Organic LETTERS

Letter

pubs.acs.org/OrgLett

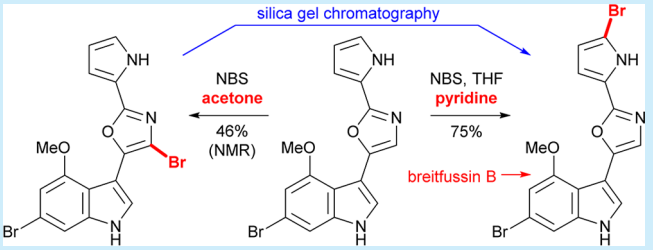
Synthesis of Breitfussin B by Late-Stage Bromination

Akbar H. Khan and Jason S. Chen*

Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

Supporting Information

ABSTRACT: The breitfussins are halogenated natural products whose structures were determined with the assistance of atomic-force microscopy. The site selectivity of *N*-bromosuccinimide-mediated bromination of a model breitfussin core was found to be strongly dependent on solvent selection; use of acetone led to oxazole bromination, and use of a pyridine-containing mixture led to pyrrole bromination. This tunable site-selective bromination was used in a protecting-group-free synthesis of breitfussin B that proceeded in 9.2% yield over 12 reactions and five chromatographic separations. A bromooxazole analogue of breitfussin A was also prepared by late-stage bromination but isomerized on silica gel to form breitfussin B. This isomerization appeared to proceed through a unimolecular pathway.



Breitfussins A and B (**1** and **2**, Figure 1) are halogenated natural products isolated from the Arctic hydrozoan

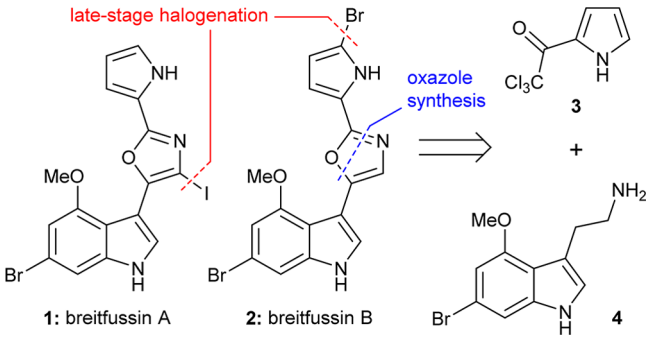


Figure 1. Retrosynthetic analysis of breitfussins A and B.

Thuiaria breitfussi collected at Bjørnøya (Bear Island), Norway.[1] The paucity of hydrogen atoms hamstrung NMR-based structure determination, and thus atomic-force microscopy (AFM)[2] and computational tools[3] were called upon to complete the assignment. This unprecedented AFM-assisted structure determination revealed the breitfussins to be related to the phorbazoles.[4] Of note, breitfussin A is the only known naturally occurring iodooxazole. Synthetic validation of the assigned structures was a high priority because of the promising capability of AFM as a structure elucidation tool. Recently, Hedberg, Bayer, and co-workers synthesized breitfussins A and B using Suzuki coupling reactions to join the heteroaromatic rings, thus confirming the assigned structure of these natural products.[5] Herein we report a conceptually distinct synthesis of breitfussin B through late-stage bromination of the breitfussin core.

We envisioned site-selective late-stage halogenations for the synthesis of breitfussins A and B (**1** and **2**) from a common precursor. Although site-selective halogenations of aromatic heterocycles such as pyrroles[6] and oxazoles[7] are well studied, comparatively little is known about selectivity in substrates containing multiple aromatic heterocycles. Indeed, at the time we started this research, a SciFinder search revealed no examples of halogenation of a pyrrole or oxazole (selective or otherwise) on a substrate containing both ring systems.[8,9] Therefore, we decided to investigate halogenation site selectivity on a model substrate.

Inspired by the isolation team's description of the breitfussins as highly oxidized dipeptides,[1] we envisioned synthesis of the central oxazole ring from substituted tryptamine **4** and 2-(trichloroacetyl)pyrrole (**3**) as high oxidation state surrogates for tryptophan and proline. Thus, the synthesis of a simplified model breitfussin (**8**, Scheme 1) commenced with the coupling of tryptamine (**5**) and 2-(trichloroacetyl)pyrrole (**3**) to afford amide **6** in 100% yield. DDQ-promoted heterobenzylic oxidation[10] gave ketone **7** in 84% yield. A subsequent Robinson−Gabriel reaction delivered oxazole **8** in 83% yield.

