Organic LETTERS

Letter

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A Concise Total Synthesis of Breitfussin A and B

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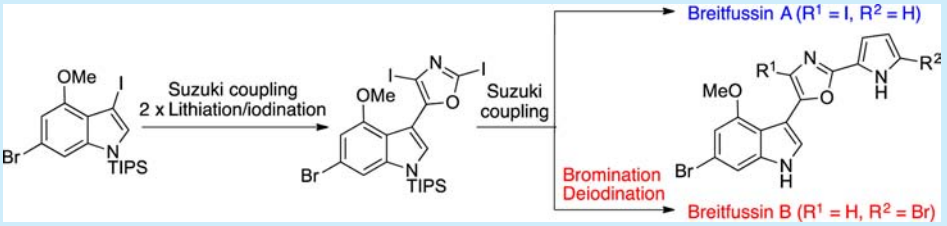
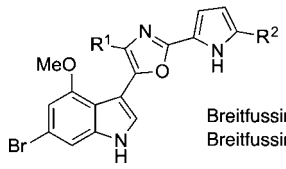
Supporting Information



ABSTRACT: The first total synthesis of breitfussin A and B is described. The approach features two palladium-catalyzed cross-couplings installing the indole and pyrrole onto the oxazole core and selective lithiation/iodination of a common indole−oxazole fragment providing 2,4-diiodinated or 2-iodinated oxazoles as potential precursors for breitfussin A and B, respectively. An unexpected acid promoted deiodination was utilized in the synthesis of breitfussin B. Comparison of the synthetic material with previously reported spectral data of isolated breitfussin A and B verified the structure of the breitfussin framework.

Breitfussin A, **1**, and B, **2**, are highly modified, halogen-rich dipeptide secondary metabolites recently discovered from the Arctic hydrozoan *Thuiaria breitfussi*.[1] The chemical structures were elucidated by combining advanced ^{13}C NMR techniques with atomic force microscopy (AFM), computer-aided structure elucidation (CASE), and calculation of ^{13}C chemical shifts by density functional theory (DFT). None of the techniques alone could provide enough information to solve the structures. Still today, highly functionalized, flat sp^2-hybridized heterocycles of natural origin carrying "NMR-silent modifications", such as halogenation and/or oxygenation, pose a significant challenge for structure elucidation.[2] The breitfussins comprise an unusual molecular framework, with the combination of an indole, oxazole, and a pyrrole. A few other natural products show structural similarities, such as the diazonamides,[3] isolated from the genus *Diazona*, which contain an indole fused to an oxazole moiety, often halogenated on the C2-position of the indole and the C4-position of the oxazole. Less complex compounds containing the indole−oxazole scaffold have been isolated from lower organisms, such as red algae[4] and bacteria.[5] The only reported case of the oxazole−pyrrole unit is within the polychlorinated phorbazoles isolated from the sponge *Phorbas sp.*[6] In addition, the halogenation of breitfussin A is unusual, with an iodinated oxazole, having no literature precedence.

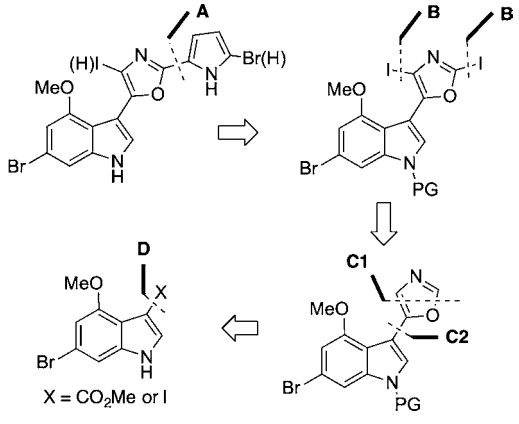
As the breitfussins have not been confirmed structurewise by chemical synthesis, and the amounts available from isolates are minor, thus not allowing for extensive biological investigation, we decided to prepare breitfussin A and B by chemical



Breitfussin A, **1** (R^1 = I, R^2 = H)
Breitfussin B, **2** (R^1 = H, R^2 = Br)

synthesis. An important point in the retrosynthetic analysis (Scheme 1) is to allow for diversification of the structures, for later structural−activity relationship (SAR) investigations of

