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Synthesis of Jenamidines A_1/A_2

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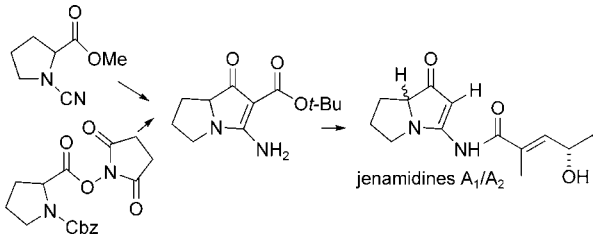
ABSTRACT



Addition of the enolate of *tert*-butyl acetate to cyanamide methyl ester 17 followed by treatment with LHMDS afforded vinylogous urea 19 in 27% yield. Vinylogous urea 19 was also obtained from 37 and *tert*-butyl cyanoacetate in 50% yield. Acylation of 19 with acid chloride 31d, followed by hydrolysis of the *tert*-butyl ester and decarboxylation with 9:1 CH_2Cl_2/TFA and very mild basic hydrolysis of the methoxyacetate ester, afforded jenamidines A_1/A_2 (3) in 45% yield. This first synthesis confirms our reassignment of the jenamidines A_1/A_2 structure.

Three bicyclic alkaloids, jenamidines A−C, were recently isolated from the culture broth of *Streptomyces* sp. (strain HKI0297).[1] Jenamidine A inhibited proliferation of the chronic myeloid leukemia cell line K-562 (GI_{50} = 1.9 μg/mL). Structure **1** was originally proposed for jenamidine A (see Figure 1). We prepared model **2**, which underwent a facile retro-Mannich reaction and had spectral data quite different from jenamidine A, suggesting that structure **1** is not correct.[2] Reexamination of the spectral data of the natural product led to revised structures for the two diastereomers of jenamidines A_1/A_2 (**3**), the two diastereomers of jenamidines B_1/B_2 (**4**), and jenamidine C (**5**).[2] Bohemamine (**6**), whose structure was determined by X-ray crystallography in 1980,[3] and the cell−cell adhesion inhibitor NP25302 (**7**),[4] whose structure was reported very recently, have the same ring system as the revised structures of jenamidines **3**−**5**.

We next turned our attention to the preparation of jenamidines A_1/A_2 (**3**), which required the development of new methods for the preparation of the novel *N*-acyl vinylogous urea in the right-hand ring. We initially explored the Pd-catalyzed coupling of triflate **8** with an amide since

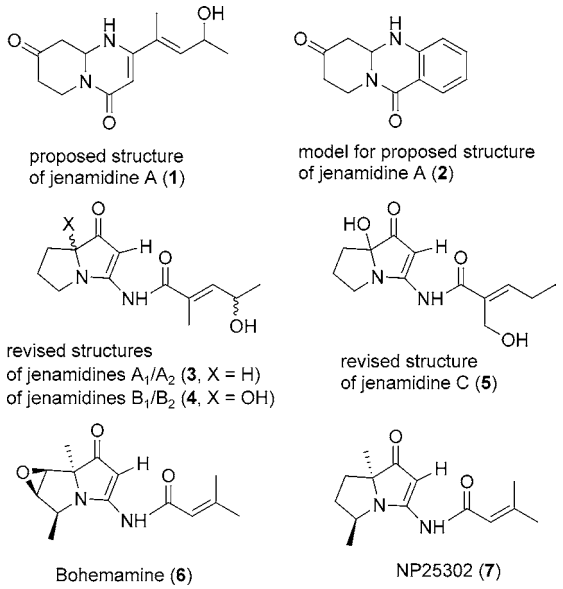


Figure 1. Structures of jenamidines and related natural products.

(1) Hu, J.-F.; Wunderlich, D.; Thiericke, R.; Dahse, H.-M.; Grabley, S.; Feng, X.-Z.; Sattler, I. *J. Antibiot.* **2003**, *56*, 747−754.
(2) Snider, B. B.; Duvall, J. R.; Sattler, I.; Huang, X. *Tetrahedron Lett.* **2004**, *45*, 6725−6727.
(3) Doyle, T. W.; Nettleton, D. E.; Balitz, D. M.; Moseley, J. E.; Grulich, R. E.; McCabe, T.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 1324−1326.
(4) Zhang, Q.; Schrader, K. K.; ElSohly, H. N.; Takamatsu, S. *J. Antibiot.* **2003**, *56*, 673−681.