We selected *N*-bromosuccinimide (NBS) as a convenient source of electrophilic bromine. Bromination of model compound **8** in acetonitrile (Table 1, entry 1) was sluggish but yielded a trace of the desired breitfussin B analogue (**9**). Although we were concerned about the possibility of competitive bromination at C4″ on the pyrrole, all of the pyrrole bromination proceeded at the C5″ position. However, even though bromooxazole **10** was not found, a surprisingly large amount of dibromide **11** was present even at low conversion, suggesting that the rate constant for the second bromination was greater than that for the initial bromination.[11]

Speculating that the higher acetonitrile solubility of the monobromide product (**9**) as compared with its precursor (**8**) may be promoting a faster second bromination, we switched solvents to THF (Table 1, entry 2). The second bromination still

Received: June 10, 2015

DOI: 10.1021/acs.orglett.5b01702
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of a Breitfussin Model System

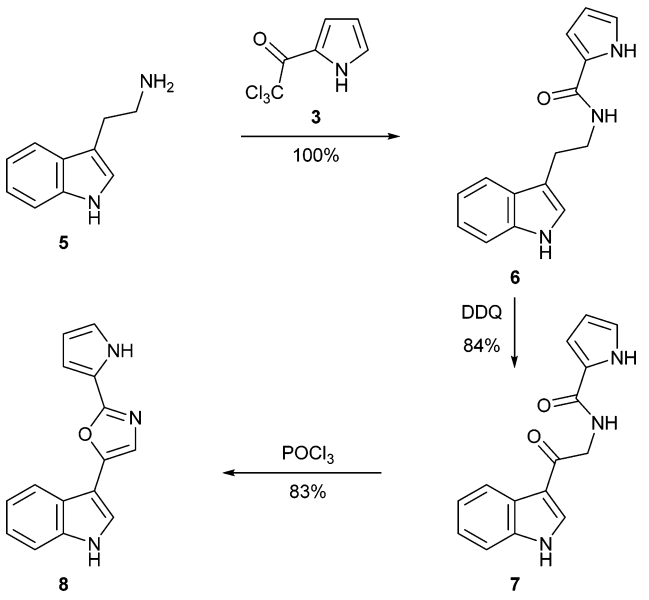
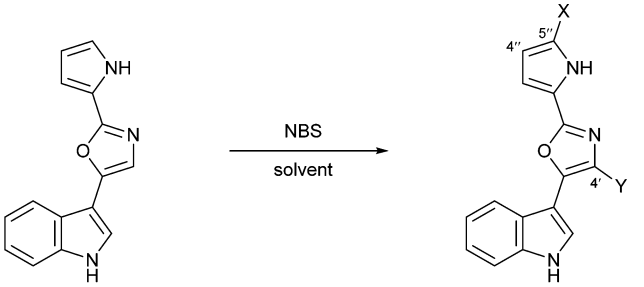


Table 1. Tuning Bromination Site Selectivity



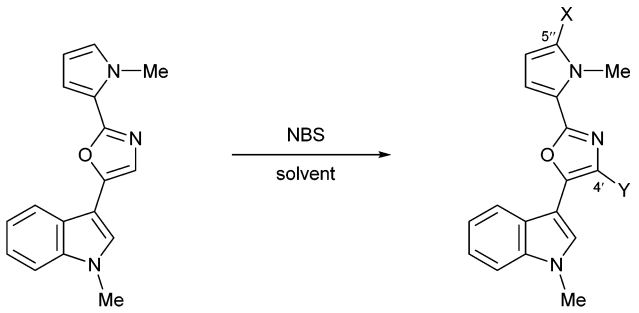
entry	NBS (equiv)	solvent	ratio **8**:**9**:**10**:**11**[a]	yield[b] (%)
1	1.0	acetonitrile	82:5:0:13	ND
2	1.0	THF	68:10:14:8	ND
3	3.0	acetone	5:12:55:28	45 (**10**)
4	1.0	acetic acid	ND[c]	ND
5	1.1	pyridine	24:76:0:0	34 (**9**)
6	1.2	THF/pyridine (19:1)	16:84:0:0	77 (**9**)

[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of the major product. [c]Low conversion to a complex mixture of products. ND = not determined.

