Intramolecular Imino Diels−Alder Reaction of a 3-Vinyl Indole: Application to a Total Synthesis of (±)-Eburnamonine

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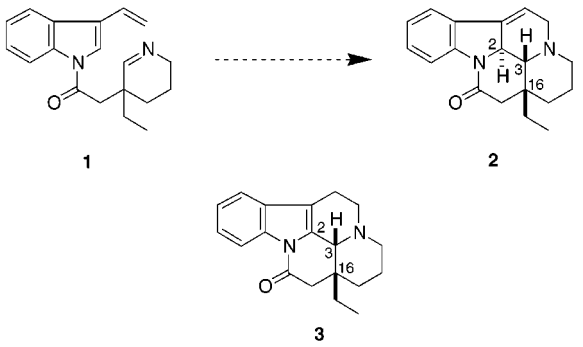
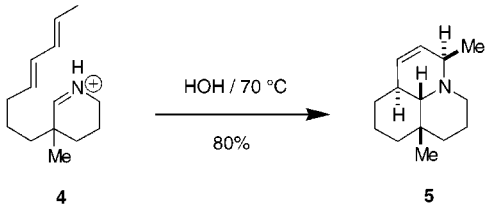
The intramolecular [4 + 2] cycloaddition of imine **1** has been examined under a variety of conditions including thermal; catalysis by acid, lithium cation, and Florisil; and the use of 5.0 M lithium perchlorate in diethyl ether. Cycloadduct **2** was transformed into (±)-eburnamonine **3** using acid catalysis. Substrate **1** was prepared by coupling indole-3-carboxaldehyde **7** with the activated *p*-nitrophenyl ester **9**. Subsequent methylenation of **10** gave rise to **11**, which upon exposure to fluoride ion provided imine **1**.

Our continuing interest in the intramolecular imino Diels−Alder reaction[2] led us to explore the [4 + 2] cycloaddition of vinyl indole imine **1** as a route to carbocyclic arrays containing nitrogen.[3] The pentacyclic system **2**, obtained from this process, is common to numerous alkaloids including eburnamonine (**3**),[4] which has received considerable attention over the years.[5] The vast majority of the syntheses of **3** reported have employed either a Pictet−Spengler or a Bischler−Napieralski cyclization to elaborate the C(2),C(3) carbon−carbon bond. The outcome of this has been that many of the syntheses of **3** have given rise to the formation of *epi*-eburnamonine wherein the D and E rings are trans fused. We detail below the synthesis of vinyl indole imine **1** and an extensive investigation into the [4 + 2] cycloaddition of **1**, which gives rise to exclusive cis ring formation between rings D and E (cf. **2**) and culminated in a total synthesis of (±)-eburnamonine (**3**).

The imino Diels−Alder strategy for elaborating pentacyclic systems such as **2** was based on a model study from our laboratory wherein iminium ion **4** was shown to undergo cycloaddition giving rise to tricyclic amine **5**.[6] On the basis of this result, it was anticipated that **1** would undergo stereospecific intramolecular imino Diels−Alder reaction leading exclusively to the formation of **2** possessing the 2,3-anti, 3,16-syn arrangement about the newly created ring system.[7] Subsequent isomerization of the olefin in **2** would provide **3**.





With respect to the cycloaddition of **1**, it is important to note that by tethering the imine to the indole nitrogen, any ambiguities regarding facial selectivity should be of no concern since there is an overwhelming bias for the vinyl indole to approach the face of the imine from the side opposite the angular ethyl group. In the case of substrate **4**, in which there is the potential for four cycloadducts being generated, a single cycloadduct is obtained that arises via an exo transition state wherein the diene approaches the iminium ion from the face opposite the quaternary methyl group.

The synthesis of vinyl indole **1**, in principle, requires coupling of 3-vinyl indole **6** with an activated ester that possesses either the imine functionality or an imine equivalent. However, in view of the fact that 3-vinylindole is very sensitive and prone to polymerization,[8] it was

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(2) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. Grieco, P. A.; Larsen, S. D.; Forbare, W. F. *Tetrahedron Lett.* **1986**, *27*, 1975. Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553. Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3, 3325. Grieco, P. A.; Parker, D. T. *J. Org. Chem.* **1988**, *53*, 3658. Also see: *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: Glasgow, 1998.

(3) For a preliminary account of this work, see: Kaufman, M. D.; Grieco, P. A. *J. Org. Chem.* **1994**, *59*, 7197.

(4) The structural assignment of eburnamonine was made in 1965 (Wenkert, E.; Wickberg, B. *J. Am. Chem. Soc.* **1965**, *87*, 1580).

(5) For an extensive compilation of syntheses of eburnamonine through 1991 see footnote 3 in ref 3 above. Also see: Palmisano, D'Anniballe, P.; Santagostino, M. *Tetrathedron* **1994**, *50*, 9487. Goes, A. D. S.; Clotilde, F.; Santamaria, J. *Tetrathedron Lett.* **1995**, *36*, 2235.

(6) Grieco, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041.

(7) A survey of the literature found no reports of 3-vinylindoles undergoing [4 + 2] cycloaddition with imines. In contrast, there are numerous reports of 3-vinylindoles reacting with more traditional dienophiles: 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*, 5, 816. Simoji, Y.; Hashimoto, T.; Furukawa, T.; Yanagisawa, H. *Heterocycles* **1993**, *36*, 123.

(8) Noland, W. E.; Sundberg, R. J. *J. Org. Chem.* **1963**, *28*, 884.

10.1021/jo9909960 CCC: $18.00
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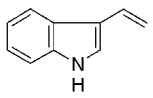
decided that the 3-vinyl substituent would be installed after acylation of the indole nitrogen. Thus, a 3-vinyl indole surrogate (cf. **7**) would be required for the coupling reaction.



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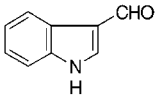
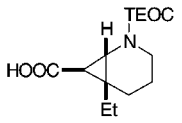


7

With respect to the imine-derived portion of **1**, we set out to prepare the activated *p*-nitrophenyl ester **9** as well as the corresponding acid chloride, which were derived from carboxylic acid **8**. It was anticipated that acylation of **7** with **9** or the corresponding acid chloride would give rise to **10**, which upon methylenation would afford **11**.



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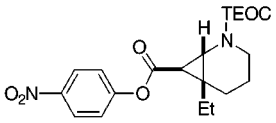

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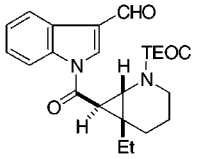

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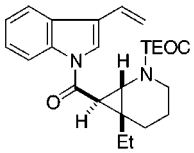
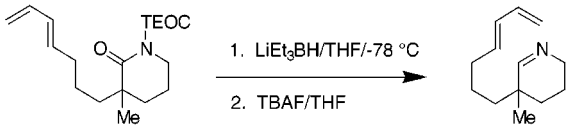


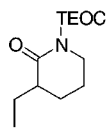
11

We have previously developed a general route to imines of type **1** by sequential reduction and fluoride-induced deprotection of *N*-(2-trimethylsilyl)ethoxycarbonyl protected lactams (cf. **12** → **13**).[6] It was anticipated[9] that exposure of the activated, *N*-(2-trimethylsilyl)ethoxycarbonyl-protected cyclopropylamine **11** to tetra-*n*-butylammonium fluoride would result in cleavage of the carbamate with concomitant formation of the key substrate imine **1** via nitrogen-induced opening of the cyclopropane ring.



12 **13**

With the cyclopropanation chemistry needed to access **8** well established,[9] attention was focused on generating the requisite enamine **15**. Thus, the dianion of *δ*-valerolactam was sequentially C-alkylated with ethyl iodide and N-acylated by treatment with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate,[10] giving rise to **14** in 69% yield. Selective reduction [$LiAl(O\text{-}t\text{-}Bu)_3$] of the lactam carbonyl followed by exposure to catalytic sulfuric acid in ether provided **15** in 92% overall yield.



