Studies on *Gelsemium* Alkaloids. Total Synthesis of (+)-Koumine, (+)-Taberpsychine, and (+)-Koumidine

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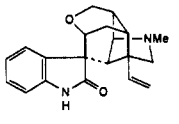
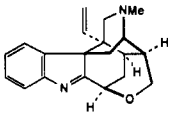
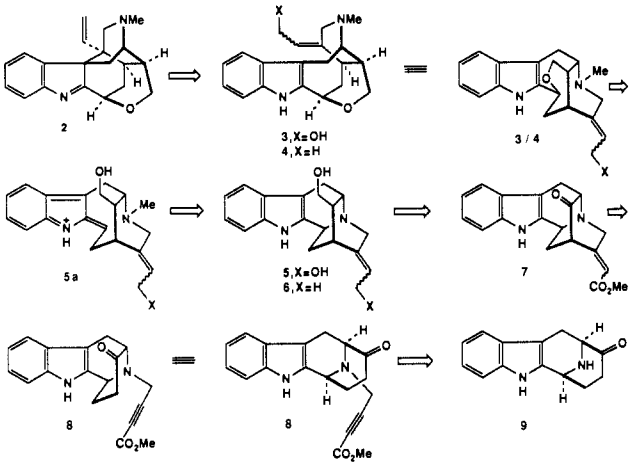
Abstract: The total synthesis of the *Gelsemium* alkaloids (+)-koumine (**2**), (+)-taberpsychine (**4**), and (+)-koumidine (**50**) has been accomplished starting from (*S*)-(−)-tryptophan (**21**). All the synthetic alkaloids are antipodal to the natural compounds. *N'*-Benzyltryptophan ((−)-**22**) was methylated to give **23** which was reductively benzylated to provide (−)-**25**. Pictet–Spengler condensation of (−)-**25** with 2-ketoglutaric acid followed by esterification gave a mixture of diastereomeric methyl esters **27**/**28**. Exposure of (+)-**27** and (−)-**28** to Dieckmann cyclization conditions provided (+)-**29** and (−)-**29**, respectively. Thus starting from a single enantiomer of tryptophan both antipodes of the tetracyclic β-ketoesters (+)-**29**/(−)-**29** are available. Since (+)-**29** was the more readily available antipode, subsequent reactions were conducted with this compound. Conversion of (+)-**29** into (+)-**31** followed conventional lines. N-Alkylation of (+)-**31** with propargyl bromide gave (+)-**33** which was converted into (+)-**36** by treatment with *t*-$BuMe_2SiOTf/Et_3N$, *n*-BuLi/$ClCO_2Me$, and $LiBF_4$. Exposure of (+)-**36** to pyrrolidine/trifluoroacetic acid gave the (*Z*)- and (*E*)-quinuclidines (+)-**37** and (+)-**38**. Methylenation of **38** with Tebbe's reagent gave **39**. Both *E* and *Z* isomers were taken through the series of transformations to give **43**, **45**, **47**, and **49** and **44**, **46**, **48**, and **50**. The structures of (+)-**37** and (+)-**43** were conclusively established by single-crystal X-ray crystallography. Fragmentation of **49** with methyl chloroformate gave **51** which was reduced with $LiAlH_4$ to give (+)-taberpsychine (**4**). Treatment of **47** with methyl chloroformate gave the 18-hydroxytaberpsychine derivative **52** which was reduced with $LiAlH_4$ to give **53**. Similarly **48** gave **55**. When the *Z* isomer **55** was exposed to the Mitsunubo conditions, (+)-koumine (**2**) was formed (40%, 72% based upon recovered **55**). The *E* isomer **53** gave (+)-koumine (**2**) in lower yields at a much reduced rate.

The alkaloids of the *Gelsemium* species are unusual in that none of them have succumbed to total synthesis.[2] The two most well-known members of this class of indole alkaloids are (+)-gelsemine (**1**)[3] and (−)-koumine (**2**).[4] Both alkaloids resisted classical structural elucidation by degradation, and eventually their structures were revealed through single-crystal X-ray crystallography.[5] The absolute configuration of (−)-koumine was established by a partial synthesis from vobasine.[6]

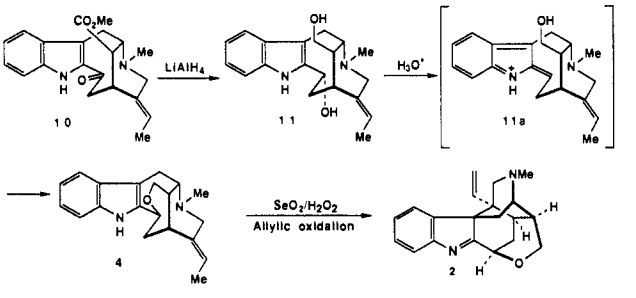




Scheme I



Scheme II



Koumine (**2**) was isolated in 1931 from the Chinese plant Kou-wen, later identified as *Gelsemium elegans* Benth.[7] Recent clinical experiments with Kou-wen on malignant tumors have given encouraging results, and good analgesic activity with no additive side effects has been reported.[8]

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(2) Joule, J. A. In *The Monoterpene Indole Alkaloids*; Interscience Publ. John Wiley and Sons, Inc.: New York, 1983; Heterocyclic Compounds, Vol. 25, Part 4, Saxton, J. E., Ed.; Chapter V, The Sarpagine–Ajmaline–Akuammicine Group, pp 201–259.

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(4) For a comprehensive recent review of gelsemium alkaloids including koumine see: Liu, Z.-J.; Lu, R.-R. *Gelsemium Alkaloids*, In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1988; Vol. 33, Chapter 2, p 83.

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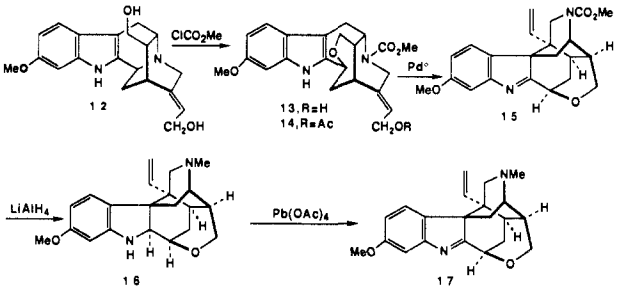
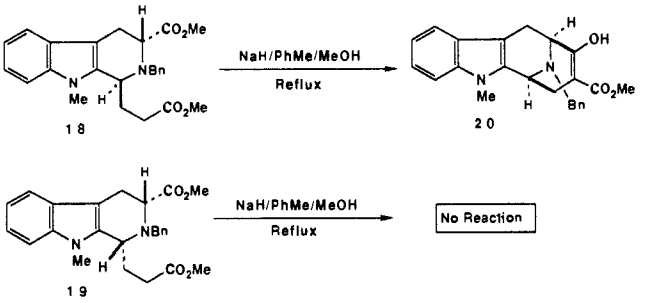
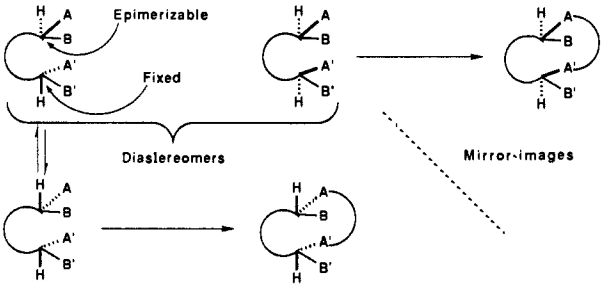
Scheme III



Scheme IV



Scheme V



Retrosynthetic and Biogenetic Considerations

Our retrosynthetic analysis of koumine (**2**) was based upon the recognition that the central part of the complex multiple-ring system contains an eight-membered ring and that crucial carbon–carbon bonds can, in principle, be made by entropically favored transannular reactions. A plausible precursor to **2** is the allylic alcohol **3** which when rewritten can be recognized as 18-hydroxyanhydrovobasindiol. Although **3** is not a known natural product, (−)-anhydrovobasindiol or (−)-taberpsychine (**4**) is a naturally occurring indole alkaloid.[9] An intramolecular S_N2' reaction should be capable of converting **3** into koumine (**2**). Fragmentation of **5** induced by electrophilic attack on the quinuclidine nitrogen atom should generate the iminium ion **5a** which upon intramolecular trapping by the primary hydroxyl group provides a viable route to **3**/**4**. The compound **6** is a known indole alkaloid called koumidine,[10] whereas the 18-hydroxy derivative **5** is not, as yet, a natural product. The compound **5** should be available from the ketone **7** by a stereospecific reductive hydroxymethylation sequence. The quinuclidine core structure of **7** should be accessible from **8** by intramolecular conjugate addition of the derived ketone enolate to the electrophilic acetylenic ester. At this point we can relate **8** to the parent 6,10-imino-5*H*-cyclooct[*b*]indole ring system **9** which is available as a single enantiomer from *S*-(−)-tryptophan.

Since we initiated research on the total synthesis of koumine (**2**), several important papers have appeared in the literature that have a direct bearing on the retrosynthetic scheme shown above and, more significantly, imply, in a structural sense, a biogenetic relationship between koumine (**2**) and the various indole alkaloids of the structural types shown in Scheme I. A partial synthesis[6] of koumine (**2**) was reported in 1986. Vobasine (**10**) on reduction with $LiAlH_4$ gave vobasindiol (**11**) which was dehydrated with aqueous sulfuric acid to provide taberpsychine (**4**). Allylic oxidation of **4** using SeO_2/H_2O_2 gave koumine albeit in modest yield (25%), Scheme II. In a similar vein Sakai[11,12] has converted 18-hydroxygardnerine (**12**) into the 11-methoxy analogue of koumine **17** by using the sequence of transformations shown in Scheme III. Fragmentation of **12**, induced by methyl chloroformate, gave **13** (cf. **3**), whose derived acetate **14** on treatment with $Pd(PPh_3)_4/NaH$ underwent a transannular S_N2' cyclization to give **15**. Reduction of **15** with $LiAlH_4$ gave **16**, which on reintroduction of the imine functionality with $Pb(OAc)_4$ gave **17**.

Both Schemes II and III closely parallel a biogenetic sequence proposed by Lounasmaa and Koskinen.[13]

There are no reported total syntheses of gelsemium or sarpagine alkaloids **5**/**6**. The only successful endeavors have involved the ajmaline family of indole alkaloids.[14]

Results

The first objective was to establish an efficient route to the tetracyclic adduct **9**, or a N^1-protected derivative, preferably as a single enantiomer. While both Yoneda[15] and more recently Cook[16] have reported the synthesis of **20**, a number of curious and unexplained facts appeared in their work. For example, Yoneda claims that the cis isomer **19** did not undergo Dieckmann cyclization, whereas the trans isomer **18** cyclizes to give **20**. This work was conducted in the racemic series. In the enantiomerically pure series derived from D-(+)-tryptophan Cook claims that under Dieckmann cyclization conditions (NaH/PhMe/MeOH, heated at reflux) **18** cyclizes to give **20**, whereas the cis compound **19** first epimerizes at C-3 to the trans compound **18** before cyclizing to the antipode of **20** (Scheme IV).

The particular conditions of the Dieckmann cyclization are ones that would be expected to cause equilibration of any carbanionic intermediates. Finally these workers also report that the trans isomer **18** cyclizes to give **20** faster than the cis isomer **19** cyclizes to give antipodal **20**. Before discussing our own results, which contradict the above, an a priori analysis of this type problem is instructive. In a general sense, if we start with two compounds whose stereochemical relationship is diastereomeric with one stereogenic center fixed (nonepimerizable and antipodal) and the other stereogenic center epimerizable, the following analysis is applicable, Scheme V.

After epimerization the diastereomers (now antipodal/mirror images) can undergo a further transformation to products which are antipodal. The rate of the last transformation must, by

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(9) Taberpsychine (**4**) was isolated from *Tabernaemontana psychotrifolia* H. B. K.; Biemann, K.; Spiteller, R. *J. Am. Chem. Soc.* **1962**, *84*, 4578. Its structure was reported in 1969 under the name of anhydrovobasindiol, and it was partially synthesized from vobasine. Dugan, J. J.; Hesse, M.; Renner, U.; Schmid, H. *Helv. Chim. Acta* **1969**, *52*, 701. Burnell, R. H.; Medina, J. D. *Can. J. Chem.* **1971**, *49*, 307.

(10) Koumidine **6** was first isolated from Chinese gelsemium (*G. elegans*): Jin, H. L.; Xu, R. S. *Acta Chim. Sinica* **1982**, *40*, 112. The geometry of the ethylidene group was recently corrected by Cordell. Schum, Y.; Cordell, G. A. *Phytochemistry* **1987**, *24*, 2875.

(11) Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongseripatana, S.; Ponglux, D. *Tetrahedron Lett.* **1986**, *27*, 4585.

(12) For synthetic approaches to the koumine-type alkaloids see: Liu, C.; Sun, S.; Yu, Q. *J. Org. Chem.* **1983**, *48*, 44. Liu, Z.; Xu, F. *Tetrahedron Lett.* **1989**, *30*, 3457.

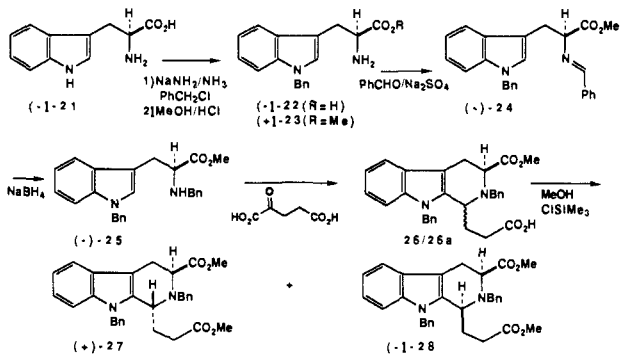
(13) Lounasmaa, M.; Koskinen, A. *Planta Medica* **1982**, *44*, 120.

(14) Synthesis of ajmaline: van Tamelen, E. E.; Shamma, M.; Burgstahler, A. W.; Wolinsky, J.; Tamm, R.; Aldrich, P. E. *J. Am. Chem. Soc.* **1958**, *80*, 5006. Masamune, S.; Ang, S. K.; Egli, C.; Nakatsuka, N.; Sakhar, S. K.; Yasunari, Y. *J. Am. Chem. Soc.* **1967**, *89*, 2506.

