Synthesis of Botryllamides and Lansiumamides via Ruthenium-Catalyzed Hydroamidation of Alkynes

Lukas J. Gooßen,* Mathieu Blanchot, Matthias Arndt, Kifah S. M. Salih

Institut für Organische Chemie, TU Kaiserslautern, Erwin-Schrödinger-Str., Building 54, 67663 Kaiserslautern, Germany
Fax +49(631)2053921; E-mail: goossen@chemie.uni-kl.de

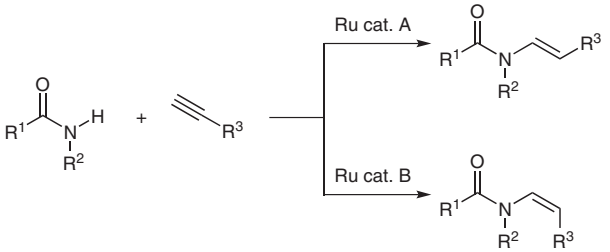
Received 26 March 2010

In memory of Keith Fagnou

Abstract: Ruthenium-catalyzed hydroamidations of alkynes allow a concise synthetic entry to both *E*- and *Z*-configured enamide natural products. This was demonstrated by the synthesis of botryllamides C and E, lansiumamides A and B, and lansamide I in 1–3 steps and 57–98% yield from simple, commercially available precursors.

Key words: alkyne, botryllamide, hydroamidation, lansamide, lansiumamide, ruthenium

The enamide group is a substructure widely present in natural products with interesting biological activities,[1] as well as fungicides,[2] metabolic drugs,[3] and functional materials.[4] Traditional synthetic entries to this substructure, for example, condensation reactions, require harsh reaction conditions and are usually not stereoselective.[5] Metal-catalyzed coupling reactions offer much milder reaction conditions but suffer from the limited availability of the vinylic precursors, for example, vinyl halides or pseudohalides.[6] Based on pioneering studies by Watanabe[7] and inspired by catalytic additions of other nucleophiles to alkynes,[8,9] we have recently developed ruthenium-catalyzed hydroamidation reactions that allow the *anti*-Markovnikov addition of various N–H nucleophiles to terminal alkynes under selective formation of either *E*- or *Z*-configured enamide derivatives (Scheme 1).[10]



Scheme 1 Hydroamidation of amides and terminal alkynes

The preparative utility of this synthetic strategy has so far been demonstrated only using rather simple model substrates. Based on the encouraging results obtained in these studies, we decided to take the next hurdle and probe the applicability of this methodology in the context of the synthesis of more complex structures, namely lansiumamides, lansamides, and botryllamides (Figure 1).

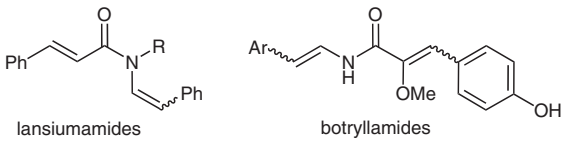


Figure 1 Structures of lansiumamides and botryllamides

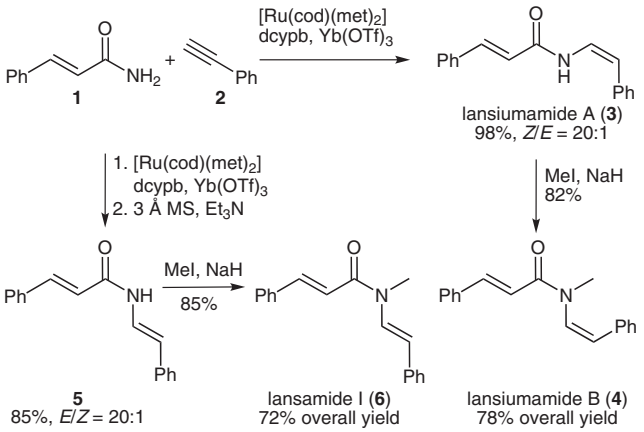
Lansiumamides including lansiumamides A and B, and lansamide I have been isolated from the leaves and fruits of *Clausena lansium*, a plant used in traditional chinese medicine for the treatment, for example, of asthma and viral hepatitis.[11] Total syntheses have been reported by Taylor[11b] (4 steps, 8–28% overall yield) and Maier[11d] (5 steps, 11–12% overall yield). Taylor generated the enamide moiety by adding vinylmagnesium reagents to isocyanates obtained via Curtius rearrangement of acyl azides. Maier et al. employed various methods to condense aldehydes with amides. In all the above syntheses, the enamides were obtained as mixtures of *E*- and *Z*-isomers in the key step.

