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Total synthesis and characterization of breitfussins A and B

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Total synthesis and characterization of breitfussins A and B

by

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William S. Jenks
Arthur Winter
Yan Zhao

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University

Ames, Iowa

2017

DEDICATION

To my family

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NOMENCLATURE

AFM	atomic-force microscopy
aq.	aqueous
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
n-Bu	butyl
t-Bu	*tert*-Butyl
°C	degrees Celsius
Calc'd	calculated
d	doublet
dba	dibenzylideneacetone
dec	decomposition
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
equiv	equivalent
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared (spectroscopy)
J	coupling constant

L	liter
m	multiplet or milli
m	meta
m/z	mass to charge ratio
μ	micro
M	molarity
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
ppm	parts per million
pyr	pyridine
q	quartet
rt	room temperature
R_f	retention factor
s	singlet
t	triplet
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
UV	ultraviolet

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ABSTRACT

The breitfussins are highly modified halogenated marine alkaloids, containing an unprecedented indole-oxazole-pyrrole structure and breitfussin A is only known iodo-oxazole containing the natural product. Due to lack of enough information from conventional tools like NMR, mass spectroscopy, and IR, their structures were determined by an unusual application of atomic-force microscopy (AFM) along with other computational tools.

In the absence of selective halogenation on oxazole-pyrrole containing a molecular frame, the site-selective halogenation was studied on the model compound of breitfussins. It has been found that the oxazole and pyrrole rings proved to be comparably reactive towards electrophilic halogenation by *N*-chlorosuccinimide (NCS), *N*-bromosuccinimide (NBS), *N*-iodosuccinimide and iodine-monochloride (ICl). Solvent and protecting group selection were found to be an effective means of tuning the halogenation site selectivity. The iodination site selectivity was controlled with the help of protecting group while acetone favoring oxazole bromination and pyridine favoring the pyrrole bromination. This tunable site-selective halogenation was used in the synthesis of breitfussin A by using only one protecting group in 14 steps with 6.5% overall yield and a protecting group-free synthesis of breitfussin B that proceeded in 9.2% yield over 12 reactions steps. A bromo-oxazole analog 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.

CHAPTER 1. NATURAL PRODUCTS IN PHARMACEUTICALS, TOTAL SYNTHESIS AND STRUCTURE REASSIGNMENT, BREITFUSSINS (A AND B) AND STRUCTURE ASSIGNMENT

1.1 Natural Products in pharmaceutical

Nature has been a great source of various chemical entities. It stands as a vast resource for various chemicals. These chemicals have been used in different fields of daily life. Some of the chemical obtained from nature are termed as natural products. Natural products are small molecules produced naturally by an organism including primary and secondary metabolites.[1] They include very small molecules, such as urea,[2] and complex structures, such as Taxol.[3] As they may only be isolable in small quantities, have interesting biological activity and chemical structures, natural product synthesis poses an interesting challenge in organic chemistry. One of the most important aspects, in which natural products have made a huge impact, is treatments of diseases. These compounds have not only saved millions of lives over the years but also improved the standard of living on this planet. For example, penicillin was discovered during World War II, and it saved millions of life over the time. Similarly, quinine was also useful in saving millions of lives.[4]

Natural products have been the backbone of traditional medicine throughout the globe and dates backs to hundreds and thousands of years. The man has searched for cures of illnesses by chewing herbs, berries, roots and barks. These compounds were used as herbal medicine without isolating and characterizing the active compounds in it. Some of these trials were very successful and useful. In last 100 - 150 years, with the

advancement of technology, people started to look for bioactive compounds in traditional medicine. Since then, natural products have been as part of medicine as an identified and characterized bioactive molecules.[5-8]

On a rough estimate, it has been found that approximately over half of the pharmaceutical compounds used in clinic today are derived from the natural products.[9] Some well-known natural product derived drugs which are being used in modern pharmaceutical care includes quinine,[10] theophylline,[11] penicillin G,[12] morphine,[13] paclitaxel,[3] digoxin, vincristine, doxorubicin, cyclosporine and vitamin A among many other examples.[14] The structures of few of them are given.

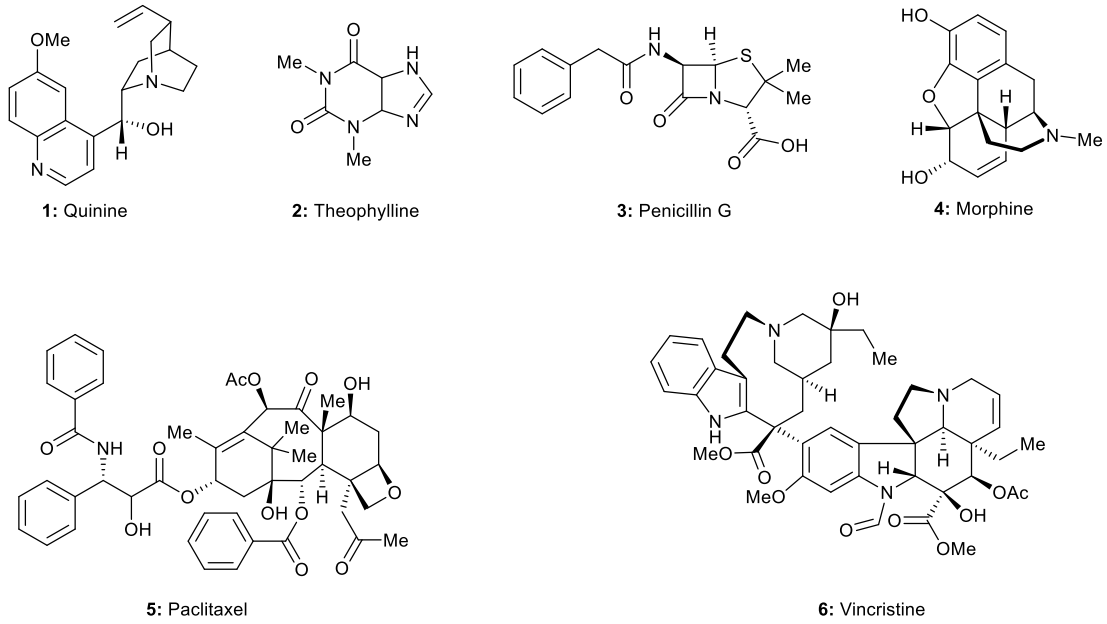


Figure 1.1. Molecular structures of some natural products in pharmaceuticals

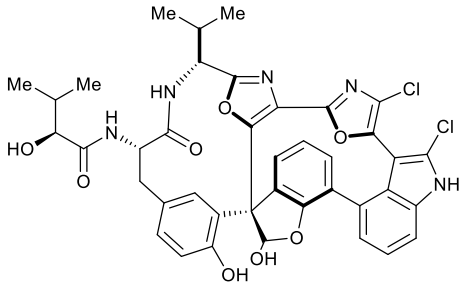
1.2 Total Synthesis and Structure Reassignment

The complete chemical synthesis of a complex molecule, often a natural product, from simple, commercially available precursors is called Total Synthesis. It is a process which does not involve the aid of biological process. If the synthesis of the natural product involves the aid of biological process, it is called semisynthesis. There are various aspects of total synthesis that is valuable to the chemistry and society. In some cases biologically intriguing natural products can be obtained only in a small amount from the natural resources or their extraction and purification from natural sources can be very expensive and time-consuming.[15,16] Total synthesis can enable the production of such compounds on a larger scale to facilitate further extensive biological investigations and medical applications. Sometimes these natural products can be synthesized from a commercially available simple molecule in the laboratory or in a chemical plant in the more cost-effective process than extracting and purifying it from nature. Thus total synthesis makes use of such natural product economically more feasible and desirable.

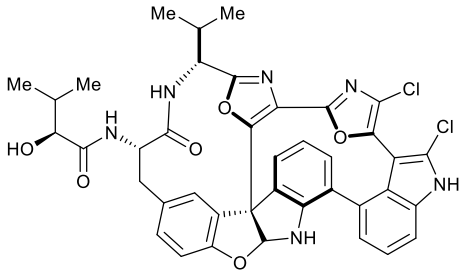
In most cases, the development of the natural product as medicine requires a change in the structure of natural products to enhance its potency[17] or improving its selectivity towards the target.[18] It also enables the way to improve HSA binding, physical and chemical properties.[17] Most of the time such modification leads to superior pharmacological properties than those possessed by the natural products by themselves in terms of efficacy and safety.[19]

One of the fundamental aspects of the total synthesis of the natural product is to provide the absolute proof of the assigned structures.[20] The structural determination of

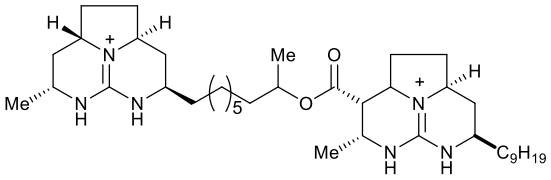
new natural product is very important for many disciplines. The structural assignment is very important in DMPK study of compounds. It may lead to new therapeutic agents or new understanding of disease biology.[21] With the advancement of new analytical tools for structure elucidation like NMR, IR, and X-ray, the role of the total synthesis in structure elucidations is probably underappreciated by most chemists today.[22] Despite many advances in analytical tools for structure elucidation, there are many examples in literature where assigned structures of natural products were incorrect, and it was corrected by the total synthesis. Almost 40% of the structure of natural products is reassigned by the help of the total synthesis. The recent notable examples, where structures of natural products were mischaracterized includes diazonamides (an incorrect structure determination by X-ray!),[23,24] cylindrospermopsin,[25] the sclerophytins,[26] batzelladine F,[27] and Azaspiracid (1, 2, and 3) [28-31] (Figure 1.2). In all cases, structures were correctly reassigned by the total synthesis of molecules. Similarly, the natural product yuremamine was isolated from the stem bark of *Mimosa hostilis* in 2005 by Callaway and co-workers.[32] The structure of yuremamine, originally proposed to be the densely functionalized dihydropyrroloindole **15** with three contiguous stereogenic centers, but after the total synthesis of compound, it was revised to the flavonoidal indole **16** by Sperry and co-workers.[33]



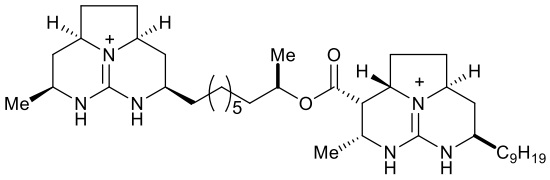
7: original structure of diazonamide A



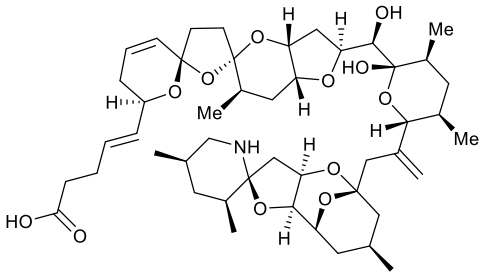
8: revised structure of diazonamide A



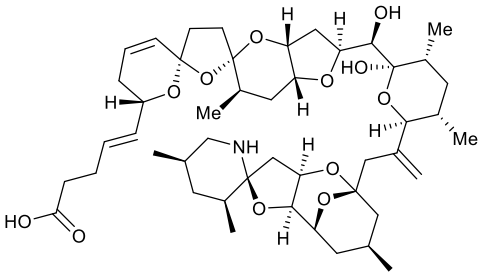
9: original structure of betzelladine F



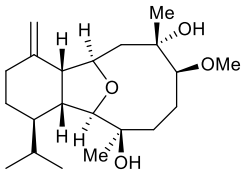
10: revised structure of betzelladine F



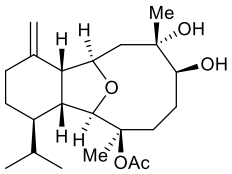
11: original structure of azaspiracid-1



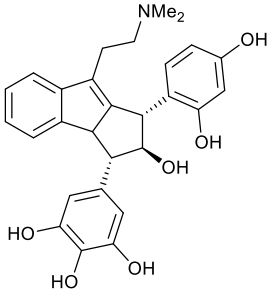
12: revised structure of azaspiracid-1



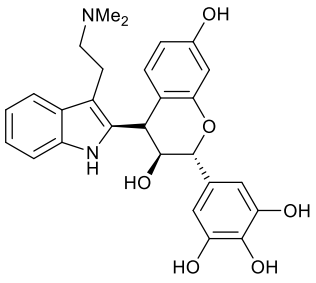
13: original structure of sclerophytin F



14: revised structure of sclerophytin F



15: original structure of yuremamine

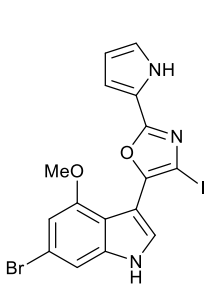


16: revised structure of yuremamine

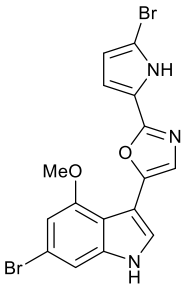
Figure 1.2. Molecular structures of some natural products reassigned by total synthesis

1.3 Breitfussin A and B and its structural assignment

In an effort to find new class of antibiotic, K. Ø. Hanssen *et al*. isolated breitfussin A and B (**17** and **18**, Figure 1.3) from the Arctic coral-like animal, *Thuiaria bretfussi* collected at Bjørnøya near Bear Island, Norway.[34] The structure elucidation of these compounds was found to be difficult. Since these compounds were only available in small amounts, preventing structure determination by x-ray crystallography. From standard techniques of mass spectrometry, NMR, IR, and UV, isolation chemists were able to identify indole, oxazole, and pyrrole unite but could not put them together to get the final structure. To determine the final structure, they took atomic-force microscopy (AFM)[35-37] image of the molecule (Figure 1.4) and overlaid the predicted structure of molecule obtained from computational tools[38] (Figure 1.5) on the AFM image. They identified that breitfussins are highly modified halogenated dipeptide, composed of an unusual molecular framework of indole, oxazole, and pyrrole (Figure 1.3). Also, breitfussin A is only known natural product with iodo-oxazole unite. Structure of the breitfussins to be related to the phorbazoles.[39,40] Since this type of structure determinations are prone to miss an assignment; it needed final proofing of structure by total synthesis. Recently, Hedberg, Bayer, and coworkers synthesized breitfussins A and B using Suzuki coupling reactions to join the heteroaromatic rings, thus confirming the assigned structure of natural products.[41, 42]



