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Synthesis of pentabromopseudilin and other arylpyrrole derivatives via Heck arylations

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ABSTRACT

Pentrabromopseudilin and other 2 and 3-arylpyrrole derivatives were synthesized through the Heck–Matsuda reaction involving endocyclic enecarbamates and *N*-protected 3-pyrrolines, respectively. The overall processes permitted an easy and efficient access to these structural motifs present in several bioactive compounds. Attempts to synthesize the compound isopentabromopseudilin led to a tribromo aryl maleimide. We hypothesize that this latter compound is the putative product arising from the unusual thermal instability of isopentabromopseudilin.

Introduction

The arylpyrrole unit is a widespread structural motif among biologically active compounds. For example, it is present on the structures of two commercial compounds, Chlorfenapyr (**1**),[1] a potent pro-insecticide, and Fludioxonil (**2**), an antifungal antibiotic used for seed treatment (Fig. 1). The latter compound was designed based on the natural product pyrrolnitrin (**3**), isolated from *Pseudomonas* sp., which displays excellent antifungal activity but unsuccessful field performance.[2]

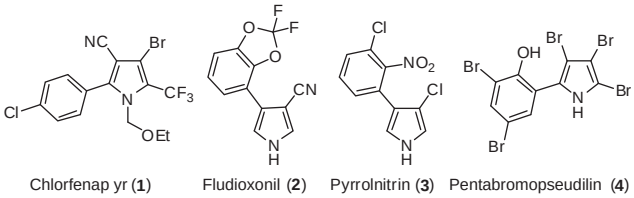
Among the natural arylpyrrole compounds we also find pentabromopseudilin (**4**), a compound first isolated from *Pseudomonas bromoutilis* in 1966[3,4] and later from *Chromobacteria*,[5] *Alteromonas luteoviolaceus*[6], and *Pseudoalteromonas* sp.[7] This interesting polybrominated natural product displays a variety of in vitro biological activities such as antibiotic, antitumor, antifungal, and phytotoxic,[8] including remarkable inhibition of human lipoxygenases[9] and myosin-dependent processes.[10–12] It's also worth mentioning that pentabromopseudilin also displays a high in vitro activity against MRSA (IC_{50} = 0.1 μM).[7]

Several syntheses of pentabromopseudilin (**4**) have been reported, and all of them share as a common feature the construction of the pyrrole nucleus from an aliphatic intermediate already containing the aromatic substituent.[6,9,12–14] Herein, we disclose a new strategy to the synthesis of this class of compounds, by attaching the aromatic substituent to a pre-formed pyrroline scaffold through an efficient Heck–Matsuda (HM) reaction.

The HM reaction, which employs arenediazonium salts as arylating agents, presents several advantages over conventional protocols, such as its practicality as an easy to perform protocol, and as a phosphine-free and air tolerant process. The more reactive nature of the arylating agent usually implies in shorter reaction times and milder reaction conditions, making this a greener and more practical alternative for the arylation of olefins.[15–17]

Previous studies from our group have already demonstrated that both 2 and 3-aryl dihydropyrroles could be obtained from the Heck–Matsuda reactions involving enecarbamates and *N*-protected 3-pyrrolines, respectively (Scheme 1).[18–20] These structures represent direct precursors to arylpyrroles, and could be transformed in these aromatic derivatives in a straightforward manner.

Herein we describe the construction of both 2 and 3-arylpyrrole cores, the application of this methodology in the total synthesis of



Chlorfenap yr (**1**) Fludioxonil (**2**) Pyrrolnitrin (**3**) Pentabromopseudilin (**4**)

Figure 1. Biologically active arylpyrroles.

