J|A|C|S COMMUNICATIONS

Published on Web 12/14/2010

Concise Total Synthesis of (+)-Lyconadin A

Takuya Nishimura, Aditya K. Unni, Satoshi Yokoshima, and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

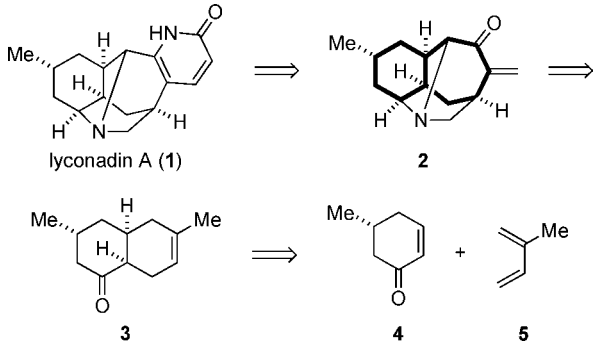
Received October 22, 2010; E-mail: fukuyama@mol.f.u-tokyo.ac.jp

Abstract: The total synthesis of lyconadin A from (*R*)-5-methylcyclohex-2-enone was accomplished. Our synthesis features the facile construction of a highly fused tetracyclic compound through a combination of an aza-Prins reaction and an electrocyclic ring opening. Transformation of the bromoalkene moiety in the tetracycle could be achieved by either a vinylogous Pummerer rearrangement or the formation and subsequent isomerization of the nitrosoalkene to furnish an α,β-unsaturated ketone, from which the pyridone ring was constructed.

Lyconadin A (**1**) was isolated in 2001 by Kobayashi and co-workers from the club moss *Lycopodium complanatum*.[1,2] Lyconadin A was shown to exhibit modest cytotoxicity against murine lymphoma L1210 cells and human epidermoid carcinoma KB cells. Closer examination revealed that lyconadin A enhanced mRNA expression for nerve growth factor (NGF) in 1321N1 human astrocytoma cells.[3] In addition to these biological activities, the unprecedented pentacyclic skeleton of lyconadin A has attracted much attention as a challenging target for total synthesis,[4] and two total syntheses of the molecule have been reported to date.[5] The first total synthesis of (+)-lyconadin A was achieved in 2007 by Beshore and Smith, who employed an intramolecular aldol/conjugate addition cascade as well as an aminoiodination reaction to construct the core tetracyclic structure. Shortly afterward, Sarpong and co-workers accomplished total syntheses of (±)- and then (+)-lyconadin A, in which a unique oxidative C−N bond-forming reaction was used to craft the pentacyclic skeleton.[6] Herein, we disclose a total synthesis of (+)-lyconadin A by means of a facile construction of both the core structure and the pyridone ring.

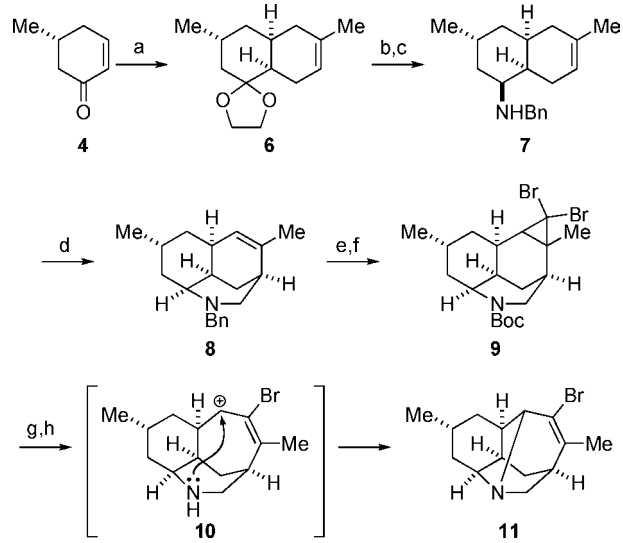
Our retrosynthetic analysis of **1** is outlined in Scheme 1. The pyridone moiety of **1** could be constructed from enone **2** according to a procedure developed in our laboratory.[7] We envisioned that construction of the carbon framework of **2**, bicyclo[5.4.0]undecane, would be achieved via a ring expansion of the *cis*-decaline system derived from **3**. Both the carbonyl group and the double bond in **3** would form the basis of the unique tertiary amine moiety. Decaline **3** could in turn be prepared through a Diels−Alder reaction.

