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Total synthesis of (+)-asperazine

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Dedicated to Professor Hisashi Yamamoto in honor of his many pioneering contributions to organic chemistry and receipt of the 2006 Tetrahedron Prize

Abstract—The first total synthesis of the structurally novel cyclotryptophan alkaloid asperazine is reported. The central step in the synthetic sequence is a diastereoselective intramolecular Heck reaction in which the substituent controlling stereoselection is external to the ring being formed. This synthesis confirmed the structure of (+)-asperazine (**1**) proposed by Crews and co-workers and provided material for additional biological studies. The in vitro cytotoxicity originally reported for the marine isolate was not confirmed with synthetic (+)-asperazine.

1. Introduction

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 (Fig. 1).[1] Asperazine was reported to display an unusual profile of cytotoxicity. Whereas no activity was seen in antibacterial (*Bacillus subtilis*) or antifungal (*Candida albicans*) assays, significant differential in vitro cytotoxicity was observed against human leukemia.[1,2] Unfortunately, further biological studies were not possible as a result of the small amount of asperazine isolated,[1] and the inability to regrow asperazine-producing *A. niger* cultures.[3]

The structure of asperazine was assigned by a combination of NMR experiments, mass spectrometry, and chemical degradation. Initial NMR investigations coupled with mass spectra indicated that asperazine contained two tryptophan and two phenylalanine units, as such showing structural similarity to WIN 64821 (**2**)[4] and ditryptophenaline.[5] However, unlike these alkaloids, asperazine was not C_2-symmetric. Further NMR analysis demonstrated that the aromatic *peri* carbon of one indole unit was attached to the quaternary benzylic carbon of a cyclotryptophan fragment (the C3–C24 linkage of **1**). Hydrolysis of asperazine provided (*R*)-phenylalanine, leading to the assignment of the *R* configuration at C15 and C37. The relative configuration of C11 and C15 followed from the absence of a five-bond coupling between these hydrogens, which is often seen in proline-containing diketopiperazines when comparable hydrogens are *cis*.[6] The relative configuration at C2, C3, and C11 was ascertained by ^{1}H NMR NOE experiments. Finally, the configurational relationship between the hexacyclic moiety and the pendant diketopiperazine was assumed based on the likelihood that (*S*)-tryptophan was the biogenetic precursor of both tryptophan fragments.

The unavailability of asperazine from natural sources, its potential selective antileukemic activity, and its uncommon structure led us to pursue its total synthesis. In 2001, we reported the first, and to date only, total synthesis of asperazine (**1**).[7] This synthesis confirmed the structure of asperazine proposed by Crews and co-workers and provided additional material for biological studies. In this paper, we report full details of this total synthesis and the experiments that led to the successful synthesis strategy. Moreover, we report that synthetic asperazine, unlike the original natural isolate, shows no significant antileukemic activity in the Corbett–Valeriote soft agar disk diffusion assay.[2]

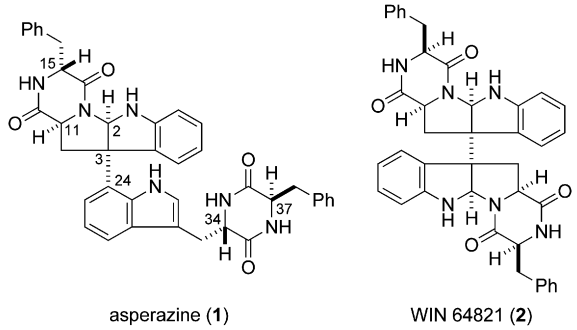

Figure 1. Structures of asperazine and WIN 64821.

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1.1. Synthesis plan

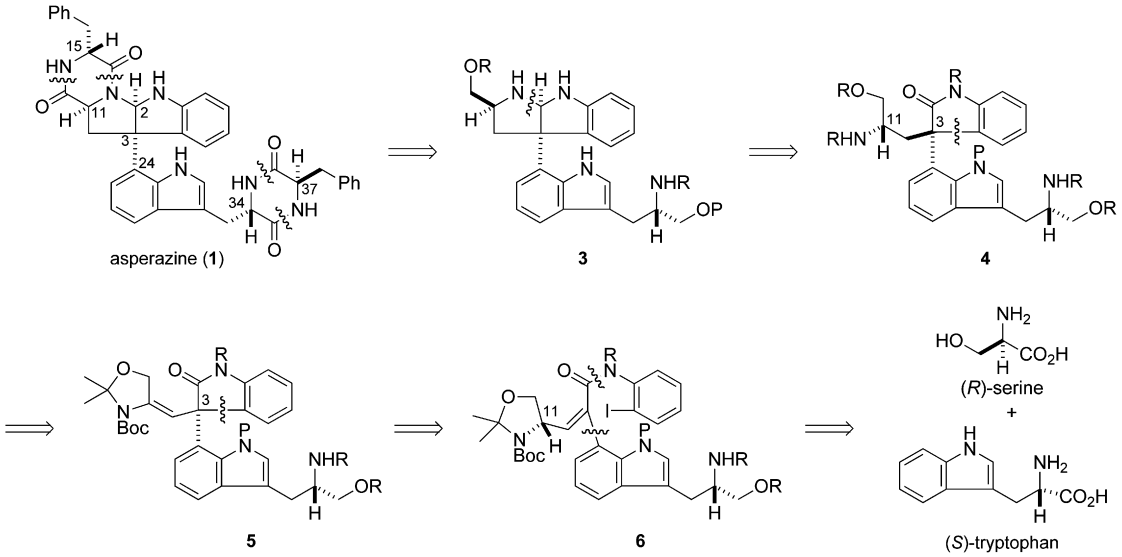
Foremost in a synthetic endeavor targeting asperazine (**1**) is the need to construct the quaternary-carbon stereocenter C3, which unites the two tryptophan-derived fragments.[8] Complicating this task, the indole unit is appended at a sterically congested *peri* aromatic carbon. Another consideration affecting our planning was the possibility that asperazine might not have the relative configuration depicted in representation **1**. We have already noted that there was no experimental evidence for the absolute configuration at C34. Moreover, it remained a possibility that the hydrolytic degradation of asperazine yielding (*R*)-phenylalanine had not cleaved both diketopiperazine units. Thus, we sought to pursue a synthetic approach in which either (*R*)- or (*S*)-phenylalanine and (*R*)- or (*S*)-tryptophan fragments could be synthetic inputs.

The strategy we chose to develop is outlined in retrosynthetic format in Scheme 1 for the specific case in which structure **1** correctly represents the three-dimensional structure of asperazine. Removing the two (*R*)-phenylalanine fragments from **1** provides *cis*-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (for simplicity, hereafter referred to as *cis*-pyrrolidinoindoline) **3**. Further disconnection of the pyrrolidine ring gives oxindole **4**. It is conceivable that this intermediate and its quaternary-carbon stereocenter could be assembled by a catalytic asymmetric intramolecular Heck reaction,[9] an approach we have employed successfully in the total synthesis of several cyclotryptamine alkaloids.[10] However, we chose to develop an alternate, potentially complimentary approach. A plausible precursor of oxindole **4** would be the dehydro congener **5**. At the outset, we entertained the possibilities that hydrogenation of the double bond of **5** to introduce the C11 stereocenter of **4** might be controlled by the nearby quaternary stereocenter C3, or if need be, by a catalyst-controlled hydrogenation.[11] We envisaged intermediate **5** arising from a diastereoselective intramolecular Heck reaction of α,β-unsaturated iodoanilide **6**, in which the serine-derived allylic stereogenic center C11 would control diastereoselection. Such an approach for constructing the pivotal C3–C24 σ-bond had several appealing features. Foremost, it would allow us to explore the ability of a stereocenter external to the ring being formed to regulate stereoselection in a Heck cyclization. Although the use of stereogenic centers in the chain connecting the reacting partners has been exploited often in the stereocontrolled construction of rings by intramolecular Heck reactions,[12] few studies have examined the influence of stereocenters external to the nascent ring.[13] A second appeal of this strategy was the anticipated ease with which the configuration of the newly formed C3 quaternary-carbon stereocenter could be ascertained. Because the configuration of the C–C π-bond and the sp^3 stereocenter C3 in Heck product **5** should be correlated by the suprafacial stereospecificity of the migratory insertion and β-hydride elimination steps, the absolute configuration at C3 should be ascertained easily from the geometry of the trisubstituted alkene. Finally, the Heck cyclization precursor **6** was seen as arising from (*S*)-tryptophan, 2-iodoaniline, and serine. As events transpired, we learned that the C11 stereocenter of precursor **6** would need to be of the *S* absolute configuration, thus deriving from (*R*)-serine, to achieve the desired stereocontrol at C3 in the pivotal Heck cyclization. At the outset, this fact was not known with certainty; thus, the ready availability of either serine enantiomer was an important consideration in the genesis of our synthesis plan.

2. Results and discussion

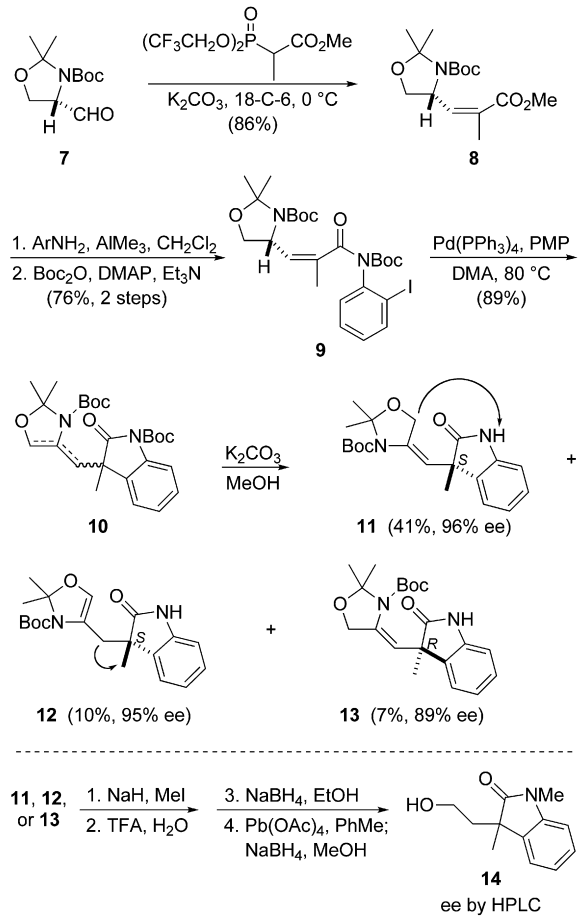
2.1. Model study for forming the C3 quaternary-carbon stereocenter

Before initiating our synthetic endeavor, we wished to examine the feasibility of the proposed diastereoselective Heck reaction in a simpler system. The synthesis of a model Heck cyclization substrate, iodoanilide **9**, is summarized in Scheme 2. Since alkene face stereoselection in the pivotal intramolecular Heck cyclization would be controlled by the



Scheme 1. Retrosynthetic disconnection of asperazine.

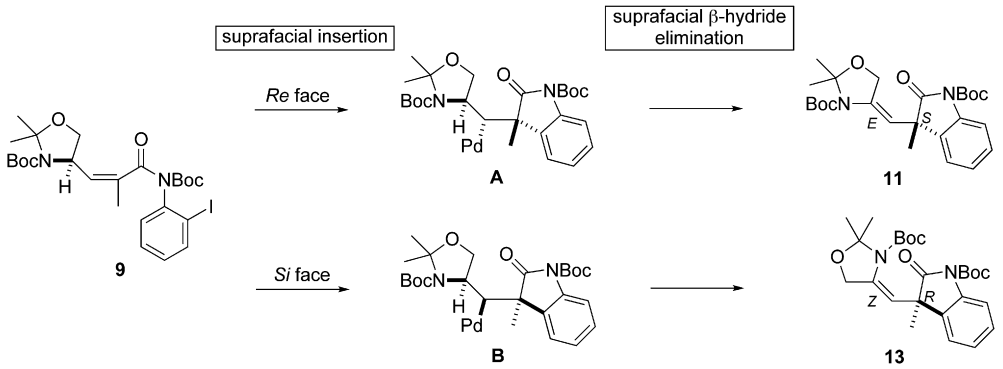
substituents at the γ-carbon of the α,β-unsaturated anilide Heck cyclization precursor, we wanted these substituents to differ considerably in size. As a result, Garner's aldehyde **7** was selected as the starting material; this commercially available precursor is easily prepared on a large scale from (*S*)-serine.[14] Stereoselective Horner–Wadsworth–Emmons olefination of aldehyde **7** provided (*Z*)-enoate **8**.[15] Weinreb amidation of this intermediate with 2-iodoaniline,[16] followed by reaction of the secondary amide product with di-*tert*-butyldicarbonate gave Heck precursor **9** in 65% overall yield from aldehyde **7**.