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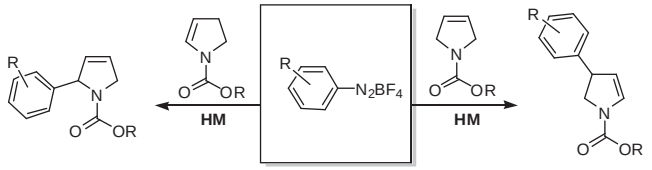


Scheme 1. Preparation of aryl dihydropyrroles by HM reaction.

pentabromopseudilin (**4**), as well as in studies toward its 3-arylated regioisomer, isopentabromopseudilin (see compound **19** ahead).

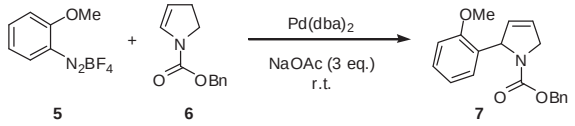
Results and discussion

Aiming at the synthesis of the 2-arylpyrrole natural product **4**, we first investigated the Heck–Matsuda reaction between enecarbamate **6**[21] and the *ortho*-methoxy benzenediazonium salt **5** (Scheme 2).

Based on our own previous results, we initiated this study employing $Pd(dba)_2$ as the catalyst and 3 equiv of NaOAc as the base, in acetonitrile as the solvent.[18] Firstly, we investigated the stoichiometry of the reaction to find out that the use of 1.5 equiv of the olefin led to improved yields of the desired 2-arylpyrroline **7** (entries 1–3, Table 1). Larger excesses of the olefin did not lead to improvements in yields (entry 4).

Secondly, we tested benzonitrile as the solvent, since it proved to be beneficial in many other Heck–Matsuda reactions.[22–24] In benzonitrile the reaction took place very quickly, but only decomposition of the starting materials was observed (entry 5). Performing the reaction at lower temperature led to lower yields (entry 6). The use of PhCN as an additive in CH_3CN did not bring any improvement in yields when compared to CH_3CN alone (entry 7). Finally, we observed that using freshly macerated NaOAc as the base resulted in cleaner and faster reactions (entries 8–9). In these cases, only a slight excess of the olefin (1.2 equiv) was necessary to obtain good yields of the desired Heck adduct **7** after just 10 min (78% isolated yield). It is worth mentioning that no isomerized Heck adducts were detected in any of these experiments.

As pentabromopseudilin (**4**) bears a free phenol in its structure, we also prepared the *o*-hydroxybenzenediazonium tetrafluoroborate (see compound **14** ahead) and reacted it with enecarbamate **6** under the same conditions described in entry 8 of Table 1. Unfortunately, no conversion was observed either in acetonitrile (at rt or under heating) or in benzonitrile.



Scheme 2. Preparation of **7** by means of the HM reaction.

Table 1
Optimization of HM reaction conditions for preparation of **7**

Entry	**5** (equiv)	**6** (equiv)	$Pd(dba)_2$ (mol %)	Solvent	Yield **7** (%)
1	1.5	1	4	CH_3CN	46–47
2	1.5	1	8	CH_3CN	43–46
3	1	1.5	4	CH_3CN	67
4	1	2	4	CH_3CN	66
5	1	1.5	4	PhCN	Decomp.
6[a]	1	1.5	4	PhCN	43
7[b]	1	1.5	4	PhCN/ CH_3CN	61
8[c]	1	1.5	4	CH_3CN	71–73
9[c]	1	1.2	4	CH_3CN	78

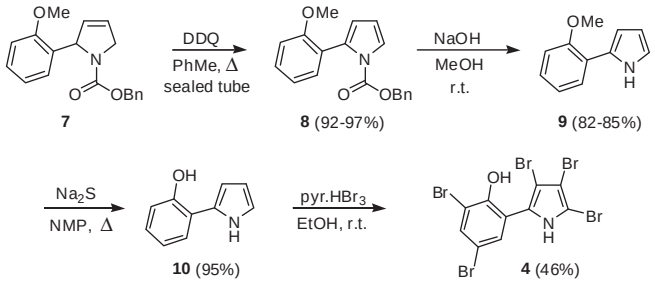
[a] Reaction performed at 0 °C.
[b] PhCN used as an additive, 10% v/v.
[c] Freshly macerated NaOAc employed.

