# Alkaloid Synthesis via Intramolecular Imino Diels–Alder Chemistry: Total Synthesis of (±)-Eburnamonine

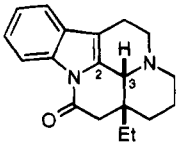
Michael D. Kaufman[1] and Paul A. Grieco*

*Ernest E. Campaigne and Marvin Carmack Laboratory of Organic Chemistry, Department of Chemistry, Indiana University, Bloomington, Indiana 47405*

*Received August 30, 1994*[⊗]

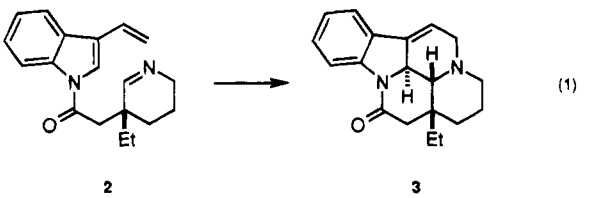
*Summary:* A novel strategy, featuring an intramolecular imino Diels–Alder reaction, for the construction of the pentacyclic framework of eburnamonine is detailed.

The pentacyclic skeleton common to the indole alkaloid eburnamonine (**1**) and related natural products has received considerable attention over the years. Since



**1**

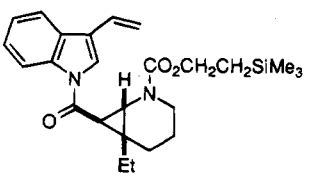
Wenkert's synthesis of racemic eburnamonine in 1965,[2] which established that the D–E ring fusion was cis, numerous total and formal syntheses of **1** have appeared in the literature.[3] With few exceptions,[3c,r] the vast majority of the published syntheses construct the C(2), C(3) carbon carbon bond via either a Pictet–Spengler or a Bischler–Napieralski cyclization. As a consequence, the majority of the syntheses of **1** have also led to the formation of *epi*-eburnamonine which possesses the trans ring fusion. In conjunction with our continuing interest in immonium ions as heterodienophiles for the Diels–Alder reaction,[4,5] we have developed a fundamentally different approach to the construction of the pentacyclic skeleton of eburnamonine (**1**) which is based on an intramolecular [4 + 2] cycloaddition of vinyl indole imine **2** (eq 1).[6] This strategy has been successfully applied to



**2** **3** (1)

a synthesis of racemic **1**.

Our plan for the elaboration of the imine functionality in vinyl indole imine **2** centered around the unmasking of a protected β-amino cyclopropanecarboxamide (cf. **4**)with concomitant opening of the cyclopropane leading



**4**

directly to **2**. The synthesis of the TEOC-protected β-amino cyclopropanecarboxyamide **4** commences with commercially available δ-valerolactam. Treatment of a 0.43 M solution of δ-valerolactam in anhydrous tetrahydrofuran with 2.0 equiv of *n*-butyllithium at 0 °C followed by sequential addition of ethyl iodide and β-(trimethylsilyl)ethyl 4-nitrophenyl carbonate[7] affords the TEOC-protected lactam **5** in 69% yield. Selective reduction of the amide carbonyl with lithium tri-*tert*-butoxyaluminum hydride at −50 °C followed by exposure to ethereal sulfuric acid provides eneamide **6** directly in 92% overall yield. Addition of ethyl diazoacetate to a suspension of copper bronze in neat eneamide **6** at 135 °C generates a separable mixture of the exo and endo cyclopropane esters **7** (R = Et) and **8** (R = Et) in 33% and 31% yield,

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1994.

(1) Abbott Predoctoral Fellow, 1993–1994.

(2) Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580.

