Asymmetric Synthesis of (−)-Eburnamonine and (+)-*epi*-Eburnamonine from (4*S*)-4-Ethyl-4-[2-(hydroxycarbonyl)ethyl]-2-butyrolactone

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The key chiral nonracemic 4,4-disubstituted 2-butyrolactone carboxylic acid, (*S*)-**4**, is readily accessible via an efficient and stereospecific dirhodium(II) tetraacetate catalyzed tertiary C−H insertion reaction of the diazomalonate (*S*)-**5**. The coupling of the acid (*S*)-**4** with tryptamine produces the amide (*S*)-**3**, which is then transformed into the aldehyde **23** and hydroxy-lactam **24**. Acid-mediated Pictet−Spengler cyclization of **23** and **24** produces the tetracyclic indole lactams (1*S*,-12b*S*)-**25a** and (1*S*,12b*R*)-**25b**. Compounds **25a** and **25b** are converted, via the lactam alcohols **30a** and **30b**, to (−)-eburnamonine (**1a**) and (+)-*epi*-eburnamonine (**1b**).

Introduction

Natural products that feature one or more quaternary centers in their molecular architecture have always served as challenging targets to synthetic organic chemists. The strategies devised to tackle the synthesis of these molecules must invariably also address the construction of the quaternary center(s). Indeed, the construction of quaternary centers has been the topic of sustained investigations[1] over the years, and more recently newer approaches addressing the enantioselective construction of quaternary centers have emerged.[2]

We have been interested in the use of 4,4-disubstituted 2-butyrolactones as intermediates in alkaloid synthesis. Interestingly, a survey of the literature revealed that neither the synthesis of these molecules nor their use as intermediates in natural product synthesis has been extensively explored. To our knowledge, only one example of the use of a 4,4-disubstituted 5-hydroxy-2-butyrolactone for the synthesis of a natural product has been reported.[3] We recently described[4] a method, based on the dirhodium(II)−carbenoid-mediated intramolecular tertiary C−H insertion reaction of β-branched diazomalonates, for the synthesis of 4,4-disubstituted 2-butyrolactones. Subsequently, we reported[5] the preparation of an appropriately functionalized 4,4-disubtituted 2-butyrolactone and demonstrated its utility as a synthetic intermediate for the synthesis of quebrachamine. Herein, we detail[6] the results of our studies on the preparation of the chiral nonracemic 2-butyrolactone carboxylic acid **4** and its use in the enantioselective synthesis of (−)-eburnamonine (**1a**), a peripheral and cerebral vasodilator,[7,8a] and its C-3 epimer, (+)-*epi*-eburnamonine (**1b**).

The strategy adopted here for the synthesis of **1a** and **1b** is conceptually different from the ones that have been reported in the recent literature.[8] Two principal approaches have been developed: the first approach utilized appropriately functionalized Δ^1- and Δ^2-piperidine derivatives[8b(ii),c,d] as key intermediates and the second approach used 3,3-disubstituted 2-butyrolactones.[8b(i),e−h]

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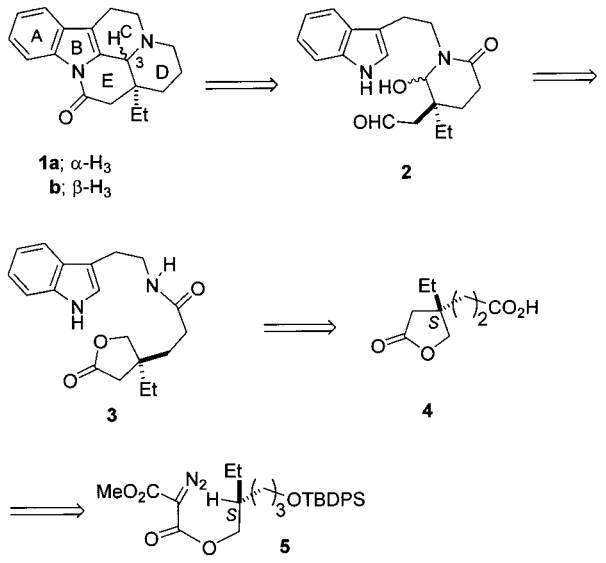
Chart 1. Retrosynthetic Analysis of Eburnamonine (1a) and *epi*-Eburnamonine (1b)



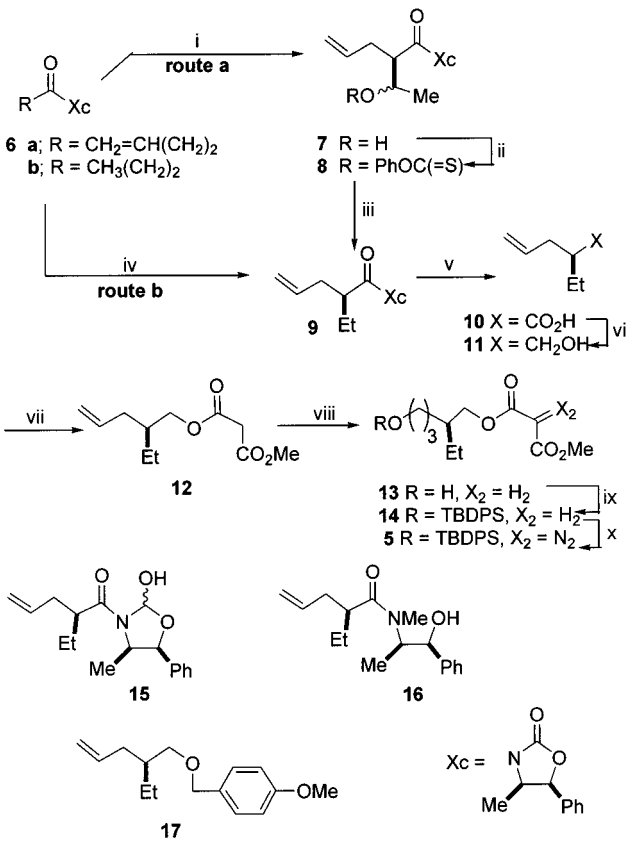
The retrosynthetic analysis for the pentacyclic indole alkaloids eburnamonine (**1a**) and *epi*-eburnamonine (**1b**) is shown in Chart 1. These compounds differ only in the stereochemistry at the D/E ring junction. Therefore, both of these compounds can be accessed from a common precursor; that is, the hydroxy-lactam aldehyde **2**. Compound **2** can be derived from the 2-butyrolactone amide **3**, which in turn, is accessible from the chiral nonracemic 2-butyrolactone carboxylic acid **4**. Compound **4** is prepared via Rh(II)-catalyzed tertiary C−H insertion reaction of the chiral nonracemic diazo compound **5**.

Results and Discussion

Preparation of (*S*)-Diazomalonate (5). The study began with the synthesis of (*S*)-2-ethyl-4-penten-1-ol (**11**), which was required for the preparation of the malonate ester **12** (Scheme 1). Two routes, a and b, for the synthesis of **11** were investigated. The first route (a) entailed an asymmetric aldol reaction coupled with the removal of the hydroxyl group in the aldol product to complete the installation of the ethyl side-chain. Thus, aldol reaction of the readily prepared *N*-(4-pentenoyl)-oxazolidinone (**6a**),[9] via its dibutylboron enolate,[10] with freshly distilled acetaldehyde gave the aldol product **7**.

Compound **7** was obtained as a mixture of two very closely moving stereoisomers that were epimeric only at the carbinol center. No attempt was made to separate the two diastereomers because the carbinol center was inconsequential to the synthesis of **9** since the hydroxyl group in **7** will be deoxygenated[11] in the next step. The secondary alcohol **7** was then converted to the phenyl thionocarbonate[12] **8**, which was then subjected to free-radical reduction using Bu_3SnH to yield compound **9**. The overall yield for this three-step sequence to form **9** was 36%. It is interesting to note that under the free-radical conditions used for the conversion **8** → **9**, the intramolecular cyclization of the secondary carbon-centered free radical onto the terminal double bond to form a cyclobutane derivative was not detected, although the process corresponded to a favored 4-exo-trig cyclization.[13] The absence of such a competing cyclization reaction may be due to the well-known[14] propensity of a (cyclobutyl)-methyl free radical-type intermediate to undergo rapid ring opening to form the more stable 1-pentenyl system.

Scheme 1[a]



[a] (i) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C; MeCHO, −78 °C, 52%; (ii) PhOC(=S)Cl, DMAP, CH_2Cl_2, 92%; (iii) Bu_3SnH, AIBN, PhMe, 75 °C, 76%; (iv) $NaN(SiMe_3)_2$, THF, −78 °C; CH_2=$CHCH_2Br$, −40 °C, 88%; (v) $LiOH·H_2O$, H_2O_2, 3:1 v/v THF−H_2O; 1.5 M $NaHSO_3$, 100%; (vi) $LiAlH_4$, Et_2O, 0 °C to room temperature; aq NaOH, 50%; (vii) $MeO_2CCH_2CO_2H$, DCC, DMAP, CH_2Cl_2, 86%; (viii) disiamylborane, THF, 0 °C; 30% H_2O_2, NaOH, 74%; (ix) TBDPS−Cl, pyridine, 0 °C, 89%; (x) MsN_3, Et_3N, MeCN, 88%.

