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Synthetic studies of *N*-reverse prenylated indole. An efficient synthesis of antifungal indole alkaloids and *N*-reverse prenylated tryptophan

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Abstract—The efficient method for the synthesis of *N*-1,1-dimethyl-2-propenyl (reverse prenyl) indole was developed by the *N*-propargylation of the indoline, partial hydrogenation of the terminal alkyne, and oxidation to the indole using chemical manganese dioxide (CMD). This method was used for the synthesis of the antifungal indole alkaloids **2**, **3**, and *N*-reverse prenylated tryptophan.

Though not commonly found in natural products, *N*-1,1-dimethyl-2-propenyl (reverse prenyl) indole structures are contained in some biologically interesting natural products. The representative example of this type of compound is asterriquinone (**1**), isolated from *Aspergillus terreus* by Yamamoto et al., which has a symmetrical benzoquinone structure attached to a *N*-1,1-dimethyl-2-propenylindole and possesses antitumor activity (Fig. 1).[1] Recently, a new antifungal *N*-reverse prenylated indole alkaloid **2** and its derivative **3** having

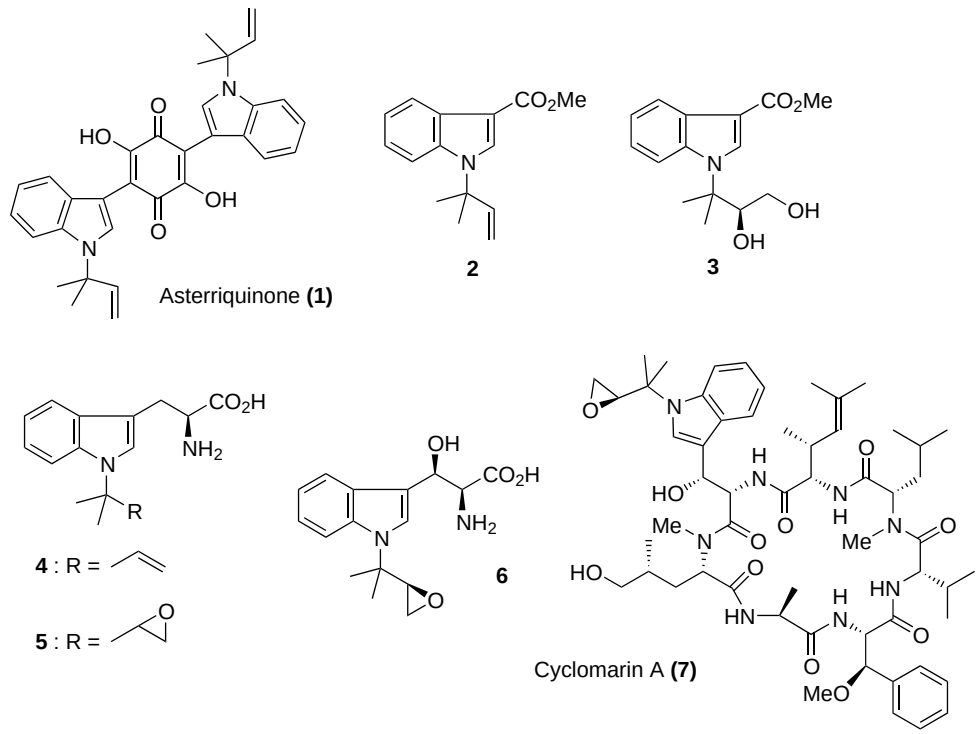

Figure 1. Natural *N*-reverse prenylated indole compounds.

Keywords: *N*-reverse prenylated indole; antifungal indole alkaloid; chemical manganese dioxide (CMD).

