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Total Synthesis of (−)-Lepistine

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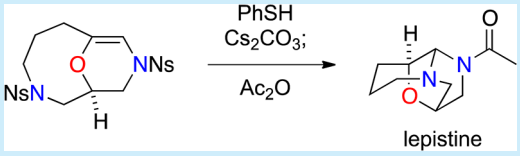
Supporting Information

ABSTRACT: The first total synthesis of (−)-lepistine has been accomplished in 11 steps from (*S*)-glycidol. The synthesis features construction of the 10-membered ring via an intramolecular epoxide opening by nosylamide, regioselective dehydration to form an enol ether, and construction of the aminal moiety induced by cleavage of the nosyl groups.



In 1975, Laing and co-workers isolated lepistine (**1**) as the major component in the mushroom *Clitocybe fasciculate*.[1] X-ray crystallography of its hydrobromide salt revealed that **1** is a tricyclic compound containing two nitrogen atoms and one oxygen atom in the skeleton (Figure 1). The two nitrogen

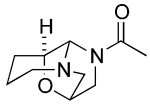
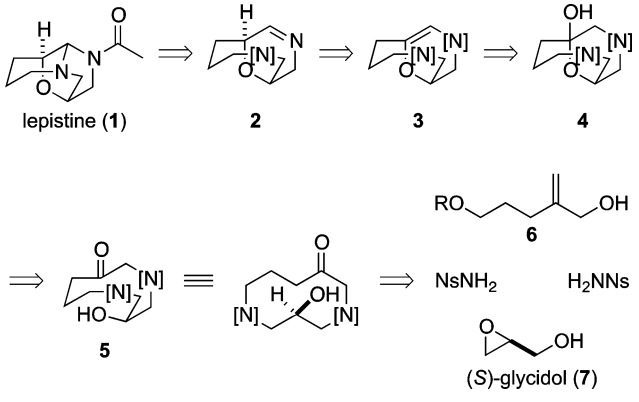


Figure 1. Structure of lepistine.

atoms constitute an aminal, which is substituted by an acetyl group. Although the unique, closely folded structure of **1** should have attracted the attention of organic chemists, no studies on lepistine, including synthesis, biological activity, or biosynthesis, have been reported to date. Herein we disclose the total synthesis of (−)-lepistine (**1**), featuring the facile construction of the tricyclic skeleton.

Our retrosynthetic analysis is illustrated in Scheme 1. The characteristic aminal moiety could be formed by intramolecular addition of a secondary amine to an imine. The requisite intermediate **2** could be derived from enamine **3**. The enamine

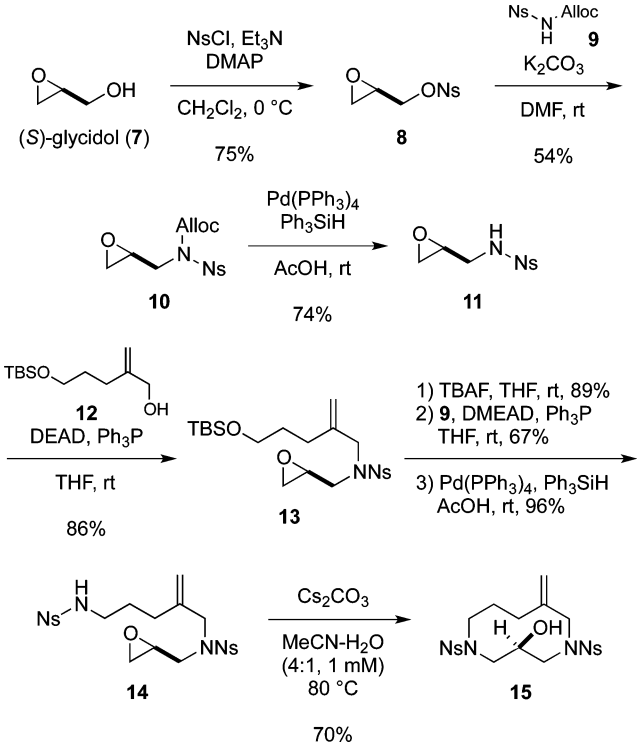
Scheme 1. Retrosynthetic Analysis



with an oxygen substituent could also be viewed as an enol ether, which in turn could be prepared via dehydration between a carbonyl and a hydroxy groups in **5**. The ketone moiety could be formed through oxidative cleavage of an olefin moiety. The 10-membered ring with a 1,3-diamino-2-propanol moiety could be constructed via sequential alkylations of nosylamides with alcohol unit **6** and glycidol (**7**).[2]

