Total Synthesis of Asperazine

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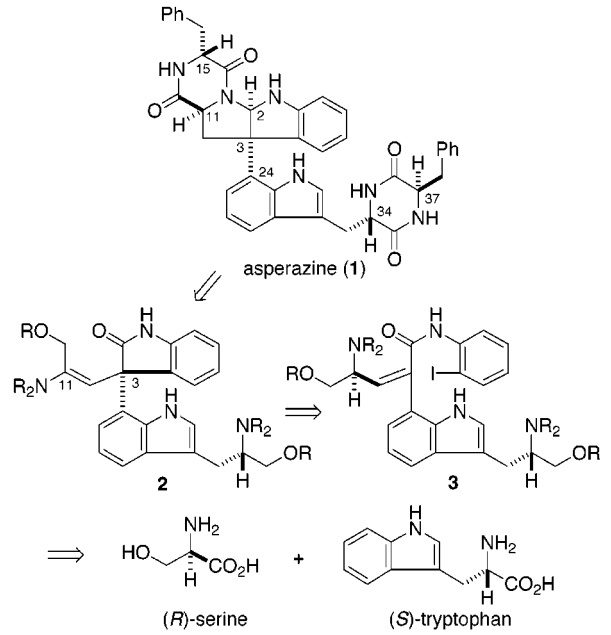
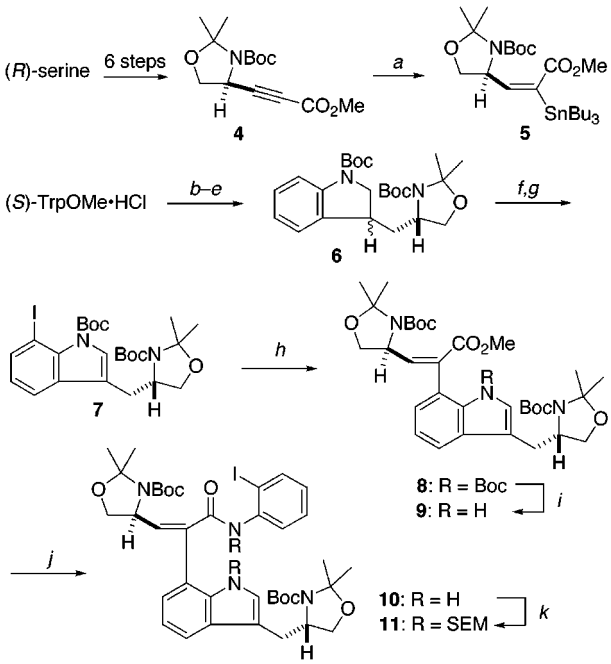
In 1997, Crews and co-workers reported the isolation of asperazine (**1**) from a saltwater culture of the fungus *Aspergillus niger* obtained from a Caribbean *Hyrtios* sponge.[1] Asperazine is a member of a large family of diketopiperazine alkaloids that contain two tryptophan units.[2] However, asperazine differs from other members of this family by having the tryptophan units linked in an unsymmetrical fashion; this bonding generates the diaryl-substituted quaternary stereocenter C3. The relative configuration of asperazine was proposed on the basis of extensive NMR investigations, whereas the absolute configuration was assigned when hydrolysis of **1** provided only (*R*)-phenylalanine.[3] Biological evaluation of asperazine revealed no antibacterial or antifungal activity but did show asperazine to exhibit significant differential cytotoxicity toward leukemia in vitro.[4] Unfortunately, further biological studies have not been possible due to the inability to regrow asperazine-producing *A. niger* cultures.[5] Herein, we report the first total synthesis of asperazine by an efficient sequence capable of providing meaningful amounts of asperazine and its congeners.