With the desired Heck adduct **7** in hand, it was subjected to aromatization with DDQ in toluene, leading to the corresponding arylpyrrole **8** in high yields (Scheme 3). A simple filtration of arylpyrrole **8** on a short pad of silica gel provided the desired product with enough purity to be used in the next step without further purification. Compound **8** was then deprotected under basic conditions to afford the free pyrrole compound **9** in an 85% isolated yield.

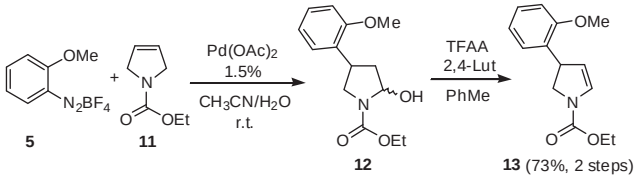
Compound **9** is a known intermediate in the synthesis of pentabromopseudilin (**4**), and we were able to successfully perform its conversion into the final product through demethylation and bromination procedures as described in the literature.[14] Overall, we have accomplished a new total synthesis of pentabromopseudilin in a 28% overall yield, over 5 steps.

Using a similar strategy, we moved toward the total synthesis of the 3-aryl compound isopentabromopseudilin (**19**). Initially, we performed the Heck–Matsuda reaction between *ortho*-methoxy benzenediazonium salt **5** and 3-pyrroline **11**, available from the ring closing metathesis reaction of the appropriated *N*-protected diallylamine.[20]

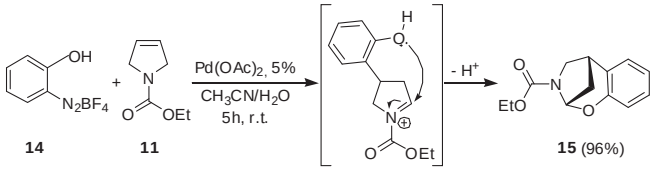
To carry out the arylation of 3-pyrroline **11**, we used a procedure described previously by us, using $Pd(OAc)_2$ as the pre-catalyst in a mixture of acetonitrile and water as the solvent.[20] Under these conditions the reaction went to completion in only 15 min. The crude reaction product was then subjected to dehydration leading to the desired arylated enecarbamate **13** in a 73% isolated yield (Scheme 4).



Scheme 3. Synthesis of pentabromopseudilin (**4**) from Heck adduct **7**.



Scheme 4. Preparation of **13** through a HM/dehydration sequence.



Scheme 5. Formation of the unprecedent tricycle **15** under HM reaction.