17: breitfussin A



18: breitfussin B

Figure 1.3. Structure of breitfussin A and B

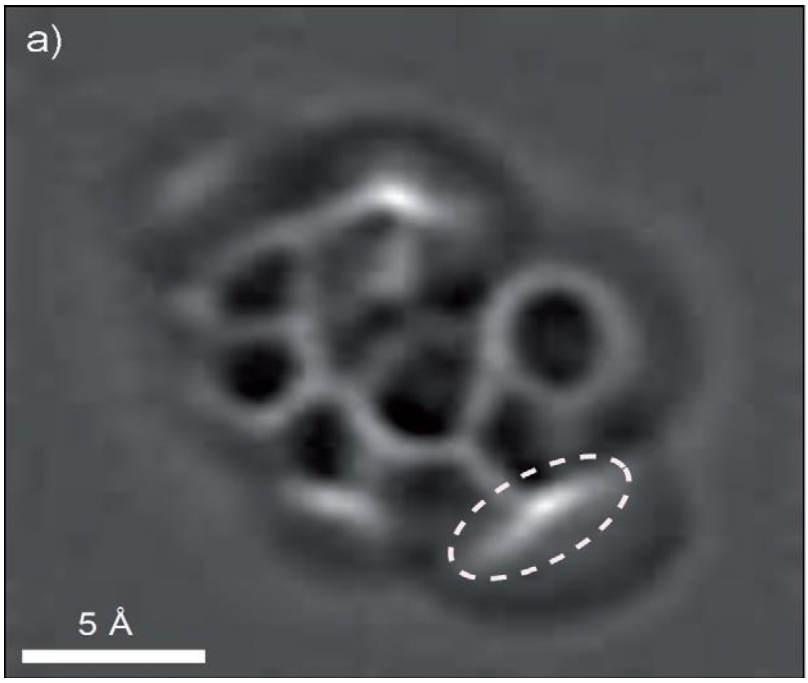


Figure 1.4 (a). AFM image of breitfussin A[34]

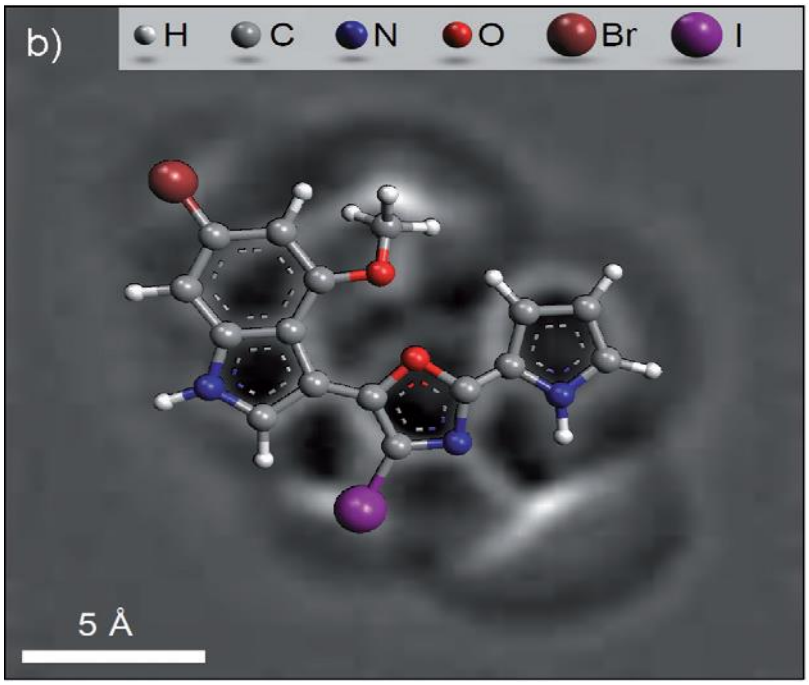


Figure 1.4 (b). AFM image of breitfussin A is overlaid with predicted structure[34]

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CHAPTER 2. SYNTHESIS OF BREITFUSSINS ANALOG AND SELECTIVE HALOGENATIONS

Part of this chapter has been published in Organic Letters Journal especially work on bromination on breitfussins analog, For reference, please see:

Khan, A. K.; Chen, J. S. *Org. Lett*. **2015**, *17*, 3718.

2.1 Introduction

Breitfussin A and B (Figure 2.1) are a series of highly modified halogenated dipeptide with very rare molecular framework alkaloids isolated from marine organism *Thuiaria bretfussi*.[1] The structure determination of these compounds was not possible by NMR, MS and IR analysis because of a low number of hydrogen atoms. The atomic-force microscopy (AFM)[2-4] and computational tools[5] were called upon to complete the assignment. This unprecedented application of AFM revealed breitfussins A and B to be unusual oxazole–pyrrole natural products related to the phorbazoles.[6,7] Of note, breitfussin A is the only known naturally-occurring iodooxazole. Synthetic validation of the assigned structures is a high priority because of the promising capability of AFM as a structure elucidation tool.

Although site-selective halogenations of aromatic heterocycles such as pyrroles[8] and oxazoles[9] are well-studied, comparatively little is known about selectivity in substrates containing multiple aromatic heterocycles. Surprisingly, a SciFinder search revealed no examples of pyrrole or oxazole halogenation (selective or otherwise) on a substrate containing both ring systems![10,11] This absence of literature on selective

halogenation on substrates containing multiple aromatic heterocycles gave us an opportunity to develop site-selective halogenation which could be utilized for the synthesis of breitfussins (A and B) and could apply to other similar systems. Here we have used the model compound to carry out selective halogenation.[12]

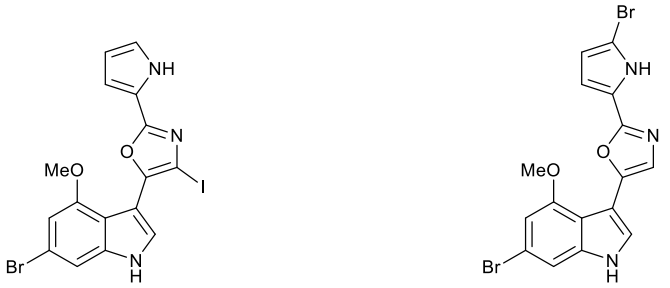


Figure 2.1. Structure of breitfussin A and B

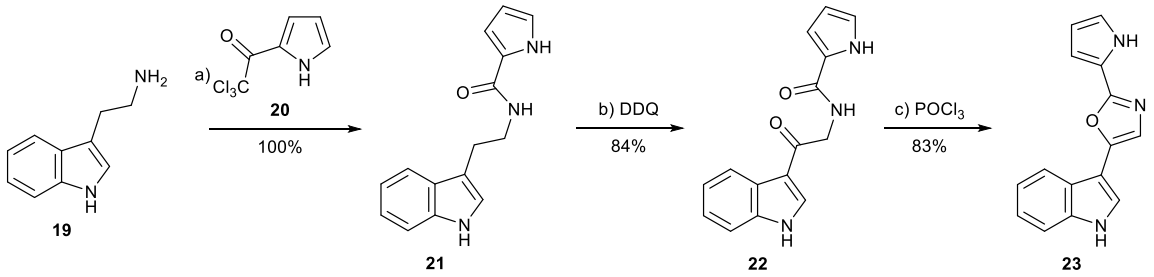
2.2 Synthesis of a Model Compound

Here we envisioned synthesis of the central model compound **23** from substituted tryptamine **19** and 2-(trichloroacetyl)pyrrole (**20**) as high oxidation state surrogates for tryptophan and proline.

Synthesis of breitfussin model compound **23** (Scheme 1) commenced with the reaction between tryptamine (**19**) and 2-(trichloroacetyl)pyrrole (**20**) to afford pure amide **21** with out purification in quantitative yield. DDQ-promoted heterobenzilic oxidation[12] of amide **21** in THF and water (9:1) mixture gave ketone amide **22** in 84% yield. A subsequent cyclization was carried out by dehydration of ketoamide **22** in the presence of

phosphoryl chloride (Robinson-Gabriel oxazole synthesis) to deliver oxazole **23** in 83% yield. The yield of oxazole formation is very affected by impurity in ketoamide which has a nonlinear effect. To get the reproducible yield, ketoamide must be purified carefully because the by-product of DDQ present as an impurity is ^{1}H NMR silent which can be detected by ^{13}C NMR.

Scheme 2.1. Synthesis of model compound **23**[a]



[a] Reagents and conditions: a) **20** (1.02 equiv), DMF, 50 °C for 3 h, 100%; b) DDQ (2.0 equiv) THF: H_2O (9:1) 0 °C for 4 h, 84%; c) $POCl_3$ in pyridine (1:5) dropwise over 5 minutes at 0 °C for 1.5 h then to 23 °C for 1.5 h, 83%; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

2.3 Selective bromination of Model Compound

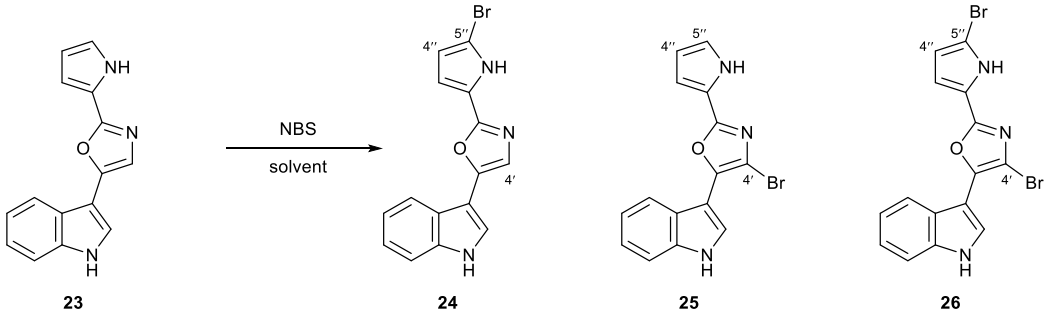
For the study of bromination on breitfussin model compound **23**, N-bromosuccinimide (NBS) was selected as a convenient source of electrophilic bromine. Bromination of model compound **23** in acetonitrile (Table 1, entry 1) was sluggish but

yielded a high amount of dibrominated product **26** even at very low conversion. The presence of high amount of dibromainted product suggests that rate of the second bromination is higher than the rate of the first bromination. 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.

Speculating that the higher acetonitrile solubility of the monobromide product (**24**) as compared with its precursor (**23**) may be promoting a faster second bromination,[13] we switched solvents to THF (Table 2.1, entry 2). The second bromination still 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.This comprable rate of bromination also suggests that reactivity of pyrrole and oxazole rings are very close and can be altered to get selectivity. To slowdown the second bromination, we ran the reaction in acetone (Table 2.1, entry 3) because of the even higher solubility of model compound **23** in this solvent. This simple change not only reduced the extent of over bromination but also enhanced the selectivity for bromooxazole **25**. 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 2.1, 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 **24**. Speculating that mixture of pyridine and NBS might be causing the decomposition of product and a low mass

recovery after the reaction. We switched to a 19:1 THF: pyridine as a solvent mixture (Table 2.1, entry 6) which delivered bromopyrrole **24** in a satisfying 77% yield.[11]

Table 2.1. Bromination study on model Compound **23**



Entry	Equiv NBS	Solvent	Ratio **23**:**24**:**25**:**26**[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 (**25**)
4	1.0	Acetic acid	ND[c]	ND
5	1.1	Pyridine	24:76:0:0	34 (**24**)
6	1.2	THF:Pyridine (19:1)	16:84:0:0	77 (**24**)

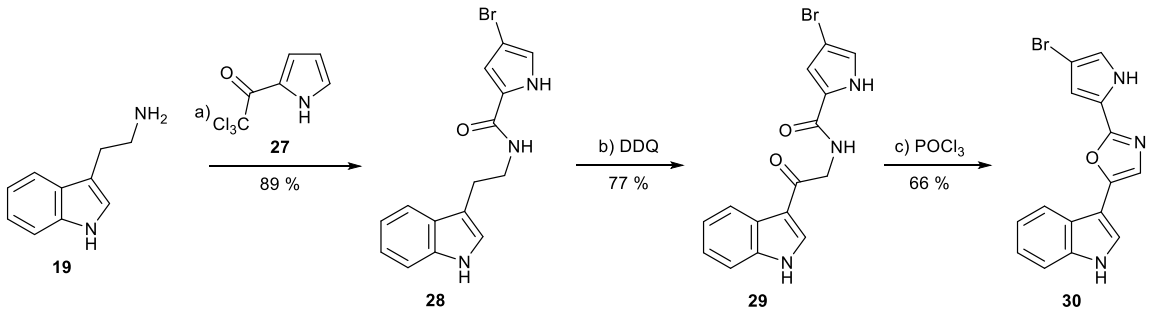
[a] Estimated by ^{1}H NMR analysis. [b] Isolated yield of the major product. [c] Low conversion to a complex mixture. ND = not determined. NBS = *N*-Bromo succinamide.

2.4 Synthesis of 4-bromopyrrole Model Compound

We have not tuned the bromination of model compound **23** to deliver 4-bromopyrrole **30** (Scheme 2.2). Bromination of the C4 position of 2-

(trichloroacetyl)pyrrole (**20**) has been reported in the literature, and it has been found to be the most reactive towards bromination with NBS. To avoid any possibility of mischaracterization of 4-bromo-pyrrole **30** as 5-bromo-pyrrole **24**, we synthesized 4-bromo-pyrrole **30** by using commercially available 4-bromo-2-(trichloroacetyl)pyrrole (**20**). The reaction between tryptamine **19** and 4-bromo-2-(trichloroacetyl)pyrrole **20** produced amide **28** in 89% yield. DDQ-promoted heterobenzilic oxidation[11] of amide **28** in THF and water (9:1) mixture gave bromo-ketoamide **29** in 77% yield. A subsequent cyclization was carried out by dehydration of bromo-ketoamide **29** in the presence of phosphoryl chloride (Robinson-Gabriel oxazole synthesis) to deliver 4-bromopyrrole **30** in 66% yield. On comparison, the NMR of 5-bromopyrrole **24** and 4-bromopyrrole **30** were found to be different, and a differential NOE was used to confirm the structure of 5-bromopyrrole **24.**

Scheme 2.2. Synthesis of model compound **30**[a]

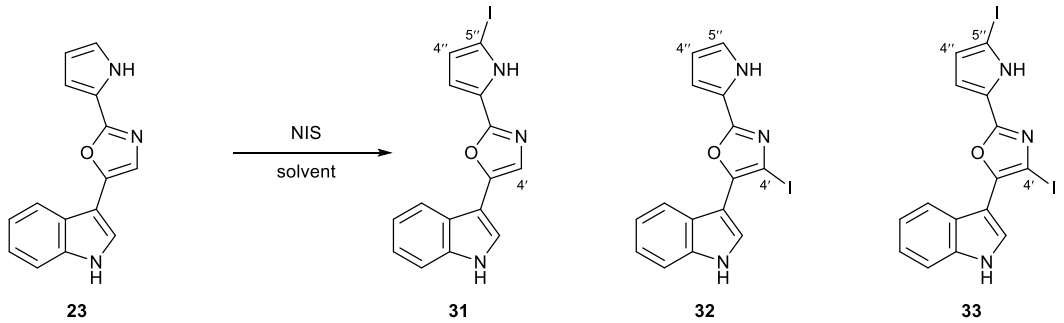


[a] Reagents and conditions: a) **27** (1.02 equiv), DMF, 50 °C for 3 h, 89%; b) DDQ (2.0 equiv) THF: H_2O (9:1) 0 °C for 6 h, 77%; c) $POCl_3$ in pyridine (1:5) dropwise over 5 minutes at 0 °C for 1.5 h then to 23 °C for 1.5 h, 66%; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

2.5 Selective Iodination of Model Compound 23

Having a successfully developed method to carry out selective bromine selectively at different sites, we turned our attention to iodination. Model compound **23** was reacted with NIS in acetone, but it resulted in decomposition of starting material with out formation desired iodo-oxazole **32** (Table 2.2, entry 1). Reaction in acetic acid again produced an inseparable mixture. When the model compound was reacted with NIS in pyridine, we encountered the similar problem of low mass recovery as in bromination resulting in low yield 28% of iodo-pyrrole **31** (Table 2.2, entry 3). After switching to THF: pyridine (19:1) solvent, the yield of iodo-pyrrole **31** (Table 2.2, entry 4) improved to 40% but was not at the level to the yield of bromo-pyrrole **24**. Here we also explored the possibility of using molecular iodine as an electrophilic iodine source. The molecular iodine was found to be unreactive.[13]

Table 2.2. Iodination study on model Compound **23**



Entry	Equiv NBS	Solvent	Ratio **23**:**31**:**32**:**33**[a]	Yield[b] (%)
1	3.0	Acetone	Decomposition	ND
2	1.0	Acetic acid	Complex mixture	ND
3	1.5	Pyridine	28:72:0:0	28 (**31**)
4	1.5	THF:Pyridine (19:1)	35:65:0:0	40 (**31**)

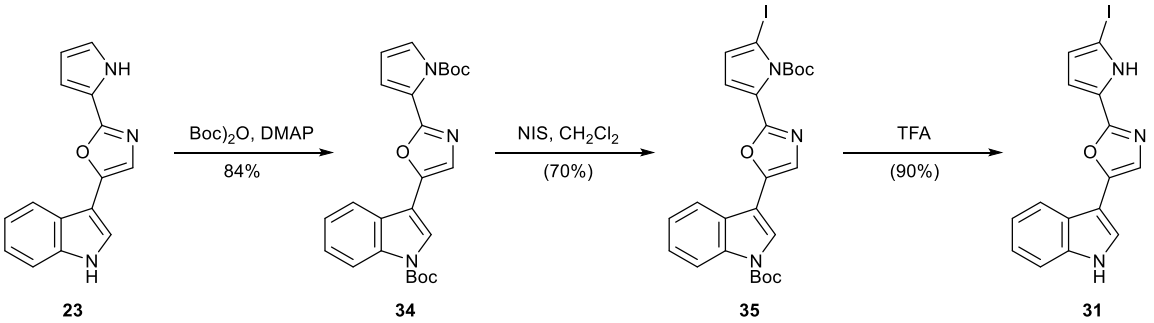
[a] Estimated by ^{1}H NMR analysis. [b] Isolated yield of the major product. ND = not determined. NIS = *N*-iodo succinamide.