Although route a provided access to alcohol **11**, the low overall yield of **9** prompted us to investigate route b. This route afforded a higher yield of **9**, which also turned out to be the more direct and preferred route. Therefore, allylation of the sodium enolate[10] derivative of the known[15] *N*-butanoyloxazolidinone **6b** with allyl bromide produced the allylated oxazolidinone **9** in 88% yield. The ^1H and ^{13}C NMR spectra as well as the specific optical rotations of compound **9** obtained via routes a and b were the same.

The removal of the oxazolidinone chiral auxiliary from **9** was not trivial. We found that the usual methods for the removal of the auxiliary group, such as by reduction with lithium aluminum hydride[15] ($LiAlH_4$), led to a mixture of the desired alcohol **11** (and the chiral auxil-

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iary), the carbinol **15**, and the *N*-methyl amino alcohol **16**. The relative proportion of **11**:**15**:**16** was, not surprisingly, found to depend on the reaction temperature. For example, compound **15** was obtained as the major byproduct when the reduction was conducted at −78 °C, whereas at −5 °C both **15** and **16** were formed. These results suggested that the oxazolidinone carbonyl moiety in compound **9** was sterically more accessible than the carbonyl moiety of the 4-pentenoyl unit; presumably the ethyl group at the α-tertiary carbon shielded the carbonyl moiety of the pentenoyl unit from attack by the $LiAlH_4$ reagent.

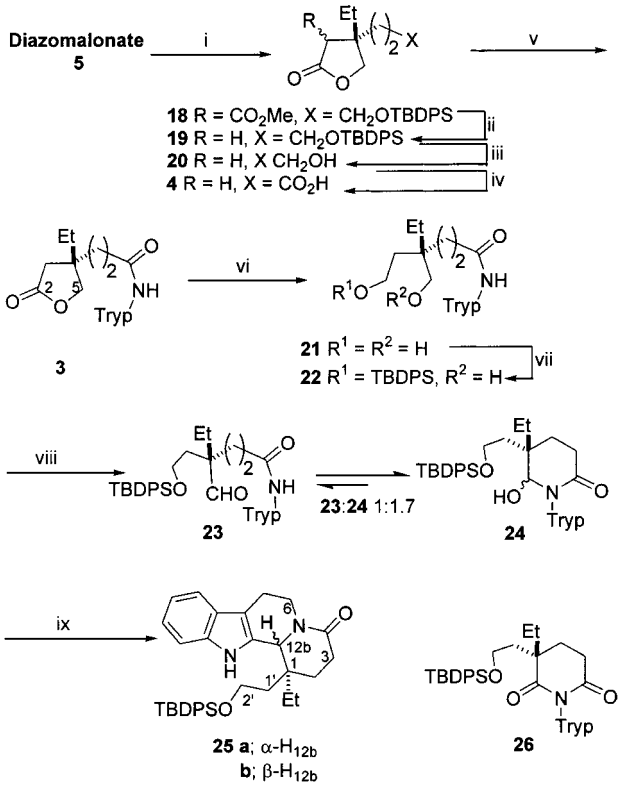
Due to the difficulties encountered in the optimization of reaction conditions for the direct removal of the oxazolidinone auxiliary, we decided to adopt a two-step procedure for the conversion of **9** to the primary alcohol **11** (Scheme 1). This entailed the hydrolysis of **9** under Evans conditions (LiOH, H_2O_2)[16] which led to a quantitative yield of the carboxylic acid **10**. The chiral (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone auxiliary was recovered in 95% yield. Subsequent reduction of **10** with $LiAlH_4$ in diethyl ether gave a 50% yield of the volatile primary alcohol **11**.

The absolute configuration of **11** was confirmed via its conversion to the 4-methoxybenzyl ether derivative **17** and comparison of the specific optical rotation of **17** with that of the known[17a] dextrorotatory (*R*)-enantiomer. Compound **17** {$[\alpha]_D$ −2.8 (*c*, 1.8, $CHCl_3$), 89% ee[17b]} was levorotaory and possessed an optical rotation that was of the same magnitude as the *R*-enantiomer {$[\alpha]_D$ +1.9 (*c*, 2.01, $CHCl_3$)}.

With the primary alcohol in hand, the next stage was to prepare the diazomalonate **5**. Esterification of **11** with α-(methoxycarbonyl)acetic acid mediated by DCC[18] produced the malonate ester **12** in 86% yield. Hydroboration−oxidation of the terminal double bond using disiamylborane[19] followed by alkaline hydrogen peroxide proceeded regioselectively and chemoselectively to furnish a good yield (81%) of the primary alcohol **13**. After protection of the hydroxyl group as the *tert*-butyldiphenylsilyl (TBDPS) ether, **14**, the malonyl unit was diazotized (MsN_3,[20] Et_3N) to obtain the diazomalonate **5**.

Preparation of (*S*)-γ-Lactone Carboxylic Acid (4) and Construction of the Tetracyclic Indole Lactam (25). In our earlier work, we found[5] that $Rh_2(OAc)_4$ was the best catalyst for effecting tertiary C−H insertion in malonate esters. Furthermore, dirhodium(II)−carbenoid insertion into configurationally defined tertiary carbon stereocenters has been found to be stereospecific and to occur with retention of configuration.[21] With these facts in mind, we were confident that the transformation **5** → **18** could be realized. Therefore, the diazomalonate **5** was

Scheme 2[a]



[a] (i) 2 mol % $Rh_2(OAc)_4$, CH_2Cl_2, reflux, 87%; (ii) 10:1 v/v DMSO−H_2O, NaCl, 110 °C, 84%; (iii) Bu_4NF, THF, 93%; (iv) CrO_3, H_2SO_4, H_2O, 95%; (v) tryptamine (Tryp), DCC, DMAP, CH_2Cl_2, 67%; (vi) $LiBH_4$, 5:1 v/v THF-MeOH, rt, 92%; (vii) TBDPS−Cl, imidazole, DMF, 92%; (viii) Py·SO_3, DMSO, Et_3N, rt, 95%; (ix) CF_3CO_2H, CH_2Cl_2, −42 °C (see text also), 95%.

treated with 2 mol % of $Rh_2(OAc)_4$, which proceeded efficiently and with high regioselectivity to provide a 1:1 diastereomeric mixture of the 4,4-disubstituted 2-butyrolactone **18** in 87% yield (Scheme 2). A small amount (8.5%) of the 2-oxetanone product,[5] which was produced via a competitive Rh(II)−carbenoid insertion into the C−H bond adjacent to the ester oxygen, was also isolated. Trace amounts (0.9%) of products derived from the interception of the Rh(II)−carbenoid intermediate by water[5] was also obtained. Subsequent decarboxylation[22] of **18** in aqueous DMSO containing NaCl proceeded smoothly to give the 2-butyrolactone **19** in 84%. The fluoride anion mediated desilylation of **19** proceeded efficiently to yield the primary alcohol **20**, which was subjected to Jones oxidation to give the carboxylic acid **4** in 95% yield.

The carboxylic acid **4** was then coupled to tryptamine (Tryp), mediated by DCC,[18] to give the amide **3**. The next step required the adjustment of the oxidation level at the C-2 and C-5 positions of the 2-butyrolactone moiety in **3**, and this was best achieved via the corresponding diol **21**. We first investigated a two-step reduction protocol: the lactone moiety was first treated with DIBAL-H to

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obtain the lactol intermediate, which was further reduced with $NaBH_4$ to produce the diol **21**. This route, however, was found to be inefficient, and only a 36% yield (over two steps) of the **21** was obtained. After further investigations, it was found that the reduction of **3** using excess $LiBH_4$ in THF−MeOH[8e] led to an excellent yield (92%) of the diol **21**.

