doi:10.1246/cl.2011.1079
Published on the web September 17, 2011

Concise Synthesis of Deformylflustrabromine, a Marine Indole Alkaloid, through a 2-Propynyl Dicobalt Hexacarbonyl Complex

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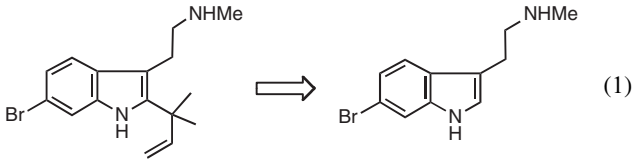
Deformylflustrabromine, a marine indole alkaloid, was synthesized from 6-bromotryptamine, a plausible biosynthetic precursor, without protection of the amino group by a two-step reverse prenylation involving the Nicholas reaction and reductive decomplexation of the resulting acetylene dicobalt hexacarbonyl complex.

Indole terpene alkaloids are a large family of naturally occurring, biologically active compounds.[1] Due to their structural diversity and various biological activities, many efforts to synthesize these compounds have been made.[2] Synthetic methods for the isoprenylation of indole derivatives, which represents the simplest modification of indole to introduce the terpene structure, have been well studied because numerous natural indole alkaloids are modified by isoprenyl groups.[3] In contrast, only a few methods of reverse prenylation have been reported and mainly involve the C-2 position of indole.[4–6] The most reliable method for the reverse prenylation of the C-2 position indole is the reaction of 3-chloroindolenine with 9-prenyl borane, developed by Danishefsky,[4] which has been applied to the total synthesis of several naturally occurring indole alkaloids.[4,7,8] Recently, Baran reported palladium-catalyzed reverse prenylation at the N-1 position of indole,[9] which enables synthesis of a variety of reverse-prenylated indoles in a single step.[10]

As part of our research program directed toward the synthesis of naturally occurring terpene-containing indole alkaloids,[11] we are interested in the reverse prenylation of the indole nucleus in order to synthesize reverse-prenylated indole natural products, such as deformylflustrabromine (**1**),[12] emindole PA,[13] sulpinine B,[14] ellamide, and aflatrem.[15] We describe herein the synthesis of deformylflustrabromine (**1**) by means of two-step reverse prenylation utilizing an acetylene dicobalt hexacarbonyl complex.[16]

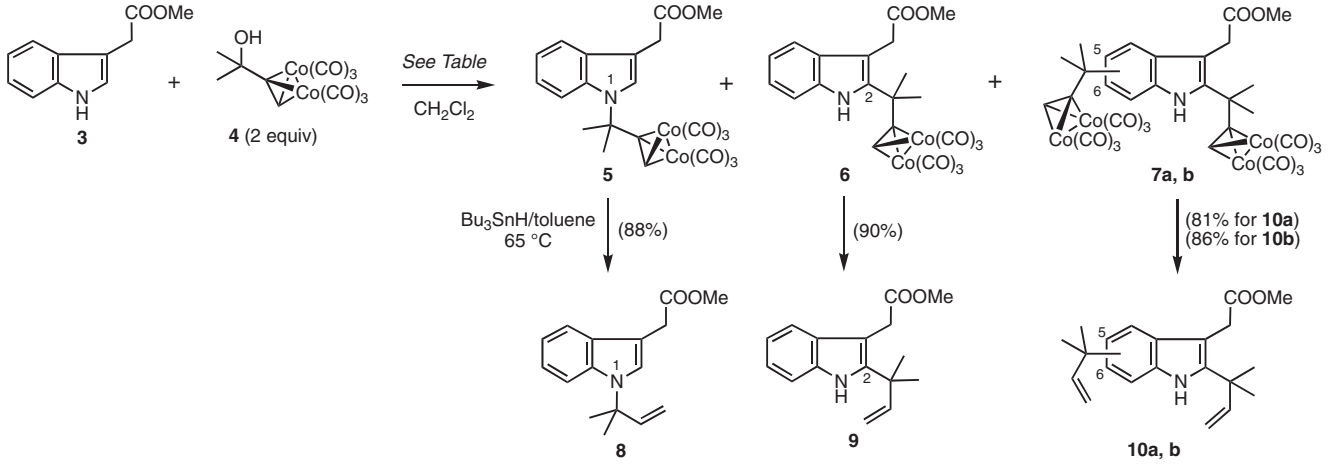


(1)

