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Structure Reassignment and Synthesis of Jenamidines A_1/A_2, Synthesis of (+)-NP25302, and Formal Synthesis of SB-311009 Analogues

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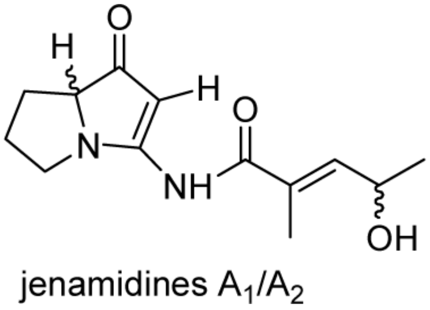
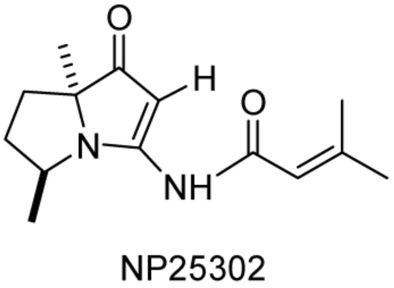
Abstract

The proposed structures of jenamidines A, B, and C (**1**−**3**) were revised to jenamidines A_1/A_2, B_1/B_2, and C (**8**-**10**). Jenamidines A_1/A_2 (**8**) were synthesized from activated proline derivative **43** by conversion to **26** in two steps and 50% overall yield. Acylation of **26** with acid chloride **38d** gave **39d**, which was deprotected with TFA and then mild base to give **8** in 45% yield from **26**. (−)-*trans*-2,5-Dimethylproline ethyl ester (**49**) was prepared by the enantioselective Michael reaction of ethyl 2-nitropropionate (**51**) and methyl vinyl ketone (**50**) using modified dihydroquinine **60** as the catalyst. Further elaboration converted **49** to natural (+)-NP25302 (**12**). A Wittig reaction of proline NCA (**76**) with ylide **79** gave **72** as a 9/1 E/Z mixture in 27% yield completing a one step formal synthesis of SB-311009 analogues.

Introduction

Structure Revision

Sattler and co-workers reported the isolation of jenamidines A, B, and C (**1**−**3**) from the culture broth of *Streptomyces* sp. (strain HKI0297) in 2003 (see Figure 1).[1] Jenamidine A inhibits proliferation of the chronic myeloid leukemic cell line K-562 with a GI_{50} of 1.9 μg/mL. The structures were determined by HRMS, IR, UV and a series of NMR spectroscopic experiments. One of the most striking features of these structures is that the ketone in jenamidine A is in a different position than in jenamidines B and C.

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Supporting Information Available. Details of experimental procedures and characterization for all of compounds not reported in the experimental section; copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

Our examination suggested that the aminal hydrogen H_{9a} in jenamidine A should absorb further downfield than the observed value of δ 3.94 and that carbons C^7 and C^9 of **1**, which are adjacent to a ketone, should absorb further downfield than the observed values of δ 27.5 and 28.8, respectively.[2] In addition, one of the H_9's absorbs at δ 1.53, which is further upfield than expected for a proton next to a ketone. The methylene carbons of the analogous compound *N*-acetyl-4-piperidinone absorb between δ 40.6−44.9 and the methylene protons absorb between δ 2.4−2.6 and 3.7−4.0.[3]

These expectations were confirmed by the synthesis of tricycle **6**, which is a good model for the piperidinone moiety of the proposed structure of jenamidine A (see Scheme 1). Reaction of 2,3-dihydro-4-pyridinone (**4**)[4] with isatoic anhydride (**5**) and Et_3N in THF for 8 h in a sealed tube at 80 °C provided 29% (65% based on recovered **4**) of the surprisingly unstable tricyclic piperidinone **6**. Analysis of the NMR spectral data of **6** confirmed our doubts regarding the structure proposed for jenamidine A. H_{9a} of **6**, which is adjacent to two nitrogens, absorbs at δ 5.12 (dd, *J* = 3.7, 9.2 Hz). The methylene groups adjacent to the ketone absorb between δ 2.4 and 2.6. The three CH^2 carbons absorb at δ 47.8, 40.9 and 39.7. These data are consistent with those expected for this structure.[5] Treatment of **6** with dilute acid resulted in a facile retro-Mannich reaction to give **7**[6] quantitatively. Partial conversion of **6** to **7** occurred during flash chromatography on silica gel suggesting that structure **1** would not survive the isolation protocol for jenamidine A.

These observations suggested that the three methylene carbons of jenamidine A might be part of a pyrrolidine ring with the ketone elsewhere in the molecule. Eventually, we considered the unusual ketene aminals **8**, **9**, and **10** as possible structures for jenamidines A, B, and C (see Figure 2). A literature search established that two compounds containing the identical ring system have been isolated. The structure of bohemamine (**11**) was determined in 1980 by X-ray crystallography.[7] NP25302 (**12**), the deoxy analogue of bohemamine was recently reported[8] and shown to inhibit the adhesion of HL-60 cells to CHO-ICAM-1 cells with an IC_{50} of 24 μM. The ^1H and ^{13}C NMR spectral data for **12** correspond well with those reported for jenamidine A, aside from the expected differences resulting from the methyl groups and differing side chains.[2a] The NMR spectral data for the jenamidine A side chain correspond well with those reported for ethyl 4-hydroxy-2*E*-methylpenten-2-oate ester.[9] The unusual UV absorption at 326 nm (log ε 3.32) in the jenamidines is probably due to the *N*-acyl vinylogous urea[10] and is also present in bohemamine (335 nm)[7] and NP25302 (334 nm).[8]

Careful analysis of the ^1H and ^{13}C NMR spectra indicated that jenamidine A is a mixture of two compounds.[2a] The ^{13}C NMR spectrum contains doubled peaks between 0.02 and 0.1 ppm apart for all carbons except C_5, C_6, and $C_{6'}$. Similarly, the ^1H NMR spectrum showed two peaks separated by 0.04 ppm around δ 5.65 for H_2. Jenamidine A was therefore renamed jenamidines A_1/A_2 because the natural product is a pair of diastereomers. Presumably, epimerization of the ring fusion hydrogen α to the ketone occurs readily. Jenamidine B is renamed jenamidines B_1/B_2 because the NMR spectra indicate that this compound is also a mixture of diastereomers.[2a] The third member of the family, which has only one stereocenter, remains jenamidine C, most likely as a mixture of enantiomers because the optical rotation of jenamidine C (**10**) ($[\alpha]^{22}_D$ +1.8) is lower than that of jenamidines A^1/A_2 (**8**) and jenamidines B_1/B_2 (**9**) ($[\alpha]^{22}_D$ +6.8 and +8.4, respectively).[1]

These structures are also biosynthetically reasonable. Jenamidines B_1/B_2 (**9**) can be formed by hydroxylation of jenamidines A_1/A_2 (**8**), while jenamidine C (**10**) can be formed by bis hydroxylation of jenamidines A_1/A_2 precursor **13**, which lacks the side chain hydroxy group (see Scheme 2).

Results and Discussion

Synthesis of Jenamidines A_1/A_2 (8)

We now turned to the synthesis of jenamidines A_1/A_2 (**8**), which required the development of new methods for the preparation of the novel *N*-acyl vinylogous urea in the right hand ring. A wide variety of approaches proved to be unsuccessful. For instance, we attempted to convert the known keto lactam **15**[11] to enol triflate **14a**, which should undergo Pdcatalyzed amidation as recently reported for related systems (see Scheme 3).[12] Unfortunately, reaction of **15** with NaH and Tf_2O gave only the unstable pyrrole bis triflate **16**.[13] Use of excess NaH and Tf_2O gave crude (90% pure) **16** in 91% yield, which was isolated in only 17% yield. Although we could cleanly couple 2-methyl-2-butenamide[14] with the enol triflate prepared from dimedone, initial attempts at Pd-catalyzed couplings of amides with **16** were unsuccessful. Attempted preparation of vinylogous urea **14b** by reaction of keto lactam **15** with NH_3 gave complex mixtures that did not contain **14b**.[15]

We then turned to the preparation of a vinylogous urea by the addition of an enolate to a cyanamide. Deprotection of the Boc group of Weinreb amide **17**[11a] with TFA in CH_2Cl_2 and reaction of the liberated amine with CNBr[16] and $NaHCO_3$ in EtOH afforded cyanamide **18** in 84% yield (see Scheme 4). Addition of methylmagnesium bromide gave the methyl ketone, which could not be cyclized to give **14b**. Cyanamide **18** was then treated with the lithium enolate of *tert*-butyl acetate in an attempt to form keto ester **20**, which we hoped would cyclize to form the desired vinylogous urea. However, we obtained a mixture of **22** (32%), **23** (21%), and **24** (30%). Presumably, the stabilized tetrahedral intermediate **19** cyclized to the cyanamide to form bicyclic intermediate **21** more rapidly than it lost *N*-methoxymethylamine to give keto ester **20**. Work up provided urea keto ester **24**, which underwent cyclodehydration to give **22** and **23**. The double bond stereochemistry of **23** was established by an NOE between the alkene and ring fusion hydrogens; the chemical shift of the alkene hydrogen, δ 5.19 is consistent with that expected for the (*Z*)-isomer.[17] Imidazolone **22** is the thermodynamic product because treating a solution of **23** in $CDCl_3$ with one drop of TFA cleanly isomerized **23** to **22**.

The Weinreb amide appeared to be a poor choice of electrophile because the tetrahedral intermediate **19** was too stable and cyclized to give **21** more rapidly than it decomposed to give keto ester **20**. A simple ester should be better because the tetrahedral intermediate will decompose rapidly to give **20**, which could then cyclize to give the desired product **26**. Fortunately, this proved to be the case. Acid catalyzed esterification of proline[18] and cyanation[16] with CNBr and $NaHCO_3$ in EtOH gave the known cyanamide **25** (see Scheme 5).[19] Cyanamide methyl ester **25** was added to a solution of the lithium enolate of *tert*-butyl acetate (2.3 equiv) in THF at −45 °C.[20] The solution was stirred for 1 h at −45 °C to give keto ester **20**, treated with 1.2 equiv of LHMDS in THF, and stirred at 25 °C for 2 h to give the desired product **26** in 27% yield. Byproduct **28** was formed in 24% yield by the addition of the enolate to the cyanamide to give **27**, which then cyclized to the methyl ester to form the alkylidene imidazolidinedione **28**.[21] The stereochemistry of the double bond was established by an NOE between the alkene proton and the methylene group. The methyl ester of **25** is less electrophilic than the Weinreb amide of **17** so that the enolate added to both the methyl ester and the cyanamide.

Vinylogous urea **26** has the ring system of jenamidines A_1/A_2 with an additional *tert*-butyl carboxylate, which we hoped we could remove by hydrolysis and decarboxylation either before or after the introduction of the side chain amide. Reaction of **26** with 9:1 CH_2Cl_2/TFA effected hydrolysis, but did not provide the desired vinylogous urea **14b**.

Acylation of **26** with 2.5 equiv of NaH and 2.2 equiv of tigloyl chloride for 2 h afforded a mixture of the desired product amide **29** and the bis-acylated product pyrrole **30** (see Scheme

6). Stirring the crude mixture in 9:1 CH_2Cl_2/TFA for 15 h effected hydrolysis of the *tert*-butyl esters of **29** and **30** and the enol ester of **30** and decarboxylation to give jenamidines A_1/A_2 model **31** in 69% overall yield from **26**. The spectral data of the ring portion of **31** correspond very closely to those of the natural product, supporting the assignment of **8** as the structure of jenamidines A_1/A_2.