Botryllamides were first isolated from the marine ascidian *Botryllus tyreus* as a complex mixture of ten structurally closely related derivatives.[12] They display activity as selective inhibitors of the ABCG2 multidrug transporter.[12c] While some of them have previously been prepared using traditional methods for enamide synthesis (4 steps, 20% yield),[12d] there are no published syntheses of botryllamides C and E.

The synthesis of the above compounds can greatly be simplified when employing Ru-catalyzed hydroamidation reactions to access the enamide moiety. The key advantage of this strategy is that the stereoselectivity of the reaction is controlled by the catalyst system, so that both (*E*)- and (*Z*)-enamide products can selectively be synthesized from the same, easily accessible amide and alkyne starting materials.

Lansiumamide A (**3**) is thus accessible in a single step from commercially available phenylacetylene (**2**) and cinnamide (**1**) in the presence of a ruthenium catalyst (Scheme 2). We tested various catalyst systems and found that this transformation is most effectively promoted by a bimetallic catalyst generated in situ from bis(2-methallyl)cycloocta-1,5-diene-ruthenium(II), 1,4-bis(dicyclo-

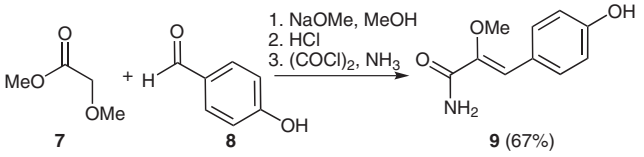
SYNLETT 2010, No. 11, pp 1685–1687
Advanced online publication: 04.06.2010
DOI: 10.1055/s-0029-1219961; Art ID: G10310ST



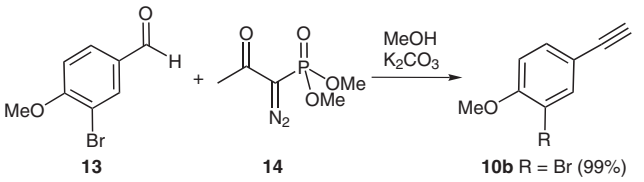
Scheme 2 Syntheses of lansiumamides A and B and lansamide I

hexylphosphino)butane (dcypb), and ytterbium triflate [$Yb(OTf)_3$] in a DMF–water mixture. Within six hours, the desired lansiumamide A (**3**) is formed in 98% yield and a *Z*/*E* ratio of 20:1.[10c] Methylation of **3** according to Maier's protocol[11d] gave lansiumamide B (**4**) in 82% yield. Lansamide I (**6**) was synthesized from the same starting materials using the *E*-selective protocol, in which a hydroamidation under the above conditions is combined with an in situ double-bond isomerization (Scheme 2). This way, the (*E*)-enamide **5** was obtained in 85% yield and an *E*/*Z* ratio in excess of 20:1. The methylation proceeded in 85% yield, so that overall, lansamide I (**6**) was obtained in 72% yield over two steps (Scheme 2).

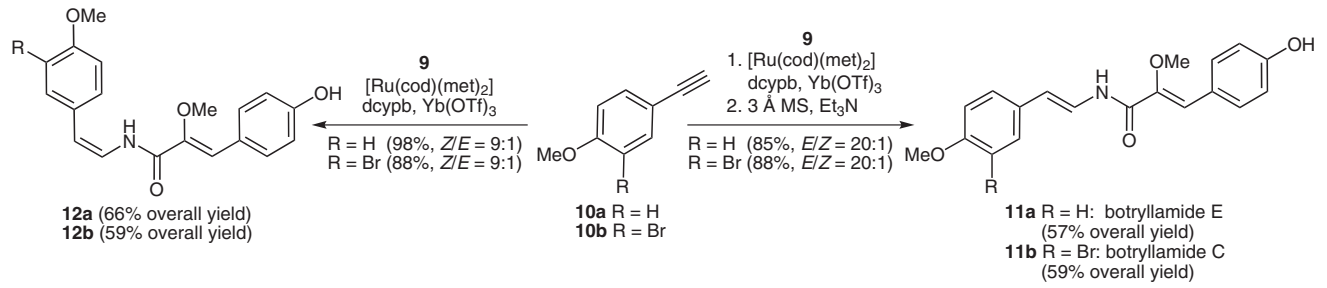
The hydroamidation strategy was similarly effective for the preparation of botryllamides C and E (**11a**,**b**). In both



