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Synthesis of Aza Bicyclic Enones via Anionic Cyclization: Application to the Total Synthesis of (–)-Brunsvigine

Chin-Kang Sha,* An-Wei Hong, and Chien-Ming Huang

Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan, ROC

cksha@mx.nthu.edu.tw

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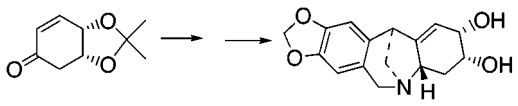
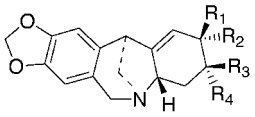
ABSTRACT



(-)-brunsvigine

A general approach to the synthesis of aza bicyclic enones was developed via a simple two-step annulation involving a Mitsunobu protocol and anionic cyclization. According to this strategy the total synthesis of (–)-brunsvigine was accomplished with 12% overall yield.

Montanine-type alkaloids first isolated[1] by Wildman et al. in 1955 belong to a subclass of *Amaryllidaceae* alkaloids. These natural products **1**−**6** have the core structure of the 5,11-methanomorphanthridine ring system and differ only in the configurations of stereocenters at C-2 and C-3.[2]



1-6

	R_1	R_2	R_3	R_4	
1	H	OH	H	OH	(-)-brunsvigine
2	H	OH	OH	H	(-)-pancracine
3	H	OMe	OH	H	(-)-montanine
4	H	OMe	OMe	H	(-)-manthine
5	H	OMe	OAc	H	(-)-*O*-acetylmontanine
6	OMe	H	OH	H	(-)-coccinine

Because of this interesting pentacyclic ring structure and promising pharmacological potential, these alkaloids attract much synthetic effort. Hoshino et al. reported[3] the first total synthesis of racemic montanine, coccinine, pancracine, brunsvigine, and *O*-acetylmontanine, using reductive cyclization as a key step to assemble the pentacyclic unit. Overman and Shim developed an elegant total synthesis of racemic pancracine employing an aza-Cope rearrangement and Mannich cyclization.[4] Weinreb and Jin reported an enantioselective synthesis of (−)-coccinine and (−)-pancracine via a concerted ene reaction of allenylsilane imines.[5] Total synthesis of (+)-coccinine, a nonnatural enantiomer of (−)-coccinine was reported by Pearson and Lian who undertook cycloaddition of a 2-azaallyl anion.[6] Ikeda et al. reported a formal total synthesis of racemic pancracine based on α-carbonyl radical cyclization.[7] We reported an anionic cyclization approach to the synthesis of 5*H*-perhydroindol-3-ones.[8] As a continuation of our work in this area, we report in this Letter the first total synthesis of (−)-brunsvigine via anionic cyclization[9] of the Weinreb amide intermediate **19**.

(1) (a) Wildman, W. C.; Kaufman, C. J. *J. Am. Chem. Soc.* **1955**, *77*, 1249. (b) Dry, L. J.; Poynton, M. E.; Thompson, M. E.; Warren, F. L. *J. Chem. Soc.* **1958**, 4701. (c) Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153. (d) Wildman, W. C.; Brown, C. L. *J. Am. Chem. Soc.* **1968**, *90*, 6439.

(2) (a) Martin, S. F. The Amaryllidaceae Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1987; Vol. 30, p 252. (b) Lewis, J. R. *Nat. Prod. Rep.* **1993**, *10*, 291. (c) Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

(3) (a) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079. (b) Ishizaki, M.; Hoshino, O. *J. Org. Chem.* **1992**, *57*, 7285. (c) Ishizaki, M.; Kurihara, K.-i.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101.

(4) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

(5) (a) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050. (b) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773.

(6) Pearson, W. H.; Lian, B. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1724.

(7) Ikeda, M.; Hamada, M.; Yamashita, T.; Ikegami, F.; Sato, T.; Ishibashi, H. *Synlett* **1998**, 1246.

(8) Sha, C.-K.; Huang, S.-J.; Huang, C.-M.; Hong, A.-W.; Jeng, T.-H. *Pure Appl. Chem.* **2000**, *72*, 1773.