In light of these difficulties, we opted to modify the substrate. As shown in Scheme 2.3, Boc protection of model compound **23** proceeded in 84% yield to furnish *N*-Boc-oxazole **34**, but this led to an *increase* in pyrrole reactivity;[14] The reaction of *N*-Boc-oxazole **34** with NIS afforded *N*-Boc-5-iodopyrrole **35** in 70% yield, and subsequent deprotection with TFA resulted in the formation of 5-iodopyrrole **31** (breitfussin B analogue) in 90% yield.

To avoid the electronic influence of a carbamate, model compound **23** was converted into TIPS-protected analog **36** in 88% yield (Scheme 2.4). Oxazole

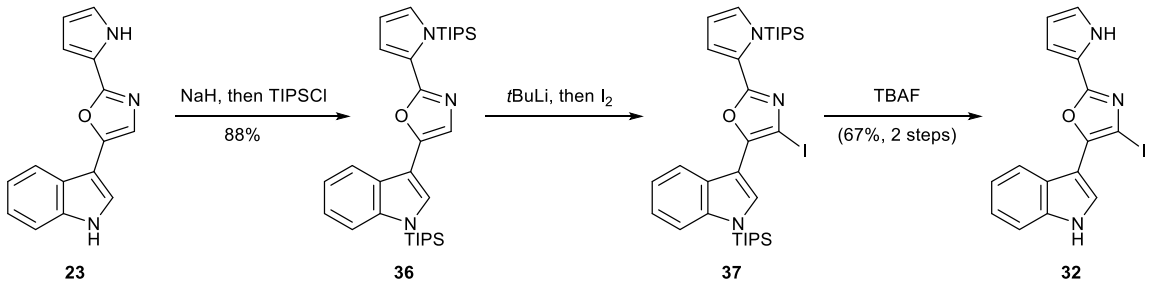
deprotonation by *t*BuLi and trapping with molecular iodine[15] and subsequent deprotection with TBAF resulted in the formation of iodooxazole **32** (breitfussin A analog) in 67% yield over 2 steps.

Scheme 2.3. Synthesis of model 5-iodopyrrole **31**[a]



[a] Reagents and conditions: a) $(Boc)_2O$ (3.00 equiv), DMAP (0.10 equiv), THF, 23 °C for 1 h, 84%; b) NIS (2.20 equiv) CH_2Cl_2, 23 °C for 24 h, 70%; c) CH_2Cl_2:TFA (9:1), 23 °C for 3.0 h, 90%; $(Boc)_2O$ = Di-*tert*-butyl dicarbonate; DMAP = 4-Dimethylaminopyridine; TFA = Trifluoroacetic acid.

Scheme 2.4. Synthesis of model compound **32**[a]



[a] Reagents and conditions: a) NaH (3.0 equiv), DMF, 0 °C for 20 min then TIPCl then 23 °C for 1.0 h, 88%; b) *t*BuLi (3.0 equiv) THF, −40 °C for 30 min then I_2 (5.0 equiv), c) TBAF (3.2 equiv) THF at 0 °C for 10 min, 67% over 2 steps; TIPCl = Triisopropylsilyl chloride; TBAF = Tetra-*n*-butylammonium fluoride.

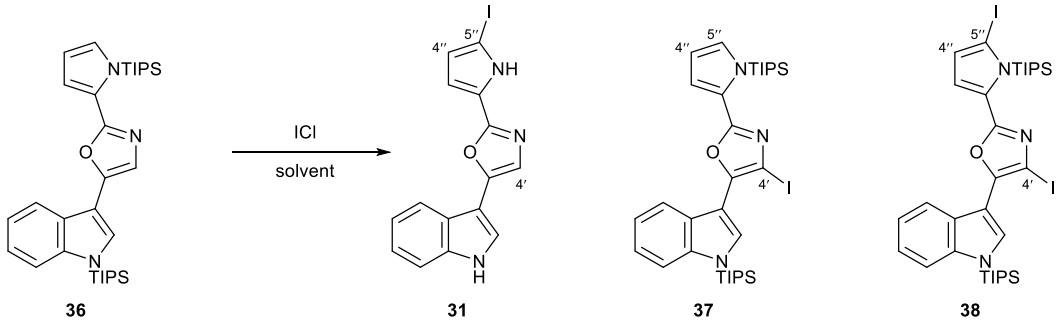
2.6 Selective Iodination of *N*-TIPS Compound 33 with Iodine Monochloride (ICl)

Although we were able to install iodine in a model compound on pyrrole and oxazole to produce 5-iodopyrrole **31** and iodooxazole **32** (breitfussin A analog) by two different methods, using NIS, and deprotonation followed by trapping with molecular iodine respectively. The synthesis of breitfussin A (**17**) by using this deprotonation method had a rare chance of success because of metal halogen exchangeable bromine was present on indole of breitfussin A. Due to the obstacle of bromine on indole of breitfussin A, a new method to place iodine on oxazole was warranted.

To install iodine directly on oxazole, we envisioned to block reactive the C5″ position of model compound **23** by placing bulky TIPS group on pyrrole. The reaction on

N-TIPS Compound **36** with iodine monochloride (ICl)[51] in THF: pyridine (19:1) led the formation of 5-iodopyrrole **31** as a major product along with *N*-TIPS iodooxazole **37** (Table 2.3, entries 1–4). We speculated that acidic nature of ICl might be causing the deprotection of *N*-TIPS at first and subsequent iodination on pyrrole furnishing 5-iodopyrrole **31**. To block the deprotection caused by the acidity of reaction mixture we used 1:1 mixture of THF and pyridine as a solvent. This led to the formation of desired *N*-TIPS iodooxazole **37** in 76% yields which were subsequently converted to iodooxazole **32** by using TBAF in 96% yield.

Table 2.3. Iodination of *N*-TIPS Compound **36** with ICl



36 **31** **37** **38**

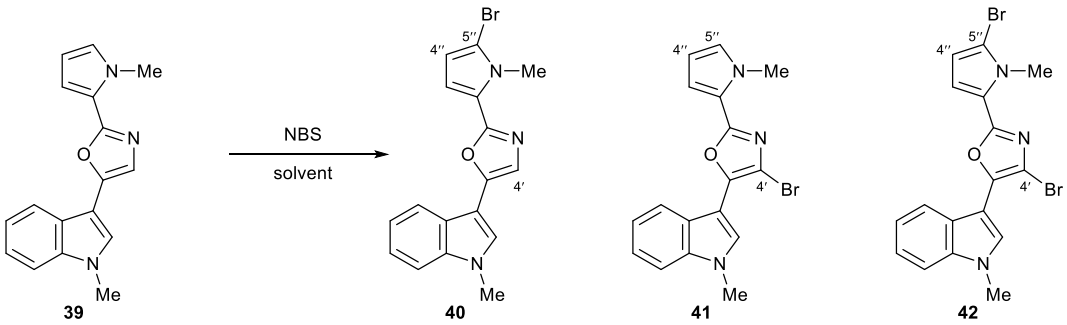
Entry	Equiv ICl	Solvent	Ratio **36**:**31**:**37**:**38**[a]	Yield[b] (%)
1	2.0	Acetone	Decomposition	ND
2	2.0	Acetic acid	Complex mixture	ND
3	2.0	THF:Pyridine (19:1)	15:55:30:0	35 (**31**)
4	2.0	THF:Pyridine (1:1)	5:0:95:0	76 (**37**)

[a] Estimated by ^{1}H NMR analysis. [b] Isolated yield of the major product. ND = not determined. ICl = Iodine monochloride.

2.7 Mechanistic Role of Acidic N-H Hydrogen in Selectivity

We also investigated the reaction of *N*-methylated model compound **35** with NBS in an attempt to shed some light on the reasons for the observed solvent-dependent bromination site selectivity (Table 2.4, entries 1–4). In our bromination study on model compound **23,** we found that reactivity of pyrrole and oxazole were very close towards nucleophilic bromination. We thought that hydrogen bonding of acidic N-H on pyrrole with pyridine might be playing a crucial role in selectivity and substitution of acidic hydrogen should lead to loss of selectivity. On the reaction of the *N*-methylated model compound, **38** with NBS resulted in nonselective bromination. The site selectivities of the bromination reactions run in acetone and THF: pyridine are at odds with those observed for *N*-unmethylated model compound **23**; this indicates that acidic N-H hydrogen on pyrrole is very crucial to get selectivity. But more studies will be required to elucidate the mechanistic role of pyridine in the selective formation of bromopyrrole **24**. In place of pyridine other organic bases like DMAP, imidazole, and triethylamine gave similar selectivity but lower yields.

Table 2.4. Bromination study on *N*-methylated model compound **36**



entry	equiv NBS	Solvent	ratio **39**:**40**:**41**:**42**[a]	yield[b] (%)
1	1.0	THF	2:9:60:29	43 (**40**), 23 (**41**)
2	3.0	Acetone	0:22:0:78[c]	ND
3	1.0	Acetone	43:37:12:8	36 (**40**)
4	1.2	THF:pyridine (19:1)	7:31:44:18	28 (**40**) 44 (**41**)

[a] Estimated by ^{1}H NMR analysis. [b] Isolated yield of the major product. [c] Low conversion to a complex mixture. ND = not determined. NBS = *N*-bromo succinamide.

2.8 Conclusion

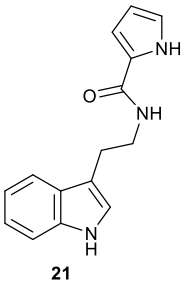
In conclusion, selective halogenations delivered breitfussin analogs with both natural and unnatural halogenation patterns. The rates of pyrrole and oxazole halogenation were found to be comparable. Site-selective bromination was achieved by adjusting the reaction solvent, and site-selective iodination was achieved by altering the substrate and reagents. These results will be useful not only for the synthesis of

halogenated target molecules such as breitfussins A and B but also for preparation of halogenated building blocks for palladium-catalyzed cross-coupling reactions.[16] Our NMR spectroscopic comparisons support the assigned structures of breitfussins A and B, and we are pursuing their total synthesis in order to complete the structure validation.

2.9 General Procedures

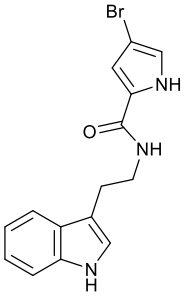
Unless otherwise noted, all reactions were performed with stirring under an argon atmosphere under anhydrous conditions. Reagents were purchased at the most economical grade. Dry tetrahydrofuran (THF) and *N*, *N*-dimethylformamide (DMF) were obtained by passing HPLC-grade solvents through commercial solvent purification systems. NBS was recrystallized from acetic acid. Unless otherwise noted, all other chemicals were used as received, without purification. Flash column chromatography was performed using Grace Davison Davisil silica gel (60 Å, 35–70 μm). Yields refer to chromatographically- and spectroscopically- (^{1}H NMR) homogeneous samples. Thin-layer chromatography (TLC) was performed on Grace Davison Davisil silica TLC plates using UV light and common stains for visualization. NMR spectra were calibrated using a residual undeuterated solvent as an internal reference. Apparent couplings were determined for multiplets that could be deconvoluted visually.

2.10 Selected Experimental, Physical, and Spectral Data



21

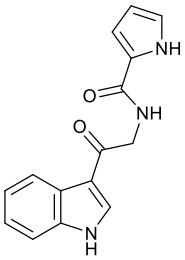
Amide 21. To a solution of 2-(trichloroacetyl)pyrrole (**20**, 6.76 g, 31.8 mmol, 1.02 equiv) in 10 mL of DMF was added tryptamine (**19**, 5.00 g, 31.2 mmol, 1.00 equiv). The mixture was stirred at 50 °C for 3 hours, then cooled to room temperature and diluted with EtOAc (2 × 500 mL). The combined organic layers was washed with water (2 × 500 mL) and saturated NaCl solution (500 mL), then dried over anhydrous $MgSO_4$ and concentrated to give pure amide **21** as a brown solid (7.93 g, 100%). **21**: R_f = 0.55 (80% EtOAc / hexanes); IR (thin film): ν_{max} = 3403, 3315, 2925, 1616, 1558, 1520 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.40 (s, 1H), 10.79 (s, 1H), 8.10 (t, *J* = 5.7 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.33 (d, *J* = 8.0, 1H), 7.16 (d, *J* = 2.1, 1H), 7.06 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.98 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 6.83 (dt, *J* = 1.4, 2.6 Hz, 1H), 6.73 (ddd, *J* = 3.6, 2.4, 1.5 Hz, 1H), 6.07 (dt, *J* = 3.5, 2.4 Hz, 1H), 3.49 (m, 2H), 2.91 (t, *J* = 7.7) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.6, 136.2, 127.3, 126.5, 122.5, 121.1, 120.9, 118.3, 118.1, 112.0, 111.4, 109.6, 108.4, 39.2, 25.5 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{16}N_3O^+$ [M + H^+]: 254.1288, found: 254.1287.