(3) (a) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941. (b) Klatte, F.; Rosentreter, U.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 879. (c) Buzas, A.; Herrison, C.; Lavielle, G. *C. R. Acad. Sci. Ser. C* **1976**, *283*, 763. (d) Novak, L.; Rohaly, J.; Szantay, C. *Heterocycles* **1977**, *6*, 1149. (e) Cousterousse, G.; Buendia, J.; Toromanoff, E.; Martel, J. *Bull. Soc., Chim. Fr., Part 2* **1978**, 355. (f) Wenkert, E.; Hudlicky, T.; Showalter, H. D. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (g) Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540. (h) Bolsing, E.; Klatte, F.; Rosentreter, U.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1902. (i) Buzas, A.; Jacquet, J.-P.; Lavielle, G. *J. Org. Chem.* **1980**, *45*, 32. (j) Wenkert, E.; Halls, T.; Kwart, L.; Magnusson, G.; Showalter, H. D. *Tetrahedron* **1981**, *37*, 4017. (k) Irie, K.; Ban, Y. *Heterocycles* **1981**, *15*, 201. (l) Massiot, G.; Oliveira, F. S.; Levy, J. *Tetrahedron Lett.* **1982**, *23*, 177. (m) Imanishi, T.; Miyasha, K.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1982**, *30*, 1521. (n) Rahman, A.; Sultana, M. *Z. Naturforsch., B.* **1982**, *37*, 793. (o) Imanishi, T.; Miyashita, K.; Nakai, A.; Inoue, M.; Hanaoka, M. *Chem. Pharm. Bull.* **1983**, *31*, 1191. (p) Szabo, L.; Sapi, J.; Kalaus, G.; Argay, G.; Kalman, A.; Baitz-Gacs, E.; Tamas, J.; Szantay, C. *Tetrahedron*, **1983**, *39*, 3737. (q) Kalaus, G.; Malkieh, M.; Katona, I.; Peredy, M.; Koritsanszky, T.; Kalaman, A.; Szantay, C. *J. Org. Chem.* **1985**, *50*, 3760. (r) Magnus, P.; Pappalardo, P.; Southwell I. *Tetrahedron* **1986**, *42*, 3215. (s) Shono, T.; Matsumura, Y.; Ogaki, M.; Onomura, O. *Chem. Lett.* **1987**, 1447. (t) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953. (u) Wasserman, H.; Kuo, G. *Tetrahedron Lett.* **1989**, *30*, 873. (v) Karvinen, E.; Lounasmaa, M. *Heterocycles* **1992**, *34*, 1773. (w) Takano, S.; Yonaga, M.; Morimoto, M.; Ogasawarak, K. *J. Chem. Soc. Perkin Trans. 1* **1985**, 305. (x) Hakam, K.; Thielmann, M.; Thielmann, T.; Winterfeldt, E. *Tetrahedron* **1987**, *43*, 2035. (y) Node, M.; Nagasawa, H.; Fuji, K. *J. Am. Chem. Soc.* **1987**, *109*, 7901. (z) Node, M.; Nagasawa, H.; Fuji, K. *J. Org. Chem.* **1990**, *55*, 517. (aa) Meyers, A. I.; Romine, J.; Robichaud, A. J. *Heterocycles* **1990**, *30*, 339. (bb) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525.

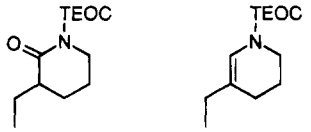
(4) (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553. (c) Grieco, P. A.; Larsen, S. D.; Fobare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975. (d) Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3325. (e) Grieco, P. A.; Parker, D. T. *Ibid.* **1988**, *53*, 3658. (f) Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, *29*, 5855.

(5) For a review of the imino Diels–Alder reaction see: Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, p 401.

(6) For the all carbon variant of the imino Diels–Alder reaction illustrated in eq 1 see: Eberle, M. K.; Shapiro, M. J.; Stucki, R. *J. Org. Chem.* **1987**, 4661. Simoji, Y.; Saito, F.; Tomita, K.; Morisawa, Y. *Heterocycles* **1991**, *32*, 2389. Simoji, Y.; Tomita, K.; Hashimoto, T.; Saito, F.; Morisawa, Y.; Mizuno, H.; Yorikane, R.; Koike, H. *J. Med. Chem.* **1992**, *35*, 816.

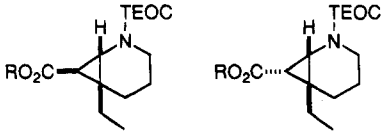
(7) Rosowsky, A.; Wright J. E. *J. Org. Chem.* **1983**, *48*, 1539. Carpino, L. A.; Tsao, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 358.

0022-3263/94/1959-7197$04.50/0 



5 6

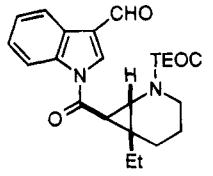
respectively.[8] Interestingly, treatment of a solution of



7 8

ester **8** (R = Et) in methylene chloride with 0.15 equiv of boron trifluoride etherate at 0 °C gives rise to an 84% isolated yield of **7** (R = Et) along with an 8% recovery of **8** (R = Et). The facile Lewis acid catalyzed transformation of **8** (R = Et) into **7** presumably occurs *via* the corresponding ketene immonium salt. Saponification of ester **7** (R = Et) gave rise to the corresponding acid in near quantitative yield.