The differentiation of the two primary alcohol units in **21** was addressed. We were certain that the regioselective protection of the less-hindered nonneopentylic primary alcohol could be readily achieved. However, this operation proved not to be trivial. We initially explored the selective formation of the mono-benzoate and mono-*tert*-butyldimethylsilyl ether, under various reaction conditions. For example, when the diol **21** was treated with 1 mol equiv of benzoyl chloride in dry pyridine no benzoate (mono and/or di) product was obtained. Interestingly, when the benzoylation was conducted in the presence of a catalytic amount (10 mol %) of *N*,*N*-diisopropylethylamine (Hunig's base) and using a mixture of pyridine and chloroform (1:5 v/v) as solvent, equal amounts of the mono- (**21** $R^1 = Bz$, $R^2 = H$) and dibenzoates (**21** $R^1 = R^2 = Bz$) were obtained, and a very small amount (<2%) of starting diol **21** was also recovered. To achieve efficient monoprotection of **21** and to obtain a good yield of the desired monoprotected product, we investigated the reaction of **21** with the bulkier *tert*-butyldimethylsilyl chloride. However, under the improved reaction conditions (pyridine/$CHCl_3$, catalytic amounts of Hunig's base) alluded to above, no silylation occurred, and only unreacted diol **21** was recovered. On the other hand, silylation of the diol **21** in a mixture of imidazole and DMF[23] afforded a 1.7:1 ratio of the mono- (**21**, R^1 = TBDMS, $R^2 = H$) to bis- (**21**, $R^1 = R^2$ = TBDMS) silyl ethers. It was eventually found that the best method consisted of the use of the sterically more demanding TBDPS-chloride in imidazole/DMF;[23] under these conditions the mono-silyl ether **22** was obtained as the predominant product (mono:bis; 14:1) and in a high yield of 93%. It is useful to note that no silyl ether product was formed when the silylation was conducted in either pyridine or pyridine/$CHCl_3$ containing a catalytic amount of Hunig's base.

With the hydroxyl groups differentiated, the oxidation of the neopentylic primary alcohol moiety in **22** to the aldehyde **23** was investigated. Several oxidation methods were considered, and on the basis of literature reports[8e,24] on the mildness of the tetrapropylammonium perruthenate (TPAP)-catalyzed oxidation reaction conditions toward the indole nucleus, we treated the alcohol **22** with 5 mol % of TPAP in the presence of *N*-methylmorpholine *N*-oxide (NMMO, 1.5 mol equiv; powdered 4A molecular sieves). The oxidation reaction was slow and after 24 h was incomplete as judged by TLC; the desired aldehyde **23** was obtained in only 34% yield and starting alcohol **22** (14%) was recovered.

Ley and co-workers have reported[24] that the TPAP oxidations can be accelerated by the use of acetonitrile as cosolvent. Employing the same initial conditions (5 mol % TPAP, 1.5 equiv of NMMO) as before, the alcohol **22** was oxidized in a mixture of CH_2Cl_2 and acetonitrile (10:1 v/v). There was, however, no enhancement in the overall rate of oxidation (reaction time was 22 h), but the yield of the aldehyde **23** was increased to around 43% and no starting alcohol **22** was detected. Also, under these mild oxidation conditions, we were surprised to obtain the unusable glutarimide **26** (14%), which was formed from further oxidation of the hydroxy-lactam **24**. Although the yield of **23** was slightly improved, it was deemed unacceptable in the context of our projected synthesis of the vinca alkaloids **1a** and **1b**.

Therefore the oxidation of **22** using pyridine−SO_3 (Py·SO_3) complex in DMSO[25] was investigated. We were pleased to find that when alcohol **22** was treated with Py·SO_3 (7 equiv) in DMSO containing Et_3N,[25a] the aldehyde **23** and the hydroxy-lactam **24** were formed in a combined yield of 95%, and in a ratio of 1:1.7. The glutarimide **26** was not produced under these conditions.

The ^1H NMR spectrum of the hydroxy-lactam **24** revealed that it was a 1:1 mixture of C-6 epimers. This ratio was based on the integration of the H-6 doublets centered at δ 4.37 and δ 4.72, respectively.

The stage was set for the Pictet−Spengler[26] cyclization of the aldehyde **23** and hydroxy-lactam **24** to form the tetracyclic compounds **25**. In preliminary studies, we have found that the cyclization of the pure hydroxy-lactam **24** under thermal conditions (toluene, 110 °C) gave a modest 56% yield of the tetracycles **25**. On the other hand, the cyclization of the pure aldehyde **23** under the same conditions did not afford the products **25**. These initial results indicated that the cyclization proceeded via the more reactive hydroxy lactam **24**. Thus, for the efficient conversion of the mixture of the aldehyde **23** and hydroxy-lactam **24** to **25**, it was reasoned that the use of an acidic medium would be beneficial because it would favor formation of the acyl iminium intermediate from the hydroxy-lactam **24** as well as promote the ring-chain tautomerism of the aldehyde **23** in favor of the hydroxy-lactam **24**.

This line of reasoning was confirmed by the smooth cyclization of the mixture of **23** and **24** in refluxing glacial acetic acid[8b] to give a diastereomeric mixture of two tetracyclic indoles **25a** and **25b**, which were readily separated by chromatography. The ratio of **25a**:**25b**, based on isolated yields, was 1:2.

In an effort to delineate cyclization reaction conditions that would favor the formation of more of the α-epimer **25a**, we examined the Pictet−Spengler cyclization of the mixture of **23** and **24** under two other acidic conditions. The first employed Nafion-H[27] (50 mol %), as a heterogeneous acid catalyst, in refluxing toluene. This also yielded a 1:2 ratio of **25a** and **25b**. The second set of conditions we examined was modeled after the cyclization conditions developed by Schultz and Pettus.[8e] This entailed conducting the cyclization in a mixture of trifluoroacetic acid (5 equiv) in dichloromethane at −42 °C. This, however, led to a 1:3 ratio of the tetracyclic indoles **25a** and **25b**.

Further efforts to acquire more of the α-epimer **25a** led us to investigate the feasibilty of the BF_3-mediated equilibration of the β-epimer **25b**. We were encouraged by the work of Fuji and co-workers who demonstrated[8b(i)]

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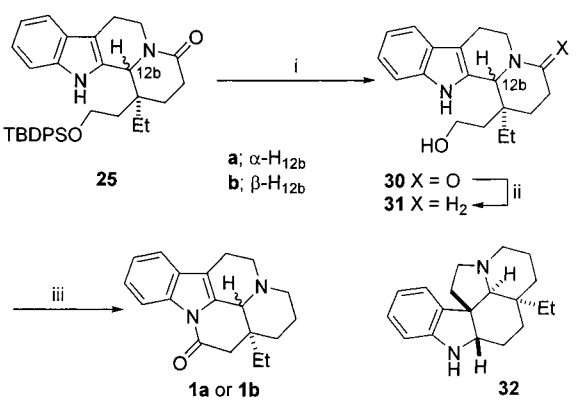
(26) (a) Review: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (b) Yu, P.; Cook, J. M. *J. Org. Chem.* **1998**, *63*, 9160 and references therein.

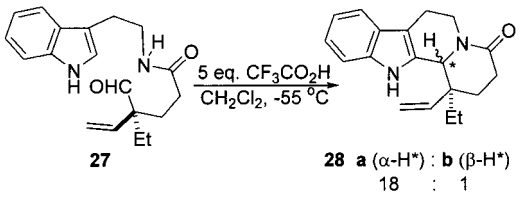
Scheme 3[a]



[a] (i) Me_3SiCl, MeOH, 0 °C: **30a** (96%), **30b** (97%); (ii) $LiAlH_4$, THF, 20 min, reflux: **31a** (30%), **31b** (84%); (iii) For **1a**: Py·SO_3, DMSO, Et_3N, rt; then TPAP, NMMO, CH_2Cl_2, 4A MS, 33%; For **1b**: TPAP, NMMO, CH_2Cl_2, 4A MS, 55%.

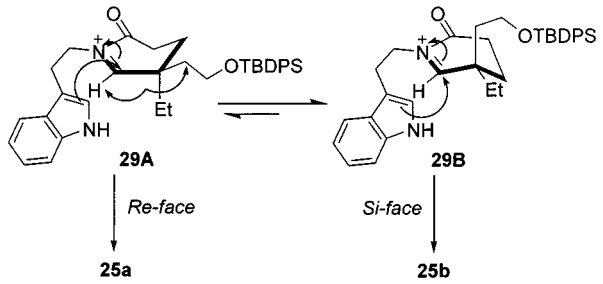
that the treatment of the pure alcohol **30b** (see Scheme 3) with of BF_3 etherate at 35−40 °C for 10 h yielded a 1:1 equilibrium ratio of **30a**:**30b**. With compound **25b**, it was reasoned that under Fuji's reaction conditions fluoride anion-mediated desilylation (**25b** → **30b**) as well as epimerization of the C-12b stereocenter could be effected in one operation. However, it should be noted that we do not know the exact order by which these two processes occur. Thus, when a solution of pure β-epimer **25b** in neat BF_3·etherate was heated at 40 °C for 10 h a 91% yield of the mixture of **30a** and **30b** was obtained. Disappointingly, the ratio of **30a**:**30b** was found to be 1:4. Prolonged heating[28] did not result in any increase in the amount of the α-epimer **30a**.

