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Total Synthesis of (+)-Okaramine J Featuring an Exceptionally Facile N-Reverse-prenyl to C-Prenyl Aza-Claisen Rearrangement

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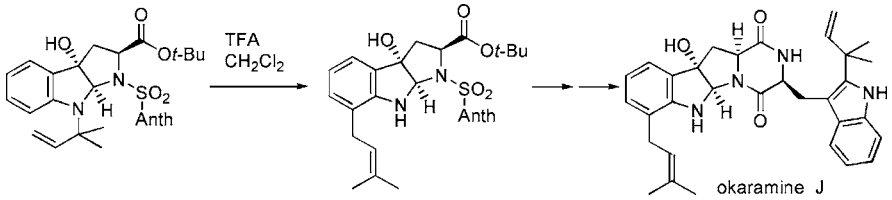
ABSTRACT



The convergent total synthesis of (+)-okaramine J was achieved in a longest linear sequence of 12 steps from L-tryptophan *tert*-butyl ester. A key reaction was the acid-catalyzed room-temperature aza-Claisen rearrangement of a N-reverse-prenylated hexahydro[2,3-*b*]pyrroloindole to a C-prenylated derivative.

The okaramines are a family of indole alkaloids isolated[1] by Hayashi's group from fermentation extracts of *Penicillium simplicissimum* and *Aspergillus aculeatus* cultured on okara[2] (the soybean residue from soymilk production). Biogenetically, these natural products are derived from the L-Trp-L-Trp diketopiperazine by prenylation and further skeletal reorganization (Figure 1). Many display potent insecticidal activity upon oral administration to the third instar larvae of silkworms, e.g., LD_{50} of 8 μg/g of diet for okaramines A and C.

Despite the unusual structural features and in vivo bioactivity, there were no reports of synthetic efforts directed toward the okaramines when we initiated our program. The austamides, alkaloids derived from the Trp-Pro diketopiperazine, contain a similar azocine ring to okaramine A and

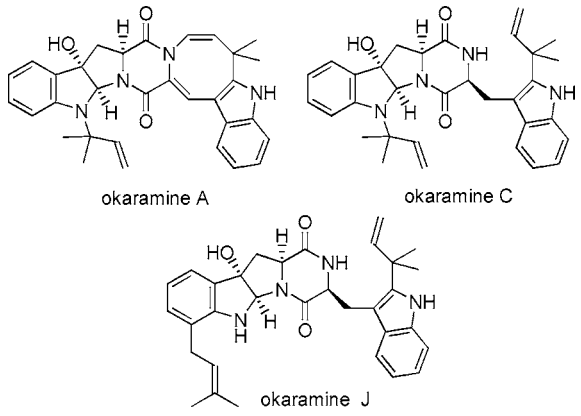


Figure 1. Examples of okaramine alkaloids.

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(1) (a) Murao, S.; Hayashi, H.; Takiuchi, K.; Arai, M. *Agric. Biol. Chem.* **1988**, *52*, 885−886. (b) Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1988**, *52*, 2131−2133. (c) Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1989**, *53*, 461−469. (d) Hayashi, H.; Fujiwara, T.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1991**, *55*, 3143−3145. (e) Hayashi, H.; Asabu, Y.; Murao, S.; Arai, M. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 246−250. (f) Hayashi, H.; Sakaguchi, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 804−806. (g) Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod.* **1999**, *62*, 315−317. (h) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1910−1920. (i) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 103−110.

(2) O'Toole, D. K. *J. Agric. Food Chem.* **1999**, *42*, 363−371.