The side chain was then prepared by a modification of Adam's procedure for the ethyl ester.[9] Ylide **32**[22] was prepared from *tert*-butyl 2-bromopropionate by conversion of the bromide to an iodide, reaction of the iodide with triphenylphosphine, and treatment of the phosphonium salt with aqueous NaOH (see Scheme 7). Aldehyde **33**[23] was prepared from *S*-methyl lactate by first protecting the alcohol as the TBDMS ether and then reducing the ester with DIBALH. Reaction of aldehyde **33** with ylide **32** in CH_2Cl_2 for 2 h provided α,β unsaturated ester **34**[9] in 67% yield. Due to the incompatibility of the TBDMS group with the formation of the acid chloride, the alcohol was deprotected with pyr•HF in THF to give alcohol **35** in 99% yield. Initially we chose to protect the alcohol as an acetate ester. Reaction of **35** with AcCl, DMAP, and pyridine in THF gave **36a** in 99% yield, which was deprotected in 9:1 CH_2Cl_2/TFA to give acetoxy acid **37a** in 99% yield. Stirring **37a** in oxalyl chloride gave crude acid chloride **38a**, which was used without purification.

Reaction of vinylogous urea **26** with NaH and acid chloride **38a** followed by hydrolysis and decarboxylation with 9:1 CH_2Cl_2/TFA as described above for the preparation of **31** gave jenamidines A_1/A_2 acetate (**39a**) in 84% yield (see Scheme 8). To our surprise, hydrolysis using KOH in methanol/water or K_2CO_3 in MeOH for 12 h at 25 °C afforded primarily **14b**. The “amide” and acetate were cleaved at similar rates. Since the nitrogen of the “amide” of **39a** is part of a vinylogous urea, the “amide” is actually a vinylogous acyl urea. Acyl ureas are rapidly hydrolyzed in basic methanol.[24] Vinylogous urea **14b** is polar and hard to work with; initial attempts to reacylate it were unsuccessful. This is ironic since **14b** was our initial target. The *tert*-butyl ester of **26**, which we thought was undesirable, turns out to facilitate handling and acylation, and can then be easily removed with TFA in CH_2Cl_2.

Initial attempts at milder or enzymatic selective cleavage of the acetate of **39a** were unpromising. Acid-labile protecting groups were appealing since they would be cleaved by the 9:1 CH_2Cl_2/TFA used for the hydrolysis of the *tert*-butyl esters. Unfortunately, most acid-labile protecting groups are not compatible with the formation of acid chloride **38**. The TBDMS group has been used with mixed anhydrides,[25] but acylation of **26** with mixed anhydrides formed from tiglic acid proceeded in significantly lower yield than with the acid chloride. Unfortunately, application of Wissner's procedure[26a] for making TBDMS ether-containing acid chlorides to the acid prepared by hydrolysis of **34** converted the allylic OTBDMS group to an allylic chloride.

We then examined more base labile ester protecting groups. Dichloroacetate, chloroacetate, and methoxyacetate esters are hydrolyzed 10,000, 700 and 20 times faster then acetate esters, respectively.[27] Alcohol **35** was protected with dichloroacetyl chloride, chloroacetyl chloride, or methoxyacetyl chloride to give **36b-d**, respectively, in good yield. Acidic hydrolysis proceeded smoothly to give **37b-d**, which were transformed into the corresponding acid chlorides **38b-d**.

Reaction of **38b** with vinylogous urea **26** gave only 29% of jenamidine A_1/A_2 dichloroacetate (**39b**), but the deprotection proceeded smoothly with $NaHCO_3$ in MeOH at 0 °C for 30 min to give jenamidines A_1/A_2 (**8**) in quantitative yield. The dichloroacetate could be selectively cleaved, but was too unstable for the coupling and decarboxylation reactions. Reaction of chloroacetate **38c** with **26** gave **39c** in a still unacceptable 31% yield, which could also be cleaved by $NaHCO_3$ in MeOH for 1 h at 25 °C to give **8** cleanly.

The best compromise was the methoxyacetate protecting group. Acylation of **26** with acid chloride **38d**, hydrolysis of the *tert*-butyl ester and decarboxylation with 9:1 CH_2Cl_2/TFA gave crude jenamidines A_1/A_2 methoxy acetate (**39d**) in ~70% yield based on analysis of the ^1H NMR spectrum. Flash chromatography provided pure **39d** in 39% yield and jenamidines A_1/A_2 (**8**) in 18% yield. Since **8** was not present in the crude product, hydrolysis occurred during chromatography. Pure **39d** was treated with K_2CO_3 in methanol for 6 h at 0 °C to give **8** in 56% yield (70% based on recovered **39d**), recovered **39d** in 20% yield, and **14b** resulting from cleavage of the amide in 18% yield. A more efficient procedure involved hydrolysis of crude **39d** with K_2CO_3 in MeOH at 0 °C for 24 h to give jenamidines A_1/A_2 in 45% overall yield from **26**, **39d** in 11% overall yield from **26**, and traces (<5%) of **14b**.

The spectral data of synthetic jenamidines A_1/A_2 (**8**) are identical to those of the natural product thereby confirming the revised structure we proposed. Both synthetic and natural jenamidines A_1/A_2 are a 1:1 mixture of diastereomers. Even though **26** was prepared from (*S*)-proline and **33** was prepared from (*S*)-methyl lactate, we obtained **8** as a mixture of diastereomers. The ring fusion hydrogen is readily epimerized and this stereocenter is lost in the formation of the bis acylated intermediate analogous to **30**, which will give a mixture of diastereomers on hydrolysis. In the ^1H NMR spectrum of **8** in CD_3OD, the ring fusion hydrogen, H_{7a}, integrates for only ~0.5, suggesting that partial deuterium exchange has occurred. In the ^{13}C NMR spectrum, C_2 and C_7 absorb as four peaks since a separate peak is observed for the H_{7a} and D_{7a} isomer of each diastereomer.[28]

The optical rotation of synthetic **8**, $[\alpha]_D$ +4.2, is very similar to that of the natural product, $[\alpha]_D$ +6.8.[1] Therefore natural jenamidines A_1/A_2 (**8**) could also be a mixture of isomers at the ring fusion and the (*S*) isomer on the side chain. However, since both rotations are for mixtures of diastereomers, it is also possible that the natural product is a mixture of isomers on the side chain.

The three-step sequence from vinylogous urea **26** and acid chloride **38d** to jenamidines A_1/A_2 (**8**) proceeded in 45% yield, which was acceptable given the instability of the amide linkage in base. The one-pot preparation of **26** from cyanamide **25** provided adequate quantities of material, but the 27% yield left room for improvement. Coupling of various *N*-acetyl amino acid derivatives **40** with ethyl cyanoacetate had been reported to give **41**, which cyclized on treatment with 8% HCl in EtOH at reflux to provide **42** in 18−51% overall yield (see Scheme 9).[29] We examined variants of this procedure because the acid-catalyzed cyclization used to convert **41** to **42** is not compatible with the *tert*-butyl ester of **26**.

Reaction of Cbz-proline *N*-hydroxysuccinimide ester (**43**) with the enolate of *tert*-butyl cyanoacetate and NaH in benzene for 3 h gave crude **44**, which was hydrogenated (1 atm) over 10% Pd/C in MeOH for 2 h to provide **45** as complex mixture of keto/enol tautomers. Fortunately, crude **45** cyclized on standing for 1 d to give **26** in 50% overall yield from **43**. Using this sequence, which has not been fully optimized, jenamidines A_1/A_2 (**8**) are now available from commercially available **43** in 5 steps and 23% overall yield.

Synthesis of NP25302 (12)

We now turned to applying what we had learned in the synthesis of jenamidines A_1/A_2 (**8**) to the synthesis of NP25302 (**12**). Acylation of **46** followed by acid-catalyzed hydrolysis and decarboxylation should be straightforward because the problematic side chain alcohol of jenamidines A_1/A_2 is not present in NP25302 (see Scheme 10). Vinylogous urea **46** can be prepared by addition of the enolate of *tert*-butyl acetate to cyanamide **47** or by the addition of *tert*-butyl cyanoacetate to **48**. Both **47** and **48** should be readily accessible from *trans*-2,5-dimethylproline ethyl ester (**49**).

The challenging portion of this synthesis is the efficient and stereospecific preparation of **49**. 2,5-Dimethylproline has been prepared, but the stereochemistry was not addressed.[30] Feringa reported the Yb(OTf)$_3$-catalyzed Michael addition of ethyl 2-nitropropionate (**51**) to methyl vinyl ketone (**50**) to give **52** in 99% yield (see Scheme 11).[31] Hydrogenation (35 psi) of **52** over Pd/C for 3 d gave a 2:1 mixture of hydroxylamines **53** and **54** in 69% yield.[31] We decided to reexamine this hydrogenation in an attempt to improve the stereoselectivity and complete the reduction to give **49**.

Reaction of **50** and nitro ester **51** with 0.1 equiv of DABCO in CH_2Cl_2 gave **52** in 98% yield (see Scheme 12). Reduction under Feringa's conditions[31] gave a 2:1 mixture of **53** and **54** as reported. The stereoselectivity problem was eventually overcome by developing a two-step route that gave **53** selectively. Reductive cyclization of **52** over Pd/C for 15 h at 1 atm of H_2 provided nitrone **55**. Further reduction over PtO_2 for 8 h at 1 atm of H_2 gave a >20:1 mixture of hydroxylamines **53** and **54** in quantitative yield. The stereochemistry of **53** was confirmed by an NOE observed between the proton α to the nitrogen and both methyl groups, showing that H-5 and Me-2 are on the same face of the proline ring. Presumably, hydrogen approaches from the less sterically hindered side of the proline ring with the quaternary methyl rather than the carboethoxy group. It is not clear why the selectivity achieved with Pt is so much better than that obtained with Pd.

There are numerous reports of the reduction of nitro ketones to pyrrolidines rather than *N*-hydroxy pyrrolidines.[32] We suspect that steric hindrance retards hydrogenolysis of **53** and **54**. The N-OH bond of **53** can be reduced by stirring with Zn(Cu) in refluxing acetic acid to give the required *trans*-2,5-dimethylproline ethyl ester (**49**). The NMR spectra of **49** and **53** are very similar, but the IR spectra show the expected peaks for an OH in **53** at 3446 cm^{-1} (neat) and for an NH in **49** at 3345 cm^{-1} (neat).[33]

The need for three separate steps to reduce **52** to **49** was unappealing. We thought that addition of acid might accelerate the hydrogenation of **55** over Pd. This led to the development of a one-pot reductive cyclization of **52** that gave **49** stereospecifically. Hydrogenation (1 atm) of **52** as before over 10% Pd/C with Na_2SO_4 in EtOH gave nitrone **55**. Concentrated hydrochloric acid (3 equiv) was added and the hydrogenation was continued at 3.3 atm for 36 h to provide amine **49**•HCl with >20:1 stereoselectivity. An NOE observed between the proton α to the nitrogen and both methyl groups in **49**•HCl confirmed the trans relationship of the methyl groups. Hydrogenation of **52** in the presence of HCl, without first reducing to the nitrone at neutral pH, was not as clean.

The conversion of **49** to **46** could be carried out via *N*-hydroxysuccinimide ester **48** (analogously to the conversion of **43** to **26)** or cyanamide **47** (analogously to the conversion of **25** to **26**). The first route was much more efficient for the preparation of jenamidines A_1/A_2 intermediate **26**. However, we chose to use cyanamide **47** for two reasons. First, it takes only one step to make **47** from **49**; at least three steps will be needed to prepare **48**. Second, the two methyl groups in cyanamide **47** should decrease the reactivity of the cyanamide more than that of the ester so that enolate addition should occur selectively to the ester. The low yield of **26** from cyanamide **25** resulted from addition of the enolate to the ester and cyanamide at similar rates.

Reaction of **49**•HCl with excess $NaHCO_3$ and CNBr in EtOH for 2 h at 25 °C gave cyanamide **47** in 75% overall yield from nitro keto ester **52** (see Scheme 13). Addition of **47** to the lithium enolate of *tert*-butyl acetate at −45 to 25 °C in THF gave β-keto ester **57** as a mixture of keto/enol tautomers as the major product instead of the expected bicyclic product **46**. The two methyl groups prevent the addition of the enolate to the cyanamide, but they also retard the cyclization of **57** to give the desired and expected product **46**. This cyclization failed under a variety of conditions, but eventually was efficiently accomplished by treatment with *t*-BuOK in *t*-BuOH in a sealed tube at 135 °C for 15 h toafford bicyclic vinylogous urea **46** in 49% yield from cyanamide **47**.