Scheme 2. Model study of the proposed diastereoselective intramolecular Heck reaction.

We quickly discovered that the desired Heck cyclization took place efficiently when iodoanilide **9** was exposed to 20 mol % $Pd(PPh_3)_4$ and excess 1,2,2,6,6-pentamethylpiperidine (PMP) in *N*,*N*-dimethylacetamide (DMA) at 80 °C for 6 h. These conditions produced three isomeric oxindole products **10**. After initial resolution of this mixture on silica gel, and further separation after the Boc-protecting group had been selectively removed from the oxindole nitrogen by reaction with K_2CO_3 in MeOH, oxindole alkene isomers **11**, **12**, and **13** were isolated, respectively, in 41%, 10%, and 7% overall yields from Heck precursor **9**. NMR spectra, in conjunction with the diagnostic ^1H NMR NOE enhancements for isomers **11** and **13** depicted in Scheme 2, readily established that oxindoles **11** and **13** were *E* and *Z* stereoisomers produced in the initial Heck cyclization, whereas **12** was a product of subsequent double bond migration.[17]

The absolute configuration at the newly formed quaternary-carbon stereocenter of oxindoles **11**–**13** was determined as follows. During a previous investigation in our laboratories, a convenient HPLC method for measuring the enantiomeric purity of 1,3-dimethyl-3-(2-hydroxyethyl)oxindole (**14**) was developed and the absolute configuration of this 3,3-disubstituted oxindole established.[18] Thus, oxindoles **11**–**13** were individually transformed into oxindole **14** by the four-step sequence summarized in Scheme 2. This study revealed that **11** and **12** were *S* enantiomers of similar, high (95–96% ee) enantiomeric purity, whereas oxindole **13** had the *R* absolute configuration and a slightly lower enantiomeric purity (89% ee). Several conclusions could be drawn. First, as anticipated from mechanistic considerations, the absolute configuration of the quaternary-carbon stereocenter and the geometry of the alkene are correlated in such a way that the configuration of the quaternary stereocenter of the primary Heck products **11** and **13** can be ascertained from the configuration of the double bond. This analysis is explicitly developed in Scheme 3. Second, oxindole product **12** is derived almost exclusively from the major Heck product **11**. Thus, diastereoselectivity in the initial Heck cyclization was an encouraging 9:1, with insertion occurring preferentially from the α-*Re* face of α,β-unsaturated amide **9**. Third, there is a slight loss of enantiomeric purity in forming the *R* Heck product **13**, likely arising from a small amount of this product being formed from *S* oxindole **12** by a second double bond migration. Finally, if stereoselection in the pivotal intramolecular Heck reaction in the fully constituted series

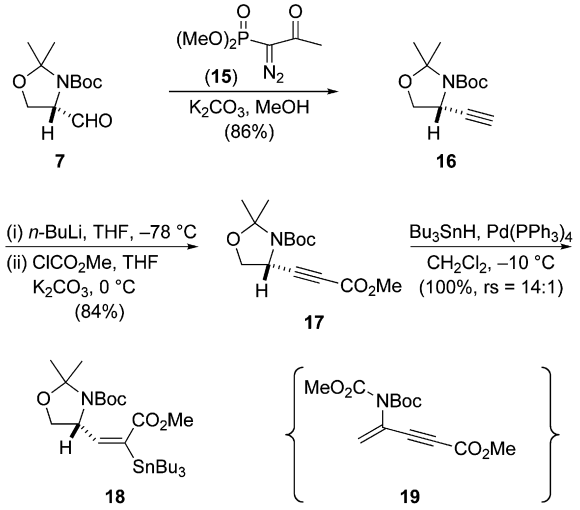


Scheme 3. The expected relationship of the quaternary-carbon stereocenter and double bond of the oxindole products formed from the Heck cyclization of alkenyl iodide **9**.

occurs in similar fashion to that observed in this model series, the Heck cyclization substrate would need to be assembled from (*R*)-serine as depicted in Scheme 1.

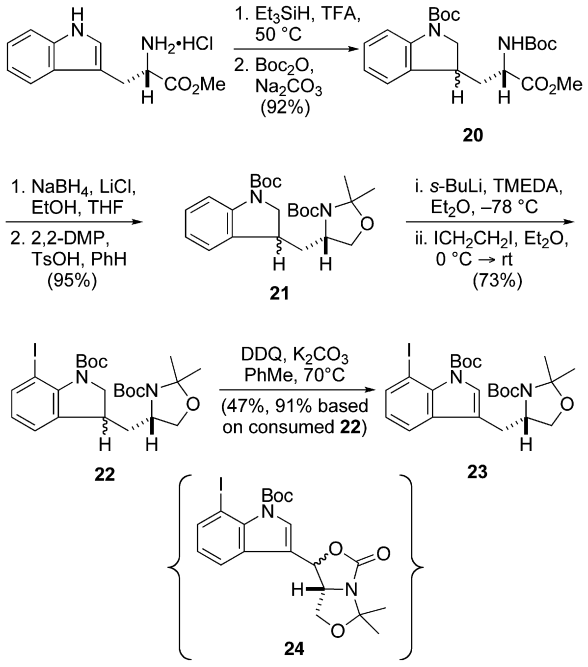
2.2. Initial studies in the (*S*)-serine series

Contemporaneous with the model study described in the previous section, we initiated the synthesis of a more elaborate Heck cyclization substrate having a suitably protected (2-amino-2-carboxyethyl)-1*H*-indol-7-yl substituent at the α-carbon of the α,β-unsaturated anilide Heck cyclization precursor **6** (Scheme 1). Because it was not yet clear at the time what the absolute configuration of the γ stereocenter would need to be, we chose to use less expensive (*S*)-serine in these studies. On the basis of our earlier success in introducing bulky substituents at the hindered *peri* carbon of indoline fragments,[10b–d] we pursued a strategy in which a Stille cross-coupling would be a key step.[19] The requisite stannane **18** was assembled from the *S* enantiomer **7** of Garner's aldehyde (Scheme 4).[14] Initially, we examined the elaboration of aldehyde **7** to alkynoate **17** according to a literature procedure.[20] In our hands, this sequence was not satisfactory as both the formation of the 1,1-dibromoalkene intermediate and its conversion to alkynoate **17** were irreproducible, with enyne **19** being formed as a byproduct. Following another literature precedent,[21] aldehyde **7** was allowed to react with diazoketophosphonate **15**,[22] giving alkyne **16** in 86% yield. The competitive formation of enyne **19** was avoided when the lithium acetylide derivative of alkyne **16** was quenched in an inverse fashion with methyl chloroformate, providing alkynoate **17** in 84% yield. Hydrostannylation[23] of this intermediate was best carried out using 3 mol % of $Pd(PPh_3)_4$ and 2 equiv of Bu_3SnH in CH_2Cl_2 at −10 °C. These conditions delivered vinyl stannane **18**, a 14:1 mixture of regioisomers, in nearly quantitative yield. The use of an excess of Bu_3SnH was necessitated by the palladium-catalyzed decomposition of this reagent to give hexabutylditin and hydrogen gas. In an attempt to avoid the use of an excess of the tin reagent, alternate catalysts such as $Pd_2(dba)_3\cdot CHCl_3$, $Pd(PPh_3)_2Cl_2$, $Pd(dppf)Cl_2$, and $Rh(PPh_3)_2Cl$ were screened; however, all gave inferior results.



Scheme 4. Preparation of vinyl stannane **18**.

With vinyl stannane **18** in hand, we turned to the synthesis of 7-iodotryptophan derivative **23** (Scheme 5). Although functionalizing the 7-position of an indole is a difficult task, the 7-position of *N*-(*tert*-butoxycarbonyl)indolines is readily functionalized by *ortho* lithiation.[24] With such a conversion in mind, (*S*)-tryptophan methyl ester hydrochloride was reduced with Et_3SiH in trifluoroacetic acid[25] and both nitrogens were masked with Boc groups to yield indoline **20** as an inconsequential mixture of epimers. Reduction of this intermediate with $NaBH_4$, followed by reaction of the product with 2,2-dimethoxypropane (2,2-DMP) and catalytic *p*-toluenesulfonic acid gave indoline **21** in high yield. Upon reaction of this intermediate with 1.4 equiv of *s*-BuLi at −78 °C in the presence of TMEDA, followed by inverse quenching of the resulting aryllithium reagent into a 0 °C ether solution of diiodoethane, the 7-iodo derivative **22** was formed in 73% yield.[24] The use of less *s*-BuLi (1.0 or 1.2 equiv) in the initial lithiation step, for up to 2 h at −78 °C, did not result in complete lithiation as confirmed by deuterium quenching experiments.



Scheme 5. Preparation of iodotryptophan derivative **23**.

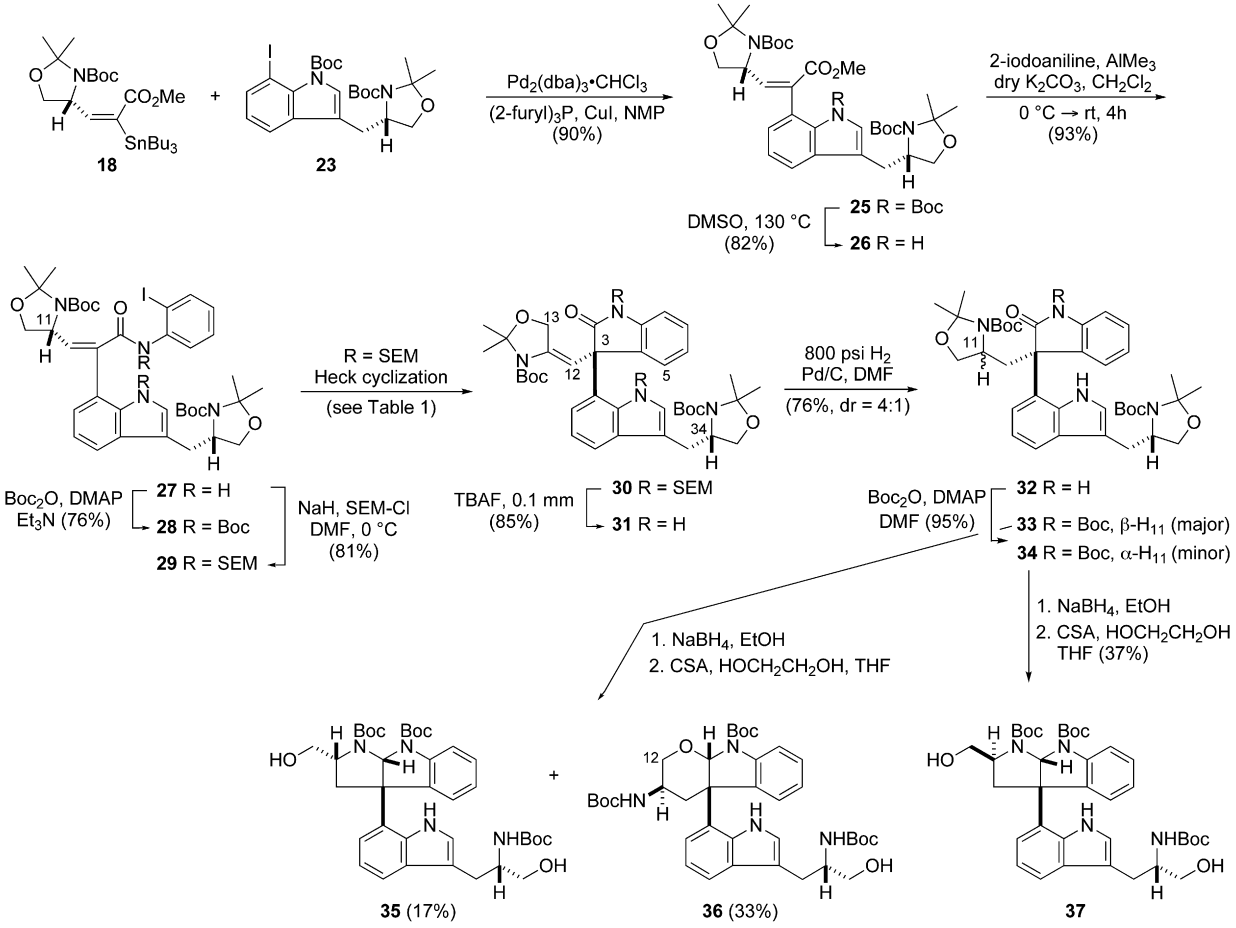
Dehydrogenation of iodoindoline **22** to indole analog **23** turned out to be more challenging than anticipated. Reaction of **22** with DDQ at 70 °C in toluene successfully oxidized the indoline ring, but also led to partial cleavage of the Boc and isopropylidene protecting groups. Inclusion of K_2CO_3 to buffer the hydroquinone byproduct eliminated these side reactions; however, significant amounts of the over-oxidation product **24** were produced. Switching to quinone reagents having lower oxidation potentials, such as *o*- or *p*-chloranil, did not improve this reaction. The best solution we found was to use DDQ and stop the reaction at approximately 50% conversion. Thus, heating a mixture of indoline **22**, DDQ, and K_2CO_3 in toluene at 70 °C for 12 h provided a readily separable mixture of iodotryptophan derivative **23** and the starting indoline **22**. Iodotryptophan derivative **23** was isolated in 47% yield (91% yield based on consumed

