## Synthesis of ( $\pm$ )-7-Hydroxylycopodine

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ABSTRACT



A six step synthesis of  $(\pm)$ -7-hydroxylycopodine has been achieved in 5% overall yield. In the key step, a Prins cyclization of a bicyclic keto alkyne in 60% H<sub>2</sub>SO<sub>4</sub> forms a tricyclic dihydroxy amino ketone.

Sauroine (**3**, 7,8-dihydroxylycopodine), from *Huperzia* saururus,<sup>1a</sup> was reported in 2004 and shown in 2009 to improve memory retention in the step-down test in male Wistar rats, significantly increasing hippocampal plasticity (see Scheme 1).<sup>1b</sup> The lycopodium alkaloids are a large and extensively studied alkaloid family.<sup>2</sup> Huperzine A, the medicinally most significant lycopodine alkaloid as a potential treatment for Alzheimer's disease, functions as an acetyl-cholinesterase inhibitor but may have other roles as has been addressed in several recent reviews.<sup>3</sup>



Lycopodine (1) has been synthesized many times over the past 40 years<sup>4</sup> but is still a significant target with the first synthesis in optically pure form reported by Carter in 2008.<sup>4j</sup> 8-Hydroxylycopodine (2, clavolonine) has been known for many years and has been synthesized by Wenkert in racemic form and recently by Evans and Breit in optically pure form.<sup>5</sup> 7-Hydroxylycopodine (4) was

(3) For recent reviews on huperzine A for treatment of Alzheimer's disease, see: (a) Hostettmann, K.; Borloz, A.; Urbain, A.; Marston, A. *Curr. Org. Chem.* **2006**, *10*, 825–847. (b) Zhu, D.-Y.; Tan, C.-H.; Li, Y.-M. In *Medicinal Chemistry of Bioactive Natural Products*; Liang, X.-T., Fang, W.-S., Eds.; WILEY-VCH: New York, 2006; pp 143–182. (c) Bai, D. *Pure Appl. Chem.* **2007**, *79*, 469–479. (d) Little, J. T.; Walsh, S.; Aisen, P. S. *Exp. Opin. Invest. Drugs* **2008**, *17*, 209–215. (e) Desilets, A. R.; Gickas, J. J.; Dunican, K. C. Ann. Pharmacother. **2009**, *43*, 514–518.

(4) (a) Stork, G.; Kretchmer, R. A.; Schlessinger, R. H. J. Am. Chem. Soc. 1968, 90, 1647–1648. (b) Ayer, W. A.; Bowman, W. R.; Joseph, T. C.; Smith, P. J. Am. Chem. Soc. 1968, 90, 1648–1650. (c) Kim, S.; Bando, Y.; Horii, Z. Tetrahedron Lett. 1978, 2293–2294. (d) Heathcock, C. H.; Kleinman, E. F.; Binkley, E. S. J. Am. Chem. Soc. 1982, 104, 1054–1068. (e) Schumann, D.; Müller, H.-J.; Naumann, A. Liebigs Ann. Chem. 1982, 1700–1705. (f) Kraus, G. A.; Hon, Y. S. J. Am. Chem. Soc. 1985, 107, 4341–4342. Heterocycles 1987, 25, 377–386. (g) Padwa, A.; Brodney, M. A.; Marino, J. P.; Sheehan, S. M. J. Org. Chem. 1997, 62, 78–87. (h) Greico, P. A.; Dai, Y. J. J. Am. Chem. Soc. 1998, 120, 5128– 5129. (i) Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. Angew. Chem., Int. Ed. 1998, 37, 636–637. (j) Yang, H.; Carter, R. G.; Zakharov, L. N. J. Am. Chem. Soc. 2008, 130, 9238–9239. (k) Yang, H.; Carter, R. G. J. Org. Chem. 2010, 75, 4929–4938. (l) For a review of Iycopodine syntheses, see: Hudlický, T.; Reed, J. W. The Way of Synthesis; Wiley-VCH: Weinheim, 2007; pp 573–602.

(5) (a) Wenkert, E.; Broka, C. A. J. Chem. Soc., Chem. Commun. 1984, 714–715. (b) Evans, D. A.; Scheerer, J. R. Angew. Chem., Int. Ed. 2005, 44, 6038–6042. (c) Laemmerhold, K. M.; Breit, B. Angew. Chem., Int. Ed. 2010, 49, 2367–2370.

