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Total Synthesis of the Ambigols: A Cyanobacterial Class of Polyhalogenated Natural Products

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03784 Read Online

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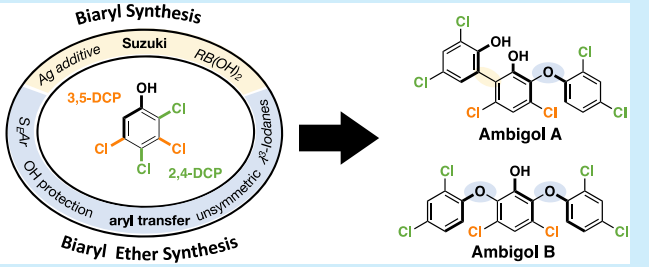
ABSTRACT: The first total synthesis of all members of the cyanobacterial natural product class of the ambigols is described. Key steps of the synthetic strategy are the formation of sterically demanding mono- and bis-iodonium salts to install the required biaryl ether structural elements and Suzuki cross-coupling giving straightforward access to the biaryl bonds. The synthetic methods are also utilized to construct unnatural or hypothetical ambigols that are still awaiting discovery from Nature.



Polychlorinated organic compounds are known not only for their structural and functional diversity but also for their negative environmental impact.[1] Compounds such as the man-made polychlorinated diphenyl ethers (PCDEs) and biphenyls (PCBs) accumulate as persistent and bioaccumulative substances in the human food chain and can ultimately lead to deleterious health effects in animals and humans, e.g., causing liver damage, teratogenicity, and immunotoxicity.[2−5]

In addition to chlorinated substances of anthropogenic origin, Nature offers diverse biological sources, such as the ambigols (**1**−**5**, Figure 1) from the terrestrial blue-green alga *Fischerella ambigua*[6] or structurally related polybrominated diphenyl/s ethers (**6** and **7**, PBBs/DEs) from the marine γ-proteobacteria *Pseudoalteromonas spp.*[7] All these compounds not only bear multiple chlorine/bromine substituents but also have biaryl (Scheme 1, yellow) and/or biaryl ether (Scheme 1, blue) structural elements in common. We have previously shown that two cytochrome P450 enzymes, *ab2* and *ab3*, which are part of the 14.3 kb *ab* biosynthetic gene cluster, selectively install these structural features found in the ambigols using dichlorophenol building blocks (Scheme 1a),[8]

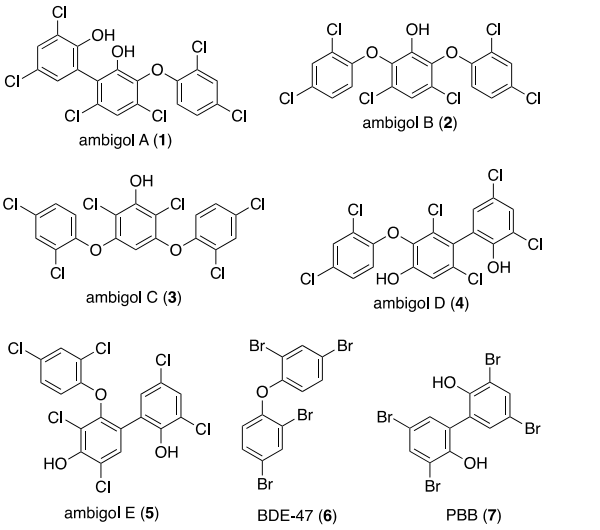
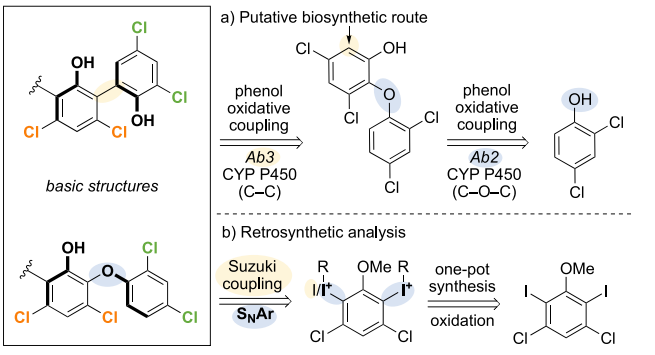


