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A Short Synthetic Route to (+)-Austamide, (+)-Deoxyisoaustamide, and (+)-Hydratoaustamide from a Common Precursor by a Novel Palladium-Mediated Indole → Dihydroindoloazocine Cyclization

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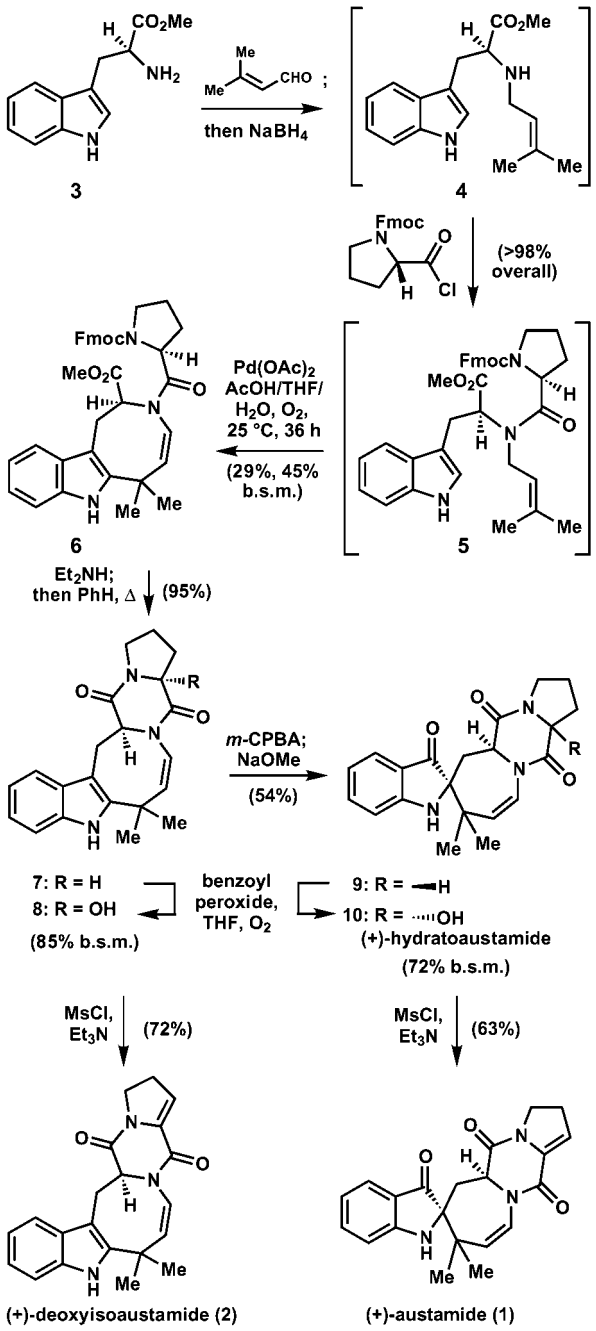
Fungi utilize tryptophan along with other amino acids and prenyl (isoprenoid) groups to form a large assortment of natural centa-molecules (molecular weights in the hundreds) which exhibit a range of potent biological effects (e.g. antimicrobial, insecticidal, and anthelmintic).[1,2] A subset of this class that either contains or is derived biosynthetically from the unusual indoloazocine tricyclic subunit presents a novel structural challenge that attracted our attention. Described herein is the first enantioselective total synthesis of (+)-austamide (**1**) and its naturally occurring relatives **2** and **10** (Scheme 1)[3] from a common intermediate by a short and novel route. The only previously reported work in this area is Kishi's pioneering synthesis of racemic austamide in 29 steps.[4] The key step in the present synthesis is a new multistage, palladium-mediated conversion of an *N*-prenylated tryptophan derivative to the dihydro-indoloazocine tricycle in one step.