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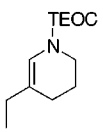
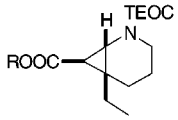
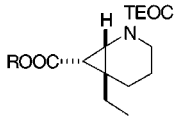


15

Cyclopropanation of **15** was conducted employing the method of Wenkert.[9a] Excess ethyl diazoacetate was added dropwise to a suspension of copper−bronze in neat **15** at 135 °C. The exo and endo cyclopropanes **16** and **17**, which were isolated as a 1.1:1 mixture in 65% yield, could be readily separated by chromatography. Both cyclopropyl esters were saponified to their respective carboxylic acids upon treatment with sodium hydroxide in ethanol−water−tetrahydrofuran (3:1:1). Exo ester **16** gave rise to **8** in essentially quantitative yield. In contrast, the highly hindered endo ester **17** provided **18** in only 66% yield.

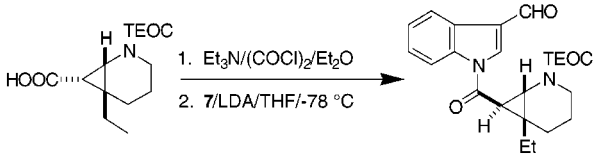


16 R = Et
19 R = Cl

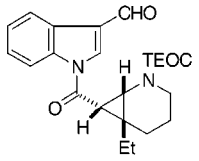


17 R = Et
18 R = H
20 R = Cl

Our initial attempt to couple exo acid **8** with indole-3-carboxaldehyde **7** relied on acid chloride **19**. The acid chloride **19**, prepared from **8**, was added as a solution in tetrahydrofuran to a solution of the lithium amide of **7** cooled to −78 °C. The reaction was complete in a few minutes; however, the yield of the coupled product **10** was only 52%. Interestingly, subjection of the endo acid **18** to identical reaction conditions gave rise to the exo carboxamide **10** in similar yield! The endo isomer **21**, the anticipated product derived from acid chloride **20**, could not be detected.



18 **10**



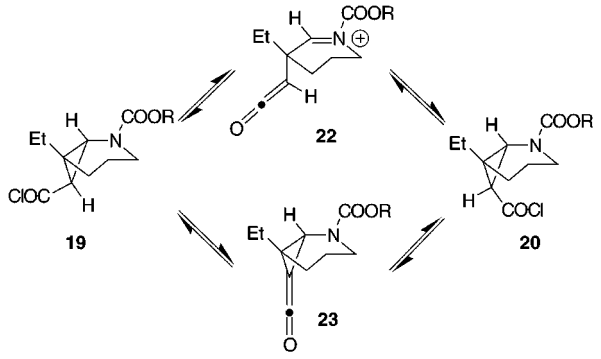
21

The formation of the exo amide **10** from endo acid **18** was quite unexpected. While it could be suggested that the excess base present in the coupling reaction epimerized the initially formed endo amide **21**, this explanation seems unlikely considering that esters **16** and **17** do not interconvert during basic hydrolysis. A more likely explanation is that the exo acid chloride **19** is formed prior to the introduction of lithiated **7**. In this regard, two possibilities emerge. Assuming that the endo acid **18** does give rise initially to endo acid chloride **20**, then it might be postulated that an equilibrium exists between **19** and **20** by way of either ketene iminium ion **22** or ketene **23**. While **22** could form spontaneously from **20**,

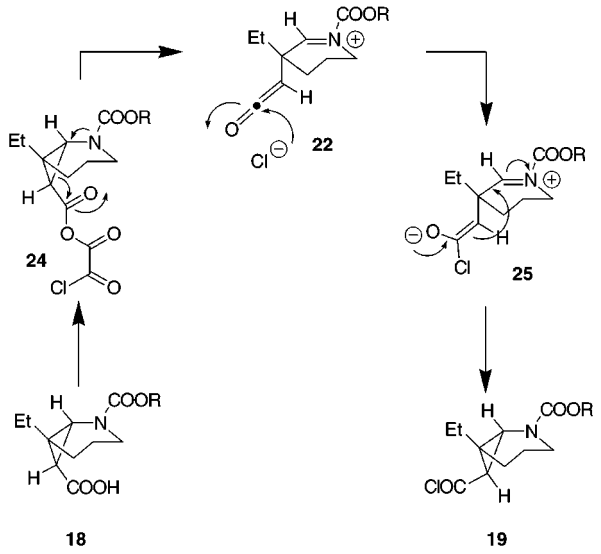
(9) (a) Wenkert, E.; Hudlicky, T.; Showalter, H. D. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (b) Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27. (c) Wenkert, E.; Halls, T.; Kwart, L.; Magnusson, G.; Showalter, H. D. *Tetrahedron* **1981**, *37*, 4017. (d) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953.

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

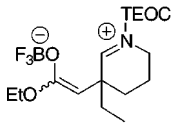
the formation of ketene **23** would require the presence of catalytic base to effect dehydrochlorination of **20**.



Alternatively, it may be that the endo acid chloride **20** does not form at all upon exposure of the endo carboxylic acid **18** to oxalyl chloride and base. In view of the hindered nature of the endo carboxylate, it is conceivable that the piperidine ring sufficiently shields the carboxyl in the initially formed mixed anhydride **24** to render attack by chloride ion slow relative to ketene formation (cf. **22**). Nucleophilic attack of chloride on ketene **22** followed by sterospecific intramolecular trapping of the iminium ion by enolate **25** would give rise to exo acid chloride **19** irreversibly.

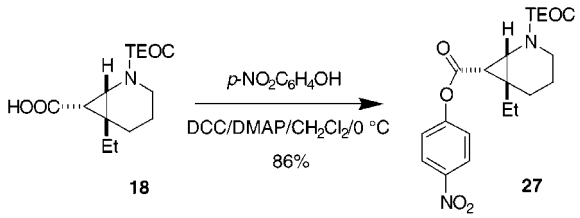


The apparent epimerization of endo acid **18** or endo acid chloride **20** suggested that it might be possible to equilibrate cyclopropane esters **16** and **17** by judicious choice of Lewis acid catalyst. This was indeed realized through the agency of catalytic boron trifluoride etherate. Thus, exposure of a solution of pure endo ester **17** in methylene chloride to 0.15 equiv of boron trifluoride etherate at 0 °C gave rise to a 10.5:1 mixture of exo ester **16** and endo ester **17** with a 92% material balance. The "equilibration" presumably occurs via the iminium ion-enolate **26**. Since exo ester **16** was never subjected to boron trifluoride etherate, it is not clear if the 10.5:1 ratio of **16**:**17** represents a true equilibrium ratio.[11] Nevertheless, a single equilibration of cyclopropane ester **17** allowed access to cyclopropane ester **16** in 60% overall yield from enecarbamate **15**.



26

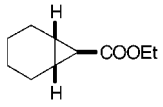
With a way to maximize production of exo ester **16**, attention was turned to a more reliable procedure for the conversion of **16** into **10**. The eventual solution proved to be the use of the activated *p*-nitrophenyl ester **9**, mp 77.5−78.5 °C, which was made available in 86% yield from exo acid **8** by dicyclohexylcarbodiimide facilitated esterification at 0 °C with the aid of 4-(dimethylamino)-pyridine [it also proved possible to esterify the endo acid **18** in this manner without epimerization (cf. **18** → **27**)]. Treatment of **9** with 1.2 equiv of *N*-lithioindole-3-carboxaldehyde afforded the coupled amide **10** in a reproducible 77% yield.