28

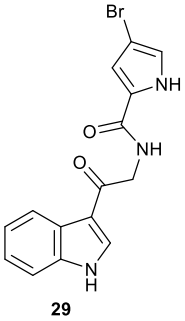
Amide 28 was prepared in 89 % yield in the same manner. **28**: R_f = 0.74 (80 % EtOAc / hexanes); IR (thin film): ν_{max} = 3410, 2940, 1704, 1632, 1565, 1455 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.81 (s, 1H), 10.80 (s, 1H), 8.23 (t, *J* = 5.7 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 7.07 (ddd, *J* = 8.0, 7.0, 1.0 Hz,

1H), 6.98 (ddd, *J* = 7.9, 7.0, 0.9, 1H), 6.97 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.83 (t, *J* = 1.9 Hz, 1H), 3.49 (m, 2H), 2.91 (t, *J* = 7.5 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 159.56, 136.24, 127.25, 127.13, 122.62, 121.03, 120.93, 118.28, 118.23, 111.82, 111.38, 111.24, 94.88, 25.38 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{15}BrN_3O^+$ [M + H^+]: 332.0393, found: 332.3970.



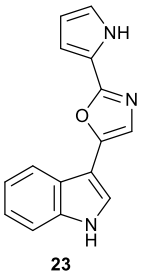
22

Ketoamide 22. To a solution of amide **21** (1.05 g, 4.0 mmol, 1.0 equiv) in 20 mL of a THF:H_2O mixture (9:1) at 0 °C was added DDQ (1.81 g, 8.0 mmol, 2.0 equiv). The resultant red solution was stirred at 0 °C for 4 hours, then diluted with EtOAc (200 mL). The organic layer was washed with saturated $NaHCO_3$ solution (4 × 200 mL) until the aqueous layer remained colorless. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to give a brown solid. Flash column chromatography (100% EtOAc) gave pure ketoamide **22** (893 mg, 84%) as a brown solid. **22**: R_f = 0.20 (80% EtOAc / hexanes); IR (thin film): ν_{max} = 3414, 3207, 1631, 1562, 1517, 1438 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.01 (s, 1H), 11.46 (s, 1H), 8.48 (d, *J* = 3.1 Hz, 1H), 8.28 (t, *J* = 5.9, 1H), 8.16 (d, *J* = 7.8 Hz, 1H), 7.49 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.22 (m, 1H), 7.19 (m, 1H), 6.87 (dt, *J* = 1.5, 2.6 Hz, 1H), 6.85 (ddd, *J* = 3.7, 2.5, 1.5 Hz, 1H), 6.11 (dt, *J* = 3.6, 2.4 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.7, 160.9, 136.4, 133.5, 126.2, 125.4, 122.8, 121.8, 121.4, 121.2 114.0, 112.2, 110.2, 108.6, 45.6 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{14}N_3O_2^+$ [M + H^+]: 268.1081, found: 268.1079.



29

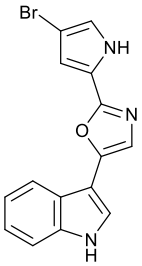
Bromo-ketoamide 29 was prepared in 77 % yield in the same manner. **29**: R_f = 0.43 (80 % EtOAc / hexanes); IR (thin film): ν_{max} = 3409, 2936, 1703, 1620, 1562, 1450 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.10 (s, 1H), 11.86 (s, 1H), 8.47 (d, *J* = 3.1 Hz, 1H), 8.43 (t, *J* = 5.9 Hz, 1H), 8.16 (d, *J* = 7.7 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.22 (m, 1H), 7.19 (m, 1H), 7.01 (dd, *J* = 2.9, 1.6 Hz, 1H), 6.94 (dd, *J* = 2.5, 1.7 Hz, 1H), 4.60 (d, *J* = 5.9 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.35, 159.89, 136.41, 133.55, 126.81, 125.43, 122.89, 121.86, 121.34, 121.16, 114.03, 112.19, 111.76, 95.02, 45.65 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{13}BrN_3O_2^+$ [M + H^+]: 346.0186, found: 346.0192.



23

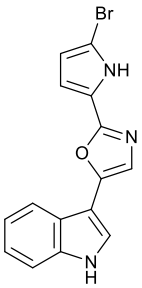
Oxazole 23. To a solution of ketoamide **22** (267 mg, 1.0 mmol) in 3.5 mL of pyridine at 0 °C was added $POCl_3$ (0.7 mL) dropwise over 5 minutes. The mixture was stirred at 0 °C for 1.5 hours, then at 23 °C for another 1.5 hours. The mixture was diluted with EtOAc (250 mL), washed with cold saturated $NaHCO_3$ solution (250 mL), water (250 mL), and saturated NaCl solution (250 mL), then dried over $MgSO_4$ and concentrated to give a brown solid. Flash column chromatography (60% EtOAc / hexanes) gave pure oxazole **23** (207 mg, 83% yield) as a tan solid. **23**: R_f = 0.36 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3358, 1631, 1406 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.82 (s, 1H), 11.56 (s, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 2.7 Hz, 1H), 7.47 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.45 (s, 1H), 7.21 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.97 (dt, *J* = 1.5, 2.6, Hz, 1H), 6.75 (ddd, *J* = 3.5, 2.5, 1.5 Hz, 1H), 6.21 (dt, *J* = 3.5, 2.4 Hz, 1H) ppm; ^{13}C NMR

(150 MHz, DMSO-d_6): δ = 154.0, 146.1, 136.4, 123.5, 123.1, 122.1, 121.6, 120.1, 120.0, 119.9, 119.6, 112.0, 109.33, 109.30, 103.9 ppm; HRMS (ESI-QTOF): calcd for $C_{15}H_{12}N_3O^+$ [M + H^+]: 250.0975, found: 250.0982.



30

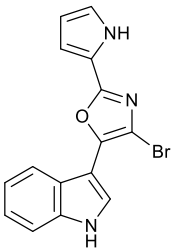
Oxazole 30 was prepared in 66 % yield in the same manner. **30**: R_f = 0.58 (50 % EtOAc / hexanes); IR (thin film): ν_{max} = 3406, 2924, 1499, 1424 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.21 (s, 1H), 11.59 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.48 (s, 1H), 7.48 (d, [peak overlaps singlet at 7.48], 1H), 7.21 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 7.16 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 7.12 (dd, *J* = 2.9, 1.6 Hz, 1H), 6.81 (dd, *J* = 2.5, 1.7 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.64, 146.74, 136.37, 123.44, 123.43, 122.19, 121.35, 121.04, 120.17, 119.98, 119.69, 112.07, 110.73, 103.66, 95.97 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{11}BrN_3O^+$ [M + H^+]: 328.0085, found: 328.0086.



24

Bromopyrrole 24. To a solution of model compound **23** (30 mg, 0.12 mmol, 1.0 equiv) in 4 mL of a THF:pyridine mixture (19:1) at 0 °C was added NBS (25 mg, 0.14 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 30 min, then diluted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over Na_2SO_4 and concentrated to give a brown solid. Flash column chromatography (30% EtOAc / hexanes) gave pure bromopyrrole **24** (30 mg, 77% yield) as a tan solid. **24**: R_f = 0.50 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3405, 2925, 1704, 1499, 1426 cm^{-1};

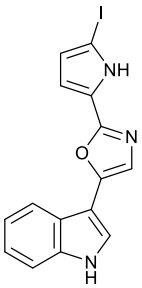
^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.60 (s, 1H), 11.59 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 2.6 Hz, 1H), 7.48 (d, [peak overlaps singlet at 7.48], 1H), 7.48 (s, 1H), 7.21 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.16 (ddd, J = 7.8, 7.1, 1.0 Hz, 1H), 6.74 (dd, J = 3.7, 2.6 Hz, 1H), 6.27 (dd, J = 3.7, 2.3 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.8, 146.4, 136.4, 123.43, 123.35, 122.2, 121.8, 120.1, 120.0, 119.7, 112.1, 111.7, 110.8, 103.8, 102.0 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{11}BrN_3O^+$ [M + H^+]: 328.0080, found: 328.0081.



25

Bromooxazole 25. To a solution of model compound **23** (50 mg, 0.20 mmol, 1.0 equiv) in 4 mL of acetone at 0 °C, was added NBS (36 mg, 0.20 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 30 minutes, then extra NBS (71 mg, 0.40 mmol, 2.0 equiv) was added and the mixture was stirred for an additional 5 minutes at 0 °C. The reaction was quenched by addition of 10 wt% Na_2SO_3 (10 mL), then extracted with EtOAc (40 mL). The organic phase was washed with water (40 mL) and saturated NaCl solution (40 mL), then dried over $MgSO_4$ and concentrated to give a brown solid. Flash column chromatography (30% EtOAc / hexanes) gave pure bromooxazole **25** (29 mg, 45% yield) as a tan solid. **25**: R_f = 0.48 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3212, 2927, 1619, 1457 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.02 (s, 1H), 11.75 (s, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.98 (d, J = 2.7 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.24 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H), 7.19 (ddd, J = 8.1, 7.1, 1.1 Hz, 1H) 7.03 (dt, J = 1.5, 2.6 Hz, 1H), 6.85 (ddd, J = 3.7, 2.5, 1.5 Hz, 1H), 6.25 (dt, J = 3.5, 2.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.2, 143.1, 135.9, 124.4, 124.1, 122.6, 122.5, 120.45, 120.37, 118.9, 112.1, 110.5, 109.8,

108.3, 101.9 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{11}BrN_3O^+$ [M + H^+]: 328.0091, found: 328.0083.

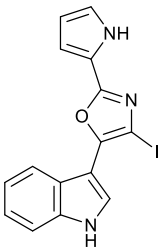


31

Iodopyrrole 31. ***Procedure (a):*** To a solution of model compound **23** (30 mg, 0.12 mmol, 1.0 equiv) in 4 mL of a THF:pyridine mixture (19:1) at 0 °C was added NIS (40 mg, 0.18 mmol, 1.5 equiv). The mixture was stirred at 0 °C for 30 min, then diluted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over Na_2SO_4 and concentrated to give a dark green solid. Flash column chromatography (30 % EtOAc / hexanes) gave pure iodopyrrole **31** (18 mg, 40 % yield) as a yellow solid.

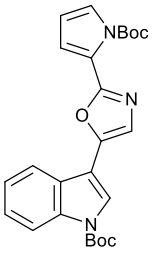
Procedure (b): A solution of iodopyrrole **34** (46 mg, 0.08 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2:TFA (9:1) was stirred at 23 °C for 3 hours. The mixture was diluted with EtOAc (25 mL). The organic phase was washed with water (25 mL) and saturated NaCl solution (20 mL), then dried over Na_2SO_4 and concentrated to give a dark green solid. Flash column chromatography (30 % EtOAc / hexanes) gave pure iodopyrrole **31** (27 mg, 90 % yield) as a yellow solid. **31**: R_f = 0.59 (50 % EtOAc / hexanes); IR (thin film): ν_{max} = 3407, 3126, 2919, 1704, 1615, 1495, 1457 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.36 (s, 1H), 11.58 (s,1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.48 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.46 (s, 1H), 7.21 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.16 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.68 (d, *J* = 3.5 Hz, 1H), 6.38 (d, *J* = 3.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.70, 146.31, 136.37, 124.43, 123.41, 123.33, 122.14, 120.10,

119.95, 119.66, 118.88, 112.06, 111.77, 103.77, 69.65 ppm; HRMS (ESI-QTOF): calcd for $C_{15}H_{11}IN_3O^+$ [M + H^+]: 375.9941, found: 375.9941.



32

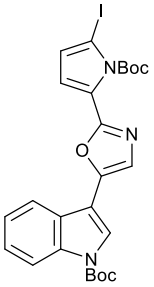
Iodooxazole 32. To a solution of crude iodooxazole **37** (0.089 mmol theoretical, 1.0 equiv) in 1 mL of THF at 0 °C was added TBAF (1.0 M in THF, 285 μL, 0.285 mmol, 3.2 equiv). The mixture was stirred at 0 °C for 10 minutes, then diluted with ether (50 mL). The organic layer was washed with water (2 × 50 mL) and saturated NaCl solution (50 mL), then dried over $MgSO_4$ and concentrated to give a tan solid. Flash column chromatography (25 % EtOAc / hexanes) gave pure iodooxazole **32** (22 mg, 67 % yield over two steps) as a white solid. **32**: R_f = 0.63 (50 % EtOAc / hexanes); IR (thin film): ν_{max} = 3401, 2924, 1515, 1455, 1416 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.98 (s, 1H), 11.70 (s, 1H), 8.07 (d, *J* = 2.7 Hz, 1H), 8.04 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.23 (ddd, *J* = 7.9, 7.1, 1.1 Hz, 1H), 7.19 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.00 (dt, *J* = 1.5, 2.6 Hz, 1H), 6.81 (ddd, *J* = 3.5, 2.4, 1.5 Hz, 1H), 6.24 (dt, *J* = 3.5, 2.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 155.83, 147.42, 135.83, 124.66, 124.41, 122.37, 122.35, 120.42, 120.36, 118.94, 112.09, 110.19, 109.59, 102.45, 78.27 ppm; HRMS (ESI-QTOF) calcd for $C_{15}H_{11}IN_3O^+$ [M + H^+]: 375.9941, found: 375.9936.



34

Carbamate 34. To a solution of oxazole **23** (50 mg, 0.20 mmol, 1.0 equiv) and Boc anhydride (131 mg, 0.60 mmol, 3.0 equiv) in 1 mL of THF was added DMAP (3 mg, 0.02 mmol, 0.1 equiv). The mixture was stirred at 23 °C for one hour, then quenched with water (5 mL) and diluted with ether

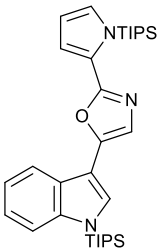
(50 mL). The organic layer was washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over $MgSO_4$ and concentrated to give a yellow solid. Flash column chromatography (15 % EtOAc / hexanes) gave pure carbamate **34** (76 mg, 84 % yield) as a white solid. **34**: R_f = 0.38 (20 % EtOAc/Hexanes); IR (thin film): ν_{max} = 2948, 2868, 1452 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 7.3 Hz, 1H), 7.91 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 3.2, 1.8, Hz,1H), 7.46 (s, 1H), 7.41 (dt, *J* = 0.9, 7.8 Hz, 1H), 7.35 (dt, *J* = 0.6, 7.6 Hz, 1H), 6.77 (dd, *J* = 3.4, 1.7 Hz, 1H), 6.32 (t, *J* = 3.4 Hz, 1H), 1.69 (s, 9H), 1.43 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 154.61, 149.39, 148.49, 146.43, 135.77, 126.74, 125.35, 124.64, 123.54, 123.06, 122.65, 121.01, 120.36, 119.01, 115.65, 111.16, 109.61, 84.65, 84.35, 28.29, 27.79 ppm; HRMS (ESI-QTOF): calcd for $C_{25}H_{28}N_3O_5^+$ $[M + H^+]$: 450.2023, found: 450.2026.