(15) Yoneda, N. *Chem. Pharm. Bull.* **1965**, *13*, 622 and 1231. Hobson, J. D.; Raines, J.; Whiteoak, R. J. *J. Chem. Soc.* **1963**, 3495. Cloudsdale, I. S.; Kluge, A. F.; McClure, N. L. *J. Org. Chem.* **1982**, *47*, 919. References to the 6,10-imino-5*H*-cyclooct[*b*]indole ring system.

(16) Zhang, L.-L.; Cook, J. M. *Heterocycles* **1988**, *27*, 2795. Sverens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; Dipierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535. Trudell, M. L.; Cook, J. M. *J. Am. Chem. Soc.* **1989**, *111*, 7504.

Scheme VI



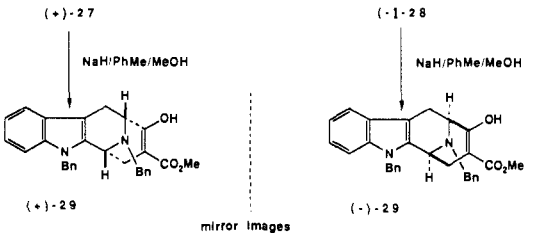
definition, be the same. Therefore, if the last step is the slowest, both diastereomers will be transformed at the same rate. Whereas if epimerization is the slowest step, naturally it will be overall rate determining. Consequently if the diastereomers are transformed to antipodal products at a different rate, the rate-determining step is epimerization. Applying this argument to the specific problem of the conversion of **18**/**19** into **20** and its mirror image, since the rates of conversion of **18**/**19** into **20** are different, the rate-determining step is C-3 epimerization. The trans compound **18** *cannot* undergo Dieckmann cyclization to **20** directly without the formation of an azabicyclo[3.3.1]inside–outside system, which is obviously impossible, especially under thermodynamic control. The cis compound **19**, in the absence of other steric effects, should be the thermodynamically more stable diastereomer since the C-3 CO_2Me and C-1 $CH_2CH_2CO_2Me$ substituents can occupy a 1,3-diequatorial relationship, although $A^{(1,3)}$ strain between the N^1-alkyl group and the C-1 propionate may favor the trans isomer. Regardless, only the 1,3-diaxial conformer of the cis isomer can undergo the Dieckmann cyclization.

(*S*)-(−)-Tryptophan **21** was converted into its N^1-benzyl derivative **22** (95%) by treatment with sodamide (2.2 equiv)/$PhCH_2Cl$ in liquid ammonia.[17] Conversion of **22** into the methyl ester **23** (68%) (dry HCl/MeOH)[17,18] followed by condensation with benzaldehyde (PhH/Na_2SO_4) and reduction of the imine **24** with sodium borohydride in methanol gave (−)-*N*,*N'*-dibenzyltryptophan methyl ester **25** (95% from **23**). By using Cooks[19] recent improvement of the Pictet–Spengler condensation, **25** was treated with 2-ketoglutaric acid/benzene at reflux with provision for the removal of water and the resulting acids **26** (67%) esterified ($MeOH/ClSiMe_3$) to give a mixture of diastereomeric methyl esters **27**/**28** (ca. 2:1) (80%) (Scheme VI).

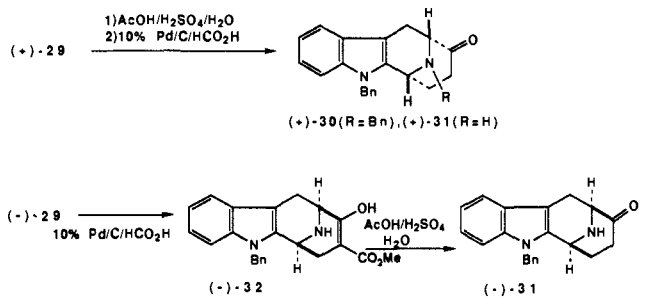
While **27** and **28** could be separated by chromatography over silica gel, they were more conveniently separated on a large scale by fractional crystallization from methanol. The major diastereomer **27** was isolated in 58% yield. The minor diastereomer **28** could be isolated in a pure form by chromatography of the mother liquors. Assignment of the stereochemistry was initially based upon extensive studies by the Sakai group[20] and ^{13}C NMR data comparisons with data reported by Bailey and Hollinshead.[21] Typically *N*-benzylmethylene carbons for 1,3-cis disubstituted tetrahydro-β-carbolines resonate about 7 ppm downfield of the corresponding peaks in the trans isomers. The major isomer **27** exhibited an α-amino benzylic methylene ^{13}C resonance at 52.63 ppm, while the minor isomer **28** resonated at 61.15 ppm.

Treatment of **28** with NaH/PhMe/MeOH heated at reflux gave (+)-**29** (88%) in 5 h, whereas the trans isomer **27** required 15 h to be converted into (−)-**29** (72%). The antipodal relationship between **29** and **30** is demonstrated by rotational data, **29** $[\alpha]_D^{25}$ +160° (*c* 0.985, CH_2Cl_2), **30** $[\alpha]_D^{25}$ −158° (*c* 0.990, CH_2Cl_2). The enantiomeric purities of **29** and **30** were confirmed by an ^1H NMR study[22] of these compounds in the presence of the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol[23] in benzene-d_6 (Scheme VII).

Scheme VII



Scheme VIII



Beginning with a single enantiomer of tryptophan both enantiomers of the tetracyclic β-ketoester (+)-**29**/(−)-**29** are available. The absolute configuration shown for (−)-**29** corresponds to the natural configuration for koumine. The above results are in agreement with the analysis described in Scheme V and represents experimental results that were reproduced many times by different workers. We have taken both antipodes (+)-**29** and (−)-**29** through the entire sequence but will only describe the so-called (+)-unnatural series in the text since this material was more readily available.

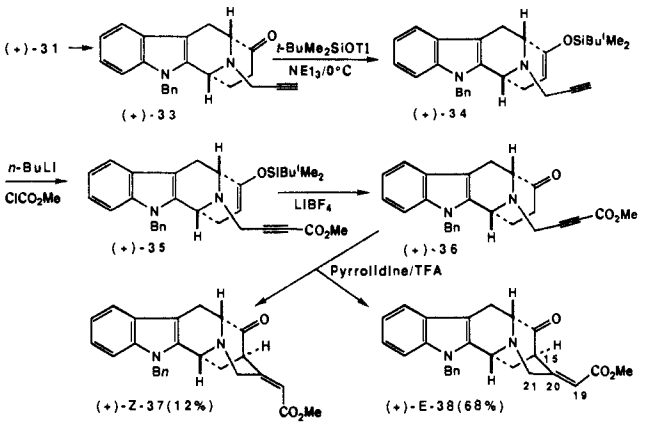
The major enantiomer (+)-**29** was hydrolyzed and decarboxylated under standard conditions[24] in $AcOH/H_2SO_4/H_2O$ at reflux. Although the reaction was very slow (7 days), the ketone (+)-**30** was isolated in 99% yield. Catalytic transfer hydrogenation[25] with 10% Pd/C in 88% formic acid cleanly gave the monodebenzylated ketone (+)-**31**. In reverse order, (−)-**29** was exposed to the catalytic transfer hydrogenation conditions to give (−)-**32** (72%). Decarboxymethylation of (−)-**32** gave (−)-**31** (86%). The optical purity of each enantiomer was retained through both sequences, (+)-**31** $[\alpha]_D^{23}$ +104° (*c* 1.05 CH_2Cl_2) and (−)-**31** $[\alpha]_D^{28}$ −98° (*c* 1.08 CH_2Cl_2). Decarboxylation followed by debenzylation proceeds in an overall yield of 84%, whereas the reverse sequence proceeds in 62% overall yield. Both enantiomeric forms of **31** are available and for the major enantiomer (+)-**31**, in 20% overall yield through 10 steps from (*S*)-(−)-tryptophan. Correspondingly starting from (*R*)-(+)-tryptophan, (−)-**31** (natural series) is the major enantiomer (Scheme VIII).

The next phase of the synthesis involved alkylation of the bridged N-atom with a linear C_4 unit and the formation of the quinuclidine ring system. While we looked at a number of variations for the construction of the quinuclidine framework, only one route was successful.

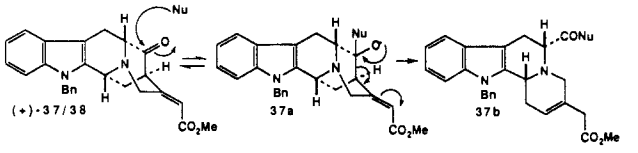
N-Alkylation of the amine (+)-**31** with propargyl bromide/EtOH[26] gave the propargylamine (+)-**33** (60%). Treatment of

(17) Yamada, S.; Shioiri, T.; Itaya, T.; Hara, T.; Matsueda, R. *Chem. Pharm. Bull.* **1965**, *13*, 88.
(18) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 2, p 926.
(19) Zhang, L. H.; Cook, J. M. *Heterocycles* **1988**, *27*, 1357. See also ref 16.
(20) Shimizu, M.; Ishikawa, M.; Komoda, Y.; Nakajima, T.; Yamaguchi, K.; Sakai, S. *Chem. Pharm. Bull.* **1984**, *32*, 1313.
(21) Bailey, P. D.; Hollinshead, S. P. *Heterocycles* **1987**, *26*, 389.
(22) Pirkle, W. H.; Burlingame, T. G.; Beare, S. D. *Tetrahedron Lett.* **1968**, *3*, 5849.
(23) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384.
(24) Furniss, B. S.; Hannaford, A. J.; Rogers, V.; Smith, P. W. G.; Tatchell, A. R. *Practical Organic Chemistry*, 4th ed.; Vogel, A. I., Ed.; Longmans: New York, 1978; p 437.
(25) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.

Scheme IX



Scheme X

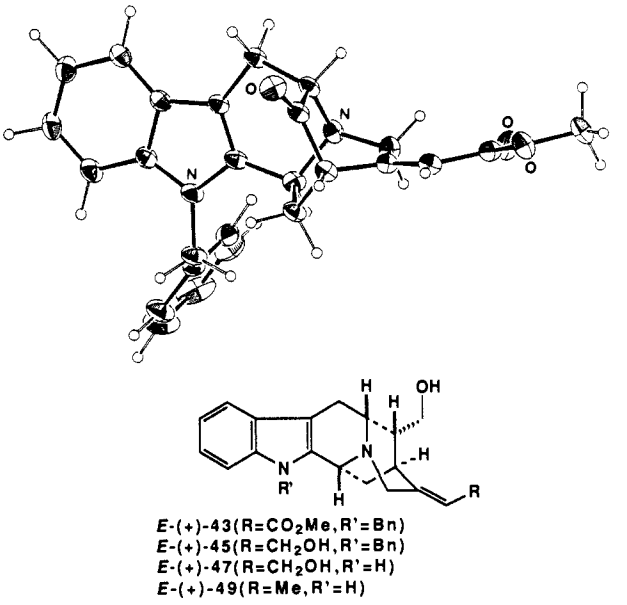


(+)-33 with *t*-$BuMe_2SiOTf/NEt_3$/O °C in dry CH_2Cl_2 gave the enol ether (+)-34 (82%). Deprotonation of (+)-34 with *n*-BuLi/THF/−78 °C to −30 °C followed by quenching the so-formed acetylide anion with methyl chloroformate gave the α,β-unsaturated acetylenic ester (+)-35 in 76% yield after purification.

Initially we attempted a fluoride ion mediated deprotection of the dimethyl *tert*-butylsilyl enol ether 35 expecting that the enolate would readily be trapped by the α,β-unsaturated acetylenic ester to give the quinuclidines 37/38. Treatment of 35 with a wide range of reagents that are well-precedented to deprotect trialkylsilyl enol ethers, KF Triton B,[27] KF 18-crown-6, KF benzyltriethylammonium chloride, CsF,[28] naked fluoride, $KF{\cdot}2H_2O$ benzyltriethylammonium chloride,[29] $BF_3{\cdot}OEt_2$,[30] and tetrabutylammonium fluoride[31] gave reaction mixtures that typically consisted of a mixture of the ketone 36 and the required quinuclidine, *Z* and *E* olefinic ester isomers 37/38 but always in very poor yields and difficult to purify, Scheme IX.

Apparently the nonenolizable carbonyl group in 37/38 causes a retro-Dieckmann fragmentation process to take place under the conditions used to release the enolate anion from 35, Scheme X.

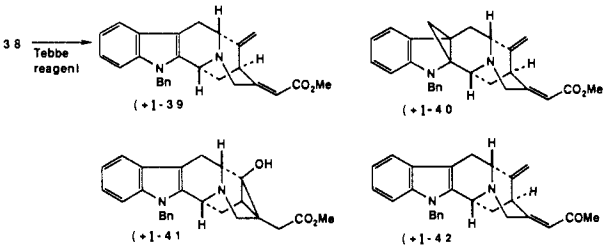
Since the keto ester 36 was readily prepared by treatment of 35 with $LiBF_4/H_2O/THF$,[32] we exposed 36 to a number of conditions (both acidic and basic) to promote intramolecular Michael cyclization to give 37/38. A wide variety of reagents such as DABCO, DBU, 2,6-di-*tert*-butyl-4-methylpyridine, $NaN(SiMe_3)_2$, AgOAc, camphorsulfonic acid, *p*-TsOH, and $TiCl_4$ were ineffective, but eventually it was found that 1.2 equivs of lithium diisopropylamide/THF/−78 °C to 0 °C over 2 days gave 37/38 as a separable 1:1 mixture of *E* and *Z* α,β-unsaturated esters in 60% yield after purification. The assignment of *E* and *Z* isomers was readily made by comparison of their ^1H NMR spectra. The *Z* isomer (+)-37 exhibited two doublets of doublets at 4.45 and 4.20 ppm (*J*'s = 19.9, 2.2 and 19.9, 2.6 Hz), while the unshielded C-21 protons of the *E* isomer 38 appeared as a broad singlet at 3.90 ppm. Similarly the C-15 proton of the *E* isomer (+)-38 appeared as a multiplet at 4.65–4.64 ppm, while the unshielded C-15 proton in the *Z* isomer (+)-37 appeared at 3.06–3.05 ppm. These assignments were confirmed by a single-crystal X-ray crystallographic structure determination of the *Z* isomer (+)-37. Figure 1 shows an ORTEP representation.[33] While both 37/38 were available, it was found that the reaction (LDA/THF/−78 °C to 0 °C) did not scale-up satisfactorily. Eventually it was discovered that treatment of (−)-36 with pyrrolidine (0.2 equiv) and trifluoroacetic acid (0.2 equiv) in dry benzene heated at reflux for 19 h gave 37/38 (12% and 68%). It should be noted that 37 equilibrates to a mixture of 37/38 on standing in solution, as does 38.