starting material) together with 48% yield of iodoindoline **22**, which could be recycled.

The final steps in the construction of Heck cyclization precursors **28** and **29** are summarized in Scheme 6. Stille cross-coupling of stannane **18** and iodide **23** to form α,β-unsaturated ester **25** took place in excellent yield using trifurylphosphine as the ligand[26] and CuI as an additive.[27] However, all attempts to elaborate this intermediate to 2-iodoanilide congeners failed. For example, both direct Weinreb aminolysis of ester **25** with 2-iodoaniline[16] and coupling of the acid derived from **25** with this aniline using Mukaiyama's salt,[28] procedures we have previously used to construct related Heck cyclization precursors,[18] were unsuccessful. Reasoning that the steric bulk of the Boc substituent of the indole was the cause, this group was selectively removed by thermolysis of tri-Boc precursor **25** in DMSO at 130 °C. After chromatographic removal of the minor Stille product derived from the small contaminate of the β-stannane in coupling partner **18**, isomerically pure enoate **26** was isolated in 82% yield. Using a slight modification of Weinreb's procedure[16] in which we added dry K_2CO_3 to minimize the cleavage of acid-labile protecting groups, the condensation of 2-iodoaniline with enoate **26** delivered anilide **27** in 93% yield. NMR analysis showed that this product was a single alkene stereoisomer, whose *Z* configuration was confirmed by ^{1}H NMR NOE experiments.

To favor productive conformations for the Heck cyclization, the anilide nitrogen atom needed to be protected. Attempts to selectively protect this nitrogen resulted in partial functionalization of the indole nitrogen as well. As a result, Boc and SEM protecting groups were placed on both free nitrogens to give rise to Heck cyclization precursors **28** and **29**. Encouraged by the results in the model series, the first Heck cyclization was attempted with Boc precursor **28**. Unfortunately, no reaction conditions were found to effect cyclization of this intermediate. For example, heating of anilide **28** with 40 mol % of $Pd(PPh_3)_4$ and excess PMP in DMA at 80 °C for 72 h resulted only in the formation of palladium containing adducts.[29]

Much more encouraging were the results obtained with the SEM substrate **29**. A survey of cyclization conditions indicated that Pd^0 catalysts containing trifurylphosphine ligands gave the best results; salient experimental results are summarized in Table 1. Under the optimum conditions identified, heating unsaturated iodoanilide **29**, 10 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 1 equiv of $(2\text{-furyl})_3P$, and excess PMP in DMA at 90 °C for 8 h led to the formation of a single detectable oxindole product **30**, which was isolated in 78% yield. The structure of this product was readily secured after the SEM groups were removed from the oxindole and indole fragments.[30] Particularly diagnostic was the strong NOESY correlation observed between H5 and the C13 methylene



Scheme 6. Heck cyclization and elaboration of product **30** to *cis*-pyrrolidinoindoline **35**.

Table 1. Heck cyclization of SEM substrate **29**

Entry	Conditions	Products
1	19 mol % $Pd(PPh_3)_4$, PMP, DMA, 80 °C, 24 h	**29**:**30** (1:1)
2	35 mol % $Pd(PPh_3)_4$, PMP, DMA, 80 °C, 24 h	**30** (52%)
3	16 mol % $Pd(PPh_3)_4$, PMP, MeCN, 80 °C, 18 h	Trace reduction product[a]
4	21 mol % $Pd(PPh_3)_4$, PMP, PhMe, 100 °C, 24 h	**29** and reduction product[a]
5	19 mol % $Pd(PPh_3)_4$, K_2CO_3, DMA, 80 °C, 18 h	Reduction product[a] only
6	33 mol % Pd(dppf)Cl_2, PMP, DMA, 70–90 °C, 2 d	**30** (40%)[b]
7	18 mol % $Pd_2(dba)_3\cdot CHCl_3$, Ph_3As (144 mol %), PMP, DMA, 100 °C, 2 h	No reaction
8	10 mol % $Pd_2(dba)_3\cdot CHCl_3$, Ph_3P (40 mol %), PMP, DMA, 100 °C, 22 h	**30** (56%)
9	27 mol % $Pd(OAc)_2$, Ph_3P (54 mol %), Ag_3PO_4, DMA, 90 °C, 24 h	**30** (39%)
10	25 mol % $Pd(OAc)_2$, Ph_3P (50 mol %), PMP, DMA, 90 °C, 24 h	**30** (56%)
11	7.5 mol % $Pd_2(dba)_3\cdot CHCl_3$, $(2\text{-fur})_3P$ (90 mol %), PMP, DMA, 80 °C, 30 h	**30** (67%)
12	10 mol % $Pd_2(dba)_3\cdot CHCl_3$, $(2\text{-fur})_3P$ (100 mol %), PMP, DMA, 90 °C, 8 h	**30** (78%)

[a] Deiodo-**29**.
[b] A 2:1 mixture of isomers.

group, which is consistent with **31** being either the (*E*)-alkylidene isomer or the endocyclic isomer resulting from double bond migration. The NMR chemical shift of the C12 vinylic hydrogen of **31** (δ 6.33) was more similar to that of the (*E*)-alkylidene Heck product **11** (δ 6.05) than the chemical shift of the vinylic hydrogen (C13) of endocyclic isomer **12** (δ 5.70), allowing the double bond position of Heck product **31** to be specified.[31] Thus, the absolute configuration at the quaternary-carbon stereocenter C3 of the Heck product **31** is *S*, opposite to what was the proposed configuration of this stereocenter of asperazine (**1**).[1]

Although we now realized that a Heck cyclization precursor analogous to **29** in which the C11 stereocenter has the *S* absolute configuration would be required for a total synthesis of the proposed structure of asperazine (**1**), we had sufficient supplies of hexacyclic intermediate **31** on hand to allow us to explore additional steps in the synthesis in this epimeric series.[32] With the Heck reaction realized, we turned to generate the C11 stereocenter and form the pyrrolidine ring (Scheme 6). To no surprise, we found that hydrogenation of the hindered trisubstituted double bond of Heck product **30** was extremely difficult. For example, under forcing conditions (1200 psi H_2, 2 equiv of 10% Pd/C, EtOAc, 23 °C, 56 h) only 30% of the double bond of **30** was reduced.[33] Fortunately, analog **31**, whose double bond is more accessible by virtue of lacking a protecting group on the indole nitrogen, underwent hydrogenation under less forcing conditions (10% Pd/C, DMF, 800 psi H_2, 23 °C) to give dihydro product **32**, an inseparable 4:1 mixture of C11 epimers, in 76% yield. In an attempt to increase the diastereoselectivity of this reaction, alternate catalysts (Rh/alumina, $RhCl(PPh_3)_3$, and Crabtree's catalyst) and solvents (EtOH, EtOAc, and PhH) were screened. In all cases, results were inferior to those realized with Pd/C. To facilitate reduction of the oxindole carbonyl group, the oxindole nitrogens of hydrogenation products **32** were selectively protected with Boc groups. At this point, the C11 epimers of Boc products **33** and **34** could be separated; however, their relative configuration at C11 could not yet be determined.

To assign the relative configuration of epimers **33** and **34**, as well as work out chemistry for forming the *cis*-pyrrolidinoindoline moiety, these products were elaborated in an identical fashion: the oxindole carbonyl group was selectively reduced with $NaBH_4$ at room temperature in ethanol and then a slight excess of camphorsulfonic acid (CSA) was added to the crude hemiaminals to promote dehydrative cyclization. The minor hydrogenation product **34** gave *cis*-pyrrolidinoindoline **37** in 37% yield, whereas, the major diastereomer **33** provided a mixture of the corresponding *cis*-pyrrolidinoindoline **35** (17% yield) and 2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole **36** (33% yield). In DMSO-d_6 at 100 °C, the ^1H NMR spectrum of **35** displayed two NH signals and two OH signals, whereas the spectrum of hydropyranoindoline **36** showed the presence of three NH signals and only one OH signal. The relative configuration at C11 of the epimeric pyrrolidinoindoline products could now be determined by ^1H NMR NOE experiments. The correlation of H5 to the C12 methylene hydrogen that exhibited a weak NOE to the C11 methine hydrogen was particularly diagnostic in defining the relative configuration of indolyl *cis*-pyrrolidinoindoline **35** (Fig. 2).

2.3. Total synthesis of (+)-asperazine

The total synthesis of asperazine commenced with the *R* enantiomer of Garner's aldehyde (*ent*-**7**) (Scheme 7).[14] The seven reactions needed to transform this precursor into the Heck cyclization substrate **41** were carried out in the same manner, and with comparable yields, as those utilized to prepare diastereomer **29**. The critical intramolecular Heck reaction of α,β-unsaturated iodoanilide **41** proceeded in 66% yield at 90 °C in DMA containing 6 equiv of PMP using the catalyst generated from $Pd_2(dba)_3\cdot CHCl_3$ (10 mol %) and trifurylphosphine (1 equiv). As in the Heck cyclization of diastereomer **29**, only a single Heck product **42**, having the *E* configuration of the trisubstituted double bond, was isolated.