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were the subject of total synthesis by Hutchison and Kishi[3] and, more recently, Baran and Corey.[4]

Our initial target was okaramine C, the simplest of the alkaloids with high biological activity. Disconnection across the diketopiperazine ring and removal of the N-reverse-prenyl group gives two known amino acid fragments (Figure 2)

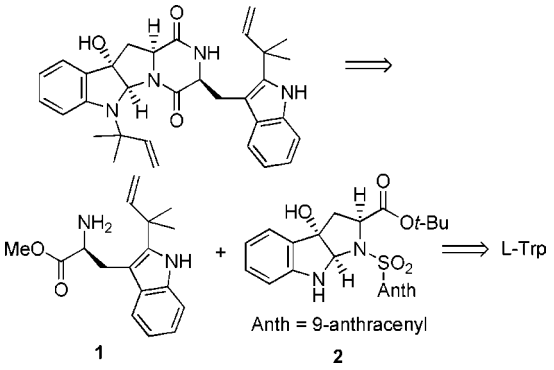
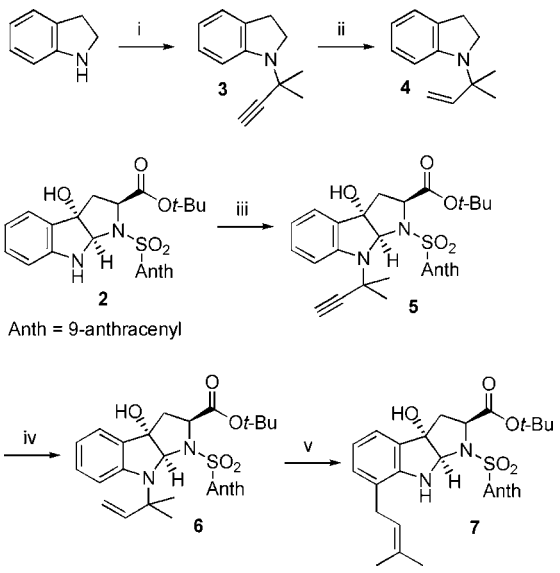


Figure 2. Retrosynthesis of okaramine C.

elegantly prepared by Danishefsky in the course of other endeavors. The indole C-2 reverse-prenylated derivative **1**, made in four steps from L-Trp methyl ester, featured in the total syntheses[5] of gypsetin and brevianamide E. The hexahydro[2,3-*b*]pyrroloindole **2** was obtained as a single diastereomer in four steps by oxidative Witkop cyclization of L-Trp *tert*-butyl ester and was an intermediate in the total synthesis[6] of himastatin.

With **1** and **2** in hand, our next challenge was the N-reverse-prenylation of **2**. This was first investigated with indoline as a simpler model. Alkylation with a propargylic bromide in an adaptation of Hennion's conditions,[7,8] where the chloride was employed, gave **3** (Scheme 1), which was smoothly hydrogenated using Lindlar's catalyst to the alkene **4**. Not for the first time in this project, these results were not readily extrapolated to the real system. The alkylation of **2** was sluggish and proceeded in poorer yield, albeit with

Scheme 1[a]



[a] Reagents and conditions: (i) 1.2 equiv of $HC{\equiv}CC(CH_3)_2Br$, 10 mol % CuCl, 1.2 equiv of *i*-Pr_2NEt, THF, 3 h, 65%; (ii) 1 atm H_2, 5 wt % Lindlar's catalyst, EtOAc, 3 h, 95%; (iii) 1.2 equiv of $HC{\equiv}CC(CH_3)_2Br$, 20 mol % CuCl, 1.2 equiv of *i*-Pr_2NEt, THF, 3 days, 55% (+39% recovered **2**); (iv) 1 atm H_2, 20 wt % Pd/Al_2O_3, EtOAc, 1.5 h, 99%; (v) 5 equiv of TFA, CH_2Cl_2, 16 h, 84%.

recovery of 39% starting material. The resulting alkyne **5** was refractory to Lindlar hydrogenation, and a more active catalyst was necessary. The reaction time was carefully optimized to avoid over-reduction to the alkane.

The *tert*-butyl ester of **6** was then deprotected with TMSOTf buffered with 2,6-lutidine.[9] Surprisingly, this was accompanied by rearrangement of the N-reverse-prenyl group to the C-prenylated analogue. Similarly, treatment of **6** with TFA produced rearranged **7** in good yield with the *tert*-butyl ester intact. We believe these transformations are charge-accelerated aza-Claisen rearrangements. The aza-Claisen rearrangement of aromatic allylamines was first studied by Carnahan and Hurd.[10] In the case of *N*-allylaniline itself, pyrolysis was unsuccessful, largely producing aniline and other uncharacterized materials. Later,[11] Hurd and Jenkins achieved a 42% yield of *o*-allylaniline in refluxing xylene and zinc chloride. Most subsequent examples[12,13] of aza-Claisen rearrangements have employed this principle of

(3) (a) Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 539−542. (b) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786−6788.