The preference for the formation of the β-epimer **25b** over the α-epimer **25a** was intriguing. Literature reports on similar Pictet−Spengler cyclization reactions indicated that the cyclization normally resulted in the formation of the C-12b α and β epimers in almost equal amounts (ratio of α:β = 1∼1.3:1).[8b(i),29a] The absence of diastereocontrol during the cyclization was attributed to a lack of stereochemical differentiation of the π-face of the iminium moiety because of the similar steric size of the C-1 geminal substituents. Recent studies,[8e,29b] however, have also suggested that the nature of the geminal substituents at the quaternary carbon center adjacent to the carbocation site may play a subtle but important role in governing the diastereoselectivity of the reaction. For example, Schultz and Pettus[8e] reported that the Pictet−Spengler cyclization of the aldehyde **27** (eq 1) proceeded with high diastereoselectivity to give an 18:1 ratio of **28a**:**28b**. The high diastereoselectivity of the reaction was



(Eq. 1)

ascribed to $\pi-\pi$ interaction between the C-1 β-vinyl substituent and the indole moiety of the acyl iminium ion intermediate. This, in turn, helped to deliver the indole unit to the β-face of the iminium unit. Returning to the formation of **25a** and **25b**, the diastereoselectivity of the cyclization can be understood if the key bond formation step in the presumed acyl iminium ion intermediate involved the more stable reactive conformer **29B**.



Conformer **29A** is less preferred because it is destabilized by an unfavorable $A^{1,2}$ interaction[30] between the pseudoequatorial, bulky *tert*-butyldiphenylsilyloxyethyl group and the iminium C−H unit. Approach of the indole moiety to the conformer **29B** would occur from the less-hindered *Si*-face of the iminium moiety leading to the formation of **25b**. The composite results from the acid-mediated cyclization reaction of **23**/**24** and from the BF_3-mediated equilibration reaction of **25b** are in accord with this line of reasoning. That is, product **25b** was a kinetically and thermodynamically favored product under the reaction conditions studied.

The structure of each of the diastereomers **25a** and **25b** were fully characterized by ^1H and ^{13}C NMR spectroscopy, including COSY-45, HETCOR, and HMQC. The characteristic ^1H and ^{13}C resonances for the **25a** and **25b** are collected in Table 1.

In the ^1H NMR spectra, it was found that the H-12b, NH, and the C-2′ methylene hydrogens in the silyloxyethyl moiety in **25a** are shielded relative to those in **25b**, with the exception of the C-3 methylene hydrogens (2H-3). The latter set of hydrogens resonated at lower field in **25a** compared to the same set in **25b**.

Interestingly, the ^{13}C NMR spectra of **25a** and **25b** showed that there was no significant difference in the chemical shifts of the C-3 and C-12b resonances between **25a** and **25b**. However, the C-2′ signal in the silyloxyethyl moiety and the C-1 quaternary carbon resonance in **25a** appeared at lower chemical shifts (shielded) when compared to the C-2′ and C-1 signals in the **25b**.

The structure of compound **25a**[31a] was confirmed by its conversion to the primary alcohol **30a** (vide infra), and comparison of its ^1H NMR spectrum with that reported in the literature.[8e] The syn relative stereochemistry of the silyoxyethyl substituent at the quaternary center (C-1) and the C-12b hydrogen in compound **25b** was ascertained by NOE measurements.[31b]

(27) Registered trademark of Dupont Co. (a) Review: Olah, G. A.; Iyer, P. S.; Prakash, G. S. K. S*ynthesis* **1986**, 573. (b) Wee, A. G. H.; Liu, B.-S. *Tetrahedron* **1994**, *50*, 609.

(28) We found that on extended heating, a small amount of an unidentified polar compound was beginning to form as shown by TLC analysis.

(29) (a) Wenkert, E.; Hudlicky, T. *J. Org. Chem*. **1988**, *53*, 1953. (b) See also ref 8c. This study reported that the cyclization gave a 5.7:1 ratio of the C-12b β-epimer:α-epimer. The steric size of the CO_2Et group is relatively smaller than the ethyl group (*A* values are −1.1∼1.2 kcal/mol and −1.75 kcal/mol, respectively; see Smith, M. B.; March, J. *Advanced Organic Chemistry*, 5th ed.; Wiley-Interscience: New York, 2001; p 174). It is concievable that the β-CO_2Et at the quaternary carbon center might be involved in the stabilization of the carbocation center via interaction of one of the lone-pairs of electrons on the ester carbonyl oxygen with the vacant p-orbital of the carbocation. This would result in the shielding of the β-face of the iminium moiety.

(30) Johnson, F. *Chem. Rev*. **1968**, *68*, 375.

Table 1. Selected ^{1}H and ^{13}C Resonances for 25a and 25b

^{1}H	25a	25b	^{13}C	25a	25b
2H-3	m, 2.43−2.55	m, 2.38−2.49	C-3	29.1	29.1
H-12b	s, 4.75	s, 5.18	C-12b	60.9	60.9
CH_2CH_2OSi	"t", 3.59	m, 3.90−4.06	CH_2CH_2OSi	59.8	60.5
NH	s, 7.82	s, 9.38	C-1	38.9	39.3

Assembly of Eburnamonine (1a) and *epi*-Eburnamonine (1b). Each of the two epimers **25a** and **25b** served as the key intermediate in the synthesis of the vinca alkaloids (−)-eburnamonine (**1a**) and (+)-*epi*-eburnamonine (**1b**), respectively. The synthesis of **1b**, as shown in Scheme 3, was first investigated.

The TBDPS protecting group in **25b** was removed using methanol−Me_3SiCl to afford the known[8b(i)] lactam alcohol **30b** in high yield. The reduction of **30b** using $LiAlH_4$ to the amino alcohol **31b** was not straightforward. In previous studies[5] we have found that such reductions required a reaction time of at least 15 h. However, the use of the same reaction time (15 h) for this reduction step (**30b** → **31b**) was found to be detrimental to the yield of the desired product; only 40% of the known[8b(i)] amino alcohol **31b** was obtained, and no starting **30b** was recovered. After careful monitoring (TLC) of the reduction reaction, we were pleased to find that when the reaction time was shortened to 20 min, an 84% yield of **31b** was realized. Subsequent oxidation of **31b** using TPAP/NMMO[8e] gave a 55% yield of (+)-*epi*-eburnamonine (**1b**), whose spectral data and optical rotation were in accord with published data.[7b]

For the synthesis of (−)-eburnamonine (**1a**) (Scheme 3), the silyl ether **25a** was desilylated (methanolic−Me_3SiCl) to give the lactam alcohol[8b(i),e] **30a**. The lactam carbonyl in **30a** was treated briefly (30 min) with $LiAlH_4$ to afford a modest yield (30%) of **31a**.[8b(i),e] No starting material was recovered. It is not clear to us at this time why there is a marked decrease in the efficiency of the $LiAlH_4$ reduction of **30a** compared to **30b**.

Next, the amino alcohol **31a** was oxidized with Py·SO_3/DMSO/Et_3N[24a] to obtain the corresponding aldehyde which, without further purification, was subjected to further oxidation using TPAP/NMMO[8e] to afford a 33% yield of (−)-eburnamonine (**1a**). The ^{1}H and ^{13}C NMR data as well as specific optical rotation of **1a** were in accord with the published data.[8b(i),e]

In view of the fact that both **30a** and **30b** have been converted to (−)-aspidospermidine (**32**),[8b(i),e] the present work also constitutes a formal synthesis of this alkaloid.

Conclusions

A new approach toward the enantioselective synthesis of vinca alkaloids as exemplified by eburnamonine and *epi*-eburnamonine is presented. The approach featured the use of a chiral nonracemic 4,4-disubstituted 2-butyrolactone **19**, which was readily prepared, via a stereospecific Rh(II)−carbenoid-mediated tertiary C−H insertion reaction with retention of configuration, from the diazo compound **5**. Conversion of **19** to the carboxylic acid **4** followed by coupling with tryptamine gave **3**. Readjustment of the oxidation level of the C-2 and C-5 carbons of the lactone moiety in **3** led to the aldehyde **23**/hydroxylactam **24**. Acyl iminium-based Pictet−Spengler cyclization of **23**/**24** gave the tetracylic indoles **25a** and **25b**, which served as advanced intermediates for the total synthesis of the alkaloids (−)-eburnamonine (**1a**) and (+)-*epi*-eburnamonine (**1b**), respectively, as well as for the formal synthesis of (−)-aspidospermidine **32**. Further studies on the use of 4,4-disubstituted 2-butyrolactones in natural product synthesis is in progress.

Experimental Section

Melting points are uncorrected and were measured on a Kofler hot-stage melting point apparatus. Only diagnostic absorptions in the infrared spectrum are reported. ^{1}H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra were recorded in $CDCl_3$, unless otherwise stated. Tetramethylsilane ($\delta_H = 0.00$) and the $CDCl_3$ resonance ($\delta_C = 77.0$) were used as references. Proton assignments were made using double irradiation experiments and confirmed, where necessary, by COSY-45 experiments. ^{13}C assignments were made using DEPT-135, HETCOR, and HMQC experiments. Elemental analyses and high-resolution mass spectral analysis (EI, 70 eV) and chemical ionization mass spectral analyses were performed at the Chemistry Department, University of Saskatchewan, Canada. Tetrahydrofuran and diethyl ether were dried by distillation from sodium/benzophenone ketyl. Dichloromethane and triethylamine were dried by distillation from CaH_2. Flash chromatography[32] was used for the purification of reaction products. All air and moisture sensitive reactions were conducted under a static pressure of argon, and reaction progress was monitored by thin-layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminum backed sheets. Dirhodium(II) tetraacetate and Nafion-H were purchased from Strem Chemicals Inc., MA, and Aldrich Chemical Co., WI, respectively.