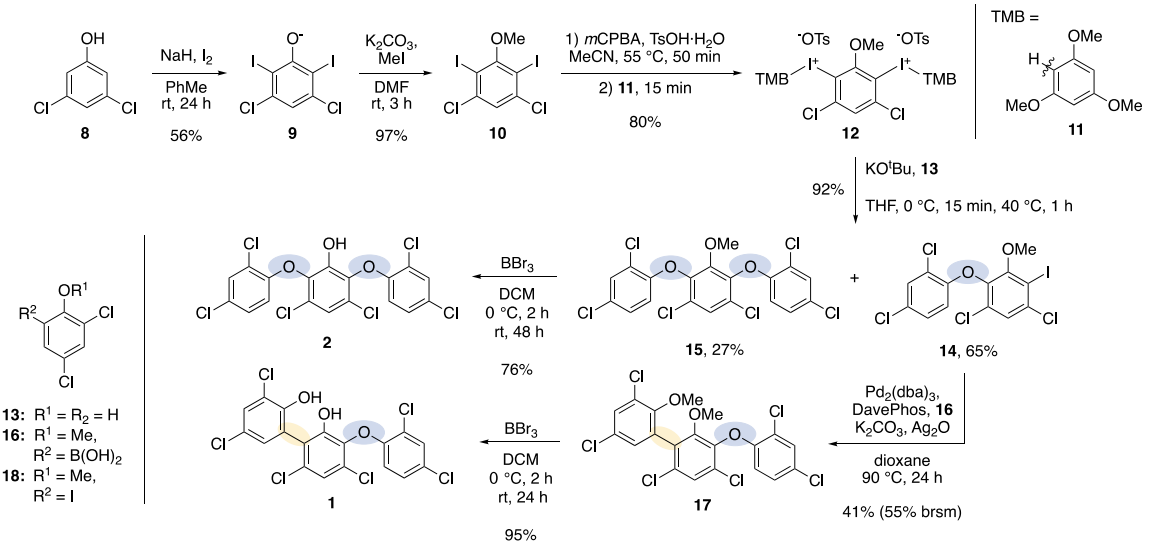
Figure 1. Structures of natural products produced by the terrestrial cyanobacterium *Fischerella ambigua* (**1**−**5**) and the marine γ-proteobacteria *Pseudoalteromonas spp.* (**6**, **7**).

Scheme 1. (a) Biosynthetic Assembly of Ambigols A (1) and B (2) and (b) Retrosynthetic Analysis



Received: November 13, 2020

Scheme 2. Synthesis of Ambigol A (1) and B (2)[a]



[a]C−O−C biaryl ether (blue) and C−C biphenyl (yellow) bond formation.

in analogy to previous work by Moore et al. on PBDE biosynthesis.[9]

The ambigols are interesting not only from a structural point of view but also in terms of biological effects. Ambigol A (**1**) is a strong inhibitor of cyclooxygenase (in the range of the drug indometacin), a relevant activity in the development of nonsteroidal antirheumatic drugs.[6] In addition, **1** exhibits antibiotic (against *B. megaterium* and *subtilis*), antiviral (HIV-1 reverse transcriptase inhibition), and cytotoxic (L6 myoblast cells) activities. Interestingly, ambgiol B (**2**) shows generally lower biological activities in the above indications.[10] Ambigol C (**3**), which is structurally very similar to **2**, but with a different substitution pattern at the central building block, exhibits strong antibacterial activity against *B. megaterium* (IC_{50}: 7.0 ng/mL) and has weak antiplasmodial and trypanocidal effects.[11] Ambigols D (**4**) and E (**5**), which were recently isolated by Niedermeyer et al., were shown to increase prodigiosin production in *Serratia* spp.[12] In-depth investigations of all these biological effects are impeded by low production titers and long fermentation times (30 to 40 days of incubation) of the natural producer *F. ambigua*. Synthetic access to the ambigols has the potential to solve these problems and to enable future functional evaluation of this interesting natural product class. We thus set out to develop chemical routes to all known ambigols.