E-(+)-43(R=CO_2Me,R'=Bn)
E-(+)-45(R=CH_2OH,R'=Bn)
E-(+)-47(R=CH_2OH,R'=H)
E-(+)-49(R=Me,R'=H)

Figure 1.

Scheme XI



At this stage we needed to homologate the carbonyl group in 37/38 to a hydroxymethyl group in a stereospecific manner. Both conventional Wittig methylenation and the Corey dimethylsulfoxonium methylide[34] did not produce any useful results. Recently transition-metal carbenoid complexes have gained wide spread use as methylenating agents for base sensitive substrates. Treatment of 38 with Lombardo's reagent[35] ($TiCl_4/Zn/CH_2Br_2$) in CH_2Cl_2 for 1 h at 20 °C gave a mixture of 39 (24%) and unexpectedly 40 (20%). It is possible that the cyclopropane is produced from a Simmons–Smith type reagent, $BrCH_2ZnBr$ present in the Lombardo reagent. Particularly problematic in this procedure, especially on a large scale (>1 g) was the lack of reliable reproducibility of the yields of 39. Using the Takai procedure[36] (replacing CH_2Br_2 by CH_2I_2) gave 39/40 (1:1), and if the Lombardo reagent was prepared by using a Zn–Cu couple

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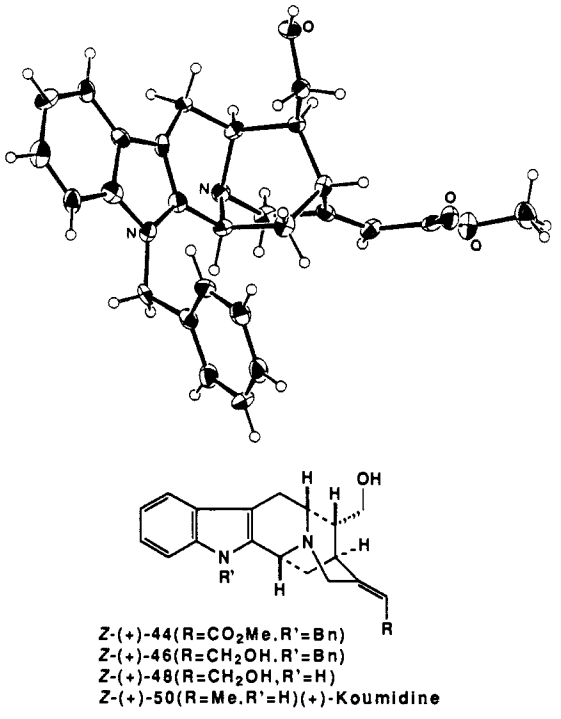


Figure 2.

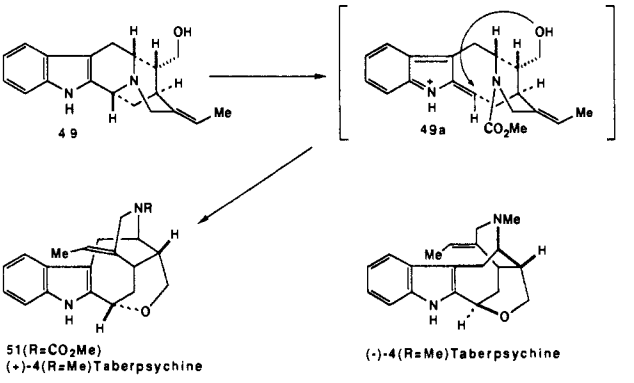
rather than Zn dust the cyclopropanol **41** was the major product (Scheme XI).

Since the ill-defined Lombardo reagent did not provide a reproducible supply of **39**, we examined the Tebbe reagent.[37] The preparation of the Tebbe reagent was best carried out by using the Grubbs procedure.[38] Treatment of **38** with the Tebbe reagent in THF gave the required *exo*-methylene adduct **39** (63%) and the methyl ketone **42** (15%) (after acidic workup). This procedure was reproducible and provided **39** in gram quantities.

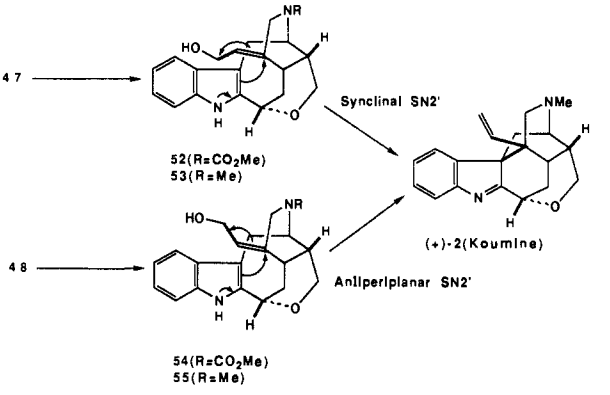
Hydroboration of **39** proved to be particularly difficult; however, it was eventually found that treatment of **39** with a freshly prepared solution of diisoamylborane in THF at 0 °C/12 h gave **43** (69%). The stereochemistry of the newly introduced hydroxymethyl group was determined by single-crystal X-ray crystallography (Figure 2).[33] Application of the same methylenating/hydroborating sequence to **37** gave **44**. Reduction of (*E*)-**43** with DIBAL-H/PhMe at room temperature gave **45** (89%). Similarly **44** gave **46** (92%). The indole *N'*-benzyl protecting group in **45** was removed reductively by treatment with $Na/NH_3/-78$ °C to give **47** (81%). Likewise **46** gave **48** (91%) which is the 18-hydroxy derivative of (+)-koumidine (**50**). When **46** was treated with Na/NH_3 at −30 °C (cf. −78 °C) the C-18 hydrogenolysis product (+)-koumidine (**50**) was isolated in 95% yield. Comparison with an authentic sample of (−)-koumidine (^1H NMR, ^{13}C NMR, IR, TLC, $[\alpha]_D$) demonstrated their structural identity and antipodal relationship and furthermore confirms Cordell's reassignment of the stereochemistry of the ethylidene group.[10] Similarly **47** gave **49** (63%). Fragmentation of the (*E*)-ethylidene isomer **49** by treatment with methyl chloroformate/MeOH/$NaHCO_3$ gave **51** (52%), presumably via the extended iminium ion **49a** (Scheme XII).

Reduction of **51** with $LiAlH_4$/THF/heated at reflux 18 h, gave (+)-taberpsychine (**4**) (67%). Comparison with an authentic sample of (−)-taberpsychine (^1H NMR, IR, HRMS, $[\alpha]_D$, and TLC) demonstrated their structural identity and antipodal relationship.[9] Since (−)-taberpsychine has been converted into (−)-koumine (**2**) by treatment with SeO_2/H_2O_2 (see Scheme II)

Scheme XII



Scheme XIII



this constitutes a formal synthesis of (+)-koumine, but since the conversion of **4** into **2** only proceeds in very modest yields (25%) we carried the 18-hydroxy derivatives **47** and **48** through to (+)-koumine. Treatment of **47** with MeO_2CCl/CH_2Cl_2/room temperature/5 h gave the 18-hydroxytaberpsychine derivative **52** (61%, 93% based upon recovered starting material). Reduction of **52** with $LiAlH_4$/THF/reflux 3 h gave (+)-18-hydroxytaberpsychine (**53**) (78%). Similarly the *Z* isomer **48** gave **55** via **54** (33%). When the *Z* isomer **55** was treated with diethyl azodicarboxylate/Ph_3P/imidazole(catalyst)/NaH in dry THF heated at reflux it was cleanly converted into (+)-koumine (**2**) (40%, 72% based upon recovered **55**). Surprisingly when the *E* isomer **53** was exposed to the above Mitsunubo conditions, (+)-koumine (**2**) was formed in lower yields (34%, no recovered starting material) and at a much reduced rate. Substantial degradation to intractable byproducts was observed. While the effect of double bond geometry on the rate and product distribution in the S_N2' reaction has not been previously considered, in this particular situation it is a factor that influences the relative $\Delta G^{\ddagger}$'s between the transition states leading to koumine (Scheme XIII).

In the *Z* isomer **55** the developing π-system is *antiperiplanar* to the indole 2,3-double bond, whereas in the *E* isomer **53** the relationship between the developing vinyl group and the 2,3-double bond can be viewed as *synclinal*. Obviously we cannot discount that the different rates of cyclization of **53** and **55** to koumine is a reflection of the ease of formation of the phosphonium ion leaving group in the Mitsunubo reaction and therefore peculiar to the specific substrates **53**/**55**. Nevertheless there must be energy differences between synclinal and antiperiplanar transition states in the S_N2' reaction in the same way that there are for aldol reactions and related transformations. It should be instructive to investigate this possible stereoelectronic effect in simpler substrates (intra- and intermolecular) to ascertain whether or not it is a real factor in coming to a more complete understanding of the often controversial S_N2' reaction mechanism. We are currently starting this study.[41]

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Experimental Section

Melting points were taken on a Thomas-Hoover capillary tube apparatus and are uncorrected. Boiling points are uncorrected. Optical rotations were performed on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded on a Perkin-Elmer 298 grating spectrometer either neat, as Nujol mulls, or in $CHCl_3$ as indicated. Ultraviolet spectra were recorded on a Perkin-Elmer 554 spectrometer in the indicated solvents. Proton NMR spectra were recorded either on a Nicolet NT-360 360 MHz, a Varian EM390 90 MHz, a Bruker AM 500 500 MHz or a Varian XL-300 300 MHz spectrometer as indicated, in $CDCl_3$, and are reported in ppm downfield from TMS. Carbon-13 NMR spectra were recorded on a Varian XL-300 spectrometer at 75 MHz in $CDCl_3$ and are also reported in ppm downfield from TMS. Mass spectra were recorded on a Kratos MS 80 spectrometer. Elemental analyses were performed by Midwest Microlab in Indianapolis, IN. Routine monitoring of reactions were performed by using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. Preparative-layer chromatography was performed by using Merck 60 F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated solvents on Merck 60H F_{254} silica gel.

Air- and moisture-sensitive reactions were carried out under usual inert atmosphere techniques. Reactions requiring anhydrous conditions were performed in glassware dried by a Bunsen flame or in an oven at 140 °C, then cooled under argon, and performed under a blanket of argon. Solvents and commercial reagents were dried and purified before use: Et_2O and THF were distilled from sodium benzophenone ketyl; CH_2Cl_2, Et_3N, DMSO, pyrrolidine, *tert*-butyl alcohol, diisopropylamine, benzene, toluene, and hexanes were distilled from calcium hydride under argon.

(*S*)-(−)-*N'*-Benzyltryptophan (22). Following the reported procedure,[17] metallic Na (10.4 g, 452 mmol) was added, in small pieces, to liquid NH_3 (1000 mL) containing $Fe(NO_3)_3 \cdot 9H_2O$ (0.6 g, 1.5 mmol) cooled to −78 °C. After the mixture had turned grayish-black, (*S*)-(−)-tryptophan (**21**) (40.0 g, 196 mmol) was washed into the solution with a minimum of anhydrous Et_2O. The mixture was allowed to come to reflux. After 20 min freshly distilled benzyl chloride (22.5 mL, 196 mmol) was added dropwise over a 10-min period, and the mixture stirred overnight to allow the solvent to evaporate. The resulting solid was dissolved in hot water (1500 mL) and precipitated by the addition of glacial acetic acid (70 mL). The solid was filtered and washed with water (400 mL), 50% EtOH/H_2O (400 mL), 95% EtOH/H_2O (400 mL), and Et_2O (400 mL). The crude product was dried for 3 days over silica gel at 0.1 mmHg, to yield the crude product **22** (54.8 g, 95%) as a tan solid: mp 208–211 °C (lit.[17] 211–212 °C); IR (Nujol) 3600, 2760, 2600, 1627, 1604 cm^{-1}.

(*S*)-(−)-*N'*-Benzyltryptophan Methyl Ester (23). Following the reported procedure,[17] *N'*-benzyltryptophan (**22**) (54.7 g, 185 mmol) was added to methanol at 0 °C. Anhydrous HCl gas was then bubbled into the suspension for 1 h and the resulting clear mixture stirred overnight under argon. The solvent was removed, and the resulting oil dissolved in MeOH (200 mL). Addition of Et_2O caused formation of a precipitate which was filtered and dried under vacuum to yield the methyl ester hydrochloride (46.7 g, 73%) as a crystalline salt. A sample was crystallized from MeOH/Et_2O: mp 203.5–204 °C (lit.[17] mp 198–198.5 °C); $[\alpha]_D^{24}$ +22° (*c* 0.44, 95% EtOH); UV (95% EtOH) λ_{max} (ϵ) 220 (28 500), 285 nm (5540); ^1H NMR (360 MHz, DMSO-d_6) δ 8.8–8.5 (2 H, br), 7.6 (1 H, m), 7.42–7.05 (9 H, m), 5.37 (2 H, s), 4.19 (1 H, m), 3.58 (3 H, s), 3.36–3.22 (2 H, m); CIMS, *m/e* 309 (M − Cl), 292, 249, 220, 91 (base).

