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Synthesis of NP25302

Kiri Stevens,[†] Andrew J. Tyrrell,[†] Sarah Skerratt,[‡] and Jeremy Robertson*,[†]

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, U.K., and Pfizer Global Research and Development, Ramsgate Road, Sandwich CT13 9NJ, U.K.

jeremy.robertson@chem.ox.ac.uk

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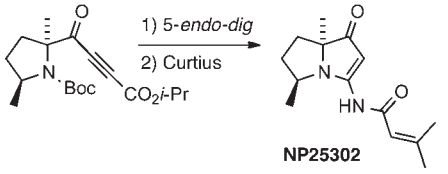
ABSTRACT



An efficient synthesis of NP25302 is presented that relies on 5-*endo-dig* *N*-cyclization to establish the bicyclic core and Curtius rearrangement to install the *N*-acyl vinylogous urea functionality.

Bohemamine (**1**, Figure 1) was the first reported member of a small class of alkaloids defined by a 3-*N*-acylamino-tetrahydropyrrolizine core.[1] Subsequent members, all of bacterial origin, include jenamidines A–C **2**–**4**,[2] NP25302 **5**,[3] bohemamines B **6** and C **7**, and a chlorinated bohemamine **8**.[4] Jenamidine A inhibits the growth of chronic myeloid leukemia K-562 cells (GI_{50} = 1.9 μg mL^{-1}),[2] and both bohemamine and NP25302 inhibit the adhesion of human promyelocytic leukemia HL-60 cells to Chinese hamster ovary cells expressing intercellular adhesion molecule ICAM-1 (CD54) (IC_{50} = 24.3 and 27.2 μg mL^{-1}, respectively).[3]

With only one exception,[5] the vinylogous urea functionality in these natural products[6] and their non-natural

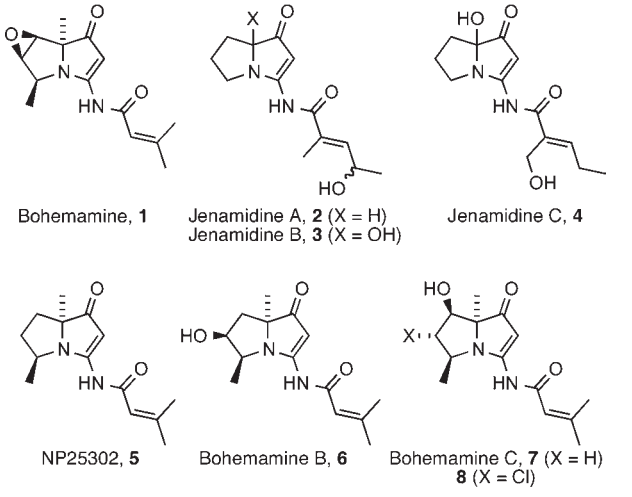


Figure 1. Known alkaloids of the bohemamine type.

analogues[7] has been established synthetically by either *N*- or *C*-cyclization onto a tethered nitrile. We present a fundamentally different approach, based on Curtius rearrangement (Scheme 1), for which current literature precedent is confined to pyridone[8] and pyridazine[9]

[†] University of Oxford.
[‡] Pfizer Global Research and Development.

(1) 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.
(2) (a) Isolation and proposed structure: Hu, J.-F.; Wunderlich, D.; Thiericke, R.; Dahse, H.-M.; Grabley, S.; Feng, X.-Z.; Sattler, I. *J. Antibiot.* **2003**, *56*, 747. (b) Structural reassignment: Snider, B. B.; Duvall, J. R.; Sattler, I.; Huang, X. *Tetrahedron Lett.* **2004**, *45*, 6725.
(3) Zhang, Q.; Schrader, K. K.; ElSohly, H. N.; Takamatsu, S. *J. Antibiot.* **2003**, *56*, 673.
(4) Bugni, T. S.; Woolery, M.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2006**, *69*, 1626.
(5) Contini, A.; Erba, E.; Trimarco, P. *ARKIVOC* **2008**, (xii), 136.
(6) (a) Snider, B. B.; Duvall, J. R. *Org. Lett.* **2005**, *7*, 4519. (b) Duvall, J. R.; Wu, F.; Snider, B. B. *J. Org. Chem.* **2006**, *71*, 8579.
(7) (a) Volovenko, Y. M. *Chem. Heterocycl. Compd.* **1998**, *33*, 854. (b) Katritzky, A. R.; Vincek, A. S.; Steel, P. J. *Heterocycles* **2008**, *76*, 1401. (c) Tverdokhlebov, A. V.; Denisenko, A. V.; Tolmachev, A. A.; Volovenko, Y. M.; Shishkina, S. V.; Shishkin, O. V. *Synthesis* **2009**, 1265. (d) Nestorak, I. Y.; Tverdokhlebov, A. V.; Tolmachev, A. A.; Volovenko, Y. M. *Heterocycles* **2010**, *81*, 611.
(8) (a) Heyns, K.; Vogelsang, G. *Chem. Ber.* **1954**, *87*, 1440. (b) Cannon, W. N.; Jones, R. G. *J. Org. Chem.* **1957**, *22*, 1722.
(9) (a) Boger, D. L.; Coleman, R. S. *J. Org. Chem.* **1986**, *51*, 3250. (b) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1987**, *109*, 2717.