Results and Discussion. From a synthetic perspective, the biaryl cross-links in the ambigols can be established by transition-metal catalyzed cross-coupling reactions. In the structurally related but only dimeric PBBs and PBDEs (e.g., **6** and **7**, Figure 1) this was successfully achieved by Suzuki cross-coupling reactions (Scheme 1b, yellow),[12,13] thus also rendering this the method of choice for ambigol assembly. For the installation of the biaryl ether bonds a number of different established reactions is available. This includes copper-catalyzed Ullmann coupling, palladium-catalyzed Buchwald−Hartwig reaction, and nucleophilic aromatic substitution (S_NAr).[14,15] In this work, the formation of the biaryl ether bonds by aryl transfer reaction using electrophilic λ^3-iodonium salts was applied. The use of iodonium salts in aryl transfer reactions offers many advantages and has also successfully been applied in PBDE synthesis.[16,17] Most importantly, these hypervalent iodine compounds are directly accessible by one-pot reactions by oxidation of the corresponding iodinated precursor (hence giving fast access to all required regioisomeric iodonium salts), are stable, and can be readily purified due to their high polarity.[18−21] This compound class is thus perfectly suited for a streamlined synthesis of all ambigols.

The route to ambigols A (**1**) and B (**2**) started with the selective *ortho* double iodination of 3,5-dichlorophenol (**8**) by electrophilic aromatic substitution (S_EAr) using NaH/I_2 to give **9** in 56% yield.[22] After *O*-protection of the aryl diiodide **9** using potassium carbonate and iodomethane (97%), oxidation of **10** using *m*CPBA, *p*-toluenesulfonic acid, and trimethoxybenzene (TMB) provided direct access to bisiodonium salt **12** in 80% yield.[23−26] The following arylation reaction of **12** with a nucleophile (here phenol **13**) takes place via a T-shaped Ar_2I-Nu intermediate, leading to an aryl iodine side product and the desired biaryl ether by reductive elimination.[27,28] When using λ^3-iodonium salt with unsymmetric substitution at the iodonium center(s), such as **12**, two theoretical T-shaped intermediates are possible. However, chemoselectivity studies have shown that in general the less electron-rich and/or sterically demanding aryl group (*ortho* effect) is transferred to the nucleophile.[28] Accordingly, when subjecting **12** to an aryl transfer reaction with 2,4-dichlorophenol (**13**) as the nucleophile, the central 3,5-dichlorophenol of **12** is transferred to the nucleophile with the electron-rich trimethoxybenzene serving as a "dummy group". The aryl transfer reaction led to the monoarylated main product **14** in 65% yield and the double-arylated trimeric **15** in 27% yield (Scheme 2). This reaction thus conveniently gave access to the two central intermediates **14** and **15** for ambigol A (**1**) and B (**2**) synthesis, respectively. Deprotection of **15** by BBr_3-mediated *O*-demethylation delivered **2** in 76% yield. The formation of the biphenyl bond present in ambigol A (**1**) was realized by Suzuki reaction. The reaction conditions were initially optimized for such electronically demanding substrates using a structurally related model system (coupling of 1,5-dichloro-3-iodo-2-methoxybenzene to (3,5-dichlororo-2-methoxyphenyl) boronic acid; see Supporting Information, Chapter 2.3) by

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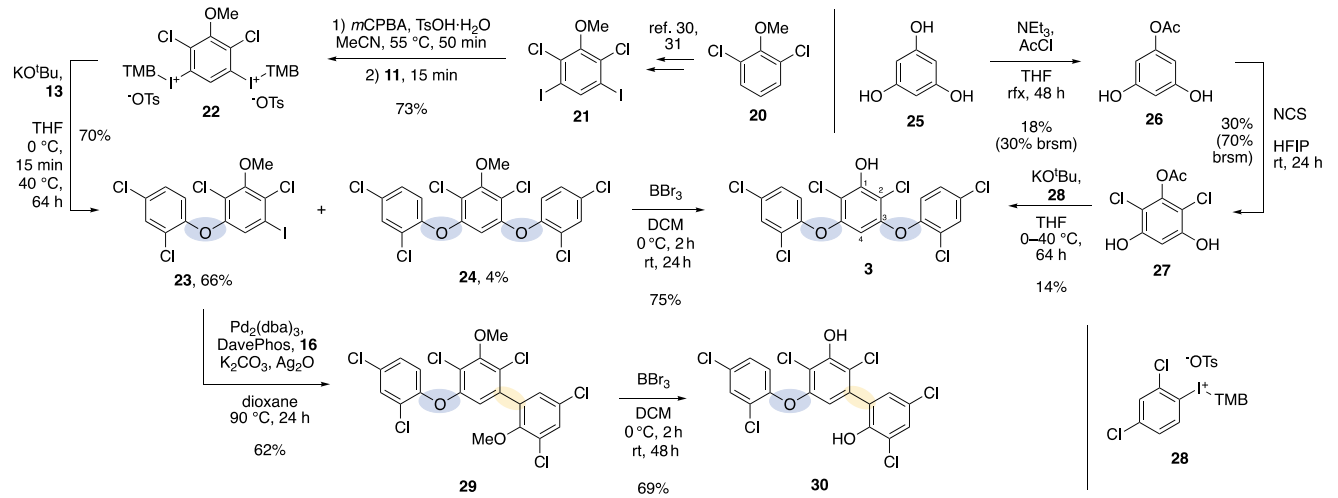
Scheme 3. Dual Approach for the Total Synthesis of Ambigol C (3) and C−C Coupled Analogue 30