<sup>(1) (</sup>a) Ortega, M. G.; Agnese, A M.; Cabrera, J. L. *Tetrahedron Lett.* **2004**, *45*, 7003–7005. (b) Vallejo, M. G.; Ortega, M. G.; Cabrera, J. L.; Carlini, V. P.; Rubiales de Barioglio, S.; Almiron, R. S.; Ramirez, O. A.; Agnese, A. M. *J. Nat. Prod.* **2009**, *72*, 156–158; note that the methyl group of sauroine is attached to the wrong carbon.

<sup>(2)</sup> For recent reviews on lycopodium alkaloids, see: (a) Kobayashi, J.; Morita, H. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Elsevier: San Diego, CA, 2005; Vol. 61, pp 1–57. (b) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752–772. (c) Hirasawa, Y.; Kobayashi, J.; Morita, H. *Heterocycles* **2009**, *77*, 679–729.

Scheme 1. Retrosynthesis of 7-Hydroxylycopodine



reported in 2004.<sup>6</sup> The bridgehead hydroxy group of sauroine (**3**) and 7-hydroxylycopodine (**4**) precludes the use of most of the methods that have been developed for lycopodine and clavolonine synthesis, but they also make aldol and Prins approaches more attractive. We decided to synthesize 7-hydroxylocopodine (**4**) first and then modify that route to prepare sauroine (**3**) with the additional 8-hydroxy group so that these molecules will be available for further biological evaluation.

We planned to construct the final ring of **4** from dihydroxy ketone **5** by a modified Oppenauer oxidation—aldol reaction sequence as developed by Heathcock in his lycopodine synthesis<sup>4d</sup> (see Scheme 1) and later used by Kraus and Carter.<sup>4f,j,k</sup> We planned to prepare the  $\beta$ -hydroxycyclohexanone of **5** from diketone **6** by an intramolecular aldol reaction. The 2-oxopropyl side chain of **6** should be available by Wacker oxidation of the allyl side chain of **7**, which will be prepared by hydrolysis of enol ether **8**. This route is appealing because Wiesner reported an efficient synthesis of **15**, the analogue of **8** with an *N*-methyl substituent.<sup>7b</sup> We were concerned about the stereochemistry of the ring fusion that will be introduced by protonation of the enol ether of **8** because related work from Wiesner's laboratory led to the synthesis of 12-epilycopodine.<sup>7c,d</sup> Nevertheless, the brevity of this approach was very appealing.

Before addressing the synthesis of **5**, we chose to carry out a model study for the preparation of the tricylic framework with an *N*-methyl rather than a protected *N*-hydroxypropyl group. Reaction of 3-bromopropylamine hydroScheme 2. Unsuccessful Approach to Diketone



bromide (9), 5-methyl-1,3-cyclohexanedione (10), and 2,6lutidine in ethanol at 130 °C afforded the enamide which underwent an intramolecular alkylation to give racemic 11 (see Scheme 2).<sup>7b,8,9</sup> Alkylation of 11 with iodomethane using NaH in THF gave 12 in 48% yield from 10. Following Wiesner's procedure, vinylogous amide 12 was heated in isopropyl iodide at 55 °C for 42 h to provide cation 13, which was treated with allylmagnesium bromide to give 15 in 55% yield from 12. Hydrolysis of the enol ether of 15 with 1 M hydrochloric acid afforded a 1.7:1 mixture of stereoisomeric ketones in 77% yield. Unfortunately, we were unable to prepare 18 by a Wacker oxidation of keto amino alkene 15, although amino alkenes have been successfully oxidized to amino methyl ketones.<sup>10</sup>

We then attempted to prepare methyl ketone 18 by hydrolysis of alkyne 14. Addition of propargylmagnesium bromide to cation 13 gave ketone 14 in 42% yield from 12. Hydration of the triple bond of 14 with HgO in 1:1 MeOH/ 1 M aqueous  $H_2SO_4$  at 65 °C also failed to give the desired methyl ketone 18. Instead we obtained dienone 16 in 39% yield. A plausible mechanism for the formation of 16 involves the desired hydration of the alkyne to give 18, which under the acidic conditions undergoes a retro conjugate addition to give amino diketone 17. Condensation

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<sup>(9)</sup> For the preparation of related vinylogous amides by this method, see: (a) Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J., III. J. Org. Chem. 1993, 58, 1935–1938.
(b) Zhao, Y.; Zhao, J.; Zhou, Y.; Lei, Z.; Li, L.; Zhang, H. New J. Chem. 2005, 29, 769–772.