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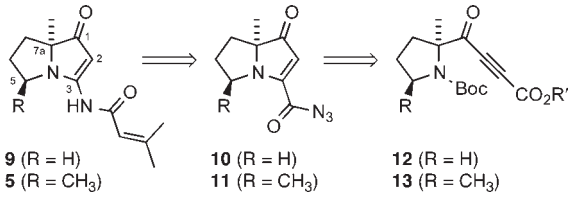
Scheme 1. Key Stages in the Synthesis of NP25302 **5** and *nor*-NP25302 **9** [R′ = Alkyl]



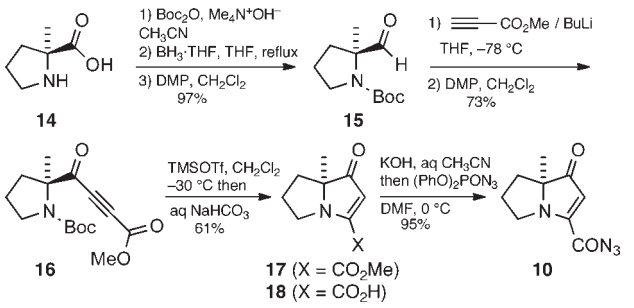
substrates. In addition, we describe the first application of a 5-*endo-dig N*-cyclization[10−12] to the synthesis of a pyrrolizidine-type ring system.[13]

Initially, the viability of the key 5-*endo-dig* and Curtius steps was tested in a readily accessible system leading to (+)-*nor*-NP25302 **9**. *N*-Protection of (*S*)-2-methylproline **14**[14] and an efficient reduction/oxidation sequence furnished aldehyde **15** (Scheme 2). Building on model studies,[15] in which various functionalized alkynyl organometallics were added to *N*-Boc-prolinal, the addition of lithiated methyl propiolate[16] provided ketone **16** after oxidation with Dess−Martin periodinane (DMP). The sequence from (*S*)-methylproline to ketone **16** was extremely efficient (71% over five steps), with no purification of intermediates required.

The first key step to be addressed, the 5-*endo-dig N*-cyclization (→ **17**), was unsuccessful using the Hg(II)-mediated conditions described in the closest precedent for such a process.[12,17] However, mild *N*-deprotection with *p*-toluenesulfonic acid,[18] followed by addition of solid $NaHCO_3$, provided acceptable yields (up to 59%) of the bicyclic product **17**. Alternatively, use of TMSOTf at low temperature to effect the Boc-deprotection[19] gave a slightly improved yield, and for convenience, this method is preferred.

Carboxylic acid **18** was isolated following alkaline hydrolysis (LiOH, aq CH_3CN) of ester **17**, but standard protocols[20] for conversion of carboxylic acids into acyl azides failed with this compound. The intermediate lithium carboxylate was also found to be rather unreactive toward activation (e.g., with ethyl chloroformate), but the potassium carboxylate was sufficiently nucleophilic in DMF to react with diphenylphosphoryl azide[21] and, following optimization, acyl azide **10** was obtained reproducibly in excellent overall yield from ester **17**.

Scheme 2. Synthesis of Curtius Rearrangement Precursor **10**



It was our intention to trap the isocyanate derived from acyl azide **10** by addition of an isobutenyl organometallic to provide *nor*-NP25302 directly. In practice, thermolysis of the azide led to rapid polymerization, presumably of the intermediate isocyanate, and compatible isobutenyl nucleophiles for trapping *in situ* were not found. Instead, rearrangement was effected in the presence of a variety of alcohols to provide carbamates **19**−**22** (Scheme 3). Each of these was acylated with 2,2-dimethylacryloyl chloride (**28**) but the so-formed *N*-acyl carbamates **23**−**26** could not be deprotected (→ **9**) without complication. In most attempts amine **27** was formed. In one case (**26**), deprotection was accompanied by migration of the dimethylacryloyl group to the C(2) position; in other cases, the dimethylacryloyl fragment was removed preferentially. Eventually, the Curtius rearrangement was performed in the presence of water to provide amine **27** which was then acylated using the conditions described in Snider's synthesis of NP25302 to afford (+)-*nor*-NP25302 **9**.