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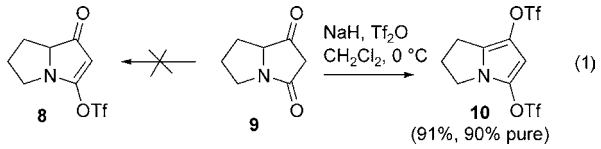
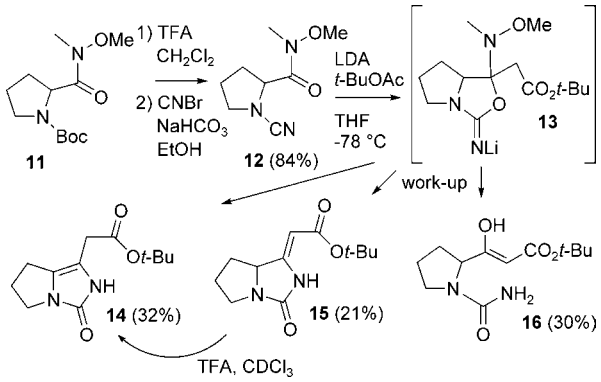
a broadly applicable Pd-catalyzed amidation of enol triflates was recently reported.[5] Unfortunately, reaction of known keto lactam **9**[6] with NaH and Tf_2O gave only the unstable pyrrole bis triflate **10**. Use of excess NaH and Tf_2O gave crude (90% pure) **10** in 91% yield, which was isolated in pure form in only 17% yield (see eq 1). Although we were able to cleanly couple 2-methyl-2-butenamide[7] with the enol triflate prepared from 5,5-dimethyl-1,3-cyclohexanedione, initial attempts at Pd-catalyzed couplings of amides with **10** were unsuccessful. Attempted preparation of vinylogous urea **33** (see Scheme 5) by reaction of keto lactam **9** with NH_3 led to complex mixtures.



We then turned our attention to preparing the vinylogous urea by addition of an enolate to a cyanamide. Hydrolysis of the Boc group of Weinreb amide **11** and reaction of the liberated amine with CNBr and $NaHCO_3$ in EtOH afforded cyanamide **12** in 84% yield (see Scheme 1). Addition of the

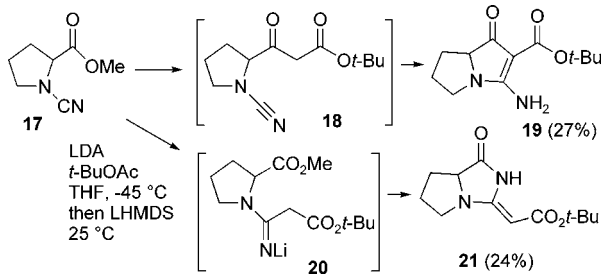
Scheme 1



lithium enolate of *tert*-butyl acetate to **12** provided 30% of the enol tautomer of urea β-keto ester **16**, 21% of imidazolidinone **15**, and 32% of imidazolone **14**. Presumably the lithium alkoxide of the initially formed tetrahedral intermediate adds to the cyanamide to give **13**. Workup affords urea keto ester **16**, which can undergo cyclodehydration to give **14** and **15**. Imidazolone **14** is the thermodynamic product since treating a solution of **15** in $CDCl_3$ with one drop of TFA cleanly isomerized **15** to **14**.

The Weinreb amide appeared to be a poor choice because the initially formed tetrahedral intermediate was stable, allowing the alkoxide to add to the cyanamide to form **13**. We thought that a simple ester might be a better choice because the tetrahedral intermediate should rapidly form the cyanamide keto ester **18**, which could then cyclize to form the desired product **19**. Fortunately, this proved to be the case. Cyanamide methyl ester **17**[8] was added to a solution of the lithium enolate of *tert*-butyl acetate (2.3 equiv) in THF at −45 °C.[9] The solution was stirred for 1 h at −45 °C, treated with 1.2 equiv of LHMDS in THF, and stirred at 25 °C for 2 h to give the desired product **19** (27%) (see Scheme 2). Byproduct **21** (24%) was formed by addition of

