# Synthesis of Eburnamonine and Dehydroaspidospermidine[1]

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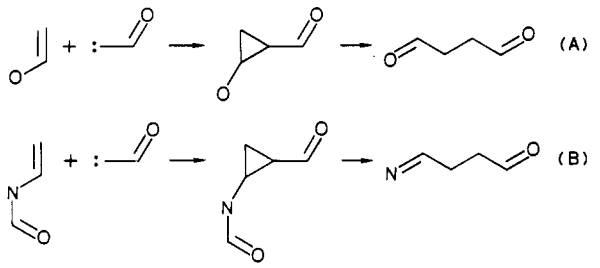
The route of synthesis of γ-imino carbonyl compounds by cyclopropanation of enamides and acid-catalyzed ring opening of the resultant β-amido cyclopropanecarboxylates has been applied to the preparation of substituted 1-piperideines and therefrom to the synthesis of the alkaloids eburnamonine, dehydroaspidospermidine, and aspidospermidine.

For some time the two-step preparation of γ-dicarbonyl compounds, outlined in the general reaction sequence A,

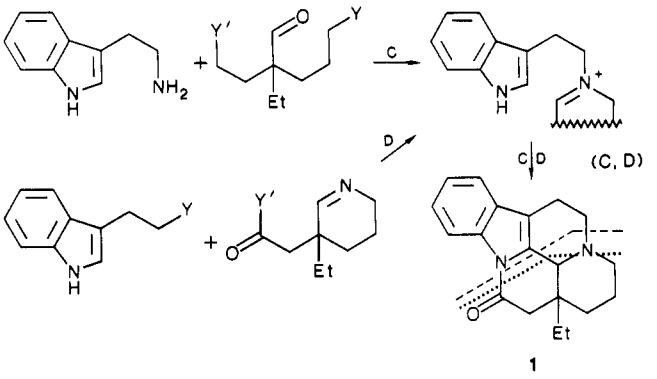



has served as the basis of synthesis of a number of natural products.[3] On one occasion it was applied to the construction of eburnamonine (1) and three Aspidosperma bases on recognition of the possibility of a uniquely substituted γ-dicarbonyl system undergoing interaction with tryptamine and multiple cyclization of the resultant iminium salt creating the desired alkaloid skeleton (Scheme I, sequence C).[4] This reaction scheme was founded on the view of the eburnamonine structure constituting a combination of two subunits, the basic nitrogen being attached to the indole-containing subunit (cf. dotted line in formula 1).

It now became of interest to introduce flexibility into the reaction scheme by operating on the general reaction sequence B for the two-step preparation of γ-imino carbonyl compounds.[5] This required the construction of a uniquely substituted γ-keto 1-piperideine, when applied to the synthesis of eburnamonine (1), and N-alkylation with a tryptophyl derivative, followed by multiple cyclization of the thus-formed iminium salt (sequence D). Such an approach to the alkaloid reflected the idea of the final structure being made up of two subunits, of which the non-indole subunit contained the basic nitrogen of the natural product (cf. dashed line in formula 1). Finally, dissection of the structurally complex Aspidosperma alkaloid dehydroaspidospermidine (2) into three subunits (cf. dotted lines in formula 2), one of which was the aforementioned γ-keto 1-piperideine, pointed to the possibility of the use of the latter intermediate also in the synthesis of dehydroaspidospermidine (2) (Scheme II, sequence E).

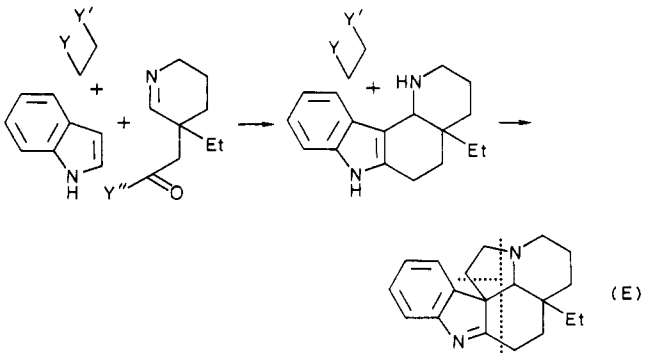
As the following discussion will reveal, the reaction sequences D and E could be realized and the scientific goals, the synthesis of eburnamonine and dehydroaspidospermidine by new reaction routes, achieved.

**Scheme I**




1

**Scheme II**




2

**Eburnamonine (13).**[6,7] The enamide needed to initiate reaction sequence B (and hence sequence D) was 1-carbomethoxy-3-ethyl-2-piperideine (**3c**). In view of its structural similarity with 3-acetyl-2-piperideine (**3a**), a compound obtained readily from commercially available β-acetylpyridine on hydrogenation,[8] the **3a** → **3c** transformation by reduction and acylation was envisaged as the simplest preparation of the desired enamide. However, despite the well-known conversion of N-unsubstituted or

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(3) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

(4) Wenkert, E.; Halls, T. D. J.; Kwart, L. D.; Magnusson, G.; Showalter, H. D. H. *Tetrahedron* **1981**, *37*, 4017 and references therein.

(5) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogoli, P. *J. Org. Chem.* **1977**, *42*, 3945.

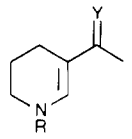
(6) For preliminary communications, see: (a) Wenkert, E.; Hudlický, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (b) Wenkert, E.; *J. Nat. Prod.* **1980**, *43*, 235.

