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A Direct and Efficient Total Synthesis of the Tubulin-Binding Agents Ceratamine A and B; Use of IBX for a Remarkable Heterocycle Dehydrogenation

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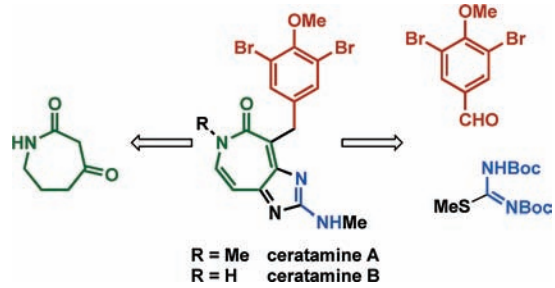
ABSTRACT



The total synthesis of the tubulin-binding agents ceratamine A and B is reported, along with des-methyl analogs, via a synthetic route that is high-yielding and operationally efficient. The synthetic route involved a Beckmann rearrangement to form an azepine ring precursor, a Knoevenagel condensation to install the benzylic side chain, and an effective imidazole annulation onto an α-aminoketone precursor with a protected *S*-methylisothiourea. Final dehydrogenation proved remarkably facile using IBX.

The marine natural products ceratamine A (**1a**) and B (**1b**) (Figure 1) were isolated from the New Guinean sponge *Pseudoceratina* sp. by Roberge and co-workers and were shown to possess antimitotic activity in a cell-based assay.[1] These unusual heterocyclic compounds join a large family of marine natural products that exhibit antimitotic activity[2,3] and were shown[4] to arrest cells in mitosis and stimulate microtubule polymerization in the absence of normally associated proteins.

The ceratamines do not compete with taxol for binding to β-tubulin, whereas taxol, the epothilones, discodermolide, and the eleuthesides bind to a common site,[5] which itself is distinct from the binding site of the *Vinca* alkaloids.[6] Thus, the ceratamines may exhibit a unique spectrum of antitumor activity.[4] Preclinical studies of the ceratamines would rely

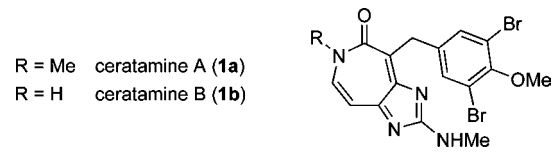


Figure 1. Structures of the ceratamines.

(1) Manzo, E.; van Soest, R.; Matainaho, L.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2003**, *5*, 4591.
(2) Beckers, T.; Mahboobi, S. *Drugs Future* **2003**, *28*, 767.
(3) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253.
(4) Karjala, G.; Chan, Q.; Manzo, E.; Andersen, R. J.; Roberge, M. *Cancer Res.* **2005**, *65*, 3040.
(5) Nogales, E.; Wolf, S. G.; Khan, I. A.; Luduena, R. F.; Downing, K. H. *Nature (London)* **1995**, *375*, 424.
(6) Bai, R.; Pettit, G. R.; Hamel, E. *J. Biol. Chem.* **1990**, *265*, 17141.

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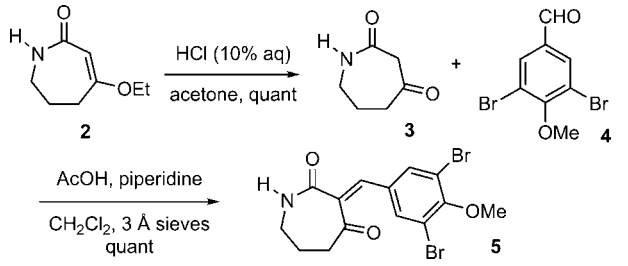
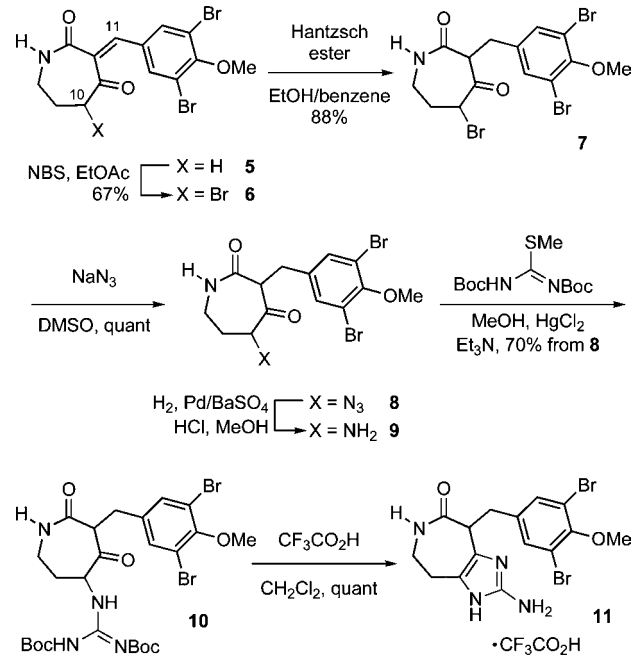
Scheme 1. Synthesis of Key Intermediate Hydroazepinedione **5**