35

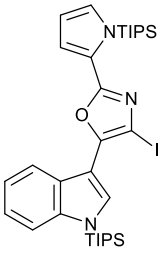
***N*-Boc Iodopyrrole 35.** To a solution of carbamate **34** (20 mg, 0.04 mmol, 1.0 equiv) in 1 mL of CH_2Cl_2 was added NIS (20 mg, 0.09 mmol, 2.2 equiv). The mixture was stirred at 23 °C for 24 hours, and then diluted with ether (25 mL). The organic phase was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over $MgSO_4$ and concentrated to give a colorless solid. Flash column chromatography (15 % EtOAc / hexanes) gave pure *N-Boc* iodopyrrole **35** (16 mg, 70 % yield) as a colorless solid. **35**: R_f = 0.43 (20 % EtOAc / hexanes); IR (thin film): ν_{max} = 2980, 2934, 1740, 1477, 1453, cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.2 Hz, 1H), 7.89 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.44 (s, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 3.6 Hz, 1H), 6.6 (d, *J* = 3.6 Hz, 1H), 1.69 (s, 9H), 1.48 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ =

153.82, 149.40, 148.38, 146.19, 135.80, 126.67, 125.42, 125.14, 123.62, 123.48, 123.19, 122.76, 120.27, 118.47, 115.71, 109.38, 86.22, 84.64, 70.15, 28.33, 27.71 ppm; HRMS (ESI-QTOF): calcd for $C_{25}H_{27}IN_3O_5^+$ [M + H^+]: 576.0990, found: 576.0998.



36

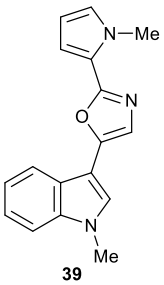
***N*-TIPS amine 36.** To a solution of oxazole **23** (100 mg, 0.40 mmol, 1.0 equiv)) in 1 mL DMF at 0 °C was added NaH (60 % dispersion in mineral oil, 29 mg, 1.20 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 20 minuties, then TIPSCl (257 μL, 1.20 mmol, 3.0 equiv). The mixture was stirred at 23 °C for one hour. The compound was extracted in diethyl ether (50 mL). The organic layer was washed with water (50 mL), saturated solution of NaCl (50 mL) then dried over $MgSO_4$ and concentrated to give a white solid. Flash column chromatography (5 % EtOAc / hexanes) gave pure **36** (198 mg, 88% yield) as a white solid. **36**: R_f = 0.74 (20 % EtOAc / hexanes); IR (thin film): ν_{max} = 2980, 2933, 1760, 1740, 1609, 1476, 1453, cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.88 – 7.85 (m, 1H), 7.57 (s, 1H), 7.56 – 7.54 (m, 1H), 7.29 (s, 1H), 7.27 – 7.22 (m, 2H), 7.07 (dd, *J* = 2.7, 1.5, 1H), 7.05 (dd, *J* = 3.4, 1.5 Hz, 1H), 6.38 (dd, *J* = 3.4, 2.8 Hz, 1H), 1.84 (septet, *J* = 7.5 Hz, 3H), 1.75 (septet, *J* = 7.5 Hz, 3H), 1.18 (d, *J* = 7.5 Hz, 18H), 1.14 (d, *J* = 7.5 Hz, 18H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 155.54, 146.34, 141.54, 129.37, 128.64, 127.62, 126.06, 122.52, 120.94, 120.81, 120.00, 116.53, 114.43, 110.60, 108.03, 18.49, 18.23, 13.54, 12.95 ppm; HRMS (ESI-QTOF) calcd for $C_{33}H_{52}N_3OSi_2^+$ [M + H^+]: 562.3643, found: 562.3650.



37

***N*-TIPS iodooxazole 37. *Procedure (a)*:** To a solution of TIPS amine **36** (50 mg, 0.089 mmol, 1.0 equiv) in 1 mL of THF at –40 °C was added *t*BuLi (1.7 M in pentane, 157 μL, 0.27 mmol, 3.0 equiv). The mixture was stirred at –40 °C for 30 minutes, then a solution of iodine (113 mg, 0.44 mmol, 5.0 equiv) in 1 mL of THF added. The reaction mixture was warmed to 23 °C, then quenched by addition of 10 wt % Na_2SO_3 (10 mL). The mixture was extracted with ether (25 mL). The organic layer was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over $MgSO_4$ and concentrated to give crude iodooxazole **32** along with partially-desilylated products as a white solid.

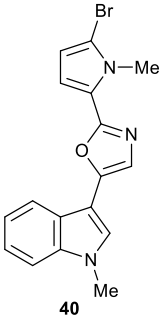
***Procedure (b)*:** To a solution of TIPS amine **36** (50 mg, 0.089 mmol, 1.0 equiv) in 1 mL of pyridine THF (19:1) at –40 °C was added ICl (1.0 M in CH_2Cl_2, 178 μL, 0.18 mmol, 2.0 equiv) drop by drop over 30 min, then reaction was warmed to 0 °C over 3 hours. Again ICl (1.0 M in CH_2Cl_2, 45 μL, 0.045 mmol, 0.5 equiv) was added. After 5 min reaction mixture was quenched by addition of 10 wt % Na_2SO_3 (10 mL). The mixture was extracted with ether (25 mL). The organic layer was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over $MgSO_4$ and concentrated to give crude iodooxazole **33** as a white solid.



39

***N*-Methylated compound 39**. To a solution of N-unmethylated compound **23** (50 mg, 0.20 mmol, 1.0 equiv) in 1 mL of DMF at 0 °C was added NaH (60% dispersion in mineral oil, 15 mg, 0.60 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 15 minutes, then methyl iodide (38 μL, 0.60 mmol, 3.0 equiv) was added. The mixture was stirred at 23 °C for 30 minutes, then extracted

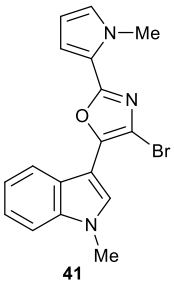
with EtOAc (50 mL). The organic layer was washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over Na_2SO_4 and concentrated to give a white solid. Flash column chromatography (30% EtOAc / hexanes) gave pure N-methylated compound **39** (53 mg, 95% yield) as a white solid. **39**: R_f = 0.20 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 3258, 2919, 2853 1631, 1406 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 7.90 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.49 (s, 1H), 7.28 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.21 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 7.02 (t, *J* = 2.1 Hz, 1H), 6.81 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.17 (dd, *J* = 3.8, 2.6 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.6, 145.6, 136.9, 127.3, 127.2, 123.8, 122.2, 120.7, 120.3, 120.0, 119.7, 111.4, 110.4, 108.0, 102.8, 36.2, 32.7 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{16}N_3O^+$ [M + H^+]: 278.1288, found: 278.1258.



40

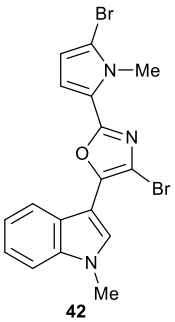
Bromopyrrole 40, bromooxazole 41, and dibromide 42. To a solution of model compound **39** (25 mg, 0.09 mmol, 1.0 equiv) in 2 mL of a THF:pyridine mixture (19:1) at 0 °C was added NBS (19 mg, 0.11 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 15 min, then diluted with EtOAc (50 mL). The organic phase was washed with water (50 mL) and saturated NaCl solution (50 mL), then dried over Na_2SO_4 and concentrated to give a brown solid. Flash column chromatography (15% EtOAc / hexanes) gave pure bromopyrrole **40** (9.0 mg, 28%), bromooxazole **41** (14 mg, 44%), and dibromide **42** (5.3 mg, 13%) as white solids. **40**: R_f = 0.35 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 2923, 2858, 1621, 1607, 1511, 1402 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 7.91 (dt, *J* = 8.0, 09 Hz, 1H), 7.88 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.53 (s, 1H), 7.28 (ddd, *J* =

8.1, 7.1, 1.0 Hz, 1H), 7.21 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.89 (d, *J* = 4.0 Hz, 1H), 6.40 (d, *J* = 4.0 Hz, 1H), 4.01 (s, 3H), 3.87 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.7, 145.9, 136.9, 127.5, 123.7, 122.2, 120.4, 119.9, 119.7, 111.8, 111.2, 110.5, 107.7, 102.6, 34.5, 32.8 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{15}BrN_3O^+$ [M + H^+]: 356.0393, found: 356.0384.



41

41: R_f = 0.36 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 2920, 2850, 1622, 1600, 1507, 1412 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.03 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.24 (ddd, *J* = 7.9, 7.1, 0.9 Hz, 1H), 7.09 (t, *J* = 2.1 Hz, 1H), 6.90 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.20 (dd, *J* = 3.8, 2.6 Hz, 1H), 3.98 (s, 1H), 3.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.7, 142.8, 136.4, 128.3, 128.1, 124.4, 122.5, 120.8, 120.2, 119.6, 112.4, 110.6, 108.4, 108.0, 100.8, 36.2, 32.9 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{15}BrN_3O^+$ [M + H^+]: 356.0393, found: 356.0380.



42

42: R_f = 0.42 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 2924, 2852, 1621, 1506, 1412 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.05 (s, 1H), 8.00 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.31 (ddd, *J* = 8.2, 7.1, 1.0 Hz, 1H), 7.24 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.99 (d, *J* = 4.1 Hz, 1H), 6.44 (d, *J* = 4.1 Hz, 1H), 3.98 (s, 3H), 3.91 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 152.7, 143.2, 136.4, 128.5, 124.4, 122.6, 121.2, 120.9, 120.3, 112.8, 111.6, 110.6, 108.8, 107.8, 100.7, 34.6, 33.0 ppm; HRMS (ESI-QTOF) calcd for $C_{17}H_{14}Br_2N_3O^+$ [M + H^+]: 433.9498, found: 433.9502.

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(i) Wipf, P.; Yokokawa, F. *Tetrahedron Lett.* **1998**, *39*, 2223.

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CHAPTER 3. TOTAL SYNTHESIS OF BREITFUSSINS (A AND B) AND ISOMERISM STUDIES

Part of this chapter has been published in Organic Letters Journal especially work on bromination on breitfussins analog, For reference, please see:

Khan, A. K.; Chen, J. S. *Org. Lett*. **2015**, *17*, 3718.

3.1 Introduction

Breitfussins A and B (Figure 3.1) are highly modified and halogenated dipeptide natural products isolated from the Arctic hydrozoan *Thuiaria breitfussi*.[1] These compounds are composed of a rare molecular frame of indole, oxazole, and pyrrole. Natural products containing oxazole are relatively rare, and breitfussin A is only known iodo-oxazole containing the natural product. These compounds are recently identified halogenated oxazole derivative and a new class of marine alkaloids related to phorbazoles and diazonamides. The traditional methods of structure determination (NMR, IR, MS, UV) were not sufficient to assign the structure of breitfussins. Non-tradition methods, atomic force microscopy (AFM)[2-4] imaging and other computational tool,[5] were called upon to determine final structure of these molecules. Due to the unprecedented use of AFM, in structure determination of breitfussins, the total synthesis will provide a final proof of the structure. It may help to open the possibility of AFM as structure elucidation tool in combination with other analytical tools. Hedberg, Bayer, and coworkers synthesized breitfussins A and B using Suzuki coupling reactions to join the heteroaromatic rings, thus confirming the assigned structure of these natural products.[6,7]

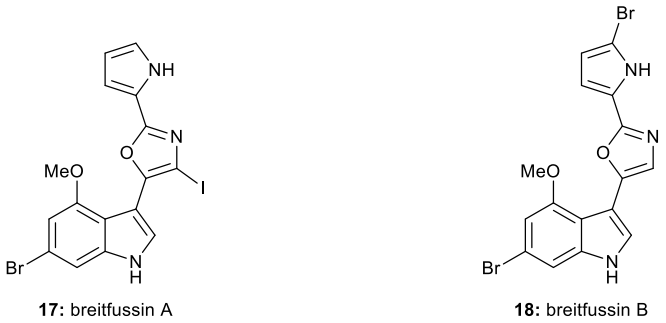


Figure 1.3. Structure of breitfussin A and B

3.2 Retrosynthetic Analysis of Breitfussins

In our retrosynthetic analysis, we envisioned site-selective late-stage halogenations for the synthesis of breitfussins A and B (**17** and **18**) from a common precursor oxazole (**43**) (Figure 3.2) by using our developed methods for selective halogenation on breitfussins analog.

Inspired by the isolation team's description of the breitfussins as highly-oxidized dipeptides,[34] we envisioned synthesis of the central oxazole ring by Robinson-Gabriel oxazole synthesis from β-amidoketone (**44**) moiety at the center of the molecule. This β-amidoketone (**45**) compound can be synthesized from substituted tryptamine **45** and 2-(trichloroacetyl)pyrrole (**20**) as high oxidation state surrogates for tryptophan and proline. The substituted tryptamine is not commercially available, and its synthesis has not been reported. Thus retrosynthetic analysis led us to the substituted indole (**46**). This substituted indole is commercially available but not radially. It is also very expensive (~ \$700/gm), we envisioned the synthesis of the indole from commercially available substituted benzyl aldehyde (**48**) by using Hemetsberger indole synthesis.

