ORGANIC LETTERS

2012
Vol. 14, No. 5
1326–1329

[C+NC+CC] Coupling-Enabled Synthesis of Influenza Neuramidase Inhibitor A-315675

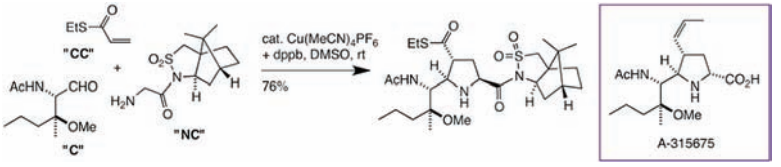
Philip Garner,*,† Laksiri Weerasinghe,† Wiley J. Youngs,‡ Brian Wright,‡ Dean Wilson,§ and Dylan Jacobs§

Department of Chemistry, Washington State University, Pullman, Washington 99164-4630, United States, Department of Chemistry, University of Akron, Akron, Ohio 44325, United States, and Vertex Pharmaceuticals Inc., Cambridge, Massachusetts 02139, United States

ppg@wsu.edu

Received January 26, 2012

ABSTRACT



An efficient synthesis of the neuramidase inhibitor A-315675 is reported. The fully functionalized pyrrolidine core of the target is assembled in one pot via an *exo*-selective asymmetric [C+NC+CC] coupling reaction.

The *endo*-selective[1] and *exo*-selective[2] asymmetric [C+NC+CC] coupling reactions provide stereo complementary routes to highly functionalized pyrrolidines (Scheme 1).[3] In each of these multicomponent reactions, the key C−C bond-forming step involves a [3 + 2] cycloaddition of a metalated azomethine ylide (formed by condensation of the C- and NC-components) with an electronically activated dipolarophile (CC-component). The most obvious advantage of the [C+NC+CC] coupling reaction over existing [3 + 2] cycloaddition art is the ability to employ enolizable and chiral aldehyde C-components without unwanted enolization or enamine formation that could result in α-epimerization and undesired side reactions. These aymmetric [C+NC+CC] coupling reactions turn out to be remarkably general toward a variety of dipolarophiles. The absolute stereochemistry is controlled in a predictable manner by Oppolzer's camphorsultam auxiliary, which can be removed post-coupling by *N*-acyl sultam reduction or methanolysis. In light of the widespread occurrence of pyrrolidines in natural products and modern pharmacopeia, we anticipated that the [C+NC+CC] coupling methodology would be useful for the synthesis of pyrrolidine-based targets. In our first application of this methodology, the *endo*-selective asymmetric [C+NC+CC] coupling reaction formed the basis for an efficient synthetic entry to the cyanocycline family of natural products.[4] We now report our first application of the *exo*-selective asymmetric [C+NC+CC] coupling reaction in the form of a short and stereocontrolled synthesis of the antiviral agent A-315675.

A-315675 (**4**) and its isopropyl ester prodrug, A-322278 (**5**), are potent neuramidase (NA) inhibitors that can be used to treat influenza (Scheme 2).[5] Like the currently marketed neuramidase inhibitors zanamavir (Relenza, **2**) and oseltamivir (Tamiflu, **3**), A-315675 prevents viral

† Washington State University.
‡ University of Akron.
§ Vertex Pharmaceuticals Inc.

(1) Garner, P.; Kaniskan, H. U.; Hu, J.; Youngs, W. J.; Panzner, M. *Org. Lett.* **2006**, *8*, 3647.

(2) Garner, P.; Hu, J.; Parker, C. G.; Youngs, W. J.; Medvetz, D. *Tetrahedron Lett.* **2007**, *48*, 3867.