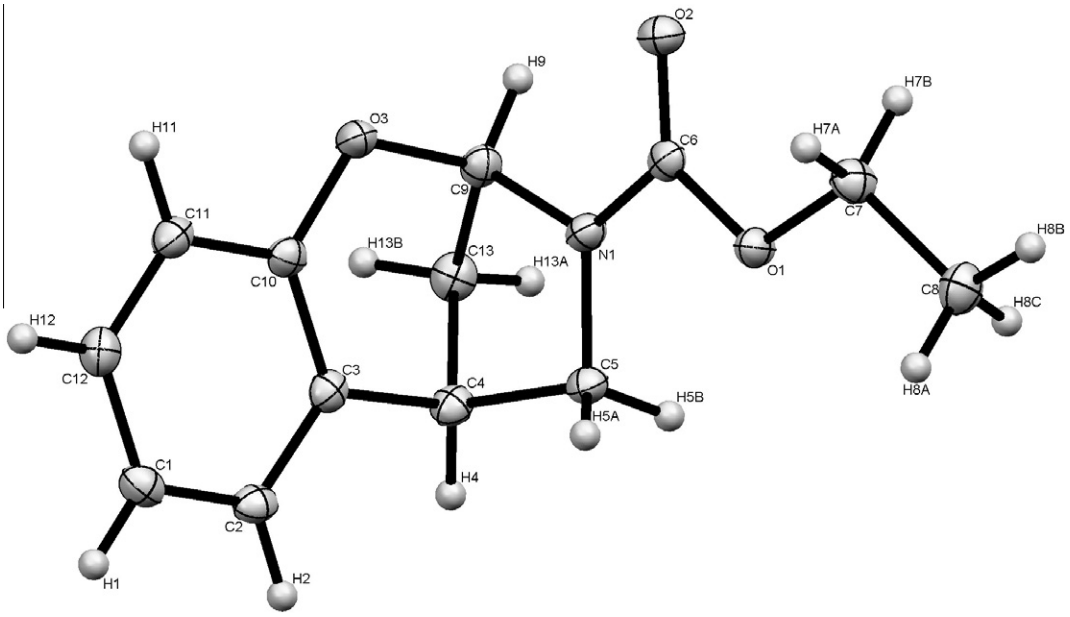


Figure 2. Ortep diagram for tricyciclic compound **15**. Displacement ellipsoids are drawn at 50% probability level. H atoms are shown as small spheres of arbitrary radius.

In spite of the formation of lactamol **12** in the process—due to the acidification of the reaction medium—its intermediacy in the overall process is beneficial, since previous attempts to drive the reaction to the endocyclic enecarbamate in this kind of transformation proved to be troublesome.[19,20] This difficulty is probably related to the high reactivity of the enecarbamate product under the Heck–Matsuda conditions, leading to undesired byproducts and diarylated compounds, for instance.

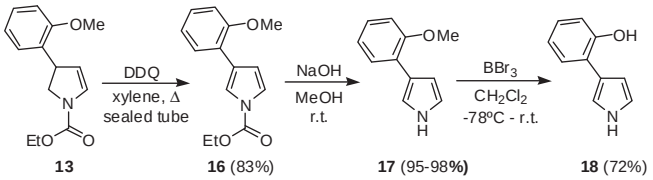
Interestingly, when the *o*-hydroxyl benzenediazonium salt **14** was subjected to the Heck–Matsuda reaction (5 mol % of Pd, 5 h) the tricyclic compound **15** was obtained in a 96% isolated yield (Scheme 5). This curious compound results from the intramolecular attack of the free phenol group onto the transient *N*-acyliminium ion formed in the course of reaction.

This new tricyclic compound, an unusually thermostable *N,O*-acetal, was fully characterized by spectroscopic methods and its structure was confirmed by X-ray crystallography (Fig. 2 see details in the supplementary data).

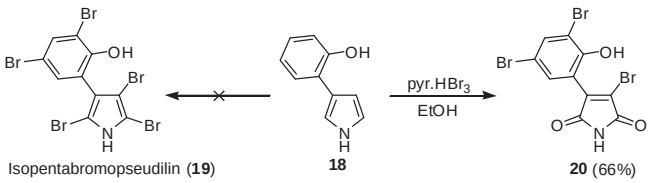
Continuing our efforts toward the synthesis of isopentabromopseudilin (**19**), the Heck adduct **13** was then subjected to aromatization employing DDQ in xylene (Scheme 6), leading to the 3-arylpyrrole derivative **16** in ~83% yield.[25] As before, the reaction was very clean and a simple filtration on a short pad of silica gel afforded compound **16** with enough purity to be used in the next step without further purification.

The *N*-carboethoxy arylpyrrole **16** was then deprotected under basic conditions to afford the arylpyrrole **17** in excellent yield and purity, after a simple extractive work-up. Demethylation of arylpyrrole **17** proved challenging, and after much experimentation, we found out that the use of 5 equiv of BBr_3 as the demethylating agent leads to the desired phenol derivative **18** in a 72% isolated yield.