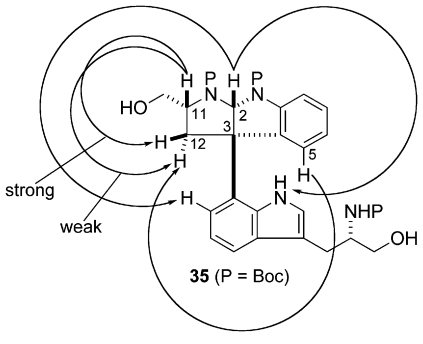
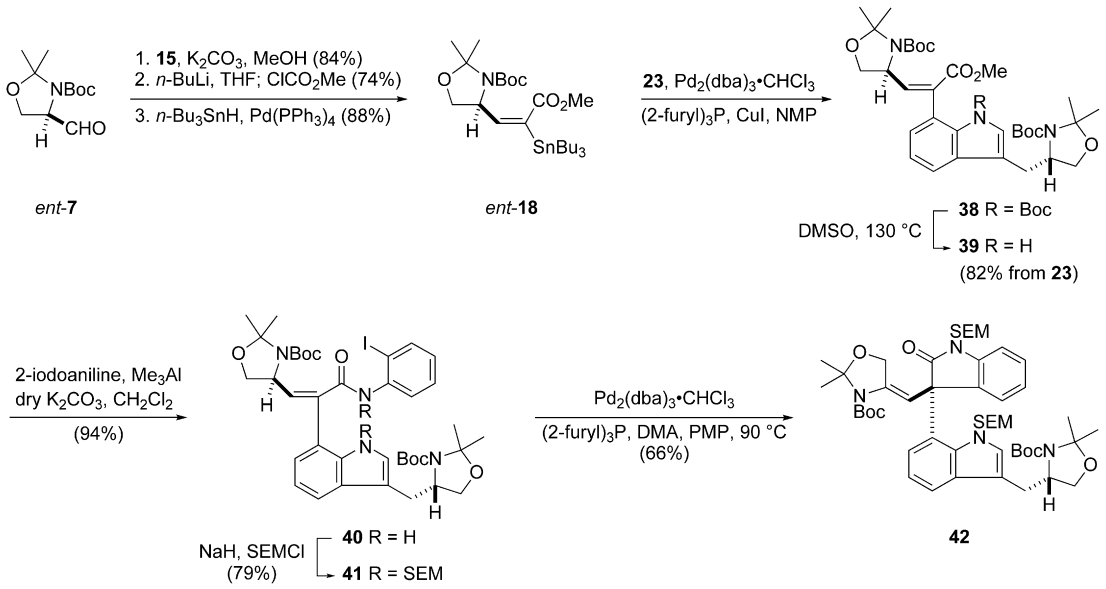


Figure 2. ^1H NMR NOE data for intermediate **35**.



Scheme 7. Diastereoselective Heck cyclization to form oxindole **42**.

Our thoughts on the origin of diastereoselection in the Heck cyclization forming oxindole **42** are the following. Because of the high degree of steric congestion about the trisubstituted double bond of precursor **41**, we believe that the Boc-protected oxazoline fragment is likely oriented to place the smallest substituent at C11, hydrogen, toward palladium (Fig. 3).[34,35] When the aryl palladium fragment approaches the double bond from the favored direction depicted in Figure 3, the carbonyl oxygen of the anilide and the *N*-Boc substituent at C11 project away from each other. Approach from the alternate alkene stereoface is disfavored because it places these groups in close proximity.

The elaboration of Heck product **42** to indolyl *cis*-pyrrolidinoindoline **47** is outlined in Scheme 8. After removing the SEM groups from **42**, catalytic hydrogenation of alkenyl oxindole **43** at 1000 psi over Pd/C in DMF at room temperature provided dihydro product **44** in 95% yield as a 4:1 mixture of C11 epimers. To avoid the problem encountered earlier of competitive cyclization of the C12 hydroxyl group to form a 2,3,4,4a,9,9a-hexahydropyrano[2,3-*b*]indole product (see Scheme 6), we chose to mask the primary hydroxyl groups prior to attempting to form the *cis*-pyrrolidinoindoline ring system. Toward this end, intermediate **44** was exposed to 1 M HCl in dioxane at 50 °C to cleave the oxazolidine and Boc substituents. Without purification, the resulting diamine diol was allowed to react with a large excess of di-*tert*-butyldicarbonate and NaOH under phase transfer conditions.[36] The C11 epimers were separated on silica gel to provide epimers **45** and **46** in 17% and 59% yields, respectively. Reduction of major product **46** with lithium triethylborohydride at −78→0 °C afforded a mixture of epimeric hemiaminals, which cyclized upon addition of ethereal HCl.[37] Selective cleavage of the two carbonates with methanolic KOH at room temperature delivered *cis*-pyrrolidinoindoline diol **47** in 79% yield from precursor **46**.

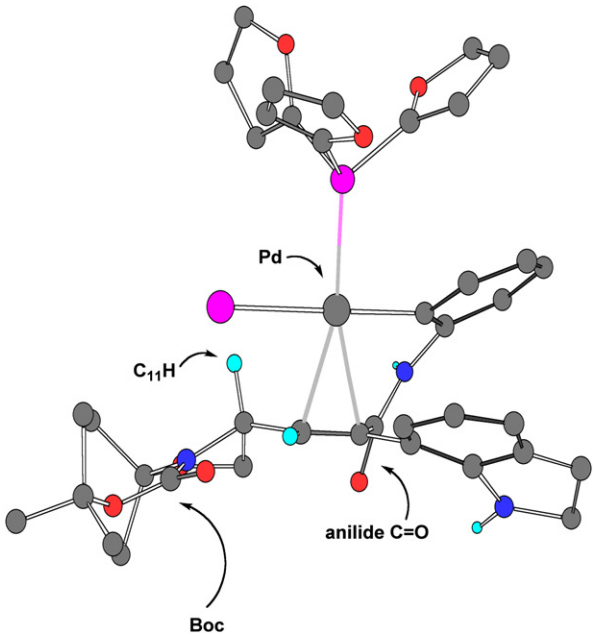
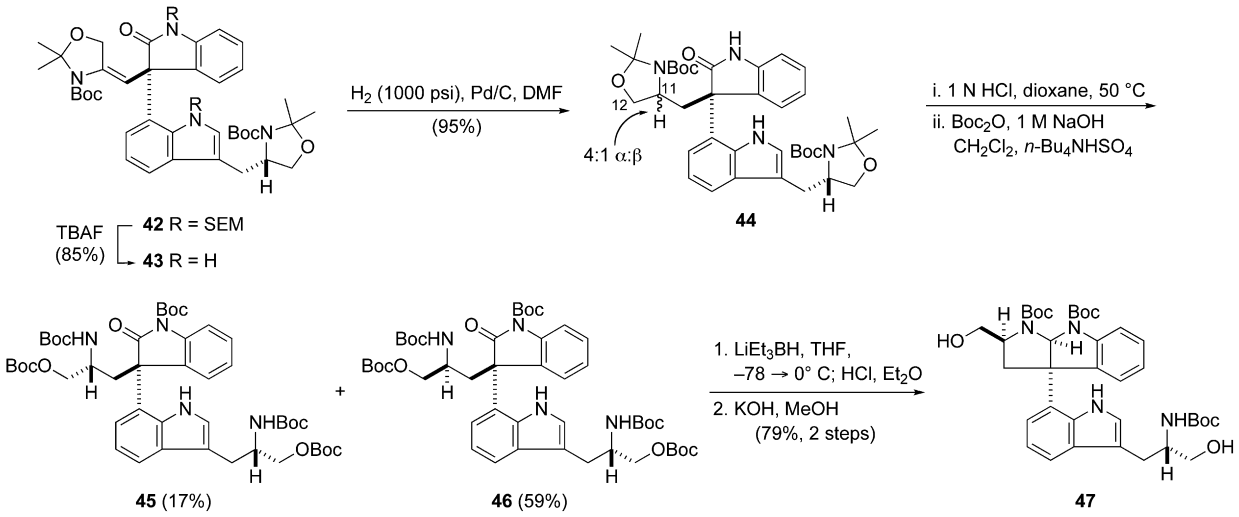


Figure 3. Model of the insertion step in the intramolecular Heck reaction to form oxindole **42**; most hydrogens are removed for clarity.

We turned to the introduction of the two remaining diketopiperazine units present in asperazine (Scheme 9). The first issue was oxidation of the primary alcohol groups of diol **47** to give diacid **48**, a conversion that was made challenging by the presence of the unmasked indole substituent. Many one- and two-step oxidation procedures (e.g., PDC, Jones' reagent, ruthenium(VIII) oxidants, TEMPO, $KMnO_4$, AgO, and Pt/O_2) were surveyed. In the end, only one sequence was found to be efficient: oxidation of diol **47** to the corresponding dialdehyde with DMSO and sulfur trioxide·pyridine complex,[38] followed by sodium chlorite oxidation of the crude dialdehyde to give diacid **48**.[39] Coupling of this intermediate with (*R*)-phenylalanine methyl ester hydrochloride mediated by HATU[40] provided dipeptide **49** in 65% overall yield from diol **47**.

All that remained to complete the total synthesis of asperazine (**1**) was to cleave the three Boc-protecting groups of

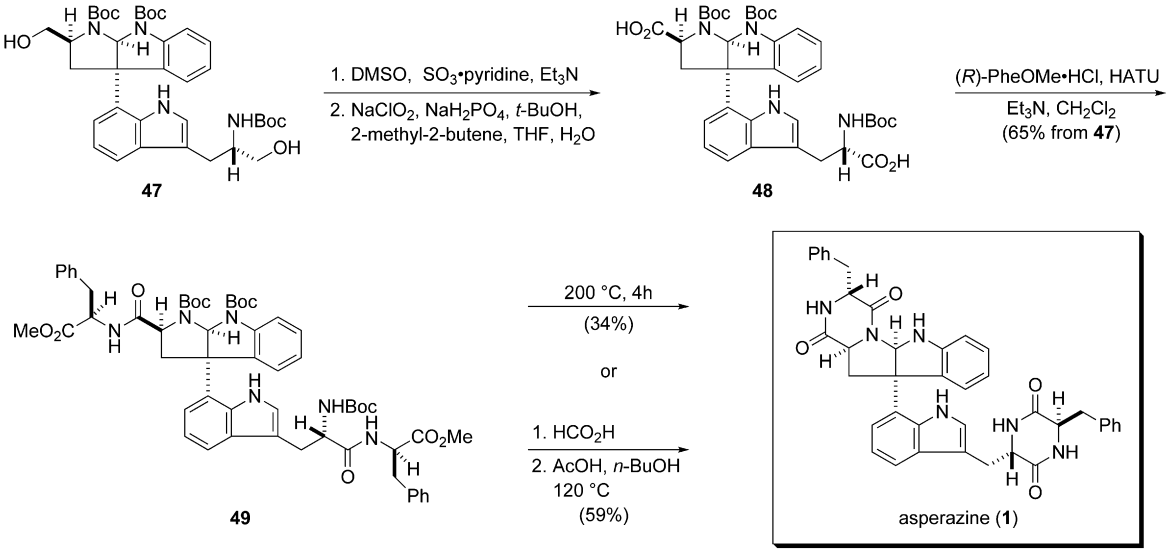


Scheme 8. Elaboration of Heck product **42** to *cis*-pyrrolidinoindoline **47**.

intermediate **49** and cyclize, with loss of methanol, to form the two diketopiperazine rings. To our delight, this series of five reactions could be accomplished in a single step[41] by heating **49** at 200 °C for 4 h under a stream of argon. This reaction provided asperazine (**1**) and two presumed stereoisomers[42] in a 70:3:2 ratio. Purification of this mixture by preparative reverse-phase HPLC provided pure asperazine (**1**) in 34% yield. However, it was more efficient to carry out this conversion in two steps: cleavage of the three *tert*-butoxycarbonyl protecting groups of dipeptide **49** with formic acid at room temperature,[43,44] followed by heating the crude deprotected dipeptide in *n*-butanol at 120 °C for 24 h in the presence of acetic acid.[45] After preparative thin-layer chromatography, asperazine (**1**), $[\alpha]_D$ +95.7 (*c* 0.2, MeOH), was isolated in 59% yield from this sequence. 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] Moreover, synthetic asperazine and a sample of the natural product were co-eluted from a C18 reverse-phase HPLC column (31% MeCN/69% H_2O, v/v). 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 (see Supplementary data).