The completion of the synthesis was now trivial. Acylation of **46** with 3-methyl-2-butenoyl chlorideand NaH in THF at 25 °C for 2 h gave **58**, which was stirred in 9:1 CH_2Cl_2/TFA for 15 h to give (±)-NP25302 (**12**) in 88% yield from **46**.

Enantioselective Synthesis of Natural (+)-NP25302 (12)

Enantioselective synthesis of (+)-NP25302 will require carrying out an enantioselective Michael reaction of ethyl 2-nitropropionate (**51**) and methyl vinyl ketone (**50**) to give optically pure **52**. Feringa prepared **52** in 72% ee using Al-Li-2,2′-dihydroxybinaphthyl, prepared in situ from LAH and 2.45 equiv of (*R*)-BINOL, as the asymmetric catalyst.[34] Deng and coworkers have developed bifunctional cinchona alkaloids such as **59** that efficiently catalyze enantioselective Michael additions to α,β-unsaturated carbonyl compounds.[35] The modified dihydroquinine **60** was synthesized analogously to **59**[35b] from hydrocupreine[36] by protection of the phenol with TIPSCl and imidazole in DMF in 95% yield, arylation of the alcohol with 4,6-dichloro-2,5-diphenylpyrimidine and KOH in toluene at 115 °C for 1 h, and deprotection of the TIPS group with aqueous HF in CH_3CN to give **60** in 50% overall yield (see Figure 3).

Michael addition of **51** to **50** with 10 mol% of catalysts **59** and **60** at −20 °C for 3 days gave quantitative yields of (−)-**52** **(**80% ee) and (+)-**52** **(**90% ee), respectively (see Scheme 14). Reaction with **59** at 23 °C was complete in 5 h, but the enantioselectivity dropped to 66%. At −50 °C, the reaction with **59** proceeded too slowly and did not go to completion. The enantioselectivity was determined by chiral HPLC analysis of the ethylene glycol ketal derived from **52** as described by Feringa.[34]

Carrying out the sequence developed in the racemic series starting from (−)-**52** (80% ee) gave (+)-**49** and (−)-NP25302 (80% ee) with $[\alpha]^{22}_D$ −60 (*c* 1.0, MeOH) while the natural product has $[\alpha]^{22}_D$ +115 (*c* 1.1, MeOH). The synthesis of natural (+)-NP25302 (90% ee) with $[\alpha]^{22}_D$ +70 (*c* 1.0, MeOH) was completed from (+)-**52** (90% ee) via (−)-**49**.

Although chiral HPLC established the enantiomeric excess of **52**, we still needed to assign the absolute configuration. We thought that this could be best carried out at the stage of the dimethylproline derivative **49**. Initial attempts to form a crystalline salt from (−)-**49** with (+)-camphor-10-sulfonic acid for x-ray crystallography failed, although this approach has been used to determine the absolute configuration of a 2-methylproline ester.[37] Hoye has prepared the diastereomeric Mosher amides **61** and **62** from (2*R*,5*R*)-2,5-dimethylpyrrolidine and showed that the NMR spectra are remarkably different as indicated on the structures (see Figure 4).[38] Conformational studies indicated that the dominant conformation has the trifluoromethyl group syn to the carbonyl as shown. One methyl group, presumably that adjacent to the carbonyl, absorbed at δ 1.30 and 1.32 in the two diastereomers. As expected, the methyl group adjacent to the phenyl group in **62** (δ 0.10) is shifted upfield 0.99 ppm from the methyl group in **61** (δ 1.09). Similarly, the methine hydrogen in **61** adjacent to the phenyl group (δ 3.19) is shifted upfield 1.24 ppm from the methine hydrogen in **62** (δ 4.43).

There were some concerns regarding the application of this procedure to determining the absolute stereochemistry of (−)-**49**. The amine component of Hoye's Mosher amides **61** and **62** is C_2-symmetric so that there is only one conformer. Although Mosher amides **63** and **64** can exist as two conformers, we expected that the conformer with the smaller carbonyl group adjacent to the more hindered side bearing the ester group would be much more stable so that the shielding effects on the secondary methyl group and methine hydrogen should be similar to those observed in **61** and **62**. Acylation of (−)-**49** with both *R*- and *S*-Mosher acid chlorides[39] gave the corresponding *S*- and *R*-Mosher amides, **63** and **64**, respectively. The shielding effects are almost identical to those observed in the pseudo-enantiomeric amides **61** and **62**, establishing that the (−)-**49** obtained from catalyst **60** is the (2*S*,5*S*) isomer and that natural (+)-NP25302 (**12**) is the (4*S*,7*S*) isomer. Synthetic **12** with 90% ee has $[\alpha]_D$ +70 indicating that optically pure material should have $[\alpha]_D$ +78, rather than +115 as reported. This is not due to degradation of the 90% ee of **52** during the reductive cyclization to give **49** because the NMR spectrum of crude Mosher amides **63** and **64** prepared from (−)-**49** indicated the presence of a 20:1 mixture of isomers (90% ee).

Approaches toward the synthesis of jenamidines B_1/B_2 (9)

Jenamidines B_1/B_2 (**9**) differ from jenamidines A_1/A_2 (**8**) by the presence of an additional hydroxy group on the ring fusion. Attempted oxidation of jenamidines A_1/A_2 acetate (**39a**) under a variety of conditions gave a complex mixture of products as expected for a functionally dense, base-labile compound. Attempted hydroxylation of **26** was equally unsuccessful as was epoxidation of the *N*-acetyl enol acetate of **26** prepared with 2 equiv of AcCl and 2 equiv of THF at 25 °C.

α-Acetoxylation of ketones can be achieved with $Mn(OAc)_3$ and $Pb(OAc)_4$.[40,41] Reaction of **26** with $Mn(OAc)_3$ was not promising, but reaction with 2 equiv of $Pb(OAc)_4$ in refluxing benzene for 9 h proceeded cleanly, but with modest material balance (45%) to give a compound in 39% yield whose structure was eventually established to be **65** based on ^1H and ^{13}C NMR, IR and mass spectral data (see Scheme 15). The ^1H NMR spectrum showed NH_2 protons at δ 8.28 and 7.95. The absorption for H^4 at δ 6.04 (dd, 1, J = 6.1, 6.7) is consistent with a proton adjacent to a nitrogen and an acetate.[42,43] We expected that acetoxylation at C_4 should occur from the convex face to give **65** with the acetates cis. This was supported by molecular mechanics calculations. MMX calculations with conformational searching using PCMODEL predicted vicinal coupling constants for H_4 (dd, J = 8.0, 7.1) for **65**, which correspond well with the observed values, and (dd, J = 6.7, 2.8) for the other diastereomer with the acetates trans, which do not correspond well with the observed values. An NOE was observed between H_4 and $H_{6\alpha}$ as expected for a calculated distance of 3 Å in **65**. The calculated distance between H_4 and the closest H_6 in the other isomer is 4 Å, which is too far for an NOE to be observed.

We hoped that oxidation of **26** with only 1 equiv of $Pb(OAc)_4$ would occur selectively at the ring fusion to give **67**. Unfortunately, oxidation of **26** with 1 equiv of $Pb(OAc)_4$ in refluxing benzene gave a 3:2 mixture of the desired monoacetate **67**, and the undesired regioisomer **66** and traces of bis acetate **65**. A similar reaction at room temperature was selective for the undesired regioisomer giving a 1:5 mixture of **67** and **66**. Slow flash chromatography using 39:1 CH_2Cl_2/MeOH as eluent afforded pure **66**, but the acetate of the desired regioisomer **67** exchanged with methanol to give **68**. The relative stereochemistry of **66** was not established, but it is tentatively assigned assuming that oxidation occurs on the less hindered convex face. The facile oxidation adjacent to the amide nitrogen was unexpected because we thought that the position adjacent to the ketone should be more easily oxidized. However, there is limited precedent for oxidation adjacent to an amide nitrogen with $Pb(OAc)_4$[43] and electrochemical oxidation adjacent to amide nitrogens occurs readily.[44] Complex mixtures were obtained from $Pb(OAc)_4$ oxidation of the **29**/**30** mixture or **31** and attempts to prepare jenamidines B_1/B_2 analogues from **68** were not promising. In conclusion, acetoxylation with $Pb(OAc)_4$ at the ring fusion could be accomplished to give **67**, but acetoxylation adjacent to the nitrogen occurred at a competitive rate to give **66** and bis acetate **65** indicating that application of this method to the synthesis of jenamidines B_1/B_2 (**9**) will not be straightforward.

Formal synthesis of SB-311009 analogues. We isolated **23** from an unsuccessful approach to jenamidines A_1/A_2. While looking for analogous compounds to help us confirm the structure of **23**, we came across SB-253514 (**70**), which was isolated by Readshaw and coworkers from the culture broths of *Pseudomonas fluorescens* strain DSM11579 in 2000.[45] The glycosidic linkage was hydrolyzed enzymatically to give the alcohol SB-311009 (**69**) (see Scheme 16).[45c] SB-253514 is a potent and selective inhibitor (IC_{50} = 51 nM) of lipoprotein-associated phospholipase A_2 ($LpPLA_2$), the enzyme responsible for the conversion of phosphatidylcholine to lysophosphatidylcholine and oxidized fatty acids during the conversion of low density lipoprotein to its oxidized form.[45a] Pinto prepared **74**, in which R is a variety of long alkyl chains, and found that these analogues were 2–4 times more biologically active than **69** or **70**.[46] A five-step sequence converted *N*-Boc-proline (**71**) to the unsaturated 2-trimethylsilylethyl ester **72** in 7% overall yield. Deprotection of the 2-trimethylsilylethyl ester with TBAF gave acid **73** in 100% yield, which was coupled with an amine using EDCI to give **74**.

We thought that **72** and related esters could be prepared in a single step by a Wittig reaction between the *N*-carboxyanhydride (NCA) of proline (**76**) and a stabilized ylide such as **77** or **79** (see Scheme 17). Bateson reported that the Wittig reaction of the NCA of the cyclohexylidene aminal of homoserine with ylide **77** in EtOAc gave the enoate in 81% yield.[47] To the best of our knowledge, this is the only report of a Wittig reaction on an NCA although Wittig reactions on succinic and phthalic anhydrides have been extensively studied.[48]

Proline-NCA (**76**) was prepared by reaction of proline (**75**) with triphosgene at 40 °C in THF followed by the addition of triethylamine at 0 °C.[49] Proline-NCA is very unstable because nucleophiles initiate polymerization,[50] so freshly prepared **76** in THF was used for all reactions. Reaction of **76** with ylide **77** in EtOAc following Bateson's procedure gave no **78**. Eventually we found that heating **76** and **77** in toluene at reflux provided **78** as a >9:1 *E*/*Z* mixture in a highly variable 10–20% yield from proline. Fortunately, reaction of proline NCA (**76**) with **77** in toluene at 150 °C in a microwave oven for 15 min (75 psi) reproducibly afforded enoate **78** as a >9:1 *E*/*Z* mixture of isomers in 35% yield. The alkene hydrogen absorbs at δ 5.66 in the *E*-isomer and δ 5.05 in the *Z*-isomer as observed by Pinto for the isomers of **72**.

Hydrolysis of the methyl ester of **78** to give acid **73** could not be accomplished under a variety of typical hydrolysis conditions. This is consistent with the observation that cleavage of the glycosidic linkage of SB-253514 (**70**) to give SB-311009 (**69**) could not be achieved with either acid or base, possibly due to the instability of the cyclic carbamate.[45c] The cleavage could only be achieved enzymatically.[45c]

We therefore decided to prepare 2-trimethylsilylethyl ester **72** since Pinto had hydrolyzed this to give acid **73** with TBAF.[46] The Wittig reaction of **76** with ylide **79**[51] in toluene at 150 °C for 15 min in a microwave oven gave Pinto's intermediate **72** in 27% overall yield from proline as a >9:1 E/Z mixture of stereoisomers with spectra identical to those provided by Dr. Pinto. This completes a formal synthesis of SB-311009 analogues, which is a significant improvement over the earlier procedure which required 5 steps and proceeded in 7% yield.