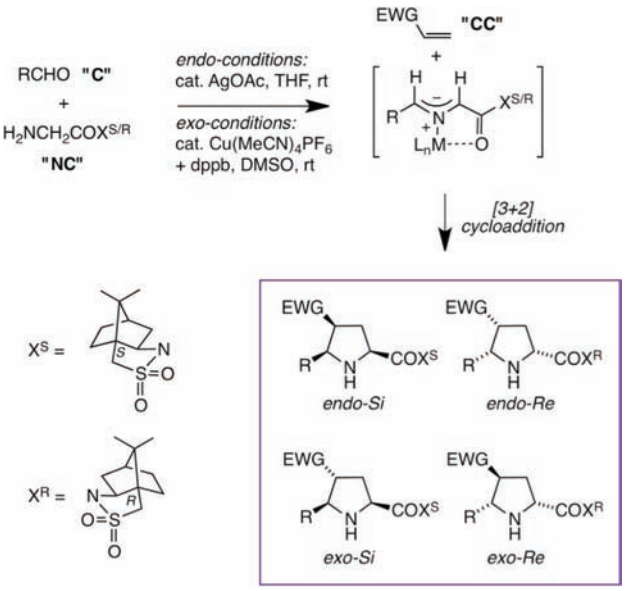
(3) For an account of our development of the asymmetric [C+NC+CC] coupling reaction, see: Garner, P.; Kaniskan, H. U. *Curr. Org. Synth.* **2010**, *7*, 348.

(4) (a) Kaniskan, H. U.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460. (b) Garner, P.; Kaniskan, H. U.; Keyari, C. M.; Weerasinghe, L. *J. Org. Chem.* **2011**, *76*, 5283–5294.

(5) Maring, C.; McDaniel, K.; Krueger, A.; Zhao, C.; Sun, M.; Madigan, D.; DeGoey, D.; Chen, H.-J.; Yeung, M. C.; Flosi, W.; Grampovnik, D.; Kati, W.; Klein, L.; Stewart, K.; Stoll, V.; Saldivar, A.; Montgomery, D.; Carrick, R.; Steffy, K.; Kempf, D.; Molla, A.; Kohlbrenner, W.; Kennedy, A.; Herrin, T.; Xu, Y.; Laver, W. G. Presented at 14th International Conference on Antiviral Research, *Antiviral Res.* 2001, *50*, A76; Abstract 129.

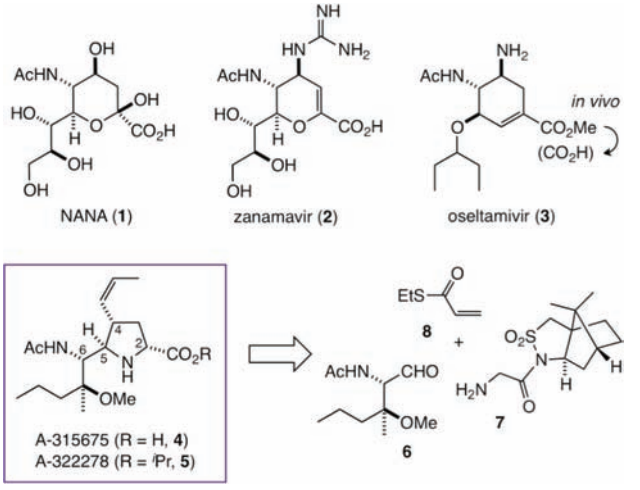
10.1021/ol3002128
Published on Web 02/17/2012

Scheme 1. Asymmetric [C+NC+CC] Coupling Reaction



replication by competitively binding to the NA active site and preventing the enzyme from cleaving *N*-acetyl neuramimic acid (NANA, **1**) units located on cell surface glycoproteins. This, in turn, prevents the release of new virus particles from the infected cell. Interestingly, A-315675 and A-322278 retained significant antiviral activity against a number of oseltamivir-resistant mutants,[6] highlighting their potential use against drug-resistant influenza. Since it is likely that antibiotic-resistant influenza strains will continue to evolve, a versatile chemistry platform that provides synthetic access to A-315675 and other pyrrolidine-based NA inhibitors would be most valuable. Three asymmetric syntheses of A-315675 have been reported to date, the first by medicinal chemists at Abbott Laboratories,[7] the second by Hanessian and co-workers,[8] and the most recent by Chida and co-workers.[9] Abbott chemists have also reported an asymmetric synthesis of A-322278.[10] We felt that our *exo*-selective asymmetric [C+NC+CC] coupling reaction would be ideally suited for the rapid assembly of the A-315675 pyrrolidine core, wherein the key [C+NC+CC] bond disconnection (Scheme 2) leads to the merger of α-acetamidoaldehyde **6**, 1(*S*)-glycylsultam **7**, and ethyl thioacrylate (**8**). The thioester would serve as both dipolarophile activator and a masked aldehyde, enabling the introduction of the (*Z*)-propenyl substituent at C4 via a Wittig reaction. Since the [C+NC+CC] coupling reaction necessarily produces a 2,5-*cis* disposed pyrrolidine, the synthetic plan would also require inversion of the carboxylic acid moiety at C2.