appeared to be faster than the first, but not by as large a margin. Interestingly, monobromination now proceeded at both the pyrrole and the oxazole at comparable rates. In an attempt to suppress the second bromination, we ran the reaction in acetone (Table 1, entry 3) because of the even higher solubility of model compound **8** in this solvent. This simple change not only reduced the extent of overbromination but also enhanced the selectivity for bromooxazole **10**. Emboldened by this result, we decided to screen other solvents in the hope of achieving selective pyrrole bromination. We speculated that solvents that can strongly interact with either the nitrogen lone pair of the oxazole ring or the acidic hydrogen of the pyrrole ring likely offered the best hope of altering the bromination selectivity. Bromination in acetic acid (Table 1, entry 4) gave a complex mixture of products. Use of pyridine as solvent (Table 1, entry 5) shut down oxazole bromination but led to low mass recovery after aqueous workup and a low isolated yield of bromopyrrole **9**. Switching to a 19:1 THF/pyridine mixture (Table 1, entry 6) delivered bromopyrrole **9** in a satisfying 77% yield. Attempts to iodinate the oxazole ring of model compound **8** using iodine, *N*-iodosuccinimide, or iodine monochloride were unsuccessful.

We also investigated the reaction of *N*-methylated model compound **12** with NBS in an attempt to shed some light on the reasons for the observed solvent-dependent bromination site selectivity (Table 2, entries 1–4). The site selectivities of the

Table 2. Bromination of an *N*-Methylated Analogue



entry	NBS (equiv)	solvent	ratio **12**:**13**:**14**:**15**[a]	yield[b] (%)
1	1.0	THF	2:9:60:29	43 (**14**), 23 (**15**)
2	3.0	acetone	0:22:0:78[c]	ND
3	1.0	acetone	43:37:12:8	36 (**13**)
4	1.2	THF/pyridine (19:1)	7:31:44:18	28 (**13**) 44 (**14**)

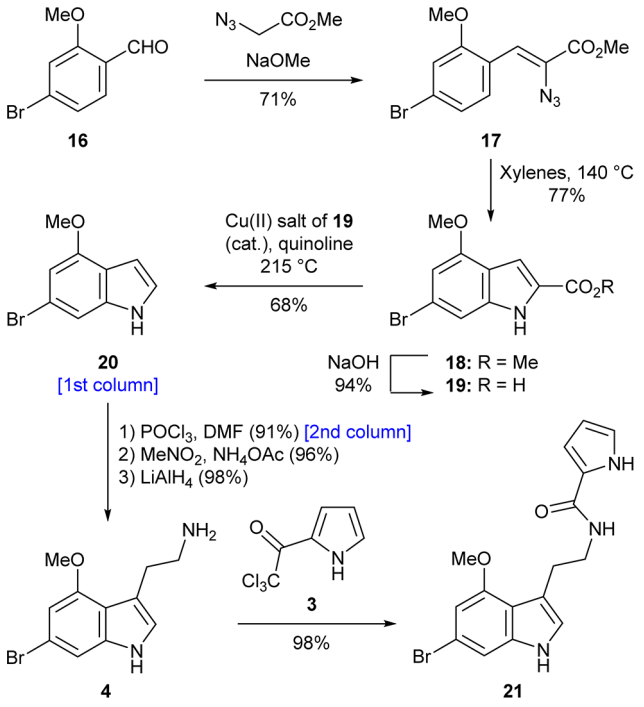
[a]Determined by ^{1}H NMR analysis of the crude reaction mixture. [b]Isolated yield of the major products. [c]A significant amount of tribromide was also observed. ND = not determined.

bromination reactions run in acetone and in THF/pyridine are at odds with those observed for *N*-unmethylated model compound **8**; more studies will be required in order to elucidate the mechanistic role of pyridine in the selective formation of bromopyrrole **9**.

We then turned our attention to the synthesis of breitfussin B (**2**). Our synthesis of substituted indole **20** (Scheme 2) paralleled the previously reported synthesis of a similar indole differing in the presence of a benzyl ether instead of a methyl ether.[12] This route was chosen because of it had been employed on gram scale and required only one chromatographic separation. Thus, commercially available aldehyde **16** was condensed with methyl azidoacetate to form azidoester **17**, which precipitated from the reaction mixture in 71% yield. Thermolysis of azidoester **17** resulted in a Hemetsberger indole synthesis;[13] indole derivative **18** crystallized in 77% yield upon cooling of the reaction mixture. Saponification of the methyl ester of intermediate **18** afforded carboxylic acid **19** in 94% yield without purification. Ten percent of carboxylic acid **19** was converted into the corresponding copper(II) salt, which served as a catalyst for the thermal decarboxylation[14] of carboxylic acid **19** to deliver indole **20** in 68% yield after column chromatography. Vilsmeier–Haack formylation afforded a 3-substituted aldehyde in 91% yield after column chromatography. A Henry reaction with nitromethane (96% yield) and the subsequent lithium aluminum