Scheme 2

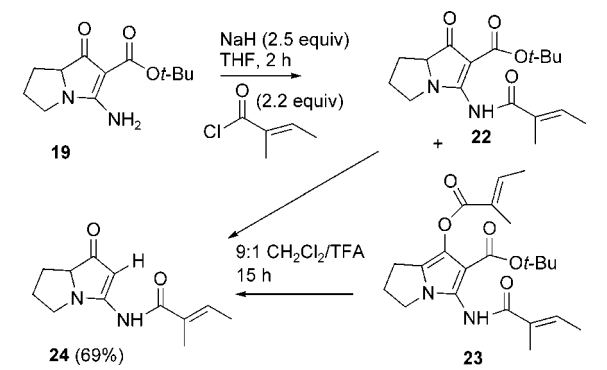


the enolate to the cyanamide to give **20**, which then cyclized to the methyl ester to form the alkylidene imidazolidinone **21**.[10] The methyl ester of **17** is less electrophilic than the Weinreb amide of **12** so that the enolate added to both the methyl ester and the cyanamide.

Vinylogous urea **19** has the ring system of jenamidines A_1/A_2 with an additional carboxylic acid, which we hoped that we could remove by hydrolysis and decarboxylation either before or after the introduction of the side chain. Reaction of **19** with 9:1 CH_2Cl_2/TFA effected hydrolysis but did not provide the desired vinylogous urea **33** (see Scheme 5).

Acylation of **19** with 2.5 equiv of NaH and 2.2 equiv of tigloyl chloride for 2 h afforded a mixture of the desired amide **22** and the bis-acylated product pyrrole **23** (see Scheme 3). Treatment of the crude mixture with 9:1 CH_2Cl_2/TFA for 15 h effected hydrolysis of the *tert*-butyl esters of **22** and **23** and the enol ester of **23** and decarboxy-

Scheme 3

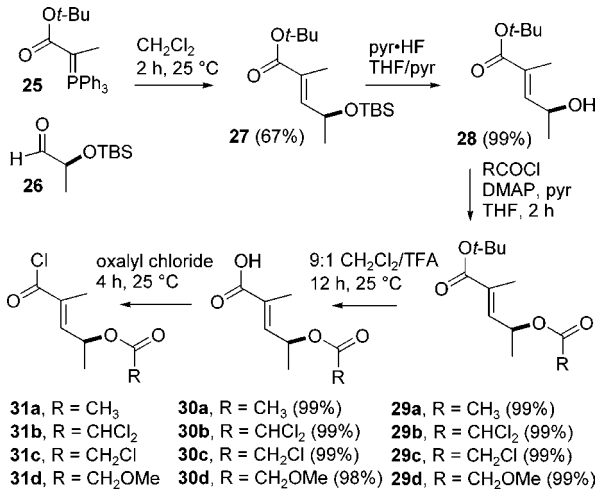


(5) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749−4752.
(6) (a) Murray, A.; Proctor, G. R.; Murray, P. J. *Tetrahedron* **1996**, *52*, 3757−3766. (b) Galeotti, N.; Poncet, J.; Chiche, L.; Jouin, P. *J. Org. Chem.* **1993**, *58*, 5370−5376.
(7) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T.; Date, T.; Okamura, K.; Inagaki, S. *J. Org. Chem.* **1991**, *56*, 6556−6564.

lation to afford jenamidines A_1/A_2 model **24** in 69% overall yield. The spectral data of the ring portion of **24** correspond very closely to those of the natural product, supporting the assignment of **3** as the revised structure of jenamidines A_1/A_2.

The side chain was then prepared by a modification of Adam's procedure for the ethyl ester.[11] Reaction of ylide **25**[12] with aldehyde **26**[13] in CH_2Cl_2 for 2 h provided ester **27** in 67% yield (see Scheme 4). Deprotection with pyr·HF gave