To a suspension of the hydrochloride salt (46.7 g, 135 mmol) in EtOAc (600 mL) was added 5% aqueous NaOH (200 mL). After 2 h of rapid stirring an insoluble precipitate was filtered off and rinsed with EtOAc (1000 mL). The organic phase was separated and the combined organic layers washed with brine and dried ($MgSO_4$). Removal of solvent gave crude **23** (38.8 g, 93%) as a yellow-brown oil. An analytical sample was prepared by Kugelrohr distillation: bp 190 °C at 0.3 mmHg; $[\alpha]_D^{23}$ +9.5° (*c* 0.75, CH_2Cl_2); IR (neat) 3370, 3330, 1730, 1612, 1605, 1550 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.62 (1 H, d, *J* = 7.6 Hz), 7.31–7.08 (8 H, m), 6.99 (1 H, s), 5.27 (2 H, s), 3.87–3.81 (1 H, m), 3.67 (3 H, s), 3.28 (1 H, dd, *J* = 14.3, 4.9 Hz), 3.07 (1 H, dd, *J* = 14.3, 7.4 Hz), 1.85 (2 H, br s); EIMS, *m/e* 309 (M^+ + 1), 308 (M^+), 292, 249, 220, 91 (base); HRMS *m/e* calcd for $C_{19}H_{20}N_2O_2$ 308.1526, Found: 308.1526.

(*S*)-(−)-*N*,*N'*-Dibenzyltryptophan Methyl Ester (25). A solution of methyl ester **23** (38.8 g, 125 mmol) in benzene (500 mL) was treated with benzaldehyde (13.9 mL, 125 mmol). After stirring the mixture for 12 h under an argon atmosphere, anhydrous $MgSO_4$ (20 g) was added, and stirring was continued for 3 h. The mixture was filtered to remove $MgSO_4$, and the solvent was evaporated in vacuo to give the crude imine **24** (51 g) as a pale yellow-brown oil: $[\alpha]_D^{23}$ −198° (*c* 1.25, CH_2Cl_2); IR (neat) 1730, 1704, 1640 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.88 (1 H, s), 7.68–7.64 (3 H, m), 7.42–7.10 (9 H, m), 6.94 (2 H, d, *J* = 8.0 Hz), 6.88 (1 H, s), 5.18 (2 H, s), 4.28 (1 H, dd, *J* = 9.0, 4.6 Hz), 3.75 (3 H, s), 3.57 (1 H, dd, *J* = 14.3, 4.6 Hz), 3.26 (1 H, dd, *J* = 14.3, 9.6 Hz).

A solution of crude imine **24** (51.0 g) in MeOH (500 mL) was treated with sodium borohydride (5 g, 132 mmol) in small portions over 10 min. The mixture was stirred at 25 °C for 1 h. Removal of the solvent in vacuo gave a yellow oil which was diluted with water (350 mL) and extracted with EtOAc (2 × 400 mL). The combined organic extracts were washed with water (200 mL) and brine and dried ($MgSO_4$). Removal of solvent in vacuo followed by flash chromatography over silica gel gave, on elution with EtOAc/hexanes (1.5:5), **25** (47.4 g, 95%) as a colorless oil: $[\alpha]_D^{24}$ −4.1° (*c* 1.50, CH_2Cl_2); IR (neat) 3330, 1725 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 206 (26 500), 222 (25 200), 286 nm (4600); ^1H NMR (360 MHz, $CDCl_3$) δ 7.58 (1 H, d, *J* = 7.8 Hz), 7.37–7.04 (13 H, m), 6.95 (1 H, s), 5.25 (2 H, s), 3.83 (1 H, d, *J* = 12.7 Hz), 3.66 (1 H, d, *J* = 12.7 Hz), 3.66 (1 H, t, *J* = 6.6 Hz), 3.58 (3 H, s), 3.19 (1 H, dd, *J* = 19.9, 6.6 Hz), 3.15 (1 H, dd, *J* = 19.9, 6.6 Hz). Anal. Calcd for $C_{26}H_{26}N_2O_2$: C, 78.36; H, 6.58; N, 7.03. Found: C, 77.91; H, 6.35; N, 6.90.

(1*R*,3*S*)-(+)-2,9-Dibenzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (26) and (1*S*,3*S*)-(+)-2,9-Dibenzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionic Acid (26a). A solution of the dibenzyl ester **25** (47.4 g, 119 mmol) in 1:1 benzene/dioxane (800 mL) was treated with 2-ketoglutaric acid (20.0 g, 137 mmol). The solution was heated at reflux for 24 h with removal of the water by the use of a Dean-Stark apparatus. Removal of solvent followed by flash chromatography over silica gel gave, on elution with EtOAc/hexanes (1:1), **26/26a** (38.5 g, 67%) as a 2:1 mixture of diastereomers. This mixture was used directly in the next step: IR ($CHCl_3$) 3620–2200, 1728, 1710 cm^{-1}.

(1*R*,3*S*)-(+)-Methyl 2,9-Dibenzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (27) and (1*S*,3*S*)-(+)-Methyl 2,9-Dibenzyl-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-1-propionate (28). A solution of acids **26** (140 g, 290 mmol) in anhydrous MeOH (1.5 L) was treated with chlorotrimethylsilane (170 mL, 1300 mmol). The solution was stirred at 25 °C overnight. Removal of solvent in vacuo and purification by flash chromatography over silica gel gave, on elution with CH_2Cl_2, **27** and **28** (114 g, 80%) as a 2:1 mixture of diastereomers. The crude mixture was dissolved in boiling MeOH and cooled overnight to yield pure trans epimer **27** (51.5 g, 36%) as colorless needles: mp 144–145 °C; $[\alpha]_D^{23}$ +13.5° (*c* 1.10, CH_2Cl_2); IR ($CHCl_3$) 1728 cm^{-1}; UV (hexanes) λ_{max} (ϵ) 212 (17 600), 226 (29 900), 282 nm (9800); ^1H NMR (360 MHz, $CDCl_3$) δ 7.61–7.58 (1 H, m), 7.23–7.11 (9 H, m), 7.05–7.02 (2 H, m), 6.90–6.87 (2 H, m), 5.36 (1 H, d, *J* = 17.3 Hz), 5.20 (1 H, d, *J* = 17.3 Hz), 4.11 (1 H, dd, *J* = 10.5, 6.0 Hz), 3.82 (3 H, s), 3.74 (1 H, d, *J* = 13.3 Hz), 3.65 (1 H, dd, *J* = 10.5, 3.1 Hz), 3.40 (3 H, s), 3.23 (1 H, d, *J* = 13.3 Hz), 3.15 (1 H, dd, *J* = 10.5, 13.1 Hz), 3.10 (1 H, dd, *J* = 24.6, 6.0 Hz), 2.47 (1 H, ddd, *J* = 17.2, 9.5, 5.8 Hz), 2.26 (1 H, dt, *J* = 17.2, 5.5 Hz), 1.96–1.73 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 173.63 (s), 173.28 (s), 138.79 (s), 137.78 (s), 137.40 (s), 135.51 (s), 129.33 (d), 128.59 (d), 127.90 (d), 127.14 (d), 126.75 (d), 126.05 (d), 121.63 (d), 119.39 (d), 118.18 (d), 109.69 (d), 107.23 (s), 55.97 (d), 53.24 (d), 52.04 (q), 51.21 (q), 46.51 (t), 29.64 (t), 28.11 (t), 20.26 (t); Anal. Calcd for $C_{31}H_{32}N_2O_4$: C, 74.98; H, 6.49; N, 5.64. Found: C, 74.72; H, 6.66; N, 5.89.

Chromatography of the mother liquor over silica gel, eluting with 10–30% EtOAc in hexanes allowed recovery of additional pure trans diester **27** (26 g), plus pure cis diester **28** (34 g) as colorless needles: mp 114–117 °C (from MeOH); $[\alpha]_D^{22}$ −14.7° (*c* 0.75, CH_2Cl_2); IR ($CHCl_3$) 1728 cm^{-1}; UV (hexanes) λ_{max} (ϵ) 215 (25 700), 226 (33 000), 283 nm (6400); ^1H NMR (360 MHz, $CDCl_3$) δ 7.61–7.59 (1 H, m), 7.26–7.11 (11 H, m), 6.93–6.86 (2 H, m), 5.39 (1 H, d, *J* = 17.0 Hz), 5.23 (1 H, d, *J* = 17.0 Hz), 3.90 (1 H, dd, *J* = 7.2, 1.6 Hz), 3.82 (1 H, d, *J* = 13.2 Hz), 3.69 (3 H, s), 3.62 (1 H, d, *J* = 13.2 Hz), 3.47 (3 H, s), 3.41 (1 H, dd, *J* = 16.2, 1.6 Hz), 3.10 (1 H, dd, *J* = 16.2, 7.2 Hz), 2.69 (1 H, ddd, *J* = 17.3, 9.4, 5.8 Hz), 2.42 (1 H, dt, *J* = 17.3, 5.4 Hz), 1.88–1.79 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 174.05 (s), 173.91 (s), 138.66 (s), 137.90 (s), 137.37 (s), 134.56 (s), 129.11 (d), 128.59 (d), 128.18 (d), 127.11 (d), 126.90 (d), 126.03 (d), 121.58 (d), 119.20 (d), 118.30 (d), 109.64 (d), 105.53 (s), 61.15 (t), 57.80 (d), 53.65 (d), 51.85 (q), 51.22 (q), 46.46 (t), 29.61 (t), 27.23 (t), 18.01 (t). Anal. Calcd for $C_{31}H_{32}N_2O_4$: C, 74.98; H, 6.49; N, 5.64. Found: C, 74.65; H, 6.69; N, 5.85.

(6*R*,10*R*)-(+)-Methyl 5,12-Dibenzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (+)-(29). A solution of trans diester **27** (12.7 g, 25.6 mmol) in anhydrous toluene (50 mL) was added to a stirred suspension of NaH (57% oil dispersion, 3.0 g, 70 mmol), previously washed with hexanes (5 × 10 mL), in toluene (50 mL) under argon in a Dean-Stark apparatus. The mixture was heated to

reflux, followed by dropwise addition of MeOH (0.7 mL, 17 mmol) in toluene (10 mL) over a period of 2 h, making sure the syringe needle remained below the solution surface. The solution was heated at reflux for 16 h. The mixture was cooled and quenched with glacial acetic acid (6.5 mL), diluted in benzene (200 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 60 mL). The organic layer was then washed with water (100 mL) and brine (100 mL) and dried ($MgSO_4$). Removal of solvent in vacuo and purification of the residue by flash chromatography on silica gel gave, on elution with EtOAc/hexanes (1:5), (+)-**29** (8.56 g, 72%) as a colorless foam. An analytical sample was crystallized from EtOAc/MeOH to give (+)-**29** as colorless needles: mp 148–150 °C; $[\alpha]_D^{23}$ +160° (*c* 0.985, CH_2Cl_2); IR ($CHCl_3$) 1660, 1620 cm^{-1}; UV (hexanes) λ_{max} (ϵ) 226 (28 000), 258 nm (9600); ^1H NMR (360 MHz, $CDCl_3$) δ 11.98 (1 H, s), 7.57–7.54 (1 H, m), 7.34–7.20 (8 H, m), 7.18–7.10 (3 H, m), 6.90–6.86 (2 H, m), 5.28 (1 H, d, *J* = 17.0 Hz), 5.14 (1 H, d, *J* = 17.0 Hz), 3.98 (1 H, d, *J* = 5.0 Hz), 3.79 (1 H, d, *J* = 5.9 Hz), 3.77 (1 H, d, *J* = 13.5 Hz), 3.62 (3 H, s), 3.61 (1 H, d, *J* = 13.5 Hz), 3.24 (1 H, dd, *J* = 16.2, 5.9 Hz), 2.98 (1 H, d, *J* = 16.2 Hz), 2.74 (1 H, br dd, *J* = 15.6, 6.0 Hz), 2.23 (1 H, dd, *J* = 15.6, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 172.48 (s), 171.72 (s), 137.93 (s), 137.49 (s), 136.75 (s), 133.94 (s), 128.71 (d), 128.20 (d), 127.27 (d), 127.15 (d), 126.81 (s), 125.88 (d), 121.58 (d), 119.41 (d), 118.22 (d), 109.43 (d), 106.20 (s), 94.09 (s), 55.83 (t), 55.07 (d), 51.29 (q), 48.74 (d), 46.45 (t), 28.25 (t), 21.88 (t). Anal. Calcd for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.07; N, 6.03. Found: C, 77.45; H, 5.97; N, 6.16.

(6*R*,10*S*)-(-)-Methyl 5,12-Dibenzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (-)-(29). As above a solution of the cis diester (-)-**28** (1.98 g, 4.00 mmol) was converted into (-)-**29** (1.64 g, 88%) in 4 h. Crystallization from EtOAc/MeOH gave colorless needles: mp 141–145 °C; $[\alpha]_D^{25}$ −158° (*c* 0.990, CH_2Cl_2). Anal. Calcd for $C_{30}H_{28}N_2O_3$: C, 77.56; H, 6.07; N, 6.03. Found: C, 78.06; H, 5.93; N, 6.09. IR and ^1H NMR data were identical to (+)-**29**.

^1H NMR Chiral Shift Study of β-Ketoesters (+)-29 and (-)-29. A reference 360 MHz ^1H NMR spectrum of (+)-**29** (5 mg) in C_6D_6 (0.5 mL) was recorded: δ 12.66 (1 H, s), 7.60–7.57 (1 H, m), 7.25–6.85 (11 H, m), 6.55 (2 H, d, *J* = 7.1 Hz), 4.64 (1 H, d, *J* = 17.2 Hz), 4.57 (1 H, d, *J* = 17.2 Hz), 3.85 (1 H, d, *J* = 5.5 Hz), 3.82 (1 H, t, *J* = 3.5 Hz), 3.53 (1 H, d, *J* = 13.5 Hz), 3.44 (1 H, d, *J* = 13.5 Hz), 3.20 (3 H, s), 3.10 (2 H, d, *J* = 3.5 Hz), 2.72 (1 H, dd, *J* = 15.4, 5.5 Hz), 2.24 (1 H, d, *J* = 15.4 Hz).

A spectrum of (+)-**29** (2.5 mg) and (-)-**29** (2.5 mg) plus the chiral solvating agent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (8.9 mg, 3 equiv) in C_6D_6 (0.5 mL) was recorded, which gave useful signals attributable to the separate enantiomers at 12.63 and 12.61, 3.54 and 3.53, 3.50 and 3.49, and 3.19 and 3.18 ppm as 1:1 doublets. A spectrum of (+)-**29** (5 mg) plus the shift reagent (8.9 mg, 3 equiv) in C_6D_6 (0.5 mL) contained only one of each doublet peak at 12.63, 3.53, 3.49, and 3.19 ppm. A spectrum of (-)-**29** (5 mg) plus shift reagent (8.9 mg, 3 equiv) in C_6D_6 (0.5 mL) contained only the opposite peaks of each doublet at 12.61, 3.54, 3.50, and 3.18 ppm. Close inspection of the 12.6 ppm enolic proton signals showed no evidence for any enantiomeric impurity in either the (+)- or (-)- compounds, leading to an estimation of >95% ee for each compound.