In conclusion, the proposed structures of jenamidines (**1–3**) have been revised to **8-10**. The revised structural assignment has been confirmed by the synthesis of jenamidines A_1/A_2 (**8**). The first total synthesis of natural (+)-NP25302 (**12**) was completed both stereospecifically and enantioselectively. $Pb(OAc)_4$ oxidation of jenamidines A_1/A_2 intermediate **26** gave access to jenamidines B_1/B_2 precursors, but indicated that oxidation α to the amide occurred at a rate comparable to oxidation α to the ketone. A one-step formal synthesis of SB311009 analogues was completed *via* a Wittig reaction with proline-NCA to give **72**.

Experimental Section

Preparation of 26 from Cbz-Proline *N*-Hydroxysuccinimide Ester (43)

tert-Butyl cyanoacetate (0.68 mL, 4.8 mmol) was added dropwise to a solution of NaH (160 mg, 4.0 mmol, 60% dispersion in mineral oil) in 8 mL of dry benzene at rt. The resulting slurry was stirred for 1 h and treated with **43** (554 mg, 1.6 mmol) in 2 mL of dry benzene. The mixture was stirred for an additional 3 h at 25 °C, quenched with H_2O, and extracted with Et_2O. The aqueous layer was acidified with 2 M HCl resulting in the formation of a white precipitate, which dissolved upon addition of CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $MgSO_4$ and concentrated to give **44**.

A solution of crude **44** in 25 mL of MeOH was stirred with 10% Pd/C (170 mg, 0.16 mmol) under 1 atm of H_2 at 25 °C for 2 h. The mixture was filtered through Celite and concentrated to give crude **45**, which cyclized on standing for 24 h at 25 °C to give crude **26**. Flash chromatography on silica gel (95:5 EtOAc/MeOH) gave 190 mg (50%) of **26**: mp 200−203 °C; $[\alpha]^{22}_D$ −62.2 (*c* 1.1, MeOH); UV (MeOH) λ_{max} nm (log ε) 211(4.17), 241 (4.21), 264 (4.11); ^1H NMR ($CDCl_3$) 8.00 (br, 1, NH), 5.42 (br, 1, NH), 3.87 (dd, 1, *J* = 6.7, 9.8), 3.34 −3.42 (m, 1), 3.20−3.28 (m, 1), 2.06−2.26 (m, 3), 1.54−1.60 (m, 1), 1.55 (s, 9); ^{13}C NMR ($CDCl_3$) 193.1, 174.0, 164.9, 90.5, 79.9, 69.7, 46.6, 28.5 (3 C), 27.6, 26.7; IR (KBr) 3475, 3077, 1714, 1638; HRMS (DEI) calcd for $C_{12}H_{18}N_2O_3$ (M^+) 238.1317, found 238.1315.

tert-Butyl (4*S*)-4-[[(*tert*-Butyl)dimethylsilyl]oxy]-2-methylpent-2*E*-enoate (34)

A solution of (1-*tert*-butoxycarbonylethylidene)triphenylphosphorane (**32**)[22] (1.9 g, 4.7 mmol) in 18 mL of dry CH_2Cl_2 was added to 2-[[(*tert*-butyl)dimethylsilyl]oxy]-propanal (**33**)[23] (730 mg, 3.8 mmol) in 8 mL of dry CH_2Cl_2. The mixture was stirred at 25 °C for 2 h and quenched with 25 mL of H_2O. The layers were separated and the organic layer was dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (98:2 hexanes/EtOAc) yielded 770 mg (67%) of **34**: ^1H NMR ($CDCl_3$) 6.57 (br d, 1, *J* = 8.5), 4.59 (dq, 1, *J* = 8.5, 6.7), 1.78 (d, 3, *J* = 1.2), 1.49 (s, 9), 1.22 (d, 3, *J* = 6.7), 0.88 (s, 9), 0.05 (s, 3), 0.04 (s, 3); ^{13}C NMR ($CDCl_3$) 167.3, 144.7, 126.8, 80.1, 66.0, 28.0 (3 C), 25.8 (3C), 23.4, 18.1, 12.5, −4.7, −4.8; IR (neat) 1710; HRMS (DCI/NH_3) calcd for $C_{16}H_{36}NO_3Si$ (MNH_4^+) 318.2464, found 318.2455.

tert-Butyl (4*S*-4-Hydroxy-2-methylpent-2*E*-enoate (35)

Silyl ether **34** (300 mg, 1.0 mmol) in 2 mL of THF was added to 18 mL of a 1.4 M solution of pyridine•HF (5 mL pyridine•$(HF)_x$, 20 mL THF, 20 mL pyridine). The mixture was stirred for 4 h in an Eppendorf tube, slowly quenched with saturated sodium bicarbonate solution, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield 185 mg (99%) of pure **35**: ^1H NMR ($CDCl_3$) 6.58 (br d, 1, *J* = 8.3), 4.67 (dq, 1, *J* = 8.3, 6.1), 1.83 (d, 3, *J* = 1.5), 1.49 (s, 9), 1.31 (d, 3, *J* = 6.1); ^{13}C NMR ($CDCl_3$) 167.2, 143.0, 129.0, 80.5, 64.9, 28.0 (3 C), 22.6, 12.6; IR (neat) 3421, 1707; HRMS (DCI/NH^3) calcd for $C_{10}H_{22}NO_3$ (MNH_4^+) 204.1600, found 204.1606.

tert-Butyl (*S*)-4-Methoxyacetoxy-2-methylpent-2*E*-enoate (36d)

Methoxyacetyl chloride (0.15 mL, 1.6 mmol) was added slowly to a solution of alcohol **35** (185 mg, 0.99 mmol), pyridine (0.17 mL, 2.12 mmol), and DMAP (12 mg, 0.1 mmol) in 15 mL of dry THF under N_2 resulting in a white precipitate. The mixture was stirred for 2 h at 25 °C, filtered, diluted with EtOAc, washed successively with 2 M HCl, water, saturated sodium bicarbonate solution, and water, dried over $MgSO_4$, and concentrated to give 255 mg (99%) of pure **36d**: ^1H NMR ($CDCl_3$) 6.51 (br d, 1, *J* = 8.9), 5.73 (dq, 1, *J* = 8.9, 6.1), 4.03 (s, 2), 3.45 (s, 3), 1.88 (d, 3, *J* = 1.5), 1.49 (s, 9), 1.36 (d, 3, *J* = 6.1); ^{13}C ($CDCl_3$) 169.4, 166.6, 137.6, 131.3, 80.7, 69.8, 68.2, 59.3, 27.9 (3 C), 19.7, 12.8; IR (neat) 1756, 1709; HRMS (DCI/NH_3) calcd for $C_{13}H_{26}NO_5$ (MNH_4^+) 276.1811, found 276.1809.

(*S*)-4-Methoxyacetoxy-2-methylpent-2*E*-enoic acid (37d)

A solution of ester **36d** (255 mg, 0.98 mmol) in 5 mL of 9:1 CH_2Cl_2:TFA was stirred for 12 h at 25 °C. The mixture was diluted with H^2O and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 194 mg (98%) of pure **37d**: ^{1}H NMR ($CDCl_3$) 11.0 (br s, 1, OH), 6.74 (d, 1, *J* = 8.8), 5.74 (dq, 1, *J* = 8.8, 6.4), 4.05 (s, 2), 3.45 (s, 3), 1.93 (s, 3), 1.38 (d, 3, *J* = 6.4); ^{13}C NMR ($CDCl_3$) 172.8, 169.5, 141.3, 129.0, 69.7, 68.1, 59.3, 19.4, 12.4; IR (neat) 3187, 1753, 1696; HRMS (DCI/NH_3) calcd for $C_9H_{18}NO_5$ (MNH_4^+) 220.1185, found 220.1189.

Conversion of 37d to the Acid Chloride

A solution of acid **37d** (194 mg, 0.96 mmol) in 8 mL of oxalyl chloride was stirred for 4 h at 25 °C under N_2. Excess oxalyl chloride was removed under reduced pressure to give (*S*)-4-methoxyacetoxy-2-methylpent-2*E*-enoyl chloride (**38d**), which was used immediately: ^{1}H NMR ($CDCl_3$) 6.98 (d, 1, *J* = 8.6), 5.73 (dq, 1, *J* = 8.6, 6.7), 4.06 (s, 2), 3.46 (s, 3), 2.00 (s, 3), 1.42 (d, 3, *J* = 6.7).

Jenamidines A_1/A_2 (8), Jenamidines A_1/A_2 4'-Methoxyacetate (39d), and 3-Amino-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (14b)

Vinylogous urea **26** (106 mg, 0.44 mmol) and NaH (60% dispersion in mineral oil, 45 mg, 1.1 mmol) were stirred in 10 mL of dry THF under N_2 for 10 min. Acid chloride **38d** (0.96 mmol) in 3 mL of dry THF was added and the resulting solution was stirred for 2 h, quenched with brine, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 196 mg of a mixture of mono and bis acylated products. A solution of the mixture in 10 mL of 9:1 CH_2Cl_2:TFA was stirred for 15 h, neutralized with saturated sodium bicarbonate solution, saturated with NaCl and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to afford jenamidines A_1/A_2 4'-methoxyacetate (**39d**) as the major product and no jenamidines A_1/A_2 (**8**), as expected. Flash chromatography on silica gel (97:3 CH_2Cl_2/MeOH to 90:10 CH_2Cl_2/MeOH) gave 55 mg (39%) of **39d**, followed by 20 mg (18%) of a mixture of **8** and other decomposition products.

A solution of a second batch of crude **39d** (prepared as before from 96 mg (0.40 mmol) of **26**, 42 mg (1.0 mmol) of NaH, and 0.96 mmol of **38d** followed by TFA hydrolysis) was stirred in 10 mL of MeOH containing 10 drops of H_2O and 200 mg of Na_2CO_3 at 0 °C for 24 h. The mixture was filtered through silica gel and concentrated to give a 4:1:1 mixture of **8**, **39d**, and **14d**. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave 14 mg (11% from **26**) of **39d** and 45 mg (45% from **26**) of **8**, while **14b** was recovered along with a complex mixture of products upon flushing the silica gel with MeOH.

Data for **39d** as a 1:1 mixture of diastereomers: ^{1}H NMR (CD_3OD) 6.345 (br d, 1 × 0.5, *J* = 8.0), 6.340 (br d, 1 × 0.5, *J* = 8.0), 5.72–5.80 (m, 1), 5.64 (s, 1), 4.07 (s, 2 × 0.5), 4.06 (s, 2 × 0.5), 3.95 (dd, 1, *J* = 8.8, 8.8), 3.40–3.47 (m, 1), 3.42 (s, 3 × 0.5), 3.41 (s, 3 × 0.5), 3.20–3.26 (m, 1), 2.10–2.25 (m, 3), 1.994 (s, 3 × 0.5), 1.991 (s, 3 × 0.5), 1.50–1.60 (m, 1), 1.41 (d, 3 × 0.5, *J* = 6.1), 1.40 (d, 3 × 0.5, *J* = 6.1); ^{13}C NMR (CD_3OD) 204.7, 173.4, (171.39, 171.37), (169.4, 169.3), (138.04, 138.00), (134.20, 134.18), 93.9, 70.7, 70.5, (69.4, 69.3), (59.54, 59.52), 49.3, 28.8, 27.5, 19.8, (13.29, 13.26); IR (neat) 1744, 1702, 1636, 1563, 1506; HRMS (DCI/NH_3) calcd for $C_{16}H_{23}N_2O_5$ (MH^+) 323.1607, found 323.1609.