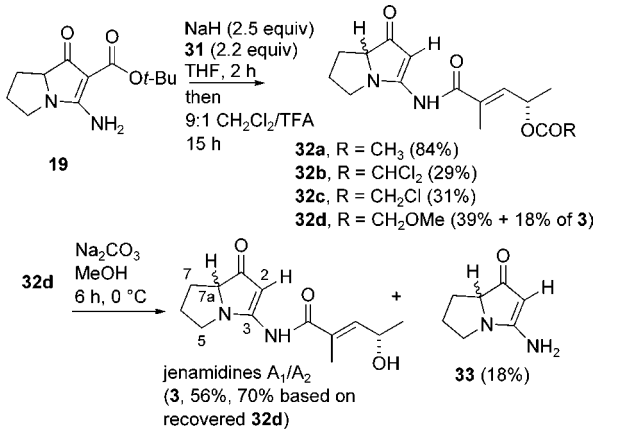
Scheme 4



hydroxy ester **28** in 99% yield. Initially, we chose to protect the side chain alcohol as an acetate ester. Reaction of **28** with AcCl, DMAP and pyridine in THF gave **29a** in 99% yield, which was deprotected with 9:1 CH_2Cl_2/TFA to give acetoxy acid **30a** in 99% yield. Stirring **30a** in oxalyl chloride gave crude acid chloride **31a**, which was used without purification.

Reaction of **19** with NaH and **31a** followed by hydrolysis and decarboxylation with 9:1 CH_2Cl_2/TFA as described above for the preparation of **24** afforded jenamidines A_1/A_2 acetate (**32a**) in 84% yield (see Scheme 5). Unfortunately, we were unable to cleave the acetate protecting group of **32a** without also cleaving the side chain amide to give a complex mixture containing some **33**. Since the nitrogen of the amide of **32a** is part of a vinylogous urea, the amide is a vinylogous acyl urea and is therefore easily cleaved under basic conditions. We considered using an acid-labile protect-

Scheme 5



ing group for the side chain alcohol that would be cleaved by the 9:1 CH_2Cl_2/TFA used for hydrolysis of the *tert*-butyl ester. Unfortunately, such a protecting group would not be compatible with acid chloride **31**, and we were unable to cleanly acylate **19** with mixed anhydrides.

We then examined more base labile ester protecting groups.[14] Dichloroacetate acid chloride **31b** was prepared analogously, but reaction with **19** afforded **32b** in only 29% yield. Fortunately, hydrolysis of **32b** with $NaHCO_3$ in MeOH for 30 min at 25 °C gave jenamidines A_1/A_2 (**3**) in 71% yield. Reaction of chloroacetate **31c** with **19** afforded **32c** in a still unacceptable 31% yield, which could also be cleaved by $NaHCO_3$ in MeOH for 1 h at 25 °C to give jenamidines A_1/A_2 (**3**) cleanly.

The best compromise was the methoxyacetate protecting group. Acid chloride **31d** was prepared in high yield from hydroxy ester **28**. Coupling of **31d** with **19**, hydrolysis of the *tert*-butyl ester, decarboxylation with 9:1 CH_2Cl_2/TFA, and flash chromatography on silica gel gave **32d** in 39% yield and jenamidines A_1/A_2 (**3**) in 18% yield. Partial cleavage of the methoxyacetate occurs on chromatography. Hydrolysis of **32d** with Na_2CO_3 in MeOH for 6 h at 0 °C provided **3** in 56% yield (70% based on recovered **32d**) and 18% of **33** resulting from cleavage of the amide. Hydrolysis of **32d** with $NaHCO_3$ in MeOH for 20 h at 25 °C afforded only **33** indicating the sensitivity of the amide side chain to basic hydrolysis. The most efficient procedure involved hydrolysis of crude **32d** with Na_2CO_3 in MeOH for 24 h at 0 °C to give jenamidines A_1/A_2 (**3**) in 45% overall yield from **19** and **32d** in 11% overall yield from **19**.

The spectral data of synthetic **3** are identical to those of the natural product, which is also an approximately 1:1 mixture of diastereomers. Even though **19** was prepared from (*S*)-proline and aldehyde **26** was prepared from (*S*)-lactic acid, we obtained **3** 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

(8) Prasit, P.; Falgueyret, J.-P.; Oballa, R.; Rydzewski, R.; Okamoto, O. PCT Int. Appl. WO 2001077073; *Chem. Abstr.* **2001**, *135*, 318414j.

(9) For similar syntheses of keto esters from esters, see: (a) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Izawa, K. *Org. Lett.* **2002**, *4*, 447−449. (b) Honda, Y.; Katayama, S.; Kojima, M.; Suzuki, T.; Izawa, K. *Tetrahedron Lett.* **2003**, *44*, 3163−3166.