Scheme 1. Retrosynthetic Analysis



Our synthesis commenced with a Diels−Alder reaction between isoprene and known enone **4**,[8] according to Overman's conditions,[9] to afford *cis*-octaline **6** (Scheme 2). After cleavage of the acetal,[10] the resulting ketone was subjected to reductive amination with benzylamine to furnish **7** with complete stereoselectivity. Upon treatment with formalin under acidic conditions, **7** underwent an aza-Prins reaction to give tricyclic compound **8**.[9,11] Replacement of the benzyl group on the nitrogen atom with a Boc group by a one-pot operation, followed by dibromocyclopropanation under biphasic conditions, afforded **9**.[12] After cleavage of the Boc group with trifluoroacetic acid (TFA), the resulting amine was heated under reflux in pyridine to induce ring expansion and formation of a C−N bond to furnish tetracyclic compound **11** in 96% yield in two steps. This reaction might involve electrocyclic ring opening of the dibromocyclopropane moiety with loss of a bromide ion to generate allylic cation **10**,[13] which might be intramolecularly intercepted by the secondary amine.

Scheme 2[a]



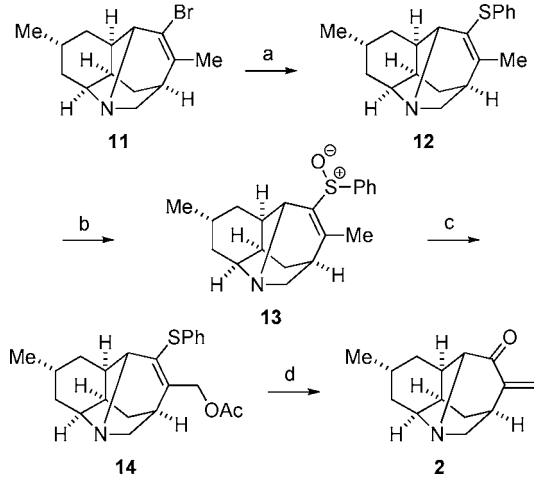
[a] Reagents and conditions: (a) $TMSOCH_2CH_2OTMS$, TMSOTf, isoprene, CH_2Cl_2, −78 °C, 71%. (b) $FeCl_3/SiO_2$, acetone, rt, 91%. (c) $BnNH_2$, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, 50 °C, 99%. (d) HCHO(aq), AcOH, SiO_2, 60 °C, 81%. (e) H_2, $Pd(OH)_2/C$, MeOH; Boc_2O, 94%. (f) $CHBr_3$, $BnNEt_3Cl$, *i*-PrOH, NaOH(aq), CH_2Cl_2, 0 °C to rt, 61%. (g) TFA, CH_2Cl_2, rt. (h) Pyridine, reflux, 96% (two steps).

Having achieved the efficient construction of the tetracyclic skeleton, we next focused on the transformation of **11** into enone **2**. Attempted oxidation of the double bond using a variety of oxidants, including OsO_4, *m*-chloroperoxybenzoic acid (*m*CPBA), *N*-bromosuccinimide, and Br_2 with or without acids, did not give

10.1021/ja109516f © 2011 American Chemical Society

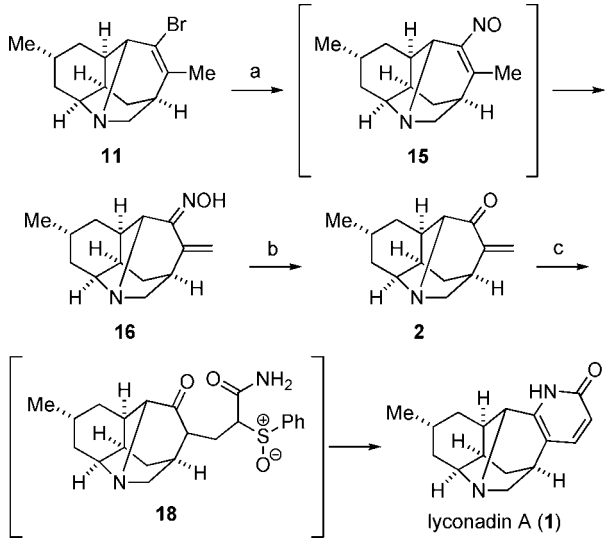
the desired product. After extensive investigations, we found that a halogen−lithium exchange of **11** could be carried out by reaction with *t*-BuLi in THF at −78 °C, and two different routes from the resulting alkenyllithium to enone **2** were established. Thus, treatment of the resulting alkenyllithium with diphenyl disulfide furnished sulfide **12** (Scheme 3). Oxidation of **12** with *m*CPBA and a subsequent vinylogous Pummerer rearrangement gave **14**,[14] which was subjected to acid hydrolysis in the presence of mercury(II) sulfate to afford enone **2**. On the other hand, treatment of the alkenyllithium with isoamyl nitrite afforded oxime **16** (Scheme 4). This reaction might proceed via formation and isomerization of nitrosoalkene **15**, and subsequent hydrolysis of oxime **16** under acidic conditions afforded enone **2**. While the yield remained somewhat low because of the in situ formation of the acidic oxime, the latter protocol enabled the more straightforward transformation

Scheme 3[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, −78 °C; PhSSPh, 88%. (b) *m*CPBA, TFA, CH_2Cl_2, 0 °C, 98%. (c) Ac_2O, CSA, toluene, reflux, 86%. (d) H_2SO_4, $HgSO_4$, H_2O, 70 °C, 63%.