(6*R*,10*R*)-(+)-5,12-Dibenzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (30). A solution of the β-ketoester **29** (20.0 g, 43 mmol) in $HOAc/H_2SO_4/H_2O$ (12:1.5:8, 250 mL) was degassed by sonication with an ultrasonic bath under vacuum. The mixture was then heated at reflux for 3 days. The solution was cooled, diluted with EtOAc (1000 mL), and washed with saturated aqueous Na_2CO_3 in 150-mL portions, until the aqueous extracts were basic to pH paper. The organic layer was washed with brine and dried ($MgSO_4$). Removal of the solvent in vacuo gave **30** (17.3 g, 99%) as a pale yellow foam. Crystallization from Et_2O produced colorless needles: mp 141.5–142.5 °C; $[\alpha]_D^{23}$ +170° (*c* 1.00, CH_2Cl_2); IR ($CHCl_3$) 1710 cm^{-1}; UV (hexanes) λ_{max} (ϵ) 212 (31 000), 223 (35 000), 283 nm (7900); ^1H NMR (360 MHz, $CDCl_3$) δ 7.57–7.55 (1 H, m), 7.36–7.10 (11 H, m), 6.90–6.88 (2 H, m), 5.27 (1 H, d, *J* = 17.0 Hz), 5.16 (1 H, d, *J* = 17.0 Hz), 3.98 (1 H, br s), 3.78 (1 H, d, *J* = 6.7 Hz), 3.69 (1 H, d, *J* = 13.3 Hz), 3.63 (1 H, d, *J* = 13.3 Hz), 3.30 (1 H, dd, *J* = 17.0, 6.7 Hz), 2.74 (1 H, d, *J* = 17.0 Hz), 2.45–2.30 (2 H, m), 2.16–2.06 (1 H, m), 1.81–1.75 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 209.79 (s), 137.96 (s), 137.43 (s), 137.00 (s), 132.87 (s), 128.75 (d), 128.60 (d), 128.29 (d), 127.42 (d), 127.16 (d), 126.57 (s), 125.71 (d), 121.87 (d), 119.53 (d), 118.24 (d), 109.51 (d), 106.51 (s), 64.89 (d), 56.08 (t), 48.78 (d), 46.40 (t), 34.26 (t), 29.84 (t), 20.38 (t). Anal. Calcd for $C_{28}H_{26}N_2O$: C, 82.73; H, 6.45; N, 6.89. Found: C, 82.40; H, 6.38; N, 6.91.

(6*R*,10*R*)-(+)-5-Benzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (+)-(31). A solution of (+)-**30** (3.91 g, 9.6 mmol) in 88% formic acid (40 mL) was purged with argon for 15 min, 10% palladium on carbon (2.0 g), was added, and the mixture was stirred for 2 h at room temperature. The catalyst was filtered through Celite and rinsed with MeOH. The solvent was removed in vacuo, and the residue was diluted with EtOAc (150 mL) and washed with saturated aqueous Na_2CO_3 until basic to pH paper. The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent in vacuo and purification of the residue by chromatography over silica gel gave, on elution with 1% Et_3N in EtOAc, (+)-**31** (2.6 g, 85%) as a colorless foam. Crystallization from EtOAc produced colorless needles: mp 170–172 °C; $[\alpha]_D^{25}$ +104° (*c* 1.05, CH_2Cl_2); IR ($CHCl_3$) 1710 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 203 (22 000), 224 (26 000), 283 nm (5900); ^1H NMR (360 MHz, $CDCl_3$) δ 7.50–7.48 (1 H, m), 7.26–7.08 (6 H, m), 6.94–6.91 (2 H, m), 5.31–5.18 (2 H, m), 4.26 (1 H, br s), 3.91 (1 H, d, *J* = 6.9 Hz), 3.15 (1 H, dd, *J* = 16.6, 6.9 Hz), 2.83 (1 H, d, *J* = 16.6 Hz), 2.60 (1 H, br), 2.41–2.25 (2 H, m), 2.16–2.02 (1 H, m), 1.87–1.81 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 210.39 (s), 137.48 (s), 136.76 (s), 134.92 (s), 128.75 (d), 127.42 (d), 126.60 (s), 125.61 (d), 121.90 (d), 119.51 (d), 118.41 (d), 109.48 (d), 107.20 (s), 59.51 (d), 46.35 (t), 44.86 (d), 34.77 (t), 31.33 (t), 25.75 (t); EIMS, *m/e* 316 (M^+), 288, 259 (base), 225, 197, 168, 91; HRMS, *m/e* calcd for $C_{21}H_{20}N_2O$ 316.1575, found 316.1560. Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.56; H, 6.48; N, 8.95.

(6*R*,10*R*)-(-)-Methyl 5-Benzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole-8-carboxylate (-)-(32). A solution of (-)-**29** (0.52 g, 1.1 mmol) in 88% formic acid (5 mL) was flushed with argon and then stirred with 10% Pd/C (0.26 g) for 1 h. The catalyst was filtered through Celite and rinsed with methanol. After evaporation in vacuo the residue was diluted with EtOAc (75 mL), washed with saturated aqueous Na_2CO_3 (10 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated, and the residue was chromatographed over silica gel, eluting with EtOAc to give (-)-**32** (0.295 g, 72%) as a colorless foam: $[\alpha]_D^{27}$ −26° (*c* 1.00, CH_2Cl_2); IR ($CHCl_3$) 3500–2200, 1658, 1618 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 202 (21 000), 226 (26 000), 254 nm (7400); ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.50 (1 H, m), 7.26–7.07 (6 H, m), 6.93–6.89 (2 H, m), 5.28 (1 H, d, *J* = 17.1 Hz), 5.19 (1 H, d, *J* = 17.1 Hz), 4.33 (1 H, d, *J* = 5.5 Hz), 4.03 (1 H, dd, *J* = 5.3, 0.8 Hz), 3.60 (3 H, s), 3.15 (1 H, dd, *J* = 16.0, 5.3 Hz), 3.08 (1 H, dd, *J* = 16.0, 0.8 Hz), 2.71 (1 H, dd, *J* = 15.8, 5.5 Hz), 2.27 (1 H, d, *J* = 15.8 Hz); ^{13}C NMR ($CDCl_3$) δ 172.34 (s), 171.66 (s), 137.48 (s), 136.55 (s), 135.50 (s), 128.73 (d), 127.30 (d), 126.87 (s), 125.81 (d), 121.69 (d), 119.47 (d), 118.19 (d), 109.45 (d), 106.71 (s), 94.22 (s), 51.33 (q), 50.07 (d), 46.42 (t), 44.86 (d), 29.23 (t), 26.40 (t); HRMS, *m/e* calcd for $C_{23}H_{22}N_2O_3$ 374.1630, found 374.1626.

(6*R*,10*R*)-(-)-5-Benzyl-9-oxo-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (-)-(31). A solution of (-)-**29** (184 mg, 0.49 mmol) in acetic acid/H_2SO_4/H_2O (12:1.5:8, 2 mL) was degassed and then heated under reflux for 4 days. The solution was diluted with EtOAc (25 mL) and washed with saturated aqueous Na_2CO_3 (3 × 5 mL). The combined aqueous solution was back extracted with EtOAc (15 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$), evaporated in vacuo, and chromatographed over silica gel, eluting with 2% Et_3N in EtOAc to give (-)-**31** (133 mg, 86%) as a pale yellow foam: $[\alpha]_D^{28}$ −98° (*c* 1.08, CH_2Cl_2); HRMS, *m/e* calcd for $C_{21}H_{20}N_2O$ 316.1575, found 316.1567. Other spectra were identical to (+)-**31**.

(6*R*,10*R*)-(+)-5-Benzyl-9-oxo-12-(prop-2-ynyl)-6,7,8,9,10,11-hexahydro-6,10-imino-5*H*-cyclooct[*b*]indole (33). To a solution of keto amine **31** (2.3 g, 7.3 mmol) in absolute EtOH (25 mL) was added propargyl bromide (80 wt % in toluene, 4.0 mL, 35.7 mmol) and anhydrous K_2CO_3 (5.0 g, 36.2 mmol). The mixture was stirred under argon at room temperature for 12 h. The mixture was filtered through Celite and washed with EtOAc. The solvent was removed in vacuo, and the residue was purified by silica gel chromatography, eluting with 10–50% EtOAc in hexanes to give **33** (1.5 g, 60%) as a colorless foam: $[\alpha]_D^{23}$ +152° (*c* 1.03, CH_2Cl_2); IR ($CHCl_3$) 3330, 1710 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 203 (20 000), 224 (25 000), 282 nm (5400); ^1H NMR (360 MHz, $CDCl_3$) δ 7.43 (1 H, d, *J* = 7.0 Hz), 7.20–7.02 (6 H, m), 6.87 (2 H, d, *J* = 8.1 Hz), 5.27 (1 H, d, *J* = 17.0 Hz), 5.17 (1 H, d, *J* = 17.0 Hz), 4.20 (1 H, br s), 3.84 (1 H, d, *J* = 6.8 Hz), 3.24 (2 H, d, *J* = 2.5 Hz), 3.13 (1 H, dd, *J* = 17.2, 6.8 Hz), 2.64 (1 H, d, *J* = 17.2 Hz), 2.33–2.27 (2 H, m), 2.11 (1 H, t, *J* = 2.5 Hz), 2.05–1.95 (1 H, m), 1.78–1.72 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 208.82 (s), 137.39 (s), 137.09 (s), 132.07 (s), 128.79 (d), 127.49 (d), 126.38 (s), 125.72 (d), 122.02 (d), 119.60 (d), 118.24 (d), 109.50 (d), 106.22 (s), 79.33 (s), 72.93 (d), 63.82 (d), 49.58 (d), 46.51 (t), 41.20 (t), 33.90 (t), 29.45 (t), 20.03 (t); EIMS, *m/e* 354 (M^+), 326, 297, 258, 206, 168, 91 (base); HRMS, *m/e* calcd for $C_{24}H_{22}N_2O$ 354.1732, found 354.1733.

(6*R*,10*R*)-(+)-5-Benzyl-9-[(*tert*-butyldimethylsilyl)oxy]-12-(prop-2-ynyl)-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole (34). A solution of ketone **33** (1.54 g, 4.4 mmol) in CH_2Cl_2 was treated with Et_3N (1.8 mL, 13.3 mmol) and stirred under argon for 15 min. *tert*-Butyl-

dimethylsilyl trifluoromethanesulfonate (1.6 mL, 6.9 mmol) was then added over a 15-min period. The mixture was stirred at room temperature for 30 min. EtOAc (50 mL) was added, and the solution was washed with saturated aqueous Na_2CO_3 (2 × 10 mL) and brine. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by silica gel chromatography using EtOAc/hexanes (1:3) to give **34** (1.66 g, 82%) as a white foam: $[\alpha]_D^{22}$ +66° (*c* 1.02, CH_2Cl_2); IR ($CHCl_3$) 3310, 1670, 1609 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 202 (37 000), 227 (41 000), 283 nm (9800); ^1H NMR (360 MHz, $CDCl_3$) δ 7.50–7.46 (1 H, m), 7.22–7.02 (6 H, m), 6.89–6.87 (2 H, m), 5.27 (1 H, d, *J* = 17.1 Hz), 5.18 (1 H, d, *J* = 17.1 Hz), 4.55 (1 H, dd, *J* = 5.5, 1.9 Hz), 4.11 (1 H, d, *J* = 5.4 Hz), 3.60 (1 H, d, *J* = 5.7 Hz), 3.34 (1 H, dd, *J* = 16.1, 2.5 Hz), 3.28 (1 H, dd, *J* = 16.1, 2.5 Hz), 2.97 (1 H, dd, *J* = 16.1, 5.7 Hz), 2.81 (1 H, d, *J* = 16.1 Hz), 2.67 (1 H, br dd, *J* = 16.4, 4.7 Hz), 2.14 (1 H, t, *J* = 2.5 Hz), 1.90 (1 H, dd, *J* = 16.4, 5.5 Hz), 0.88 (9 H, s), 0.09 (3 H, s), 0.00 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 150.20 (s), 137.67 (s), 136.82 (s), 134.06 (s), 128.65 (d), 127.26 (d), 127.21 (s), 125.88 (d), 121.26 (d), 119.15 (d), 118.16 (d), 109.37 (d), 106.18 (s), 97.81 (d), 79.97 (s), 72.49 (d), 55.43 (d), 48.92 (d), 46.48 (t), 41.30 (t), 29.28 (t), 25.65 (q), 21.28 (t), 17.95 (s), −4.36 (q), −4.58 (q); EIMS, *m/e* 468 (M^+), 429, 377, 297, 257, 209, 152 (base); HRMS, *m/e* calcd for $C_{30}H_{36}N_2OSi$ 468.2597, found 468.2604.