(10) For similar compounds, see: (a) Zhao, M.-X.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron* **2002**, *58*, 1309−1316. (b) Ceder, O.; Stenhede, U. *Acta Chem. Scand.* **1973**, *27*, 2221−2223.

(11) Adam, W.; Renze, J.; Wirth, T. *J. Org. Chem.* **1998**, *63*, 226−227.

(12) Giner, J.-L. *Tetrahedron Lett.* **2002**, *43*, 5457−5459.

(13) (a) Hirama, M.; Shigemoto, T.; Itô, S. *J. Org. Chem.* **1987**, *52*, 3342−3346. (b) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

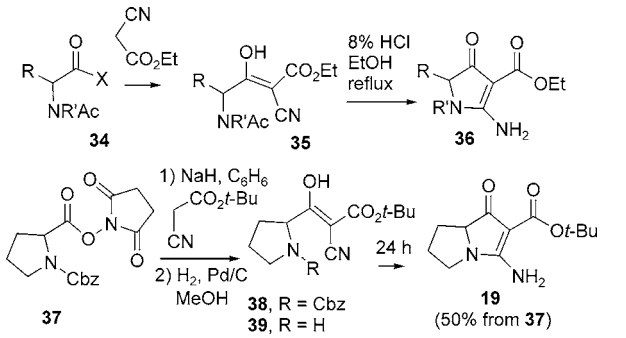
(14) Kocieñski, P. J. *Protecting Groups*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2005; pp 333−337.

analogous to **23**, which will give a mixture of diastereomers on hydrolysis. In the proton NMR spectrum of **3** in CD_3OD, the ring fusion hydrogen, H-7a, integrates for only ~0.5, suggesting that partial deuterium exchange has occurred. 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.[15] H-2 slowly exchanges with CD_3OD over several hours as was noted for the natural product.[2] The optical rotation of synthetic **3**, $[\alpha]_D$ 4.2, is very similar to that of the natural product, $[\alpha]_D$ 6.8.[1] Therefore, natural jenamidines A_1/A_2 (**3**) 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 isomers, it is also possible that the natural product is a mixture of isomers on the side chain.

The three-step sequence from vinylogous urea **19** and acid chloride **31d** to jenamidines A_1/A_2 (**3**) proceeded in acceptable yield, given the instability of the amide linkage. The one-pot preparation of **19** from cyanamide **17** provided adequate quantities of material, but the 27% yield left room for improvement. Coupling of various *N*-acetyl amino acid derivatives **34** with ethyl cyanoacetate has been reported to give **35**, which cyclized on treatment with 8% HCl in EtOH at reflux to provide **36** in 18−51% overall yield (see Scheme 6).[16] The reported spectral data of **36** are comparable to those of **19**. We examined variations of this procedure because the acid-catalyzed cyclization used to convert **35** to **36** is not compatible with the *tert*-butyl ester of **19**.

Reaction of Cbz-proline *N*-hydroxysuccinimide ester (**37**) with *tert*-butyl cyanoacetate and NaH in benzene for 3 h gave crude **38**, which was hydrogenated (1 atm) over 10% Pd/C in MeOH for 2 h to give crude **39** with a very complex NMR spectrum. Fortunately, crude **39** cyclized on standing for 1 d to give **19** in 50% overall yield from **37**. Using this sequence, which has not been fully optimized, jenamidines A_1/A_2 (**3**) are now available in 23% overall yield.

Scheme 6



In conclusion, addition of the enolate of *tert*-butyl acetate to cyanamide methyl ester **17** followed by treatment with LHMDS afforded vinylogous urea **19** in 27% yield. Vinylogous urea **19** can be obtained more easily from **37** and *tert*-butyl cyanoacetate in 50% yield. Acylation of **19** with acid chloride **31d**, followed by hydrolysis of the *tert*-butyl ester and decarboxylation with 9:1 CH_2Cl_2/TFA and very mild basic hydrolysis of the methoxyacetate ester afforded jenamidines A_1/A_2 (**3**) in 45% yield. This first synthesis confirms our reassignment of the jenamidines A_1/A_2 structure. Extension of this approach to the syntheses of jenamidines B_1/B_2, jenamidine C, and NP25302 is currently in progress.

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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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