(7) For previous syntheses, see: (a) Bartlett, M. F.; Taylor, W. I. *J. Am. Chem. Soc.* **1960**, *82*, 5941. (b) Wenkert, E.; Wickberg, B. *Ibid.* **1965**, *87*, 1580. (c) Cartier, D.; Lévy, J.; LeMen, J. *Bull. Soc. Chim. Fr.* **1976**, 1961. (d) Costerousse, G.; Buendia, J.; Toromanoff, E.; Martell, J. *Ibid.* **1978**, II-355. (e) Hermann, 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. (f) Bölsing, E.; Klatte, F.; Rosentreter, V.; Winterfeldt, E. *Chem. Ber.* **1979**, *112*, 1902. (g) Irie, K.; Okita, M.; Wakamatsu, T.; Ban, Y. *Nouv. J. Chem.* **1980**, *4*, 275. (h) Irie, K.; Ban, Y. *Heterocycles* **1981**, *15*, 201.

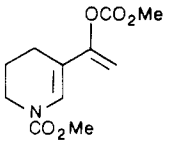
(8) Wenkert, E.; Dave, K. G.; Haglid, F.; Lewis, R. G.; Oishi, T.; Stevens, R. V.; Terashima, M. *J. Org. Chem.* **1968**, *33*, 747.

0022-3263/88/1953-1953$01.50/0 

N-monoalkylated vinylogous amides into vinylogous amines (i.e. enamines) with lithium aluminum hydride,[9] such reductions of amide vinylogue **3a** (8 h refluxing in dioxane) yielded unstable enamine **3b** (15%),[10] whose immediate interaction with methyl chlorocarbonate and triethylamine gave enamide **3c** (94%). The low product yield of the hydride reduction prompted consideration of an alternate operation based on vinylogous imide **3d**, whose preparation (91% overall yield) involved treatment of compound **3a** with methyl chlorocarbonate and triethylamine and exposure of the resultant mixture of 3-acetyl-1-carbomethoxy-2-piperideine (**3d**) and its enol carbonate (**4**)[11] to aqueous acid.



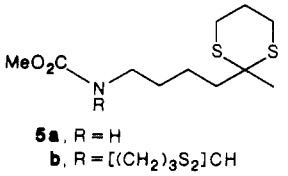
**3a**: R = H, Y = O
**b**: R = H, Y = $H_2$
**c**: R = $CO_2Me$, Y = $H_2$
**d**: R = $CO_2Me$, Y = O



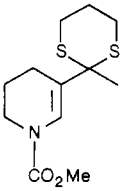
**4**

In an attempt at thioketal formation and subsequent desulfurization, imide **3d** was caused to react with propane-1,3-dithiol, but the reaction went badly awry. With boron trifluoride as catalyst it gave acylic thioketal urethane **5a** (82%) at elevated temperature and substance **5b** (67%) when allowed to react at 0 °C. With hydrogen bromide acting as a catalyst the reaction led to the formation of the desired ketal **6** (48%), accompanied by ketals **5a** and **5b**. This extraordinary result revealed a strong tendency for conjugate addition to the $\alpha,\beta$-unsaturated keto function of imide **3d** and for the 2-thiolated piperidine intermediate **7a** to undergo ring unravelling (i.e. acid-catalyzed, mercaptan-induced retro-Dieckmann condensation). It is conceivable that the successful production of ketal **6** in the hydrogen bromide promoted reaction reflects the intermediacy of 2-bromopiperidine **7b** and its survival until chromatographic workup and that the thermal decomposition of the thioorthoformamide moiety of urethane **5b** (i.e. the **5b** → **5a** conversion) proceeds by way of intermediate salt **8** and the trapping thereof by mercaptan.

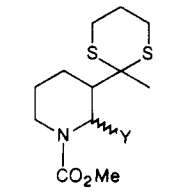
Treatment of thioketal **6** with Raney nickel produced enamide **3c** (93%), the starting compound of the reaction sequence B. Decomposition of ethyl diazoacetate in the enamide over copper bronze[12] gave cyclopropanecarboxylate **9** (95%) in a ca. 2:1 exo–endo ratio.[13] Acid hydrolysis of the latter afforded carbinol amide lactone **10a** (90%), while alkaline hydrolysis yielded the carbinol amine



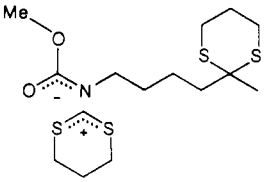
**5a**, R = H
**b**, R = [$(CH_2)_3S_2$]CH



**6**

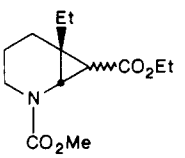


**7a**, Y = $HS(CH_2)_3S$
**b**, Y = Br

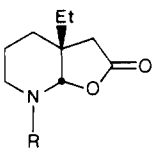


**8**

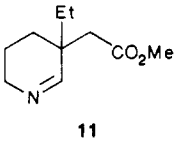
lactone **10b** (88%). Treatment of the latter with methanolic hydrogen chloride transformed the lactone into fragile imino ester **11**. Since both lactone **10b** and ester **11** represent the $\gamma$-imino carbonyl system (the first in masked form), their build-up from enamide **3c** completed reaction sequence B.



