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Short, Enantioselective Total Synthesis of Okaramine N

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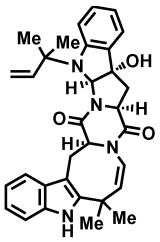
The okaramines are a family of biologically active tryptophan-derived heptacyclic and octacyclic alkaloids produced by a strain of the fungus *Penicillium simplicissum* (ATCC 90288) and first described by Prof. H. Hayashi and co-workers.[1] To date, no synthesis of any member of this group of complex natural products has been reported. We describe herein a remarkably simple synthesis of okaramine N (**1**)[1a] that takes advantage of a powerful new Pd-promoted construction of the dihydroindoloazocine cyclic subsystem that was recently devised and applied to the austamide family of pentacyclic dihydroindoloazocine alkaloids.[2]

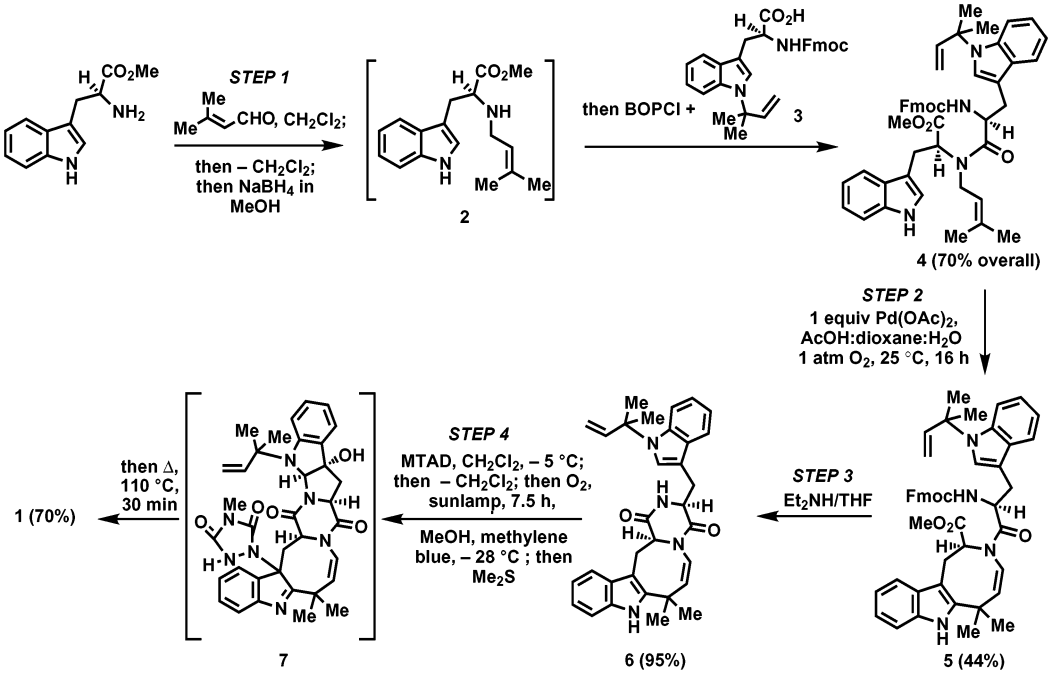


okaramine N (1)

Although we were successful in developing an extremely simple-looking route to **1** and in demonstrating the power of the Pd methodology for generating the dihydroindoloazocine system, we were surprised and repeatedly humbled by the large number of completely unforeseen roadblocks. Many key transformations in alternative routes to **1**, which a priori seemed likely to succeed, failed completely. In many respects, the development of the synthesis of **1**, which is outlined in Scheme 1, was similar to finding a way up a vertical cliff that offers just a limited number of small cracks and handholds.