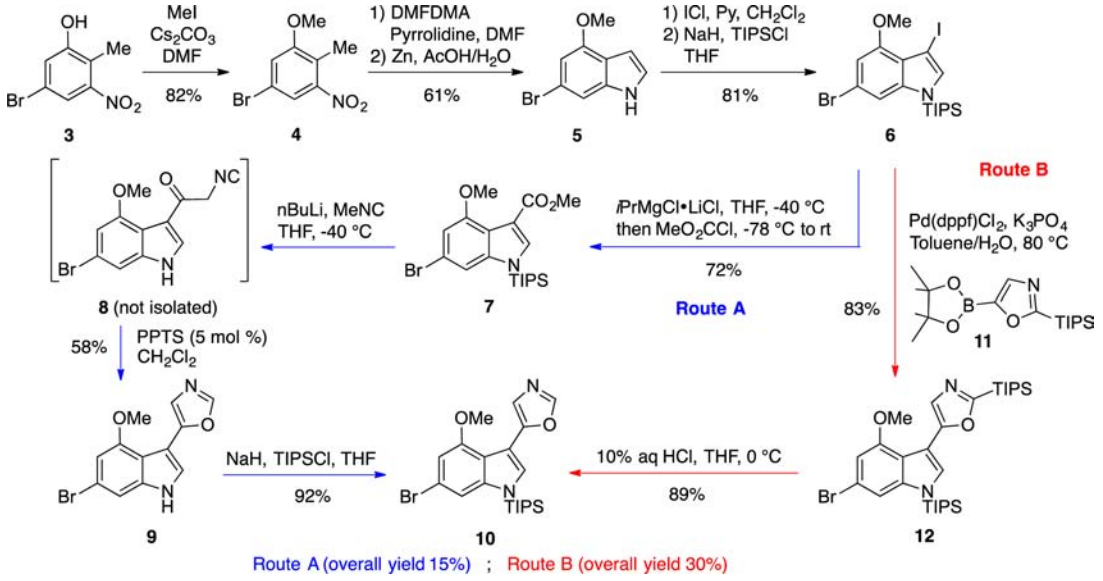
Scheme 1. Retrosynthetic Analysis of the Breitfussins



Received: November 18, 2014
Published: December 16, 2014

   dx.doi.org/10.1021/ol503348n | *Org. Lett.* 2015, 17, 122−125

Scheme 2. Synthesis of Precursor 10



potential biological activity. Initial disconnection **A** of the pyrrole moiety suggests a late-stage metal-catalyzed cross-coupling, which would be followed by an electrophilic bromination of the C2-position of the pyrrole in the case of breitfussin B. The next disconnection **B** indicates a stepwise iodination of the oxazole core, as breitfussin A requires iodination of the oxazole at C2 and C4, while for breitfussin B only one iodine should be introduced at the C2-position of the oxazole. This difference calls for an efficient and modular strategy, allowing for the formation of both derivatives. The common oxazole precursor for breitfussin A and B is further disconnected in **C1** or **C2**. The former disconnection **C1** corresponds to the Schöllkopf reaction,[7] giving an indole methyl ester and a metalated methyl isocyanide as synthons, while the latter disconnection **C2** corresponds to a cross-coupling of an oxazole and an indole. The final disconnection **D** gives 4-methoxy-6-bromo-1-*H*-indole, which is available via the classical Leimgruber−Batcho indole synthesis.[8]

The synthesis commenced with the methylation of the readily available phenol derivative **3**[9] (Scheme 2), employing methyl iodide and cesium carbonate in DMF at rt, to give **4** in good yield. Next, **4** was subjected to Leimgruber−Batcho indole synthesis, employing *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) with pyrrolidine in DMF according to standard conditions.[8b] The resulting vinyl pyrrolidine intermediate was not further purified, but used directly in the subsequent reduction step due to its low stability. Reductive ring closure was carried out in acetic acid/water/THF with zinc powder as the reducing agent at 80 °C to give indole **5** in 61% yield (calculated from **4**) after column chromatography. Attempts to convert indole **5** directly into a 3-methoxycarbonyl derivative (desilylated **7**) via the 3-trichloroacetyl derivative obtained by standard treatment[10] (pyridine, Cl_3CCOCl, heat) and a subsequent basic haloform reaction in methanol were unsuccessful. Indole **5** proved to be unreactive toward trichloroacetyl chloride, even when heated at higher temperatures, and treatment with Lewis acids such as Et_2AlCl led to decomposition. At best, an 18% yield of desilylated **7** could be obtained. Vedejs and Barda report the 3-carboxymethyl ester formation of an electron-rich indole (4-benzyloxy-substituted) under challenging circumstances as part of studies toward Diazonamide A.[11] In their case, it was necessary to brominate the C3-position, protect the N1-position, and subsequently perform bromine/lithium exchange at C3 prior to quenching with methyl chloroformiate. Such a sequence would not be compatible with the 6-bromo substituent of indole **5**, which would be susceptible to bromine/lithium exchange. Instead, we found that iodination (ICl in pyridine) at C3 of indole **5**, and subsequent TIPS-protection, gave **6** in 81% yield over the two steps. TIPS-protected 3-iodo-indole **6** underwent smooth iodine/magnesium exchange at −40 °C by treatment with *i*PrMgCl·LiCl in THF for 15 min, without any trace of halogen/metal exchange at the C6-position. The resulting mixture was further cooled to −78 °C, quenched with methyl chloroformate, and allowed to reach rt over 1 h, giving 3-methoxycarbonyl substituted indole **7** in 72% yield. Next, oxazole formation from **7** was attempted following the Schöllkopf protocol.[7] After treatment of **7** with methyl isocyanide/*n*BuLi at −78 °C to rt, a mixture of deprotected isonitrile intermediate **8**, as well as unprotected oxazole **9** and TIPS-protected oxazole **10**, was isolated. The ratio varied in an irreproducible way when attempts were made to quench more carefully in order to avoid TIPS-deprotection of the N1-position and to promote oxazole cyclization. The best conditions yieldwise were to allow for the complete deprotection during workup, thus mainly providing isonitrile **8**. To avoid bromine/lithium exchange during the reaction, it was necessary to quench in a reverse fashion by siphoning the cold (0 °C) reaction mixture into a bicarbonate solution. The crude isonitrile intermediate **8** was treated with catalytic amounts of PPTS in CH_2Cl_2 to recyclize the oxazole core resulting in **9** in reasonable yield (58% yield over two steps). Compound **9** was subsequently reprotected to give **10** in excellent yield.