**9**

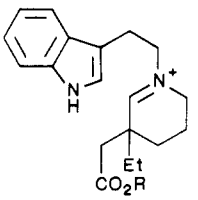


**10a**, R = $CO_2Me$
**b**, R = H
**c**, R = ($\beta$-indolyl)$CH_2CH_2$

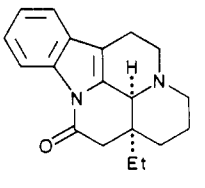


**11**

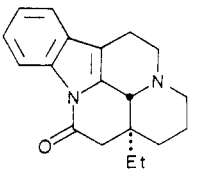
Heating a dimethylformamide solution of tryptophyl bromide and sensitive imino ester **11** gave a mixture (31%) of eburnamonine (**13**) and its isomer **14** as well as unlactamized, tetracyclic esters (30%) and acids (10%). Pentacylic lactam formation was improved by the use of carbinol amine lactone **10b** as cyclization substrate. *N*-Alkylation of amine **10b** with tryptophyl bromide yielded the carbinol amine lactone **10c** (60%),[4] whose exposure to hot glacial acetic acid led to a ca. 1.3:1 mixture (87%) of (±)-eburnamonine (**13**) and (±)-epieburnamonine (**14**). The lack of strong stereochemical preference in the cyclizations reflects the similar steric bulk of the ethyl and acetic ester (or acid) groups $\alpha$ to the cyclizing imino carbon in intermediates **12a** and **12b**. In this context the exclusive formation of (±)-eburnamonine (**13**) (60%)[4] (presumably via intermediate **12c**) on thermolysis of carbinol amine lactone **10c** without solvent was most welcome.



**12a**, R = Me
**b**, R = H
**c**, R = -



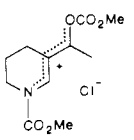
**13**



**14**

**Dehydroaspidospermidine (18).**[14] Carbinol amine lactone **10b**, a masked form of a $\gamma$-imino carbonyl system, was suited ideally as starting material for the reaction sequence E. By analogy with previous condensations of

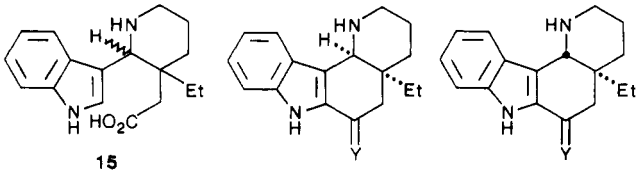
(9) (a) Leete, E.; Marion, L. *Can. J. Chem.* **1953**, *31*, 775. (b) Nugrady, T.; Doyle, T. W. *Ibid.* **1964**, *42*, 485.
(10) For a synthesis of **3b** from acyclic precursors, see: Ziegler, F. E.; Kloek, J. A.; Zoretic, P. A. *J. Am. Chem. Soc.* **1969**, *91*, 2342.
(11) The formation of this unusual enol carbonate indicates that N-acylation may proceed by a circuitous route: (a) acylation at the most basic site of **3a** (i.e. at oxygen), (b) N-deprotonation, (c) N-acylation, and (d) loss of methyl chlorocarbonate from the resultant salt i. Deprotonation of the latter, however, would produce **4**.



i

(12) Cf. Hodgkins, J. E.; Flores, R. T. *J. Org. Chem.* **1963**, *28*, 3356.
(13) For previous cyclopropanations of *N*-acylhydropyridines, see: Wenkert, E.; Broquet, C. *Synth. Commun.* **1979**, *9*, 689.
(14) For previous syntheses, see: (a) Giri, V. S.; Ali, E.; Pakrashi, S. C. *J. Heterocycl. Chem.* **1980**, *17*, 1133. (b) Ban, Y.; Yoshida, K.; Goto, J.; Oishi, T.; Takeda, E. *Tetrahedron* **1983**, *39*, 3657.

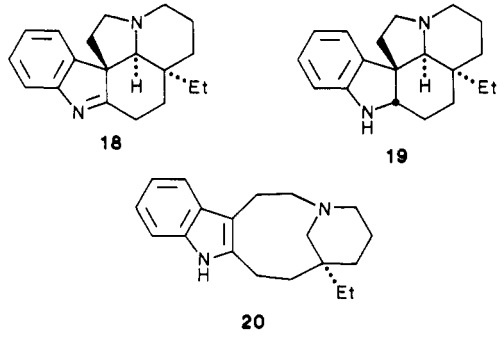
indole with 1- or 2-piperideines,[8,15] interaction of lactone **10b** with indole in aqueous acetic acid produced a mixture of amino acids **15** (89%), whose treatment with polyphosphoric acid yielded a ca. 2:1 mixture (94%) of ketones **16a** and **17a**. Reduction of each isomer with lithium aluminum hydride at elevated temperature[16] afforded (97%) tetracycles **16b** and **17b**, respectively, whose relative configurations were determined by $^{13}C$ NMR spectroscopy.[17]



**15** **16** **17**

**a**, Y = O
**b**, Y = $H_2$

When an ethylene bromide solution of amine **16b** and potassium carbonate was heated for a short time,[18] it resulted in the formation of (±)-dehydroaspidospermidine (**18**) (32%).[14] Reduction of the latter with lithium aluminum hydride yielded (±)-aspidospermidine (**19**) (70%).[19] In view of previous transformations of pentacycle **18** into (±)-quebrachamine (**20**) by borohydride reduction at elevated temperature,[4,14a] the present work also constitutes a formal total synthesis of the latter natural base.