The first step in the synthesis of okaramine N (**1**) was the assembly of the tetracyclic intermediate **4** from (*S*)-tryptophan methyl ester by reductive N-alkylation with 3-methyl-2-butenal (Schiff base formation in CH_2Cl_2, removal of CH_2Cl_2, reaction of the Schiff base with $NaBH_4$ in MeOH at 0 °C for 30 min, and removal of MeOH in vacuo to give **2**)[2] (Scheme 1), followed by acylation of **2** with the tryptophan derivative **3**. Reaction of **3** (synthesized as described below) with 1.2 equiv of diisopropylethylamine and 1.2 equiv of bis(2-oxo-3-oxazolidyl)phosphinic chloride (BOPCl) afforded the corresponding mixed anhydride, which was allowed to react with **2** at 0 °C for 3 h to afford **4** in 70% overall yield.[3] The second step of the synthesis, cyclization of **4** to form the pentacycle **5**, was accomplished under conditions similar to those defined earlier for Pd-promoted dihydroindoloazocine formation.[2] Thus, treatment of **4** with 1 equiv of $Pd(OAc)_2$ in 1:3.5:1 acetic acid−dioxane−water at 23 °C for 16 h provided **5** in 38% isolated yield[3] (44% yield based on recovered starting material). Despite the presence of two indole subunits in **4**, only the N-unsubstituted subunit appeared to react, and only eight-membered ring formation was observed (only traces of seven-membered cyclization product[2] could be detected). The yield of the transformation **4** → **5** was not diminished upon scale-up to the gram level. Exposure of **5** to excess diethylamine in THF at 0−23 °C for 6 h resulted in Fmoc cleavage and cyclization to form the diketopiperazine **6** (95%).[3] In principle, the synthesis of okaramine N (**1**) from **6** might be accomplished by $^1\Delta g$ O_2-mediated photooxi-

Scheme 1. Enantioselective Synthesis of Okaramine N



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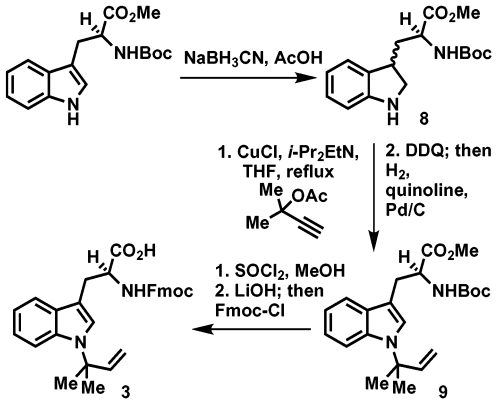
Scheme 2. Synthesis of **3**

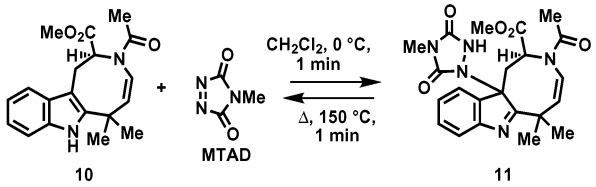


dation of the *tert*-prenylated indole subunit followed by cyclization. In actuality, photooxidation of **6** occurs most rapidly at the N-unsubstituted indole subunit. Further, when the *tert*-prenylated indole subunit is attacked by $^1\Delta g$ O_2, the predominating reaction is cleavage of the indole 2,3-π-bond to form an *N*-formyl kynurenine system. These facts led us to develop a new method for the selective differentiation of the two indole subunits of **6** that involves a novel application of the commercially available "ene" reaction reagent *N*-methyltriazolinedione (MTAD). The bisindole **6** underwent highly selective reaction with MTAD in CH_2Cl_2 at -5 °C for 10 min to form exclusively the ene product at C(3) of the N-unsubstituted indole subunit. Subsequent photooxidation (methylene blue as a photosensitizer in MeOH at -28 °C for 7.5 h with irradiation by a sunlamp) followed by reduction of the resulting product by Me_2S in MeOH (from -28 to -10 °C over 3 h) afforded the hydroxylated octacycle **7** cleanly together with a minor amount of diastereomer (ratio of **7** to diastereomer of ca. 5). Thermolysis of the mixture of **7** and the diastereomer at 110 °C for 30 min and chromatographic isolation[3] furnished okaramine N (**1**) in 70% yield from **6**, based on recovered **6** (ca. 50%, due to incomplete photooxidation).