Data for jenamidines A_1/A_2 (**8**) as a 1:1 mixture of diastereomers: $[\alpha]^{22}_D$ 4.2 (*c* 0.6, MeOH), lit.[1] $[\alpha]^{22}_D$ 6.8 (*c* 0.7, MeOH); UV λ_{max}^{MeOH} nm (log ε) 240 (4.29), 282 (3.84), 3.26 (4.02); ^1H NMR (CD_3OD) 6.37 (d, 1, *J* = 7.9), 5.67 (s, 1 × 0.5), 5.63 (s, 1 × 0.5), 4.67 (dq, 1, *J* = 6.5, 7.9), 3.92−3.98 (m, 1), 3.42−3.49 (m, 1), 3.18−3.26 (m, 1), 2.08−2.24 (m, 3), 1.92 (s, 3), 1.50−1.60 (m, 1), 1.31 (d, 3 × 0.5, *J* = 6.5), 1.29 (d, 3 × 0.5, *J* = 6.5); ^{13}C NMR (CD_3OD) (204.69, 204.57), (173.61, 173.48), (169.84, 169.82), (143.67, 143.65), (131.62, 131.60), (93.82, 93.80, 93.76, 93.75), (70.77, 70.67), (65.31, 65.25), 49.29, 28.80, (27.51, 27.47, 27.40, 27.37), (22.68, 22.64), 12.92; IR (neat) 2973, 1699, 1634, 1557, 1504, 1404, 1244, 1139, 1059; HRMS (DCI/NH_3) calcd for $C_{13}H_{19}N_2O_3$ (MH^+) 251.1396, found 251.1394. The ^1H and ^{13}C NMR spectrum are identical to those of the natural product.[1,2a] H_{7a} is approximately 50% exchanged with deuterium. C_2 (93.7−93.8) and C_7 (27.3−27.5) absorb as four peaks since the carbon for each diastereomer absorbs separately for the proton and deuterium isomers due to the isotope shift.[28]

Pure **39d** (30 mg, 0.093 mmol) was stirred in 2 mL of MeOH containing 5 drops of H_2O and 50 mg of Na_2CO_3 at 0 °C for 6 h. The mixture was filtered through silica gel and concentrated. Flash chromatography on silica gel (90:10 CH_2Cl_2/MeOH) gave 6 mg (20%) of recovered **39d**, followed by 13 mg (56%, 70% based on recovered **39d**) of **8** and 2.5 mg (18%) of **14b**.

Data for **14b**: ^1H NMR (CD_3OD) 4.50 (s, 1), 3.90 (dd, 1, *J* = 6.7, 9.1), 3.28−3.35 (m, 1), 3.12 −3.20 (m, 1), 2.05−2.25 (m, 3), 1.40−1.48 (m, 1); ^{13}C NMR (CD_3OD) 197.5, 178.5, 72.1, 47.7, 29.3, 28.2 (C-2 was not observed because H-2 exchanged with D); HRMS (DEI) calcd for $C_7H_{10}N_2O$ (M^+) 138.0793, found 138.0789.

Ethyl *trans*-2,5-Dimethyl-2-pyrrolidinecarboxylate (49)

A solution of **52** (886 mg, 4.08 mmol) in 16 mL of EtOH containing 10% Pd on activated carbon (430 mg, 0.41 mmol) and Na_2SO_4 (580 mg, 4.08 mmol) was stirred under 1 atm of H_2 at 25 °C for 20 h to give nitrone **55**. Concd HCl (1 mL) was added and the mixture was stirred in a Parr Shaker under 50 psi of H_2 at 25 °C for 36 h. The mixture was filtered through Celite and concentrated to give **49**•HCl containing <5% of the diastereomer **56** •HCl, which was used without purification in the next step: ^1H NMR ($CDCl_3$) 11.0 (br s, 1, NH), 8.7 (br s, 1, NH), 4.32 (q, 2, *J* = 7.0), 4.10−4.20 (m, 1), 2.45−2.51 (m, 1), 2.22−2.30 (m, 1), 2.05−2.15 (m, 1), 1.88 (s, 3), 1.60−1.72 (m, 1), 1.59 (d, 3, *J* = 6.7), 1.36 (t, 3, *J* = 7.0). The ^1H NMR spectrum of **49**•HCl in $CDCl_3$ containing excess $NaHCO_3$ to convert it back to the free amine is identical to that of **49** prepared by Zn(Cu) reduction of hydroxylamine **53**.

(−)-**49**·HCl was prepared analogously from (+)-**52**: $[\alpha]^{22}_D$ −44.5 (*c* 0.6, MeOH).

Ethyl 1-Cyano-2,5-dimethyl-2-pyrrolidinecarboxylate (47)

$NaHCO_3$ (1.7 g, 20.4 mmol) and CNBr (520 mg, 4.9 mmol) were added to a solution of **49**•HCl (prepared from 4.08 mmol of **52**) in 20 mL of EtOH and the resulting mixture was stirred for 2 h at 25 °C. H_2O was added and the solution was stirred for 15 min and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 599 mg (75% from **52**) of cyanamide **47**: ^1H NMR ($CDCl_3$) 4.18−4.27 (m, 2), 3.82 (ddd, 1, *J* = 6.1, 6.1, 9.1), 2.40−2.46 (m, 1) 2.02−2.10 (m, 1), 1.75−1.84 (m, 1), 1.61 (s, 3), 1.50−1.60 (m, 1), 1.38 (d, 3, *J* = 6.1), 1.31 (t, 3, *J* = 7.0); ^{13}C NMR ($CDCl_3$) 172.9, 114.5, 68.0, 61.8, 58.3, 37.1, 32.0, 23.0, 19.5, 14.0; IR (neat) 2208, 1737; HRMS (EI) Calcd for $C_{10}H_{16}N_2O_2$ (M^+) 196.1212, found 196.1206.

(−)-**47** was prepared analogously from (−)-**49**•HCl: $[\alpha]^{22}_D$ −34.3 (*c* 0.6, MeOH).

tert-Butyl 1-Cyano-2,5-dimethyl-β-oxo-2-pyrrolidinepropanoate (57)

tert-Butyl acetate (0.84 mL, 6.2 mmol) was added dropwise over a period of 10 min to a freshly prepared solution of LDA (5.4 mmol in 14 mL of THF) at −45 °C under N_2. The solution was stirred for 15 min and treated with cyanamide **47** (467 mg, 2.4 mmol) in 5 mL of dry THF. The mixture was stirred for 1 h at −45 °C and 2 h at 25 °C, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give crude **57**, which was used without purification. An analytical sample was prepared by flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) to give pure **57** as a 2:1 keto/enol mixture: ^{1}H NMR ($CDCl_3$) 5.25 (s, 1 × 0.33), 3.75−3.86 (m, 1), 3.62 (d, 1 × 0.66, J = 15.9), 3.55 (d, 1 × 0.66, J = 15.9), 2.54 (ddd, 1 × 0.66, J = 2.4, 6.7, 13.4), 2.38 (ddd, 1 × 0.33, J = 1.8, 6.7, 12.8), 1.95−2.05 (m, 1), 1.65−1.80 (m, 1), 1.60 (s, 3 × 0.33), 1.54 (s, 3 × 0.66), 1.40 −1.55 (m, 1), 1.51 (s, 9 × 0.33), 1.48 (s, 9 × 0.66), 1.40 (d, 3 × 0.33, J = 6.1), 1.38 (d, 3 × 0.66, J = 6.1); ^{13}C NMR ($CDCl_3$) 203.1, 177.1, 172.6, 166.0, 114.7, 114.6, 89.7, 82.2, 81.5, 73.4, 67.4, 59.8, 58.9, 45.3, 37.2, 35.8, 31.8, 31.6, 28.1 (3 C × 0.33), 27.9 (3 C × 0.66), 23.7, 21.9, 19.5, 19.4; IR (neat) 2207, 1742, 1716; HRMS (ES) Calcd for $C_{14}H_{23}N_2O_3$ (MH^+) 267.1709, found 267.1704.

tert-Butyl 3-Amino-5,7a-dimethyl-5,6,7-trihydro-1-oxo-1H-pyrrolizine-2-carboxylate (46)

Crude **57** (prepared from 2.4 mmol of **47**) was stirred in 10 mL of *t*-BuOH with 3.5 mL of a 1.0 M solution of *t*-BuOK in *t*-BuOH under N_2 in a sealed tube submerged in a 135 °C oil bath. After 15 h, the mixture was cooled, diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave 310 mg (49% over 2 steps) of **46**: mp 247−249 °C; ^{1}H NMR ($CDCl_3$) 8.20 (br s, 1, NH), 5.98 (br s, 1, NH), 3.94−4.04 (m, 1), 2.36−2.47 (m, 1), 1.74−1.92 (m, 2), 1.66−1.73 (m, 1), 1.55 (s, 9), 1.33 (d, 3, J = 6.7), 1.31 (s, 3); ^{13}C NMR ($CDCl_3$) 195.8, 170.6, 166.2, 90.7, 79.9, 75.3, 53.9, 35.3, 29.2, 28.5 (3 C), 24.4, 17.3; IR (neat) 3454, 1705, 1635; HRMS (ES) Calcd for $C_{14}H_{23}N_2O_3$ (MH^+) 267.1709, found 267.1696.

(−)-**46** was prepared analogously from (−)-**47**: $[\alpha]^{22}_D$ −21.3 (c 0.3, MeOH).

(±)-NP25302 (12)

Vinylogous urea **46** (150 mg, 0.56 mmol) and NaH (60% dispersion in mineral oil, 40 mg, 1.0 mmol) were stirred in 10 mL of dry THF under N_2 at 25 °C for 10 min. A solution of 3,3-dimethylacryloyl chloride (95 mg, 0.80 mmol) in 2 mL of dry THF was added and the resulting mixture was stirred for 2 h, quenched with H_2O, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give 233 mg of crude **58**, which was stirred in 15 mL of a 9:1 CH_2Cl_2/TFA solution for 15 h at 25 °C. The mixture was neutralized with saturated sodium bicarbonate solution, saturated with NaCl, and extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated to give crude NP25302. Flash chromatography on silica gel (95:5 CH_2Cl_2/MeOH) gave 122 mg (88%) of pure; (±)-NP25302 (**12**): mp 193−195 °C; UV (MeOH) λ_{max} nm (log ε) 252 (4.09), 282 (3.82), 334 (3.73); ^{1}H NMR($CDCl_3$) 10.38 (br s, 1, NH), 6.01 (s, 1), 5.80 (s, 1), 4.05−4.13 (m, 1), 2.41−2.52 (m, 1), 2.21 (s, 3), 1.90 (s, 3), 1.77−1.88 (m, 2), 1.64−1.71 (m, 1), 1.34 (s, 3), 1.17 (d, 3, J = 6.5); ^{13}C NMR ($CDCl_3$) 205.5, 167.3, 164.2, 158.2, 117.6, 93.5, 74.8, 54.8, 35.4, 28.2, 27.8, 24.6, 20.4, 17.4; IR (KBr) 3296, 3206, 2974, 1710, 1641, 1572, 1507, 1140; HRMS (ES) Calcd for $C_{14}H_{21}N_2O_2$ (MH^+) 249.1603, found 249.1593. The ^{1}H and ^{13}C NMR spectra are identical to those of an authentic sample.[8]

(+)-NP25302 (**12**) (90 mg) was prepared analogously from (−)-**46**: mp 227−230 °C, lit.[8] mp 229−230 °C; $[\alpha]^{22}_D$ +70 (c 1.0, MeOH), lit.[8] $[\alpha]^{22}_D$ +115.5 (c 1.1, MeOH).

(−)-NP25302 (**12**) (25 mg) was prepared analogously from (−)-**52** via (+)-**49**, (+)-**47**, and (+)-**46**: mp 224−227 °C; $[\alpha]^{22}_{D}$ −60 (*c* 1.0, MeOH).