deformylflustrabromine (1) **2**

In our approach, we planned to introduce a reverse prenyl group to indole through the reverse prenylation of *N*-methyl-6-bromotryptamine (**2**), during the late stage of synthesis as a plausible biosynthetic precursor (eq 1). To realize the reverse prenylation of **2**, we intended to employ a Friedel–Crafts-type reaction utilizing a 2-propynyl dicobalt hexacarbonyl complex,[17] which is known as the Nicholas reaction.[18]

We first examined the Nicholas reaction of methyl 3-indoleacetate (**3**) as a model substrate with acetylene cobalt complex **4** to determine the regioselectivity of the reaction (Scheme 1). The Nicholas reaction of several indole derivatives has been reported; indole itself preferentially reacts with **4** at the C-3 position,[19] while the reaction of 3-substituted indole, such as Cbz-protected tryptamine, with acetylene cobalt complex **4** gives a N-1-substituted product as a major product and N-1 and C-5 or C-6 disubstituted products as minor products.[20] In contrast to these previous results, we found that the reaction of **3** and two equivalents of acetylene cobalt complex **4** in the presence of $HBF_4 \cdot OEt_2$ gave a mixture (approximately 1:1) of products **7a** and **7b** in 58% yield (Table 1, Entry 1). In this reaction, two molecules of acetylene cobalt complex **4** were introduced to the



Scheme 1. Nicholas reaction of **3** with acetylene cobalt complex **4** and reductive decomplexation.

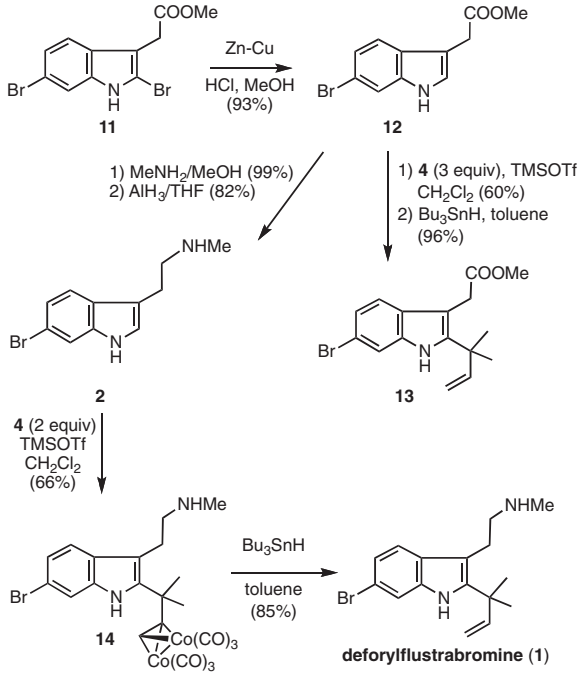
Table 1. Nicholas reaction of **3** with acetylene cobalt complex **4** in the presence of a variety of acid

Entry	Acid (equiv)	Temp /°C	Products/%		
			5	**6**	**7a**, **7b** (5-:6-)
1	$HBF_4 \cdot OEt_2$ (3)	20	0	0	58 (1:1)
2	$BF_3 \cdot OEt_2$ (3)	0	0	0	51 (1:1)
3	TMSOTf (3)	0	0	28	54 (1:1)
4	Tf_2NH (3)	0	0	14	53 (1:1)
5	$Sc(OTf)_3$ (0.4)	20	62	6	0
6	$InBr_3$ (0.4)	0	76	0	23 (1:1)
7	TMSOTf (0.4)	0	87	0	0
8	Tf_2NH (0.4)	0	83	0	0