Methylenation of aldehyde **10** was accomplished by treatment of **10** with a slight excess of methylene triphenylphosphorane, prepared from sodium bis(trimethylsilyl)amide and methyl triphenylphosphonium bromide. The sensitive vinyl indole **11**, obtained in 86% yield, could be stored for several weeks in solution at −78 °C with minimal decomposition.

With the availability of **11**, the stage was set for cleavage of the carbamate and liberation of the imine functionality. Unfortunately, the fragile nature of the indole amide bond was not fully appreciated. For example, attempted cleavage of the TEOC group with tetra-*n*-butylammonium fluoride afforded none of the desired imine **1**. Instead, only 3-vinylindole and the known lactone **28** were isolated. The fragile imine **1** was accessed by action of anhydrous cesium fluoride in *N*,*N*-dimethylformamide. The reaction required 40 h at ambient temperature and provided **1** in 66% yield. Use of predried benzyltrimethylammonium fluoride in tetrahydrofuran with crushed 4 Å molecular sieves[12] gave rise to an improved procedure for the generation of **1**. Thus, treatment of **11** with 8.0 equiv of benzyltrimethylammonium fluoride at 45 °C afforded imine **1** in 81% yield. The reaction rate at ambient temperature was negligible,

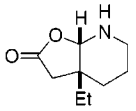
(11) It has been reported that upon exposure to potassium ethoxide, pure ester ***i*** equilibrates to an 7.3:1 mixture of exo and endo esters as determined by GC analysis. See: Hodgkins, J. E.; Flores, R. J. *J. Org. Chem.* **1963**, *28*, 3356.



i

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

presumably due to the low solubility of the benzyltrimethylammonium fluoride in tetrahydrofuran. The sensitive imine **1** could be rapidly chromatographed on silica gel. Upon standing, it slowly undergoes decomposition. Imine **1** was best used immediately.



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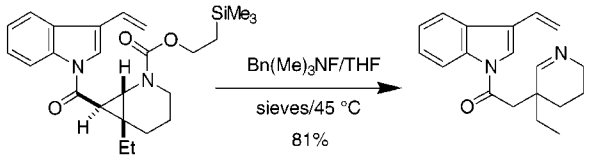
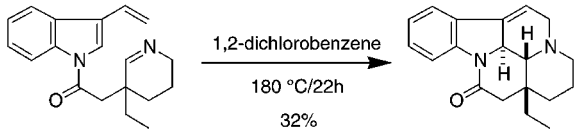


11 **1**

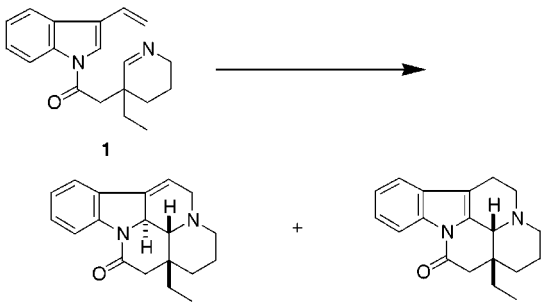
With imine **1** in hand, the key Diels−Alder cyclization was attempted. Heating a 0.005 M solution of purified imine **1** in 1,2-dichlorobenzene (180 °C) afforded, after 22 h, a 32% yield of crystalline **2**, mp 119.0−120.5 °C, along with recovered **1** (47%). ^{1}H NMR analysis initially confirmed the trans relationship (J = 9.9 Hz) between the two methine protons in pentacyclic lactam **2**. Confirmation of the cis relationship between the D and E ring fusion was obtained by single-crystal X-ray analysis.[13] Notably, no eburnamonine was formed in the reaction.



1 **2**

Whereas the thermal [4 + 2] cycloaddition proceeded slowly, the acid-catalyzed reaction was much more efficient. Acid catalysis resulted in shorter reaction times, higher yields, and partial isomerization of **2** into (±)-eburnamonine (**3**) (Table 1). As the data in Table 1 indicate, yields were good to excellent in all cases studied. While the thermal imino Diels−Alder reaction required heating at 180 °C, cycloaddition of **1** in benzene occurred at 50 °C in the presence of 1.0 equiv of trifluoroacetic acid (Table 1, entry 1). Under these conditions, cycloadduct **2** does not isomerize into (±)-eburnamonine. As entries 2−6 of Table 1 illustrate, raising the reaction temperature (benzene at reflux) results in complete conversion of **1** into **2** and **3** after only a few hours. While the transformation of **2** into **3** varies with time and equivalents of added acid, it is clear that this conversion is significantly slower than the initial cycloaddition (cf. Table 1, entries 2 and 4). Entries 5 and 6 of Table 1 reveal that catalytic acid is less effective than stoichiometric acid at promoting the isomerization of **2** into (±)-**3**. The best isolated yield of (±)-**3** was obtained with 1.1 equiv of trifluoroacetic acid in benzene at reflux (Table 1, entry 4).

Table 1. Acid-Catalyzed Cycloaddition of Imine 1[a]



1 **2** **3**

			yield[b] (%)		
entry	conditions	time (h)	**2**	**3**	**1**
1	1.0 equiv TFA, 50 °C	46	60		25
2	1.1 equiv TFA, refux	3	70	5	
3	1.0 equiv CSA, reflux	5	65	7	
4	1.1 equiv TFA, reflux	40	20	60	
5	0.1 equiv TFA, reflux	48	45	23	
6	0.1 equiv CSA, reflux	48	56	22	
7[c]	0.1 equiv CSA, rt	60	96		

[a] All reactions were conducted in benzene unless noted otherwise. [b] Isolated yields. [c] Reaction conducted in 5.0 M $LiClO_4 \cdot Et_2O$.

The best yield of cycloadduct **2**, however, was obtained at ambient temperature in 5.0 M lithium perchlorate−diethyl ether containing 0.1 equiv of camphorsulfonic acid (Table 1, entry 7).[14] The reaction is slow, requiring 60 h to go to completion, but affords the Diels−Alder adduct **2** in a remarkable 96% yield. This result was a surprise in view of the abysmal performance of simpler model systems undergoing cycloaddition in 5.0 M lithium perchlorate−diethyl ether.[6] Equally remarkable was the fact that no eburnamonine could be detected in the crude reaction product.

The cycloaddition of **1** could also be performed in 5.0 M lithium perchlorate−diethyl ether containing no added acid catalyst (Table 2, entry 1).[15] This finding prompted a brief investigation into the use of other lithium salts of weakly coordinating anions as possible catalysts for this reaction. These results are illustrated in Table 2. Interestingly, lithium perchlorate in benzene at reflux catalyzed the cycloaddition as effectively as protic acids despite the heterogeneous nature of the reaction system (Table 2, entry 2). Reetz and Gansäuer[16] have reported a single example of an imino Diels−Alder reaction catalyzed by 20 mol % lithium perchlorate as a suspen-

(13) Cycloadduct **2** crystallizes in space group $P1$ with cell dimensions at −173 °C of a = 8.697(5) Å, b = 10.404(6) Å, c = 8.507(5) Å, α = 93.60(3)°, β = 99.66(3)°, γ = 83.07(3)°, V = 752.60 Å^3, D_c 1.299 g cm^{-3}, 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. Complete crystallographic data can be obtained from the Indiana University Molecular Structure Center, Bloomington, IN 47405 (report no. 94110).