(6*R*,10*R*)-(+)-Methyl 5-Benzyl-9-[(*tert*-butyldimethylsilyl)oxy]-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole-12-but-2-ynoate (35). A solution of silyl enol ether **34** (7.0 g, 15 mmol) in dry THF (75 mL) was cooled to −78 °C under argon, and a solution of *n*-BuLi (30.3 mmol) in hexanes (13.0 mL) was slowly added over a 30-min period. After 15 min at −78 °C, methyl chloroformate (5.8 mL, 75.1 mmol) was added, and the solution was slowly warmed to −30 °C. The reaction was quenched with H_2O (30 mL) and warmed to room temperature. The mixture was diluted with EtOAc (500 mL), washed with H_2O (2 × 50 mL) and brine, and dried ($MgSO_4$). Removal of the solvent in vacuo and chromatography over silica gel, eluting with 10–30% EtOAc in hexanes, gave **35** (6.0 g, 76%) as a colorless foam: $[\alpha]_D^{21}$ +66° (*c* 1.00, CH_2Cl_2); IR ($CHCl_3$) 2220, 1711, 1672, 1608 cm^{-1}; UV (95% EtOH) λ_{max} (ϵ) 202 (35 000), 227 (36 000), 283 nm (7700); ^1H NMR (360 MHz, $CDCl_3$) δ 7.49–7.46 (1 H, m), 7.26–7.03 (6 H, m), 6.85 (2 H, d, *J* = 6.7 Hz), 5.27 (1 H, d, *J* = 17.1 Hz), 5.16 (1 H, d, *J* = 17.1 Hz), 4.57 (1 H, dd, *J* = 5.5, 1.8 Hz), 4.04 (1 H, d, *J* = 5.3 Hz), 3.63 (3 H, s), 3.54 (1 H, d, *J* = 5.6 Hz), 3.45 (1 H, d, *J* = 17.1 Hz), 3.43 (1 H, d, *J* = 17.1 Hz), 2.95 (1 H, dd, *J* = 16.1, 5.6 Hz), 2.82 (1 H, d, *J* = 16.1 Hz), 2.65 (1 H, br dd, *J* = 16.3, 5.3 Hz), 1.90 (1 H, dd, *J* = 16.3, 5.5 Hz), 0.89 (9 H, s), 0.10 (3 H, s), 0.00 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 153.59 (s), 150.00 (s), 137.56 (s), 136.88 (s), 133.57 (s), 128.69 (d), 127.27 (d), 127.05 (s), 125.81 (d), 121.41 (d), 119.20 (d), 118.15 (d), 109.37 (d), 106.06 (s), 97.75 (d), 84.48 (s), 76.12 (s), 55.66 (d), 52.48 (q), 49.20 (d), 46.46 (t), 41.41 (t), 29.35 (t), 25.62 (q), 21.06 (t), 17.93 (s), −4.38 (q), −4.45 (q); EIMS, *m/e* 526 (M^+), 468, 429, 316, 259, 152 (base), 91; HRMS, *m/e* calcd for $C_{32}H_{38}N_2O_3Si$ 526.2652, found 526.2652.

(6*R*,10*R*)-(+)-Methyl 5-Benzyl-9-oxy-6,7,10,11-tetrahydro-6,10-imino-5*H*-cyclooct[*b*]indole-12-but-2-ynoate (36). A solution of silyl enol ether **35** (1.4 g, 2.7 mmol) in dry THF (30 mL) was treated with lithium tetrafluoroborate (1.0 M in CH_3CN, 2.7 mmol). The mixture was heated at reflux for 3 days. After cooling, the mixture was diluted with EtOAc (400 mL), washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). Removal of the solvent in vacuo gave **36** (1.0 g, 91%) as a colorless foam: $[\alpha]_D^{26}$ +160° (*c* 0.50, CH_2Cl_2); IR ($CHCl_3$) 2220, 1710, 1607, 1262 cm^{-1}; UV (*p*-dioxane) λ_{max} (ϵ) 231 (29 000), 283 nm (9300); ^1H NMR (360 MHz, $CDCl_3$) δ 7.52 (1 H, d, *J* = 7.6 Hz), 7.29–7.13 (6 H, m), 6.95–6.92 (2 H, m), 5.38 (1 H, d, *J* = 17.1 Hz), 5.26 (1 H, d, *J* = 17.1 Hz), 4.23 (1 H, br s), 4.12 (1 H, d, *J* = 6.9 Hz), 3.74 (3 H, s), 3.47 (2 H, s), 3.22 (1 H, dd, *J* = 17.3, 6.9 Hz), 2.77 (1 H, d, *J* = 17.3 Hz), 2.46–2.38 (2 H, m), 2.16–2.08 (1 H, m), 1.87–1.81 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 208.25 (s), 153.36 (s), 137.28 (s), 137.16 (s), 131.63 (s), 128.79 (d), 127.49 (d), 126.24 (s), 125.64 (d), 122.15 (d), 119.66 (d), 118.27 (d), 109.47 (d), 106.17 (s), 83.56 (s), 76.32 (s), 64.06 (d), 52.56 (q), 49.89 (d), 46.49 (t), 41.03 (t), 33.73 (t), 29.47 (t), 19.98 (t); EIMS, *m/e* 412 (M^+), 355 (base), 316, 259, 168, 91; HRMS, *m/e* calcd for $C_{26}H_{24}N_2O_3$ 412.1787, found 412.1787.

(*Z*)-(2*S*,6*R*,12b*R*)-(+)-Methyl 12-Benzyl-13-oxo-1,2,3,4,5,6,7,12,12b-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (37) and (*E*)-(2*S*,6*R*,12b*R*)-(+)-Methyl 12-Benzyl-13-oxo-1,2,3,4,5,6,7,12,12b-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (38). A solution of ketone **36** (1.00 g, 2.43 mmol), pyrrolidine (40.1 mL, 0.46 mmol), and trifluoroacetic acid (38 mL, 0.46 mmol) in benzene (20 mL) was heated at reflux for 19 h. The solution was cooled, diluted with EtOAc (100 mL), and washed with saturated aqueous Na_2CO_3 (2 × 20 mL) and brine. The organic layer was dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was chromatographed over silica gel, eluting with 20–70% EtOAc in hexanes to yield *Z*-(+)-**37** (140 mg, 14%) and *E*-(+)-**38** (708 mg, 71%).

(*Z*)-(+)-37: An analytical sample was crystallized from CH_2Cl_2/MeOH; mp 236–238 °C (dec); $[\alpha]_D^{25}$ +250° (*c* 1.00, CH_2Cl_2); IR ($CHCl_3$) 1712, 1650, 1618 cm^{-1}; UV (*p*-dioxane) λ_{max} (ϵ) 231 (37 000), 283 nm (10 000); ^1H NMR (360 MHz, $CDCl_3$) δ 7.54–7.52 (1 H, m), 7.28–7.09 (6 H, m), 7.01–6.98 (2 H, m), 5.80 (1 H, t, *J* = 2.4 Hz), 5.22 (1 H, d, *J* = 17.0 Hz), 5.16 (1 H, d, *J* = 17.0 Hz), 4.45 (1 H, dd, *J* = 19.9, 2.2 Hz), 4.26 (1 H, dd, *J* = 9.4, 2.7 Hz), 4.20 (1 H, dd, *J* = 19.9, 2.6 Hz), 3.72 (3 H, s), 3.56 (1 H, d, *J* = 6.4 Hz), 3.34 (1 H, dd, *J* = 15.7, 1.0 Hz), 3.09 (1 H, dd, *J* = 15.7, 6.4 Hz), 3.06–3.05 (1 H, m), 2.24 (1 H, ddd, *J* = 13.2, 9.4, 2.0 Hz), 1.97 (1 H, dt, *J* = 13.2, 3.4 Hz); ^{13}C NMR ($CDCl_3$) δ 215.54 (s), 166.09 (s), 157.78 (s), 137.40 (s), 137.20 (s), 137.03 (s), 128.89 (d), 127.62 (d), 126.58 (s), 126.14 (d), 122.02 (d), 119.62 (d), 118.65 (d), 115.84 (d), 109.35 (d), 104.96 (s), 64.55 (d), 55.91 (t), 52.00 (d), 51.33 (q), 48.79 (d), 46.72 (t), 36.45 (t), 22.50 (t); EIMS, *m/e* 412 (M^+), 384 (base), 353, 325, 293, 259, 233, 168, 125, 91; HRMS, *m/e* calcd for $C_{26}H_{24}N_2O_3$ 412.1787, found 412.1786.

(*E*)-(+)-38: $[\alpha]_D^{25}$ +140° (*c* 0.75, CH_2Cl_2); IR ($CHCl_3$) 1723, 1660, 1615 cm^{-1}; UV (*p*-dioxane) λ_{max} (ϵ) 230 (33 000), 283 nm (11 000); ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (1 H, d, 7.4 Hz), 7.29–7.09 (6 H, m), 6.98 (2 H, d, *J* = 7.5 Hz), 5.84 (1 H, s), 5.24 (1 H, d, *J* = 17.0 Hz), 5.17 (1 H, d, *J* = 17.0 Hz), 4.65–4.64 (1 H, m), 4.25 (1 H, dd, *J* = 9.4, 2.3 Hz), 3.90 (2 H, s), 3.69 (3 H, s), 3.55 (1 H, d, *J* = 6.4 Hz), 3.37 (1 H, d, *J* = 15.7 Hz), 3.05 (1 H, dd, *J* = 15.7, 6.4 Hz), 2.25 (1 H, ddd, *J* = 13.1, 9.4, 1.0 Hz), 1.99 (1 H, dt, *J* = 13.1, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 214.78 (s), 165.43 (s), 154.85 (s), 137.39 (s), 137.21 (s), 136.86 (s), 128.90 (d), 127.63 (d), 126.59 (s), 126.04 (d), 122.06 (d), 119.62 (d), 118.68 (d), 116.01 (d), 109.36 (d), 105.12 (s), 64.43 (d), 55.90 (t), 51.36 (q), 49.26 (d), 46.68 (t), 45.83 (d), 35.46 (t), 22.46 (t); EIMS, *m/e* 412 (M^+), 384 (base), 293, 259, 168, 125, 91; HRMS, *m/e* calcd for $C_{26}H_{24}N_2O_3$ 412.1787, found 412.1787.

Lombardo Reagent. Following the reported procedure[35] CH_2Br_2 (2.0 mL, 28 mmol) was added to Zn dust (5.75 g, 87.9 mmol) in dry THF (50 mL) at −78 °C with efficient overhead stirring. After 10 min, $TiCl_4$ (2.3 mL, 21 mmol) was added dropwise over 20 min. The reaction mixture was warmed to 0 °C over 2.5 h and then stored in a refrigerator (5 °C) until needed.

(*E*)-(2*S*,6*R*,12b*R*)-(+)-Methyl 12-Benzyl-13-methylene-1,2,3,4,5,6,7,12,12b-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (39) and (*E*)-(2*S*,6*R*,7a*S*,12a*R*,12b*R*)-(+)-Methyl 12-Benzyl-7a,12a-methano-13-methylene-1,2,3,4,5,6,7,7a,12,12a,12b-decahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (40). A solution of ketone **38** (256 mg, 0.62 mmol) in dry CH_2Cl_2 (10 mL) was treated with approximately 5 g of Lombardo's reagent. After stirring for 2 h at room temperature the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL) and filtered through Celite. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The residue was purified by chromatography over silica gel eluting with 20–50% EtOAc in hexanes to give the cyclopropane **40** (35.5 mg, 21%) and the desired olefin **39** (62.6 mg, 24%) as colorless foams.

Olefin (39): mp 175 °C (from MeOH); $[\alpha]_D^{24}$ +54° (*c* 1.2, CH_2Cl_2); IR ($CHCl_3$) 1709, 1660 cm^{-1}; UV (*p*-dioxane) λ_{max} (ϵ) 235 (35 000), 284 nm (10 000); ^1H NMR (360 MHz, $CDCl_3$) δ 7.55–7.53 (1 H, m), 7.26–7.19 (4 H, m), 7.15–7.09 (2 H, m), 7.00–6.98 (2 H, m), 5.70 (1 H, s), 5.25 (1 H, d, *J* = 17.0 Hz), 5.14 (1 H, d, *J* = 17.0 Hz), 5.03 (1 H, d, *J* = 2.7 Hz), 4.98 (1 H, d, *J* = 2.1 Hhz), 4.57 (1 H, d, *J* = 2.5 Hz), 4.13 (1 H, dd, *J* = 9.2, 2.3 Hz), 3.85 (1 H, br d, *J* = 3.5 Hz), 3.75 (2 H, s), 3.69 (3 H, s), 3.25 (1 H, dd, *J* = 15.5, 5.7 Hz), 3.05 (1 H, d, *J* = 15.5 Hz), 1.98 (1 H, dd, *J* = 12.4, 9.7 Hz), 1.74 (1 H, dt, *J* = 12.4, 3.3 Hz); ^{13}C NMR ($CDCl_3$) δ 166.02 (s), 162.75 (s), 150.25 (s), 138.39 (s), 137.38 (s), 137.09 (s), 128.70 (d), 127.35 (d), 127.18 (s), 125.96 (d), 121.32 (d), 119.18 (d), 118.21 (d), 111.18 (d), 109.29 (d), 108.11 (t), 104.28 (s), 56.45 (q), 50.91 (d), 50.91 (t), 48.85 (d), 46.56 (t), 37.24 (d), 34.73 (t), 26.40 (t); EIMS, *m/e* 410 (M^+), 319, 259, 149, 91 (base); HRMS, *m/e* calcd for $C_{27}H_{26}N_2O_2$ 410.1994, found 410.1993. Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 80.00; H, 6.38; N, 6.82. Found: C, 79.51; H, 6.40; N, 6.86.

Cyclopropane (40): IR ($CHCl_3$) 1710, 1650, 1610, 900 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (5 H, m), 7.14 (1 H, ddd, *J* = 7.3, 1.3, 0.5 Hz), 7.01 (1 H, ddd, *J* = 7.8, 7.5, 1.3 Hz), 6.72 (1 H, td, *J* = 7.4, 1.0 Hz), 6.55 (1 H, dd, *J* = 7.8, 0.3 Hz), 5.61 (1 H, dd, *J* = 2.0, 1.5 Hz), 4.90 (1 H, d, *J* = 2.9 Hz), 4.67 (1 H, d, *J* = 2.3 Hz), 4.45 (1 H, t, *J* = 3.0 Hz), 4.23 (1 H, d, *J* = 15.0 Hz), 4.13 (1 H, d, *J* = 15.0 Hz), 3.67 (3 H, s), 3.52 (1 H, dd, *J* = 18.3, 1.9 Hz), 3.43 (1 H, dd, *J* = 18.4, 2.0 Hz), 3.29 (1 H, br d, *J* = 6.9 Hz), 3.21 (1 H, dd, *J* = 10.0, 4.3 Hz), 2.55 (1 H, dd, *J* = 13.7, 0.7 Hz), 2.24 (1 H, dt, *J* = 13.2, 4.0 Hz), 1.37 (1 H, ddd, *J* = 13.0, 10.2, 2.6 Hz), 1.17 (1 H, d, *J* = 4.1 Hz), 0.13 (1 H, d, *J* = 4.0 Hz); EIMS, *m/e* 424 (M^+), 333, 234, 91 (base);

HRMS, *m/e* calcd for $C_{28}H_{28}N_2O_2$ 424.2152, found 424.2156.