**18** **19** **20**

## Experimental Section

Melting points were determined on a Reichert micro hotstage apparatus and are uncorrected. Ultraviolet spectra of methanol solutions were recorded on a Cary-17 spectrophotometer and infrared spectra of films of oils or chloroform solutions of solids on Perkin-Elmer 137 and Beckman IR-8 spectrophotometers. $^1H$ NMR spectra of deuteriochloroform solutions were measured on a Varian XL-100-15 spectrometer and mass spectra on Finnigan 3300 LRMS and C.E.C. 21-11013 HRMS instruments. TLC, thick-layer and column chromatographic, separations were executed on silica gel 60-PF-254.

**Methyl 5-Acetyl-1,2,3,4-tetrahydropyridine-1-carboxylate (3d).** Methyl chlorocarbonate (15.6 g, 162 mmol) was added dropwise over a 15-min period into a stirring solution of 10.1 g (81 mmol) of 3-acetyl-2-piperideine (**3a**) and 8.16 g (81 mmol) of triethylamine in 100 mL of dry tetrahydrofuran at 0 °C, and the stirring was continued at room temperature for 4 h. Concentrated hydrochloric acid (5 mL) was added and the mixture extracted with methylene chloride. The extract was filtered through a silica pad and the filtrate evaporated. Kugelrohr distillation (130–140 °C/0.3 Torr) gave 13.4 g (91%) of liquid vinylogous imide **3d**: UV $\lambda_{max}$ 280 nm ($\epsilon$ 34 000); IR [C=O] 1710 (s), [C=O, C=C] 1650 (m), 1620 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 1.6–1.9 (m, 2, $H_2$-5), 2.0–2.4 (m, 2, $H_2$-4), 2.28 (s, 3, Me), 3.5–3.7 (m, 2 $H_2$-6), 3.85 (s, 3, OMe), 7.98 (s, 1, H-2); MS, *m/e* (relative intensity) 183 ($M^+$, 27), 168 (base), 81 (29), 58 (24), 43 (73), 42 (45). Anal. Calcd for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.90; H, 7.20; N, 7.66.

Without acid treatment on workup the above reaction gave a 2:1 **3d–4** mixture, from which there could be isolated liquid carbonate **4** on thick-layer TLC (development with dichloromethane) and Kugelrohr distillation (140–160 °C/0.5 Torr): IR [C=O] 1760 (s), 1700 (s), [C=C] 1640 (s), [C=$CH_2$] 850 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 1.8–2.3 (m, 4, $H_2$-5, $H_2$-4), 3.59 (t, 2, $J$ = 6 Hz, $H_2$-6), 3.76 (s, 3, carbonate OMe), 3.85 (s, 3, OMe), 4.7–4.9 (m, 2, olefinic Hs), 7.1–7.3 (m, 1, H-2); MS, *m/e* (relative intensity) 241 ($M^+$, 14), 165 (base), 54 (75), 47 (48). Anal. Calcd for $C_{11}H_{15}O_5N$: C, 54.77; H, 6.27; N, 5.81. Found: C, 54.65; H, 6.40; N, 5.73.

**6-[(Methoxycarbonyl)amino]-2-hexanone Propylene Thioketal (5a).** A mixture of 1.00 g (5.5 mmol) of urethane **3d**, 1.00 g (9.8 mmol) of 1,3-propanedithiol, and 10 drops of boron trifluoride etherate was heated at 90 °C for 1 h. A 10% solution of sodium bicarbonate was added and the neutralized mixture extracted with methylene chloride. The extract was evaporated and the residue chromatographed. Elution with dichloromethane gave 1.17 g (82%) of viscous oily urethane **5a**: IR ($CHCl_3$) [NH] 3440 (m), [C=O] 1705 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 1.5–2.2 (m, 8, methylenes), 1.60 (s, 3, Me), 2.7–3.0 (m, 4, 2 $SCH_2$), 3.1–3.3 (m, 2, $NCH_2$), 3.64 (s, 3, OMe); MS, *m/e* (relative intensity) 263 ($M^+$, 72), 249 (40), 200 (35), 188 (65), 167 (80), 133 (base), 119 (92), 88 (75), 59 (64). Anal. Calcd for $C_{11}H_{21}O_2NS_2$: C, 50.19; H, 8.04; N, 5.32. Found: C, 49.80; H, 7.91; N, 5.31.

**Thioketal 5b.** A solution of 1.00 g (9.8 mmol) of 1,3-propanedithiol and 10 drops of boron trifluoride etherate was added to a solution of 1.00 g of urethane **3d** in 5 mL of chloroform at 0 °C and the mixture kept at room temperature for 1 h. Workup as above led to the recovery of 200 mg (20%) of starting urethane, 143 mg (10%) of thioketal **5a**, and 1.40 g (67%) of crystalline thioketal **5b**: mp 118–124 °C (hexane–$CH_2Cl_2$); IR [C=O] 1700 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 1.5–2.4 (m, 10, methylenes), 1.56 (s, 3, Me), 2.6–3.1 (m, 8, 4 $SCH_2$), 3.1–3.5 (m, 2, $NCH_2$), 3.75 (s, 3, OMe), 5.21 (s, 1, $S_2CH$); MS, *m/e* (relative intensity) 381 ($M^+$, 48), 306 (55), 279 (15), 133 (98), 128 (base), 119 (97), 59 (95); exact mass, *m/e* 381.0919 (calcd for $C_{15}H_{27}O_2NS_4$ *m/e* 381.0924).