(4) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904−7905.

(5) (a) Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025−7026. (b) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964−11975.

(6) (a) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2993−2995. (b) Kamenecka, T. M.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2995−2998. (c) Kamenecka, T. M.; Danishefsky, S. J. *Chem. Eur. J.* **2001**, *7*, 41−63.

(7) Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908−4912.

(8) For related amine propargylations with esters, see: (a) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S.-I. *J. Org. Chem.* **1994**, *59*, 2282−2284. (b) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 1, 6517−6522. (c) Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 7277−7280.

(9) Borgulya, J.; Bernauer, K. *Synthesis* **1980**, 545−547.

(10) Carnahan, F. L.; Hurd, C. D.; *J. Am. Chem. Soc.* **1930**, *52*, 4586−4595.

(11) Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418−1423.

(12) For purely thermal rearrangements of aromatic allyl or propargylamines, see: (a) Marcinkiewicz, S.; Green, J.; Mamalis, P. *Tetrahedron* **1961**, *14*, 208−222. Scheurer, H.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 478−489. (b) Prasad, D. V.; Darbarwar, M. *Synth. Commun.* **1988**, *18*, 881−887. (c) Majumdar, K. C.; Bhattacharyya, T. *Tetrahedron Lett.* **2001**, *42*, 4231−4233.

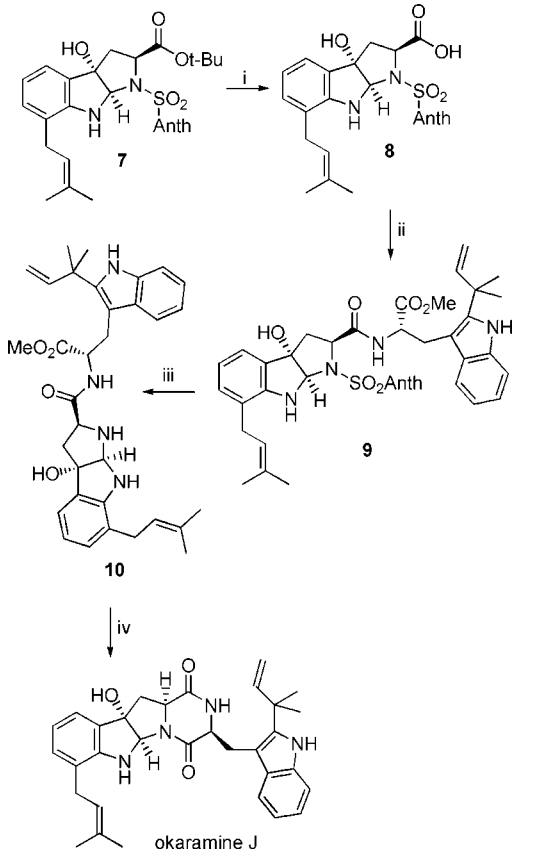
(13) For charge-accelerated aza-Claisen rearrangements, see: (a) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, 4661−4664. (b) Schmid, M.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 105−124. (c) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978−1032. (d) Barmettler, P.; Hansen, H.-J. *Helv. Chim. Acta* **1990**, *73*, 1515−1573. (e) Lai, G.; Anderson, W. K. *Tetrahedron Lett.* **1993**, *34*, 6849−6852. (f) Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095−5100. (g) Anderson, W. K.; Lai, G. *Synthesis* **1995**, 1287−1289. (h) Lai, G.; Anderson, W. K. *Tetrahedron* **2000**, *56*, 2583−2590. (i) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621−625.

charge acceleration either by protic or Lewis acid catalysis or by using quaternary anilinium substrates. In addition, the reactions are typically carried out at >100 °C.