Because there was some ambiguity concerning the relative configuration of the diketopiperazine rings,[1,3] we developed a flexible synthetic strategy that would allow for ready access to asperazine, its diastereomers, and derivatives thereof. The fundamental challenge in a stereocontrolled synthesis of asperazine is forming the quaternary stereocenter C3. Although this challenge could have been addressed using an asymmetric Heck reaction,[6] we chose to develop an alternate approach in which the quaternary center would evolve from an uncommon diastereoselective Heck cyclization (**3** → **2**) (Scheme 1).[7] Two significant advantages of this strategy were envisaged: (1) the enamine (or enamide) functionality of **2** would provide a good handle for introduction of the C11 stereocenter, and (2) facial selectivity of the pivotal Heck cyclization could be ascertained easily from the geometry of the trisubstituted double bond of **2** because the newly formed sp^2 and sp^3 stereocenters (C11 and C3, respectively) would be correlated by the stereospecifity of the migratory insertion and β-hydride elimination steps.[6] Indole **3** was seen as arising from (*R*)-serine and (*S*)-tryptophan. This general approach, employing α-amino acid building blocks, would allow access to asperazine as well as a diversity of analogues.

Scheme 1



Scheme 2[a]



[a] Key:[8] (a) *n*-Bu_3SnH, $(Ph_3P)_4Pd$, CH_2Cl_2, −10 °C, 88%; (b) Et_3SiH, TFA, 50 °C; (c) Boc_2O, aq Na_2CO_3, dioxane; (d) $NaBH_4$, LiCl, EtOH, THF; (e) 2,2-dimethoxypropane, *p*-TsOH, PhH, 87% (over four steps); (f) *s*-BuLi, TMEDA, Et_2O, −78 °C; ICH_2CH_2I, 73%; (g) DDQ, K_2CO_3, PhMe, 70 °C, 47% (48% recovered sm); (h) **5**, $Pd_2(dba)_3$•$CHCl_3$, (2-furyl)$_3$P, CuI, NMP; (i) DMSO, 130 °C, 84% (over two steps); (j) 2-iodoaniline, Me_3Al, K_2CO_3, CH_2Cl_2, 94%; (k) NaH, SEMCl, DMF, 0 °C, 79%.

The synthesis began with the assembly of iodoanilide **11**, the Heck cyclization precursor, utilizing a Stille cross-coupling reaction to form the demanding C3−C24 bond (Scheme 2). The stannane-coupling partner **5** was formed as a 16:1 mixture of regioisomers (α:β) by palladium-catalyzed hydrostannylation[9] of serine-derived ynoate **4**.[10] Halide-coupling partner **7** was synthe-

(1) Varoglu, M.; Corbett, T. H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **1997**, *62*, 7078−7079.

(2) (a) Hibino, S.; Choshi, T. *Nat. Prod. Rept.* **2001**, *18*, 66−87 and earlier reviews in this series. (b) Anthoni, U.; Christophersen C.; Nielsen, P. H. In *Alkaloids Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: London, 1999; Vol. 13, pp 163−236.

(3) The absolute configuration of C2, C3, and C11 was assigned on the basis of the absence of a five-bond (∼1 Hz) coupling constant between C11 and C15. The absolute configuration at C34 could not be assigned by NMR methods and was postulated on the basis of biogenetic considerations.[1]

(4) Only 28 of over 20 000 purified organic compounds have shown leukemia selectivity in the Corbett−Valeriote disk diffusion assay.[1]

(5) Personal communication to L.E.O. from Professor Phillip Crews.

(6) (a) Donde, Y.; Overman, L. E. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; Chapter 8G. (b) Shibasaki, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1996; pp 119−151.

(7) Heck reactions in which the stereoinducing element is external to the ring being formed are uncommon. For two recent examples, see: (a) Overman, L. E.; Paone, D. V.; Stearns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702−7703. (b) Buezo, N. D.; Mancheno, O. G.; Carretero, J. C. *Org. Lett.* **2000**, *2*, 1451−1454.