We considered the possibility that a diastereoisomer of asperazine in which C34 and C37 (or C2, C3, C11, and C15) were epimeric to **1** would not be distinguishable from **1** by NMR comparisons. However, such a diastereomer should be discernible by CD analysis. Most revealingly, subtracting the CD spectra of cyclo-(*S*)-Trp-(*R*)-Phe from that of **1** and adding back that of cyclo-(*R*)-Trp-(*S*)-Phe generates a predicted CD spectrum for the C34, C37 epimer of asperazine (**1**) that is readily distinguished from the CD spectrum of **1**.

Synthetic asperazine was tested by Frederick Valeriote against L1210 leukemia, Colon38, H116 colon cancer, and



Scheme 9. Final steps in the total synthesis of (+)-asperazine (**1**).

H125 lung cancer using the Corbett–Valeriote soft agar disk diffusion assay that had been employed in the initial bioassays of natural asperazine.[1,2] Synthetic asperazine showed low cytotoxicity against all three cell lines.[46] This surprising result prompted us to repurify synthetic asperazine and repeat the bioassays; again no significant cytotoxicity against L1210 leukemia was seen. This finding suggests that a minor component of the natural isolate is likely responsible for the observed L1210 cytotoxicity in the initial biological evaluations of asperazine.[1] Because the physical properties of synthetic and natural asperazine compared well, we feel it is less likely that the relative and absolute configuration of natural asperazine differs from that depicted in structure **1**.

3. Conclusion

The first total synthesis of asperazine (**1**) was accomplished in 22 steps from readily available amino acid starting materials. A pivotal step in the sequence is a diastereoselective intramolecular Heck reaction (**41**→**42**) in which the substituent controlling stereoselection is external to the ring being formed. The efficiency of this step provides an excellent example of the notable utility of intramolecular Heck reactions for forming highly congested quaternary-carbon stereocenters. This synthesis confirmed the structure of (+)-asperazine (**1**) proposed by Crews and co-workers and provided material for additional biological studies. The in vitro cytotoxicity originally reported for the marine isolate was not confirmed by the repetition of these studies with synthetic (+)-asperazine.

4. Experimental

4.1. General

Air-sensitive reactions were carried out under an atmosphere of argon. Concentrations were performed under reduced pressure (ca. 15 mm) with a rotary evaporator, unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, and dichloromethane were degassed with argon and then passed through two 4×36 inch columns of anhydrous neutral A-2 alumina (8×14 mesh; LaRoche Chemicals; activated under a flow of argon at 350 °C for 3 h) to remove H_2O.[47] Toluene was degassed with argon and then passed through one 4×36-inch column of Q-5 reactant (Engelhard; activated under a flow of 5% hydrogen/nitrogen at 250 °C for 3 h) to remove oxygen then through one 4×36-inch column of anhydrous neutral alumina to remove H_2O.[47] Methanol was distilled from Mg turnings at atmospheric pressure under a N_2 atmosphere. Triethylamine, pyridine, diisopropylethylamine, diisopropylamine, acetonitrile, benzene (PhH), and methyl chloroformate were distilled from CaH_2 at atmospheric pressure under a N_2 atmosphere. *N*,*N*-Dimethylacetamide (DMA), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), and 1,2,2,6,6-pentamethylpiperidine (PMP) were distilled from CaH_2 under reduced pressure (ca. 10 mm). $Pd_2(dba)_3\cdot CHCl_3$,[48] $Pd(PPh_3)_4$,[49] and (*R*)-BINAP[50] were prepared according to established procedures. Molarities of organolithium reagents were established by titration with menthol/fluorene.[51]

4.2. Synthesis of (4*S*)-4-[2-methoxycarbonyl-2-(tributylstannanyl)vinyl]-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (*ent*-18)

A modification of the general procedure of Guibe was employed.[23] A degassed solution of *n*-Bu_3SnH (7.50 mL, 27.9 mmol) and CH_2Cl_2 (25 mL) was added by syringe pump (0.5 mL/h) to a degassed solution of *ent*-**17**[20,52] (4.00 g, 14.1 mmol), $(Ph_3P)_4Pd$ (500 mg, 0.433 mmol), and CH_2Cl_2 (100 mL) at −10 °C. The solution was concentrated for 18 h after the addition was complete. The crude residue was purified by silica gel chromatography (49:1, 33:1, 24:1, 19:1, 13:1, 9:1 hexanes/EtOAc) to give 7.15 g (88%) of *ent*-**18**, a clear oil, as a 16:1 mixture of regioisomers in favor of α-stannane: ^{1}H NMR (500 MHz, C_6D_6, 70 °C) δ 6.42 (td, J=30.4, 7.7 Hz, 1H), 5.24 (br, 1H), 4.13 (dd, J=9.0, 6.8 Hz, 1H), 3.82 (dd, J=9.0, 3.1 Hz, 1H), 3.43 (s, 3H), 1.73 (s, 3H), 1.62–1.56 (m, 6H), 1.54 (s, 3H), 1.43 (s, 9H), 1.40–1.31 (m, 6H), 1.06–1.03 (m, 6H), 0.91 (t, J=7.3 Hz, 9H); ^{13}C NMR (125 MHz, C_6D_6, 70 °C) δ 170.1, 156.7, 152.1, 135.8, 94.5, 79.5, 69.7, 58.7, 50.9, 29.3, 28.5, 27.5, 27.3, 24.4, 13.7, 10.9; IR (neat) 2957, 2929, 2872, 1704, 1604, 1382, 1199 cm^{-1}; MS (CI) *m*/*z* 518.1932 (518.1933 calcd for $C_{22}H_{40}NO_5Sn$, M−*t*-Bu). Anal. Calcd for $C_{26}H_{49}NO_5Sn$: C, 54.37; H, 8.60; N, 2.44. Found: C, 54.60; H, 8.73; N, 2.51. Diagnostic data for the β-regioisomer of stannane *ent*-**18**: a second vinylic hydrogen (δ 6.21) was observed as a triplet of doublets with coupling constants corresponding to an allylic ^{1}H coupling ($^3J(^1H)$=1.5 Hz) and an allylic ^{117}Sn coupling ($^3J(^{117}Sn)$=30.8 Hz).

4.3. Preparation of iodoindole 23

4.3.1. 3-[(2*S*)-2-*tert*-Butoxycarbonylamino-2-methoxycarbonylethyl]-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (20). A modification of the general procedure of McKenzie was employed.[25a] Triethylsilane (120 mL, 751 mmol) was added by syringe pump (2.5 mL/min) to a solution of (*S*)-TrpOMe·HCl (22 g, 86 mmol) and TFA (260 mL) at rt. After stirring the mixture at 50 °C for 2 h, the volatiles were removed by distillation (65 °C, 20 mm). The crude residue was dissolved in saturated aqueous $NaHCO_3$ (200 mL) and extracted with CH_2Cl_2 (200 mL×6). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 22 g of the known indoline.[25b] A solution of Boc_2O (42.0 mL, 183 mmol) and dioxane (110 mL) was added slowly (5 mL/min) to a solution of the crude indoline, Na_2CO_3 (28.0 g, 264 mmol), and H_2O (110 mL) at rt. After stirring for 1.5 h at rt, the cloudy mixture was concentrated, and the residue was partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (400 mL). The aqueous layer was extracted with EtOAc (300 mL×3), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (6:1, 3:1, 2:1 hexanes/EtOAc) to give 33.4 g (92% over two steps) of **20**, a clear oil, as a 3:2 mixture of diastereomers: ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 7.62 (t, J=7.5 Hz, 1H), 7.20 (d, J=7.4 Hz, 1H), 7.15 (app q, J=6.6 Hz, 1H), 6.94 (t, J=7.4 Hz, 1H), 6.88 (br, 1H, NH), 4.23–4.18 (m, 1H, minor isomer), 4.16–4.11 (m, 1H, major isomer), 4.06–4.01 (m, 1H), 3.664 (s, 3H), 3.658 (s, 3H,

major isomer), 3.64–3.60 (m, 1H), 3.43–3.35 (m, 1H), 2.15–2.10 (m, 1H), 1.92–1.84 (m, 1H), 1.531 (s, 9H, major isomer), 1.529 (s, 9H, minor isomer), 1.43 (s, 9H, minor isomer), 1.42 (s, 9H, major isomer); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 171.9 (both), 154.7 (both), 151.2 (both), 141.6 (major), 141.5 (minor), 133.8 (major), 133.7 (minor), 127.0 (minor), 126.9 (major), 123.5 (minor), 123.4 (major), 121.5 (both), 113.7 (both), 79.8 (both), 78.0 (both), 53.3 (minor), 52.7 (major), 52.0 (minor), 51.6 (major), 51.0 (both), 36.3 (minor), 36.2 (major), 35.8 (minor), 35.3 (major), 27.6 (both×2); IR (neat) 3352, 2977, 2932, 1746, 1704, 1602, 1487, 1393, 1171 cm^{-1}; MS (ESI) *m/z* 443.2162 (443.2158 calcd for $C_{22}H_{32}N_2NaO_6$, M+Na).

4.3.2. 3-[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-ylmethyl]-2,3-dihydroindole-1-carboxylic acid *tert*-butyl ester (21). Sodium borohydride (490 mg, 13.0 mmol) was added to a stirring mixture of **20** (2.16 g, 5.14 mmol), LiCl (550 mg, 13.0 mmol), and THF (22 mL) at rt. After 5 min, EtOH (30 mL) was added. The cloudy mixture was stirred at rt for 5 h and quenched at 0 °C by careful addition of saturated aqueous NH_4Cl (25 mL) and H_2O (75 mL). This mixture was extracted with EtOAc (100 mL×3), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give the corresponding amino alcohol. Diagnostic data: MS (ESI) *m/z* 415.30 (415.22 calcd for $C_{21}H_{32}N_2NaO_5$, M+Na). *p*-Toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) was added to a solution of this crude product, 2,2-dimethoxypropane (6.00 mL, 48.8 mmol), and PhH (25 mL) at rt. After 3 h at rt, the solution was concentrated and partitioned between MTBE (methyl *tert*-butyl ether, 100 mL) and saturated aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with MTBE (100 mL×3), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (13:1, 9:1, 6:1, 4:1 hexanes/EtOAc) to give 2.11 g (95% over two steps) of **21** as a colorless foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.30 (br, 1H), 7.23–7.10 (m, 2H), 7.00–6.90 (m, 1H), 4.25–3.55 (br m, 5H), 3.40–3.15 (br m, 1H), 2.25–1.70 (br m, 2H), 1.65–1.35 (br m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$)[53] δ 152.5, 152.4, 152.2, 151.7, 151.3, 142.5, 134.2, 127.9, 127.3, 124.3, 123.8, 122.3, 122.1, 114.7, 93.9, 93.8, 93.4, 80.5, 80.1, 80.0, 79.9, 67.7, 67.4, 66.5, 56.0, 55.6, 55.2, 54.1, 53.7, 53.2, 39.9, 39.0, 37.1, 36.7, 28.6, 28.4, 27.9, 27.7, 27.0, 26.9, 24.4, 23.1; IR (neat) 2978, 2934, 1698, 1602, 1487, 1392 cm^{-1}; MS (ESI) *m/z* 455.2531 (455.2522 calcd for $C_{24}H_{36}N_2NaO_5$, M+Na). Anal. Calcd for $C_{24}H_{36}N_2O_5$: C, 66.64; H, 8.39; N, 6.48. Found: C, 66.77; H, 8.34; N, 6.48.