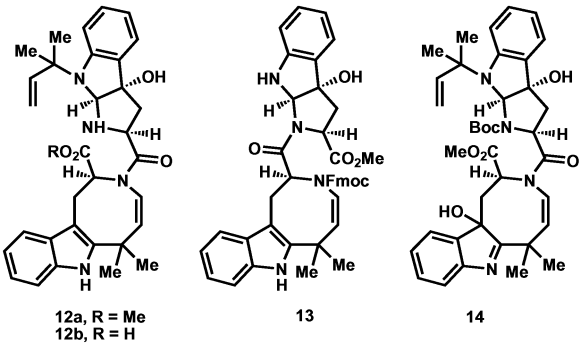
The synthesis of *tert*-prenylated indole **3** was accomplished as illustrated in Scheme 2. (*S*)-*N*-Boc-tryptophan methyl ester was converted to the known indoline **8** in 60% yield using excess $NaBH_3CN$ (10 equiv) in HOAc at 23 °C for 12 h.[4] The *tert*-prenyl group was installed with formation of **9** by the following sequence: (1) copper(I)-catalyzed alkylation with 2-acetoxy-2-methyl-3-butyne (0.1 equiv of CuCl, 1.1 equiv of *i*-Pr_2NEt, THF, reflux, 95%);[5] (2) dihydroindole → indole dehydrogenation by treatment with DDQ (1.05 equiv, 0 °C, 20 min); and (3) selective reduction of ethynyl to vinyl (1 atm H_2, cat. 10% Pd−C, MeOH containing quinoline, 87% yield for two steps). The Boc-protecting group was then removed from **9** (1.5 equiv of $SOCl_2$, MeOH, 50 °C for 2 h) and the resulting amino ester was saponified to the amino acid (15 equiv of LiOH, THF−H_2O 3:1, 0 °C, 2 h). Schotten−Baumann acylation of the amino acid with FmocCl (CH_2Cl_2 added, 10% aqueous Na_2CO_3, 1.1 equiv of FmocCl, 0 °C, 10 min, 81% overall yield) gave **3**.

Crucial to the success of the synthesis of **1** which is outlined in Scheme 1 was the use of the MTAD reagent for selectively protecting one of the indole subunits in **6** so as to allow site-specific photosensitized oxidation of the other (less reactive) indole subunit. Selective and reversible thermal ene reaction of MTAD with an indole derivative is further exemplified in Scheme 3 by the instantaneous and quantitative conversion of **10** to **11** and the reformation of **10** from **11** simply by heating. This is a new and general process with considerable promise in the chemistry of indoles that will be delineated in a separate publication.

Scheme 3. Reversible Ene Reaction of a Dihydroindoloazocine with MTAD



In the introductory paragraph, it was stated that our attempts to synthesize okaramine N by alternative routes led to the surprising failure of reactions that we had expected to proceed in the required way. For example, we were not able to cyclize methyl ester **12a** or acid **12b** to the corresponding diketopiperazine under a wide variety of conditions. In addition, many attempts to convert **13** to the corresponding diketopiperazine met only with failure. Another obstacle was presented by the tendency of *tert*-prenylated intermediates such as **14** to undergo rapid ortho Claisen rearrangement upon acid treatment or heating above 120 °C. Finally, attempts to add the *tert*-prenyl group to des-*tert*-prenyl **1** at the end of the synthesis were unsuccessful.



In summary, the first synthetic route to a member of the okaramine family of polycyclic bisindole alkaloids has been developed by careful choreography of a number of powerful synthetic transformations.

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Supporting Information Available: Detailed experimental procedures for all compounds and full characterization of compounds **1**, **3**, **4**, **6**, and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 103−110 and 1519−1521. (b) Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod.* **1999**, *62*, 315−317. (c) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 1910−1920. (d) Hayashi, H.; Sakaguchi, A. *Biosci., Biotechnol., Biochem.* **1998**, *62*, 804−806. (e) Hayashi, H.; Asabu, Y.; Murao, S.; Arai, M. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 246−250. (f) Hayashi, H.; Fujiwara, T.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1991**, *55*, 3143−3145. (g) Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1989**, *53*, 461−469.
(2) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904−7905.
(3) This product was isolated by silica gel chromatography as an amorphous powder. Solvents used for elution: for **4**, a hexanes−EtOAc gradient; for **5**, a hexanes−ether gradient; for **6**, a hexanes−EtOAc gradient; and for **1**, MeOH−CH_2Cl_2 or EtOAc.
(4) For a previously reported four-step preparation of **8**, see: Dinh, T. D.; Van Vranken, D. L. *J. Pept. Res.* **1999**, *53*, 465−474.
(5) (a) Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908−4912. (b) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282−2284. (c) Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277−7280.

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