The pathway of synthesis is shown in Scheme 1. (*S*)-Tryptophan methyl ester was converted to the Schiff base with 3-methyl-2-butenal in CH_2Cl_2 (4 Å molecular sieves at 23 °C for 3 h) which, after removal of CH_2Cl_2, was reduced with $NaBH_4$ in CH_3OH (0 °C, 30 min) to form **4**. Removal of solvent and reaction with *N*-(9-fluorenylmethoxycarbonyl) (Fmoc) (*S*)-prolyl chloride in CH_2Cl_2 at 23 °C produced the coupled amide **5** (>98% yield from **3**), which was isolated simply by removal of solvent and used directly in the next step. Although the key step in the synthesis, cyclization of **5** to **6**, was beyond the scope of known methods for the construction of eight-membered rings, we were able to discover a workable new method. Treatment of **5** with 1 equiv of $Pd(OAc)_2$ in 1:1:1 THF−H_2O−HOAc at 23 °C under 1 atm of O_2 for 36 h afforded after flash chromatography on silica gel the desired indoloazocine **6** (29% from **3**; 45% based on recovered starting material **5**). Fmoc cleavage (excess Et_2NH in THF at 23 °C) and heating of the resulting amino ester at reflux in C_6H_6 produced the diketopiperazine **7**, $[\alpha]_D^{23}$ +170 (*c* 0.5, $CHCl_3$) (95% from **6**). The synthesis of (+)-austamide (**1**) was accomplished in four steps from **6**, which followed parts of the Kishi synthesis of (±)-austamide,[4] including the following: (1) epoxidation of the 2,3-bond of the indole subunit in **7** with subsequent C−O cleavage to form a 3-hydroxy indoline that was then converted diastereoselectively to the spirocyclic oxindole **9** by heating with $NaOCH_3$ in CH_3OH at reflux for 45 min; (2) radical-initiated α-hydroxylation of the proline subunit in **9** (benzoyl peroxide, O_2, in THF at 55 °C), followed by reduction of hydroperoxide to hydroxyl with $(CH_3)_2S$ to form (+)-hydratoaustamide (**10**); and (3) dehydration with CH_3SO_2Cl−Et_3N in CH_2Cl_2 to give **1**, $[\alpha]_D^{23}$ +133 (*c* 0.03, EtOH). The spectroscopic data for synthetic **1** matched those reported previously.[3−6]

In a similar way (+)-deoxyisoaustamide (**2**) was synthesized from **7** by (1) radical-initiated α-hydroxylation at C(2) of the proline subunit to form **8** and (2) dehydration of **8** with CH_3SO_2Cl−Et_3N−CH_2Cl_2 to give **2**, $[\alpha]_D^{23}$ +100, in $CHCl_3$.

Scheme 1. First Enantioselective Total Syntheses of (+)-Austamide (**1**) and (+)-Deoxyisoaustamide (**2**)



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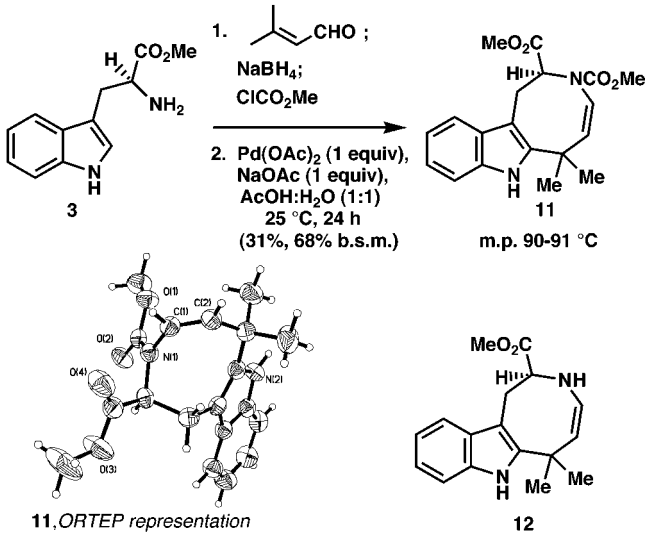
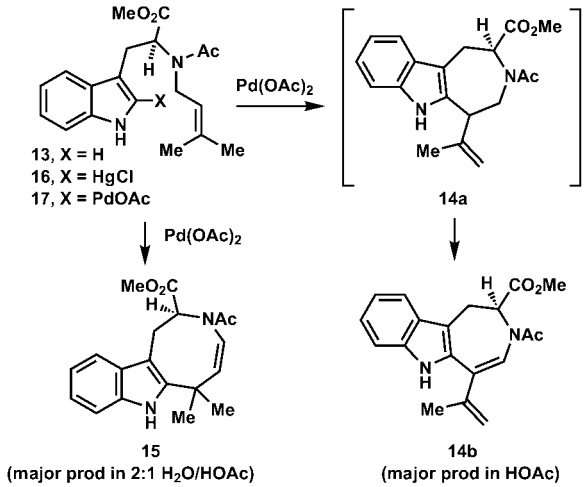
The successful formation of the dihydroindoloazocine system was initially demonstrated by the experimental conversion of (*S*)-tryptophan methyl ester (**3**) to the cyclization product **11** in 31%