Scheme 2. Construction of the Imidazo[4,5-*d*]azepine System



on synthetic material as a result of the low natural abundance of these agents, typical for sponge-derived secondary metabolites.

The ceratamines possess an unusual imidazo[4,5-*d*]azepine ring system that presumably results from the oxidative coupling of a brominated tyrosine and a histidine. Dibromotyrosine-containing natural products are typical of sponges of the order *Verongida*, which includes the genus *Pseudoceratina*, and many such metabolites possess interesting biological activity.[7] There have been two reports by Andersen and co-workers[8] on attempted syntheses of the ceratamines, which although unsuccessful provided important analogs and information on structure activity relationships. (Waly was the first to report the synthesis of the imidazo[4,5-*d*]azepine ring system.[9]) Herein, we report a direct and efficient synthesis of ceratamine A and B that uses a synthetic strategy that involved the initial construction of a functionalized aminohydroazepinone skeleton, condensation with *S*-methylisothiourea to install the aminoimidazole ring, and a straightforward dehydrogenation to the azepine ring system.

Key synthetic intermediate hydroazepinedione **5** (Scheme 1) could be synthesized in good yield by an efficient series of transformations starting from known ε-lactam **2**, readily prepared from 3-ethoxy-2-cyclohexenone by Beckmann rearrangement.[10] Acid-promoted hydrolysis of the ethyl enol ether (25 °C, 1 h) revealed the β-ketoamide of **3** in quantitative yield. Knoevenagel condensation of **3** with 3,5-dibromoanisaldehyde (**4**)[11] (25 °C, 1 h) provided **5** in quantitative yield.

At this stage, acid-promoted bromination[12] of **5** occurred readily (Amberlyst-15, 25 °C, 24 h) to provide the α-bromoketone **6** (Scheme 2). Initially, we planned to functionalize **6** by displacement of the C10 bromide with a nitrogen-based nucleophile such as a protected guanidine, to directly install the 2-aminoimidazole ring, or azide for a more indirect route. These nitrogen-based nucleophiles underwent conjugate addition to C11 of the benzylidene β-ketoamide of **6**, in preference to displacement of the bromide. In an attempt to block conjugate addition, **6** was treated with sodium thiophenolate, which displaced the C10 bromide. In light of this lose-lose scenario, we elected to reduce **6**, although this would necessitate a subsequent reoxidation at a later stage.

The Hantzsch ester[13] proved to be the most suitable reagent for conjugate reduction of the double bond of **6** and provided the desired product **7** in excellent yield (25 °C, 12 h) without over-reduction of the α-bromide. Attempted imidazole annulation with α-bromoketone **7** using N-Boc guanidine led to an unprecedented Favorskii rearrangement leading to the corresponding tetrahydropyridone carboxylic acid guanidide,[14] details of which will be communicated separately.

However, displacement of the C10 bromide of **7** with azide occurred cleanly (25 °C, 1 h) and provided azidoketone **8** in quantitative yield. Although metal-catalyzed hydrogenolysis of the azide was not the most obvious method for reduction because of the potentially labile aryl bromides, using the more typical reductant Ph_3P was unsuccessful because the adjacent ketone intercepted the intermediate phosphinimine

(7) Fistularins: Aiello, A.; Fattorusso, E.; Menna, M.; Pansini, M. *Biochem. Syst. Ecol.* **1995**, *23*, 377. Psammaplins: Piña, I. C.; Gautschi, J. T.; Wang, G.-Y.-S.; Sanders, M. L.; Schmitz, F. J.; France, D.; Cornell-Kennon, S.; Sambucetti, L. C.; Remiszewski, S. W.; Perez, L. B.; Bair, K. W.; Crews, P. *J. Org. Chem.* **2003**, *68*, 3866. Ma'edamines: Hirano, K.; Kubota, T.; Tsuda, M.; Watanabe, K.; Fromont, J.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 8107.