(2*S*)-[5-(*tert*-Butyldiphenylsilyloxy)-2-ethylpentyl]-α-diazo-α-(methoxycarbonyl)acetate (5). Compound (*S*)-**14** (4.3 g, 9.1 mmol) was dissolved in dry MeCN (30 mL), and the solution was cooled to 0 °C. Mesyl azide (1.3 mL, 14 mmol) was added followed by dry Et_3N (2.5 mL, 18 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 10 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aqueous NaOH and water. The aqueous layer was reextracted with more CH_2Cl_2. The combined organic layers were dried, filtered, and evaporated. Chromatographic purification (7:1 and then 2:1 v/v PE: Et_2O) of the crude product gave 5.9 g (88%) of the diazo product **5** as a viscous oil. $[\alpha]_D$ +3.3 (*c* 1.5, $CHCl_3$). IR ν_{max} (neat): 2135, 1761, 1737, 1695 cm^{-1}. ^{1}H NMR: δ 0.89 (t, 3H, J = 7.2 Hz), 1.05 (s, 9H), 1.27−1.70 (m, 7H), 3.64 (t, 2H, J = 6.0 Hz), 3.83 (s, 3H), 4.15 (d, 2H, J = 5.8 Hz), 7.30−7.40 (m, 6H), 7.60−7.75 (m, 4H). ^{13}C NMR: δ 10.9, 19.2, 23.6, 26.7, 26.8, 29.6, 38.6, 52.5, 63.9, 67.7, 127.6, 129.5, 133.9, 135.5, 160.9, 161.6. Anal. Calcd for $C_{27}H_{36}N_2O_5Si$: C, 65.29; H,7.31; N, 5.64. Found: C, 65.34; H, 7.29; N, 5.54.

(4*S*)-4-[3-(*tert*-Butyldiphenylsilyloxypropyl)-4-ethyl-3-(methoxycarbonyl)dihydro-2(3*H*)-furanone(18). Thethree-necked round-bottom flask was fitted with a reflux condenser and a pressure-equalizing addition funnel. The whole apparatus was flame dried under a stream of Ar before use. $Rh_2(OAc)_4$ (0.105 g, 0.24 mmol) was placed in the reaction flask, and dry CH_2Cl_2 (400 mL) was added, under Ar. The suspension was heated to reflux. A solution of the diazo compound **5** (5.92 g, 12 mmol) in dry CH_2Cl_2 (400 mL) was added dropwise over

(31) (a) NOE measurements were not done for compound **25a** because a solution of **25a** in $CDCl_3$ was found to have decomposed upon extended storage. We do not know the exact length of time of storage because the experiments were conducted at the Prairie Regional NMR center in Winnipeg, Manitoba. We have, however, observed that a clear solution of **25a** in $CDCl_3$ turned light brown when left standing on the bench overnight (~18 h). TLC analysis of the solution showed that a polar material, which does not correspond to the primary alcohol **30a**, was formed. No further attempts were made to characterize this unknown material. (b) See Supporting Information, Figure S1, for details.

(32) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923.

a period of 6 h. After addition was complete, the reaction mixture was refluxed for an additional 14 h, then cooled to room temperature, and the mixture was filtered through a Celite pad. The filtrate was evaporated, and the crude mixture was purified by chromatography (2:1 v/v PE−Et_2O) to yield the desired oily γ-lactone **18** (4.90 g, 87%), two diastereomeric β-lactones (0.48 g, 8.5%), and some water insertion products (0.048 g, 0.8%). γ-Lactone **18**: obtained as a 1:1 mixture of diastereomers based on the integration of the ester methoxy singlets. $[\alpha]^{23}_D$ −4.7 (*c* 1.6, $CHCl_3$). IR υ_{max} (neat): 1787, 1737 cm^{-1}. ^1H NMR: δ 0.90 and 0.91 (t, 3H, J = 7.2 Hz), 1.04 (s, 9H), 1.31−1.70 (m, 6H), 3.27 and 3.28 (s, 1H), 3.55−3.70 (m, 2H), 3.71 and 3.76 (s, 3H), 4.03 and 4.07 (d, 1H, J = 8.6 Hz), 4.19 (d, 1H, J = 8.6 Hz), 7.35−7.45 (m, 6H), 7.60−7.70 (m, 4H). Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.20; H, 7.74. Found: C, 69.00; H, 7.92. β-Lactones [2.8:1 ratio of "β-lactone 1" (0.35 g): "β-lactone 2" (0.12 g)]. "β-Lactone 1": IR υ_{max} (neat): 3071, 1836, 1754 cm^{-1}. ^1H NMR: δ 0.93 (t, 3H, J = 7.4 Hz), 1.05 (s, 9H), 1.25−1.80 (m, 7H), 3.65 (t, 2H, J = 5.7 Hz), 3.80 (s, 3H), 4.12 (1H, d, J = 4.6 Hz), 4.64 (dd, 1H, J = 9.1, 4.6 Hz), 7.30−7.48 (m, 6H), 7.62−7.75 (m, 4H). "β-Lactone 2": IR υ_{max} (neat): 3072, 1835, 1746 cm^{-1}. 1H NMR: δ 0.92 (t, 3H, J = 7.4 Hz), 1.07 (s, 9H), 1.25−1.80 (m, 7H), 3.67 (t, 2H, J = 5.7 Hz), 3.83 (s, 3H), 4.15 (d, 1H, J = 4.6 Hz), 4.64 (dd, 1H, J = 8.6, 4.6 Hz), 7.34−7.48 (m, 6H), 7.60−7.75 (m, 4H).

(4*S*)-4-[3-(*tert*-Butyldiphenylsilyloxypropyl)-4-ethyldihydro-2(3*H*)-furanone (19). γ-Lactone **18** (0.72 g, 1.53 mmol) was dissolved in DMSO (2 mL) containing NaCl (90 mg, 1.53 mmol). Water (60 μL, 3.1 mmol) was added, and the mixture was heated at 110 °C for 12 h. The mixture was cooled to room temperature, and water (2 mL) was added. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine and then dried. The filtered solution was evaporated, and the crude product was purified by chromatography (4:1 and then 2:1 v/v PE: Et_2O) to give (*S*)-**19** (0.53 g, 84%) as a colorless liquid. $[\alpha]_D$ −3.3 (*c* 1.5, $CHCl_3$). IR υ_{max} (neat): 1778 cm^{-1}. ^1H NMR: δ 0.87 (t, 3H, J = 7.2 Hz), 1.05 (s, 9H), 1.42−1.58 (m, 6H), 2.31(s, 2H), 3.65 (t, 2H, J = 5.1 Hz), 3.96 (d, 1H, J = 8.6 Hz), 4.03 (d, 1H, J = 8.6 Hz), 7.35−7.40 (m, 6H), 7.60−7.70 (m, 4H). ^{13}C NMR: δ 8.4, 19.2, 26.8, 27.3, 29.0, 32.2, 40.0, 42.5, 63.7, 77.1, 127.7, 129.7, 133.7, 135.5, 177.1. Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.08; H, 8.49.

(4*S*)-4-Ethyl-4-(3-hydroxypropyl)dihydro-2(3*H*)-furanone (20). Compound **19** (0.40 g, 1 mmol) was dissolved in THF (5 mL), and the solution was cooled to 0 °C. Bu_4NF (0.51 mL, 0.51 mmol, 1 M in THF) was added dropwise, and the mixture was stirred at room temperature for 40 min. Water (1 mL) was added, THF was evaporated, and the residual oil was chromatographed (1:1 v/v PE: EtOAc) to give 0.16 g (93%) of **20** as a viscous oil. $[\alpha]^{24}_D$ −4.5 (*c* 1.7, $CHCl_3$) IR υ_{max} (neat): 3600−3125, 1770 cm^{-1}. ^1H NMR: δ 0.88 (t, 3H, J = 7.7 Hz), 1.40−1.60 (m, 6H), 1.60−1.88 (br hump, 1H), 2.35(s, 2H), 3.66 (br s, 2H), 4.03 (s, 2H). ^{13}C NMR: δ 8.4, 27.2, 29.0, 32.2, 39.8, 42.5, 62.6, 77.0, 177.1. Anal. Calcd for $C_9H_{11}O_3$: C, 62.77; H, 9.36. Found: C, 62.57; H, 9.16.