Cyclopropanol 41. According to the reported procedure,[36] a suspension of Zn dust (235 mg, 3.6 mmol) in glacial acetic acid (2.0 mL) was treated with $Cu(OAc)_2$ (20 mg, 0.1 mmol). The desired Zn–Cu couple formed instantly and was washed thoroughly with Et_2O. The Zn–Cu couple was then suspended in dry THF (2.0 mL). The suspension was treated with CH_2I_2 and stirred at 50 °C for 2 h. $TiCl_4$ (1.0 M in CH_2Cl_2, 1.0 mmol) was added, and the mixture was stirred at room temperature for 30 min. A solution of **38** (100 mg, 0.24 mmol) in THF (1.0 mL) was added, and the mixture was stirred at room temperature for 16 h. The reaction was quenched by addition of saturated aqueous K_2CO_3 (0.5 mL), which caused vigorous evolution of gas. The resulting light blue slurry was filtered through Celite and washed with EtOAc. Removal of solvent and purification of the residue by preparatory TLC gave, on elution with MeOH/EtOAc (1:9), the cyclopropanol **41** (74 mg, 74%) as a colorless foam: IR ($CHCl_3$) 3600–3110, 1730 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54–7.51 (1 H, m), 7.32–7.05 (6 H, m), 7.00–6.96 (2 H, m), 5.19 (1 H, d, J = 17.2 Hz), 5.11 (1 H, d, J = 16.7 Hz), 3.94 (1 H, d, J = 8.6 Hz), 3.72 (3 H, s), 3.70 (1 H, d, J = 4.1 Hz), 3.24–3.20 (1 H, m), 3.04 (1 H, d, J = 11.8 Hz), 2.91 (1 H, d, J = 11.9 Hz), 2.74 (1 H, d, J = 16.7 Hz), 2.39 (1 H, d, J = 16.7 Hz), 2.03 (1 H, ddd, J = 13.7, 9.4, 0.8 Hz), 1.49 (1 H, ddd, J = 13.8, 4.2, 1.0 Hz), 1.28–1.23 (1 H, m), 1.01 (1 H, d, J = 3.9 Hz); CIMS, *m/e* 414 (M^+), 397, 387, 341 (base), 259, 168, 91; HRMS, *m/e* calcd for $C_{26}H_{26}N_2O_3$ 414.1945, found 414.1946.

Preparation of Tebbe's Reagent. According to the reported procedure,[38] commercially available titanocene dichloride was purified by Soxhlet extraction with CH_2Cl_2. A three-necked flask was charged with purified titanocene dichloride (1.6 g, 6.4 mmol), and a commercially available solution of trimethylaluminum (2.0 M in toluene, 6.4 mL, 12.8 mmol) was added. The mixture was stirred for 3 days at room temperature to give a solution of Tebbe's reagent in toluene.

(*E*)-(2*S*,6*R*,12b*R*)-(+)-Methyl 12-Benzyl-13-methylene-1,2,3,4,5,6,7,12,12b-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (39) and (*E*)-(2*S*,6*R*,12b*R*)-(+)-Methyl 12-Benzyl-13-methylene-18-oxo-18-methoxy-1,2,3,4,5,6,7,12,12b-octahydro-2,6-methanoindolo[2,3-*a*]quinolizine-3-ethylidenoate (42). A solution of ketone **38** (203 mg, 0.49 mmol) in dry THF (3.0 mL) was treated with a solution of Tebbe's reagent in toluene (800 μL). The mixture was stirred at room temperature for 40 min. After this time the mixture was quenched with 2 M aqueous NaOH (0.5 mL) and stirred at room temperature overnight to allow for complete decomposition of the aluminum and titanium salts. The resulting bright yellow suspension was filtered through Celite, washed with EtOAc, and the solvent was removed in vacuo. Purification of the residue by preparatory TLC gave, on elution with EtOAc–hexanes (1:1), the previously reported *exo*-methylene compound **39** (128 mg, 63%) and the α,β-unsaturated ketone **42** (30 mg, 15%): IR ($CHCl_3$) 1695, 1630 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.55–7.22 (1 H, m), 7.29–7.08 (6 H, m), 7.00–6.98 (2 H, m), 6.08 (1 H, s), 5.26 (1 H, d, J = 17.1 Hz), 5.14 (1 H, d, J = 17.0 Hz), 5.02 (1 H, d, J = 2.8 Hz), 4.96 (1 H, d, J = 2.2 Hz), 4.57 (1 H, br d, J = 2.4 Hz), 4.09 (1 H, dd, J = 9.8, 2.8 Hz), 3.82 (1 H, br d, J = 3.7 Hz), 3.70–3.66 (2 H, m), 3.22 (1 H, dd, J = 15.5, 5.6 Hz), 3.04 (1 H, dd, J = 15.5, 1.1 Hz), 2.18 (3 H, s), 1.95 (1 H, td, J = 10.0, 1.6 Hz), 1.71 (1 H, dt, J = 12.3, 3.6 Hz); EIMS, *m/e* 394 (M^+), 351, 303, 259, 168, 131, 91; HRMS, *m/e* calcd for $C_{27}H_{26}N_{20}$ 394.2047, found 394.2042.

(*E*)-(+)-(16*S*)-12-Benzyl-10-desoxy-18-oxo-18-methoxysarpagine (43). A solution of commercially available BH_3–THF (1.0 M in THF, 5.0 mL) was treated with 2-methyl-2-butene (2.0 M in THF, 5 mL) at −5 °C to give a 0.5 M solution of diisoamylborane in THF.

A solution of olefin **39** (370 mg, 0.90 mmol) in DMF (5 mL) was added to the diisoamylborane at 0 °C. The solution was warmed to room temperature and stirred for 4 h. Ten percent aqueous NaOH was then added (3 mL) followed by 30% H_2O_2 (4 mL). The mixture was stirred for 1 h at room temperature. The mixture was washed with CH_2Cl_2 (2 × 15 mL), and the combined organic extracts were dried (Na_2SO_4). Purification of the residue by silica gel chromatography gave, on elution with 10% MeOH/Et_2O, the alcohol **43** (225 mg, 58%) as a colorless foam: mp 125 °C (THF, Et_2O 1:1); $[\alpha]_D^{22}$ +61.4° (*c* 0.50, CH_2Cl_2); IR ($CHCl_3$) 3700–3300, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.47 (1 H, m), 7.24–7.07 (6 H, m), 6.97–6.95 (2 H, m), 5.67 (1 H, t, J = 1.7 Hz), 5.21 (1 H, d, J = 17.0 Hz), 5.09 (1 H, d, J = 17.0 Hz), 4.00–3.96 (2 H, m), 3.64 (3 H, s), 3.61–3.55 (2 H, m), 3.49 (1 H, dd, J = 10.7, 6.9 Hz), 3.43 (1 H, dd, J = 10.7, 4.9 Hz), 3.22 (1 H, dd, J = 10.7, 8.0 Hz), 2.99–2.90 (2 H, m), 2.15–2.10 (1 H, m), 1.61–1.51 (1 H, m); ^{13}C NMR (C_6D_6) δ 167.6 (s), 166.3 (s), 138.7 (s), 138.2 (s), 137.6 (s), 129.0 (2C, d), 127.5 (d), 127.0 (s), 126.2 (2C, d), 121.8 (d), 119.8 (d), 118.9 (d), 110.5 (d), 109.9 (d), 106.5 (s), 60.9 (t), 56.9 (t), 52.2 (d), 50.7 (q), 48.3 (d), 46.4 (t), 42.1 (d), 28.2 (d), 25.7 (t), 22.7 (t); EIMS, *m/e* 428 (M^+), 411 (base), 397, 357, 321, 258, 91; HRMS, *m/e* calcd for $C_{27}H_{28}N_2O_3$ 428.2101, found 428.2102. Seventy percent yield can be obtained on a small scale.

(*Z*)-(+)-(16*S*)-12-Benzyl-10-desoxy-18-oxo-18-methoxysarpagine (44). The above procedure was performed on the *Z* olefinic isomer **37** (370 mg, 0.90 mmol) to give, after chromatography on flash silica gel (EtOAc eluant), 225 mg (58% yield) of **44** as a white foam. Additionally 25.7 mg (7%) of the starting *exo*-methylene compound was recovered: $[\alpha]_D$ +31.3° (*c* 0.65, CH_2Cl_2); IR ($CHCl_3$) 3700–3300, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.54–7.51 (1 H, m), 7.29–7.09 (6 H, m), 7.03–6.99 (2 H, m), 5.77 (1 H, t, J = 2.5 Hz), 5.27 (1 H, d, J = 17.3 Hz), 5.16 (1 H, d, J = 17.3 Hz), 4.30 (1 H, dd, J = 20.0, 2.3 Hz), 4.09–3.97 (2 H, m), 3.72 (3 H, s), 3.67 (1 H, dd, J = 10.5, 6.8 Hz), 3.58 (1 H, dd, J = 10.8, 5.3 Hz), 3.34 (1 H, dd, J = 10.6, 8.9 Hz), 3.05 (1 H, dd, J = 15.7, 5.4 Hz), 2.95 (1 H, dd, J = 16.6, 1.7 Hz), 2.57 (1 H, dd, J = 5.6, 3.4 Hz), 2.32–2.26 (1 H, m), 1.76–1.58 (2 H, m); EIMS (*m/e*) 428 (M^+), 427, 397, 258, 168, 91 (base); HRMS, *m/e* calcd for $C_{27}H_{28}N_2O_3$ 428.2101, found 428.2092.

(*E*)-(+)-(16*S*)-12-Benzyl-10-desoxy-18-hydroxysarpagine (45). A solution of ester **43** (542 mg, 1.3 mmol) in dry benzene (5 mL) was treated with diisobutylaluminum hydride (1.0 M in toluene, 5.0 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched by the addition of MeOH (520 μL). The resulting mixture was stirred at room temperature overnight. The resulting suspension was filtered through Celite and washed with MeOH. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel to give, after elution with 10% MeOH/EtOAc, **45** (430 mg, 85%) as a colorless foam: $[\alpha]_D^{22}$ +38.8° (*c* 0.74, CH_2Cl_2); IR ($CHCl_3$) 3700–3300, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.53–7.50 (1 H, m), 7.29–7.08 (6 H, m), 7.01–6.98 (2 H, m), 5.45 (1 H, t, J = 7.0 Hz), 5.28 (1 H, d, J = 16.8 Hz), 5.16 (1 H, d, J = 17.2 Hz), 4.12 (2 H, t, J = 6.6 Hz), 4.05 (1 H, dd, J = 9.1, 4.0 Hz), 3.72–3.54 (4 H, m), 3.27 (1 H, dd, J = 10.6, 9.5 Hz), 2.98–2.86 (3 H, m), 2.20–2.16 (1 H, m), 1.77–1.60 (1 H, m); EIMS, *m/e* 400 (M^+), 399, 382, 258, 167, 90 (base); HRMS, *m/e* calcd for $C_{26}H_{28}N_2O_2$, 400.2152, found 400.2151.

(*Z*)-(+)-(16*S*)-12-Benzyl-10-desoxy-18-hydroxysarpagine (46). The above reduction was performed on the corresponding *Z* olefinic isomer **44** (205 mg, 0.48 mmol) with diisobutylaluminum hydride (1 M in toluene, 1.44 mL, 1.44 mmol). The compound **46** (176 mg, 91.9% yield) was isolated after preparative thin-layer chromatography (2.0 mm, silica gel plate) eluting with 20% MeOH/Et_2O; $[\alpha]_D$ +19.4° (*c* 0.50, CH_2Cl_2); IR ($CHCl_3$) 3700–3300 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.57–7.52 (1 H, m), 7.36–7.12 (6 H, m), 7.04–7.02 (2 H, m), 5.43 (1 H, dd, J = 8.1, 4.2 Hz), 5.29 (1 H, d, J = 16.8 Hz), 5.16 (1 H, d, J = 16.7 Hz), 4.17–4.00 (3 H, m), 3.80 (1 H, d, J = 18.1 Hz), 3.63–3.52 (3 H, m), 3.25 (1 H, dd, J = 10.9, 8.5 Hz), 2.99 (2 H, d, J = 4.2 Hz), 2.44–2.20 (3 H, m), 1.73 (1 H, t, J = 11.6 Hz), 1.61 (1 H, ddd, J = 3.6, 3.6, 12.9 Hz); EIMS (*m/e*) 400 (M^+), 399, 382, 369, 259, 168, 91 (base); HRMS, *m/e* calcd for $C_{26}H_{28}N_2O_2$ 400.2152, found 400.2154.

(*E*)-(+)-(16*S*)-10-desoxy-18-hydroxysarpagine (47). A solution of diol **45** (160 mg, 0.40 mmol) in THF (8 mL) was cooled to −78 °C. NH_3 (20 mL) was then condensed into the flask small pieces of Na metal (37 mg, 1.6 mmol) were added, and the solution was stirred for 1.5 h at −78 °C. While still at −78 °C the solution was quenched by addition of saturated aqueous NH_4Cl. The ammonia was allowed to evaporate overnight. The aqueous solution was extracted with CH_2Cl_2 (2 × 20 mL) and then extracted with *n*-BuOH (2 × 20 mL). The solvent was removed in vacuo, and the residue was purified by preparatory TLC to give, on elution with 30% EtOAc/hexanes, the deprotected compound **47** (113 mg, 91%) as a colorless foam: $[\alpha]_D^{24}$ −2.7° (*c* 0.55, MeOH); ^1H NMR (360 MHz, DMSO-d_6) δ 7.34 (1 H, d, J = 7.7 Hz), 7.25 (1 H, d, J = 8.5 Hz), 6.99 (1 H, t, J = 7.0 Hz), 6.92 (1 H, t, J = 7.6 Hz), 5.27 (1 H, t, J = 7.0 Hz), 4.50 (1 H, t, J = 1.2 Hz), 4.23 (1 H, t, J = 4.3 Hz), 4.02 (1 H, dd, J = 9.8, 2.8 Hz), 3.95 (2 H, br d, J = 5.0 Hz), 3.59 (1 H, t, J = 6.4 Hz), 3.53 (1 H, br s), 3.51–3.24 (3 H, m), 2.92–2.80 (3 H, m), 2.67 (1 H, dd, J = 15.9, 5.8 Hz), 2.00–1.65 (4 H, m); EIMS, *m/e* 310 (M − 2), 309, 293, 279, 169; HRMS, *m/e* calcd for $C_{19}H_{24}N_2O_2$ 312.1839, found (M^+ − 2) 310.1675.