This model study had established an efficient nine-step synthesis of *nor*-NP25302 from proline derivative **14**, and it was expected that the extra methyl group at C(5) in NP25302 would not complicate the route. (±)-*trans*-2,5-Dimethylproline derivative **29** (Scheme 4) was prepared in two high-yielding steps from ethyl 2-nitropropionate in a modification

(10) 5-*Endo-dig N*-cyclization onto alkynols: (a) Smith, C. R.; Bunnelle, E. M.; Rhodes, A. J.; Sarpong, R. *Org. Lett.* **2007**, *9*, 1169. (b) Yan, B.; Zhou, Y.; Zhang, H.; Chen, J.; Liu, Y. *J. Org. Chem.* **2007**, *72*, 7783. (c) Bunnelle, E. M.; Smith, C. R.; Lee, S. K.; Singaram, S. W.; Rhodes, A. J.; Sarpong, R. *Tetrahedron* **2008**, *64*, 7008. (d) Friel, D. K.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 9942.

(11) 5-*Endo-dig N*-cyclization onto alkynones: Gouault, N.; Le Roch, M.; Cornee, C.; David, M.; Uriac, P. *J. Org. Chem.* **2009**, *74*, 5614.

(12) Application in natural product synthesis [(+)-preussin from (*S*)-phenylalanine]: Overhand, M.; Hecht, S. M. *J. Org. Chem.* **1994**, *59*, 4721.

(13) Related 6-*endo-dig* cyclizations: (a) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702. (b) Ward, T. R.; Turunen, B. J.; Haack, T.; Neuenswander, B.; Shadrick, W.; Georg, G. I. *Tetrahedron Lett.* **2009**, *50*, 6494. (c) Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019. (d) Niphakis, M. J.; Turunen, B. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6793. (e) Pepe, A.; Pamment, M.; Georg, G. I.; Malhotra, S. V. *J. Org. Chem.* **2011**, *76*, 3527.

(14) Beck, A. K.; Blank, S.; Job, K.; Seebach, D.; Sommerfeld, Th. *Org. Synth.* **1995**, *72*, 62.

(15) Tyrrell, A. J. D. Phil. Thesis, University of Oxford, Oxford, U. K., 2008.

(16) Midland, M. M.; Tramontano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(17) Use of AcOH as the solvent instead of CH_3NO_2 gave some product (16%), and replacement of the reported $Hg(OAc)_2$ with $Hg(OCOCF_3)_2$ raised the yield to 38%.

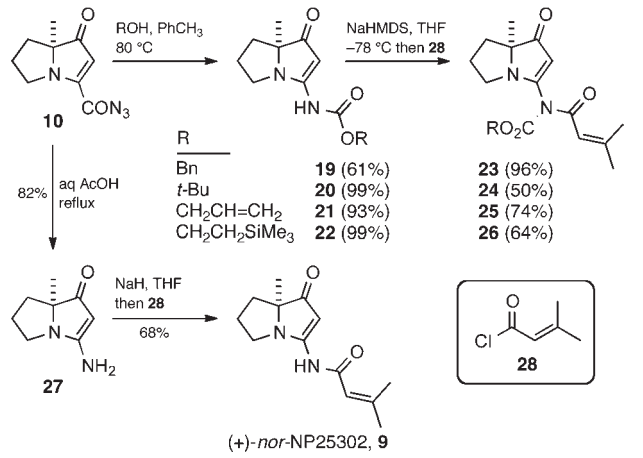
(18) These conditions were found to be preferred in a related system: Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624.

(19) *Cf.* Bastiaans, H. M. M.; van der Baan, J. L.; Ottenheijm, H. C. J. *J. Org. Chem.* **1997**, *62*, 3880.

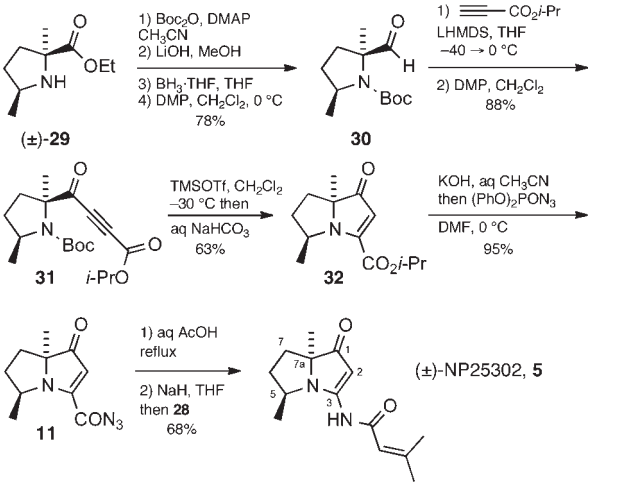
(20) For example: $(PhO)_2PON_3/Et_3N$ in toluene or toluene/*t*-BuOH was hampered by the limited solubility of acid **18** in these solvents; clean preparation of the acid chloride, in readiness for substitution with azide, could not be achieved.