[2-Oxo-2-[2-(Trimethylsilyl)ethoxy]ethyl]triphenylphosphonium bromide was prepared as previously described.[51] A solution of 2-(trimethylsilyl)ethanol (143 μL, 1.0 mmol) and triethylamine (140 μL, 1 mmol) in 1 mL of dry CH_2Cl_2 was added to a solution of bromoacetyl bromide (87 μL, 1 mmol) in 2 mL of dry CH_2Cl_2. The mixture was stirred overnight, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed successively with 2 M HCl and brine, dried over $MgSO_4$, and concentrated. The resulting oil was stirred with triphenylphosphine (525 mg, 2 mmol) in EtOAc for 24 h at rt. The precipitated salt was collected and used in the next step.

2-(Trimethylsilyl)ethyl (2-*E*)-[7a*S*)-Tetrahydro-3-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-1-ylidene]-acetate (72)

Triethylamine (0.11 mL, 0.80 mmol) was added to the above phosphonium salt (400 mg, 0.80 mmol) in 2 mL of toluene in a microwave tube. The mixture was stirred for 30 min under N_2 to generate ylide **78**. A solution of **76** in 2 mL of dry THF (prepared from 0.52 mmol of proline) was then added. The mixture was heated at 150 °C at 100 psi for 15 min in a microwave. After cooling, the mixture was concentrated to give crude **72** as a 9:1 mixture of the *E* and *Z* products. Flash chromatography on silica gel (CH_2Cl_2) gave 3 mg of a 6:1 mixture of (*E*)-**72** and (*Z*)-**72**, followed by 39 mg (27%) of pure (*E*)-**72**: $[\alpha]^{22}_{D}$ -141 ($_c$ 0.9, MeOH); UV (MeOH) λ_{max} nm (log ε) 212 (4.00), 238 (4.12); ^{1}H NMR ($CDCl_3$) 5.64 (d, 1, *J* = 1.8), 4.92 (ddd, 1, *J* = 7.3, 7.3, 1.8), 4.15−4.28 (m, 2), 3.69 (ddd, 1, *J* = 8.0, 8.0, 11.3), 3.26−3.35 (m, 1), 2.59−2.67 (m, 1), 2.05−2.19 (m, 2), 1.55−1.66 (m, 1), 0.99−1.04 (m, 2), 0.05 (s, 9); ^{13}C NMR 166.4, 165.3, 156.8, 95.9, 64.2, 62.6, 45.9, 30.3, 26.3, 17.3, −1.5 (3 C); IR (neat) 1805, 1713, 1667; HRMS (CI) Calcd for $C_{13}H_{22}NO_4Si$ (MH^+) 284.1318, found 284.1313. The ^{1}H NMR spectral data for (*E*)-**72** are identical to those provided by Dr. Ivan Pinto.[46]

The ^{1}H NMR peaks for (*Z*)-**72** in the mixture are identical to those in an NMR spectrum of (*Z*)-**72** provided by Dr. Pinto:[46] ^{1}H NMR ($CDCl_3$) 5.05 (d, 1, *J* = 1.5), 4.35−4.45 (m, 1), 4.15−4.25 (m, 2), 3.60−3.75 (m, 1), 3.20−3.30 (m, 1), 2.00−2.30 (m, 3), 1.60−1.70 (m, 1), 0.99−1.05 (m, 2), 0.05 (s, 9).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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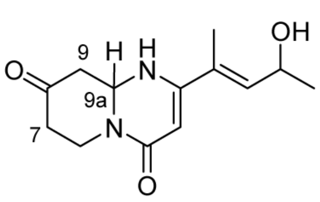
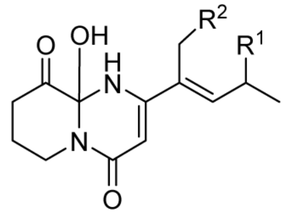
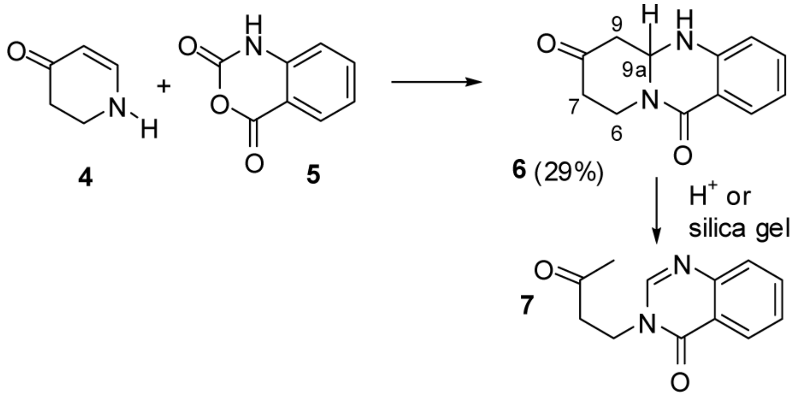


proposed structure
of jenamidine A (**1**)



proposed structures
of jenamidine B (**2**, R^1 = OH, R^2 = H)
of jenamidine C (**3**, R^1 = H, R^2 = OH)

FIGURE 1.
Proposed structures of jenamidines A, B, and C.



SCHEME 1.
Synthesis of Model 6

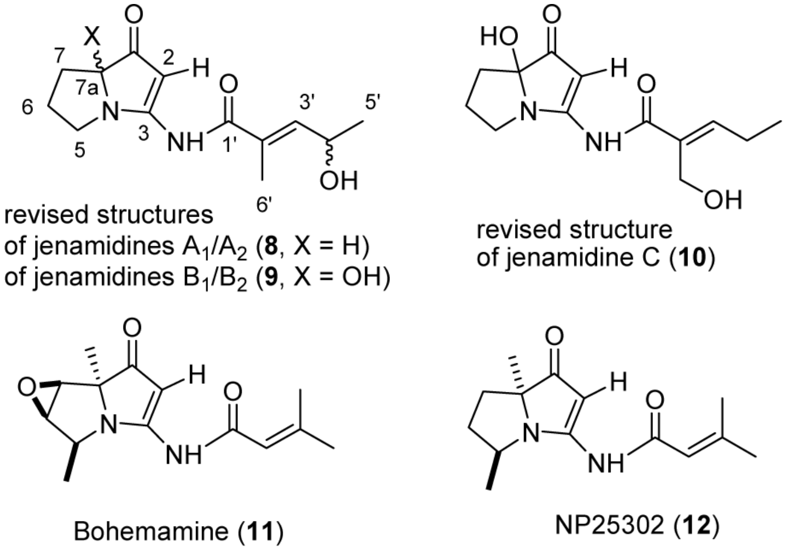
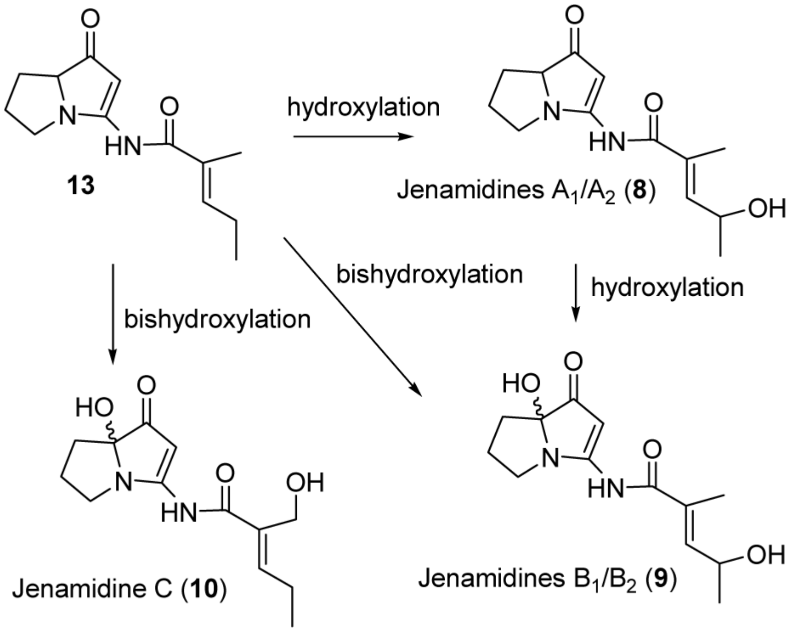


FIGURE 2.

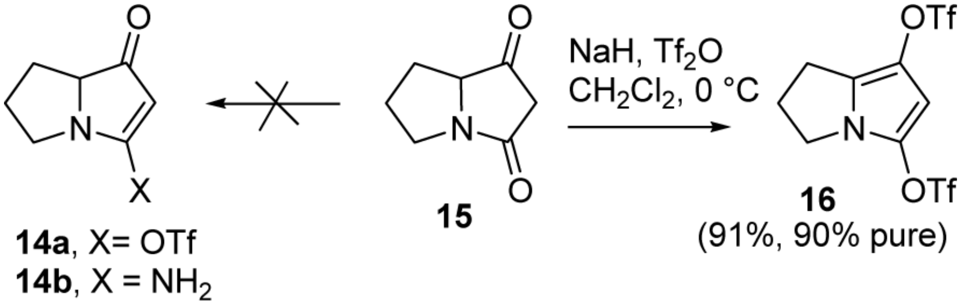
Bohemamine, NP25302, and revised structures of jenamidines A$_1$/A$_2$, B$_1$/B$_2$, and C.



Results and Discussion

SCHEME 2.

Possible Late Steps in the Biosynthesis of Jenamidines A_1/A_2, B_1/B_2, and C

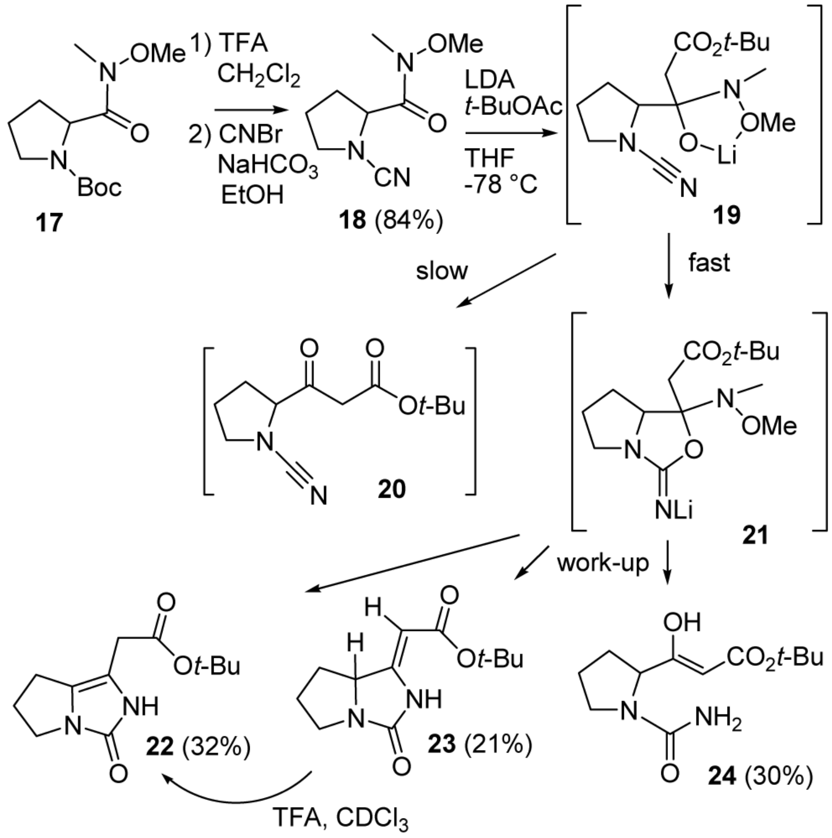


14a, X= OTf
14b, X = NH_2

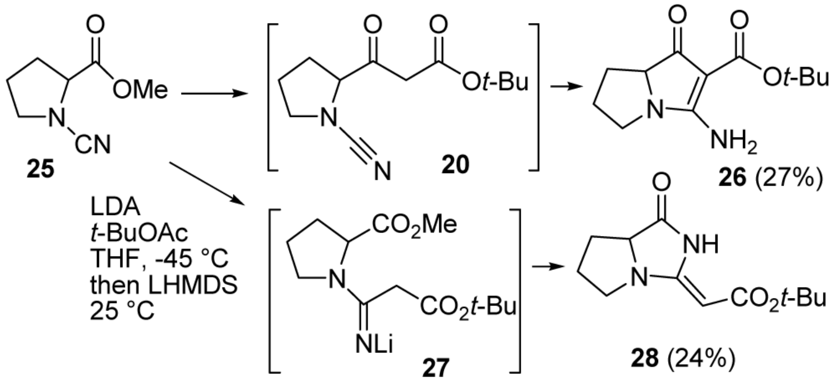
15

16
(91%, 90% pure)

SCHEME 3.