(4*S*)-4-Ethyl-4-[2-(hydroxycarbonyl)ethyl]dihydro-2(3*H*)-furanone (4). Jones reagent was added dropwise to a solution of **20** (0.62 g, 3.6 mmol) in acetone (40 mL) at 0 °C until the orange color of the oxidant persisted. A few drops of 2-propanol was added and then followed by water (1 mL). The mixture was evaporated, and the resulting mixture was mixed with saturated NaCl. The mixture was extracted with EtOAc. The organic layers were washed with brine, dried, filtered, and evaporated to give a **4** (0.66 g, 98%) as a colorless oil. $[\alpha]^{24}_D$ −7.1 (*c* 1.4, $CHCl_3$) IR υ_{max} (neat): 3500−2500, 1770, 1710 cm^{-1}. ^1H NMR: δ 0.90 (t, 3H, J = 7.4 Hz), 1.52 (q, 2H, J = 7.4 Hz), 1.78−1.88 (m, 2H), 2.20−2.39 (m, 4H), 4.00 (d, 1H, J = 9.2 Hz), 4.06 (d, 1H, J = 9.2 Hz). ^{13}C NMR: δ 8.4, 28.8, 29.1, 30.6, 39.6, 42.4, 76.5, 176.5, 178.4. Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.17; H, 7.59.

Amide 3. The carboxylic acid **4** (0.076 g, 0.41 mmol) was dissolved in CH_2Cl_2 (10 mL) at 0 °C, and DCC (0.10 g, 0.5 mmol) was added. After for 1 h, tryptamine (0.080 g, 0.5 mmol) was added, and the mixture was stirred for 15 h at room temperature. The precipitate was removed by filtration, and the residue was washed with CH_2Cl_2. The filtrate was washed with 5% HCl, water, saturated $NaHCO_3$, and brine, dried, and concentrated. Chromatographic purification (1:1 and 1:2 v/v PE:EtOAc) of the crude oil yielded the amide **3** (0.090 g, 67% yield). $[\alpha]^{24}_D$ −2.9 (*c* 0.9, $CHCl_3$) IR υ_{max} (neat): 3314, 1770, 1650 cm^{-1}. ^1H NMR: δ 0.83 (t, 3H, J = 7.7 Hz), 1.40 (q, 2H, J = 7.7 Hz), 1.67−1.78 (m, 2H), 1.93−2.05 (m, 2H), 2.20 (s, 2H), 2.94 (t, 2H, J = 6.6 Hz), 3.56 (dt, 2H, J = 6.8, 6.3 Hz), 3.88 (d, 1H, J = 8.4 Hz), 3.94 (d, 1H, J = 8.4 Hz), 5.93 (bt, 1H, J = 5.7 Hz), 6.95−7.6 (m, 5H), 8.68 (bs, 1H). ^{13}C NMR: δ 8.5, 25.2, 29.3, 31.3, 31.6, 39.4, 40.0, 42.4, 76.7, 111.5, 112.6, 118.6, 119.4, 122.1, 122.3, 127.4, 136.5, 172.1, 177.3. HRMS Calcd for $C_{19}H_{24}N_2O_3$: 328.1787. Found: 328.1787.

(4*S*)-*N*-[2-(Indole-3-yl)-ethyl)]-4-ethyl-4-hydroxymethyl-6-hydroxyhexamide (21). To a solution of amide **3** (0.054 g, 0.16 mmol) in THF (1 mL)−MeOH (0.2 mL) at 0 °C was added $LiBH_4$ solution (0.4 mL, 0.8 mmol, 2 M in THF). The mixture was stirred at room temperature for 48 h, cooled to 0 °C, and quenched with saturated NH_4Cl solution (0.5 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried, filtered, and evaporated to leave a viscous oil. Chromatographic purification of the oil (20:1 v/v CH_2Cl_2: MeOH) gave the diol **21** (0.05 g, 92% yield). $[\alpha]^{24}_D$ +1.3 (*c* 2.0, MeOH). IR υ_{max} (film): 3328, 1633 cm^{-1}. ^1H NMR: δ 0.77 (t, 3H, J = 7.7 Hz), 1.16 (q, 2H, J = 7.4 Hz), 1.32−1.55 (m, 3H), 1.68−1.86 (m, 1H), 2.06 (t, 2H, J = 6.9 Hz), 2.97 (t, 2H, J = 6.3 Hz), 3.27 (bs, 2H), 3.53−3.74 (m, 5H), 4.48 (bs, 1H), 5.81 (bt, 1H, J = 5.6 Hz), 7.0−7.66 (m, 5H), 8.35 (bs, 1H). ^{13}C NMR: δ 7.3, 25.1, 26.8, 27.4, 30.2, 38.8, 39.8, 58.2, 67.1, 111.3, 112.4, 118.6, 119.5, 122.2, 127.3, 136.4, 174.2.

(4*S*)-*N*-[2-(3-Indolyl)ethyl)]-4-ethyl-4-hydroxymethyl-6-*tert*-butyldiphenylsiloxyhexamide (22). To a solution of diol **21** (0.23 g, 0.69 mmol) in DMF (5 mL) was added *tert*-butyldiphenylsilyl chloride (0.21 g, 0.76 mmol) followed by addition of imidazole (0.12 g, 1.7 mmol). The mixture was stirred at −20 °C for 4 h and then 12 h at room temperature. The reaction was quenched with saturated NaCl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried, filtered, and concentrated. Chromatographic separation (1:1 v/v PE: Et_2O and 1:1 PE:EtOAc) gave monosilyl ether **22** (0.36 g, 92% yield) as a thick oil. $[\alpha]^{24}_D$ −6.9° (*c* 0.4, $CHCl_3$). IR υ_{max} (film): 3414, 3304, 3048, 1650 cm^{-1}. ^1H NMR: δ 0.75 (t, 3H, J = 7.4 Hz), 1.04 (s, 9H), 1.11−1.31 (m, 2H), 1.39−1.60 (m, 4H), 1.87−2.12 (m, 2H), 2.95 (t, 2H, J = 6.9 Hz), 3.29 (s, 2H), 3.50−3.75 (m, 5H), 5.53 (bt, 1H, J = 5.6 Hz), 7.0 (d, 1H, J = 2.2 Hz), 7.06−7.25 (m, 2H), 7.30−7.50 (m, 7H), 7.50−7.70 (m, 5H), 8.10 (bs, 1H, NH). ^{13}C NMR: δ 7.3, 18.9, 25.2, 26.0, 26.7, 28.8, 30.3, 36.5, 39.4 (39.7), 60.2, 66.7, 111.2, 112.7, 114.9, 118.6, 119.3, 122.0, 127.3, 129.8, 133.0, 135.5, 136.3, 173.7. HRMS Calcd for $C_{35}H_{46}N_2O_3Si$: 570.3278. Found: 570.3274.

A small amount of bis-silyl ether **21** (R^1 = R^2 = TBDPS) (0.038 g, 6% yield) was also isolated. $[\alpha]^{24}_D$ −2.6 (*c* 1.9, $CHCl_3$). IR υ_{max} (neat): 3428, 3294, 3070, 1658 cm^{-1}. ^1H NMR: δ 0.67 (t, 3H, J = 7.4 Hz), 1.00 (s, 9H), 1.03 (s, 9H), 1.15−1.30 (m, 2H), 1.38−1.60 (m, 4H), 1.64−1.77 (m, 2H), 2.87 (t, 2H, J = 6.9 Hz), 3.26 (s, 2H), 3.46 (q, 2H, J = 6.9 Hz), 3.63 (t, 2H, J = 7.4 Hz), 5.02 (bt, 1H, J = 5.7 Hz), 6.83 (d, 1H, J = 2.3 Hz), 7.04−7.22 (m, 2H), 7.24−7.43 (m, 7H), 7.52−7.67 (m, 5H), 7.79 (bs, 1H). ^{13}C NMR: δ 7.5, 19.1, 19.4, 25.3, 26.5, 26.9, 27.0, 29.9, 30.9, 36.2, 39.4, 60.2, 67.3, 111.3, 113.0, 118.7, 119.5, 122.0, 127.3, 129.6, 133.7, 134.0, 135.6, 135.8, 136.4, 173.2. HRMS Calcd for $C_{51}H_{64}N_2O_3Si_2$: 808.4456. Found: 808.4459.