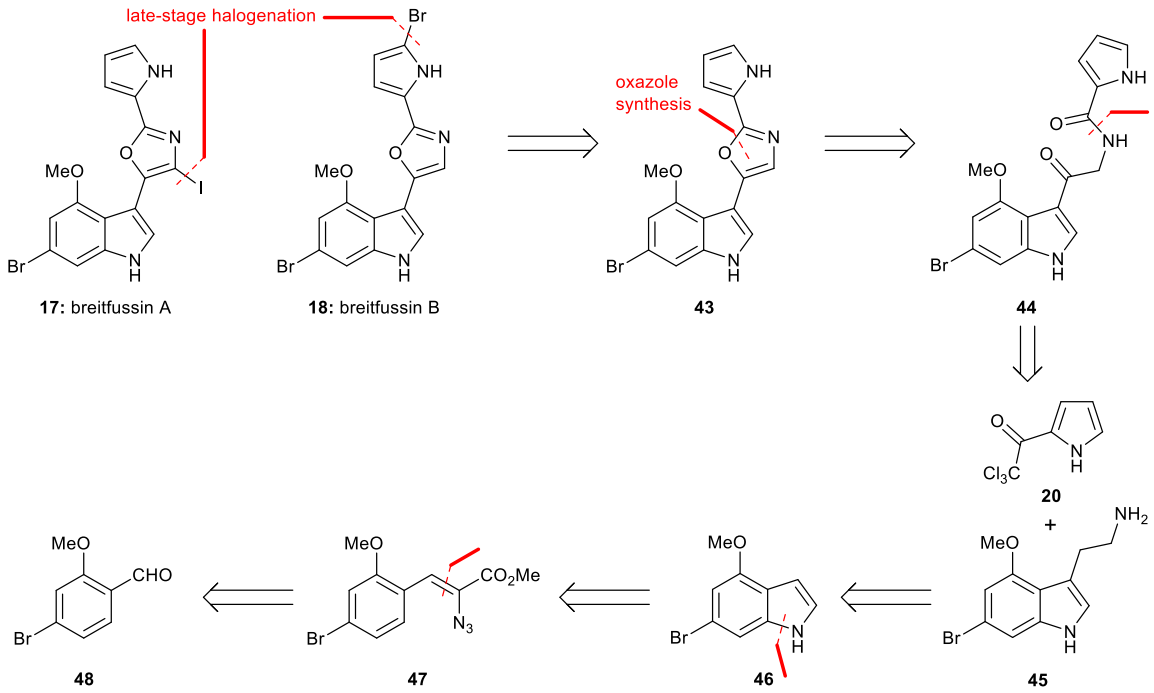


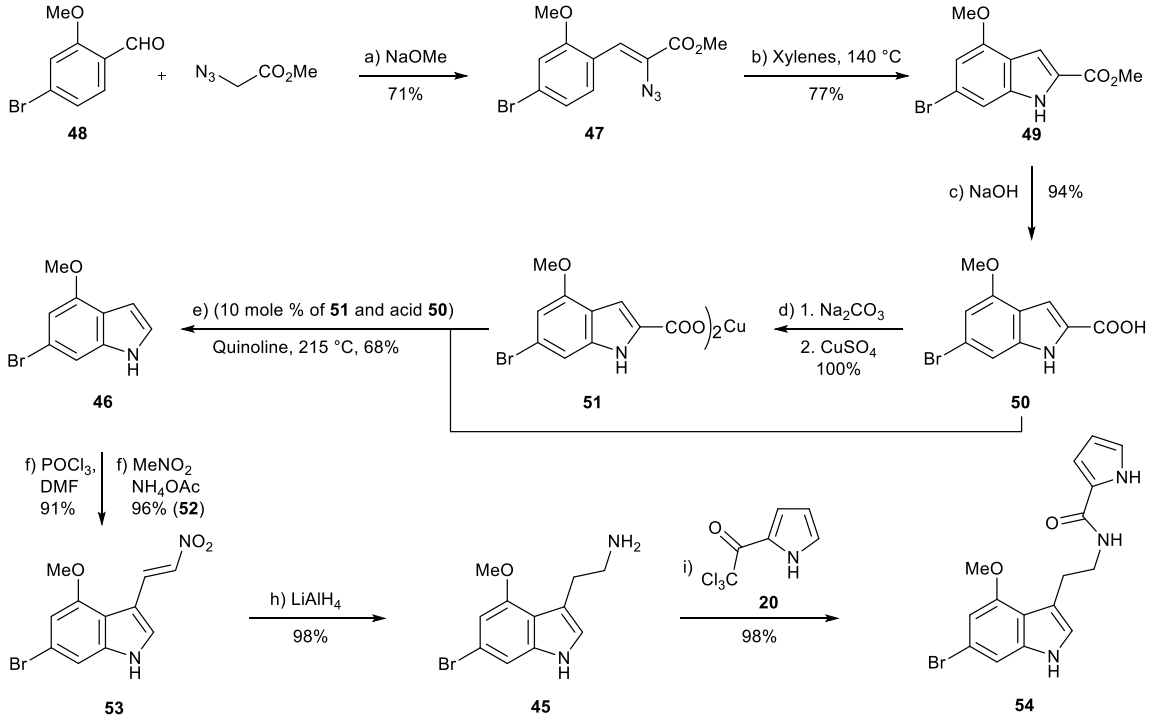
Figure 3.2. Retrosynthetic analysis of breitfussins

3.3 Synthesis of substituted amide 54

For the synthesis of substituted indole **46** (Scheme 3.1), we have used Hemetsberger indole synthesis because it has been used for the synthesis of similar indole.[8] Furthermore, this route was chosen because it had been employed for synthesis of indole on a gram scale and required only one chromatographic separation. Thus, commercially-available aldehyde **48** was condensed with methyl azidoacetate, which was obtained by reaction between chloroacetate and azide, to form azido ester **47**. On cooling, azido ester precipitates out from the reaction mixture. On scale-up of this reaction, we determined that yield was irreproducible. After careful analysis of reaction byproduct, we found that on a large scale, product azido ester **47** was undergoing decomposition by

hydrolysis when the reaction was quenched with ice at room temperature. To get reproducible yield, the reaction mixture was cooled to 0 °C at first, and then ice-water was added. This change in quenching procedure resulted in the formation of azidoester **47** in 71% yield reproducibly. Thermolysis of azido ester **47** in xylenes under degassed (absence of oxygen) condition resulted, a Hemetsberger indole synthesis;[9] 2-methyl carboxy indole **49.** It was crystallized out in 77% yield upon cooling of the reaction mixture. Saponification of the methyl ester of intermediate **49** afforded carboxylic acid **50** in 94% yield without purification. For the decarboxylation of acid to produce indole, ten percent of carboxylic acid **50** was converted into the corresponding copper(II) salt **51**, which served as a catalyst for the thermal decarboxylation[10] of carboxylic acid **50** to deliver indole **46** in 68% yield after column chromatography. This is the first column chromatography used for the purification of indole over five steps. Vilsmeier–Haack formylation of indole **46** afforded a 3-substituted aldehyde **52** in 91% yield after column chromatography. The obtained 3-substituted aldehyde **52** was subjected to a Henry reaction with nitromethane. It produced nitro-indole derivative **53** in 96% yield as crystalline compound after cooling to room temperature. The subsequent reduction of nitro-indole derivative **53** with lithium-aluminiumhydride resulted in substituted tryptamine (**45**) in 98% yield. Both reactions proceeded sufficiently cleanly that no purification was necessary. The reaction substituted tryptamine **45** with 2-(trichloroacetyl)pyrrole (**20**) resulted in the formation of substituted amide **54** in 98% yield without purification.

Scheme 3.1. Synthesis of substituted amide **54**[a]



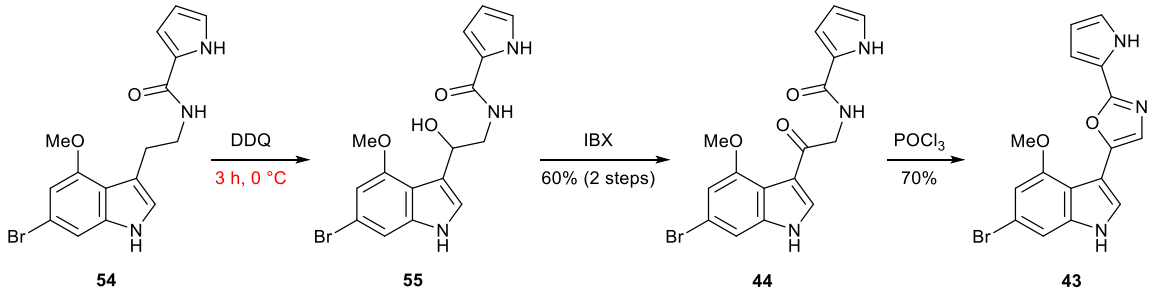
[a] Reagents and conditions: a) **48** (1.0 equiv), then NaOMe (5.0 equiv), MeOH, 0 °C for 30 min then 23 °C for 2 h, 71%; b) **49** xylene, 140 °C, 30 min, 77%; c) 3 M aq NaOH reflux for 6.0 h, then HCl, 94%; d) Na_2CO_3 (0.5 equiv) heat to dissolve then $CuSO_4$; e) (10 mole % of **51** and acid **50**) then heated to 215 °C for 5.0 h, 68%; f) $POCl_3$ (1.3 equiv) DMF at 0 °C for 15 min then **46**, 30 min at 0 °C then NaOH to make basic, 100 °C for 30 min, 91%; g) NH_4OAc (1.0 equiv), nitromethane, 100 °C for 12 h, 96%; h) $LiAlH_4$ (6.0 equiv), at 0 °C for 15 min then 70 °C for 5.0 h, 98%; i) **20** (1.02 equiv), DMF, 23 °C for 6.0 h; $LiAlH_4$ = lithium-aluminiumhydride.

3.4 Synthesis of oxazole 43

In our synthesis of breitfussin model compound **23**, amide **21** was oxidized by an aqueous solution of DDQ to yield ketoamide **22** (Scheme 2.1) with out any problem but oxidation of amide **54** by an aqueous solution of DDQ to yield ketoamide **44** (Scheme 3.2) was not to the optimal level. Unfortunately, a small amount of debrominated ketoamide **56** (<10%) was also formed, and this undesired contaminant proved chromatographically inseparable both at this stage and at later stages in the synthesis.

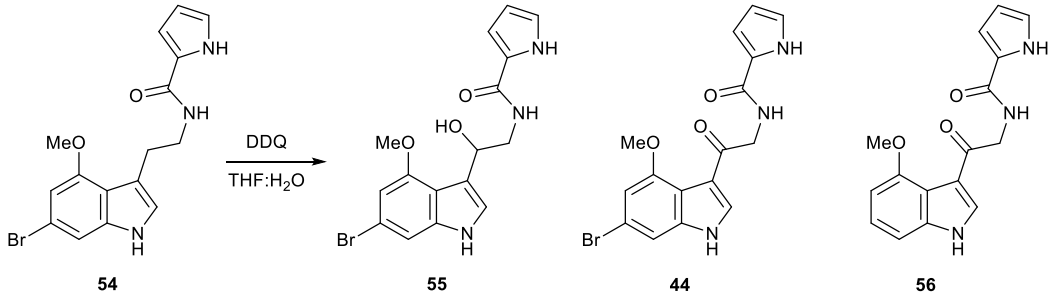
The debromination yield was minimized by adjusting the solvent composition and tuning the substrate and reagent concentrations, but we were unsuccessful in shutting down the debromination pathway during the DDQ oxidation of amide **54** into ketoamide **44**. After monitoring reaction carefully over time with H NMR, we noticed that there was no debromination during the initial oxidation of amide **54** into benzylic alcohol **55 (**Table 3.1**)**, and the crude material could be cleanly oxidized by IBX to form ketoamide **44** (Scheme 3.2) without formation of debrominated side product **56**. During monitoring of debrominated product with NMR, we did not calculate the amount of benzylic alcohol **55** or ketoamide **44** produced because NMR peaks of these compounds overlap and could not be calculated separately. 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 **44** gave oxazole **43** in 70% yield after column chromatography.

Scheme 3.2. Synthesis of substituted oxazole **43**[a]



[a] Reagents and conditions: a) DDQ (3.0 equiv), THF:H_2O (9:1), 0 °C for 3.0 h; b) IBX (3.0 equiv), THF, 23 °C for 3.0 h, 60% over 2 steps; c) $POCl_3$ in pyridine (1:5) dropwise over 5 minutes at 0 °C for 1.5 h then to 23 °C for 1.5 h, 71%; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; IBX = 2-iodoxybenzoic acid.

Table 3.1. Monitoring of debromination keto-amide **56** by NMR analysis

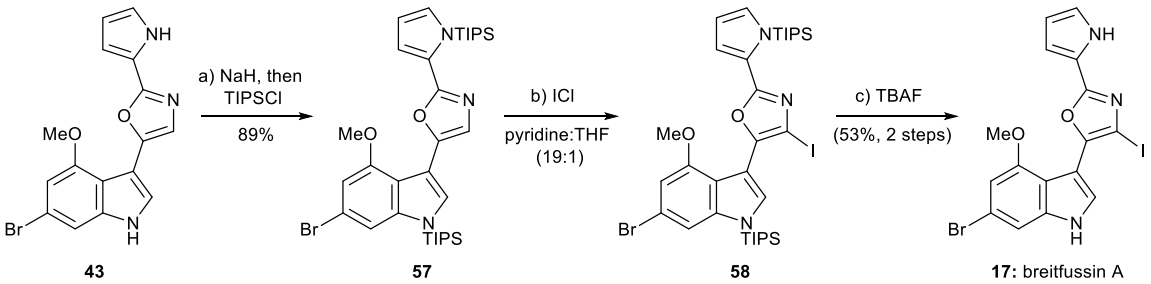


Entry	Time (h)	Temperature °C	% of keto-amide **44**	% of debrominated keto-amide **56**
1	1.0	0	ND	0
2	1.5	0	ND	0
3	2.0	0	ND	0
4	2.5	0	ND	0
5	3.0	0	ND	0
6	3.5	0	ND	>2
7	6.0	0	51	9

3.5 Synthesis of breitfussin A (17)

To follow the method developed on our model compound **23** to carry out iodination on oxazole, we converted oxazole **43** into *N*-TIPS oxazole **57** in 89% yield by using sodium hydride and TIPSCl. The *N*-TIPS oxazole **57** was subjected to iodine monochloride (ICl) in pyridine: THF (19:1) and subsequent deprotection by TBAF to furnish breitfussin A (**17**) in 53% yield over two steps. This iodination was carried out in a very careful way to avoid over iodination. At first reaction mixture was cooled to −40 °C in pyridine: THF (19:1) mixture (THF was used to avoid freezing of pyridine) then 0.8 equivalent of ICl was added drop by drop over the period of 30 min, and the reaction was warmed to 0 °C over three hours. 0.5 equivalent of ICl was added at 0 °C and then quenched after 5 minutes with a saturated solution of sodium thiosulfate. The NMR spectroscopic data for synthetic breitfussin A (**17**) was identical to that reported for the natural substance.[11]

Scheme 3.3. Synthesis of breitfussin A (**17**) [a]



[a] Reagents and conditions: a) NaH (3.0 equiv), DMF, 0 °C for 20 min then TIPCl then 23 °C for 1.0 h, 89%; b) ICl (0.8 equiv), pyridine:THF (19:1) , −40 °C to 0 °C over 3.0 h,

then ICl (0.5 equiv) and quenched in 5 min; c) TBAF (3.2 equiv) THF at 0 °C for 10 min, 53 % over 2 steps; IC = Iodine monochloride; TIPCl = Triisopropylsilyl chloride; TBAF = Tetra-*n*-butylammonium fluoride.

3.6 Synthesis of breitfussin B (18) and Isomerism study

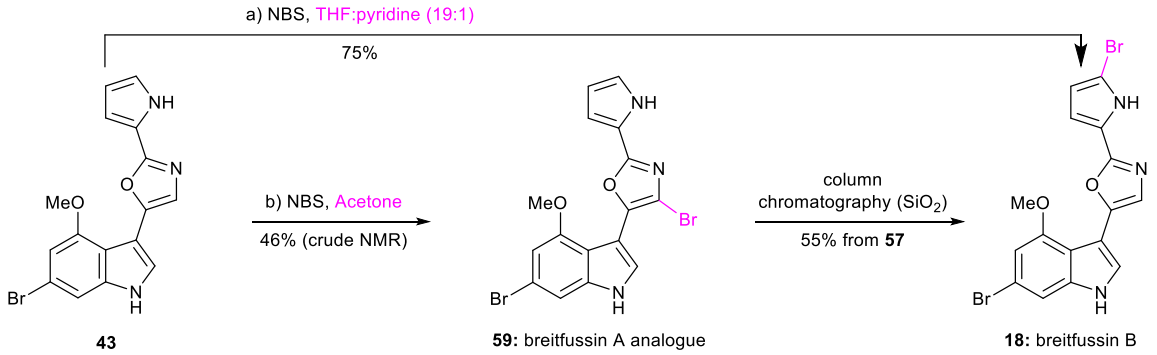
To synthesize breitfussin B (**18**), we followed the bromination condition developed in our model study; intermediate **43** was subjected to the action of NBS in a 19:1 mixture of THF and pyridine to deliver breitfussin B (**18**) in 75% yield after column chromatography. The NMR spectroscopic data for synthetic breitfussin B (**18**) was identical to that reported for the natural substance.[11,12]

Here we decided to get a bromo analog of breitfussin A by using our develop method for bromination of oxazole on model compound (**23**). The oxazole **43** was brominated in acetone in order to generate bromooxazole **59**, an analog of breitfussin A (**17**). 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 (**18**) (29% yield) and a dibrominationed product **60** (16% yield). The crude mixture was stable for at least a week, but flash column chromatography in silica gel isomerized bromooxazole **59** into bromopyrrole **18** (i.e., breitfussin B).[11] 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 (**18**); the facile silica gel-promoted isomerization provides access to breitfussin B (**18**) even if the bromination conditions favor bromooxazole **59**.