C-2 position and the C-5 or C-6 position of the indole product. To our knowledge, this is the first example of the Nicholas reaction at the C-2 position of an indole derivative. We next performed the same reaction using one equivalent of acetylene cobalt complex **4** and obtained a complex mixture. This unexpected result prompted us to perform a screening of the acid used for the reaction of methyl 3-indoleacetate (**3**) with acetylene cobalt complex **4**. Representative results of the Nicholas reaction with two equivalents of acetylene cobalt complex **4** and several acids are shown in Table 1.[21,22] In the presence of the Lewis acid $BF_3 \cdot OEt_2$, the reaction proceeded similarly to that of Entry 1 (Entry 2). When TMSOTf or Tf_2NH was employed as an acid, monoalkylated indole **6** was obtained along with the dialkylated products **7a** and **7b** (Entries 3 and 4, respectively). Surprisingly, when the reaction was performed in the presence of catalytic amounts of acids such as $Sc(OTf)_3$, $InBr_3$, TMSOTf, and Tf_2NH, *N*-alkylated indole **5** was obtained as the major product (Entries 5–8). These results implied that product **6** might be formed through *N*-alkylated product **5** as an intermediate.[23] This speculation was supported in a separate experiment, as the treatment of **5** with TMSOTf (3 equiv) gave a mixture of compound **6** (8%), **7a** and **7b** (17%), and **3** (42%).[24] Transformation of the acetylene cobalt complex moiety of **5**, **6**, **7a**, and **7b** to a reverse prenyl group was achieved in good yields by reductive decomplexation with Bu_3SnH, a reaction that was developed in our laboratory.[25] We thus established a procedure for the two-step reverse prenylation at the N-1 position of the indole nucleus, as well as the C-2 position, although the issue of the regioselectivity has not yet been solved.

The above results indicate that the reactivity of the indole benzene moiety in the Nicholas reaction is higher than we expected. However, we envisioned that the 6-bromo substituent of an indole derivative such as **2** would suppress the Nicholas reaction at the benzene ring due to steric hindrance, resulting in a regioselective reaction at the C-2 position.

We thus examined the Nicholas reaction of methyl 6-bromoindoleacetate **12**, which was prepared in two steps from methyl 3-indoleacetate (**3**), involving (i) 2,6-dibromination of **3** with NBS,[26] and (ii) regioselective debromination of methyl 2,6-dibromoindoleacetate with a freshly prepared Zn/Cu couple in MeOH in the presence of HCl (Scheme 2). Subsequently, the Nicholas reaction of **12** with acetylene cobalt complex **4** (3 equiv) was carried out by treatment of TMSOTf (4 equiv) at room temperature to provide the desired product possessing the cobalt complex at the C-2 position in 60% yield. Using this



Scheme 2. Synthesis of deformylflustrabromine (**1**).

approach, none of the other regioisomers were obtained. As anticipated, this indicates that the bromo substituent at the C-6 position excluded substitution at the benzene ring. The acetylene cobalt moiety of the product was then transformed into a reverse prenyl group by reductive decomplexation, giving **13** in excellent yield. It is worth noting that the ester and bromo substituents are compatible with the reaction conditions of the sequential reverse prenylation.

We next investigated the Nicholas reaction of 6-bromo-*N*-methyltryptamine (**2**), which was prepared from **12** in two steps, involving *N*-methylamide formation and subsequent reduction of the amide with AlH_3.[27] The reaction of **2** with acetylene cobalt complex **4** was performed under optimized conditions in 66% yield. Again, it should be noted that the Nicholas reaction appears to be unaffected in the presence of an unprotected basic amino functional group.[28] The cobalt complex of the product smoothly underwent reductive decomplexation to provide deformylflustrabromine (**1**) in 85% yield.

In summary, we have developed a new route to deformylflustrabromine, a reverse prenyl indole alkaloid, by means of an acetylene–cobalt complex. As the reverse prenylation procedure is compatible with ester and bromo substituents, as well as basic amino groups, this modification of indole derivatives should facilitate an accessible route to synthesize diverse reverse-prenylated indole compounds, not only from simple indole derivatives, but also from naturally occurring indole alkaloids. The generality and regioselectivity of the Nicholas reaction of indole derivatives, as well as its application to complex terpene indole alkaloids, are currently under investigation in our laboratory.

This work was financially supported by a Grant-in-Aid for Scientific Research (B) from MEXT, the Naito Foundation, and the Nagase Science and Technology Foundation.

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