DOI: 10.1021/acs.orglett.5b01702
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Synthesis of Amide 21

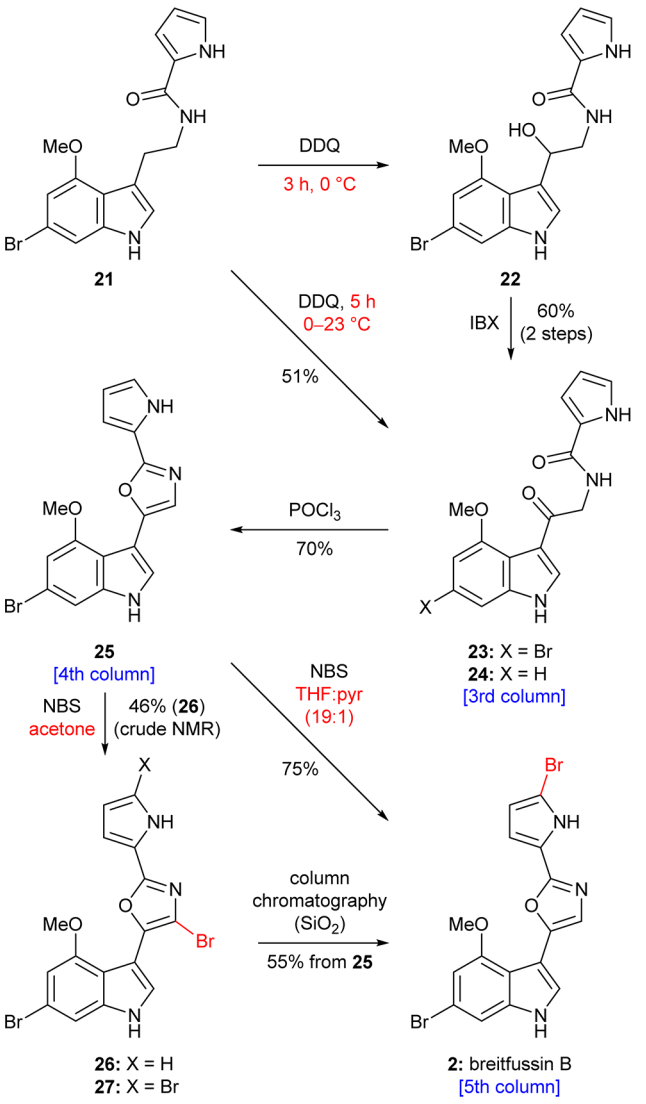


hydride-mediated reduction (98% yield) both proceeded sufficiently cleanly that no purification was necessary. Coupling of the resultant substituted tryptamine (**4**) with 2-(trichloroacetyl)pyrrole (**3**) delivered amide **21** in 98% yield without purification.

As in our synthesis of breitfussin model compound **8**, amide **21** was oxidized by an aqueous solution of DDQ to yield ketoamide **23** (Scheme 3). Unfortunately, a small amount of debrominated ketoamide **24** (<10%) was also formed, and this undesired contaminant proved chormatographically inseparable both at this stage and at later stages in the synthesis. The debromination yield was minimized by adjusting the solvent composition and tuning the substrate and reagent concentrations, but we were unsuccessful in shutting down the debromination pathway during the DDQ oxidation of amide **21** into ketoamide **23**. However, no debromination occurred during the initial oxidation to benzylic alcohol **22**, and the crude material could be cleanly oxidized by IBX to form ketoamide **23** without contamination from debrominated side product **24**. This detour added one step to the synthesis but also resulted in an improved yield (60% for the two-step process; compare with 51% for the one-step process). Robinson−Gabriel cyclization of ketoamide **23** gave oxazole **25** in 70% yield after column chromatography. Following the bromination condition developed in our model study, intermediate **25** was subjected to the action of NBS in a 19:1 mixture of THF and pyridine to deliver breitfussin B (**2**) in 75% yield after column chromatography. The NMR spectroscopic data for synthetic breitfussin B (**2**) was identical to that reported for the natural substance.[1]