(4*S*)-*N*-[2-(3-Indolyl)ethyl)]-4-ethyl-4-(2-*tert*-butyldiphenylsiloxyethyl)-5-oxopentamide (23) and (5*S*)-*N*-[2-(3-Indolyl)ethyl)]-5-ethyl-5-(2-*tert*-butyldiphenylsiloxyethyl)-6-hydroxy-δ-lactam (24). Monosilyl ether **22** (0.24 g, 0.42 mmol) was dissolved in DMSO (5 mL) at room temperature, and dry Et_3N (1.1 mL, 7.4 mmol) was added followed by addition of Py·SO_3 complex (0.48 g, 3.0 mmol) in DMSO (2 mL). The mixture was stirred at room temperature for 60 h, and then 1 M NaOH (5 mL) was added. The mixture was stirred for another 15 min and then was extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered, and concentrated. Chromatographic separation (1:1

v/v PE:Et_2O and then 1:1 v/v PE:EtOAc) gave **23** (0.083 g, 35% yield) and **24** (0.14 g, 60% yield). Compound 23: IR υ_{max} (neat): 3402, 3296, 3052, 2710, 1721, 1653 cm^{-1}. ^1H NMR: δ 0.73 (t, 3H, J = 7.4 Hz), 1.02 (s, 9H), 1.50 (q, 1H, J = 7.4 Hz), 1.51 (q, 1H, J = 7.7 Hz), 1.63−1.90 (m, 6H), 2.93 (t, 2H, J = 6.6 Hz), 3.47−3.64 (m, 4H), 5.35 (m, 1H), 6.97 (d, 1H, J = 2.2 Hz), 7.07−7.24 (m, 2H), 7.29−7.45 (m, 7H), 7.55−7.68 (m, 5H), 8.02 (bs, 1H), 9.42 (s, 1H). ^{13}C NMR: δ 7.6, 19.1, 23.7, 25.3, 26.7, 26.9, 30.7, 35.0, 39.7, 50.5, 59.7, 111.3, 112.9, 115.6, 118.7, 119.5, 122.1, 122.3, 127.8, 129.8, 133.4, 135.6, 136.4, 172.2, 205.7. HRMS Calcd for $C_{35}H_{44}N_2O_3Si$: 568.3121. Found: 568.3121.

Compound **24**: $[\alpha]^{24}_D$ +13.9 (*c* 0.9, $CHCl_3$) IR υ_{max} (film): 3420, 3300, 3050, 1625 cm^{-1}. ^1H NMR (1:1 Mixture of diastereomers, ratio was based on integration of H-6 doublets at δ 4.37 and δ 4.72): δ 0.63, 0.68 (t, 3H, J = 7.4 Hz), 1.05, 1.08 (s, 9H), 1.16−2.07 (m, 6H), 2.18−2.50 (m, 2H), 2.76 (d, 0.5H, J = 5.7 Hz), 3.00−3.20 (m, 2H), 3.46−3.73 (m, 3H), 3.77−4.09 (m, 1H), 4.37 (d, 0.5H, J = 3.4 Hz), 4.56 (d, 0.5H, J = 5.7 Hz), 4.72 (d, 0.5H, J = 2.9 Hz), 6.98−7.23 (m, 3H), 7.30−7.55 (m, 7H), 7.60−7.78 (m, 5H), 7.95 and 8.02 (bs, 1H). HRMS Calcd for $C_{35}H_{44}N_2O_3Si$: 568.3121. Found: 568.3118.

(3*S*)-*N*-[2-(3-Indolyl)ethyl)]-3-ethyl-3-(2-*tert*-butyldiphenylsiloxyethyl)glutarimide (26). IR υ_{max} (film): 3420, 3074, 1722, 1660 cm^{-1}. ^1H NMR: δ 0.78 (t, 3H), 1.03 (s, 9H), 1.5−2.09 (m, 6H), 2.63 (t, 2H, J = 6.9 Hz), 2.91 (t, 2H, J = 8.0 Hz), 3.53−3.77 (m, 2H), 4.02 (t, 2H), 7.00 (d, 1H, J = 3.0 Hz), 7.09−7.22 (m, 2H), 7.23−7.32 (m, 1H), 7.33−7.50 (m, 6H), 7.53−7.78 (m, 5H), 7.83 (bs, 1H).

(1*S*,12b*S*)-1-Ethyl-1-(2-*tert*-butyldiphenylsilyloxyethyl)-4-oxo-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizine (25a) and (1*S*,12b*R*)-1-Ethyl-1-(2-*tert*-butyldiphenylsilyloxyethyl)-4-oxo-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizine (25b). A mixture of aldehyde **23** and hydroxy-lactam **24** (0.073 g, 0.13 mmol) was dissolved in dry CH_2Cl_2 (10 mL) at −42 °C, and trifluoroacetic acid (0.065 mL, 0.78 mmol) was added dropwise. The mixture was stirred at −42 °C and then allowed to warm slowly to room temperature for 16 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried and concentrated. Chromatographic purification (1:1 v/v PE: EtOAc) gave the oily **25a** (18.7 mg) and **25b** (49.4 mg) and in a combined yield of 95%. Lactam **25a**: $[\alpha]^{24}_D$ −50 (*c* 0.2, $CHCl_3$) IR υ_{max} (film): 3487, 3052, 1632 cm^{-1}. ^1H NMR: δ 0.98 (s, 9H), 1.12 (t, 3H, J = 7.4 Hz), 1.20−1.37 (m, 1H), 1.66−1.98 (m, 5H), 2.43−2.55 (m, 2H), 2.63−2.83 (m, 3H), 3.59 (t, 2H, J = 6.9 Hz), 4.76 (s, 1H), 5.10−5.22 (m, 1H), 7.09−7.23 (m, 2H), 7.24−7.46 (m, 8H), 7.48−7.58 (m, 4H), 7.82 (bs, 1H). ^{13}C NMR: δ 8.3, 19.0, 21.1, 24.0, 26.8, 27.8, 29.1, 30.4, 33.9, 39.9, 41.0, 59.8, 60.9, 110.9, 113.4, 118.3, 119.8, 122.3, 126.5, 127.7, 129.7, 130.9, 133.3, 135.5, 136.1, 169.9.

Lactam **25b**: $[\alpha]^{24}_D$ + 85 (*c* 0.5, $CHCl_3$) IR υ_{max} (film): 3347, 3052, 1644 cm^{-1}. ^1H NMR: δ 0.68 (t, 3H, J = 7.4 Hz), 0.80−1.12 (m, 1H), 1.02 (s, 9H), 1.38−1.60 (m, 2H), 1.65−1.86 (m, 2H), 2.26−2.50 (m, 3H), 2.65−2.90 (m, 3H), 4.01 (bt, 2H, J = 4.0 Hz), 5.11−5.23 (m, 2H), 7.06−7.22 (m, 2H), 7.37−7.58 (m, 8H), 7.63−7.77 (m, 4H), 9.04 (bs, 1H). ^{13}C NMR: δ 7.0, 19.1, 21.3, 24.0, 26.8, 26.9, 29.1, 38.4, 39.4, 41.0, 60.5, 60.9, 111.2, 112.9, 118.0, 119.3, 121.7, 126.7, 128.1, 130.2, 130.4, 131.6, 132.2, 132.3, 135.5, 135.7, 136.0, 170.0. HRMS Calcd for $C_{35}H_{42}N_2O_2Si$: 550.3016. Found: 550.3018.

Equilibration of Lactam (25b) Using BF_3·Etherate. Pure **25b** (50 mg, 0.09 mmol) was dissolved in freshly distilled BF_3·etherate (1.3 mL). The mixture was heated at 40 °C for 10 h. The reaction mixture was then cooled to 0 °C in an ice−water bath, and ice cold aqueous $NaHCO_3$ (8 mL) was added. The mixture was stirred briefly and then extracted with CH_2Cl_2. The combined organic layers were dried, filtered, and evaporated. Purification by column chromatography (8:1 and 4:1 v/v CH_2Cl_2: acetone) afforded compound **30b** (21 mg) and compound **30a** (5 mg), and in a combined yield of 91%. Compounds **30a** and **30b** showed identical ^1H NMR spectral data as detailed below for **30a** and **30b**.

(1*S*,12b*S*)-1-Ethyl-1-(2-hydroxyethyl)-4-oxo-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizine (30a). Compound **25a** (0.020 g, 0.036 mmol) was dissolved in dry MeOH (1 mL), and the solution was cooled to 0 °C. Trimethylsilyl chloride (0.016 g, 0.14 mmol) was added dropwise to the methanolic solution at 0 °C. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Methanol was evaporated, the residue was treated with $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried, filtered, and evaporated to leave a solid residue. Chromatographic purification (8:1 and 4:1 v/v CH_2Cl_2: acetone) gave pure **30a** (10.8 mg, 96% yield). mp 285−286 °C (dec) (lit.[8b(i)] mp 263−265 °C). $[\alpha]^{24}_D$ −192.3 (*c* 0.13, MeOH) {lit.[8b(i)] $[\alpha]^{24}_D$ −195.5 (*c* 0.16, MeOH)}. IR υ_{max} (KBr): 3272, 3054, 1604 cm^{-1}. ^1H NMR (DMSO-d_6): 1.07 (t, 3H, J = 7.4 Hz), 1.30−1.64 (m, 2H), 1.65−2.12 (m, 3H), 2.30−2.43 (m, 2H), 2.49−2.90 (m, 3H), 3.11−3.50 (m, 3H), 4.18 (t, 1H, J = 5.2 Hz), 4.83 (s, 1H), 4.86−5.02 (m, 1H), 6.91−7.12 (m, 2H), 7.34−7.51 (m, 2H), 10.23 (bs, 1H).