<sup>(10)</sup> For examples of Wacker oxidations in the presence of an amine, see: (a) Li, W.-D.; Wang, Y.-Q. Org. Lett. 2003, 5, 2931–2934. (b) Berry, M. B.; Craig, D.; Jones, P. S.; Rowlands, G. J. Beilstein J. Org. Chem. 2007, 3, no. 39.

Scheme 3. Synthesis of Model Tricyclic Hydroxy Ketone 24



of the amine with the cyclohexanone will then give the fully conjugated  $\delta$ -amino dienone 16. This suggests that decomposition of 18 might be responsible for the failure of the Wacker oxidation of 15.

Fortunately, the alkyne of 14 provided us with another method to form the desired tricyclic hydroxy ketone 5. Wiesner reported that reaction of 15 in 75% H<sub>2</sub>SO<sub>4</sub> for 12 h afforded 22 in 70% yield as a single isomer with unknown regio- and stereochemistry. Hydrolysis of enol ether 15 afforded ketone 19, which underwent a Prins cyclization to give secondary cation 20 (see Scheme 3). A 1,5-hydride shift afforded tertiary cation 21, which lost a proton to give **22**. The desired stereochemistry with a  $\beta$ -hydrogen, which would result from formation of trans-fused bicylic ketone 19, was suggested on the basis of kinetic and thermodynamic conformational arguments. However, later work from this group leading to two syntheses of the undesired 12-epi-lycopodine<sup>7c,d</sup> raises questions about this stereochemical suggestion. Amino alkene 22 is not useful for lycopodine synthesis because the functionality is now in the wrong ring.

We decided to subject alkyne **14** to these acidic conditions with the hope that hydrolysis of the enol ether and cyclization would give vinyl cation **23** analogously to the formation of secondary cation **20**. A 1,5-hydride shift cannot occur in **23** because the hydrogen is too far from the vacant Scheme 4. Synthesis of 7-Hydroxylycopodine (4)



sp<sup>2</sup> orbital. Cation **23** should react with water to give an enol that will tautomerize to the desired tricylic ketone **24**. We were delighted to find that reaction of **14** in 60% aqueous H<sub>2</sub>SO<sub>4</sub> for 8 h afforded tricylic amino hydroxy ketone **24** in 70% yield. Prins reactions with alkynes are uncommon but known.<sup>11</sup> The isolation of  $\beta$ -hydroxy ketones from Prins reactions of keto alkynes is not usually observed but occurs here because ring strain prevents dehydration to form the enone with a bridgehead double bond. The stereochemistry of **24** was assigned from NOE studies as described in detail in the Supporting Information. The stereoisomer derived from the cis-fused bicyclic ketone was not formed, possibly because the trans-fused bicyclic ketone is 1.4 kcal/mol more stable than the cis isomer as determined by molecular mechanics calculations.

For the synthesis of 7-hydroxylycopodine precursor **5** we simply needed to replace the methyl group of **14** with a 3-hydroxypropyl group. Crude enaminoketone **11** was alkylated with  $I(CH_2)_3OTBS^{12}$  using NaH in 1:1 THF/DMF for 18 h at 25 °C to give **25** in 50% yield from

<sup>(11)</sup> For examples of Prins additions of ketones and aldehydes to alkynes, see: (a) Rodini, D. J.; Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 3857–3860. (b) Keirs, D.; Overton, K.; Thakker, K. J. Chem. Socy, Chem. Commun. **1990**, 310–311. (c) Harding, C. E.; King, S. L. J. Org, Chem. **1992**, 57, 883–886. (d) Wempe, M. F.; Grunwell, J. R. J. Org. Chem. **1995**, 60, 2714–2720. (e) Balog, A.; Geib, S. J.; Curran, D. P. J. Org. Chem. **1995**, 60, 345–352. (f) Rhee, J. U.; Krische, M. J. Org. Lett. **2005**, 7, 2493–2495. (g) Jin, T.; Yamamoto, Y. Org. Lett. **2007**, 9, 5259–5262. (h) Miranda, P. O.; Ramírez, M. A.; Martín, V. S.; Padrón, J. I. Chem.—Eur. J. **2008**, *14*, 6260–6268. (i) Chavre, S. N.; Choo, H.; Lee, J. K.; Pae, A. N.; Kim, Y.; Cho, Y. S. J. Org. Chem. **2008**, *73*, 7647–7471.