extensive screening of the catalyst system, base, solvent, and additives (Table S1). The reaction outcome was evaluated after 24 h by HPLC analysis (Figure S1). In summary, approximately 60% of the tested reaction conditions resulted in exclusive substrate protodeboronation. Product formation was observed with $PdCl_2(dppf)$ or $Pd_2(dba)_3$ in combination with phosphine ligands as the catalyst system and 1,4-dioxane as the solvent (Table S1, entries 14, 15, 17, 18, 22, 23). However, protodeboronation was also observed in these reactions. Use of $Pd_2(dba)_3$ and DavePhos showed the best results (Tables S1, entry 23). The reaction was performed with silver(I) oxide as the additive to increase the transmetalation rate of Pd and to facilitate halogen-hydroxide exchange.[29,30] The ambigol A precursor (**17**) was obtained in a yield of 41% (55% based on reisolated starting material = brsm). Final *O*-demethylation of **17** with BBr_3 delivered ambigol A (**1**) in a yield of 95%.

Ambigol A (**1**) and other members of this natural product family contain biaryl axes with three *ortho* substituents, which might thus be rotationally stable. As this aspect has not been covered in the literature, we set out to test rotational stability, exemplarily for **1**. Sufficient separation of the atropoisomers indeed succeeded by HPLC on chiral reversed-phase material at low temperature (5 °C; see Supporting Information), permitting isolation of enriched fractions of both rotational isomers. Reanalysis of this material under identical chromatographic conditions over time revealed a fast equilibration within only 1−2 h at room temperature (Figure S96).

Ambigol C (**3**) was accessible in analogy to ambigol B (**2**), by using 2,4-dichloro-1,5-diiodo-3-methoxybenzene (**21**) in the formation of the symmetric bisiodonium salt **22** (Scheme 3). The starting material can be obtained in 74% yield from a double directed silylation of anisole **20** followed by iododesilylation with iodine chloride.[31,32] The subsequent aryl transfer with the iodonium salt led to 66% of the monoarylated species **23** and to only 4% of the desired diarylated intermediate **24**. The latter was *O*-demethylated with BBr_3 furnishing ambigol C (**3**) in 75% yield. To our surprise, the NMR data of synthetic **3** were markedly different from the published data of the corresponding natural product.[10] In particular, the chemical shift at position 4 showed significant differences: δ_H = 6.01 ppm, δ_C = 101.9 ppm (reported: δ_H = 7.18 ppm, δ_C = 121.8 ppm). Interestingly, the reported shifts at that position correspond almost perfectly to the signals found in ambigol B (**2**) (Supporting Information (SI), Chaper 2.2). However, in-depth 2D NMR analysis (see SI, Figures S33−35) of synthetic **3** was in good agreement with the targeted published natural product structure. Given the differences in NMR data of synthetic and published **3**, along with the unsatisfactory low yield in the aryl transfer reaction, we decided to establish an additional, alternative route to **3** for unambiguous structural verification. The starting material **26** for this approach was obtained by esterification of phloroglucinol (**25**) with acetyl chloride under basic conditions. However, almost only the triacetylated product was obtained when the reaction was carried out at room temperature. Heating the reaction shifted the product outcome in favor of the mono- (**26**, 18%, 30% brsm) and diacetylated compound (26%, 40% brsm). Regioselective chlorination of monoacetylated phloroglucinol (**26**) with *N*-chlorosuccinimide (NCS) in hexafluoro-2-propanol (HFIP) delivered dichlorinated compound **27** (30% yield, 70% brsm).[33] This reaction had to be stopped prior to completion to circumvent increasing formation of the trichlorinated byproduct over time (15% after 22 h). The final aryl transfer using 2,4-dichloro-1-iodobenzene-containing iodonium salt **28** directly provided ambgiol C (**3**) in a yield of 14%. The analytical data of **3** from both synthetic routes matched perfectly, hence firmly corroborating that the published structure of **3** was indeed synthesized. Despite the low overall yield of the second synthesis of **3**, it is an important alternative to the route using bisiodonium salt **22**, particularly due to low step count and cheap starting materials.