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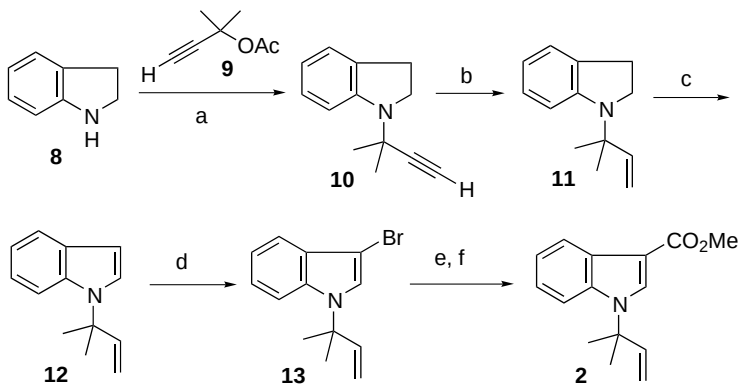
a 2,3-dihydroxy-1,1-dimethylpropyl unit were isolated from the basidiomycete *Asporpium caryae*.[2] Another class of the *N*-reverse prenylated indole is the tryptophan derivatives **4** and **5**, and the latter has a 2,3-epoxy-1,1-dimethylpropyl unit on the indole nitrogen. These tryptophan derivatives are found in the cyclic peptides, rufomycins (illamycins), and some of these peptides have shown useful antibiotic properties.[3] Moreover, the novel tryptophan derivative **6** has emerged as the anti-inflammatory cyclic peptide, cyclomarin A (**7**),[4] which was isolated from the marine bacterium *Streptomyces* sp. by Fenical et al. Cyclomarin A (**7**) is currently undergoing preclinical trials as an anti-inflammatory and an antiviral agent by Phytera, Inc.[4b] In spite of their structural novelties and attractive biological activities, synthetic studies of the *N*-reverse prenylated indole and its related compounds have not been reported to date. As a part of our program for the total synthesis of cyclomarin A (**7**), we now wish to report the efficient synthesis of the *N*-reverse prenylated indole and its application to the synthesis of the antifungal indole alkaloids **2**, **3** and *N*-reverse prenylated tryptophan **4**.

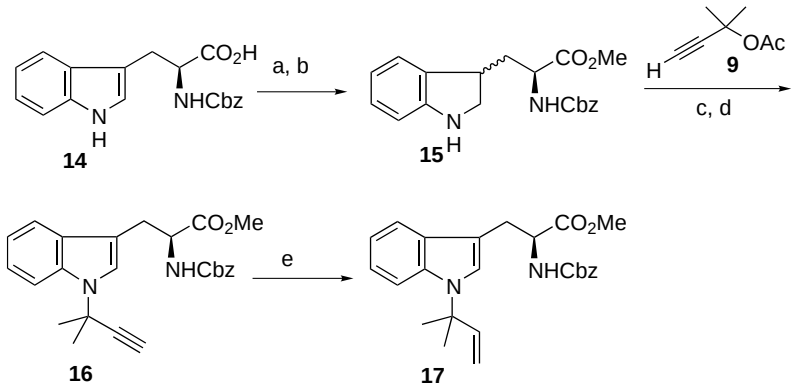
To construct the *N*-reverse prenylated indole **12**, we first attempted the *N*-propargylation of the indole followed by partial hydrogenation of the resulting terminal alkyne, the method of which was applied to the synthesis of the *N*-reverse prenylated valine for the total synthesis of muscoride A independently developed by Wipf and Pattenden.[5] However, the direct *N*-propargylation of the indole did not proceed at all under the various conditions due to the low nucleophilicity of the indole nitrogen. Accordingly, we used indoline (**8**) as a precursor of the indole. Treatment of the indoline (**8**) with 3-acetoxy-3-methylbut-1-yne in the presence of copper(I) chloride[6] provided the *N*-propargyl indoline (**10**) in 90% yield, as shown in Scheme 1. The terminal alkyne **10** was partially hydrogenated using Lindlar's catalyst to form the alkene **11** in 91% yield, which was oxidized to the indole using MnO_2 (CMD; chemical manganese dioxide)[7] to afford the *N*-reverse prenylated indole (**12**) in 86% yield. Next, we tried to convert the *N*-reverse prenylated indole (**12**) to the antifungal indole alkaloids **2** and **3**. The C-3 bromination of the indole ring with NBS in DMF gave the bromide **13** in 96% yield. Lithiation of the resulting bromide **13** with *t*-BuLi followed by methoxycarbonylation afforded the natural indole alkaloid **2** in 89% yield. Interestingly, no C-2 carbonylation of the indole ring was observed in this reaction, though some 3-lithioindoles are known to be prone to the 3→2 migration of lithium.[8] We speculated that the steric hindrance at the C-2 position of the indole ring by the *N*-reverse prenyl group would cause the selective C-3 carbonylation.