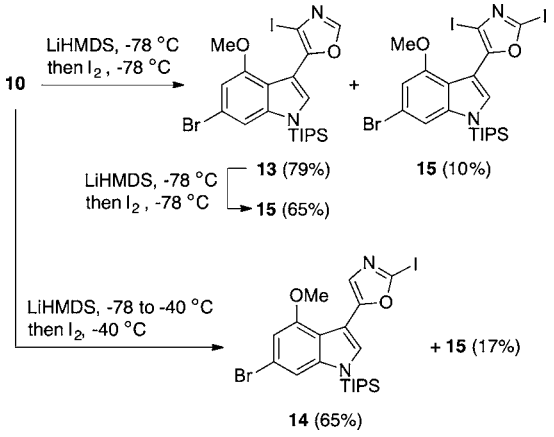
Since the Schöllkopf route (Scheme 2, route A depicted in blue) provided a poor overall yield, including challenging purifications, a Pd-catalyzed cross-coupling approach (Scheme 2, route B depicted in red) was investigated next. Reaction of 2-TIPS-protected oxazole-4-pinacol-boronic ester **11**[12] with the 3-iodo indole **6** under standard Pd-catalyzed coupling conditions ($Pd(dppf)Cl_2$, K_3PO_4, toluene/H_2O 2:1, 50 °C) gave **12** in reasonable yield (83%). Rault and co-workers

dx.doi.org/10.1021/ol503348n | *Org. Lett.* 2015, 17, 122−125

reported deprotection of the oxazole C2 TIPS-group for a similar reaction (typical reaction conditions: $Pd(PPh_3)_4$, Na_2CO_3, dioxane/H_2O, 80 °C).[12] In our case the TIPS protection on C2 remained under the reaction conditions, but could be selectively removed by treatment of **12** with 10% aq HCl to give **10** in good yield. Thus, the TIPS protection on C2 of the oxazole appears to be more acidic labile than the *N*-TIPS protection of the indole. In comparison, route B (red) turned out superior compared to the Schöllkopf route A (blue) (Scheme 2).

With the indole−oxazole fragment **10** at hand, the introduction of the iodo-substituents at C2 and C4 of the oxazole was investigated (Scheme 3). Typical oxazole reactivity