Scheme 3 Synthesis of amide **9**



Scheme 4 Synthesis of alkyne **10b**



Scheme 5 Synthesis of botryllamides E and C

syntheses, the same primary amide **9** was required. It was obtained via an aldol condensation from commercially available methyl 2-methoxyacetate (**7**) and 4-hydroxybenzaldehyde (**8**). The resulting ester was saponified in situ and converted into the corresponding primary amide **9** in an overall 67% yield (Scheme 3). Its structure was confirmed by X-ray crystal-structure analysis.[13]

Amide **9** was then treated with commercially available 4-methoxyphenylacetylene (**10a**) using the *E*-selective hydroamidation protocol to give botryllamide E (**11a**) in excellent yield (85%, *E*/*Z* = 20:1). We also synthesized the *Z*-configured isomer (**12a**, 98%, *Z*/*E* = 9:1) using the complementary hydroamidation protocol (Scheme 5).

This isomer is sensitive to *E*/*Z*-isomerization under formation of the thermodynamically favored botryllamide E (**11a**). It is thus conceivable that **12a** is also present in *Botryllus tyreus* but isomerizes quantitatively during the isolation procedure. The structure of this unnatural *Z*-configured enamide **12a** was confirmed by X-ray structure analysis (Figure 2).[14]

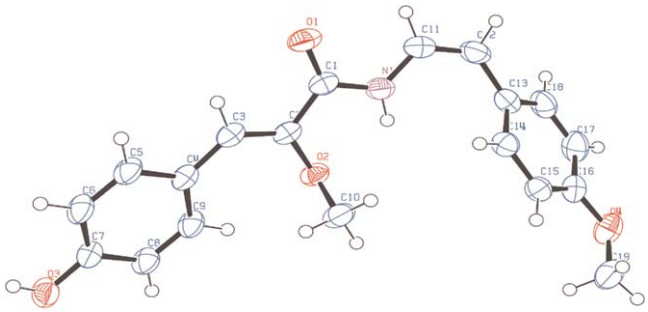


Figure 2 X-ray structure of enamides **12a**

The synthesis of botryllamide C (**11b**) was carried out analogously using the brominated phenylacetylene derivative **10b** (Scheme 4). This was synthesized in near-quantitative yield from 3-bromo-4-methoxybenzaldehyde (**13**) via a Bestmann–Ohira reaction.[15]

Again, the hydroamidation proceeded smoothly, and both the *Z*-configured enamide **12b** (88%, *Z*/*E* = 9:1) and the *E*-configured botryllamide C (**11b**, 88%, *E*/*Z* = 20:1) were obtained in high yields and selectivities (Scheme 5).

In conclusion, short and concise syntheses of lansiumamides A and B, lansamide I, as well as botryllamides C and E are possible using ruthenium-catalyzed hydroamidation reactions. Moreover, the sensitive *Z*-isomers of the

botryllamides are also accessible in high selectivity. This opens up new opportunities for the investigation of structure–activity relations for this biologically active substrate class.[12c,d]

Hydroamidation of Alkynes

An oven-dried flask was charged with the primary amide **1** or **9** (1.00 mmol), bis(2-methallyl)-cycloocta-1,5-diene-ruthenium(II) (16.0 mg, 0.05 mmol), 1,4-bis(dicyclohexylphosphinobutane (27.0 mg, 0.06 mmol), and ytterbium triflate (24.8 mg, 0.04 mmol) and flushed with nitrogen. Subsequently, dry DMF (3.0 mL), alkyne **2**, **10a**, or **10b** (2.00 mmol), and H_2O (108 μL, 6.00 mmol) were added via syringe. The resulting solution was stirred for 6 h at 60 °C. To access the (*Z*)-enamides, the reaction was worked up at this stage as detailed below. To obtain the (*E*)-enamides, 3 Å MS (500 mg) and Et_3N (200 μL) were added to the reaction mixture, and stirring was continued for 24 h at 110 °C.

For the workup, the reaction mixtures were poured into aq $NaHCO_3$ (30 mL). The resulting mixture was extracted with EtOAc (3×20 mL), the combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and the volatiles were removed in vacuo. The residue was purified by column chromatography (silica gel, EtOAc–hexane gradient). The identity and purity of the enamide products were confirmed by ^1H NMR and ^{13}C NMR spectroscopy.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are complete experimental procedures and analytical data for compounds **3–6**, **9**, **10b**, **11**, and **12**.

Acknowledgment

We thank the Deutsche Forschungsgemeinschaft for financial support and Umicore AG for generous donation of [Ru(cod)(met)$_2$], the Landesgraduiertenförderung Rheinland Pfalz and Deutscher Akademischer Austauschdienst for scholarships to M.A. and K.S.M.S.