The coupling of indole-3-carboxyaldehyde with carboxylic acid **7** (R = H) was best carried out by employing the activated *p*-nitrophenyl ester **7** (R = *p*-$NO_2C_6H_4$–), which was available in 86% yield from acid **7** (R = H) *via* a dicyclohexylcarbodimide facilitated esterification. Treatment of activated ester **7** (R = *p*-$NO_2C_6H_4$–) with 1.2 equiv of *N*-lithioindole-3-carboxaldehyde at −20 °C provides the coupled amide **9** in 77% yield. The desired



9

vinyl indole **4** was available from aldehyde **9** in 86% yield by treatment of a solution of **9** in tetrahydrofuran with triphenylphosphonium methylide at low temperature. The vinyl indole **4** proved to be quite sensitive at ambient temperature and was stored in solution at −78 °C.

In order to test our [4 + 2] cycloaddition strategy (eq 1) for the construction of the pentacyclic skeleton of eburnamonine, cleavage of the TEOC protecting group of **4** with subsequent opening of the cyclopropane was examined. The choice of fluoride source for cleavage of the (trimethylsilyl)ethyl carbamate proved critical. Use of tetra-*n*-butylammonium fluoride provided none of the desired imine **2**. However cesium fluoride in anhydrous dimethylformamide afforded imine **2** in 68%. Best results were obtained with benzyltrimethylammonium fluoride (BTAF)[9] in the presence of crushed 4Å molecular sieves. Addition of a solution of carbamate **4** in tetrahydrofuran to a suspension of BTAF-sieves in tetrahydrofuran gives rise after 8 h at 45 °C to an 81% yield of the sensitive imine **2**.

Having established a viable route to vinyl indole imine **2**, efforts were focused on the key cycloaddition process. Heating a solution of **2** in *o*-dichlorobenzene at 180 °C for 22 h provides cycloadduct **3**[10] as a crystalline compound, mp 119.0−120.5 °C, in 32% yield. No trace of eburnamonine could be detected. When **2** was exposed (3 h) to 1.1 equiv of trifluoroacetic acid in benzene at reflux, cycloadduct **3** was isolated in 70% yield along with 5% of eburnamonine **1**.[11] In an attempt to promote both the cycloaddition and the subsequent olefin isomerization, a 0.01 M solution of substrate **2** in 5.0 M lithium perchlorate−diethyl ether was treated with 10 mol % of camphorsulfonic acid.[12] No trace of eburnamonine was detected; however, a 96% yield of **3** was isolated. The isomerization of **3** into eburnamonine was carried out (12 h) at reflux in ethanolic sulfuric acid, providing crystalline **1**, mp 199.5-200.5 °C (lit.[2] mp 200−202 °C), in 80% yield.

**Acknowledgment.** This investigation was supported by a Public Health Service Research Grant from the National Institutes of General Medical Sciences (GM 33605).

**Supplementary Material Available:** Experimental and characterization data including NMR spectra (25 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) For an alternate synthesis of eburnamonine employing a cyclopropanated tetrahydropyridine, see 3t.

(9) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.

(10) Compound **3** crystallizes in space group $P\bar{1}$ with cell dimensions at −173 °C of $a$ = 8.697(5) Å, $b$ = 10.404(6) Å, $c$ = 8.507(5) Å, $\alpha$ = 93.60(3)°, $\beta$ = 99.66(3)°, $\gamma$ = 83.07(3)°, $V$ = 752.60 Å$^3$, $D_c$ 1.299 g cm$^{-1}$, $Z$ = 2. A total of 3125 reflections were measured of which 1955 were determined to be observable. All atoms, including hydrogens, were located and refined to find residuals of $R$(F) = 0.0400 and $R_w$(F) = 0.0454.

(11) During the course of purifying imine **2** on Florisil (Aldrich 200−300 mesh) a small amount of cycloadduct **3** was observed in what should have been a pure fraction of imine. Indeed, heating a 0.05 M solution of imine **2** in ethyl acetate containing an 8-fold excess of Florisil by weight gave rise after 9 h to an 82% yield of **3**. Imine **2** did not undergo the cycloaddition upon exposure to silica gel.

(12) Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663.