The main product of the aryl transfer reaction of **22** and **13**, biaryl ether **23**, was readily converted into a new ambigol analogue **30**. This was achieved by Suzuki coupling to give **29** followed by *O*-demethylation with BBr_3, delivering ambigol analogue **30** in 43% yield over two steps.

The total synthesis of ambigol D (**4**) commenced with 1,3-dichloro-2-iodo-5-methoxybenzene (**31**) which was synthesized as described previously (Scheme 4A).[8,34] The regioselective iodination to **32**, its conversion into bisiodonium salt **33**, aryl transfer reaction to **34**, Suzuki coupling to **35**, and final methoxy deprotection to ambigol D (**4**) was performed in analogy to ambigol A−C (**1**−**3**) synthesis. The selective formation of the monoarylated **34** can be achieved by adjusting the stoichiometry of 2,4-dichlorophenol (**13**) and **33**.

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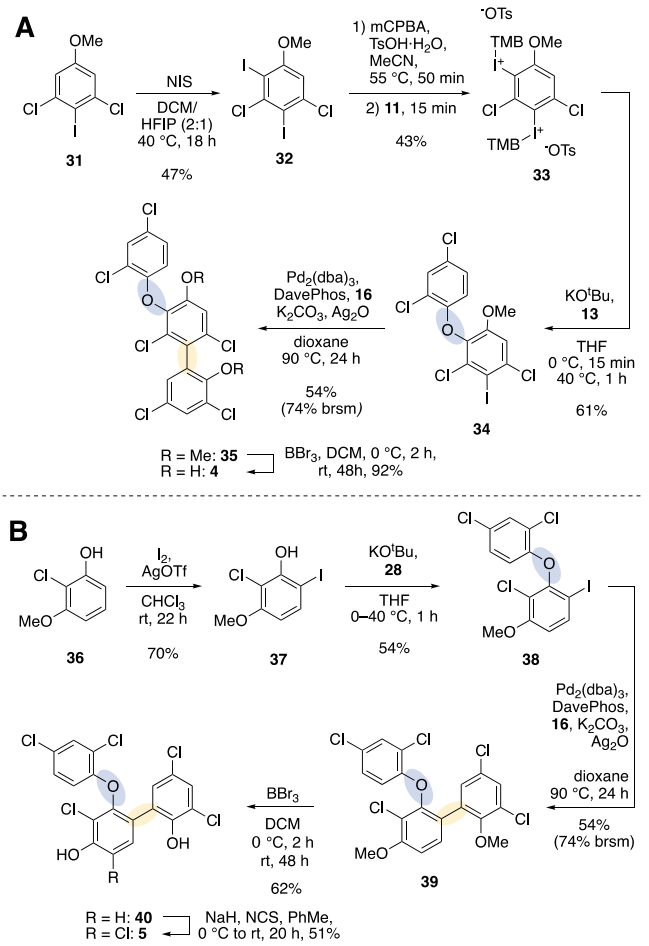
Scheme 4. Total Synthesis of Ambigol D (4) and E (5)