(8) Nodwell, M.; Riffell, J. L.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2008**, *10*, 1051. Nodwell, M.; Pereira, A.; Riffell, J. L.; Zimmerman, C.; Patrick, B. O.; Roberge, M.; Andersen, R. J. *J. Org. Chem.* **2009**, *74*, 995.

(9) Waly, M. A. *J. Prakt. Chem.* **1994**, *336*, 86.

(10) Collison, C. G.; Chen, J.; Walvoord, R. *Synthesis* **2006**, 2319.

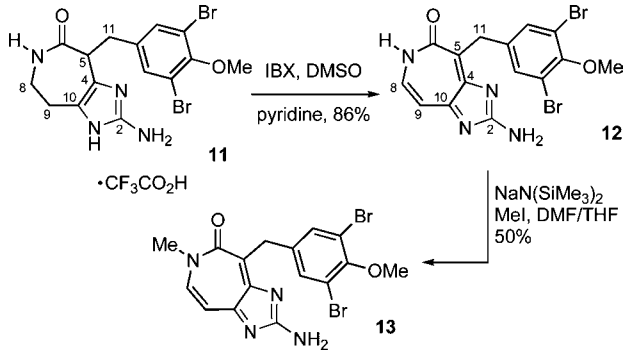
(11) Lewin, A. H.; Szewczyk, J.; Wilson, J. W.; Carroll, F. I. *Tetrahedron* **2005**, *61*, 7144.

(12) Meshram, H. M.; Reddy, P. N.; Sadashiv, K.; Yadav, J. S. *Tetrahedron Lett.* **2005**, *46*, 623.

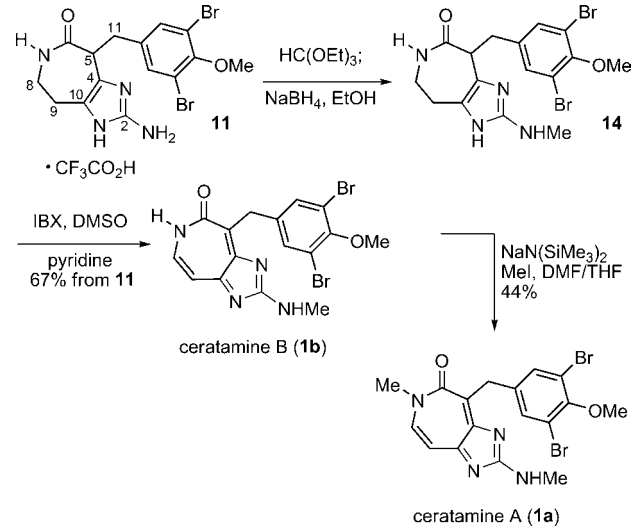
(13) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 1637. For recent use, see: Garden, S. J.; Guimaraes, C. R. W.; Correa, M. B.; de Oliveira, C. A. F.; Pinto, A. C.; de Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815. (c) Zolfigol, M. A.; Safaiee, M. *Synlett* **2004**, *5*, 827. (d) Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660.

(14) Coleman, R. S.; Campbell, E. L. Unpublished observations.

Scheme 3. Dehydrogenation to Fully Oxidized Ring System



Scheme 4. Completion of the Total Synthesis of the Ceratamines



to form a stable oxazaphospholidine (not shown).[15] Under carefully controlled conditions, however, hydrogenolysis over $Pd/BaSO_4$ catalyst (1 atm H_2, 25 °C, 2 h) afforded amine **9** in good yields without appreciable hydrogenolysis of the aryl bromides. Annulation of the 2-aminoimidazole ring of the natural products was achieved in two steps by reaction of the amine of **9** with bis-Boc-protected *S*-methylisothiourea[16] (0 °C, 1 h) to afford **10**. This reaction was facilitated by the addition of a thiophilic metal such as Hg or Ag. Acid-promoted deprotection was accompanied by a concomitant condensation reaction sequence (25 °C, 1 h) to provide the trifluoroacetate salt of **11** in quantitative yield, as a mixture of tautomers (major tautomer shown). The sequence of transformations from ε-lactam **2** to **11** occurred in an overall yield of 41% for eight synthetic operations.