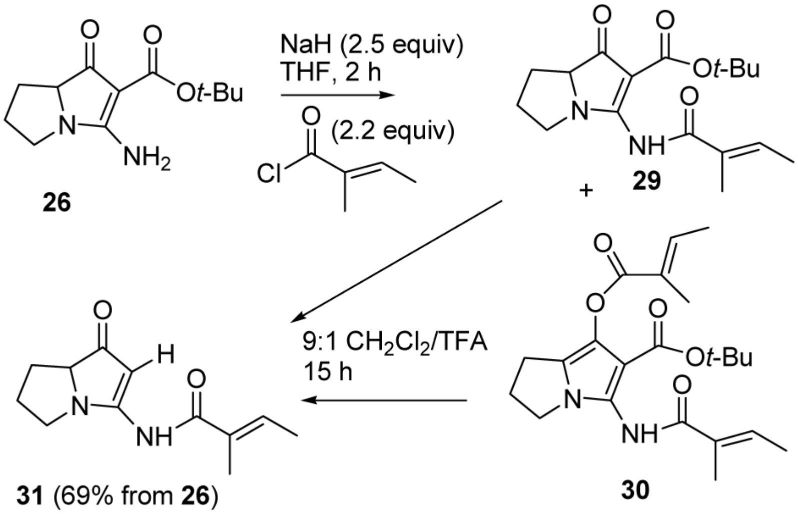

1) TFA
CH2Cl2
2) CNBr
NaHCO3
EtOH
LDA
t-BuOAc
THF
-78 °C
slow
fast
work-up
TFA, CDCl3
17
18 (84%)
19
20
21
22 (32%)
23 (21%)
24 (30%)

SCHEME 4.

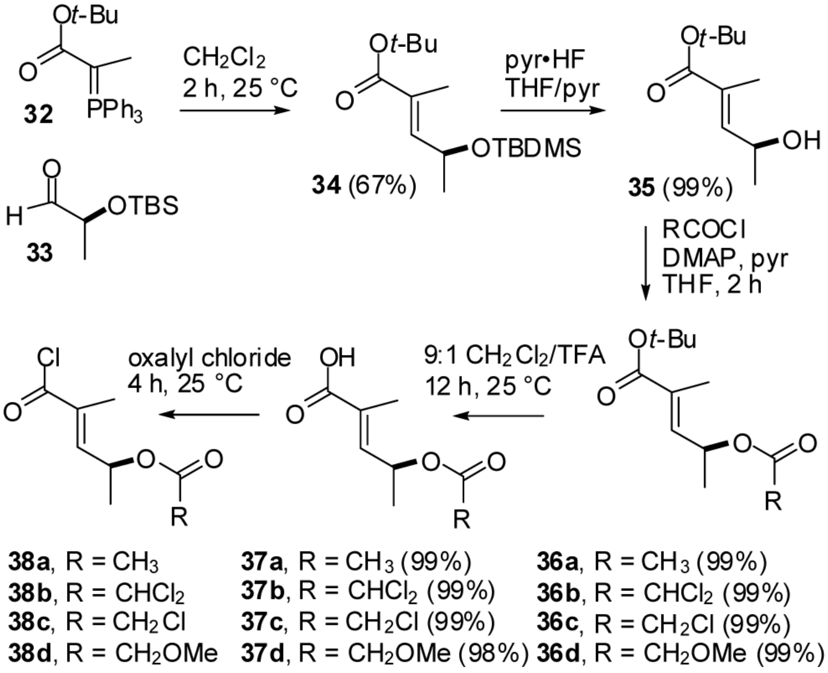


SCHEME 5.

Synthesis of Intermediate 26

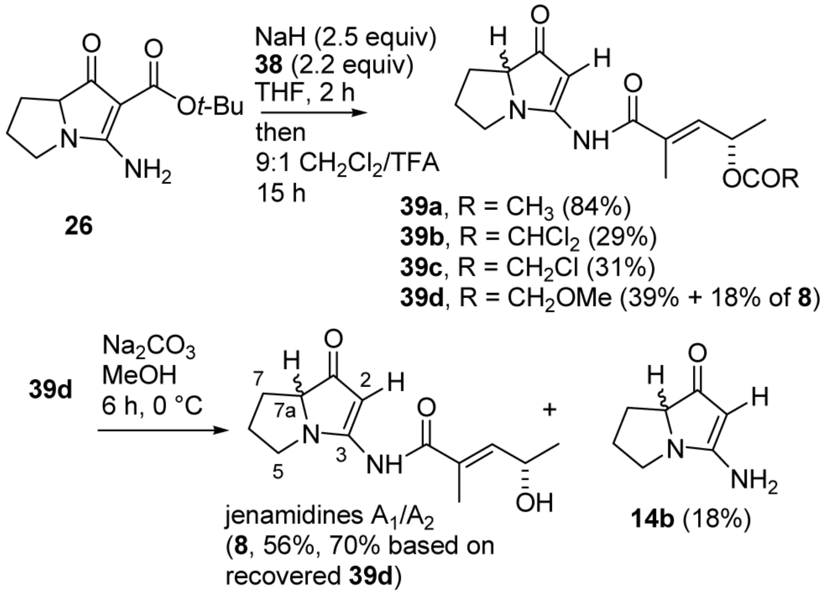


SCHEME 6.
Synthesis of Jenamidine A_1/A_2 Model 31



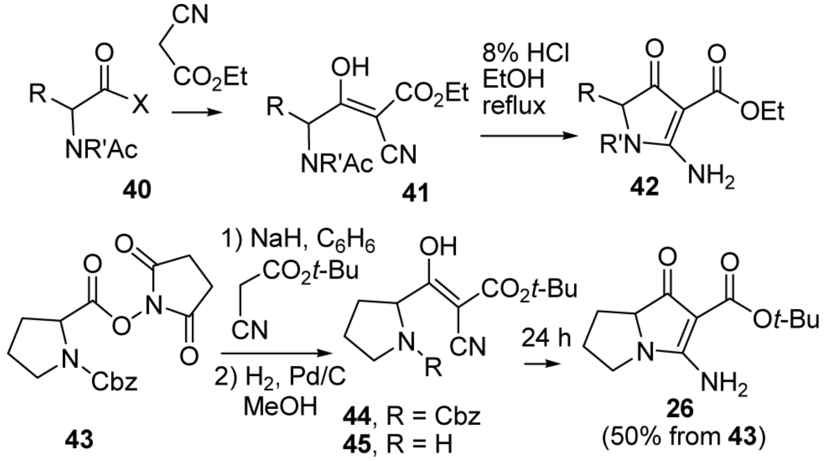
SCHEME 7.

Synthesis of Side-chain Acid Chlorides



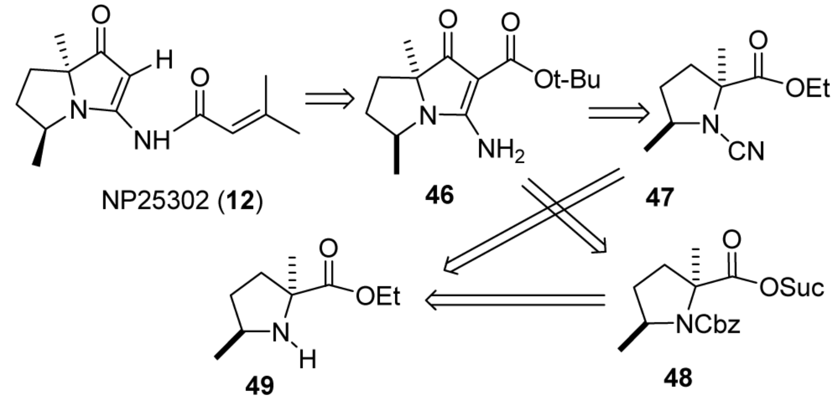
SCHEME 8.

Synthesis of Jenamidines A_1/A_2

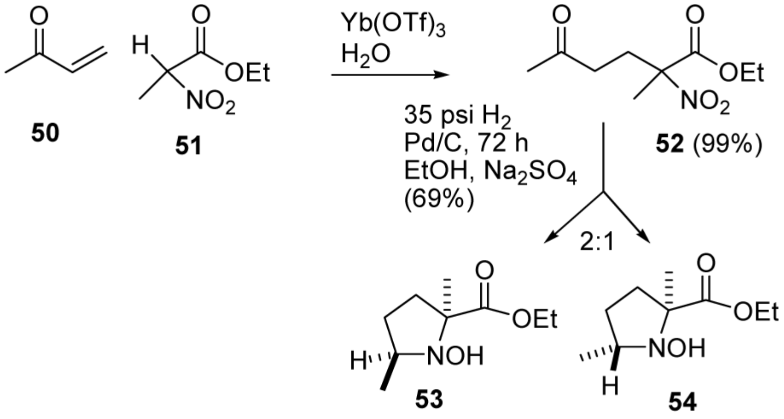


SCHEME 9.