Scheme 3. Regioselective Iodination of 10

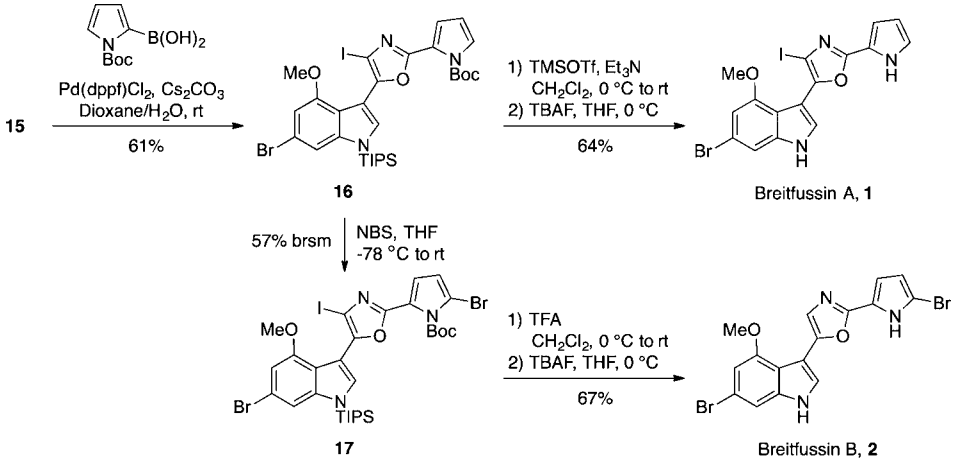


suggests that the 2-iodo-substituent should be introduced by a metalation/iodination reaction, while the 4-iodo substituent could be introduced either through electrophilic aromatic iodination or via metalation/iodination.[13] Initially, electrophilic aromatic iodination of **10** was attempted. Several electrophiles (NIS, iodine/acid, ICl) were investigated, but at best 4-iodooxazole **13** was obtained in very low yield. Attention was therefore focused on a metalation/iodination strategy.[13,14] After screening several bases (TMPMgCl·LiCl, *i*PrMgCl·LiCl, LiHMDS, NaHMDS) and electrophiles (1,2-diiodoethane, iodine), we found that the outcome of the metalation/iodination of **10** was highly dependent on the temperature of the iodination step (Scheme 3). Metalation with LiHMDS (3 equiv) at −78 °C and subsequent iodination using iodine at −78 °C gave 4-iodo derivative **13** as the major isomer (79% yield). Raising the temperature to −40 °C before addition of iodine gave predominantly the 2-iodo derivative **14** (65% yield). In both cases, 2,4-diiodinated **15** was formed in minor amounts. A second lithiation/iodination of the 4-iodo oxazole **13** gave the diiodo compound **15** in 65% isolated yield.

Next, breitfussin A was approached by the Pd-catalyzed cross-coupling between diiodooxazole **15** and *N*-Boc-2-pyrroleboronic acid (Scheme 4). Use of $Pd(dppf)Cl_2$ in dioxane/water with Cs_2CO_3 as a base at rt proved to be efficient, and the protected breitfussin A precursor **16** was obtained in 61% yield. The coupling was conducted at ambient reaction temperature (22 °C) to prevent side reactions such as cross-coupling or dehalogenation reactions at C4 of the oxazole or C6 of the indole. The only observed byproduct was material deiodinated at C2 of the oxazole. It was envisioned that the indole-TIPS and pyrrole-Boc protection groups could be cleaved off simultaneously using acidic conditions; however, employing either TFA or HCl only lead to Boc-deprotection while giving varying degrees of deiodination. Desilylated product was not observed. Stepwise deprotection of the Boc group using TMSOTf followed by desilylation using TBAF gave breitfussin A, **1**, in 64% yield over the two steps and a total yield of 7.2% over 10 steps from **3**.

In an initial attempt toward breitfussin B, the 2-iodinated oxazole **14** was submitted to cross-coupling conditions identical to those for **15**; however rather surprisingly, the reaction proved to be very slow and also led to TIPS deprotection. Screening of a number of catalysts and conditions gave no improvement (Supporting Information). The only products that could be observed were deiodinated or desilylated **14**. One may speculate that the unexpected low reactivity of 2-iodooxazole **14** compared to diiodooxazole **15** results from an electron-donating effect of the indole on the oxazole in **14**, while conjugation is attenuated in **15** as the system is more conformationally staggered due to the bulk of the 4-iodine substituent of the oxazole. As an alternative strategy, the bromination and deiodination of breitfussin A precursor **16** was envisioned (Scheme 4). Bromination of **16** at the pyrrole C2 using NBS in THF at −78 °C proceeded slowly, and **17** was isolated in 57% yield based on partial recovery of the starting material. The unexpected deiodination under acidic treatment

Scheme 4. Synthesis of Breitfussin A and B



dx.doi.org/10.1021/ol503348n | *Org. Lett.* 2015, 17, 122−125

with TFA discovered earlier could now be used to our advantage. Treatment of **17** with TFA gave the deiodinated and Boc-deprotected intermediate, which was directly desilylated using TBAF to provide breitfussin B, **2**, in 67% yield over the two steps and in a total yield of 4.3% from **3**.

Finally, comparison of the ^{13}C and ^{1}H NMR spectra at 600 MHz of **1** and **2** in DMSO-(d_6) proved to fully align with previously reported spectral data[1] (Supporting Information), thus verifying the reported structure of the breitfussin framework. In summary, we have prepared the natural products breitfussin A and B in 7.2% and 4.3% overall yields, respectively (from **3**).

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic details, and a comparison of the ^{1}H and ^{13}C NMR data of natural and synthetic **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The Research Council of Norway has supported this work by a grant to S.K.P. (224790/O30) and a travel grant to Y.G. (MabCent, 174885). Y.G. and A.B. wish to thank Prof. Trond Ø. Jørgensen (UiT The Arctic University of Norway) for his generous support.

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