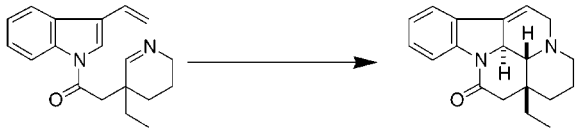
(14) For the use of catalytic camphorsulfonic acid in 5.0 M $LiClO_4 \cdot Et_2O$ to promote intramolecular [4 + 2] cycloadditions, see: Grieco, P. A.; Handy, S. T.; Beck, J. P. *Tetrahedron Lett.* **1994**, *35*, 2663. Grieco, P. A.; Beck, J. P.; Handy, S. T.; Saito, N.; Daeuble, J. F. *Tetrahedron Lett.* **1994**, *35*, 6783.

(15) To date there have been two additional reports of imino Diels−Alder reactions occurring in 5.0 M lithium perchlorate−diethyl ether solution; see: (a) Katagiri, N.; Kurimoto, A.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 1737. (b) Takemoto, Y.; Ueda, S.; Takeuchi, J.; Nakamoto, T.; Iwata, C. *Tetrahedron Lett.* **1994**, *35*, 8821.

(16) Reetz, M. T.; Gansäuer, A. *Tetrahedron* **1993**, *49*, 6025.

sion in methylene dichloride. Employing these conditions, **1** did cyclize slowly to **2** over a period of 2 weeks.

Table 2. Lithium Ion Catalyzed Cycloadditions of Imine 1[a]



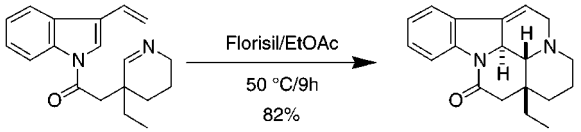
1 **2**

		yield[b] (%)	
entry	conditions	**2**	**1**
1[c]	5.0 M $LiClO_4 \cdot Et_2O$, 40 h	70	20
2	0.5 equiv $LiClO_4$, C_6H_6, 9h	81	
3	0.15 equiv $LiPF_6$, C_6H_6, 5 h	62	
4	0.15 equiv $LiBF_4$, C_6H_6, 64 h	60	20
5	0.02 equiv $LiCo[B_9C_2H_{11}]_2$, 2 h	80	

[a] All reactions were conducted at reflux unless noted otherwise. [b] Isolated yields. [c] Reaction conducted at ambient temperature.

As Table 2 indicates, other lithium salts associated with weakly coordinating anions also effectively catalyzed the reaction in benzene at reflux. Use of catalytic lithium hexafluorophosphate (Table 2, entry 3), which appears to be insoluble in benzene at reflux, resulted in complete conversion of **1** into **2** after just a few hours. Lithium tetrafluoroborate (Table 2, entry 4) exhibited some catalytic activity; however, the reaction rate was 1 order of magnitude slower. Lithium cobalt bisdicarbollide, which has been shown to catalyze the 1,4-addition of silyl ketene acetals to α,β-unsaturated carbonyl compounds,[17] was a very effective promoter of the cycloaddition, giving rise to an 80% yield of **2** in only 2 h (Table 2, entry 5). In all the cases examined in Table 2, no (±)-eburnamonine was detected. Thus, it would appear that lithium salts can be effective catalysts for imino Diels–Alder reactions of the type **1** → **2** and constitute an alternative to the use of protic acid.

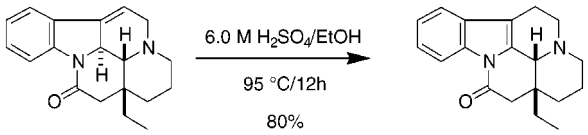
A final observation on the cycloaddition of **1** is warranted, which arose from a fortuitous discovery that occurred during chromatography of imine **1**. Purification of **1** was usually performed by silica gel chromatography with a trace of triethylamine present in the eluant. Often, the ^1H NMR spectrum of "purified" **1** exhibited trace amounts of 3-vinyl indole and lactone **28**, the usual byproducts encountered during the fluoride-induced cleavage of carbamate **11**. Concerned that these undesired products were produced during the silica gel chromatography, Florisil (magnesium polysilicate) was employed as a chromatographic support. Surprisingly, trace amounts of cycloadduct **2** were observed in what should have been pure fractions of imine **1**. Cycloadduct **2** had never been observed during chromatography on silica gel, even in the absence of added triethylamine. When a solution of imine **1** in ethyl acetate was treated with an 8-fold excess by weight of Florisil (200–300 mesh) for 40 h, a 47% yield of cycloadduct **2** was isolated along with 42% of recovered **1**. Complete conversion of **1** into **2** could be accomplished by gentle heating. Thus, heating (50 °C) a 0.05 M solution of imine **1** in ethyl acetate containing an 8-fold excess of Florisil gave rise after 9 h to **2** in 82% isolated yield.



1 **2**

In recent years, there has been increasing interest in the use of insoluble or immobilized catalysts in organic chemistry for a variety of applications, including [4 + 2] cycloadditions.[18] Diels–Alder reactions have been catalyzed by silica gel, alumina, montmorillonite clays, and zeolites.[19] Less common has been the use of Florisil.[20] With respect to imino Diels–Alder reactions, the cycloaddition of imine **1** is the first report of an imine–diene cycloaddition promoted by Florisil. Whether the enhanced reactivity of Florisil relative to protic acid (Table 1) is due to simple magnesium(II) catalysis or is a function of proximity effects imposed by the adsorption of imine **1** on the solid support is not clear at this time. It is clear, however, that Florisil represents an interesting catalyst for substrate **1** and might find application in other imino Diels–Alder reactions.

While catalysis by lithium cation and Florisil provided an excellent means of attaining pentacyclic adduct **2**, the subsequent conversion of **2** into (±)-eburnamonine (**3**) required an additional step. Best results were obtained employing deoxygenated 6.0 M sulfuric acid in ethanol at reflux (12 h). Under these conditions, synthetic (±)-**3** was made available in 80% yield from **2**. Reduced yields were obtained when the solvent was not deoxygenated. Use of weaker acids gave rise to similar yields, but only after long reaction times. For example, exposure of **2** to 10.0 equiv of trifluoroacetic aced in benzene at reflux provided racemic eburnamonine in 81% yield, but only after 90 h. Increasing the reaction temperature resulted in increased reaction rates; however, substantially lower yields were obtained. The olefin in pentacyclic substrate **2** could also be isomerized employing rhodium trichloride in ethanol at 95 °C.[21] Under these conditions, a 69% yield of (±)-**3** was isolated.



2 **3**

The crystalline (±)-eburnamonine (**3**), mp 199.5–200.5 °C [lit.[5] mp 200–202 °C], obtained from **2** was spectroscopically indistinguishable from an authentic sample of (–)-eburnamonine. The total synthesis of racemic **3** was accomplished in 11 steps [16% overall yield] from δ-valerolactam and establishes the intramolecular imino Diels–

(17) Dubay, W. J.; Grieco, P. A.; Todd, L. J. *J. Org. Chem.* **1994**, *59*, 6898.

(18) For general references, see: (a) Izumi, Y.; Urabe, K.; Onaka, M. *Zeolite, Clay, and Heteropoly Acid in Organic Reactions*; VCH: New York, 1992. (b) Smith, K., Ed. *Solid Supports and Catalysts in Organic Synthesis*; Prentice Hall: New York, 1992. (c) Clark, J. H. *Catalysis of Organic Reactions by Supported Inorganic Reagents*; VCH: New York, 1994.

(19) Pagni, R. M.; Kabalka, G. W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* **1993**, *49*, 6743.

(20) Veselvsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenkov, A. M.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175.

(21) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

Alder reaction as a viable stereocontrolled strategy for the construction of the eburnane pentacyclic skeleton.

Experimental Section

Infrared spectra were recorded in chloroform or carbon tetrachloride as indicated. High-resolution mass spectra were performed using either chemical ionization (CI) or electron impact ionization (EI) as indicated. Melting points were determined on a capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Robertson Laboratory, Inc., Madison, NJ. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded at 400 MHz, and ^{13}C magnetic resonance spectra were recorded at 100 MHz.