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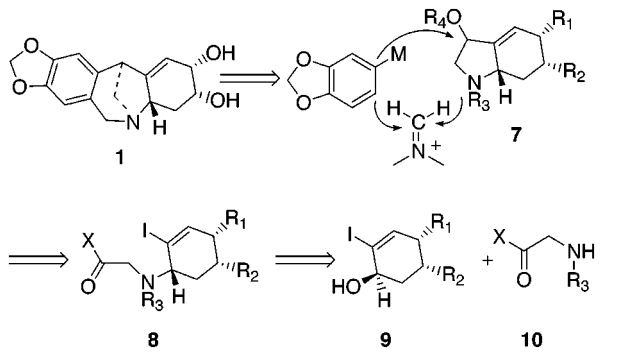
Our retro-synthetic analysis, Scheme 1, would require a facile method for the synthesis of perhydroindole **7**. We envisioned that coupling of an aryl organometallic species

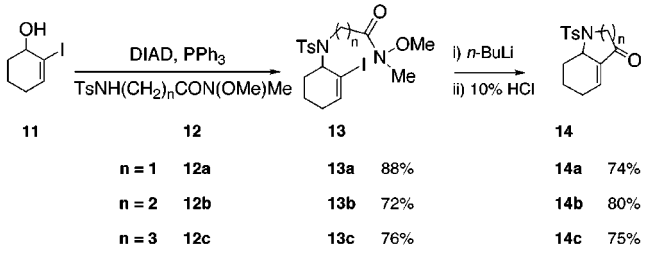
Scheme 1



with perhydroindole **7** followed by a Pictet−Spengler cyclization would provide the core structure of brunsvigine and related natural products **2**−**6**. Compound **7** could be prepared from iodo allylic alcohol **9** and a glycine unit **10** via Mitsunobu coupling (**9** + **10** → **8**) followed by anionic cyclization (**8** → **7**).

We began our investigation with the development of an efficient synthesis of perhydroindolone skeleton **14** (Scheme 2). Allylic alcohol **11**[10] was first converted into the required

Scheme 2

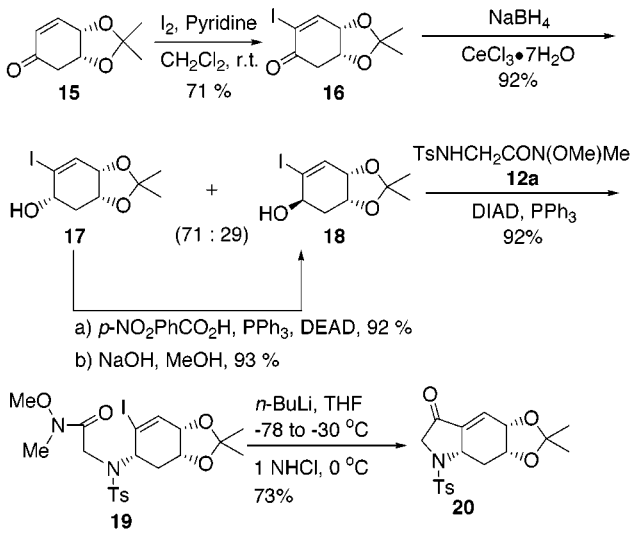


11	**12**	**13**		**14**	
	n = 1 **12a**	**13a**	88%	**14a**	74%
	n = 2 **12b**	**13b**	72%	**14b**	80%
	n = 3 **12c**	**13c**	76%	**14c**	75%

Weinreb amide intermediate **13a** using a Mitsunobu protocol.[11] Treatment of **13a** with *n*-BuLi affected metalation and anionic cyclization to give perhydroindolone **14a** in 74% overall yield. Similarly, compound **11** was reacted with compounds **12b** and **12c** to afford compounds **13b** and **13c**. Metalation of **13b** and **13c** followed by anionic cyclization gave perhydroquinolone **14b** and perhydrobenzazepinone **14c** in 80% and 75% yields, respectively. These perhydroquinolone and perhydrobenzazepinone skeletons are the core structures of several important classes of natural products, including the *Aspidosperma* and *Stemona* alkaloids.[12]

Having developed a reliable procedure for synthesis of perhydroindolone unit **14a**, we turned our attention to the total synthesis of (−)-brunsvigine. Required chiral enone **15** was obtained from (−)-quinic acid in five steps using published procedures.[13] Chiral enone **15** was then smoothly transformed into α-iodo enone **16** using Johnson's method.[14] Luche reduction[15] of iodo enone **16** in methanol at 0 °C afforded a mixture of epimeric allylic alcohols **17** and **18** in a ratio of 71:29 with 92% combined yield, Scheme 3.