Scheme 2. NANA, Neuramidase Inhibitors, and A-315675 Disconnection



In the event, the *exo*-selective [C+NC+CC] coupling of **6**,[11] **7**,[12] and **8**[13] proceeded to give the desired cycloadduct **9** in high yield (Scheme 3).[14] The diastereoselectivity of this reaction was determined to be 19:1 by HPLC−MS analysis of the crude product mixture. The structure of cycloadduct **9** was unambiguously established through its chemical correlation with an analogous cycloadduct **18** that was

(6) (a) Molla, A.; Kati, W.; Carrick, R.; Steffy, K.; Shi, Y.; Montgomery, D.; Gusick, N.; Stoll, V. S.; Stewart, K. D.; Ng, T. I.; Maring, C.; Kempf, D. J.; Kohlbrenner, W. *J. Virol.* **2002**, *76*, 5380. (b) Mishin, V. P.; Hayden, F. G.; Gubareva, L. V. *Antimicrob. Agents Chemother.* **2005**, *49*, 4515. (c) Abed, Y.; Nehme, B.; Baz, M.; Boivin, G. *Antiviral Res.* **2008**, *77*, 163. (d) Baz, M.; Abed, Y.; Nehme, B.; Boivin, G. *Antimicrob. Agents Chemother.* **2009**, *53*, 791. (e) Pizzorno, A.; Bouhy, X.; Abed, Y.; Boivin, G. *J. Infect. Dis.* **2011**, *203*, 25.

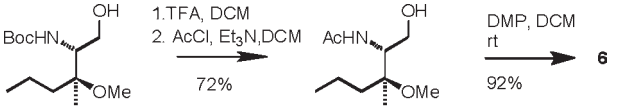
(7) (a) DeGoey, D. A.; Chen, H. J.; Flosi, W. J.; Grampovnik, D, J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. (b) Barnes, D. M.; McLaughlin, M. A.; Oie, T.; Rasmussen, M. W.; Stewart, K. D.; Wittenberger, S. J. *Org. Lett.* **2002**, *4*, 1427.

(8) Hanessian, S.; Bayrakdarian, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716.

(9) Momose, T.; Hama, N.; Higashino, C.; Sato, H.; Chida, N. *Tetrahedron Lett.* **2008**, *49*, 1376.

(10) Barnes, D. M.; Bhagavatula, L.; DeMattei, J.; Gupta, A.; Hill, D. R.; Manna, S.; McLaughlin, M. A.; Nichols, P.; Premchandran, R.; Rasmussen, M. W.; Tian, Z.; Wittenberger, S. J. *Tetrahedron: Asymmetry* **2003**, *14*, 3541.

(11) Aldehyde **6** can be prepared in 3 steps from Hanessian's intermediate **14**,[8] which is derived (in 8 steps) from D-serine.



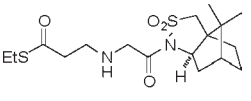
14 **15**

Large quantities of **15**, prepared by a slightly longer route that included benzyl ether formation and subsequent deprotection, were provided to us by Vertex Pharmaceuticals.

(12) Isleyen, A.; Gonsky, C.; Ronald, R. C.; Garner, P. *Synthesis* **2009**, 1261. Compound **7** is best stored as its HCl salt and the free amine regenerated immediately before use.