Unless otherwise stated, all experiments were run in oven-dried glassware under an argon atmosphere using anhydrous solvents. The solvents were dried and distilled as indicated below. Tetrahydrofuran, diethyl ether, benzene, and toluene were purified by distillation from sodium benzophenone ketyl. Diisopropylamine, triethylamine, diisopropylethylamine, hexamethylphosphoramide, dimethylformamide, and dichloromethane were purified by distillation from calcium hydride. Chloroform was purified by washing with water, drying with anhydrous magnesium sulfate, and distilling from phosphorus pentoxide. Lithium perchlorate was purchased anhydrous and was further dried at 180 °C under high vacuum for 24 h prior to use. Other reagents and solvents were reagent grade and were used as received.

E. Merck silica gel #9385 (230−400 mesh) was used for flash chromatography. Kieselgel 60 F_{254} silica plates (0.25 mm, EM Science) were used for analytical thin-layer chromatography. The plates were visualized by immersion in *p*-anisaldehyde solution, phosphomolybdic acid solution, ninhydrin solution, or cobalt(II) thiocyanate solution.

3-Ethyl-2-oxopiperidine-1-carboxylic Acid [2-(Trimethylsilyl)ethyl] Ester (14). A solution comprising 1.71 g (17.2 mmol) of distilled δ-valerolactam in 40 mL of anhydrous tetrahydrofuran under argon was degassed at −78 °C and warmed to 0 °C. To this solution was added 14.0 mL (35.0 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. After 20 min at 0 °C, 2.0 mL (25 mmol) of freshly distilled ethyl iodide was added. The reaction mixture was stirred for another 20 min at 0 °C before 4.92 g (17.3 mmol) of 2-(trimethylsilyl)-ethyl 4-nitrophenyl carbonate was added in 15 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred an additional 20 min at 0 °C and diluted with 400 mL of ether. The resulting solution was washed with water and saturated aqueous brine. The combined aqueous washings were extracted with ether. The combined organics were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The oily residue was chromatographed on 150 g of silica. Elution with hexanes−ethyl acetate (7:1) afforded 3.24 g (69%) of **14** as a pale yellow oil (Kugelrohr distillation, 130−134 °C, 1 Torr): R_f 0.25 (hexanes−ether 3:1); IR ($CHCl_3$) 1735, 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (m, 2 H), 3.79 (ddd, J = 12.9, 7.7, 5.0 Hz, 1 H), 3.66 (m, 1 H), 2.34 (m, 1 H), 2.05−1.74 (m, 4 H), 1.52 (m, 2 H), 1.11 (m, 2 H), 0.96 (t, J = 7.3 Hz, 3 H), 0.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 154.6, 65.4, 45.8, 45.2, 25.4, 24.1, 21.6, 17.6, 11.5, −1.6; high-resolution MS (EI) calcd for $C_{13}H_{25}NO_3Si$ *m/e* 271.1604, found 271.1617.

5-Ethyl-3,4-dihydro-2*H*-pyridine-1-carboxylic Acid [2-(Trimethylsilyl)ethyl] Ester (15). A solution of 2.63 g (10.3 mmol) of lithium tri-*tert*-butoxyaluminohydride in 20 mL of anhydrous tetrahydrofuran was cooled to −50 °C. To this solution was added 2.60 g (9.57 mmol) of lactam carbamate **14** in 10 mL of anhydrous tetrahydrofuran. After 15 min, the reaction mixture was warmed to −20 °C over 30 min and quenched at −20 °C by the dropwise addition of 2 mL of water. The reaction mixture was diluted with water and extracted with dichloromethane. The combined extracts were washed with saturated aqueous brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo to afford an oily residue. The residue was dissolved in 20 mL of ether. Two drops of concentrated sulfuric acid were added. The reaction mixture was stirred for 2 h at ambient temperature, dried with anhydrous potassium carbonate and magnesium sulfate, and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation to afford 2.13 g of enamide **15** as a colorless liquid, bp 100−110 °C, 1 Torr. Chromatography of the undistilled residue on 15 g of silica (hexanes−ethyl acetate 19:1) produced an additional 0.12 g of **15** (92% total yield): R_f 0.66 (hexanes−ether, 3:1); IR ($CHCl_3$) 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 and 6.56 (s, 1 H), 4.23 (m, 2 H), 3.53 (m, 2 H), 1.98 (m, 4 H), 1.81 (m, 2 H), 1.06−0.99 (m, 5 H), 0.04 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4 (153.7), 120.1 (120.5), 118.9 (119.3), 63.7 (63.6), 41.6 (41.8), 28.1, 25.0 (24.8) 21.7 (21.8), 17.7, 12.6, −1.5; high-resolution MS (EI) calcd for $C_{13}H_{25}NO_2Si$ *m/e* 255.1656, found 255.1667.

6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7β-dicarboxylic Acid 7-Ethyl Ester 2-[2-(Trimethylsilyl)ethyl] Ester (16) and 6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7α-dicarboxylic Acid 7-Ethyl Ester 2-[2-(Trimethylsilyl)ethyl] Ester (17). To a suspension of 38 mg of freshly prepared copper−bronze[11] in 1.12 g (4.41 mmol) of enamide **15** at 135 °C was added dropwise over 2 h 2.80 mL (26.6 mmol) of ethyl diazoacetate. The stirring was continued for 15 min. The cooled reaction mixture was chromatographed on 100 g of silica gel. Elution with hexanes−ether−triethylamine (9:1:0.01) afforded 493 mg (33%) of exo ester **16** as a colorless oil: R_f 0.30 (hexanes−ether 3:1); IR ($CHCl_3$) 1720, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (m, 4 H), 3.79 (br d, J = 12.6 Hz, 0.7 H), 3.64 (br d, J = 11.8 Hz, 0.3 H), 3.45 (d, J = 3.2 Hz, 0.3 H), 3.33 (d, J = 3.5 Hz, 0.7 H), 2.59 (m, 1 H), 2.01 (m, 1 H), 1.73−1.58 (m, 5 H), 1.31 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 1.00 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (170.8), 156.6 (156.0), 63.4, 60.1, 43.9, 40.8 (41.3), 33.2 (32.6), 31.1 (30.6), 25.8, 25.7, 21.4, 17.7, 14.2, 10.3, −1.6; high-resolution MS (CI) calcd for $C_{17}H_{31}NO_4Si$ *m/e* 341.2023, found 341.2027.

Further elution with hexanes−ether−triethylamine (9:1:0.01) afforded 460 mg (31%) of endo ester **17** as a colorless oil: R_f 0.23 (hexanes−ether 3:1); IR ($CHCl_3$) 1715, 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 2 H), 4.04 (m, 2 H), 3.36−3.18 (m, 2 H), 3.00 (d, J = 6.5 Hz, 0.45 H), 2.91 (d, J = 6.5 Hz, 0.55 H), 1.85−1.62 (m, 3 H), 1.58−1.47 (m, 2 H), 1.42 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.20 (m, 1H), 0.98 (m, 5H), 0.02 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (169.8), 157.0 (157.3), 63.1 (63.3), 59.8, 42.4 (42.5), 39.5 (39.7), 33.0 (32.8), 31.6 (31.3), 28.7 (28.0), 21.5 (21.6), 19.8 (19.7), 17.8 (17.6), 14.2 (14.1), 9.8, −1.5; high-resolution MS (EI) calcd for $C_{17}H_{31}NO_4Si$ *m/e* 341.2023, found 341.2021.