Oxazole **25** was also brominated in acetone in order to generate bromooxazole **26**, an analogue of breitfussin A. NMR spectroscopic analysis of the crude mixture spiked with a measured quantity of DMF (used as an internal standard) revealed a 46% yield of bromooxazole **26** along with breitfussin B (**2**) (29% yield) and a dibromination product (**27**) (16% yield). The crude mixture was stable for at least a week, but flash column

Scheme 3. Synthesis of Breitfussin B



chromatography in silica gel isomerized bromooxazole **26** into bromopyrrole **2** (i.e., breitfussin B).[15] This surprising result reveals that control of the competitive bromination of the pyrrole and oxazole rings is not necessary for the synthesis of breitfussin B (**2**); the facile silica gel promoted isomerization provides access to breitfussin B even if the bromination conditions favor bromooxazole **26**.

Unable to isolate pure bromooxazole **26**, we probed the mechanism of isomerization by TLC analysis. As shown in Figure 2, compounds **25** and **27** were not formed from bromooxazole

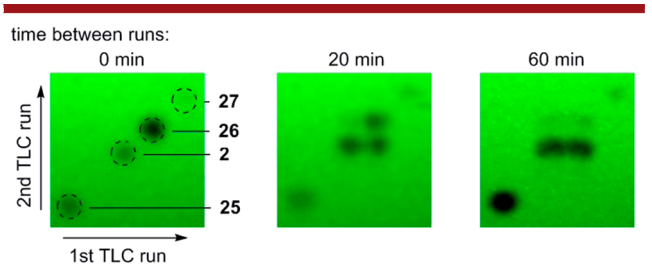


Figure 2. TLC investigation of silica-mediated isomerization. Full images of TLC plates are available in the Supporting Information.

DOI: 10.1021/acs.orglett.5b01702
Org. Lett. XXXX, XXX, XXX−XXX

26 during its isomerization into bromopyrrole **2**, suggesting a unimolecular bromine transfer.[15e] A mixture of compounds **25** and **27** did not equilibrate on silica (see the Supporting Information), further supporting the unimolecular nature of the bromine transfer. The bromine migration does not appear to be dependent on light or air. The indole methoxy group appears to be necessary for bromine migration; model compounds **9** and **10** did not equilibrate on silica even at 150 °C.

Proposing a unimolecular bromine transfer mechanism proved challenging. We speculate that the indole methoxy group likely positions silica for attack by the carbon attached to the oxazole bromine. The resultant hybridization change may allow bromine migration within the oxazole through cationic or sigmatropic rearrangements, but these pathways do not provide obvious routes to the internal redox reaction necessary for installing bromine on the pyrrole. Transfer of a bromine radical could lead to the necessary redox changes, but such a pathway likely would be bimolecular. However, since the reaction occurs on a surface, the putative radical intermediates may not have the opportunity to diffuse apart; therefore, radical mechanisms cannot be ruled out. Unfortunately, we were unable to study the reaction in solution because bromooxazole **26** decomposed when exposed to dissolved acids (e.g., aluminum chloride, boron trifluoride, and acetic acid).

In summary, we developed a tunable site-selective bromination of the breitfussin core with solvent-dependent regioselectivity. This method was applied to a protecting-group-free synthesis of breitfussin B (**2**). Bromooxazole **26** was synthesized by simply changing the bromination solvent, but it isomerized into breitfussin B (**2**) during column chromatography. Our synthesis provided breitfussin B (**2**) in 9.2% overall yield over 12 reaction steps from commercial starting materials and five chromatographic purifications (compare with 1.8% yield and 16 steps in the longest linear sequence and 10 total chromatographic purifications).[5]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, images of TLC plates, and graphical NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01702.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jschen@iastate.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Some NMR spectrometers were supported by National Science Foundation funding (CHE 0946687 and MRI 1040098). We thank D. E. Friedrichsen (Iowa State University) for technical assistance. We thank the reviewer for helpful suggestions.

■ REFERENCES

(1) Hanssen, K. Ø.; Schuler, B.; Williams, A. J.; Demissie, T. B.; Hansen, E.; Andersen, J. H.; Svenson, J.; Blinov, K.; Repisky, M.; Mohn, F.; Meyer, G.; Svendsen, J.-S.; Ruud, K.; Elyashberg, M.; Gross, L.; Jaspars, M.; Isaksson, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12238.