Scheme 4[a]



[a] Reagents and conditions: (a) *t*-BuLi, THF, −78 °C; isoamyl nitrite, 37%. (b) HCl(aq), acetone, rt to 50 °C, 88%. (c) $PhS(O)CH_2CONH_2$ (**17**), NaH, THF, 0 °C; HCl, MeOH, 40 °C, 87%.

of **11** into enone **2** in only two steps. Further investigations of the elaboration of **11** are currently underway and will be reported in due course.

To complete the total synthesis, the pyridone ring was constructed via a one-pot transformation. Thus, Michael addition of sulfinylamide **17** to the enone moiety afforded a diastereomeric mixture of adducts **18**, which, upon treatment with hydrochloric acid in methanol, underwent cyclization and desulfination to form the pyridone ring, affording lyconadin A (**1**).

In summary, the total synthesis of lyconadin A was accomplished in 11 steps (via the nitrosoalkene; 8.1% overall yield) or 13 steps (via the sulfide; 11.6% overall yield) from known enone **4**. Our synthesis features the facile construction of the highly fused tetracyclic compound **11** through a combination of an aza-Prins reaction and an electrocyclic ring opening. Transformation of the bromoalkene moiety in **11** via either a vinylogous Pummerer rearrangement or the formation and subsequent isomerization of the nitrosoalkene afforded enone **2**, from which the pyridone ring could be constructed.

Acknowledgment. We thank Prof. J. Kobayashi and Prof. T. Kubota at Hokkaido University for providing a sample of natural lyconadin A. This work was financially supported in part by Grants-in-Aid (20002004 and 22590002) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kobayashi, J.; Hirasawa, Y.; Yoshida, N.; Morita, H. *J. Org. Chem.* **2001**, *66*, 5901.
(2) For recent reviews of Lycopodium alkaloids, see: (a) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679. (b) Kobayashi, J.; Morita, H. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York; 2005; Vol. 61, pp 1−57. (c) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752.
(3) Ishiuchi, K.; Kubota, T.; Hoshino, T.; Obara, Y.; Nakahata, N.; Kobayashi, J. *Bioorg. Med. Chem.* **2006**, *14*, 5995.
(4) (a) Grant, S. W.; Zhu, K.; Zhang, Y.; Castle, S. L. *Org. Lett.* **2006**, *8*, 1867. (b) Tracey, M. R.; Hsung, R. *Abstr. Pap.−Am. Chem. Soc.* **2003**, *226*, ORGN-721.
(5) (a) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2007**, *129*, 4148. (b) Beshore, D. C.; Smith, A. B., III. *J. Am. Chem. Soc.* **2008**, *130*, 13778. (c) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222. (d) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187.
(6) Gruver, J. M.; West, S. P.; Collum, D. B.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 13212.
(7) Koshiba, T.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2009**, *11*, 5354.
(8) (a) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755. (b) Nangia, A.; Prasuna, G. *Synth. Commun.* **1994**, *24*, 1989.
(9) (a) Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 11297. (b) Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M.; Taupin, V. *J. Org. Chem.* **2010**, *75*, 7519.
(10) (a) Anderson, J. C.; Blake, A. J.; Graham, J. P.; Wilson, C. *Org. Biomol. Chem.* **2003**, *1*, 2877. (b) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.
(11) Construction of a similar structure using an intramolecular Mannich reaction has been reported. See: (a) Scott, W. L.; Evans, D. A. *J. Am. Chem. Soc.* **1972**, *94*, 4779. (b) Cheng, X.; Waters, S. P. *Org. Lett.* **2010**, *12*, 205.
(12) The dibromocyclopropanation gave the product as a 5:1 mixture of diastereomers. The stereochemistry of the major diastereomer, which was determined by a NOESY experiment, proved that the reaction occurred mainly from the convex face.
(13) For a recent review of electrocyclic reactions of dibromocyclopropanes, see: Halton, B.; Harvey, J. *Synlett* **2006**, 1975.
(14) For a recent review of the Pummerer rearrangement, see: Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832.

JA109516F