Our synthesis commenced with the construction of the 10-membered ring by using nosylamides (Scheme 2). (*S*)-Glycidol (**7**) was first converted into nosylate **8**,[3] which was treated with

Scheme 2. Construction of the 10-Membered Ring



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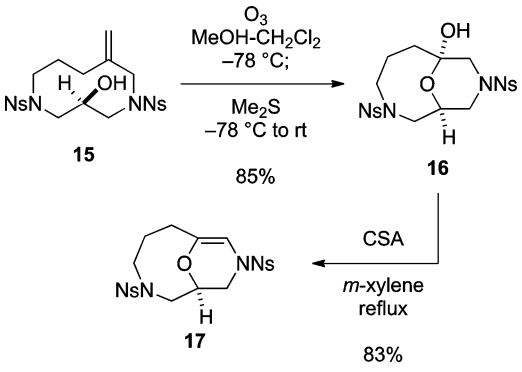
N-Alloc-*o*-nosylamide (**9**)[4] and potassium carbonate to give **10**.[5] Removal of the Alloc group by treatment with triphenylsilane and $Pd(PPh_3)_4$ in acetic acid furnished *N*-glycidyl-*o*-nosylamide (**11**),[6,7] which was subjected to the Mitsunobu reaction[8] with the known alcohol **12**[9] to give **13** in 86% yield.[10] After cleavage of the TBS ether with TBAF, another nosylamide moiety was installed via the Mitsunobu reaction with *N*-Alloc-*o*-nosylamide (**9**) to yield **14** upon cleavage of the Alloc group. Initial attempts at cyclizing the epoxynosylamide **14**[11] by treatment with cesium carbonate in acetonitrile at 80 °C for 24 h were met with difficulties, giving the desired product **15** in only 8% yield along with the recovered **14** (61%). During the course of the investigation, we found that using water as a cosolvent substantially accelerated the epoxide-opening reaction.[12] Thus, upon heating **14** with cesium carbonate in acetonitrile and water (4:1) at 80 °C for 24 h, cyclization proceeded smoothly to give **15** in 70% yield.[13]

Having constructed the 10-membered ring, we next attempted to form the enol ether (Scheme 3). Ozonolysis of

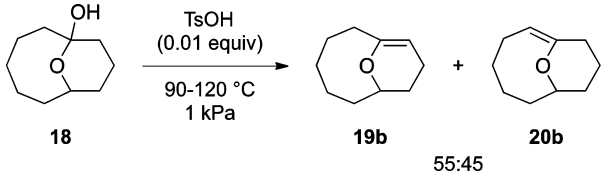
Scheme 3. Regioselective Formation of the Enol Ether



15 and subsequent workup with dimethyl sulfide afforded hemiacetal **16** in 85% yield. Dehydration of hemiacetal **16** was effected by treatment with CSA in refluxing *m*-xylene to give enol ether **17** in 83% yield with complete regioselectivity.