Unable to isolate pure bromooxazole **59**, we probed the mechanism of isomerization by TLC analysis. As shown in Figure 3.1, compounds **43** and **60** were not formed from bromooxazole **59** during its isomerization into bromopyrrole **18**, suggesting a unimolecular bromine transfer. A mixture of compounds **43** and **60** did not equilibrate on silica (see Supporting Information), further supporting the unimolecular nature of the bromine transfer. We also explored other surfaces like alumina (neutral, acidic and basic), celite and effect of acid and base on the rate of isomerization. In most of the cases, the rate of isomerization did not change to a significant amount. The bromine migration does not appear to be dependent on light or air.

We subjected breitfussin A (**17**) to similar conditions, but surprisingly it did not undergo isomerization. On heating to higher temperature breitfussin A undergoes decomposition without isomerization. The indole methoxy group appears to be necessary for bromine migration; model compounds **24** and **25** did not equilibrate on silica even at 150 °C. This observation sheds some light on the biosynthesis of breitfussin A (**17**) and B (**18**). The most likely same enzyme is responsible for halogenation (i.e., bromination and iodination) on oxazole of compound oxazole **43**, then bromo analog **60** undergoes isomerization to produce breitfussin B (**18**) while iodinated oxazole results breitfussin A (**17**) without isomerization.

Scheme 3.4. Synthesis of breitfussin B (**18**) [a]



[a] Reagents and conditions: a) NBS (1.0 equiv), THF:pyridine (19:1), 0 °C for 30 min, 75%; b) NBS (1.0 equiv), acetone, 0 °C for 10 min then (0.5 equiv) 0 °C for 5.0 min; NBS = *N*-bromo succinamide.

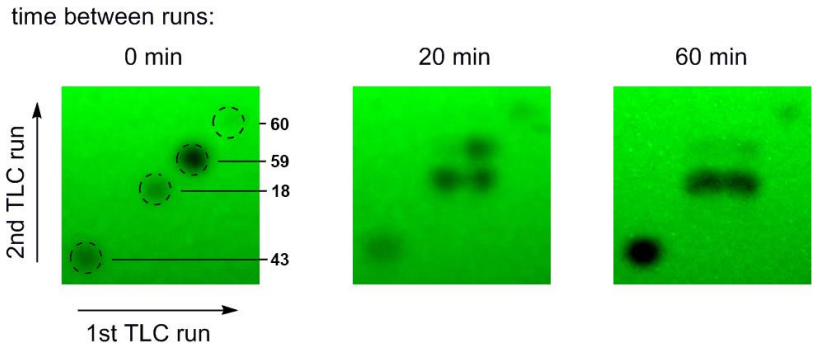


Figure 3.3. TLC investigation of silica-mediated isomerization

3.7 Conclusion

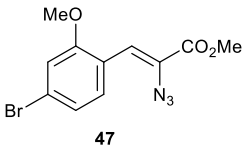
In summary, we have used our developed method of tunable site-selective halogenation of the breitfussin core to the synthesis of breitfussin A (**17**) with use of only one protecting group, and a protecting group-free synthesis of breitfussin B (**18**).

Bromooxazole **59** was synthesized by simply changing the bromination solvent, but it isomerized into breitfussin B (**18**) during column chromatography. Our synthesis provided breitfussin A (**17**) in 6.5% overall yield over 14 reaction steps and breitfussin B (**18**) in 9.2% overall yield over 12 reaction steps from commercial starting materials and 5,7 chromatographic purifications respectively. The NMR comparison of isolated natural products and synthesized molecules were found to be same.

3.8 General Procedures

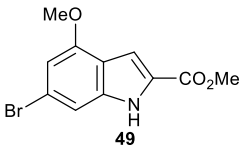
Unless otherwise noted, all reactions were performed with stirring under an argon atmosphere under anhydrous conditions. Reagents were purchased at the most economical grade. Dry tetrahydrofuran (THF) and *N*, *N*-dimethylformamide (DMF) were obtained by passing HPLC-grade solvents through commercial solvent purification systems. NBS was recrystallized from acetic acid. Unless otherwise noted, all other chemicals were used as received, without purification. Flash column chromatography was performed using Grace Davison Davisil silica gel (60 Å, 35–70 μm). Yields refer to chromatographically- and spectroscopically- (^{1}H NMR) homogeneous samples. Thin-layer chromatography (TLC) was performed on Grace Davison Davisil silica TLC plates using UV light and common stains for visualization. NMR spectra were calibrated using a residual undeuterated solvent as an internal reference. Apparent couplings were determined for multiplets that could be deconvoluted visually.

3.9 Selected Experimental, Physical, and Spectral Data



47

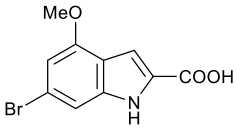
Azidoester 47. To a solution of methyl azidoacetate and aldehyde **48** (7.50 g, 35 mmol, 1.0 equiv) in 75 mL of methanol at 0 °C was added a methanolic sodium methoxide solution [prepared by dissolving solid sodium metal (4.01 g, 174 mmol, 5.0 equiv) in 100 mL of methanol at 0 °C] dropwise via cannula over 15 min. The reaction mixture was stirred at 0 °C for 30 min, then warmed to 23 °C over 2 hours. Ice water (100 g) was added to the reaction mixture, which was then immediately filtered. The precipitate was dissolved in EtOAc (300 mL), dried over Na_2SO_4, and concentrated to give pure azidoester **47** (7.71 g, 71% yield) as a white solid. **47**: R_f = 0.61 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 2951, 2853, 2124, 1713, 1585, 1481 cm^{-1}; NMR (600 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.5 Hz, 1H), 7.27 (s, 1H), 7.13 (dd, J = 8.5, 1.8 Hz, 1H), 7.02 (d, J = 1.8 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.2, 158.1, 131.7, 125.6, 124.5, 123.7, 121.2, 118.4, 114.3, 56.1, 53.1 ppm; HRMS (ESI-QTOF): compound fragments.



49

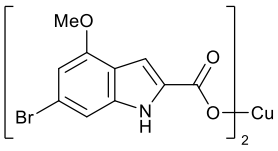
Indole 49. A deoxygenated solution of azido ester **47** (7.60 g, 24 mmol) in 50 mL of xylenes was added dropwise via cannula over 15 min to 50 mL of xylenes that had been pre-heated to 140 °C. The reaction mixture was maintained at 140 °C for 30 minutes, then cooled to 0 °C. The resultant precipitate was collected by centrifuge, then washed with hexanes (2 × 100 mL) to give pure indole **49** (5.31 g, 77% yield) as a white solid. **49**: R_f = 0.42 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 3303, 1701, 1460, 1447 cm^{-1}; ^1H NMR (600 MHz,

$CDCl_3$): δ = 8.82 (s, 1H), 7.28 (dd, *J* = 2.2, 0.8 Hz, 1H), 6.63 (d, *J* = 1.2 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 162.3, 154.9, 138.3, 126.3, 119.8, 118.1, 108.00, 106.8, 104.5, 55.8, 52.2 ppm; HRMS (ESI-QTOF): calcd for $C_{11}H_{11}BrNO_3^+$ [M + H^+]: 283.9917, found: 283.9915.



50

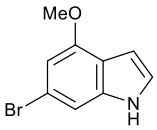
Carboxylic acid 50. A suspension of methyl ester **49** (7.00 g, 25 mmol) in 500 mL of 3 M aqueous NaOH was deoxygenated and heated to 100 °C for 6 hours. The reaction mixture was cooled to 0 °C, and 4 M aqueous HCl was added until the solution became acidic. The mixture was extracted with EtOAc (2 × 500 mL), and the organic layer was washed with saturated NaCl solution (500 mL), dried over Na_2SO_4, and concentrated to give pure carboxylic acid **50** (6.25 g, 94% yield) as a yellow solid. **50**: R_f = 0.46 (80% EtOAc / hexanes); IR (thin film): ν_{max} = 3395, 3318, 2930, 1716, 1580, 1532 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 13.02 (s, 1H), 11.91 (s, 1H), 7.19 (s, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 6.67 (d, *J* = 1.1 Hz, 1H), 3.90 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 162.3, 154.2, 138.5, 127.8, 117.7, 117.0, 109.1, 104.6, 103.4, 55.7 ppm; HRMS (ESI-QTOF): calcd for $C_{10}H_9BrNO_3^+$ [M + H^+]: 269.9766, found: 269.9747.



51

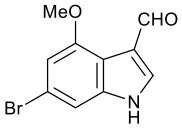
Copper carboxylate 51. To a solution of carboxylic acid **50** (1.00 g, 3.7 mmol, 2.0 equiv) and sodium carbonate (196 mg, 1.8 mmol, 1.0 equiv) in 30 mL of water at 70 °C was added a solution of copper(II) sulfate pentahydrate (462 mg, 1.8 mmol, 1.0 equiv) in 30 mL of water. The reaction mixture was cooled to 0 °C, and the resultant precipitate was filtered

and dried in a vacuum desiccator over P_2O_5 to give copper carboxylate **51** in quantitative yield as an off-white solid.



46

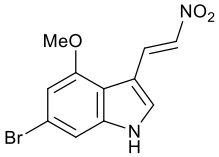
Indole 46. To a solution of carboxylic acid **50** (4.00 g, 15 mmol, 1.0 equiv) in 60 mL of distilled quinoline was added copper carboxylate **51** (0.90 g, 1.5 mmol, 0.10 equiv). The reaction mixture was deoxygenated, then stirred in a preheated 215 °C silicone oil bath. (**Caution:** This temperature is above the flash point of mineral oil.) After heating for 5 hours, the reaction mixture was cooled to room temperature and diluted with 500 mL of 10% aqueous HCl solution. The mixture was extracted with EtOAc (2 × 300 mL), and the combined organic layers was washed with water (200 mL) and saturated NaCl solution (400 mL), dried over Na_2SO_4, and concentrated to give a yellow solid. Flash column chromatography (10% EtOAc / hexanes) gave pure indole **46** (2.75 g, 68% yield based on 18.0 mmol theoretical yield) as a yellow solid. **46**: R_f = 0.44 (20% EtOAc / hexanes); IR (thin film): ν_{max} = 3424, 2940, 2839, 1581, 1494 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ = 8.13 (s, 1H), 7.18 (s, 1H), 7.08 (dd, *J* = 2.9, 2.6 Hz, 1H), 6.65 (d, *J* = 1.3 Hz, 1H), 6.62 (ddd, *J* = 3.2, 2.1, 0.8 Hz, 1H), 3.94 (s, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 153.7, 137.5, 123.1, 117.7, 115.8, 107.6, 104.0, 100.3, 55.7 ppm; HRMS (ESI-QTOF): calcd for $C_9H_9BrNO^+$ [M + H^+]: 225.9862, found: 225.9861.



52

Aldehyde 52. To 8 mL of DMF at 0 °C was added freshly distilled $POCl_3$ (0.80 mL, 8.7 mmol, 1.3 equiv). The reaction mixture was stirred for 15 min, and then a solution of indole **46** (1.50 g, 6.7 mmol, 1.0 equiv)

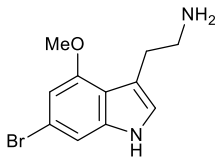
in 8 mL of DMF was added dropwise over 10 min. The resultant mixture was stirred for 30 min at 0 °C, then heated to 40 °C for one hour. The reaction mixture was then cooled to 0 °C, and 1.0 M aqueous NaOH was added dropwise until the mixture became basic. The reaction mixture was heated to 100 °C for 30 min and then cooled to room temperature, diluted with water (300 mL), and extracted with EtOAc (2 × 200 mL). The organic layer was washed with saturated NaCl solution (200 mL), dried over Na_2SO_4, and concentrated to give a white solid. Flash column chromatography (40% EtOAc / hexanes) gave pure aldehyde **52** (1.53 g, 91% yield) as a white solid. **52**: R_f = 0.41 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3226, 2958, 2862, 1644, 1516, 1437 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.29 (s, 1H), 10.27 (s, 1H), 8.06 (s, 1H), 7.31 (d, J = 1.4 Hz, 1H), 6.89 (d, J = 1.1 Hz, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 186.0, 154.3, 138.2, 130.5, 118.2, 115.6, 114.7, 108.6, 105.9, 55.9 ppm; HRMS (ESI-QTOF): calcd for $C_{10}H_9BrNO_2^+$ [M + H^+]: 253.9811, found: 253.9806.



53

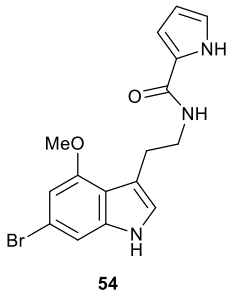
Nitroalkene 53. To a solution of aldehyde **52** (800 mg, 3.2 mmol, 1.0 equiv) in 25 mL of nitromethane at 23 °C was added ammonium acetate (192 mg, 3.2 mmol, 1.0 equiv). The reaction mixture was heated to 100 °C for 2 hours, then cooled to 0 °C for 12 hours. The reaction mixture was filtered, and the precipitate was washed with 25 mL of toluene. The combined organic layers was concentrated to give pure nitroalkene **53** (900 mg, 96% yield). **53**: R_f = 0.46 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3297, 2960, 2885, 1598, 1513, 1461 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.14 (s, 1H), 8.50 (d, J = 13.4 Hz, 1H), 8.26 (s, 1H), 8.07 (d, J = 13.4 Hz, 1H), 7.29 (dd, J = 0.6, 0.7 Hz, 1H), 6.97 (t, J = 1.3 Hz, 1H),

3.97 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.0, 139.1, 134.7, 132.9, 132.4, 116.2, 114.4, 108.7, 107.9, 106.0, 56.0 ppm; HRMS (ESI-QTOF): calcd for $C_{11}H_{10}BrN_2O_3^+$ [M + H$^+$]: 296.9869, found: 296.9871.



45

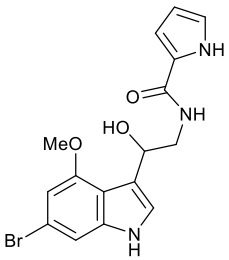
Tryptamine 45. To a solution of nitroalkene **53** (850 mg 2.9 mmol, 1.0 equiv) in 25 mL of THF at 0 °C was added $LiAlH_4$ (651 mg, 17.2 mmol, 6.0 equiv) portionwise over 15 min. Then reaction mixture was heated to 70 °C for 5 hours, then cooled to 0 °C. Excess $LiAlH_4$ was quenched by dropwise addition of 0.25 M aqueous NaOH until no further gas evolution was observed. The reaction mixture was diluted with EtOAc (300 mL), filtered through Celite, and concentrated to give pure tryptamine **45** (755 mg, 98% yield) as a tan solid. **45**: R_f = 0.23 (77% CH_2Cl_2 / 20% MeOH / 3% Et_3N); IR (thin film): ν_{max} = 3422, 2930, 1610, 1579, 1492 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.91 (s, 1H), 7.10 (d, J = 1.5 Hz, 1H), 6.97 (s, 1H), 6.55 (d, J = 1.5 Hz, 1H), 3.84 (s, 3H), 2.81 (m, 2H), 2.76 (m, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.6, 138.2, 122.2, 116.0, 113.8, 113.2, 107.5, 102.4, 55.5, 43.2, 30.9 ppm; HRMS (ESI-QTOF): calcd for $C_{11}H_{14}BrN_2O^+$ [M + H$^+$]: 269.0284, found: 269.0282.