4.3.3. 3-[(4*S*)-3-*tert*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-ylmethyl]-7-iodoindole-1-carboxylic acid *tert*-butyl ester (23). A modification of the general procedure of Iwao and Kuraishi was employed.[24] A cyclohexane solution of *s*-BuLi (5.00 mL, 1.09 M, 5.45 mmol) was added slowly (internal temperature ≤−70 °C) to a solution of **21** (1.68 g, 3.88 mmol), TMEDA (1.00 mL, 6.63 mmol), and Et_2O (38 mL). This solution was maintained at −78 °C for 20 min and then cannulated into a solution of 1,2-diiodoethane (5.50 g, 19.5 mmol) and Et_2O (38 mL) at 0 °C. The reaction was allowed to warm to rt, maintained at rt for 1 h, and poured into a solution of saturated aqueous $Na_2S_2O_3$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL). This mixture was extracted with MTBE (200 mL×3), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (13:1, 9:1, 6:1, 4:1 hexanes/EtOAc) to give 1.58 g (73%) of **22** as a colorless foam. Diagnostic data: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (br, 1H), 7.20–7.08 (br, 1H), 6.76 (br, 1H), 4.40–3.50 (br m, 5H), 3.35–3.05 (br m, 1H), 2.10–1.70 (br m, 2H), 1.70–1.30 (br m, 24H); IR (neat) 2978, 2935, 1698, 1386, 1166 cm^{-1}; MS (ESI) *m/z* 581.15 (581.15 calcd for $C_{24}H_{35}IN_2NaO_5$, M+Na).

A mixture of **22** (4.95 g, 8.86 mmol), DDQ (10.0 g, 44.1 mmol), dry K_2CO_3 (12.5 g, 90.4 mmol), and PhMe (90 mL) was stirred at 70 °C for 12 h, allowed to cool to rt, and concentrated. The crude residue was partitioned between saturated aqueous $NaHCO_3$ (200 mL) and CH_2Cl_2 (200 mL). The aqueous extract was washed with CH_2Cl_2 (200 mL×4). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (13:1, 9:1, 6:1, 4:1 hexanes/EtOAc) to give 2.36 g (48%) of recovered **22** and 2.34 g (47%) of **23** as a colorless foam: $[\alpha]_D^{24}$ −38.6, $[\alpha]_{577}^{24}$ −40.2, $[\alpha]_{546}^{24}$ −46.3, $[\alpha]_{435}^{24}$ −86.2, $[\alpha]_{405}^{24}$ −108 (*c* 0.71, $CHCl_3$); ^{1}H NMR (500 MHz, C_6D_6, major rotamer) δ 8.11 (d, *J*=7.6 Hz, 1H), 7.78 (d, *J*=7.5 Hz, 1H), 7.27 (s, 1H), 6.70 (t, *J*=7.7 Hz, 1H), 4.16 (br, 1H), 3.58–3.50 (m, 1H), 3.43–3.32 (br m, 2H), 2.68 (br t, *J*=12.2 Hz, 1H), 1.60 (s, 3H), 1.44 (s, 9H), 1.42 (s, 9H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6, major rotamer) δ 152.2, 148.3, 138.6, 134.3, 128.5, 127.9, 126.9, 124.8, 120.2, 117.5, 93.5, 83.6, 79.7, 66.2, 57.7, 28.7, 28.1, 27.9 (2), 24.5; IR (neat) 2979, 2934, 2876, 1749, 1694, 1391, 1238, 1155 cm^{-1}; MS (CI) *m/z* 556.1434 (556.1434 calcd for $C_{24}H_{33}IN_2O_5$, M).

4.4. Stille coupling to prepare 38 and deprotection to form enoate 39

A suspension of $Pd_2(dba)_3\cdot CHCl_3$ (145 mg, 0.280 mmol Pd^0), (2-furyl)$_3$P (265 mg, 1.14 mmol), and dry NMP (8 mL) in a base-washed, flame-dried 100 mL Schlenk flask was stirred for 2 h to furnish a yellow-green homogenous solution. A solution of stannane *ent*-**18** (1.70 g, 2.96 mmol), iodide **23** (1.04 g, 1.87 mmol), and NMP (12 mL) was added, and the reaction was degassed by the freeze–pump–thaw method at −78 °C three times. Copper(I) iodide (620 mg, 3.26 mmol) was added, the mixture was stirred for 19 h at rt, and the reaction was quenched by slow addition of saturated aqueous KF (10 mL). After stirring for 15 min, the mixture was diluted with MTBE (400 mL) and washed with water (300 mL) containing concentrated ammonia solution (15 mL). The aqueous layer was extracted with MTBE (200 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by silica gel chromatography (13:1, 9:1, 6:1, 4:1 hexanes/EtOAc) to give 1.19 g of **38** as a colorless foam. Diagnostic data: MS (ESI) *m/z* 736.43 (736.38 calcd for $C_{38}H_{55}N_3NaO_{10}$, M+Na).

A solution of **38** (1.19 g) and DMSO (25 mL) was degassed (bubble argon through the flask for 30 min, evacuate at 5 mm

for 15 min, and bubble argon through the flask for 30 min) and then heated at 130 °C for 6.5 h. After cooling to rt, the reaction was poured into water (200 mL) and extracted with Et_2O (50 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by silica gel chromatography (8:1, 6:1, 5:1 hexanes/EtOAc) to give 939 mg (82%) of **39** as a colorless foam: $[\alpha]_D^{24}$ −41.7, $[\alpha]_{577}^{24}$ −43.9, $[\alpha]_{546}^{24}$ −52.6, $[\alpha]_{435}^{24}$ −126, $[\alpha]_{405}^{24}$ −166 (*c* 0.79, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO, 80 °C) *δ* 10.23 (s, 1H, N*H*), 7.61 (br d, *J*=7.7 Hz, 1H), 7.13 (d, *J*=2.3 Hz, 1H), 7.01 (t, *J*=7.6 Hz, 1H), 6.92 (dd, *J*=7.2, 0.8 Hz, 1H), 6.28 (d, *J*=8.0 Hz, 1H), 5.16 (app td, *J*=7.4, 4.3 Hz, 1H), 4.29 (dd, *J*=9.0, 7.0 Hz, 1H), 4.14–4.10 (m, 1H), 3.98 (br, 1H), 3.80 (dd, *J*=7.9, 5.8 Hz, 1H), 3.74 (dd, *J*=8.8, 1.6 Hz, 1H), 3.68 (s, 3H), 3.15 (dd, *J*=13.8, 2.8 Hz, 1H), 2.81 (dd, *J*=13.8, 10.2 Hz, 1H), 1.53 (s, 6H), 1.50 (s, 3H), 1.48 (s, 9H), 1.44 (s, 9H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 80 °C) *δ* 165.8, 151.2, 151.0, 146.7, 134.0, 130.2, 127.5, 123.4, 121.7, 121.3, 118.0, 117.9, 110.9, 93.3, 92.8, 79.2, 78.7, 67.6, 65.8, 56.9, 56.1, 51.2, 28.4, 27.8, 27.7, 26.7, 25.9, 24.1, 23.4; IR (neat) 3317, 2979, 1698, 1667, 1392, 1366 cm^{-1}; MS (FAB) *m/z* 613.3363 (613.3363 calcd for $C_{33}H_{47}N_3O_8$, M). Anal. Calcd for $C_{33}H_{47}N_3O_8$: C, 64.58; H, 7.72; N, 6.85. Found: C, 64.44; H, 7.91; N, 6.75.

4.5. Elaboration of enoate 39 to Heck cyclization precursor 41

A modification of the general procedure of Weinreb was employed.[16] A toluene solution of Me_3Al (17.0 mL, 2 M, 34.0 mmol) was added slowly to a solution of 2-iodoaniline (7.51 g, 34.2 mmol) and CH_2Cl_2 (75 mL) at 0 °C. The solution was allowed to warm to rt, maintained for 1 h, and then added slowly to a vigorously stirring mixture of ester **39** (4.16 mg, 6.77 mmol), dried K_2CO_3 (12.0 g, 87.0 mmol), and CH_2Cl_2 (50 mL) at 0 °C. The mixture was allowed to warm to rt, stirred for 3 h, and quenched by dropwise addition of a solution of saturated aqueous Na/K tartrate (12.5 mL) and saturated aqueous $NaHCO_3$ (12.5 mL). After stirring at rt for 1 h, the mixture was extracted with CH_2Cl_2 (50 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (9:1, 6:1, 4:1, 3:1 hexanes/EtOAc) to give 5.10 g (94%) of **40** as a colorless foam: $[\alpha]_D^{24}$ −40.0, $[\alpha]_{577}^{24}$ −43.4, $[\alpha]_{546}^{24}$ −51.2, $[\alpha]_{435}^{24}$ −115, $[\alpha]_{405}^{24}$ −157 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO, 100 °C) *δ* 10.24 (s, 1H), 8.66 (s, 1H), 7.93 (d, *J*=8.1 Hz, 1H), 7.77 (dd, *J*=7.9, 1.3 Hz, 1H), 7.68 (d, *J*=7.3 Hz, 1H), 7.37 (td, *J*=7.7, 1.3 Hz, 1H), 7.18 (d, *J*=2.2 Hz, 1H), 7.16–7.08 (m, 2H), 6.90 (td, *J*=7.6, 1.4 Hz, 1H), 6.15 (d, *J*=8.5 Hz, 1H), 5.34–5.24 (m, 1H), 4.34 (dd, *J*=9.0, 2.2 Hz, 1H), 4.18–4.11 (m, 1H), 4.07 (dd, *J*=9.1, 4.3 Hz, 1H), 3.82 (dd, *J*=8.8, 5.6 Hz, 1H), 3.76 (dd, *J*=8.8, 1.8 Hz, 1H), 3.20 (dd, *J*=13.9, 3.3 Hz, 1H), 2.84 (dd, *J*=13.9, 10.0 Hz, 1H), 1.56 (s, 3H), 1.532 (s, 3H), 1.527 (s, 3H), 1.49 (s, 9H), 1.48 (s, 9H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO, 100 °C) *δ* 164.3, 151.4, 150.9, 138.4, 138.2, 134.0, 133.9, 128.1, 128.0, 126.2, 123.6, 123.4, 121.3, 120.8, 118.4, 118.3, 111.3, 93.2, 92.7, 91.3, 79.4, 78.6, 78.5, 67.7, 65.8, 57.0, 55.9, 28.2, 27.7, 27.6, 26.5, 25.9, 24.3, 23.4; IR (neat) 3333, 2978, 1682, 1583, 1392 cm^{-1}; MS (ESI) *m/z* 823.2522 (823.2544 calcd for $C_{38}H_{49}IN_4NaO_7$, M+Na). Anal. Calcd for $C_{38}H_{49}IN_4O_7$: C, 57.00; H, 6.17; N, 7.00. Found: C, 56.69; H, 6.21; N, 6.83.

A solution of amide **40** (4.53 g, 5.65 mmol) and DMF (35 mL) was added slowly to a stirring mixture of NaH (1.61 g, 60%, 40.3 mmol) and DMF (40 mL) at 0 °C. After 10 min, trimethylsilylethoxymethyl chloride (3.50 mL, 19.8 mmol) was added slowly. After an additional 20 min at 0 °C, the reaction was poured into saturated aqueous LiCl (300 mL) and extracted with MTBE (100 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (19:1, 13:1, 9:1, 6:1, 4:1, 3:1 hexanes/EtOAc)[54] to give 3.98 g (66%) of **41** as a colorless foam. In addition, unreacted starting material and mono-SEM-protected product [MS (ESI) *m/z* 953.48 (953.34 calcd for $C_{44}H_{63}IN_4NaO_8Si$, M+Na)] were recovered. Resubjection of these materials to the reaction conditions gave **41** in an overall yield of 79%: $[\alpha]_D^{26}$ +128, $[\alpha]_{577}^{26}$ +135, $[\alpha]_{546}^{26}$ +155, $[\alpha]_{435}^{26}$ +302, $[\alpha]_{405}^{26}$ +390 (*c* 0.78, $CHCl_3$); ^{1}H NMR[55] (500 MHz, $CDCl_3$) *δ* 8.02, 7.54, 7.41, 7.28, 6.98, 6.82, 6.51, 5.89, 5.82, 5.70, 5.26, 5.03, 4.47, 4.31, 4.16, 4.01, 3.92, 3.83, 3.72, 3.34, 3.24, 2.74, 1.76–1.45, 0.96, 0.78, 0.00, −0.13; ^{13}C NMR[56] (125 MHz, $CDCl_3$) *δ* 169.7, 152.2, 151.9, 151.8, 143.4, 141.7, 139.1, 137.4, 134.6, 134.5, 133.43, 133.35, 130.1, 128.8, 128.0, 127.9, 126.2, 121.1, 120.8, 119.7, 119.5, 118.8, 118.2, 113.6, 98.0, 94.0, 93.7, 93.5, 80.0, 79.92, 79.88, 79.8, 76.0, 68.5, 66.65, 66.57, 66.3, 58.3, 57.1, 29.7, 28.7, 28.5, 28.4, 28.0, 27.9, 27.4, 27.1, 25.0, 24.5, 23.2, 18.0, 17.8, −1.5; IR (neat) 2978, 2953, 1694, 1644, 1392, 1249 cm^{-1}; MS (ESI) *m/z* 1083.46 (1083.42 calcd for $C_{50}H_{77}IN_4NaO_9Si_2$, M+Na). Anal. Calcd for $C_{50}H_{77}IN_4O_9Si_2$: C, 56.59; H, 7.31; N, 5.28. Found: C, 56.73; H, 7.41; N, 5.25.