**3-Acetyl-1-carbomethoxy-2-piperideine Propylene Thioketal (6).** Gaseous hydrogen bromide was bubbled into a solution of 1.00 g (5.5 mmol) of ketone **3d** in 200 mL of ether at 0 °C for 10 min (at which time precipitate generation had ceased). Upon the addition of 1.00 g (9.8 mmol) of 1,3-propanedithiol the mixture was kept at room temperature for 4 h. Workup as above (cf. **5a**) resulted in the recovery of 20 mg (2%) of starting ketone and the production of 837 mg (40%) of thioketal **5b**, 72 mg (5%) of thioketal **5a**, and 710 mg (48%) of liquid thioketal **6**: IR [C=O] 1700 (s), [C=C] 1650 (s), 1615 (m), 1600 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 1.60 (s, 3, Me), 1.7–2.1 (m, 4, methylenes), 2.2–2.4 (m, 2, $H_2$-4), 2.7–2.9 (m, 4, 2 $SCH_2$), 3.5–3.7 (m, 2, $H_2$-6), 3.77 (s, 3, OMe), 7.3–7.5 (m, 1, H-2); MS, *m/e* (relative intensity) 273 ($M^+$, 10), 199 (base), 167 (60), 106 (99), 79 (65), 59 (99); exact mass, *m/e* 273.0853 (calcd for $C_{12}H_{19}O_2NS_2$ *m/e* 273.0857).

**1-Carbomethoxy-3-ethyl-2-piperideine (3c).** A mixture of 150 mg (0.55 mmol) of thioketal **6** and a tenfold excess of W-2 Raney nickel[20] in 25 mL of 95% ethanol was refluxed under nitrogen for 12 h and then cooled and filtered. Evaporation of the filtrate gave 110 mg (93%) of liquid urethane **3c**: IR [C=O] 1700 (s), [C=C] 1630 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 1.02 (t, 3, $J$ = 7 Hz, Me), 1.8–2.2 (m, 6, methylenes), 3.4–3.7 (m, 2, $H_2$-6), 3.73 (s, 3, OMe), 6.5–6.7 (m, 1, H-2); MS, *m/e* (relative intensity) 169 ($M^+$, 45), 153 (base), 140 (38), 110 (30), 95 (38), 94 (40), 59 (55), 55 (72). Anal. Calcd for $C_9H_{15}O_2N$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.52; H, 8.85; N, 8.37.

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**Cyclopropanecarboxylates 9.** Ethyl diazoacetate (17.2 g, 151 mmol) was added dropwise over a 1.5-h period into a stirring mixture of 8.00 g (47 mmol) of enamide **3c** and 400 mg of freshly prepared copper bronze[12] at 135 °C and the stirring continued for 0.5 h. Filtration of the cooled mixture and Kugelrohr distillation (110 °C/1 Torr) of the filtrate afforded 6.0 g of a mixture of ethyl maleate and fumarate. Further distillation (92–95 °C/0.008 Torr) gave 11.4 g (95%) of a ca. 2:1 exo–endo isomer mixture of liquid esters **9**: MS, *m/e* (relative intensity) 255 ($M^+$, 3), 226 (50), 182 (72), 132 (82), 41 (base). Anal. Calcd for $C_{13}H_{21}O_4N$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.00; H, 8.23; N, 5.25.

Careful chromatography and gradient elution with dichloromethane–ethyl acetate solvent mixtures led to exo isomer **9**: IR [C=O] 1725 (s), 1710 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 0.88 (t, 3, $J$ = 7 Hz, Me), 1.27 (t, 3, $J$ = 7 Hz, Me of OEt), 1.4–1.8 (m, 6, methylenes), 2.0–2.2 (m, 1, COCH), 2.6–2.7 (m, 2, $NCH_2$), 3.35 (d, 1, $J$ = 4 Hz, NCH), 3.70 (OMe), 4.13 (q, 2 $J$ = 7 Hz, $OCH_2$); $^{13}C$ NMR spectrum, detailed on formula **10** of ref 6a, as well as endo isomer **9**: IR [C=O] 1720 (s), 1705 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 0.97 (t, 3, $J$ = 7 Hz, Me), 1.24 (t, 3, $J$ = 7 Hz, Me of OEt), 1.9–2.2 (m, 7, methylenes, CH), 2.93, 3.00 (d, total of 1, $J$ = 7 Hz, NCH of each rotamer), 3.2–3.5 (m, 2, $NCH_2$), 3.67 (s, 3, OMe), 4.05 (q, 2, $J$ = 7 Hz, $OCH_2$); $^{13}C$ NMR spectrum detailed on formula **11** of ref 6a.