We next investigated the conversion of **2** to the other indole alkaloid **3** by the Sharpless asymmetric dihydroxylation[9] of the 1,1-dimethyl-2-propenyl group. Oxidation of **2** by the standard procedure with commercially available AD-mix-β (0.2% osmium, 1% $(DHQD)_2$-PHAL ligand) proceeded very slowly, but an acceptable rate (24 h at 4°C) was obtained by fortifying the AD-mix-β with up to 10% osmium and 10% ligand. After the work-up, we isolated more than a 90% yield of the diol (*R*)-**3**, but the enantiomeric excess was revealed to be only 30%.[10] After screening of the Sharpless' AD ligands as shown in Table 1, oxidation of **2** with $(DHQD)_2$-PYR produced (*R*)-**3** with an improved ee of 89%, and its absolute stereochemistry was assigned to be (*R*) in comparison with the optical rotation. The alkaloid (*S*)-**3**, having the natural configuration, was also obtained with 69% ee using the pseudoenantiomeric $(DHQ)_2$-PYR, with the usual decrease in the ee values upon changing from DHQD to DHQ.

N-Reverse prenylated tryptophan was also synthesized as shown in Scheme 2. After methyl esterification of **14**, the reduction of the indole ring with $(CF_3CO_2)_2BH{\cdot}THF$[11] afforded the indoline **15** in 96% yield. In a manner similar to our strategy, propargylation with **9** followed by CMD oxidation gave the indole **16** in good yield. Finally, partial reduction of the terminal alkyne provided the *N*-reverse prenylated tryptophan **17** as its protected form.



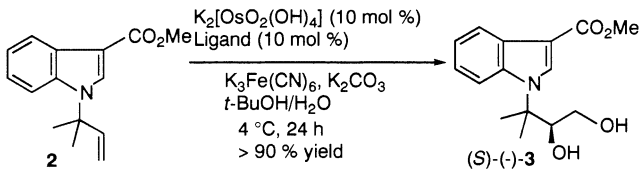
Scheme 1. (a) CuCl, *i*-Pr_2NEt, **9**, THF, 50°C, 90%; (b) H_2 (1 atm), Lindlar's catalyst, MeOH, rt, 91%; (c) MnO_2(CMD), toluene, rt, 86%; (d) NBS, DMF, 96%; (e) *t*-BuLi, THF, −78 to 0°C; (f) $ClCO_2Me$, −78 to 0°C, 89%.



Scheme 2. (a) MeI, $KHCO_3$, DMF, 0°C to rt; (b) $BH_3{\cdot}Me_2S$, TFA, THF, 0°C, 96% in two steps; (c) **9**, CuCl, *i*-Pr_2NEt, THF, 50°C, 75%; (d) MnO_2 (CMD), toluene, rt, 94%. (e) H_2 (1 atm), Lindlar's catalyst, EtOAc, rt, 95%.

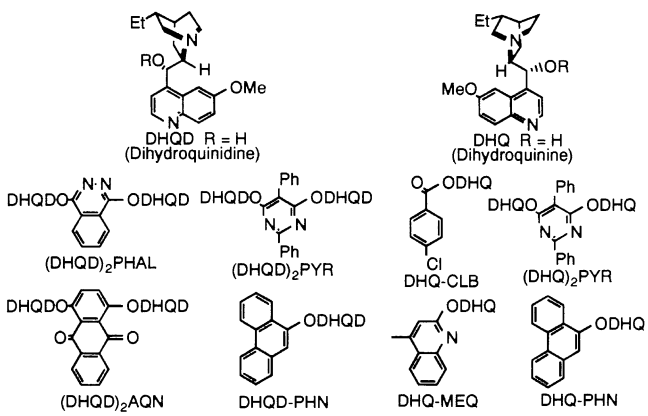
In summary, we have accomplished the efficient synthesis of *N*-1,1-dimethyl-2-propenyl (reverse prenyl) indole (**12**) and the total synthesis of the antifungal indole alkaloids **2** and **3**. We have also synthesized the *N*-reverse prenylated tryptophan as the component of some biologically active peptides. Further application of our strategy to the synthesis of the hydroxy tryptophan fragment **6** of cyclomarin A and its total synthesis are currently under way in our laboratory and will be reported in due course.

Table 1.



Entry	Ligand	% ee[a]	Abs. conf.
1	$(DHQD)_2PHAL$	30	*R*
2	$(DHQD)_2AQN$	2	*R*
3	$(DHQD)_2PYR$	89	*R*
4	DHQD-PHN	79	*R*
5	$(DHQ)_2PYR$	69	*S*
6	DHQ-MEQ	66	*S*
7	DHQ-PHN	66	*S*
8	DHQ-CLB	12	*S*

[a] Determined by chiral HPLC.[10]



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10. The ee was determined by chiral HPLC (DAICEL CHIRALPAK AD, flow rate: 1.0 ml/min, *n*-hexane:*i*-PrOH = 9:1, retention time: 16.2 min (*S*), 18.2 min (*R*)).
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