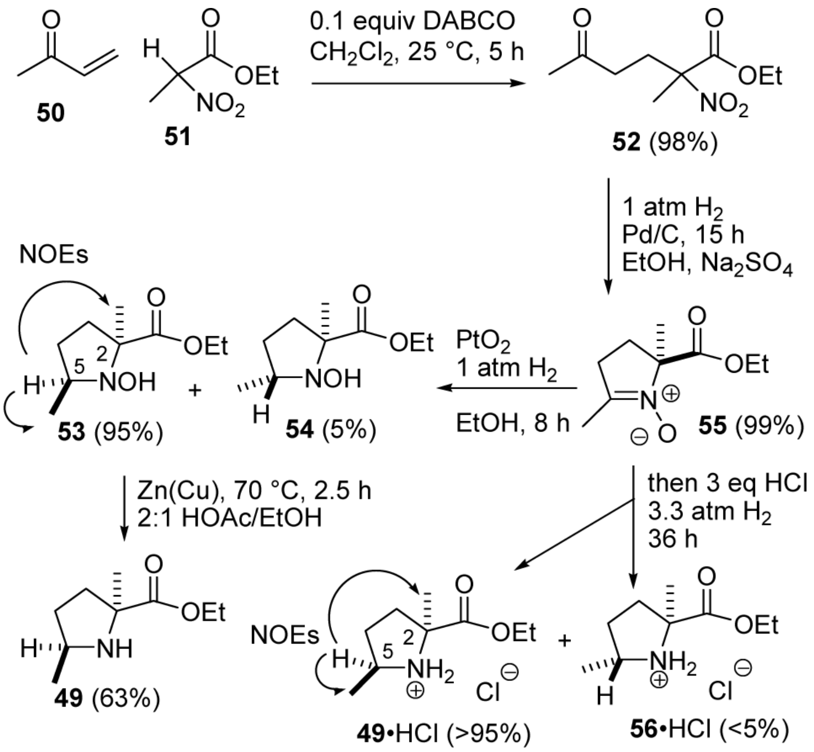
Improved Synthesis of 26



SCHEME 10.
Retrosynthesis of NP25302

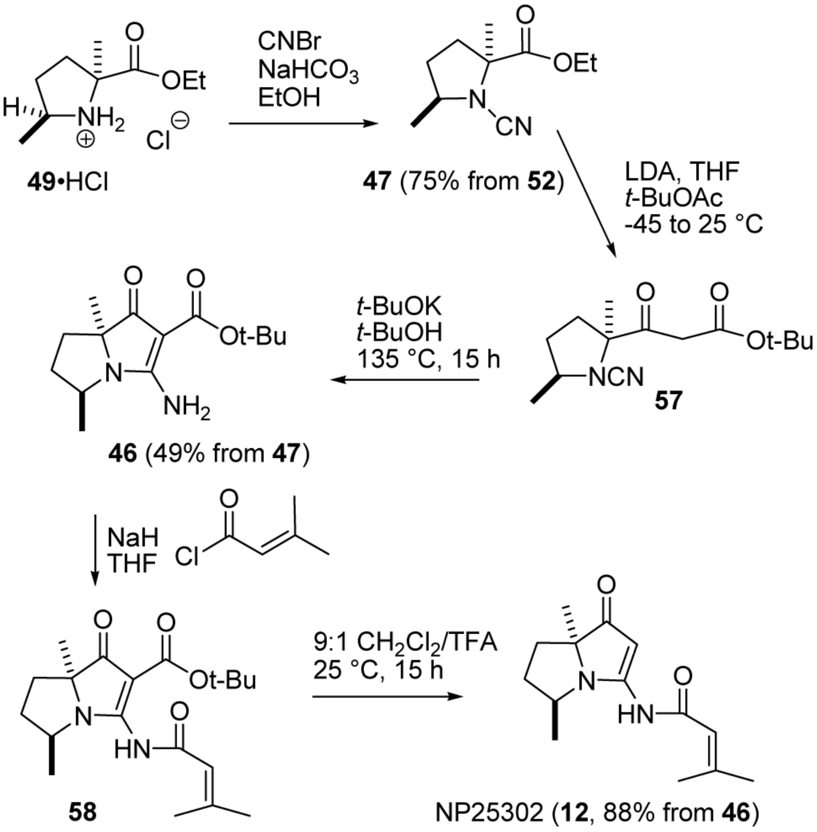


SCHEME 11.
Feringa's Synthesis of 53 and 54



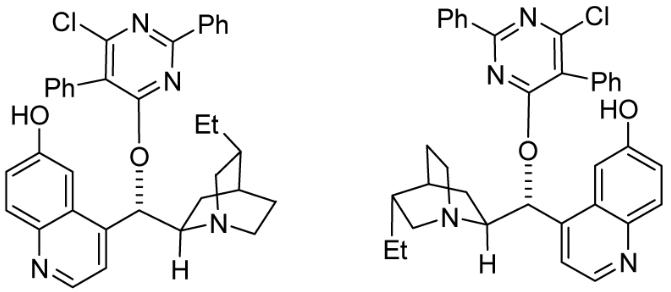
SCHEME 12.

Synthesis of *trans*-2,5-Dimethylproline Ethyl Ester (49)



SCHEME 13.

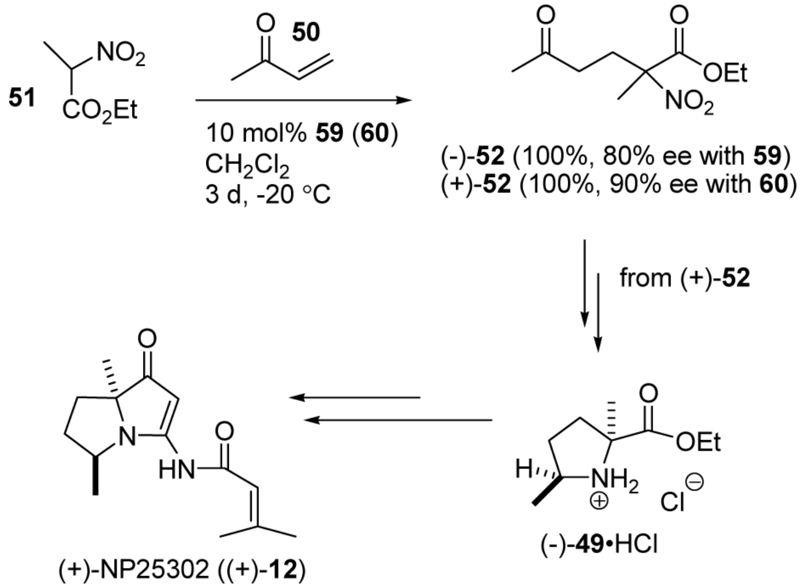
Completion of the Synthesis of (±)-NP25302 (12)



dihydroquinidine-based catalyst **59** dihydroquinine-based catalyst **60**

FIGURE 3.

Dihydroquinidine-based catalysts **59** and **60**.



SCHEME 14.

Synthesis of (+)-NP25302

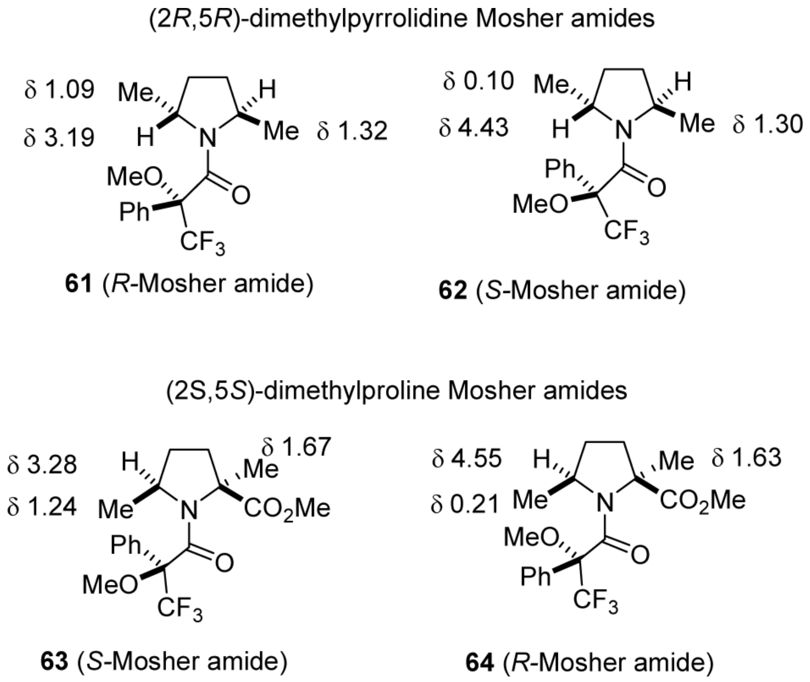
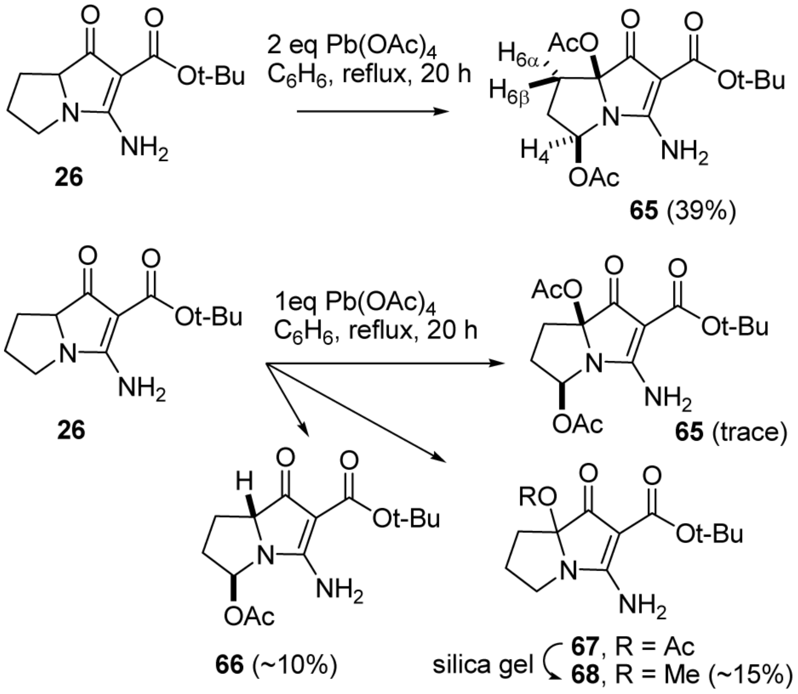
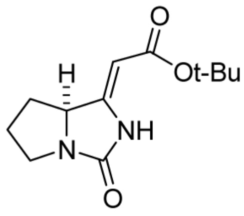


FIGURE 4.
^{1}H NMR spectral data of Mosher amides **61**-**64**.

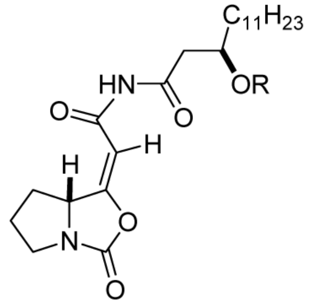


SCHEME 15.

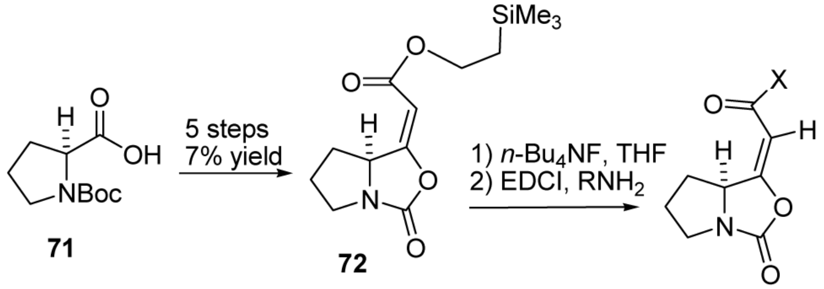
Oxidative Acetoxylation of 26



23



SB-311009 (**69**, R = H)
SB-253514 (**70**, R = rhamnose)



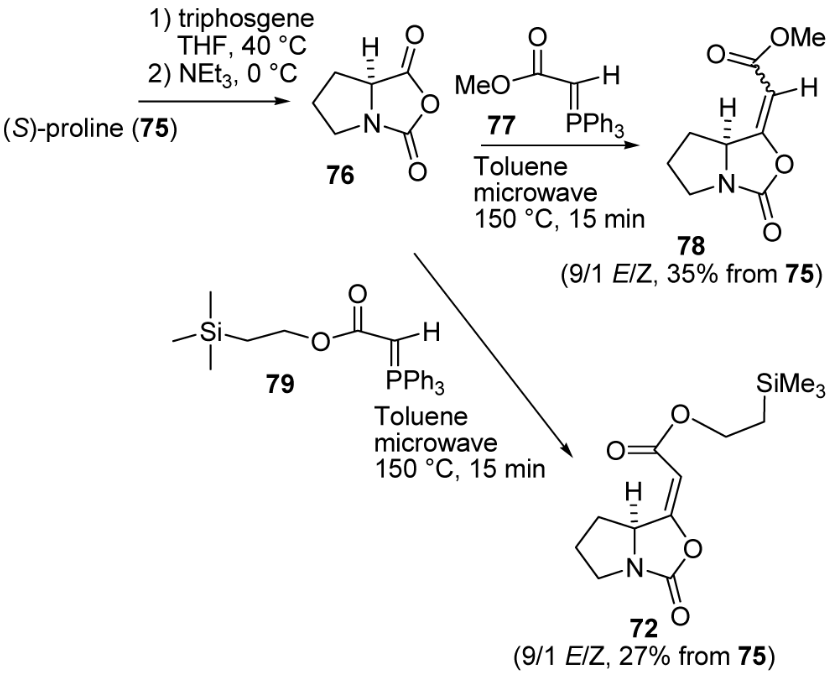
71

72

73, X = OH (100%)
74, X = NHR

SCHEME 16.

Pinto's Synthesis of SB-311009 Analogue 74



SCHEME 17.

One Step Synthesis of Intermediate 72