For the completion of the synthesis of isopentabromopseudilin (**19**), a final bromination step was required. With this objective in mind several reaction conditions employing Pyr.HBr_3 and tribromoisocianuric acid (TBCA) as bromination agents were evaluated.[26] However, under all conditions tested only the maleimide derivative **20** was obtained, probably due to a very facile pyrrole oxidation after bromination of the putative intermediates, or from the direct oxidation of the rather unstable isopentabromopseudilin (Scheme 7).[27]



Scheme 6. Preparation of arylpyrrole **18** from Heck adduct **13**.



Scheme 7. Attempted preparation of isopentabromopseudilin (**19**).

In view of this unexpected result, the brominated aryl maleimide **20** was fully characterized by spectroscopic methods. We were able to obtain a single crystal derived from co-crystallization of maleimide **20** with the pyr.HBr. The structure of this complex was elucidated by X-ray diffraction, and is shown below (Fig. 3 see details in the supplementary data).

Conclusion

This work illustrates the viability of the HM reaction as a key step in the synthesis of a variety of valuable arylpyrrole derivatives. The versatility of this approach was demonstrated by the effective synthesis of both 2 and 3-arylpyrroles. Moreover, a new total synthesis of the natural product pentabromopseudilin (**4**) was also developed. An attempted synthesis of isopentabromopseudilin (**19**) led to the exclusive formation of an interesting tribromo arylmaleimide. Isopentabromopseudilin is reported as an unstable compound which decomposes expontaneously.[27] We hypothesize that maleimide **20** is the main oxidation product resulting from the decay of isopentabromopseudilin.

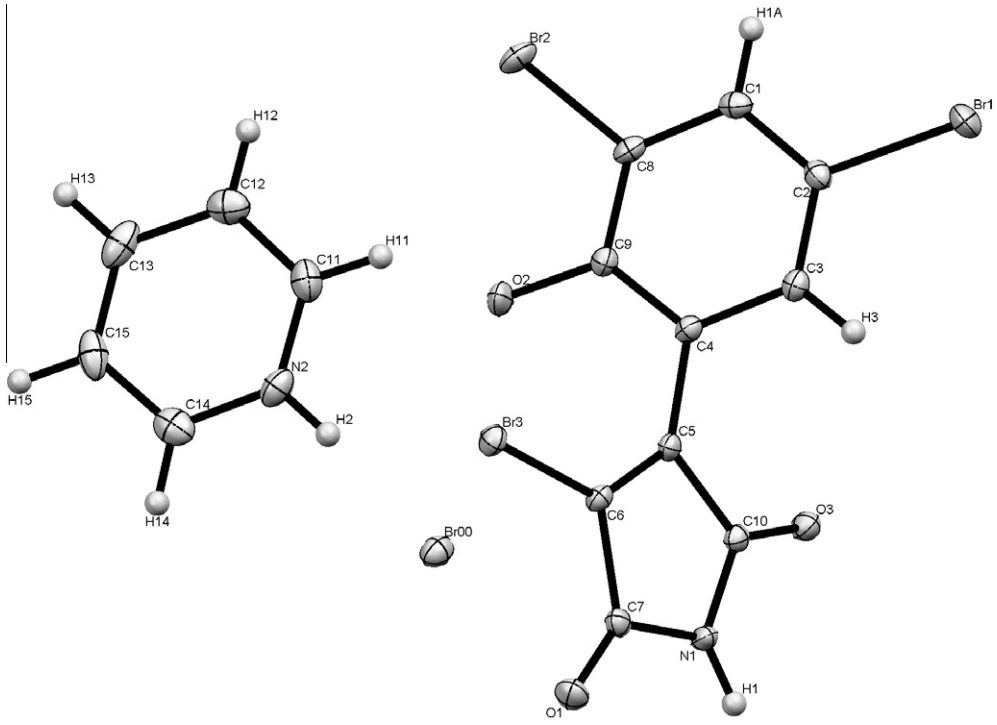


Figure 3. Ortep diagram for a co-crystal of compound **20** with pyr.HBr. Displacement ellipsoids are drawn at 50% probability level. H atoms are shown as small spheres of arbitrary radius.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.086.

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