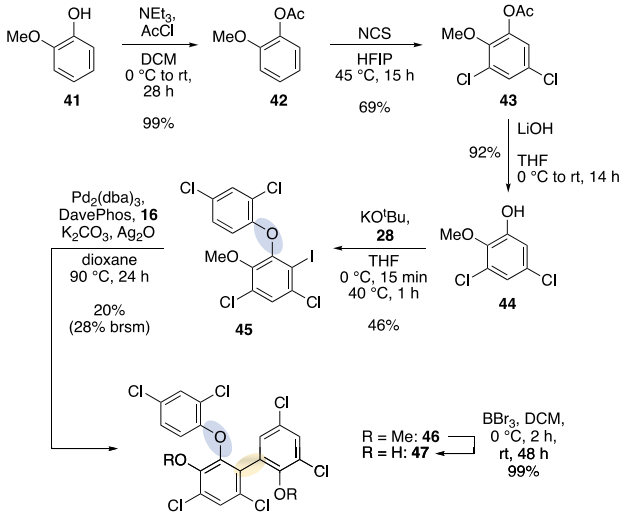
Furthermore, the site in relative *ortho*-position to the methoxy group is also stereoelectronically preferred.

Just as ambigol D (**4**), ambigol E (**5**) contains a C−O−C biaryl ether and a C−C biaryl bridge (Scheme 4B). The only difference between these two natural products is the altered connectivity at the central phenol building block. However, the direct synthesis of the required double-chlorinated precursor using NCS was not possible in this case. We therefore changed our strategy by applying a regioselective silver-catalyzed iodination of 2-chloro-3-methoxyphenol (**36**) to **37**. The latter was used in an aryl transfer reaction with **28**, delivering **38** in 54% yield. Subsequent Suzuki coupling furnished **39** in 54% yield (74% brsm), which upon deprotection gave dechloro ambigol E analogue **40**. Installation of the still missing substituent was realized by final chlorination. To achieve this, the phenol was activated by deprotonation using sodium hydride and NCS was employed as the chlorinating agent, ultimately giving ambigol E (**5**) in 51% yield.

As shown for **26** and **40**, our synthetic strategy is also an enabling tool to prepare new-to-Nature ambigols. An interesting addition to this natural product class would be analogues exclusively composed of 2,4-dichlorophenol building blocks, which do not yet have any natural counterparts.

Such a new analogue can readily be prepared from 2-methoxyphenol (**41**, Scheme 5). Acetylation of the free phenol using AcCl and NEt_3 gives **42** (99%) and facilitates subsequent regioselective dichlorination (69%) in relative *ortho*- and *para*-positions to the activating methoxy group, leading to

Scheme 5. Synthesis of the Structural Analogue 47 Only Consisting of 2,4-Dichlorophenol Units



compound **43**. Upon deacetylation to **44** in 92% yield, the liberated phenol is arylated using iodonium salt **28**, analogous to ambigol C (**3**) and E (**5**) synthesis, to furnish biaryl ether **45** in 46% yield. In the last two steps, biaryl bond formation by Suzuki coupling to **16** followed by *O*-demethylation leads to the desired analog **47** in 20% over two steps. The novel ambigol derivative **47** was thus accessible in six steps with a combined yield of 8%.

In conclusion, we report the first total synthetic access to all five natural ambigols: ambgiol A (**1**) in a six-step synthesis with an overall yield of 15%, ambgiol B (**2**) in a five-step synthesis with an overall yield of 9%, ambgiol C (**3**) in five steps with a yield of 2% or in three steps with a yield of 3%, ambigol D (**4**) and ambigol E (**5**), each in a five-step synthesis with an overall yield of 8%. The strategic combination of aryl transfer reactions with λ^3-iodonium salts and Suzuki cross-coupling chemistry to install biaryl ether and biaryl cross-links, respectively, thus gives direct access to a structurally diverse natural product family and further yet unknown synthetic analogs, such as **30**, **40**, and **47**. Application of these synthetic routes therefore contributes to broadening the structural space covered by the ambigols. Our work sets the stage for future in-depth studies on biological effects of the ambigol natural product class and novel analogs, work currently pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03784.

Experimental procedures, supplementary figures, and NMR spectra (PDF)

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https://dx.doi.org/10.1021/acs.orglett.0c03784
Org. Lett. XXXX, XXX, XXX−XXX

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

T.M.M. thanks the Stiftung der Deutschen Wirtschaft (sdw) for funding. We thank the DFG for generous financial support of the work in our laboratory (Emmy Noether Program (GU 1233/1-1)).

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