(2) (a) Gross, L.; Mohn, F.; Moll, N.; Meyer, G.; Ebel, R.; Abdel-Mageed, W. M.; Jaspars, M. *Nat. Chem.* **2010**, *2*, 821. (b) Gross, L.; Mohn, F.; Moll, N.; Liljeroth, P.; Meyer, G. *Science* **2009**, *325*, 1110. (c) Gross, L.; Mohn, F.; Moll, N.; Schuler, B.; Criado, A.; Guitián, E.; Peña, D.; Gourdon, A.; Meyer, G. *Science* **2012**, *337*, 1326.

(3) Elyashberg, M.; Williams, A. J.; Blinov, K. *Nat. Prod. Rep.* **2010**, *27*, 1296.

(4) Isolation: (a) Rudi, A.; Stein, Z.; Green, S.; Goldberg, I.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *Tetrahedron Lett.* **1994**, *35*, 2589. Synthesis: (b) Radspieler, A.; Liebscher, J. *Tetrahedron* **2001**, *57*, 4867.

(5) Pandey, S. K.; Guttormsen, Y.; Haug, B. E.; Hedberg, C.; Bayer, A. *Org. Lett.* **2015**, *17*, 122.

(6) For selected examples of electrophilic pyrrole halogenation, see: (a) Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161. (b) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221. (c) Martina, S.; Enkelmann, V.; Wegner, G.; Schlüter, A.-D. *Synthesis* **1991**, *1991*, 613. For an example of pyrrole deprotonation and halogenation, see: (d) Brittain, J. M.; Jones, R. A.; Arques, J. S.; Saliente, T. A. *Synth. Commun.* **1982**, *12*, 231. For selected examples of using protecting groups to change the site selectivity in pyrrole halogenations, see: (e) Chadwick, D. J.; Hodgson, S. T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 93. (f) Muchowski, J. M.; Solas, D. R. *Tetrahedron Lett.* **1983**, *24*, 3455.

(7) For selected examples of electrophilic oxazole halogenation, see: (a) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223. (b) Magnus, P.; McIver, E. G. *Tetrahedron Lett.* **2000**, *41*, 831. For selected examples of oxazole deprotonation and halogenation, see: (c) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, *1995*, 415. (d) Williams, D. R.; Brooks, D. A.; Meyer, K. G.; Pagel, M. *Tetrahedron Lett.* **1998**, *39*, 8023. For selected examples of halogen dance reactions on oxazoles, see: (e) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011. (f) Proust, N.; Chellat, M. F.; Stambuli, J. P. *Synthesis* **2011**, *2011*, 3083.

(8) Substrates containing both indole and oxazole ring systems were first halogenated in synthetic studies toward diazonamide A.[7a,b]

(9) The first synthesis of breitfussin B includes a pyrrole bromination in the presence of a trisubstituted oxazole.[5]

(10) Yonemitsu, O; Oikawa, Y.; Yoshioka, T.; Mohri, K. *Heterocycles* **1979**, *12*, 1457.

(11) A faster second bromination has also been observed on phenols: (a) Skraup, S.; Beifuß, W. *Ber. Dtsch. Chem. Ges. B* **1927**, *60*, 1074. (b) Tee, O. S.; Paventi, M.; Bennett, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 2233.

(12) Volgraf, M.; Lumb, J.-P.; Brastianos, H. C.; Carr, G.; Chung, M. K. W.; Muenzel, M.; Mauk, A. G.; Andersen, R. J.; Trauner, D. *Nat. Chem. Biol.* **2008**, *4*, 535.

(13) Hemetsberger, H.; Knittel, D. *Monatsh. Chem.* **1972**, *103*, 194.

(14) Piers, E.; Brown, R. K. *Can. J. Chem.* **1962**, *40*, 559.

(15) For examples of acid-catalyzed bromine migration on a pyrroles, see: (a) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221. (b) Annoura, H.; Tatsuoka, T. *Tetrahedron Lett.* **1995**, *36*, 413. For examples of acid-catalyzed bromine migration on phenols, see: (c) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358. (d) Brittain, J. M.; Newman, P. A.; de la Mare, P. B. D. *J. Chem. Soc., Perkin Trans. 2* **1981**, 32. (e) Jacquesy, J.-C.; Jouannetaud, M.-P. *Tetrahedron Lett.* **1982**, *23*, 1673. (f) Saha, K.; Lajis, N. H.; Abas, F.; Naji, N. A.; Hamzah, A. S.; Shaari, K. *Aust. J. Chem.* **2008**, *61*, 821.

DOI: 10.1021/acs.orglett.5b01702
Org. Lett. XXXX, XXX, XXX−XXX