(21) (a) Shioiri, T.; Ninomiya, K.; Yamada, S.-i. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Ninomiya, K.; Shioiri, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151.

Scheme 3. Curtius Rearrangement Trials and Completion of the Synthesis of (+)-*nor*-NP25302



Scheme 4. Synthesis of (±)-NP25302



of the literature procedure,[6b] and aldehyde **30** was obtained straightforwardly in four further steps. In contrast to the simpler aldehyde **15**, the dimethyl variant **30** was unreactive toward lithiated methyl propiolate at (the low) temperatures at which the organometallic remained stable. Related alkynyl organometallics were explored, including those derived from *tert*-butyl propiolate and propiolic acid itself; although the additions were successful, the derived ketones could not be induced to cyclize in acceptable yields. Ultimately, the use of lithiated isopropyl propiolate solved the problem. This lithium acetylide derivative has not been reported, but it proved reliable and sufficiently stable to effect efficient addition to hindered aldehyde **30**. Subsequent 5-*endo*-*dig* cyclization of the derived ketone **31** proceeded without complication under the preferred conditions for cyclization of model substrate **16**.[22] The three final steps to complete the synthesis were achieved under identical conditions and in comparable yields to the model study.

The NMR data for our synthetic NP25302 differed sufficiently from those published (see Supporting Information for details) to cast doubts on either the stereochemistry or the connectivity in the final product. However, the *trans*-relationship of the C(5) and C(7a) methyls was derived from amine **29** whose structure had been confirmed by X-ray analysis of **29**·HCl;[23] in addition, HMBC data for synthetic **5** showed an absence of H(5)–C(3) and α-H(7)–C(1) correlations, indicating approximately 90° relationships, consistent with the expected stereochemistry. It became clear that the appearance of the NMR spectra for NP25302 was affected by the quality of the solvent and the concentration of the sample.[24] For example, when the ^{1}H NMR spectrum was run in $CDCl_3$ that had been filtered through basic alumina, the two olefinic protons appeared as a single resonance [cf. lit.[3] δ_H 5.75 (1 H, s) and 6.01 (1 H, s)], but addition of TFA in 10 mol % aliquots led to splitting and shifting of the olefinic resonances until the values approached those reported. At the same time, colorless needles separated out of the NMR solvent that proved suitable for single crystal X-ray analysis. The structure (Figure 2)—the TFA salt of NP25302—confirmed the success of the synthesis.

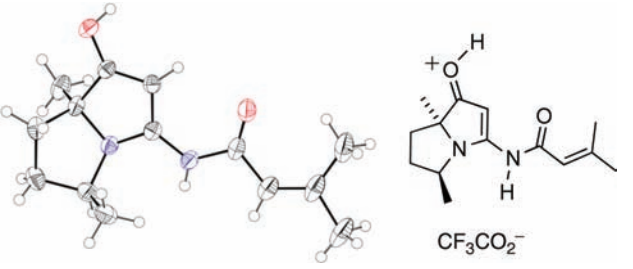


Figure 2. X-ray molecular structure of **5**·TFA [$CF_3CO_2^-$ ion omitted for clarity].

This total synthesis of (±)-NP25302 is longer than Snider's published route[6b] primarily due to the sequence of functional group interconversions required to access a suitably reactive acceptor **30** for alkynyl organometallic reagents. Nevertheless, the key 5-*endo*-*dig* cyclization and Curtius rearrangement steps successfully delivered the defining structural features of the natural product in an efficient overall synthesis (28% from **29**, average 88% yield per step).

(22) During the course of this investigtion, we found that the TMSOTf conditions for 5-*endo*-*dig* cyclization were at least as efficient with less activated analogues of alkynyl ketone **31** bearing H, CH_2OH, or CH_2OTBS in place of CO_2i-Pr. Fuller details of the scope of this cyclization will be described in due course.

(23) CCDC 834708 and 834707 contain crystallographic data for this paper (for compounds **29**·HCl and **5**·TFA, respectively). These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(24) We are very grateful to Professor Barry Snider, Brandeis University, for informative correspondence concerning the NMR spectra of natural and synthetic NP25302.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.