References and Notes

(1) (a) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990. (b) Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881. (c) Ghosh, S.; Datta, D. B.; Sen, N. *Synth. Commun.* **1987**, *17*, 299. (d) Maxwell, A.; Rampersad, D. *J. Nat. Prod.* **1989**, *52*, 411. (e) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Seijas, J. A.; Castedo, L. *Synth. Commun.* **1990**, *20*, 503.

(2) Toske, S. G.; Jensen, P. R.; Kaufman, C. A.; Fenical, W. *Tetrahedron* **1998**, *54*, 13459.

(3) Han, Y. N.; Kim, G.-Y.; Han, H. K.; Han, B. H. *Arch. Pharmacol. Res.* **1993**, *16*, 289.

(4) Yet, L. *Chem. Rev.* **2003**, *103*, 4283.

(5) (a) Dupau, P.; Le Gendre, P.; Bruneau, C.; Dixneuf, P. H. *Synlett* **1999**, 1832. (b) Wang, X.; Porco, J. A. Jr. *J. Org. Chem.* **2001**, *66*, 8215. (c) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665. (d) Boeckman, R. K. Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250. (e) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.

(6) (a) Pa, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (b) Wallace, J.; Klauber, D. J.; Chen, C.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749. (c) Brice, J. L.; Meerdink, J. E.; Stahl, S. *Org. Lett.* **2004**, *6*, 1845.

(7) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413.

(8) For addition reactions of other hydrogen-bonded nucleophiles to alkynes, see: (a) Mitsudo, T.-A.; Hori, Y.; Watanabe, Y. *J. Org. Chem.* **1985**, *50*, 1566. (b) Doucet, H.; Derrien, N.; Kabouche, Z.; Bruneau, C.; Dixneuf, P. H. *J. Organomet. Chem.* **1997**, *551*, 151. (c) Gooßen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706. (d) Pholki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (e) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 3368; *Angew. Chem.* **2004**, *116*, 3448. (f) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917. (g) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; *Angew. Chem.* **2006**, *118*, 8064.

(9) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem. Int. Ed.* **2006**, *45*, 2176; *Angew. Chem.* **2006**, *118*, 2232.

(10) (a) Gooßen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4042; *Angew. Chem.* **2005**, *117*, 4110. (b) Gooßen, L. J.; Blanchot, M.; Brinkmann, C.; Gooßen, K.; Karch, R.; Rivas-Nass, A. *J. Org. Chem.* **2006**, *71*, 9506. (c) Gooßen, L. J.; Salih, K. S. M.; Blanchot, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 8492; *Angew. Chem.* **2008**, *120*, 8620. (d) Gooßen, L. J.; Arndt, M.; Blanchot, M.; Rudolphi, F.; Menges, F.; Niedner-Schatteburg, G. *Adv. Synth. Catal.* **2008**, *350*, 2701. (e) Gooßen, L. J.; Blanchot, M.; Salih, K. S. M.; Gooßen, K. *Synthesis* **2009**, 2283. (f) Gooßen, L. J.; Blanchot, M.; Salih, K. S. M.; Karch, R.; Rivas-Nass, A. *Org. Lett.* **2008**, *10*, 4497.

(11) Isolation: (a) Lin, J.-H. *Phytochemistry* **1989**, *28*, 621; and references cited therein. Synthesis: (b) Stefanuti, I.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2000**, *41*, 3735. (c) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955. (d) Bayer, A.; Maier, M. E. *Tetrahedron* **2004**, *60*, 6665.

(12) (a) Rao, M. R.; Faulkner, D. J. *J. Nat. Prod.* **2004**, *67*, 1064. (b) McKay, M. J.; Carroll, A. R.; Quinn, R. J. *J. Nat. Prod.* **2005**, *68*, 1776. (c) Henrich, C. J.; Robey, R. W.; Takada, K.; Bokesch, H. R.; Bates, S. E.; Shukla, S.; Ambudkar, S. V.; McMahon, J. B.; Gustafson, K. R. *ACS Chem. Biol.* **2009**, *4*, 637. (d) Takada, K.; Imamura, N.; Gustafson, K. R.; Henrich, C. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1330. (e) McDonald, L. A.; Swersey, J. C.; Ireland, C. M. *Tetrahedron* **1995**, *51*, 5237.

(13) CCDC 768748 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) CCDC 768747 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59. (d) For the synthesis of the Bestmann–Ohira reagent 14, see: Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266.