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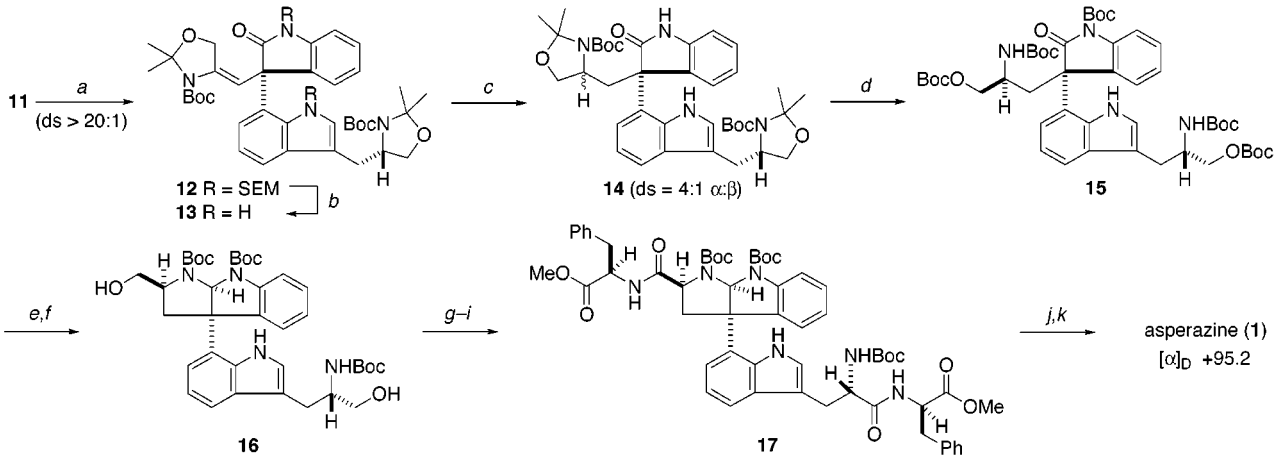
Scheme 3[a]



[a] Key:[8] (a) $Pd_2(dba)_3$·$CHCl_3$, (2-furyl)$_3$P, PMP, DMA, 90 °C, 66%; (b) Bu_4NF, 0.1 mm, 85%; (c) 1000 psi H_2, 10% Pd/C, DMF, 95%; (d) 1 N HCl, dioxane, 50 °C; Boc_2O, 1 N NaOH, Bu_4NHSO_4, CH_2Cl_2, 59%; (e) $LiEt_3BH$, THF, −78 °C → 0 °C; HCl, 0 °C → rt; (f) KOH, MeOH, 79% (over two steps); (g) SO_3·pyr, Et_3N, DMSO; (h) $NaClO_2$, NaH_2PO_4, THF, H_2O, *t*-BuOH, 2-methyl-2-butene; (i) (*R*)-PheOMe·HCl, HATU, Et_3N, CH_2Cl_2, 65% (over three steps); (j) HCO_2H; (k) 0.7 N AcOH, *n*-BuOH, 120 °C, 59%.

sized in six steps from (*S*)-TrpOMe·HCl. The indole ring of this starting material was reduced with Et_3SiH in warm TFA,[11] and then both nitrogens were acylated with Boc_2O. The ester was subsequently reduced with $LiBH_4$, and the resulting amino alcohol protected to provide indoline **6**. Ortho-lithiation[12] of **6** with *s*-BuLi and subsequent quenching with 1,2-diiodoethane installed the iodide in 73% yield. Oxidation to restore the indole was best accomplished with DDQ in warm toluene. At 52% conversion, the yield of **7** was 91%, and the recovered indoline starting material could be recycled.[13] Stille coupling of iodide **7** and stannane **5** proceeded with high efficiency to provide enoate **8**.[14,15] Selective removal of the bulky Boc-protecting group from the indole nitrogen of **8** allowed 2-iodoaniline to be incorporated by Weinreb aminolysis[16] to generate anilide **10**. Finally, protection of both the indole and the anilide nitrogens with SEM groups gave rise to **11**.