54

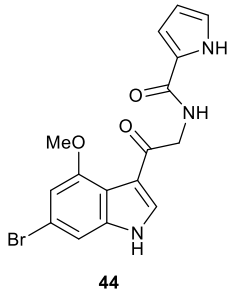
Amide 54. To a solution of tryptamine **45** (1.00 g, 3.73 mmol, 1.00 equiv) in 2 mL of DMF was added 2-(trichloroacetyl)pyrrole (**20**, 805 mg, 3.80 mmol, 1.02 equiv). The mixture was stirred for 6 hours, then diluted with CH_2Cl_2 (200 mL). The organic layer was washed with water (2 × 100 mL) and saturated NaCl solution (100 mL), then

dried over anhydrous $MgSO_4$ and concentrated to give amide **54** contaminated with a trace of 2-(trichloroacetyl)pyrrole (**3**) as a brown solid (1.33 g, 98%). This material was used unpurified in the next reaction. An analytical sample was purified by flash column chromatography (60% EtOAc / hexanes) for characterization. **54**: R_f = 0.45 (80% EtOAc / hexanes); IR (thin film): ν_{max} = 3400, 3230, 1655, 1561, 1493 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.37 (s, 1H), 10.92 (s, 1H), 7.97 (t, *J* = 5.7 Hz, 1H), 7.11 (d, *J* = 1.4 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 6.82 (dt, *J* = 2.6, 1.4 Hz, 1H), 6.72 (ddd, *J* = 3.4, 2.5, 1.5 Hz, 1H), 6.57 (d, *J* = 1.4 Hz, 1H), 6.05 (dt, *J* = 3.5, 2.4 Hz, 1H), 3.86 (s, 3H), 3.48 (q, *J* = 6.9 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 160.5, 154.6, 138.1, 126.5, 122.1, 121.0, 116.0, 113.9, 112.6, 109.6, 108.4, 107.5, 102.5, 55.5, 26.8 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{17}BrN_3O_2^+$ [M + H^+]: 362.0499, found: 362.0507.



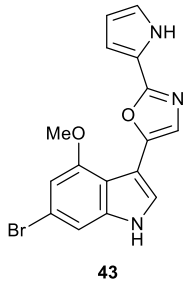
55

Alcohol 55. To a solution of unpurified amide **54** (363 mg, 1.0 mmol, 1.0 equiv) in 20 mL of a THF:H_2O mixture (9:1) at 0 °C was added DDQ (682 mg, 3.0 mmol, 3.0 equiv). The resultant red solution was stirred at 0 °C for 3 hours, then diluted with EtOAc (300 mL). The organic layer was washed with a saturated $NaHCO_3$ solution (4 × 200 mL) until the aqueous layer remained colorless. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated to give crude alcohol **55** as a brown solid. This material was used in next step without purification.



44

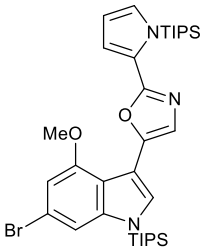
Ketoamide 44. To a solution of crude alcohol **55** (1.0 mmol theoretical, 1.0 equiv) in 5 mL of THF was added a solution of IBX (842 mg, 3.0 mmol, 3.0 equiv) in 5 mL of DMSO. The reaction mixture was stirred at 23 °C for 3 hours, then diluted with EtOAc (300 mL). The organic layer was washed with saturated $NaHSO_3$ solution (200 mL), water (300 mL), and saturated NaCl solution (300 mL), then dried over $MgSO_4$ and concentrated to give a brown solid. Flash column chromatography (80% EtOAc / hexanes) gave pure ketoamide **55** (227 mg, 60% over two steps) as a brown solid. **55**: R_f = 0.34 (80% EtOAc / hexanes); IR (thin film): ν_{max} = 3413, 3210, 1635, 1558, 1521, 1460 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.07 (s, 1H), 11.45 (s, 1H), 8.20 (t, J = 5.8 Hz, 1H), 8.17 (d, J = 3.0 Hz, 1H), 6.87 (dt, J = 2.6, 1.5 Hz, 1H), 6.83 (ddd, J = 3.8, 2.5, 1.5 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 6.11 (dt, J = 3.5, 2.4 Hz, 1H), 4.63 (d, J = 5.8 Hz, 2H), 3.89 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.2, 160.8, 153.9, 139.0, 132.6, 126.2, 121.3, 115.8, 115.7, 113.4, 110.1, 108.6, 108.1, 105.8, 55.7, 47.4 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{15}BrN_3O_3^+$ [M + H^+]: 376.0291, found: 376.0280.



43

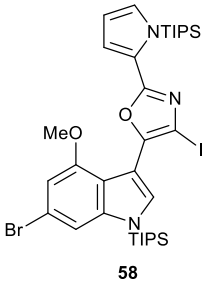
Oxazole 43. To a solution of ketoamide **44** (200 mg, 0.53 mmol) in 2.5 mL of pyridine at 0 °C was added $POCl_3$ (0.5 mL) dropwise over 5 minutes. The mixture was stirred at 0 °C for 1.5 hours, then at 23 °C for 1.5 hours. The mixture was diluted with EtOAc (250 mL), washed with cold saturated $NaHCO_3$ solution (250 mL), water (250 mL), and saturated NaCl solution (250 mL), then dried over $MgSO_4$ and concentrated to give a brown solid. Flash column

chromatography (50% EtOAc / hexanes) gave pure oxazole **43** (134 mg, 71%) as a tan solid. **43**: R_f = 0.27 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3133, 2928, 2840, 1618, 1605, 1494 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.77 (s, 1H), 11.69 (s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.34 (s, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 6.96 (dt, *J* = 2.6, 1.5 Hz, 1H), 6.73 (d, *J* = 1.5 Hz, 1H), 6.72 (m, 1H), 6.20 (dt, *J* = 3.4, 2.4 Hz, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 154.2, 153.7, 145.7, 138.5, 123.3, 122.7, 121.5, 120.0, 115.3, 112.7, 109.32, 109.3, 108.0, 104.1, 104.0, 55.6 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{13}BrN_3O_2^+$ [M + H^+]: 358.0186, found: 358.0185.



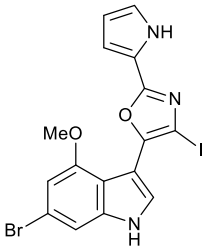
57

***N*-TIPS amine 57.** To a solution of oxazole **43** (120 mg, 0.33 mmol, 1.0 equiv)) in 1 mL DMF at 0 °C was added NaH (60 % dispersion in mineral oil, 40 mg, 1.0 mmol, 3.0 equiv). The mixture was stirred at 0 °C for 20 minuties, then TIPSCl (215 μL, 1.0 mmol, 3.0 equiv). The mixture was stirred at 23 °C for one hour. The compound was extracted in diethyl ether (50 mL). The organic layer was washed with water (50 mL), saturated solution of NaCl (50 mL) then dried over $MgSO_4$ and concentrated to give a white solid. Flash column chromatography (2 % EtOAc / hexanes) gave **57** (200 mg, 89% yield, compound contained 9% TIPS-OH as impurity and was not fully characterized, yield was calculated from H NMR analysis) as a white solid. **57**: R_f = 0.79 (20 % EtOAc / hexanes); IR (thin film): ν_{max} = 2991, 2957, 1749, 1730, 1601, 1476, cm^{-1}; HRMS (ESI-QTOF): calcd for $C_{34}H_{53}BrN_3O_2Si_2^+$ [M + H^+]: 670.2860, found: 670.2863.



58

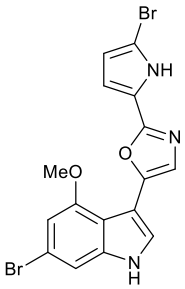
Iodo-oxazole 58. To a solution of TIPS amine **57** (150 mg, 0.24 mmol, 1.0 equiv) in 1 mL of pyridine:THF (19:1) at –40 °C was added ICl (1.0 M in CH_2Cl_2, 192 μL, 0.19 mmol, 0.8 equiv) drop by drop over 30 min, then reaction was warmed to 0 °C over 3 hours. Again ICl (1.0 M in CH_2Cl_2, 120 μL, 0.12 mmol, 0.5 equiv) was added. After 5 min reaction mixture was quenched by addition of 10 wt % Na_2SO_3 (10 mL). The mixture was extracted with ether (25 mL). The organic layer was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over $MgSO_4$ and concentrated to give crude iodooxazole **33** as a yellow solid.



17: breitfussin A

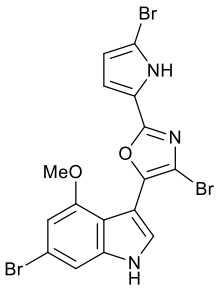
Breitfussin A (17). To a solution of crude iodooxazole **58** (0.24 mmol theoretical, 1.0 equiv) in 2 mL of THF at 0 °C was added TBAF (1.0 M in THF, 768 μL, 0.77 mmol, 3.2 equiv). The mixture was stirred at 0 °C for 10 minutes, then diluted with ether (50 mL). The organic layer was washed with water (2 × 50 mL) and saturated NaCl solution (50 mL), then dried over $MgSO_4$ and concentrated to give a tan solid. Flash column chromatography (25 % EtOAc / hexanes) gave pure breitfussin A **17** (62 mg, 53 % yield over two steps) as a white solid. **17**: R_f = 0.67 (50 % EtOAc / hexanes); IR (thin film): ν_{max} = 3463, 3167, 2952, 1528, 1407 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 11.95 (s, 1H), 11.76 (s, 1H), 7.66 (d, J = 2.69 Hz, 1H), 7.29 (d, J = 1.47 Hz, 1H), 6.96 (1H), 6.75 (d, J = 1.5 Hz, 1H), 6.68 (m, 1H), 6.20 (m, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 157.4, 154.1, 146.9, 138.4, 127.7, 122.8, 119.7, 115.7, 115.5, 110.4, 110.0, 108.4, 104.8, 101.2, 84.3,

56.2 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{12}BrIN_3O_2^+$ [M + H^+]: 483.9258, found: 483.9255.



18: breitfussin B

Breitfussin B (18). To a solution of oxazole **43** (25 mg, 0.07 mmol, 1.0 equiv) in 2 mL of a THF:pyridine mixture (19:1) at 0 °C was added NBS (13 mg, 0.07 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 30 min, then diluted with EtOAc (25 mL). The organic phase was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over Na_2SO_4 and concentrated to give a white solid. Flash column chromatography (35% EtOAc / hexanes) gave pure bromopyrrole **18** (21 mg, 75% yield) as a white solid. **18**: R_f = 0.66 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3445, 3170, 2930, 1510, 1418 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.53 (s, 1H), 11.72 (s, 1H), 7.76 (d, *J* = 2.6 Hz, 1H), 7.35 (s, 1H), 7.25 (d, *J* = 1.5 Hz, 1H), 6.73 (d, *J* = 1.5 Hz, 1H), 6.71 (d, *J* = 3.7 Hz, 1H), 6.26 (d, J = 3.7 Hz, 1H), 3.95 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.6, 153.0, 146.0, 138.5, 123.6, 122.7, 121.8, 115.4, 112.7, 111.7, 110.7, 108.0, 104.0, 103.9, 101.9, 55.6 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{12}Br_2N_3O_2^+$ [M + H^+]: 435.9291, found: 435.9287.



60

Tribromide 60. (Attempted synthesis of bromooxazole **59**.) To a solution of oxazole **43** (25 mg, 0.07 mmol, 1.0 equiv) in 2 mL of acetone at 0 °C was added NBS (12 mg, 0.07 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 10 minutes, then extra NBS (7 mg, 0.04 mmol, 0.5 equiv) was added and the mixture was stirred for an

additional 5 minutes at 0 °C. The reaction was quenched by addition of 10 wt% Na_2SO_3 (5 mL), then extracted with EtOAc (25 mL). The organic phase was washed with water (25 mL) and saturated NaCl solution (25 mL), then dried over $MgSO_4$ and concentrated to give a brown solid. Flash column chromatography (20% EtOAc / hexanes) gave pure tribromide **60** (5 mg, 14% yield) as a tan solid along with breitfussin B (**18**) (17 mg, 55%). **60**: R_f = 0.70 (50% EtOAc / hexanes); IR (thin film): ν_{max} = 3453, 3167, 1534, 1459 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ = 12.38 (s, 1H), 11.83 (s, 1H), 7.67 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 1.5 Hz, 1H), 7.13 (t, J = 2.0 Hz, 1H), 6.74 (m, 2H), 3.78 (s, 3H) ppm; ^{13}C NMR (150 MHz, DMSO-d_6): δ = 153.9, 153.6, 142.4, 137.9, 127.2, 122.4, 120.0, 115.4, 114.9, 113.2, 111.5, 108.0, 104.4, 99.6, 96.2, 55.8 ppm; HRMS (ESI-QTOF): calcd for $C_{16}H_{11}Br_3N_3O_2^+$ [M + H^+]: 514.8329, found: 514.8320.

TLC Images: TLC plates were eluted using 35% EtOAc / hexanes and visualized under a 254 nm UV lamp.

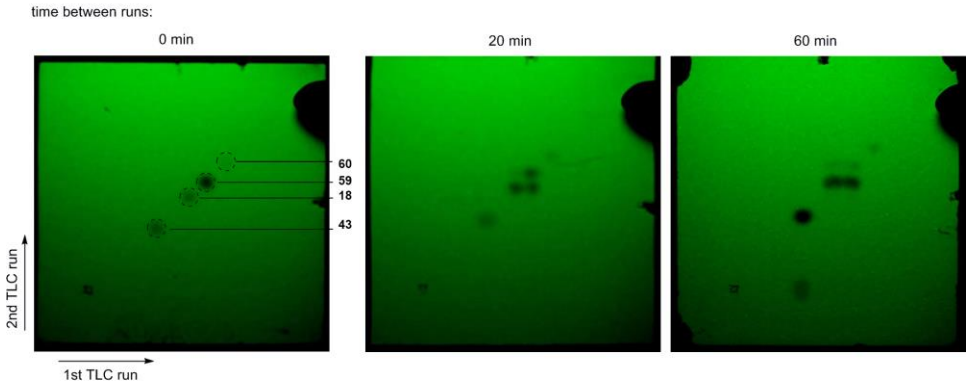


Figure S1. Time-dependent 2D TLC behavior of crude bromooxazole **59**.

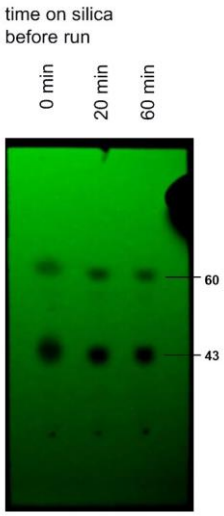


Figure S2. Time-dependent TLC behavior of a mixture of tribromide **60** and oxazole **43**.

3.10 References

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