Meier and co-workers reported that dehydration of bicyclic hemiacetal **18** produced a 55:45 mixture of regioisomers (Scheme 4),[14] suggesting that the nitrogen atom in **17** might

Scheme 4. Meier's Report



play an important role in stabilizing the olefin by means of conjugation of the lone pair.[15] Thus, DFT calculations of the related compounds were carried out to evaluate the relative stability.[16] The results strongly suggested the importance of the nitrogen atom for the relative stability of the isomers (Table 1). From the viewpoint of the carbon skeleton, the undesired isomer **20a** is more energetically favorable than the desired one **19a** (entry 1). The isomers with an ether bridge (entry 2, **19b** and **20b**) have almost the same energies, which is consistent with the Meier's report.[14] Between the isomers with a nitrogen atom (entry 3, **19c** and **20c**), the desired isomer **19c** is more

Table 1. Relative Stability of Enol Ethers at the Bridgehead Position

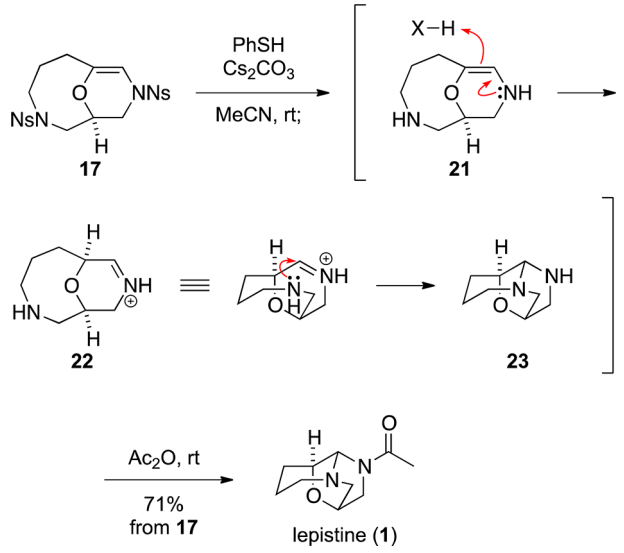
entry	X	Y	Z	isomers	ΔE^a (kcal/mol)
1	CH_2	CH_2	CH_2	**19a, 20a**	−3.40
2	CH_2	O	CH_2	**19b, 20b**	−0.21
3	CH_2	CH_2	NH	**19c, 20c**	+2.59
4	CH_2	O	NH	**19d, 20d**	+3.11
5	NH	O	NH	**19e, 20e**	+3.16
6	CH_2	O	NSO_2Ph	**19f, 20f**	+3.00

$^a\Delta E = E_{20} - E_{19}$.

favorable by 2.59 kcal/mol. Isomer **19d** or **19e** having one or two nitrogen atoms with the ether bridge is more stable than the other isomer **20d** or **20e**, respectively (entries 4 and 5). A sulfonyl group on the nitrogen atom has a negligible effect on the relative stability (entry 6).

Finally, penultimate intermediate enol ether **17** was converted into lepistine (Scheme 5). Both nosyl groups were

Scheme 5. Completion of the Synthesis



cleaved under the standard conditions to induce protonation of the liberated enamine from the less hindered side. Subsequent addition of the secondary amine to the resulting iminium ion occurred to give tricyclic aminal **23**. Since the highly polar nature of aminal **23** resisted efficient isolation, one-pot acetylation was carried out by adding acetic anhydride to afford (−)-lepistine (**1**) in 71% yield.[17]

In summary, the total synthesis of (−)-lepistine has been accomplished in 11 steps from (*S*)-glycidol (**7**). Our synthesis features construction of the 10-membered ring via an intramolecular epoxide opening by nosylamide, regioselective dehydration to form the enol ether, and construction of the aminal moiety induced by cleavage of the nosyl groups under mild conditions.

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■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

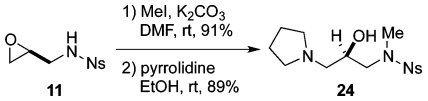
(1) Laing, M.; Warren, F. L.; White, E. P. *Tetrahedron Lett.* **1975**, *16*, 269.

(2) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 697.

(3) Shiratsuchi, M.; Kawamura, K.; Akashi, T.; Ishihama, H.; Nakamura, M.; Takenaka, F. *Chem. Pharm. Bull.* **1987**, *35*, 3691.

(4) (a) Fukuyama, T.; Cheung, M.; Kan, T. *Synlett* **1999**, 1301. (b) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

(5) The absolute configuration of **11** was determined after a two-step conversion into **24** by the modified Mosher's method. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. For details, see the Supporting Information. These results unambiguously exclude the reaction pathway via cleavage of the epoxide with **9**.