Our observation of the facile rearrangement of **6** under relatively mild conditions is unprecedented. We are unaware of any aza-Claisen rearrangements of aromatic allylamines reported at ambient temperature. We believe that the rearrangement is facilitated by a Thorpe−Ingold effect, placing the vinyl group in the desired conformation away from the bulky sulfonamide, and by the inductively electron-withdrawing nature of the other functionality present in the hexahydro[2,3-*b*]pyrroloindole. In support of this hypothesis, the simpler indoline **4** did not undergo rearrangement under the same conditions.

The formation of **7** thwarted our objective of reaching okaramine C. On the other hand, **7** is a suitable intermediate for the serendipitous total synthesis of okaramine J. Removal of the *tert*-butyl ester provided acid **8** (Scheme 2), which was coupled with **1** to furnish **9** in good yield. Reductive removal of the anthracenylsulfonamide protecting group afforded **10**. Several attempts at the direct formation of a diketopiperazine from **10** were to no avail. Instead, the methyl ester was hydrolyzed to the free amino acid, which underwent cyclization under peptide coupling conditions to give (+)-okaramine J in 49% yield. Spectra obtained with our synthetic material were identical in all respects to those of naturally isolated okaramine J.

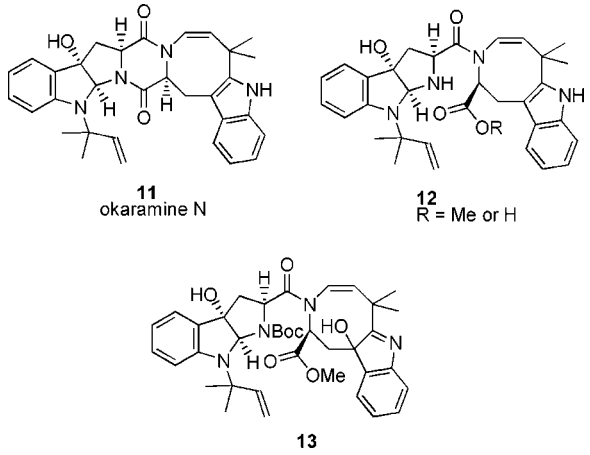
Scheme 2[a]



[a] Reagents and conditions: (i) 20 equiv of TMSOTf, 50 equiv of 2,6-lutidine, CH_2Cl_2, 3 h, 75%. (ii) 2 equiv of PyBop, 3 equiv of Et_3N, 1.1 equiv of **1**, THF, 5 h, 82%. (iii) Al/Hg, THF/H_2O, 16 h, 73%. (iv) (a) 10% KOH/MeOH, 1,4-dioxane, 16 h; (b) 1.1 equiv of HBTU, 3 equiv of *i*-Pr_2NEt, CH_2Cl_2, 7 days, 49% overall.

In summary, we have accomplished the total synthesis[14] of an okaramine alkaloid, okaramine J, by a convergent route (longest linear sequence of 12 steps from either L-Trp methyl or *tert*-butyl ester or 8 steps from the known **1** and **2**). The synthesis features the employment of a propargylic bromide for the N-reverse-prenylation of amines. This modification instead of the usual chloride or acetate is likely to be useful for less reactive amines. A key step is an unusually facile aza-Claisen rearrangement. It is tempting to speculate whether or not this process is utilized biosynthetically in Nature. We are currently modifying our route to attain the total synthesis of okaramine C, and results will be reported in due course.

Note Added in Proof. At the time of our submission, Baran, Guerrero, and Corey reported (*J. Am. Chem. Soc.* **2003**, *125*, 5628−5629) a concise total synthesis of okaramine N **11**. The paper briefly describes some failed approaches, two of which are relevant to our synthesis. The cyclization of **12** under a variety of conditions was unsuccessful (cf. our difficulties with **10**), while **13** underwent aza-Claisen rearrangement upon acid treatment or heating above 120 °C.



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Supporting Information Available: ^1H, ^{13}C, and DEPT-135 NMR spectra for all new compounds and comparison spectra of naturally isolated and synthetic (+)-okaramine J. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Portions of this work were disclosed at: (a) Royal Society of Chemistry, Perkin Division Southwest Regional Meeting, Swansea, United Kingdom, 16th December, 2002. (b) Cambridge Healthtec Institute, Advancing Library Design and Organic Synthesis, San Diego, 24th February, 2003.