Scheme 3



α-Isomer **17** was separated and converted into the required *β*-allylic alcohol **18** using Mitsunobu's procedure.[11b] Compound **18** was then reacted with compound **12a** under Mitsunobu's conditions to give **19** in 92% yield. When treated with *n*-BuLi under standard conditions, compound **19** underwent anionic cyclization to give enone **20** in 73% yield. Sodium borohydride reduction of chiral enone **20** under Luche conditions[15] afforded a single diastereomer, which was then converted into the corresponding pivaloate ester **21**, Scheme 4.

The stereochemistry of **21** was confirmed through single-crystal *X*-ray analysis.[16] CuI-promoted S_N2 displacement of

(9) Thebtaranonth, C.; Thebtaranonth, Y. *Cyclization Reactions*; CRC Press: Boca Raton, FL, 1994; Chapter 4, p 169.

(10) Compound **11** was obtained via Luche reduction (see ref 15) of 2-iodocyclohex-2-en-1-one, which was prepared via iodination of cyclohex-2-en-1-one according to Johnson's method (see ref 14).

(11) (a) Mitsunobu, O.; Jenkins, I. D.; in *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: New York, 1995; Vol. 8, p 5379. (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Uesaka, N.; Saitoh, F.; Mori, M.; Shibasaki, M.; Okamura, K.; Date, T. *J. Org. Chem.* **1994**, *59*, 5633.

(12) (a) Götz, M.; Strunz, G. M. In *Alkaloids*: *MTP International Review of Science*; Wiesnor, K., Ed.; Series 1; Butterworths: London, 1973; Vol. IX, p 143. (b) Hesse, M. In *Alkaloid Chemistry*; Wiley: New York, 1981; pp 41, 42, 176. (c) Ye, Y.; Qin, G.-W.; Xu, R.-S. *Phytochemistry* **1994**, *37*, 1201. (d) Rigby, J. H.; Laurent, S.; Cavezza, A.; Heeg, M. J. *J. Org. Chem.* **1998**, *63*, 5587.

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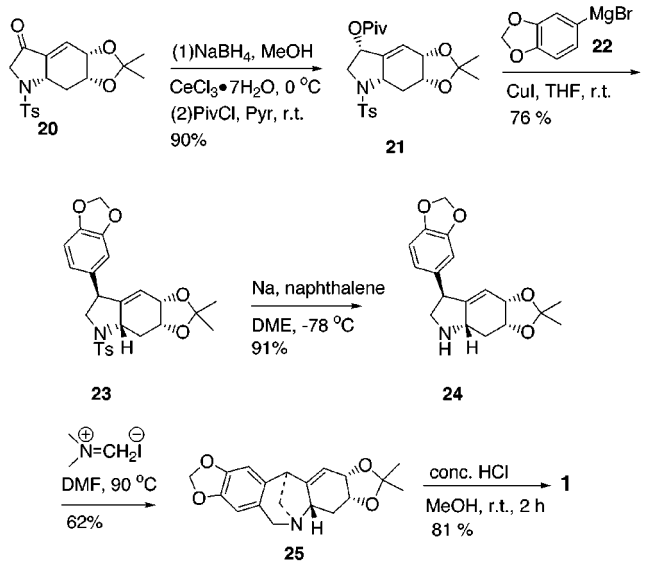
(15) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(16) X-ray data of compound **21** will be presented in a full paper.

Scheme 4



the pivaloate unit of **21** with arylmagnesium bromide **22** afforded compound **23** in 76% yield.[17] Removal of the tosyl group of **23** using sodium naphthalenide in DME at −78 °C produced amine **24**.[18] Treatment of **24** with Eschenmoser's salt[19] in DMF at 90 °C yielded compound **25**. Finally, cleavage of the acetal unit with concentrated HCl afforded (−)-brunsvigine in 12% overall yield from **15**. The optical rotation of **1** was measured, $[\alpha]_D = -76.3$ (lit. $[\alpha]_D = -76.6$).[1a,b]

In summary, we have developed an anionic cyclization approach for the synthesis of perhydroindolone **14a**, perhydroquinolinone **14b**, and perhydrobenzazepinone **14c** and applied this method for the first total synthesis of (−)-brunsvigine. Application of this method toward the total synthesis of *Stemona* alkaloids[12] is currently under investigation in our laboratory.

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