**3-(Carboxymethyl)-3-ethyl-1-(methoxycarbonyl)-2-piperidinol Lactone (10a).** A solution of 5.00 g (19 mmol) of esters **9** and 100 mL of 10% sulfuric acid solution in 20 mL of dioxane was refluxed for 18 h, cooled, and neutralized with 10% sodium bicarbonate solution. The mixture was extracted with methylene chloride and the extract evaporated. The clear, residual oil, 4.00 g (90%), solidified on standing into crystalline lactone **10a**: mp 75 °C (hexane–$CH_2Cl_2$); IR [C=O] 1770 (s), 1700 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 0.93 (t, 3 $J$ = 7 Hz, Me), 1.3–1.8 (m, 6, methylenes), 2.25, 2.40, 2.50, 2.65 (four-line AB, 2, $COCH_2$), 3.8–4.2 (m, 2, $NCH_2$), 3.76 (s, 3, OMe), 6.02 (s, 1, NCHO); MS, *m/e* (relative intensity) 227 ($M^+$, 10), 196 (65), 183 (25), 154 (base). Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.07; H, 7.46; N, 6.12.

**3-(Carboxymethyl)-3-ethyl-2-piperidinol Lactone (10b).** A solution of 1.00 g (3.9 mmol) of esters **9**, 1.0 g of potassium hydroxide, and 1 mL of water in 5 mL of diethylene glycol was heated at 110 °C for 12 h. The cooled solution was poured onto a mixture of ice and 10 mL of concentrated hydrochloric acid and brought subsequently to pH 7 by the addition of sodium bicarbonate. The mixture was extracted with methylene chloride and the extract evaporated. The clear, residual oil solidified on standing. Crystallization of the solid from hexane–$CH_2Cl_2$ gave 580 mg (88%) of crystalline lactone **10b**: mp 72 °C; IR [NH] 3400 (m), [C=O] 1740 (s) $cm^{-1}$; $^1H$ NMR $\delta$ 0.90 (t, 3, $J$ = 7 Hz, Me), 1.2–1.8 (m, 4, methylenes), 1.81 (q, 2, $J$ = 7 Hz, CH of Et), 2.15, 2.30, 2.39, 2.54 (four-line AB, 2, $COCH_2$), 2.8–3.1 (m, 2, $NCH_2$), 5.12 (s, 1, NCHO); MS, *m/e* (relative intensity) 169 ($M^+$, 18), 140 (32), 96 (base), 95 (40). Anal. Calcd for $C_9H_{15}O_2N$: C, 63.88, H, 8.93; N, 8.28. Found: C, 64.00; H, 8.86; N, 8.29.

Hydrolysis of urethane **10a** under the same conditions led to lactone **10b** with the same yield.

**3-Ethyl-3-[(methoxycarbonyl)methyl]-1-piperideine (11).** A solution of 1.00 g (5.9 mmol) of lactone **10b** in 100 mL of dry methanol, saturated with hydrogen chloride gas, was stirred at room temperature for 12 h and then neutralized with 10% sodium bicarbonate solution. Extraction of the mixture with methylene dichloride and evaporation of the extract gave crude, liquid imino ester **11**: IR [C=O] 1730 (s), [C=N] 1645 (m) $cm^{-1}$; $^1H$ NMR $\delta$ 0.86 (t, 3, $J$ = 7 Hz, Me), 1.2–1.6 (m, 6, methylenes), 2.48 (s, 2, $COCH_2$), 3.3–3.7 (m, 2, $NCH_2$), 3.53 (s, 3, OMe), 5.08 (s, 1, aldimino H); MS, *m/e* (relative intensity) 183 ($M^+$, 18), 154 (32), 110 (base). Since the material decomposed in all attempts of purification, it had to be used in crude form for N-alkylation.

**3-(Carboxymethyl)-3-ethyl-1-tryptophyl-2-piperidinol Lactone (10c).** A mixture of 200 mg (1.2 mmol) of lactone **10b**, 300 mg (1.3 mmol) of tryptophyl bromide,[21] 70 mg (0.3 mmol) of triethylbenzylammonium chloride, and 4 mL of 30% sodium hydroxide in 10 mL of benzene was stirred at 35 °C for 6 h and then at room temperature for 12 h. It was extracted with methylene chloride and the extract evaporated. Thick-layer chromatography (development with 4:1 dichloromethane–methanol) gave ca. 10% of the eburnamonines and their acids as well as 220 mg (60%) of lactone **10c**, spectrally identical with the substance obtained via reaction sequences A and C.

**Eburnamonine (13) and Epieburnamonine (14).** A solution of 180 mg (0.57 mmol) of lactone **10c** in 10 mL of glacial acetic was kept at 100 °C for 48 h. It then was cooled and neutralized with ice-cold 10% sodium bicarbonate solution. The mixture was extracted with methylene chloride and the extract evaporated. Thick-layer chromatography of the residue on alumina (development with chloroform) gave 85 mg (50%) of (±)-eburnamonine (**13**), mp 200–201 °C (lit.[7b] mp 200–202 °C), spectrally identical with an authentic sample[7b], and 63 mg (37%) of (±)-epieburnamonine (**14**): mp 132–134 °C (lit.[22] mp 134.5–136 °C), spectrally identical with the literature data.[22]

The thermolytic conversion of lactone **10c** into (±)-eburnamonine exclusively has been reported previously.[4]

**Amino Acids 15.** A solution of 1.40 g (8.3 mmol) of lactone **10b**, 1.20 g (10.2 mmol) of indole, 2 mL of dioxane, and 2 drops of concentrated hydrochloric acid in 10 mL of 10% aqueous acetic acid was stirred at 80 °C for 18 h and extracted with ether. The extract was washed with 10% aqueous acetic acid and evaporated under vacuum. Trituration of the residual oil with acetone yielded 2.10 g (89%) of a crystalline mixture of acids **15**: UV $\lambda_{max}$ 272 nm ($\epsilon$ 11 000), 280 (12 000), 290 (10 000); IR (Nujol) [OH] 3400 (br m), [NH] 3300 (br m), [$CO_2^-$] 1520 (s) $cm^{-1}$; MS, *m/e* (relative intensity) 286 ($M^+$, 15), 241 (18), 172 (40), 171 (55), 144 (95), 143 (base), 130 (55), 117 (62). Anal. Calcd for $C_{17}H_{22}O_2N_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.30; H, 7.80; N, 9.72.