4.6. Heck cyclization to form oxindole 42

A suspension of $Pd_2(dba)_3\cdot CHCl_3$ (195 mg, 0.377 mmol Pd^0), (2-furyl)$_3$P (440 mg, 1.90 mmol), and dry DMA (15 mL) in a base-washed, flame-dried 100 mL Schlenk flask was stirred for 2 h to furnish a yellow-green homogenous solution. Anilide **41** (2.00 g, 1.88 mmol), 1,2,2,6,6-pentamethylpiperidine (2.00 mL, 11.1 mmol), and DMA (5 mL) were added, and the reaction was degassed by the freeze–pump–thaw method at −78 °C three times. After 10 h at 90 °C, the reaction was allowed to cool to rt, poured into saturated aqueous LiCl (100 mL), diluted with water (100 mL), and extracted with MTBE (100 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by silica gel chromatography (12:1, 9:1, 6:1, 4:1 hexanes/EtOAc) to give 1.16 g (66%) of **42** as a colorless foam: $[\alpha]_D^{27}$ −120, $[\alpha]_{577}^{27}$ −127, $[\alpha]_{546}^{27}$ −147, $[\alpha]_{435}^{27}$ −305, $[\alpha]_{405}^{27}$ −409 (*c* 0.75, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO, 100 °C) *δ* 7.62 (d, *J*=7.4 Hz, 1H), 7.36 (td, *J*=7.7, 1.2 Hz, 1H), 7.28 (s, 1H), 7.21 (d, *J*=7.0 Hz, 1H), 7.19 (d, *J*=7.7 Hz, 1H), 7.10 (td, *J*=7.3, 0.9 Hz, 1H), 6.93 (t, *J*=7.7 Hz, 1H), 6.76 (br d, *J*=7.1 Hz, 1H), 6.41 (t, *J*=1.9 Hz, 1H), 5.71 (br, 2H), 5.19 (d, *J*=10.9 Hz, 1H), 5.14 (d, *J*=10.9 Hz, 1H), 4.16–4.10 (m, 1H), 3.83 (dd, *J*=8.2, 6.0 Hz, 1H), 3.77 (dd, *J*=12.9, 1.8 Hz, 1H), 3.73 (dd, *J*=8.7, 1.9 Hz, 1H), 3.72 (dd, *J*=13.5, 1.8 Hz, 1H), 3.62–3.54 (m, 2H), 3.46–3.39 (br m, 1H), 3.34–3.27 (br m, 1H), 3.16 (dd,

J=14.0, 3.2 Hz, 1H), 2.84 (dd, J=14.0, 10.0 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 9H), 1.45 (s, 3H), 1.44 (s, 3H), 1.43 (s, 9H), 1.41 (s, 3H), 0.92–0.75 (m, 4H), −0.04 (s, 9H), −0.07 (s, 9H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 177.1, 150.9, 149.6, 140.6, 136.8, 134.0, 133.6, 131.3, 127.9 (2), 124.5, 123.6, 122.83, 122.75, 118.6, 118.3, 112.3, 109.2, 105.5, 95.1, 92.7, 80.9, 78.7, 78.0, 69.0, 65.7, 65.1, 64.2, 63.6, 56.9, 56,7, 27.7 (2), 27.6, 26.9, 24.7, 24.4, 23.8, 17.1, 17.0, −2.06, −2.12; IR (neat) 2953, 1703, 1384, 1366, 1074 cm^{-1}; MS (ESI) m/z 955.5060 (955.5049 calcd for $C_{50}H_{76}N_4NaO_9Si_2$, M+Na). Anal. Calcd for $C_{50}H_{76}N_4O_9Si_2$: C, 64.34; H, 8.21; N, 6.00. Found: C, 64.64; H, 8.27; N, 5.93.

4.7. Elaboration of Heck product 42 to oxindole intermediate 46

A modification of a procedure reported by Kishi was employed.[30] A solution of **42** (576 mg, 0.617 mmol) and TBAF (5.0 mL, 1 M in THF, 5.0 mmol) was concentrated and placed under vacuum (≤0.1 mm) at rt for 65 h. The resulting residue was partitioned between H_2O (200 mL) and MTBE (100 mL). The aqueous layer was extracted with MTBE (75 mL×3), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. A solution of the residue, Et_3N (8 mL), and MeOH (8 mL) was maintained at 68 °C for 6 h and then concentrated. The crude residue was purified by silica gel chromatography (9:1, 6:1, 4:1, 3:1, 2:1 hexanes/EtOAc) to give 352 mg (85%) of **43** as a yellow foam: $[\alpha]_D^{26}$ −260, $[\alpha]_{577}^{26}$ −273, $[\alpha]_{546}^{26}$ −316, $[\alpha]_{435}^{26}$ −642, $[\alpha]_{405}^{26}$ −851 (c 0.74, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 10.28 (s, 1H), 9.81 (s, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.30–7.24 (m, 2H), 7.22 (d, J=2.3 Hz, 1H), 7.04 (td, J=7.6, 0.9 Hz, 1H), 6.97 (dd, J=8.2, 0.9 Hz, 1H), 6.91 (t, J=7.7 Hz, 1H), 6.74 (d, J=6.8 Hz, 1H), 6.37 (t, J=1.9 Hz, 1H), 4.15–4.10 (m, 1H), 3.90 (dd, J=12.8, 1.9 Hz, 1H), 3.82 (dd, J=8.0, 5.9 Hz, 1H), 3.73 (dd, J=8.8, 1.9 Hz, 1H), 3.61 (dd, J=12.8, 2.0 Hz, 1H), 3.18 (dd, J=14.0, 3.3 Hz, 1H), 2.83 (dd, J=14.0, 10.0 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 9H), 1.48 (s, 3H), 1.44 (s, 3H), 1.41 (s, 9H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 178.6, 150.9, 149.7, 140.8, 137.4, 133.6, 132.6, 128.4, 127.8, 124.9, 123.6, 123.3, 121.4, 119.1, 117.9, 117.7, 110.7, 109.5, 104.2, 95.0, 92.7, 80.8, 78.6, 65.7, 63.4, 56.9, 56.4, 28.1, 27.7, 27.3, 26.4, 24.8, 24.3, 23.4; IR (neat) 3379, 3260, 2979, 2936, 1694, 1620, 1471, 1385 cm^{-1}; MS (ESI) m/z 695.3409 (695.3420 calcd for $C_{38}H_{48}N_4NaO_7$, M+Na).

A mixture of **43** (400 mg, 0.595 mmol), palladium on carbon (158 mg, 10 wt %, 0.148 mmol), and DMF (12 mL) was stirred in a pressure reactor under 1000 psi of hydrogen for 24 h at rt. This mixture was filtered through Celite and the resulting filter cake was washed with MTBE (300 mL). The filtrate was washed with saturated aqueous LiCl (100 mL) and the resulting aqueous layer was extracted with MTBE (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated, and the residue was purified by silica gel chromatography (4:1, 3:1 hexanes/EtOAc) to give 383 mg (95%) of **44**, a colorless foam, as an inseparable 4:1 mixture of epimers. All characterization data were obtained on this mixture: IR (neat) 3335, 2978, 1698, 1389, 1366 cm^{-1}; MS (CI) m/z 674.3667 (674.3680 calcd for $C_{38}H_{50}N_4O_7$, M). Anal. Calcd for $C_{38}H_{50}N_4O_7$: C, 67.63; H, 7.47; N, 8.30. Found: C, 67.48; H, 7.51; N, 8.08. NMR data for the major epimer (**11**-*S*): ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 10.43 (s, 1H), 9.87 (s, 1H), 7.59–7.54 (m, 1H), 7.39 (d, J=7.4 Hz, 1H), 7.32 (td, J=7.7, 1.2 Hz, 1H), 7.17 (d, J=2.4 Hz, 1H), 7.12 (td, J=7.5, 1.0 Hz, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.97–6.91 (m, 2H), 4.15–4.08 (m, 1H), 3.83 (dd, J=8.0, 5.9 Hz, 1H), 3.77 (dd, J=8.7, 1.8 Hz, 1H), 3.73 (dd, J=8.8, 1.9 Hz, 1H), 3.65–3.54 (m, 2H), 3.14 (dd, J=14.0, 3.6 Hz, 1H), 2.93 (dd, J=13.6, 3.2 Hz, 1H), 2.80 (dd, J=14.1, 4.3 Hz, 1H), 2.61 (d, J=13.1 Hz, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.46 (s, 9H), 1.44 (s, 3H), 1.37 (s, 9H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 179.5, 150.9, 150.5, 140.9, 133.5, 129.3, 128.9, 127.9, 126.0, 123.3, 123.0, 121.0, 119.0, 118.0, 117.6, 110.9, 109.7, 92.6, 91.8, 78.8, 78.5, 65.9, 65.1, 56.9, 54.9, 54.0, 37.0, 28.1, 27.6, 27.5, 26.5, 26.4, 23.5, 23.4. NMR data for the minor epimer (**11**-*R*):[57] ^{1}H NMR (500 MHz, DMSO, 100 °C) δ 10.36 (s, 1H), 10.08 (s, 1H), 7.57 (1H), 7.41 (d, J=7.6 Hz, 1H), 7.32 (1H), 7.17 (1H), 7.12 (1H), 7.02–6.91 (3H), 4.12 (1H), 4.04–3.98 (m, 1H), 3.83 (1H), 3.72 (dd, J=8.8, 2.0 Hz, 1H), 3.29 (dd, J=8.8, 5.8 Hz, 1H), 3.15 (1H), 2.99 (d, J=14.0 Hz, 1H), 2.86–2.77 (2H), 2.49 (1H), 1.47 (s, 9H), 1.45 (s, 3H), 1.43 (s, 9H), 1.42 (s, 3H), 1.39 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, DMSO, 100 °C, diagnostic signals only) δ 178.5, 150.7, 141.1, 133.7, 130.3, 128.7, 127.9, 125.8, 123.0, 122.2, 121.0, 119.5, 117.7, 111.0, 109.8, 91.7, 78.9, 65.8, 65.0, 54.8, 54.2, 37.4, 28.0, 26.4, 26.2, 23.4.