Boron Trifluoride-Catalyzed Equilibration of Ester 17 to 16. A solution comprising 288 mg (0.843 mmol) of ester **17** in 5 mL of anhydrous dichloromethane at −20 °C was treated with 15 μL (0.12 mmol) of borontrifluoride etherate. The reaction mixture was allowed to warm to 0 °C over 1 h and stirred for 3 h at 0 °C. Triethylamine (0.2 mL, 14 mmol) was added to the reaction mixture. The solution was diluted with ether and washed with water and saturated aqueous brine. The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The isomers were separated by chromatography on 100 g of silica gel. Elution with hexanes−ether (5:1) afforded 241 mg (84%) of exo ester **16**. Further elution afforded 24 mg (8%) of endo ester **17**.

6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7β-dicarboxylic Acid 2-[2-(Trimethylsilyl)ethyl] Ester (8). To a stirred solution of 657 mg (1.92 mmol) of ester **16** in 5 mL of a solution comprising ethanol−tetrahydrofuran−water (3:1:1) at 0 °C was added 736 mg (18.4 mmol) of sodium hydroxide. The reaction was stirred for 90 min at 0 °C and 2 h at ambient temperature. The reaction mixture was quenched by the addition of water and made acidic (pH 4) with 1 N hydrochloric acid. The product was isolated by extraction with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 590 mg (99%) of acid **8** as a colorless oil that solidified on standing: IR ($CHCl_3$) 3500−2500 (br), 1690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 2 H), 3.82 (br d, J = 13 Hz, 0.65 H), 3.68 (br d, J = 13 Hz,

0.35 H), 3.51 (br d, $J = 3.4$ Hz, 0.35 H), 3.41 (br d, $J = 3.6$ Hz, 0.65 H), 2.66 (m, 1 H), 2.04 (m, 1 H), 1.76−1.64 (m, 4 H), 1.63 (br d, $J = 3.4$ Hz, 1 H), 1.34 (m, 1 H), 1.01 (m, 2 H), 0.92 (t, $J = 7.4$ Hz, 3 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (176.9), 156.7 (156.3), 63.9, 44.8, 40.9 (41.4), 34.5 (33.9), 31.0 (30.7), 26.0, 25.8, 21.4, 17.7 (17.8), 10.3, −1.5; high-resolution MS (EI) calcd for $C_{15}H_{27}NO_4Si$ *m/e* 313.1710, found 313.1696. An analytical sample was prepared by recrystallization from pentane: mp 94.5−96.0 °C. Anal. Calcd for $C_{15}H_{27}NO_4Si$: C, 57.47; H, 8.68; N, 4.47. Found: C, 57.69; H, 8.61; N, 4.31.

6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7α-dicarboxylic Acid 2-[2-(Trimethylsilyl)ethyl] Ester (18). To a stirred solution of 113 mg (0.331 mmol) of ester **17** in 0.5 mL of a solution comprised of ethanol−tetrahydrofuran−water (3:1:1) at 0 °C was added 190 mg (4.75 mmol) of sodium hydroxide. The reaction was stirred for 1 h at 0 °C and 10 h at ambient temperature. The reaction mixture was poured into water and made acidic (pH 4) with 1 N hydrochloric acid. The product was isolated by extraction with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 68 mg (66%) of acid **18** as a colorless oil that solidified on standing: IR ($CHCl_3$) 3600−2500 (br), 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (m, 2 H), 3.31−3.14 (m, 2 H), 3.03 (br d, $J = 6.2$ Hz, 0.45 H), 3.00 (br d, $J = 6.2$ Hz, 0.55 H), 1.84−1.64 (m, 3 H), 1.60−1.46 (m, 2 H), 1.41 (m, 1 H), 1.21 (m, 1 H), 1.01−0.94 (m, 5 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (175.0), 157.1 (157.6), 63.5, 42.4 (42.5), 40.5, 33.0 (32.9), 32.8 (32.3), 28.4 (27.8), 21.4 (21.6), 19.8, 17.7, 9.9, −1.5; high-resolution MS (EI) calcd for $C_{15}H_{27}NO_4Si$ *m/e* 313.1710, found 313.1705. An analytical sample was prepared by recrystallization from pentane: mp 101.5−103.0 °C. Anal. Calcd for $C_{15}H_{27}NO_4Si$: C, 57.47; H, 8.68; N, 4.47. Found: C, 57.39; H, 8.79 N, 4.38.

6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7β-dicarboxylic Acid 7-(4-Nitrophenyl) Ester 2-[2-(Trimethylsilyl)ethyl] Ester (9). To a stirred solution of 141 mg (0.45 mmol) of acid **8**, 125 mg (0.899 mmol) of *p*-nitrophenol, and 82 mg (0.67 mmol) of 4-(dimethylamino)pyridine in 2.0 mL of anhydrous dichloromethane at 0 °C was added 183 mg (0.888 mmol) of dicyclohexylcarbodiimide. The solution was stirred for 90 min at 0 °C and then poured into 50 mL of ether. The organic layer was washed exhaustively with saturated aqueous brine until the washings were no longer yellow in color. The combined aqueous washings were extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on 20 g of silica gel. Elution with hexanes−ether (2:1) afforded 168 mg (86%) of activated ester **9** as an oil that solidified on standing: R_f 0.50 (hexanes−ether 1:1); IR ($CHCl_3$) 1745, 1695, 1620, 1600 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (m, 2 H), 7.27 (m, 2 H), 4.21 (m, 2 H), 3.86 (br d, $J = 12.9$ Hz, 0.65 H), 3.72 (br d, $J = 12.6$ Hz, 0.35 H), 3.62 (br d, $J = 3.2$ Hz, 0.35 H), 3.52 (br d, $J = 3.5$ Hz, 0.65 Hz), 2.70 (m, 1 H), 2.12 (m, 1 H), 1.87 (d, $J = 3.7$ Hz, 1 H), 1.82−1.70 (m, 4 H), 1.40 (m, 1 H), 1.08−0.96 (m, 2 H), 0.96 (t, $J = 7.4$ Hz, 3 H), 0.03 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 156.5, 155.5, 145.1, 125.1 (125.0), 122.2 (122.4), 63.9, 45.8, 40.9 (41.4), 35.5 (35.0), 31.0 (30.6), 25.9, 25.8, 21.5, 18.0 (17.8), 10.5, −1.5; high-resolution MS (EI) calcd for $C_{21}H_{30}N_2O_6Si$ *m/e* 434.1874, found 434.1875. An analytical sample was prepared by recrystallization for pentane: mp 77.5−78.5 °C. Anal. Calcd for $C_{21}H_{30}N_2O_6Si$: C, 58.03; H, 6.96; N, 6.44. Found: C, 57.91; H, 7.12; N, 6.38.

6β-Ethyl-2-azabicyclo[4.1.0]heptane-2,7α-dicarboxylic Acid 7-(4-Nitrophenyl) Ester 2-[2-(Trimethylsilyl)ethyl] Ester (27). To a stirred solution of 17 mg (0.054 mmol) of acid **18**, 16 mg (0.11 mmol) of *p*-nitrophenol, and 12 mg (0.098 mmol) of 4-(dimethylamino)pyridine in 0.4 mL of anhydrous dichloromethane at 0 °C was added 22 mg (0.11 mmol) of dicyclohexylcarbodiimide. The solution was stirred for 2 h at 0 °C and then poured into 10 mL of ether. The organic layer was washed exhaustively with saturated aqueous brine until the washings were no longer yellow in color. The combined aqueous washings were extracted with ether, and the combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on 10 g of silica gel. Elution with hexanes−ether (2:1) afforded 22 mg (93%) of activated ester **27** as a colorless oil: R_f 0.50 (hexanes−ether, 1:1); IR ($CHCl_3$) 1750, 1685, 1620, 1595 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (m, 2 H), 7.28 (m, 2 H), 3.40−3.21 (m, 3 H), 1.94−1.76 (m, 4 H), 1.65 (m, 1 H), 1.50 (m, 1 H), 1.37 (m, 1 H), 1.08 (t, $J = 7.2$ Hz, 3 H), 1.00 (m, 1 H), 0.06 and 0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3 (166.9), 157.5 (156.8), 155.8 (155.5), 145.1, 125.0 (125.1), 122.7 (122.2), 63.7 (63.6), 42.8 (42.5), 41.7 (41.5), 33.9 (33.7), 32.6 (33.0), 28.3 (28.8), 21.5 (21.4), 19.6 (19.9), 17.7 (18.1), 10.0, −1.5; high-resolution MS (EI) calcd for $C_{21}H_{30}N_2O_6Si$ (M^+) *m/e* 434.1874, found 434.1873.