cyclohexanedione 10 (see Scheme 4). A solution of 25 in 2-iodopropane was heated at 55 °C for 42 h to give the intermediate cation 26, which was treated with propargylmagnesium bromide to give 27a in 40% yield from 25. Stirring 27a in 60% aqueous H<sub>2</sub>SO<sub>4</sub> for 8 h at 25 °C afforded the desired tricylic dihydroxy ketone 5 in 48% yield. The sequence was improved by adding trimethylsilylpropargyllithium, prepared by deprotonation of 1-trimethylsilylpropyne with *n*-BuLi, to cation 26 to give 27b in 51% yield. Stirring 27b in 60% sulfuric acid for 10 h at 25 °C afforded 5 in 50% yield. The stereochemistry of 5 was established by NOE studies as detailed in the Supporting Information. During the conversion of 27b to 5, the enol ether is hydrolyzed, the TBS ether and TMS alkyne are deprotected, and the keto alkyne undergoes the Prins reaction to form the third ring.

The modified Oppenauer oxidation—aldol reaction of **5** with benzophenone and KO-*t*-Bu using conditions developed by Heathcock in his lycopodine synthesis for the oxidation of the analogue of **5** lacking the tertiary hydroxy group gave a complex mixture containing  $\sim 5\%$  of the desired enone **29**.<sup>4d,13</sup> We suspect that a retro aldol reaction of the  $\beta$ -hydroxy ketone occurred under the strongly basic conditions. We eventually found that the primary alcohol could be selectively oxidized to the aldehyde with *t*-BuOMgCl and azodicarbonyldipiperidine in THF,<sup>14</sup> but all attempts to carry out the aldol reaction resulted in a retro conjugate addition with loss of acrolein to form the tricyclic secondary amine.

We therefore decided to protect the tertiary alcohol and re-examine the modified Oppenauer oxidation-aldol

(14) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. Bull. Chem. Soc. Jpn. **1977**, 50, 2773–2776.

(15) (a) Yamada, K.; Kato, K.; Nagase, H.; Hirata, Y. *Tetrahedron Lett.* **1976**, 65–66. (b) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031–1040.

reaction sequence. Both alcohol groups of 5 were differently protected in a single reaction to give 28 in 90% yield by stirring 5 for 12 h in Ac<sub>2</sub>O to form the primary acetate and adding DMSO and continuing stirring for 72 h to form the methylthiomethyl ether of the tertiary alcohol.<sup>15</sup> Keto acetate 28 was treated with KO-t-Bu (6 equiv) and benzophenone (16 equiv) in carefully degassed benzene at 110 °C for 1 h. Under these conditions, the acetate is cleaved. the resulting primary alcohol is oxidized to the aldehyde, and the aldol reaction occurs to form the enone. The methylthiomethyl protecting group is cleaved with 3 M hydrochloric acid during the workup to give 29 in 47% yield. Hydrogenation of enone 29 over PtO<sub>2</sub> with 1 atm of  $H_2$  for 10 h afforded 7-hydroxylycopodine (4) in 95% yield. The spectral data for the hydrochloride salt of 4 in CD<sub>3</sub>OD are identical to those reported for the natural product.<sup>6</sup>

In conclusion, we have developed a practical six step synthesis of  $(\pm)$ -7-hydroxylycopodine (4) that proceeds in a 5% overall yield making it readily available for further biological evaluation. The key step is the Prins reaction of **27a** or **27b** that proceeds in 60% H<sub>2</sub>SO<sub>4</sub> to give tricyclic dihydroxy amino ketone **5**. We are currently investigating methods to prepare the starting vinylogous amide **11** in optically pure form and to introduce a hydroxy group adjacent to the carbonyl group of **25** to give an intermediate that will be elaborated analogously to sauroine (**3**, 7,8dihydroxylycopodine).

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**Supporting Information Available.** Complete experimental procedures and copies of <sup>1</sup>H and <sup>13</sup>C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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