The most pressing synthetic issue remaining involved oxidation to the fully unsaturated ring system of the ceratamines, in addition to issues surrounding the installation of the correct methylation pattern of the targets. There is good precedent for the use of iodine(V) reagents to form enamides,[17a] imines,[17b] and α,β-unsaturated carbonyl compounds,[17c] but there is no precedent for formation of the C5−C4 α,β-unsaturated amide needed for the ceratamines. Nonetheless, given the number of potentially oxidizable sites in **11**, it was expected that some method(s) for the formal removal of four hydrogen atoms could be developed. In practice (Scheme 3), a remarkable, high-yielding double dehydrogenation occurred upon treatment of **11** with IBX in DMSO (35 °C, 1 h), and the fully oxidized imidazo[4,5-*d*]azepine ring system was formed cleanly to provide des-methyl ceratamine B (**12**). Methylation of the lactam nitrogen with iodomethane (−10 °C, 1 h) afforded des-methyl ceratamine A (**13**) in modest yield.

The formation of the C8−C9 enamide double bond of **12** using IBX had been examined in model systems, but the role that the electron-rich imidazole ring plays in the second oxidation is unclear. There are several mechanistic possibilities including oxidation at the benzylic position followed by elimination,[8] oxidation at C5 α to the carbonyl group, or oxidation of the imidazole ring. In any case, tautomerization occurs to form **12**, the structure of which is evident in the ^{1}H NMR spectrum in the downfield shifts of the benzylic C11−H_2 (δ 4.15, s) and C8−H_2, which change from diastereotopic multiplets at 3.43 and 3.51 ppm in **11** to an apparent triplet at 7.18 ppm in **12** ($J_{8,9}$ = 8.8 Hz).

Additional confirmation of the structure of **12** came from examination of the ^{13}C NMR spectrum. Comparing data for **12** with that reported for ceratamine B[1] showed that the most significant differences in chemical shifts occurred at C2 (Δδ 1.1 ppm), C4 (Δδ 0.8 ppm), and C10 (Δδ 0.5 ppm), closest to the site of the absent *N*-methyl group, whereas other differences were trivial (Δδ < 0.2 ppm for C5, C6, C8, C9, and C11).

Most notably, the ^{13}C NMR chemical shifts of carbons C2, C4, and C10 in **11** dramatically change from those characteristic of a 2-aminoimidazole (δ 146.5, 117.0, and 120.9) to those of a nonaromatic heterocycle in **12** (δ 176.4, 162.0, and 171.3).

Methylation of the C2-amino group at the fully oxidized stage of **12** or **13** was impractical using reductive alkylation conditions due to the sensitivity of the fully oxidized heterocyclic ring system toward reduction. However, methylation at the stage of **11** could be achieved by quantitative formation of the ethyl formimidate (80 °C, 4 h) followed by reduction with $NaBH_4$[18] (0−40 °C, 1 h) to afford **14** (Scheme 4). Oxidation of **14** with IBX (35 °C, 2 h) afforded ceratamine B (**1b**). Methylation of the lactam nitrogen (−10 °C, 1 h) afforded ceratamine A (**1a**) in modest yield. Both **1a** and **1b** provided spectral data identical with that reported for the natural products.[1]

The total synthesis of ceratamine A and B was accomplished by a direct synthetic route starting from ε-lactam **2** in 11 and

(15) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881.

(16) Guo, Z. X.; Cammidge, A. N.; Horwell, D. C. *Synth. Commun.* **2000**, *30*, 2933.

(17) (a) Nicolaou, K. C.; Mathison, C. J. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 5992. (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993.

(18) Roberts, R. M.; Vogt, P. J. *J. Am. Chem. Soc.* **1956**, *78*, 4778. Crochet, R. A., Jr.; Blanton, C. D., Jr. *Synthesis* **1974**, 55.

12 steps in an overall yield of 28% and 12%. This synthesis also provides ready access to many interesting analogs, notably, the des-methyl ceratamines **12** and **13**. A remarkable and high-yielding double dehydrogenation was the key step for introduction of unsaturation in the imidazo[4,5-*d*]azepine ring system characteristic of the natural products.

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Supporting Information Available: Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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