**Amino Ketones 16a and 17a.** A swirling mixture of 1.50 g (5.2 mmol) of amino acids **15** and 150 g of polyphosphoric acid was heated at 90 °C for 45 min and then, while ice-cold, brought to pH 10 with 10% potassium hydroxide solution. The mixture was extracted with methylene chloride. Evaporation of the extract and thick-layer chromatography (development with 9:1 $CH_2Cl_2$–methanol) of the residue gave 845 mg (61%) of crystalline ketone **16a**: mp 183–185 °C (hexane–$CH_2Cl_2$); UV $\lambda_{max}$ 232 nm ($\epsilon$ 20 500), 308 (18 900); IR [NH] 3450 (m), 3260 (w), [C=O] 1650 (s), [C=C] 1605 (m) $cm^{-1}$; $^1H$ NMR $\delta$ (acetone-$d_6$) 0.82 (t, 3, $J$ = 7 Hz, Me), 1.4–2.2 (m, 6, methylenes), 2.5–2.9 (m, 2, $COCH_2$), 2.9–3.2 (m, 2, $NCH_2$) 4.18 (s, 1, NCH), 7.2–8.2 (m, 4, aromatic Hs); MS, *m/e* (relative intensity) 268 ($M^+$, 20) 267 (14), 211 (70), 197 (65), 130 (60), 40 (base); exact mass, *m/e* 268.1584 (calcd for $C_{17}H_{20}ON_2$ *m/e* 268.1576).

Another fraction gave 455 mg (33%) of crystalline ketone **17a**: mp 226–229 °C (hexane–$CH_2Cl_2$); UV $\lambda_{max}$ 226 nm ($\epsilon$ 48 100), 310 (20 700); IR [NH] 3450 (m), 3280 (w), [C=O] 1650 (s), [C=C] 1610 (m) $cm^{-1}$; $^1H$ NMR $\delta$ (acetone-$d_6$) 0.72 (t, 3 $J$ = 7 Hz, Me), 1.0–2.0 (m, 6, methylenes), 2.44 (s, 2, $COCH_2$), 3.1–3.4 (m, 2, $NCH_2$), 4.36 (s, 1, NCH), 7.0–8.2 (m, 4, aromatic Hs); MS, *m/e* (relative intensity) 268 ($M^+$, 25), 267 (22), 211 (80), 197 (70), 130 (72), 40 (base).

**Amines 16b and 17b.** A mixture of 350 mg (1.3 mmol) of either ketone **16a** or **17a** and 6.0 g of lithium aluminum hydride in 150 mL of dry dioxane was refluxed for 18 h. Water (6 mL), 6 mL of 15% sodium hydroxide solution, and 18 mL of water were added sequentially to the cooled mixture and the composite was filtered. The organic layer of the filtrate was separated and evaporated, leaving 321 mg (97%) of crystalline amine **16b** or **17b**, respectively. Amine **16b**: mp 180–182 °C (sublimation point: ca. 140 °C); UV $\lambda_{max}$ 266 nm ($\epsilon$ 12 900), 278 (12 500), 286 (10 200), 326 (2100); IR [NH] 3490 (m), [C=C] 1620 (w), 1580 (w) $cm^{-1}$; $^1H$ NMR $\delta$ 0.86 (t, 3, $J$ = 7 Hz, Me), 1.1–2.0 (m, 8, methylenes), 2.1–2.8 (m, 4, $NCH_2$, benzyl $H_2$), 3.68 (s, 1, NCH), 6.9–7.6 (m, 4, aromatic Hs); $^{13}C$ NMR spectrum detailed on formula **4** of ref 17; MS, *m/e* (relative intensity) 254 ($M^+$, 10) 253 (8), 185 (35), 130 (25), 59 (base). Anal. Calcd for $C_{17}H_{22}N_2$: C, 80.27; H, 8.72; N, 11.01. Found: C, 80.04; H, 8.92; N, 11.01.

Amine **17b**: mp 175–177 °C (sublimation point: 145 °C); UV $\lambda_{max}$ 252 nm ($\epsilon$ 12 500), 274 (17 900), 280 (16 900), 290 (14 500), 326 (7700); IR [NH] 3490 (m), [C=C] 1620 (w), 1600 (w), 1580

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(w) $cm^{-1}$; $^1H$ NMR $\delta$ 0.80 (t, 3, $J$ = 7 Hz, Me), 1.2-2.0 (m, 8, methylenes), 2.5-3.1 (m, 2, benzyl $H_2$), 3.2-3.4 (m, 2, $NCH_2$), 3.94 (s, 1, NCH), 6.9-7.9 (m, 4, aromatic Hs); MS, $m/e$ (relative intensity) 254 ($M^+$, 12), 253 (12), 185 (40), 59 (base).