6β-Ethyl-7β-(3-formylindole-1-carbonyl)-2-azabicyclo-[4.1.0]heptane-2-carboxylic Acid 2-[2-(Trimethylsilyl)-ethyl] Ester (10). From Activated Ester 9. To a stirred solution of 49 μL (0.35 mmol) of diisopropylamine in 1 mL of anhydrous tetrahydrofuran at −78 °C was added 140 μL (0.34 mmol) of a 2.45 M solution of *n*-butyllithium in hexanes. After 15 min, 48 mg (0.33 mmol) of indole-3-carboxaldehyde in 1 mL of anhydrous tetrahydrofuran was added. Stirring was continued at −78 °C. After 30 min, 118 mg (0.272 mmol) of ester **9** was added in 2 mL of anhydrous tetrahydrofuran. The reaction was allowed to slowly warm to −20 °C over 30 min and was stirred 30 min at −20 °C. The cold reaction mixture was poured into 25 mL of aqueous pH 6 buffer solution. The crude product was isolated by extraction with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on 25 g of silica. Elution with hexanes−ethyl acetate (2:1) afforded 93 mg (77%) of amide **10** as a viscous oil: R_f 0.43 (hexanes−ethyl acetate 1:1); IR ($CHCl_3$) 1715, 1685, 1620, 1560 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.14 and 10.11 (s, 1 H), 8.35−8.18 (m, 3 H), 7.40 (m, 2 H), 4.16 (m, 2 H), 3.90 (m, 1 H), 3.83 (br d, $J = 3.2$ Hz, 0.65 H), 3.78 (br d, $J = 12.8$ Hz, 0.35 H), 2.86−2.71 (m, 1 H), 2.27 (d, $J = 3.5$ Hz, 1 H), 2.21 (m, 1 H), 1.92−1.80 (m, 2 H), 1.74 (q, $J = 7.3$ Hz, 2 H), 1.52 (m, 1 H), 1.02−0.79 (m, 2 H), 0.87 (t, $J = 7.3$ Hz, 3 H), 0.01 and −0.01 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.6, 168.6 (168.4), 156.4 (156.1), 136.3, 134.7 (134.9), 126.5 (126.4), 126.0, 125.1 (125.0), 122.1, 121.9 (121.7), 115.8 (116.0), 63.9, 45.2 (45.0), 40.8 (41.4), 37.3 (36.7), 33.3 (32.9), 25.8 (25.7), 25.5, 21.7, 17.7, 10.5, −1.6; high-resolution MS (EI) calcd for $C_{24}H_{32}N_2O_4Si$ *m/e* 440.2133, found 440.2151.

From Carboxylic Acid 8. A solution comprising 90 mg (0.29 mmol) of acid **8** in 7 mL of ether was treated with 40 μL (0.29 mmol) of triethylamine. After 5 min, the resultant solution was chilled to 0 °C and treated with 0.25 mL (2.9 mmol) of freshly distilled oxalyl chloride. The cooling bath was removed, and the heterogeneous solution was allowed to warm to ambient temperature over 1 h. The reaction was filtered through an oven-dried sintered glass filter and the solvent and excess oxalyl chloride were removed in vacuo. A 25 mL round-bottom flask was charged with 84 mg (0.58 mmol) of indole-3-carboxaldehyde and 3.0 mL of tetrahydrofuran. The resultant solution was cooled to −78 °C and was treated with 0.58 mL of a 1.0 M solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran. The resultant solution was allowed to warm to 0 °C for 15 min before being recooled to −78 °C. To this solution was added the above prepared acid chloride (**19**) in 2.0 mL of tetrahydrofuran. After 30 min, the cold solution was poured into 17 mL of phosphate buffered pH 7 solution. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo. The residue was chromatographed on 25 g of silica gel. Elution with hexanes−ethyl acetate (1:1) afforded 66 mg (52%) of amide **10**.

6β-Ethyl-7β-(3-vinyl-indole-1-carbonyl)-2-azabicyclo-[4.1.0]heptane-2-carboxylic Acid 2-[2-(Trimethylsilyl)-ethyl] Ester (11). To a stirred suspension of 54 mg (0.15 mmol) of methyltriphenylphosphonium bromide in 2 mL of anhydrous tetrahydrofuran was added 0.15 mL (0.15 mmol) of a 1.0 M solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran. The resultant bright yellow solution was

stirred for 1 h at ambient temperature and then cooled to −78 °C for 10 min. To this suspension was added 58 mg (0.13 mmol) of aldehyde **10** in 3 mL of tetrahydrofuran. The reaction was stirred for 20 min at −78 °C and then filtered (at −78 °C) through a pad of Celite. The Celite was washed with ether, and the filtrate and washings were concentrated in vacuo. The residue was chromatographed on 10 g of silica gel. Elution with hexanes−ethyl acetate (4:1) afforded 50 mg (86%) of vinyl indole **11** as a colorless oil: R_f 0.48 (hexanes−ethyl acetate 3:1); IR ($CHCl_3$) 1695, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 8.0 Hz, 1 H), 7.82 (m, 1 H); 7.53 (s, 1 H), 7.35 (m, 2 H), 6.82 (dd, J = 17.7, 11.3 Hz, 1 H), 5.83 (br d, J = 17.7 Hz, 1 H), 5.39, (br d, J = 11.3 Hz, 1 H), 4.16 (m, 2 H), 3.90 (m, 1 H), 3.76 (br d, J = 3.2 Hz, 1 H), 2.73 (m, 1 H), 2.22 (br d, J = 3.2 Hz, 1 H), 2.18 (m, 1 H), 1.84 (m, 2 H), 1.70 (m, 2 H), 1.51 (m, 1 H), 1.01−0.87 (m, 2 H) 0.86 (t, J = 7.4 Hz, 3 H), 0.03 and −0.05 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (168.0), 156.7 (156.1), 136.3, 128.5, 127.9 (128.0), 125.2, 123.6, 122.8, 120.5, 119.9 (119.7), 116.3 (116.5), 115.1 (114.9), 63.8 (63.7), 43.9 (43.6), 40.9 (41.4), 35.7 (35.2), 33.4 (33.0), 25.8, 25.7, 21.9, 17.7, 10.5, −1.6; high-resolution MS (EI) calcd for $C_{25}H_{34}N_2O_3Si$ *m/e* 438.2340, found 438.2357.