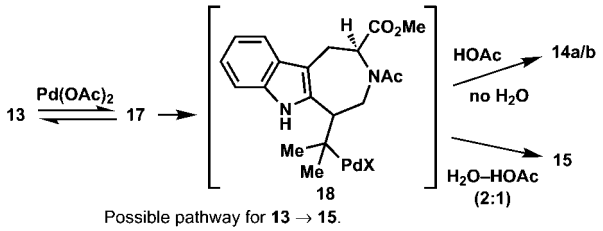


overall yield. The structure of **11** was established firmly by X-ray crystallographic analysis.[6,7] The *N*-Fmoc analogue of the methylcarbamate **11** was also synthesized from **3** by a parallel route and converted by treatment with Et_2NH to the *N*-deprotected dihydroindoloazocine **12**, a versatile intermediate for the synthesis of numerous other *N*-acyl derivatives. This series of compounds is of interest because of recent findings that the insecticidal activity of natural products such as the okaramines depends on the presence of the indoloazocine system.[8,9]



Although we have not carried out an extensive examination of the scope and mechanism of the Pd-mediated indole → dihydroindoloazocine cyclization, we have made a number of significant observations. First, water and acetic acid play an essential role in the process (THF is used to solubilize the starting tryptophan **5**, or its analog). In the absence of acetic acid, no cyclization occurs. In the absence of water, the product from the *N*-acetyl analogue **13** is mainly (4:1) the dihydroindoloazepine derivative **14b** rather than the dihydroindoloazocine **15**. However, in 2:1 H_2O−HOAc as solvent the $Pd(OAc)_2$ mediated reaction converts **13** mainly to **15**, which predominates over **14b** by 15:1. Similar results are obtained starting from the preformed chloromercury derivative **16** as with indole **13**. The rate of the $Pd(OAc)_2$-mediated cyclization is faster

Scheme 2. Possible Pathway for **13** → **15**



Possible pathway for **13** → **15**.

starting with the chloromercurated indole **16** than with the parent indole **13**, indicating that cyclization probably occurs via the palladated indole **17**, which would be the product of Heck HgX → PdX transmetalation of chloromercurial **16**.[10] Direct palladation of indoles at C(2) by Pd(II) reagents is also precedented.[11]

The simplest mechanistic interpretation of our results thus far is shown in Scheme 2 for substrate **13** via **17**. Heck cyclization of **17** could lead to the unstable organopalladium intermediate **18**, which by the usual β-H elimination would give the tetrahydroindoloazepine **14a** and Pd(0). Pd(II) dehydrogenation of **14a** through a π-allyl complex would then lead to dihydroindoloazepine **14b**. Alternatively, in 2:1 aqueous acetic as solvent C−PdX heterolysis to X^- and Pd(0) would produce a cationic intermediate that by migration of the π-electron rich β-[2-indolyl] group would result in ring enlargement and formation of the dihydroindoloazocine **15**.[12] We think it likely that there are additional significant mechanistic details which need to be taken into account because the methoxycarbonyl subunit of the tryptophan reactant appears to be essential for successful cyclization. It is striking that the simple tryptamine derivative lacking the methoxycarbonyl group (*N*-3-methyl-2-butenyl-*N*-methoxycarbonyl tryptamine) does not provide appreciable amounts of dihydroindoloazocine or indoloazepine-type product. A later paper will discuss the role of coordination by the methoxycarbonyl group of **13** (or **5**) with Pd(II) both in indole palladation and in the internal Heck reaction to form **18**.

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Supporting Information Available: Detailed experimental procedures and full characterization of new compounds (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Williams, R. M.; Stocking, E. M.; Sanz-Cervera, J. F. Biosynthesis of Prenylated Alkaloids Derived from Tryptophan. In *Topics in Current Chemistry*: Vol. 209, Biosynthesis-Terpenes and Alkaloids; Leeper, F., Vederas, J. C., Eds.; Springer-Verlag: New York, 2000; pp 97−173.
(2) Stocking, E. M.; Williams, R. M.; Sanz-Cervera, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9089−9098.
(3) (a) Steyn, P. S. *Tetrahedron Lett.* **1971**, 3331−3334. (b) Steyn, P. S. *Tetrahedron* **1973**, *29*, 107−120. (c) Sames, P. G. *Fortschr. Chem. Org. Naturst.* **1975**, *32*, 51−117.
(4) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786−6788.
(5) Hutchison, A. J. Ph.D. Dissertation, Harvard University, 1980.
(6) For experimental details, see Supporting Information.
(7) Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.
(8) (a) Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod.* **1999**, *62*, 315−317. (b) Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1989**, *53*, 461−469.
(9) Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1519−1521.
(10) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518−5526.
(11) (a) Trost, B. M.; Godleski, S. A.; Genet, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930−3931. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557−579.
(12) For analogy, see: Jensen, F. R.; Ouellette, R. J. *J. Am. Chem. Soc.* **1961**, *83*, 4477.

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