11 **24**

(6) Although the Alloc group could be cleaved in the absence of triphenylsilane, *N*-allylation of the product occurred during the workup. Using secondary amines such as pyrrolidine as nucleophiles caused the undesired cleavage of the epoxide.

(7) Yamamoto and co-workers reported the synthesis of *N*-glycidyl-*p*-nosylamide via Hf(IV)-catalyzed enantioselective epoxidation of *N*-allyl-*p*-nosylamide in 13% yield and 89% ee. The poor yield of the product may be due to the electron-withdrawing nature of the *p*-nosyl group, which can lower the reactivity of the olefin: Olivares-Romero, J. L.; Li, Z.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 5440.

(8) Mitsunobu, O. *Synthesis* **1981**, 1.

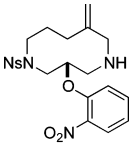
(9) (a) Perreault, S.; Rovis, T. *Synthesis* **2013**, *45*, 719. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421.

(10) The optical purity of **13** was >99% ee, which was confirmed by HPLC. For details, see the Supporting Information.

(11) For intramolecular epoxide opening reactions by sulfonamides, see: (a) Moulines, J.; Bats, J.-P.; Hautefaye, P.; Nuhrich, A.; Lamidey, A.-M. *Tetrahedron Lett.* **1993**, *34*, 2315. (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137. (c) Zhai, H.; Luo, S.; Ye, C.; Ma, Y. *J. Org. Chem.* **2003**, *68*, 8268. (d) Kokotos, C. G.; Aggarwal, V. K. *Chem. Commun.* **2006**, 2156.

(12) Acceleration of epoxide opening reactions in protic solvents has been reported. (a) Azizi, N.; Saidi, M. R. *Org. Lett.* **2005**, *7*, 3649. (b) Vilotijevic, I.; Jamison, T. F. *Science* **2007**, *317*, 1189. (c) Shimokawa, J.; Harada, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 17634.

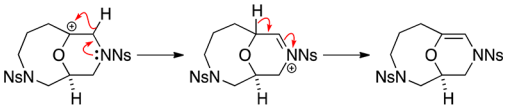
(13) Smiles rearrangement of **15**, leading to **25**, was also found to be a serious problem in the reaction. Addition of water as a cosolvent effectively inhibited the Smiles rearrangement of **15**. For details, see the Supporting Information. For Smiles rearrangement of 2- or 4-nitrobenzenesulfonamides, see: (a) Knipe, A. C.; Sridhar, N.; Loughran, A. *J. Chem. Soc., Chem. Commun.* **1976**, 630. (b) Yilmaz, I.; Shine, H. J. *J. Labelled Compd. Radiopharm.* **2006**, *25*, 1157. (c) Pizzirani, D.; Kaya, T.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2010**, *12*, 2822.



25

(14) Krämer, G.; Detert, H.; Meier, H. *Heterocycles* **2009**, *78*, 2201.

(15) Another explanation for the regioselectivity involves a 1,2-hydride shift of oxocarbenium ion **26**, leading to *N*-sulfonyliminium ion **27**, deprotonation of which gives **17**.



26 **27** **17**

(16) Conformational searches were carried out using the Conflex program at the molecular mechanics level using the MMFF force field. For the Conflex program, see: (a) Goto, H.; Osawa, E. *J. Am. Chem. Soc.* **1989**, *111*, 8950−8951. (b) Goto, H.; Osawa, E. *J. Chem. Soc., Perkin Trans. 2* **1993**, 187−198. All conformers were computed using the functional B3LYP and the 6-31G(d) basis sets as implemented in Spartan '10.

(17) The structure of the product was confirmed by ^{1}H and ^{13}C NMR, COSY, HMQC, HMBC, HRMS, and IR. Lepistine is observed as a 1:1 mixture of rotamers. Although the absolute configuration of the natural sample of lepistine was determined by X-ray crystallography (see ref 1), the optical rotation has not been reported.