**Dehydroaspidospermidine (18).** A mixture of 100 mg (0.39 mmol) of amine **16b** and 200 mg of solid, anhydrous potassium carbonate in 3 mL of redistilled 1,2-dibromoethane was heated at 140 °C for 20 min and then poured onto ice and 1 mL of concentrated hydrochloric acid. The mixture was neutralized with 10% sodium bicarbonate solution and extracted with methylene chloride. Evaporation of the extract and thick-layer chromatography of the residue on alumina (development with chloroform) led to the recovery of 60 mg of unchanged starting amine and the isolation of 35 mg (32%; 80%, based on consumed starting amine) of viscous oily (±)-dehydroaspidospermidine (**18**): UV $\lambda_{max}$ 222 nm ($\epsilon$ 22 000), 264 (9000); IR [CH, Wenkert-Bohlmann bands] 2780 (m), 2720 (m), [C=N] 1590 (m) $cm^{-1}$; MS, $m/e$ (relative intensity) 280 ($M^+$, 44), 251 (33), 210 (base), 125 (84), 124 (56); spectrally identical with a sample of natural base derived from decarboxylative hydrolysis of vincadifformine.

**Aspidospermidine (19).** A mixture of 30 mg (0.11 mmol) of imine **18** and 1.00 g of lithium aluminum hydride in 25 mL of dry ether was stirred at room temperature for 2 h and then poured into a 10% sodium hydroxide solution. It was extracted with methylene chloride and the extract evaporated. Thick-layer chromatography of the residue on alumina (development with chloroform) yielded 21 mg (70%) of crystalline (±)-aspidospermidine (**19**): mp 104-106 °C (lit.[19b] mp 108-110 °C; lit.[19c] mp 106-110°C, lit.[19d] mp 99-103 °C); MS, $m/e$ (relative intensity) 282 ($M^+$, 5), 254 (15), 124 (base); spectrally identical with a sample of the natural base.

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# Thermal and Trimethylsilyl Triflate Catalyzed Additions of Allylsilanes to Nitrones

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A new methodology is described for the coupling of allylsilanes and nitrones with trimethylsilyl triflate as a catalyst to afford homoallylhydroxylamines in yields ranging from 70% to 95%. Lower yields were obtained with shorter reaction times. The reaction also proceeds intramolecularly, giving mixtures of cis and trans tetrahydropyridines in excellent yield. The TMSOTf-catalyzed process is compared and contrasted with the thermally induced intramolecular nitrone cycloaddition.

Cycloaddition reactions of nitrones have been extensively studied and have recently been reviewed.[2] The reaction generally proceeds thermally to efficiently give cycloadducts and represents an excellent method for stereoselective carbon-carbon bond formation with concomitant introduction of additional functionality.

Recently Sakurai,[3] Kakisawa,[4] and DeShong[5] have examined the cycloaddition of nitrones with allylsilanes which proceed to give the expected isoxazolidines. We now report that the addition of allylsilanes to nitrones may be catalyzed with trimethylsilyl triflate (TMSOTf). We have found that treating a mixture of nitrone **1** and allyltrimethylsilane in methylene chloride at room temperature in the presence of TMSOTf gives a diastereomeric mixture[6] of cycloadducts **4** and homoallylhydroxylamine **6b**. The reaction is clearly catalyzed by trimethylsilyl triflate because without it temperatures >100 °C are required to achieve the usual (3 + 2) cycloaddition. Moreover,

**Table I. Trimethylsilyl Triflate Catalyzed Additions of Allylsilanes to Nitrones**

| entry | nitrone (1) | catalyst amount, equiv | reactn time (h) | % yield[b] | ratio **6b**/**4** |
|---|---|---|---|---|---|
| 1 | Ph | 1[a] | 12 | 32 | >50:1[c] |
| 2 | Ph | 1 | 36 | 90 | >50:1 |
| 3 | Ph | 0.1 | 36 | 86 | >50:1 |
| 4 | $EtO_2C$ | 0.1 | 1 | 76 | 1:4.5 |
| 5 | $EtO_2C$ | 0.1 | 50 | 71 | >50:1 |
| 6 | 3-pyridyl | 1 | 6 | 86 | 9:1 |
| 7 | 3-pyridyl | 1 | 63 | 94 | >50:1 |
| 8 | 3-pyridyl | 0.1 | 9 | 79 | 1:1.4 |

[a] $TiCl_4$ was used as catalyst. [b] Yields are for chromatographically isolated material. [c] A ratio of >50:1 indicates that the cyclic material was not detected.

TMSOTf appears to be unique in its effect on the reaction since early attempts to carry out the reaction with Lewis acids such as $SnCl_4$ and $BF_3{\cdot}Et_2O$ were generally unsuccessful, with $TiCl_4$, as the only exception, producing a 32% yield of the homoallylhydroxylamine **6b** (entry 1). An examination of Table I reveals our results to date. The reaction may be run catalytically or stoichiometrically in TMSOTf. In either case the yields are excellent (>70%). The use of 1 equiv is preferred since this leads to a single product in less time with better overall yield than the catalytic process.

A useful heuristic explaining the results involves initial silylation of nitrone **1** to form the transient electrophilic *N*-siloxyimminium ion **2** which reacts with allylsilane to give **3** (Scheme I). The fate of carbenium ion **3** may be

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