(1*S*,12b*R*)-1-Ethyl-1-(2-hydroxyethyl)-4-oxo-2,3,6,7,12,-12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizine (30b). Compound **25b** (0.050 g, 0.091 mmol) was dissolved dry MeOH (2.5 mL), and the solution was treated with trimethylsilyl chloride (0.04 g, 0.35 mmol) at 0 °C. The reaction mixture was then processed according to the procedure as described for **25a** to obtain pure **30b** (0.27 g, 97%). mp 110−113 °C. [lit. [8b(i)] mp 107−108 °C]. $[\alpha]^{24}_D$ +111 (*c* 0.54, MeOH). {[lit.[8b(i)] $[\alpha]_D$ +88.3 (*c* 0.13, MeOH), lit. $[\alpha]_D$ +98.7 (*c* 0.2, MeOH)}. IR υ_{max} (film): 3337, 3052, 1630 cm^{-1}. ^1H NMR: δ 0.70 (t, 3H, J = 7.8 Hz), 0.80−1.03 (m, 1H), 1.37−1.65 (m, 2H), 1.70−2.10 (m, 2H), 2.11−2.33 (m, 1H), 2.42−2.58 (m, 2H), 2.59−2.80 (m, 3H), 3.12 (s, 1H), 3.95−4.19 (m, 2H), 5.03−5.23 (m, 2H), 7.03−7.22 (m, 2H), 7.36 (d, 1H, J = 7.2 Hz), 7.48 (d, 1H, J = 7.2 Hz), 9.74 (s, 1H). ^{13}C NMR: δ 7.1, 21.2, 24.1, 26.9, 29.2, 37.8, 39.4, 41.1, 58.1, 61.1, 111.2, 112.5, 117.9, 119.2, 121.6, 126.6, 131.9, 136.1, 170.5.

***epi*-Eburnamonine (1b).** The lactam alcohol **30b** (33 mg, 0.11 mmol) was dissolved in dry THF (15 mL). Lithium aluminum hydride (40 mg, 1.10 mmol) was added, and the mixture was refluxed for 20 min. The mixture was cooled to 0 °C and 10% aqueous KOH (50 μL) was added. The mixture was stirred for 30 min and then was filtered through a Celite pad. The residue was washed with CH_2Cl_2. The combined CH_2Cl_2 filtrates were dried, filtered, and evaporated. The residue was purified by chromatography (6:1 and then 2:1 v/v PE−EtOAc) to give the amino alcohol **31b** (26.5 mg, 84%). mp 169−172 °C (lit. mp 173.5−175 °C). $[\alpha]^{24}_D$ +72.4 (*c* 0.38, $CHCl_3$). IR υ_{max} (film): 3475, 3450−3100, 2750, 1619, 1500 cm^{-1}. ^1H NMR: δ 0.69 (t, 3H, J = 7.4 Hz), 0.98−1.17 (m, 1H), 1.45−1.60 (m, 3H), 1.68−1.95 (m, 3H), 2.02−2.28 (m, 2H), 2.30−2.50 (m, 1H), 2.55−2.70 (m, 2H), 2.85−3.08 (m, 2H), 3.50 (s, 1H), 3.95−4.20 (m, 2H), 7.00−7.20 (m, 2H), 7.30−7.35 (m, 1H), 7.45−7.50 (m, 1H), 9.20 (br s, 1H).

The amino alcohol **31b** (7.6 mg, 0.025 mmol) and NMMO (6 mg, 0.05 mmol) were dissolved in dry CH_2Cl_2 (2 mL) containing powdered 4A molecular sieves (13 mg). TPAP (1 mg, 0.003 mmol) was added, and the mixture was stirred at room temperature overnight. The mixture was filtered through Celite, and the residue was washed twice with CH_2Cl_2. The combined CH_2Cl_2 filtrates were washed with 10% Na_2SO_3 (5 mL) and brine, and then dried, filtered, and evaporated. The residue was purified by chromatography (1:1 v/v CH_2Cl_2−acetone and then 10:1 v/v CH_2Cl_2−MeOH) to afford 4.1 mg (55%) of **1b**. mp 145−146 °C (Lit.[7b] mp 145−146 °C). $[\alpha]^{24}_D$ +158 (*c* 0.19, $CHCl_3$). [lit.[7b] $[\alpha]_D$ +168 (*c* 1.0, $CHCl_3$)]. IR υ_{max} (film): 3053, 2802, 2746, 1708 cm^{-1}. ^1H NMR: δ 0.69−1.00 (m, 4H), 1.10−1.25 (m, 1H), 1.58−1.65 (m, 1H), 1.75−2.05 (m, 3H), 2.25−3.00 (m, 6H), 3.05−3.18 (m, 3H), 7.28−7.30 (m, 2H), 7.38−7.45 (m, 1H), 8.30−8.38 (m, 1H). HRMS calcd for $C_{19}H_{22}N_2O$ (M^+): 294.1732, Found: 294.1719; HRMS calcd for $C_{19}H_{21}N_2O$ (M − 1): 293.1654, Found: 293.1652.

Eburnamonine (1a). A solution of the lactam alcohol **30a** (24.5 mg, 0.078 mmol) in dry THF (15 mL) was treated with lithium aluminum hydride (29.4 mg, 0.78 mmol) for 30 min following the procedure as outlined for the reduction of compound **30b**. The crude product was purified by chromatography (1:1 v/v PE−EtOAc) to give the amino alcohol **31a**

(6.8 mg, 30%). mp 186−189 °C (lit.[8b(i)] mp 166−168 °C; lit.[8e] mp 167−168 °C). $[\alpha]^{24}_D$ −125 (*c* 0.12, $CHCl_3$) {lit.[8b(i)] $[\alpha]_D$ −98 (*c* 1.0, $CHCl_3$)}. ^{1}H NMR: δ 1.05 (t, 3H, J = 7.3 Hz), 1.25−1.32 (m, 1H), 1.50−1.80 (m, 6H), 1.95−2.10 (m, 1H), 2.30−2.47 (m, 1H), 2.55−2.75 (m, 2H), 2.90−3.10 (m, 3H), 3.30 (br s, 1H), 3.35−3.45 (m, 1H), 3.50−3.75 (m, 2H), 7.00−7.10 (m, 2H), 7.20−7.28 (m, 1H), 7.35−7.40 (m, 1H), 7.80 (br s, 1H).

Compound **31a** (6 mg, 0.02 mmol) was dissolved in dry DMSO (0.2 mL) containing Py·SO_3 complex (23 mg, 0.14 mmol) and dry Et_3N (0.05 mL). The mixture was stirred at room temperature for 20 h. Then 1 M aqueous NaOH (1 mL) was added, and the mixture was stirred for another 15 min. The mixture was extracted with EtOAc. The combined organic layers were washed with brine and then dried, filtered, and evaporated. The crude aldehyde (6 mg) and NMMO (3 mg) were dissolved in dry CH_2Cl_2 (2 mL). Then powdered 4A molecular sieves (13 mg) was added followed by TPAP (1 mg). The mixture was stirred at room temperature for 3 h and then filtered through Celite. The residue was washed twice with CH_2Cl_2, and the combined CH_2Cl_2 filtrates were washed with 10% Na_2SO_3 (5 mL) and brine and then dried, filtered, and evaporated. The residue was purified by chromatography (1:1 v/v PE−EtOAc) to give **1a** (2 mg, 33%). mp 166−168 °C (lit.[8b(i)] mp 171−172 °C). $[\alpha]^{24}_D$ −77 (*c* 0.13, $CHCl_3$). (Lit.[8b(i)] $[\alpha]_D$ −88 (*c* 0.09, $CHCl_3$). ^{1}H NMR: δ 0.93 (t, 3H, J = 7.3 Hz), 1.01−1.15 (m, 1H), 1.35−1.80 (m, 6H), 1.95−2.15 (m, 1H), 2.38−2.60 (m, 1H), 2.57 (d, 1H, J = 13.7 Hz), 2.70 (d, 1H, J = 13.7 Hz), 2.80−3.00 (m, 1H), 3.20−3.40 (m, 1H), 4.00 (br s, 1H), 7.28−7.50 (m, 3H), 8.33−8.40 (m, 1H). HRMS calcd for $C_{19}H_{22}N_2O$ (M^+): 294.1732, Found: 294.1735; HRMS calcd for $C_{19}H_{21}N_2O$ (M-1): 293.1654, Found: 293.1661.

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Supporting Information Available: Preparation, spectral and analytical data of compounds **7**−**17**, NOE results for compound **25b**, HPLC chromatogram of benzoate derivative of alcohol **13**, and ^{1}H NMR spectra of **1a** and **1b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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