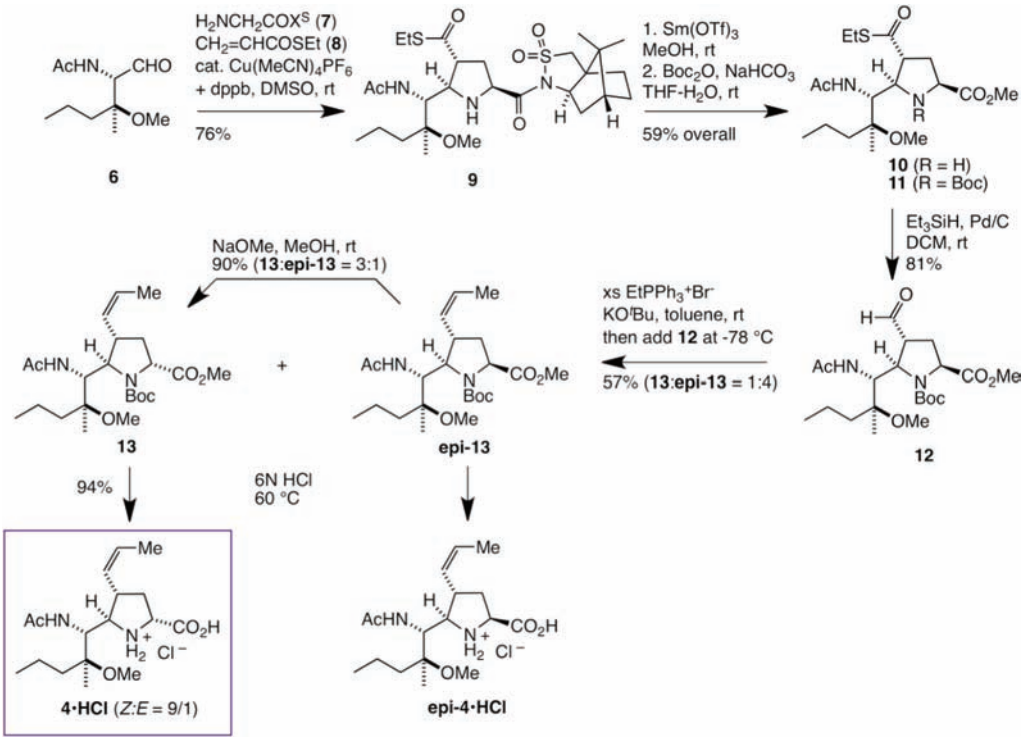
(13) Van Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. J. *Org. Chem.* **2008**, *73*, 5651.

(14) When **6**, **7**, and **8** were added at once to the catalytic mixture according to the original procedure,[2] conjugate addition product **16** was isolated (42%) in addition to the cycloadduct **9** (32%). This side reaction could be avoided by allowing **6** and **7** to react together first before adding **8**.



16

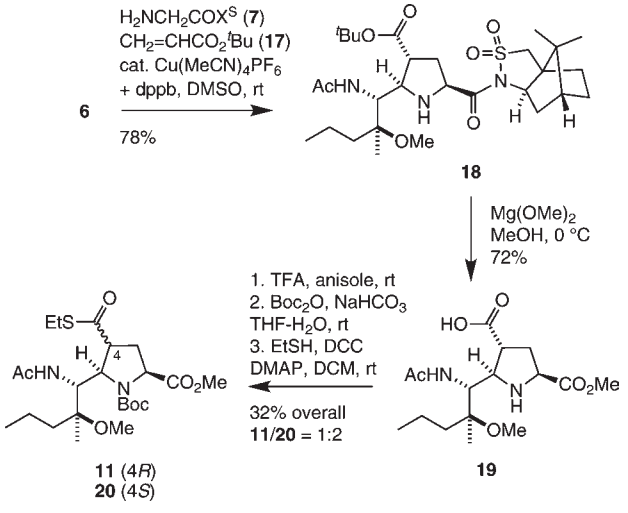
Scheme 3. [C+NC+CC] Synthesis of A-315675



characterized by X-ray crystallography (Figure 1).[15] The stereochemical outcome of these cycloadditions is in accord with our proposed transition state model for the *exo*-selective [C+NC+CC] coupling reaction. Transformation of compound **9** into the target molecule was effected in just 5 steps. First, Sm(III)-mediated methanolysis of **9** produced the methyl ester **10**, which was converted to the *N*-Boc derivative **11** in good overall yield.[16] Application of Fukuyama's Pd-catalyzed thioester reduction protocol to **11** cleanly afforded the aldehyde **12**,[17] which was immediately subjected to a Wittig reaction with the unstabilized ylide $MeCH{=}PPh_3$ at −78 °C to give a chromatographically separable 4:1 mixture of **13** and an isomer in 57% combined yield. The olefin isomer ratio could not be determined at this stage by either ^{1}H NMR or HPLC but was later shown to be 9:1.[18] The minor compound was identified as the thermodynamically favored[19] 2,5-*trans* disubstituted pyrrolidine **13**. (Note that epimerization at C4 at the thioester or aldehyde stage would be expected to retain the 4,5-*trans* relationship.) At this point, the C2 center was intentionally epimerized using NaOMe in MeOH to afford a 3:1 mixture of **13** and **epi-13** in 90% combined yield, which was separated by flash chromatography. Finally, acidic hydrolysis of the **13** produced