2-(3-Ethyl-3,4,5,6-tetrahydropyridin-3-yl)-1-(3-vinylindol-1-yl)ethanone (1). To a dry 15 mL round-bottom flask was added 149 mg (0.88 mmol) of powdered benzyltrimethylammonium fluoride. The flask was heated at 50 °C under vacuum (0.5 Torr) for 24 h, at which time 240 mg of crushed 4-Å sieves and 1.5 mL of anhydrous tetrahydrofuran were added. The heterogeneous solution was stirred vigorously at 45 °C for 90 min. Carbamate **11** (48 mg, 0.11 mmol) was added in 4.0 mL of tetrahydrofuran. Vigorous stirring was continued for 8 h at 45 °C. The cooled reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The crude product was purified by rapid chromatography on 15 g of silica gel. Elution with ethyl acetate afforded 26 mg (81%) of the imine **1** as a colorless oil: R_f 0.17 (ethyl acetate); IR (CCl_4) 1715, 1650, 1640, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 8.0 Hz, 1 H), 7.80 (dd, J = 7.2, 1.1 Hz, 1 H), 7.73 (br s, 1 H), 7.45 (s, 1 H), 7.38 (td, J = 7.6, 1.3 Hz, 1 H), 7.32 (td, J = 7.6, 1.3 Hz, 1 H), 6.80 (dd, J = 17.7, 11.8 Hz, 1 H), 5.83 (dd, J = 17.7, 1.0 Hz, 1 H), 5.40 (dd, J = 11.5, 1.0 Hz, 1 H), 3.60 (m, 2 H), 3.01 and 2.96 (AB quartet, J = 16.1 Hz, 2 H), 1.88 (m, 1 H), 1.82−1.61 (m, 5 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 167.3, 136.5, 128.6, 127.7, 125.6, 124.0, 122.4, 121.0, 119.9, 117.0, 115.6, 49.1, 42.0, 39.2, 30.2, 28.1, 19.1, 8.3; high-resolution MS (EI) calcd for $C_{19}H_{22}N_2O$ *m/e* 294.1734, found 294.1742.

(13aβ,13bβ,13cα)-13a-Ethyl-2,3,5,12,13,13a,13b,13c-octahydro-12-oxo-1*H*-indolo[3,2,1-*de*]pyrido[3,2,1-*ij*][1,5]-naphthyridine (2). In 5.0 M $LiClO_4$−Ether. To a stirred solution of 11.5 mg (0.039 mmol) of imine **1** dissolved in 3.9 mL of a 5.0 M solution of lithium perchlorate in ether was added 25 μL of a 0.16 M solution of camphorsulfonic acid in tetrahydrofuran. The reaction mixture was stirred at ambient temperature. After 60 h, the reaction mixture was partitioned between water and ether. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on 8 g of silica gel. Elution with hexanes−ethyl acetate (1:1) afforded 11.1 mg (96%) of cycloadduct **2** as an opaque film: R_f 0.46 (ethyl acetate); IR (CCl_4) 1670, 1610, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.0 Hz, 1 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.25 (td, J = 7.8, 1.0 Hz, 1 H), 7.07 (td, J = 7.5, 1.0 Hz, 1 H), 5.78 (m, 1 H), 4.80 (m, 1 H), 3.79 (dt, J = 19.6, 3.8 Hz, 1 H), 3.36 (dt, J = 19.3, 3.0 Hz, 1 H), 2.80 (td, J = 10.9, 4.0 Hz, 1 H), 2.68 (m, 1 H), 2.60 (d, J = 9.9 Hz, 1 H), 2.56 and 2.38 (AB quartet, J = 18.4 Hz, 2 H), 1.82 (m, 2 H), 1.71−1.52 (m, 4 H), 0.89 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 143.1, 134.7, 129.3, 129.2, 124.3, 120.7, 116.8, 115.5, 60.6, 55.5, 52.5, 48.5, 45.3, 36.0, 29.8, 29.5, 21.5, 7.6; high-resolution MS (EI) calcd for $C_{19}H_{22}N_2O$ *m/e* 294.1734, found 294.1739. An analytical sample was prepared by recrystallization from pentane-dichloromethane: mp 119.0−120.5 °C. Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.28; H, 7.73; N, 9.41.

Thermal Cycloaddition. A solution of 6.2 mg (0.021 mmol) of imine **1** in 4.0 mL of 1,2-dichlorobenzene was refluxed in a sealed tube at 180 °C for 22 h. The product was isolated by removal of the solvent under reduced pressure and chromatography on silica gel (5 g). Elution with ethyl acetate afforded 2.0 mg (32%) of cycloadduct **2**. Further elution with ethyl acetate allowed the recovery of 2.9 mg (47%) of imine **1**.

Trifluoroacetic Acid Catalyzed. A solution of 6.2 mg (0.021 mmol) of imine **1** in 2.2 mL of benzene at ambient temperature was treated with 48 μL (0.024 mmol) of a 0.5 M solution of trifluoroacetic acid in benzene. The resultant solution was refluxed for 3 h and then diluted with ether and washed successively with saturated aqueous bicarbonate water and saturated brine. The organic layer was dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed on 5 g of silica gel. Elution with ethyl acetate afforded 4.4 mg (70%) of cycloadduct **2**. Further elution with ethyl acetate afforded 0.3 mg (5%) of (±)-eburnamonine (**3**).

Florisil Catalyzed. A heterogeneous solution of 7.4 mg (0.25 mmol) of imine **1** and 62 mg of Florisil (Aldrich 100−200 mesh) was stirred in 0.5 mL of ethyl acetate at 50 °C for 9 h. The cooled reaction mixture was filtered, and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated in vacuo and chromatographed on 6 g of silica gel. Elution with ethyl acetate afforded 6.1 mg (82%) of cycloadduct **2**.

$LiCo(B_9C_2H_{11})_2$ Catalyzed. A solution comprising 12.5 mg (0.0424 mmol) of imine **1** and 0.3 mg (0.0009 mmol) of $LiCo(B_9C_2H_{11})_2$ in 4.0 mL of benzene was refluxed for 2 h. The cooled reaction mixture was concentrated in vacuo and chromatographed on silica gel to afford 10.0 mg (80%) of cycloadduct **2**.

(±)-Eburnamonine (3). A solution comprising 8.1 mg (0.028 mmol) of cycloadduct **2** and 0.9 mL of a 6.0 M solution of sulfuric acid in ethanol was degassed at −78 °C and then sealed under argon and heated to 95 °C. After 12 h, the cooled reaction mixture was diluted with water and made basic with a saturated aqueous sodium bicarbonate solution. The crude product was isolated by extraction with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed on 5 g of silica gel. Elution with ethyl acetate afforded 6.5 mg (80%) of (±)-eburnamonine (**3**), spectroscopically indistinguishable from a sample of (−)-eburnamonine: R_f 0.26 (ethyl acetate); IR (CCl_4) 1710, 1630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (br d, J = 7.5 Hz, 1 H), 7.43 (br d, J = 7.2 Hz, 1 H), 7.30 (m, 2 H), 3.97 (s, 1 H), 3.37−3.21 (m, 2 H), 2.90 (m, 1 H), 2.66 and 2.59 (AB quartet, J = 16.7 Hz, 2 H), 2.60 (m, 1 H), 2.49 (ddd, J = 16.9, 5.6, 2.4 Hz, 1 H), 2.41 (td, J = 12.0, 3.2 Hz, 1 H), 2.04 (m, 1 H), 1.76 (qt, J = 13.2, 3.9 Hz, 1 H), 1.66 (m, 1 H), 1.49 (br d, J = 13.4 Hz, 1 H), 1.39 (m, 1 H), 1.03 (td, J = 13.5, 3.8 Hz, 1 H), 0.93 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 134.2, 131.9, 130.0, 124.3, 123.8, 118.0, 116.2, 57.7, 50.7, 44.4, 44.3, 38.4, 28.4, 26.9, 20.6, 16.5, 7.7. An analytical sample was prepared by recrystallization from ethanol: mp 199.5−200.5 °C (lit.[4] mp 200−202 °C). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.23; H, 7.63; N, 9.49.

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Supporting Information Available: Copies of the ^1H and ^{13}C NMR spectra for compounds **1**−**3**, **10**, **11**, **14**−**17**, and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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