A modification of the general procedure of Frechet was employed.[36] A solution of **44** (302 mg, 0.448 mmol), aqueous 1 N HCl (3.2 mL), and dioxane (9.6 mL) was heated at 50 °C for 5 h. The reaction was allowed to cool to rt, and then 1 N NaOH (6 mL), 10 N NaOH (0.4 mL), and Boc_2O (0.50 mL, 2.18 mmol) were added sequentially with vigorous stirring. After 2.5 h at rt, the reaction was poured into H_2O (15 mL) and extracted with EtOAc (50 mL×3) and then $CHCl_3$ (50 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. A mixture of the residue, CH_2Cl_2 (10 mL), Boc_2O (0.50 mL, 2.18 mmol), n-Bu_4HSO_4 (15 mg, 0.044 mmol), and 1 N NaOH (10 mL) was stirred vigorously at rt for 13 h. The reaction was poured into H_2O (25 mL) and extracted with $CHCl_3$ (50 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (3.5:1, 3:1, 2:1 hexanes/EtOAc) to give 234 mg (59%) of **46** as a colorless foam, as well as 69 mg (17%) of the C11 epimer, **45** [MS (ESI) m/z 917.43 (917.45 calcd for $C_{47}H_{66}N_4NaO_{13}$, M+Na)]. Oxindole **46**: $[\alpha]_D^{26}$ −154, $[\alpha]_{577}^{26}$ −163, $[\alpha]_{546}^{26}$ −187, $[\alpha]_{435}^{26}$ −362, $[\alpha]_{405}^{26}$ −466 (c 0.68, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H, NH), 7.95 (d, J=8.0 Hz, 1H, ArH), 7.60 (d, J=6.9 Hz, 1H), 7.52 (d, J=7.2 Hz, 1H), 7.43 (t, J=7.7 Hz, 1H), 7.37 (t, J=7.4 Hz, 1H), 7.15 (s, 1H), 6.93 (t, J=7.7 Hz, 1H), 6.72 (d, J=7.1 Hz, 1H), 4.83 (br d, J=6.7 Hz, 1H), 4.20–3.97 (m, 6H, NH), 3.89 (dd, J=10.9, 3.6 Hz, 1H), 3.12–3.02 (m, 2H), 2.98 (dd, J=14.4, 8.0 Hz, 1H), 2.46 (dd, J=12.0, 9.2 Hz, 1H), 1.59 (s, 9H), 1.50 (s, 9H), 1.46 (s, 9H), 1.43 (s, 9H), 1.26 (s, 9H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 177.1, 155.3, 154.2, 153.5,

153.2, 148.8, 139.7, 134.6, 129.8, 128.9, 128.5, 126.2, 124.4, 124.2, 121.6, 121.3, 119.4 (2), 116.0, 111.4, 84.6, 82.4, 82.3, 79.4, 79.2, 69.0, 67.2, 56.1, 50.0, 47.1, 36.6, 28.4, 28.2, 28.0, 27.8, 27.7, 27.0; IR (neat) 3390, 2979, 2933, 1788, 1746, 1714, 1607, 1281, 1160 cm^{-1}; MS (ESI) *m/z* 917.4523 (917.4524 calcd for $C_{47}H_{66}N_4NaO_{13}$, M+Na). Anal. Calcd for $C_{47}H_{66}N_4O_{13}$: C, 63.07; H, 7.43; N, 6.26. Found: C, 63.16; H, 7.60; N, 5.90.

4.8. Closure of the *cis*-pyrrolidinoindoline ring to form 47

A modification of a procedure we reported earlier was employed.[37] A THF solution of $LiBEt_3H$ (0.30 mL, 1.0 M, 0.30 mmol) was added dropwise to a solution of **46** (59 mg, 0.066 mmol) and THF (4 mL) at −78 °C. After allowing the solution to warm to 0 °C, an Et_2O solution of HCl (0.38 mL, 1 M, 0.38 mmol) was added dropwise. The solution was allowed to warm to rt, maintained for 20 h, poured into H_2O (20 mL), and extracted with $CHCl_3$ (30 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give 64 mg of the crude *cis*-pyrrolidinoindoline product: MS (ESI) *m/z* 901.46 (901.46 calcd for $C_{47}H_{66}N_4NaO_{12}$, M+Na). A solution of this crude product and degassed methanolic KOH (5.0 mL, 0.356 M, 1.78 mmol) was maintained at rt for 19 h. The reaction was diluted with $CHCl_3$ (25 mL) and quenched with aqueous HCl (27 mL, 0.74 M, 2.0 mmol). The layers were separated and the aqueous layer was extracted with $CHCl_3$ (30 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by silica gel chromatography (1:1, 3:5, 1:3 hexanes/EtOAc) to give 35 mg (79% overall) of **47** as a colorless foam: ^1H NMR (500 MHz, DMSO, 100 °C) δ 9.89 (s, 1H, NH), 7.60 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=7.8 Hz, 1H), 7.29–7.22 (m, 2H), 7.11 (d, *J*=2.4 Hz, 1H), 7.01 (td, *J*=7.5, 0.9 Hz, 1H), 6.89 (t, *J*=7.6 Hz, 1H), 6.79 (d, *J*=6.8 Hz, 1H), 6.52 (s, 1H), 5.94 (br d, 1H), 4.26–4.00 (br, 1H), 4.23–4.15 (m, 1H), 3.77–3.67 (m, 1H), 3.46–3.33 (m, 3H), 3.10–2.85 (br, 1H), 3.00 (dd, *J*=13.5, 8.8 Hz, 1H), 2.92 (dd, *J*=14.6, 6.3 Hz, 1H), 2.82–2.74 (m, $2H_2$), 2.60 (t, *J*=9.5 Hz, 1H), 1.44 (s, 9H), 1.38 (s, 9H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, DMSO, 100 °C) δ 154.7, 153.7, 151.5, 140.3, 136.2, 132.2, 129.0, 127.5, 124.2, 123.7, 123.2, 122.5, 118.9, 117.7, 117.6, 116.5, 111.6, 82.5, 80.3, 78.5, 77.0, 62.7, 62.6, 60.1, 57.5, 52.9, 36.8, 27.7, 27.6, 27.4, 26.2; MS (ESI) *m/z* 701.3555 (701.3527 calcd for $C_{37}H_{50}N_4NaO_8$, M+Na).

4.9. Preparation of dipeptide 49

Sulfur trioxide·pyridine complex (26 mg, 0.16 mmol) was added to a solution of diol **47** (25.8 mg, 0.038 mmol), Et_3N (0.10 mL, 0.72 mmol), and DMSO (2 mL) at rt. After 1 h, a second aliquot of SO_3·pyr (26 mg, 0.16 mmol) was added. After an additional hour, the reaction was poured into a solution of saturated aqueous NH_4Cl (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) and extracted with EtOAc (25 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give the corresponding crude dialdehyde, which was used without purification; MS (ESI) *m/z* 697.49 (697.32 calcd for $C_{37}H_{46}N_4NaO_8$, M+Na). Sodium chlorite (45 mg, 80%, 0.40 mmol) was added in three equal portions every 45 min to a vigorously stirring mixture of the crude dialdehyde, NaH_2PO_4 (105 mg, 0.76 mmol), THF (1 mL), *t*-BuOH (0.3 mL), 2-methyl-2-butene (0.3 mL), and H_2O (1.0 mL) at rt.[39] One hour after the last addition, the mixture was poured into saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (25 mL×3). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated to give the corresponding crude diacid **48**, which was used without purification; MS (ESI) *m/z* 729.39 (729.31 calcd for $C_{37}H_{46}N_4NaO_{10}$, M+Na). *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate[40] (HATU, 51 mg, 0.13 mmol) was added to a solution of the crude diacid **48**, (*R*)-PheOMe·HCl (21 mg, 0.095 mmol), Et_3N (0.050 mL, 0.36 mmol), and CH_2Cl_2 (2 mL) at rt. After stirring for 1 h, the mixture was poured into a solution of saturated aqueous $NaHCO_3$ (20 mL) and 1 N NaOH (0.5 mL) and extracted with EtOAc (25 mL×2). The combined organic extracts were washed with a solution of saturated aqueous NH_4Cl (20 mL) and 1 N HCl (1 mL). The acidic aqueous layer was extracted with EtOAc (25 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. The crude residue was purified by preparative TLC (26:13:1 $CHCl_3$/EtOAc/MeOH) to give 25.5 mg (65% from **47**) of dipeptide **49** as a colorless foam: $[\alpha]_D^{27}$ +20.1, $[\alpha]_{577}^{27}$ +20.9, $[\alpha]_{546}^{27}$ +23.4, $[\alpha]_{435}^{27}$ +38.4, $[\alpha]_{405}^{27}$ +47.6 (*c* 0.71, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.55 (d, *J*=7.8 Hz, 1H), 7.47 (d, *J*=8.0 Hz, 1H), 7.25–7.02 (m, 12H), 6.96–6.76 (m, 5H, NH), 6.74 (s, 1H), 6.21 (d, *J*=8.0 Hz, 1H), 5.00 (br, 1H), 4.79 (dd, *J*=8.8, 2.0 Hz, 1H), 4.74 (br, 1H), 4.38 (br, 1H), 4.13 (dd, *J*=12.4, 5.8 Hz, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.24–3.07 (m, 3H), 3.06–2.98 (m, 2H), 2.95–2.86 (m, 2H), 2.74 (br, 1H), 1.53 (s, 9H), 1.44 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 171.2, 170.7, 170.0, 154.7, 152.4, 141.0, 135.9, 135.5, 133.11, 133.07, 129.3, 129.11, 129.06, 128.8, 128.6, 128.4, 128.3, 127.1, 126.8, 125.5, 124.9, 123.8, 123.5, 120.2, 119.9, 118.7, 116.1, 111.0, 82.54, 82.49, 82.1, 80.1, 62.8, 58.2, 55.0, 53.6, 52.9, 52.13, 52.10, 40.7, 38.2, 37.7, 29.7, 28.3, 28.24, 28.17; IR (neat) 3404, 2977, 2932, 1713, 1514, 1367, 1159 cm^{-1}; MS (ESI) *m/z* 1051.47 (1051.48 calcd for $C_{57}H_{68}N_6NaO_{12}$, M+Na).

4.10. (+)-Asperazine (1)

Following the general procedure of Nitecki,[43] a solution of **49** (21.7 mg, 0.0211 mmol) and HCO_2H (6 mL) was maintained at rt for 2 h. The HCO_2H was then removed as an azeotrope with heptane (15 mL×3) to give a crude residue containing the deprotected dipeptide; MS (ESI) *m/z* 729.42 (729.34 calcd for $C_{42}H_{45}N_6O_6$, M+H). Using a modification of the general procedure of Suzuki,[45] a solution of this deprotected dipeptide, AcOH (400 μL, 7.0 mmol), and *n*-BuOH (9.6 mL) was heated at reflux for 24 h. AcOH and *n*-BuOH were then removed in vacuo (0.1 mm) and the crude residue was purified by preparative TLC (9:1 chloroform/MeOH) to give 8.2 mg (59%) of asperazine (**1**) as an amorphous colorless solid. In some repetitions of this experiment, a second purification was needed, so the crude product was applied to a C18 reverse-phase HPLC column and eluted with aqueous acetonitrile (31% CH_3CN/69% H_2O, v/v) to provide pure asperazine. Material purified in this

fashion showed ^{1}H NMR spectra (in $CDCl_3$, CD_2Cl_2, and CD_3CN), ^{13}C NMR spectra (in $CDCl_3$ and CD_3CN),[58] mass spectral data, and a CD spectrum in MeOH 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] Synthetic asperazine and the natural isolate were co-eluted from a C18 reverse-phase HPLC column (31% CH_3CN/69% H_2O, v/v).

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Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra, CD spectra and HPLC chromatograms for synthetic and natural asperazine can be found. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.127.

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54. Occasionally, iodoanilide **41** would crystallize onto the silica gel during chromatography resulting in poor yields. Substituting 9:1 hexanes/benzene for pure hexanes in the solvent mixture prevented this problem. Alternatively, anilide **41** could be recrystallized from diethyl ether.
55. Coalescence of the ^{1}H NMR spectrum was not observed in DMSO-d_6 even at temperatures as high as 150 °C. As a result, the ^{1}H NMR in $CDCl_3$ at room temperature is reported; multiplicities, coupling constants, and assignments are not reported because the resonances were broad.
56. The ^{13}C NMR is also reported in $CDCl_3$ at room temperature. The number of peaks listed does not correlate to the number of carbons because of the existence of rotamers at room temperature.
57. In cases where the multiplicity and/or peak assignment was not made, the peak was obstructed by the major isomer.
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