(15) CCDC-860576 (cycloadduct **18**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/products/csd/request/.

(16) The chemical correlation of cycloadducts **9** and **18** via *N*-Boc methyl ester **11** was effected as follows. Cycloadduct **18** was converted to the methyl ester **19**, which was then processed as shown to afford an inseparable mixture of **11** and a diastereomer identified as **20**.



(17) Tokuyama, H.; Yokoshima, S.; Lin, S.-C.; Li, L.; Fukuyama, T. *Synthesis* **2002**, 1121.

(18) This Wittig reaction gave a 6:1 mixture of *Z*- and *E*-isomers employing conditions developed by Abbott chemists with similar substrates. (a) Maring, C. J.; Stoll, V. S.; Zhao, C.; Sun, M.; Krueger, A. C.; Stewart, K. D.; Madigan, D. L.; Kati, W. M.; Xu, Y.; Carrick, R. J.; Montgomery, D. A.; Kempf-Grote, A.; Marsh, K. C.; Molla, A.; Steffy, K. R.; Sham, H. L.; Laver, W. G.; Gu, Y.; Kempf, D. J.; Kohlbrenner, W. E. *J. Med. Chem.* **2005**, *48*, 3980. (b) Krueger, A. C.; Xu, Y.; Kati, W. M.; Kempf, D. J.; Maring, C. J.; McDaniel, K. F.; Molla, A.; Montgomery, D.; Kohlbrenner, W. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1692. We thank Dr. Chris Krueger (Abbott) for sharing experimental details concerning this reaction with us. The *Z*/*E* ratio improved to 9:1 when the Wittig reaction was performed at −78 °C.[9]

(19) Molecular mechanics calculations (ChemBio3D version 12.0, MM2) suggested that **13** (E_T = 36.6 kcal/mol) is more stable than its 2,5-*cis* epimer (E_T = 38.1 kcal/mol).

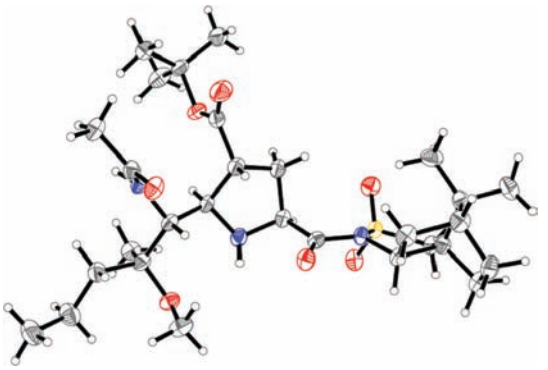


Figure 1. ORTEP diagram from the X-ray crystallographic analysis of cycloadduct **18**.

A-315675 (**4**) as its HCl salt in high yield. The *Z*/*E*-selectivity of the Wittig reaction was determined to be 9:1 at this stage by ^{1}H NMR spectroscopy. The ^{1}H and ^{13}C NMR data obtained on our material was identical with that reported by Hanessian.[8] Similarly, hydrolysis of **epi-13** produced **epi-4·HCl**.

In summary, we have completed a short (17 steps from D-serine) asymmetric synthesis of the neuramidase inhibitor A-315675. Noteworthy aspects of this synthesis include the application of our *exo*-selective asymmetric [C+NC+CC] coupling reaction to furnish the target's highly functionalized pyrrolidine ring and the effective use of a thioester moiety as both a dipolarophile activator and aldehyde surrogate.

Acknowledgment. This project was supported by Vertex Pharmaceuticals.

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

The authors declare no competing financial interest.