With **11** in hand, we turned to the pivotal Heck reaction (Scheme 3). After extensive experimentation, it was found that heating of **11** with 20 mol % $Pd_2(dba)_3$·$CHCl_3$ and 100 mol % (2-furyl)$_3$P in the presence of excess 1,2,2,6,6-pentamethylpiperidine (PMP) provided a single hexacyclic product **12** in 66% yield. Removal of the SEM-protecting groups[17] from **12** gave **13**. At this point, ^{1}H NOE analysis revealed the *E* stereochemistry of the exocyclic double bond, establishing that carbopalladation had occurred from the desired face. Survey experiments demonstrated that hydrogenation of the C11−C12 double bond of protected oxindole **12** would be extremely difficult. Fortunately, hydrogenation of **13** could be realized over Pd/C in DMF at 1000 psi H_2 to provide oxindole **14** in 95% yield as a 4:1 mixture of C11 epimers.

To complete the synthesis of asperazine (**1**), we needed to form the pyrrolidine ring and both diketopiperazines. To this end, removal of the acetonides of **14** with 1 N HCl and exhaustive Boc-protection of the resulting product provided **15**.[18] Low-temperature reduction of **15** with $LiEt_3BH$ gave a mixture of hemiaminals which cyclized to form the desired pyrrolidine ring upon addition of ethereal HCl. Selective cleavage of the carbonates yielded diol **16**.[19] Oxidation of **16** with SO_3·pyridine, $NaClO_2$ oxidation of the resulting dialdehyde, and finally HATU-mediated coupling of this crude diacid with (*R*)-PheOMe·HCl provided tetrapeptide **17**. Removal of the three Boc groups of **17** with formic acid and subsequent cyclization to form both diketopiperazines in refluxing butanol containing acetic acid[20] delivered asperazine (**1**) in 59% yield from **17**.[21]

In summary, the first total synthesis of asperazine was accomplished in 22 steps from readily available amino acid starting materials. This synthesis confirms the structure of asperazine and provides yet another example of the tremendous utility of intramolecular Heck reactions for forging highly congested quaternary carbon centers.

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Supporting Information Available: Experimental procedures and characterization data for key transformations (preparation of **8**, **9**, **12**, **14**, and **1**), copies of ^{1}H and ^{13}C NMR spectra of these compounds, tables comparing NMR spectra of synthetic and natural **1**, and the CD spectrum of synthetic **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For abbreviations not defined in *J. Org. Chem.* **2001**, *66*, 24A, see Supporting Information.

(9) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857−1867.

(10) Reginato, G.; Mordini, A.; Caracciolo, M. *J. Org. Chem.* **1997**, *62*, 6187−6192.

(11) Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *44*, 4809−4813.

(12) Iwao, M.; Kuraishi, T. *Heterocycles* **1992**, *34*, 1031−1038.

(13) At longer reaction times, oxidation at C1 of the indole side chain was observed.

(14) (a) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359−5364. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 3, 9585−9595.

(15) Stannane **5** was a 16:1 mixture of regioisomers; trace amounts of *β*-coupled product were separated after removal of the indole-protecting group.

(16) Lipton, M. F.; Basha, A.; Weinreb, S. M. *Org. Synth.* **1978**, *59*, 49−53.

(17) Moreno, O. F.; Kishi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 8180−8181.

(18) At this point, the diastereomers could be separated by silica gel chromatography. The C11 epimer of **15** was isolated in 17% yield.

(19) That the major isomer produced in the hydrogenation step had the desired configuration at C11 could now be established by ^{1}H NOE analysis of **16**.

(20) Suzuki, K.; Sasaki, Y.; Endo, N.; Mihara, Y. *Chem Pharm. Bull.* **1981**, *29*, 233−237.

(21) Synthetic asperazine showed ^{1}H NMR spectra in three solvents, ^{13}C NMR spectra in two solvents, and mass spectral data that compared favorably to those of the natural isolate.[1] The optical rotation of synthetic asperazine, $[\alpha]_D$ +95.7 (*c*, 0.2, MeOH) was higher than that reported for the natural material, $[\alpha]_D$ +52 (*c*, 0.2, MeOH);[1] however, CD spectra were nearly identical.