selectivity of the hydrogen abstraction (1,5- vs 1,7-) reflects the conformational flexibility of the system. Other byproducts arising from a possibly competing 1,6-hydrogen abstraction were not observed. This process seems unlikely, because of the higher bond dissociation energy of the relevant unactivated C−H bond.[10]

Focusing our attention to the configurational integrity of this photoredox reaction, an enantiomerically pure sample of 1,2-naphthoquinone **9** was prepared from the resolved enantiomer

Scheme 7. Rationale for Stereoretentive Photoredox Reaction



DOI: 10.1021/acs.orglett.8b01475
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of **7** obtained by preparative HPLC on a chiral stationary phase.[19] Hence, according to the procedure in Scheme 6, (+)-**7** was converted to the model substrate (−)-**9**. The absolute stereochemistry of (+)-**7** and (−)-**9** were assigned as (*S*).[20]

1,2-Naphthoquinone (−)-**9**, thus obtained, was irradiated with a xenon lamp (CH_3CN, at room temperature (rt)), which gave spiroacetal (−)-**10** in 69% yield (Table 2, entry 1).[21] The enantiomeric excess (ee) of (−)-**10** was 53% ee, as assessed by HPLC analysis on a column with chiral stationary phase (see the HPLC analysis in Figure 1).[19] As will be discussed later (vide infra, Scheme 8), the absolute configuration of the major enantiomer (−)-**10** was (*R*), proving that the photochemical reaction proceeded preferentially in a *retentive* manner.

In order to improve the configurational integrity, we optimized various reaction parameters and started with a solvent screening. It turned out that the solvent effect is substantial, in that polar solvents[22] led to both higher ee and yield of (−)-**10** (Table 2, entries 1 and 6, as the solvents CH_3CN and MeOH). Notably, when methanol was used (Table 2, entry 6), (−)-**10** was isolated in 77% ee. By contrast, other protic solvents, such as ethanol and isopropyl alcohol, led to lower yield and ee (Table 2, entries 7 and 8).

By lowering the reaction temperature, we were able to further raise the ee of **10** (Table 3).[21] At −78 °C, pleasingly, almost complete stereochemical retention was observed (98% ee) (Table 3, entry 3). Unfortunately, the yield decreased substantially (34%), because of the low solubility of (−)-**9** in methanol at low temperature, forming precipitates. Using CH_3CN as a cosolvent (MeOH:CH_3CN = 3:1, Table 3, entry 4), the reaction remained homogeneous, even at −78 °C, and photoirradiation smoothly converted quinone (−)-**9** to spiroacetal (−)-**10** in 68% yield with almost perfect configurational integrity (98% ee; see the HPLC analysis in Figure 1).[19]

Scheme 7 shows our rationale for the observed stereochemical outcome of the reaction. In an ideal case, after the initial photoexcitation and 1,5-hydrogen abstraction in **G**, the following sequential process, **H** → **I** → **J**, proceeds rapidly enough, relative to the bond rotation on the tether moiety, and leads to the stereoretentive spiroacetal formation. On the other hand, erosion of the configurational integrity occurs in the case where the bond rotation competes and the inverted conformers **K** and/or **L** intervene. Under unoptimized conditions, the configurational integrity was lost, which could easily be explained by the conformational flexibility of the compound.

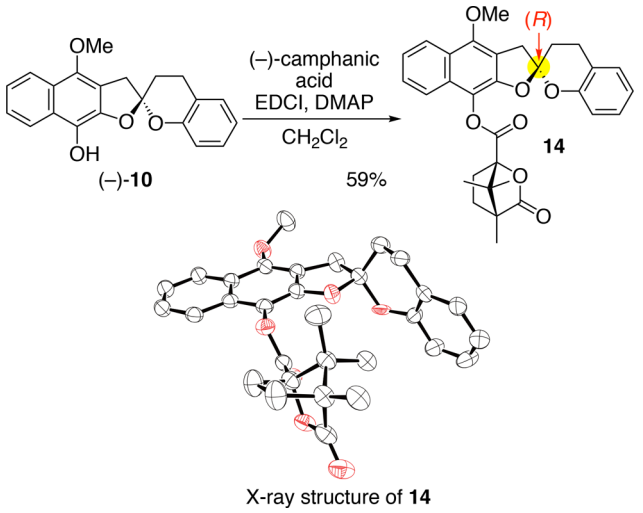
With our optimized reaction conditions, we secured high chemical yield and excellent configurational integrity for the reaction of (−)-**9** → (−)-**10**. We gained insight into the key factors responsible for the observed outcome and our interpretation is as follows:

(1) Polar solvents have a tendency to give better yields, which could be attributed to the acceleration of the electron-transfer step to form the zwitterionic species.[23]
(2) Protic solvents—in particular, methanol—lead to excellent ee values, probably because of the strong solvation effect via hydrogen bonding in **H** and/or **I**, thus reducing the conformational flexibility of the relevant intermediate(s).
(3) Lower reaction temperatures significantly improve the optical purity, which could be ascribed to the retardation of conformational changes, while the reaction rate itself is not affected.

STEREOCHEMICAL PROOF

The assignment of the stereochemistry of key compound (−)-**10** was realized after conversion to ester **14**. The absolute stereochemistry was confirmed as (*R*) by the X-ray diffraction (XRD) analysis of camphanate **14** (see Scheme 8).

Scheme 8. Absolute Configuration of (−)-10 and X-ray Structure of 14[a]



[a]Disordered atoms are omitted for clarity.

In summary, we have developed a promising approach to the enantioselective total synthesis of γ-rubromycin via the photoredox reaction of 1,2-naphthoquinone at the C2 position on chromane, allowing the enantiospecific construction to the spiroacetal moiety. Further studies toward the total synthesis is actively pursued in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01475.

Full experimental procedure, characterization data, and NMR spectra for all new compounds (PDF)

Accession Codes

CCDC 1837042 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.8b01475
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This research was supported by JSPS KAKENHI Grant Nos. JP16H06351 and JP26810018, and Grant for Basic Science Research Projects from The Sumitomo Foundation. We are grateful to Prof. Hidehiro Uekusa and Dr. Haruki Sugiyama (Tokyo Institute of Technology) for X-ray diffraction analysis. We thank one of the referees, who suggested a kinetic isotope effect, which will be examined in due course.

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(15) The structure of spiroacetal **10** was identified by extensive 2D NMR experimentation. For details, see the Supporting Information.

(16) Even when the reaction was performed for a longer time under the same conditions (60 min), 1,2-quinone **9** still slightly remained, while the yields of the product **10** and byproduct **11** were almost unchanged.

(17) Bicyclic compound **11** was obtained as a single diastereomer. For details, see the Supporting Information.

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(19) Analytical HPLC conditions: **7**; DAICEL CHIRALPAK IF (0.46 cm φ × 25 cm), solvent: hexane/*i*-PrOH = 99/1, 25 °C, flow rate = 1 mL/min, UV: 254 nm, t_R = 14.5 min for (*S*)-isomer and 17.1 min for (*R*)-isomer. **10**; DAICEL CHIRALPAK IB (0.46 cm φ × 25 cm), solvent: hexane/EtOAc = 85/15, 25 °C, flow rate = 1 mL/min, UV: 254 nm, t_R = 8.9 min for (*R*)-isomer and 10.1 min for (*S*)-isomer.

(20) For details, see the Supporting Information.

(21) Tables 2 and 3 do not show the yields of the side product **11** and recovered naphthoquinone **9**, which are shown in the Supporting Information.

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DOI: 10.1021/acs.orglett.8b01475
Org. Lett. XXXX, XXX, XXX−XXX