(+)-18-Hydroxykoumidine (48). The (*Z*)-diol **46** (160 mg, 0.40 mmol) was treated with sodium metal (37 mg, 1.60 mmol) by using the procedure described above. Chromatography on a 2.0-mm silica gel plate (30% MeOH/EtOAc eluant) gave **48** (113 mg, 91% yield): $[\alpha]_D^{24}$ −2.7° (*c* 0.55, MeOH); IR ($CHCl_3$) 3600-3066, 2920, 1680, 1625, 1615 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.36 (1 H, d, J = 7.5 Hz), 7.27 (1 H, d, J = 7.28 Hz), 7.01 (1 H, td, J = 7.05, 1.5 Hz), 6.93 (1 H, td, J = 8.1, 1.2 Hz), 5.30–5.34 (1 H, m), 4.02 (1 H, br d, J = 6.6 Hz), 3.94 (2 H, t, J = 5.7 Hz), 3.69 (1 H, d, J = 18.0 Hz), 3.56 (1 H, d, J = 18.0 Hz), 3.47–3.26 (5 H, m), 2.94 (1 H, d, J = 9.6 Hz), 2.86 (1 H, d, J = 15.6 Hz), 2.36 (1 H, br s), 2.10–2.06 (1 H, m), 1.76 (1 H, td, J = 12.3, 1.5 Hz), 1.67 (1 H, dt, J = 12.9, 3.6 Hz); EIMS (*m/e*) 310 (M^+ − 2 H), 309, 293, 279, 169 (base).

(*E*)-(+)-(16*S*)-10-desoxysarpagine (49). Anhydrous ammonia was condensed into a round-bottomed flask which had been cooled to −30 °C and fitted with a dry-ice condenser. The (*E*)-diol **45** (108 mg, 0.27 mmol) was added and treated with sodium metal (35 mg, 1.52 mmol) for 2 h at −30 °C. The intensely blue solution was quenched by addition of anhydrous NH_4Cl (500 mg). The condenser was removed, and the flask was warmed to room temperature allowing most of the ammonia to evaporate. Water (50 mL) and CH_2Cl_2 (75 mL) were added, and the organic layer was separated, washed with brine (50 mL), and dried (Na_2SO_4). Purification was effected by using preparative thin-layer chromatography (2.0-mm, silica gel plate eluted twice with 25% MeOH/Et_2O) to give **49** (50 mg, 63% yield) as a white amorphous solid. Additionally the debenzylated compound **47** (21 mg, 25%) was isolated as a byproduct: ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (1 H, br s), 7.47 (1 H, dd, J = 8.1, 2.4 Hz), 7.30 (1 H, dd, J = 8.1, 2.4 Hz), 7.15 (1 H, ddd, J = 6.9, 6.9, 1.6 Hz), 7.10 (1 H, ddd, J = 6.9, 6.9, 1.6 Hz), 5.24 (1 H, qt, J = 6.7, 1.8 Hz), 4.07 (1 H, dd, J = 8.4, 4.8 Hz), 3.78–3.70 (1 H, m), 3.65–3.60 (1 H, m), 3.56 (1 H, d, J = 6.0 Hz), 3.53 (1 H, d, J = 6.9 Hz), 3.24 (1 H, dd, J = 10.5, 9.3 Hz), 2.92 (1 H, d, J = 1.8 Hz), 2.90 (1 H, dd, J = 16.2, 2.7 Hz), 2.50 (1 H, t, J = 8.1 Hz), 2.12–2.22 (1 H, m), 1.82–1.77 (2 H, m), 1.64 (3 H, dd, J = 7.2, 1.6 Hz); EIMS (m/e) 293 (M^+), 276, 263, 169 (base); HRMS (m/e) calcd for $C_{19}H_{21}N_2O$ ($M^+ - H$) 293.1655, found 293.1662.

(+)-Koumidine (50). Anhydrous ammonia (10 mL) was condensed into a round-bottomed flask, cooled to −30 °C, and equipped with a dry-ice condenser. The (*Z*)-diol **46** (27 mg, 0.068 mmol) was added as a solution in THF (2 mL), followed by sodium metal (6.5 mg, 0.28 mmol). The intensely blue solution was stirred for 1 h, and then anhydrous NH_4Cl (100 mg) was added. The cooling bath and condenser were removed, and the majority of the ammonia was allowed to evaporate. The reaction was partitioned between water (50 mL) and CH_2Cl_2 (50 mL) and dried (Na_2SO_4). Chromatography on a 0.5-mm preparative silica gel plate (35% MeOH/Et_2O eluant) gave (+)-koumidine **50** (19 mg, 95% yield). Thin-layer chromatographic comparison of synthetic (+)-koumidine with natural (−)-koumidine (silica gel, petroleum ether, PhH, EtOAc, Et_2NH, 25:10:10:4) gave an identical R_f; $[\alpha]_D^{24}$ +11.1° (c 0.360, MeOH); IR ($CHCl_3$) 3300–3150, 1710, 1620, 1590, 1560, 1450 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 10.86 (1 H, s), 7.35 (1 H, dt, J = 7.7, 0.9 Hz), 7.26 (1 H, dt, J = 8.0, 0.9 Hz), 6.99 (1 H, ddd, J = 8.1, 8.1, 1.1 Hz), 6.92 (1 H, ddd, J = 7.8, 7.8, 1.1 Hz), 5.26–5.21 (1 H, m), 3.99 (1 H, dd, J = 10.1, 3.2 Hz), 3.62 (1 H, d, J = 17.8 Hz), 3.51 (1 H, d, J = 17.8 Hz), 3.37 (1 H, dd, J = 10.7, 5.6 Hz), 3.28 (1 H, dd, J = 10.6, 6.6 Hz), 2.91 (1 H, t, J = 9.4 Hz), 2.84 (1 H, dd, J = 15.6, 1.0 Hz), 2.69 (1 H, dd, J = 15.3, 5.8 Hz), 2.35 (1 H, dd, J = 6.0, 3.3 Hz), 2.07–2.00 (1 H, m), 1.75–1.70 (1 H, m), 1.64 (1 H, dt, J = 12.9, 3.5 Hz), 1.54 (3 H, d, J = 6.8 Hz); ^{13}C NMR (500 MHz, DMSO-d_6) δ 143.39, 138.49, 135.99, 125.98, 120.10, 118.07, 117.51, 112.15, 110.89, 104.46, 58.96, 53.54, 51.96, 48.98, 42.65, 33.57, 28.41, 22.27, 12.18; EIMS (m/e) 294 (M^+), 293, 231, 181, 169, 168, 131, 119, 69 (base); HRMS (m/e) calcd for $C_{19}H_{22}N_2O$ 294.1712, found 294.1710.

***N*-Carbomethoxytaberpsychine (51) and (+)-Taberpsychine (4).** A solution of the above *E* hydrogenolysis product **49** (32.4 mg, 0.11 mmol) in THF (2.5 mL) was treated, at room temperature, with saturated aqueous Na_2CO_3 solution (1.0 mL) followed by addition of methyl chloroformate (17.6 μL, 0.23 mmol). The reaction mixture was vigorously stirred for 4 h and then filtered to remove the white precipitate which had formed. The filtrate was concentrated and chromatographed on a 0.5-mm silica gel plate (Et_2O eluant) to provide the carbamate **51** (20.0 mg, 52% yield) which was used directly in the next step.

The carbamate **51** (18.6 mg, 0.052 mmol) was dissolved in dry THF (2 mL) and treated with a solution of lithium aluminum hydride in THF (212 μL of 1 M solution, 0.212 mmol). The reactants were warmed to reflux temperature for 18 h and then cooled. Water (10 mL) was added, and the resulting mixture was extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL) and dried Na_2SO_4. Purification was effected by using preparative thin-layer chromatography (0.25 mm, silica gel plate) eluted twice with Et_2O/MeOH/NH_4OH, 90:8:2) to give (+)-taberpsychine (**4**) (10.8 mg, 67%) as a white amorphous solid in 35% overall yield from compound **49**. Thin-layer chromatographic comparison of synthetic (+)-taberpsychine with natural (−)-taberpsychine (silica gel, EtOAc/MeOH/NH_4OH, 90:8:2) gave an identical R_f; $[\alpha]_D^{24}$ +296° (c 0.110, MeOH); IR ($CHCl_3$) 3480, 3050–2850, 1605, 1470, 1350 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.0 (1 H, br s), 7.67 (1 H, d, J = 7.9 Hz), 7.37 (1 H, d, J = 8.1 Hz), 7.15 (1 H, t, J = 7.1 Hz), 7.08 (1 H, t, J = 7.1 Hz), 5.34 (1 H, q, J = 1.0 Hz), 5.32 (1 H, d, J = 1.0 Hz), 3.89 (1 H, dd, J = 11.0, 9.8 Hz), 3.51 (1 H, br s), 3.45 (3 H, s), 3.27 (3 H, s), 3.26 (1 H, d, J = 14.8 Hz), 3.16–3.06 (2 H, m), 2.96 (1 H, d, J = 14.2 Hz), 2.61 (1 H, t, J = 1.7 Hz), 2.57–2.45 (1 H, m), 1.98 (1 H, ddd, J = 14.0, 9.7, 1.4 Hz), 1.72 (2 H, dd, J = 5.8, 1.9 Hz); EIMS (m/e) 308 (M^+), 293, 281, 243, 231, 219, 181, 169, 131, 118, 100, 87 (base); HRMS, m/e calcd for $C_{20}H_{24}N_2O$ 308.1887, found 308.1883.

(+)-18-Hydroxy-*N*-carbomethoxytaberpsychine (52). A solution of the (*E*)-diol **47** (260 mg, 0.84 mmol) in THF (20 mL) was treated, under anhydrous conditions, with methyl chloroformate (150 μL, 1.85 mmol) at room temperature for 5 h. The reaction was neutralized with aqueous Na_2CO_3 (1 mL) and then partitioned between EtOAc (100 mL) and water (50 mL). The organic layer was washed with brine (50 mL) and dried (Na_2SO_4). Purification was effected by using preparative thin-layer chromatography (1.0-mm, silica gel plate eluted with 10% MeOH/Et_2O) to give **52** (112 mg, 36%) along with recovered starting material (159 mg, 61%). The yield based on starting material reacted was 93%: $[\alpha]_D^{24}$ +25.1° (c 0.490, DMF); ^1H NMR (300 MHz, $CDCl_3$) δ 8.29 and 8.26 (1 H, two br s), 7.63 (1 H, d, J = 7.8 Hz), 7.33–7.10 (3 H, m), 5.64 (1 H, m), 5.16 (1 H, d, J = 9.8 Hz), 4.60–3.78 (5 H, m), 3.77 and 3.75 (3 H, two s), 3.60–3.20 (4 H, m), 2.55 (1 H, m), 2.34 (1 H, m), 2.15 (1 H, m). Signals are doubled due to carbamate resonance: EIMS (m/e) 368 (M^+), 337, 293, 268 (base), 231, 220, 206, 193; HRMS m/e calcd for $C_{21}H_{24}N_2O_4$ 368.1737, found 368.1737.

18-Hydroxytaberpsychine (53). The *N*-carbomethoxy derivative **52** prepared above (20.2 mg, 0.05 mmol) was dissolved in dry THF (4 mL) and treated with lithium aluminum hydride solution (1 M in THF, 400 μL, 0.40 mmol). The reaction was heated to reflux temperature for 3 h and then cooled to room temperature. Water (50 μL) was added, followed by 15% NaOH solution (50 μL), and then additional water (150 μL). The resulting suspension was filtered, and the filtrate was chromatographed on a 0.5-mm silica gel plate eluted with 35% MeOH/EtOAc to provide **53** (12.5 mg, 78% yield): IR 3480 (br s), 3300, 1590 cm^{-1}; ^1H NMR (360 MHz, DMSO-d_6) δ 8.41 (1 H, s), 7.65 (1 H, d, J = 7.6 Hz), 7.34 (1 H, d, J = 7.9 Hz), 7.13 (1 H, t, J = 7.2 Hz), 7.06 (1 H, d, J = 7.2 Hz), 5.38 (1 H, t, J = 6.5 Hz), 5.18 (1 H, d, J = 9.4 Hz), 4.68 (1 H, br s), 4.19–4.16 (1 H, m), 4.03–3.99 (1 H, m), 3.84 (1 H, t, J = 10.8 Hz), 3.68 (1 H, t, J = 6.5 Hz), 3.26–3.23 (2 H, m), 3.11–3.05 (1 H, m), 2.85 (1 H, d, J = 14.4 Hz), 2.59 (3 H, s), 1.98 (1 H, dd, J = 9.7, 13.7 Hz), 1.85–1.83 (1 H, m); EIMS (m/e) 324 (M^+), 306 (base), 293, 263, 223; HRMS m/e calcd for $C_{20}H_{24}N_2O_2$ 324.1839, found 324.1831.

***Z*-Isomer of 18-Hydroxytaberpsychine (55).** The (*Z*)-diol **48** (60 mg, 0.194 mmol), prepared above, was treated with methyl chloroformate (53 μL, 0.450 mmol) in THF (10 mL), under anhydrous conditions. The reaction was stirred at room temperature for 16 h. Saturated Na_2CO_3 solution (1 mL) was added, and the mixture was partitioned between EtOAc (50 mL) and water (20 mL). The organic layer was washed with brine (20 mL) and dried (Na_2SO_4). Chromatography on a 0.5-mm silica gel plate gave the desired *N*-carbomethoxy compound **54** (31 mg, 43%) along with recovered starting material (15 mg, 25%) and some starting material which had been carbomethoxylated on the indole nitrogen (12 mg, 17%).

The *N*-carbomethoxy derivative **54** (30 mg, 0.082 mmol) was dissolved in dry THF (10 mL) and treated with a solution of lithium aluminum hydride in THF (1 M, 410 μL, 0.41 mmol). The reaction mixture was heated to reflux temperature for 3 h. The cooled solution was then hydrolyzed with water (50 μL), 15% NaOH solution (50 μL), followed by additional water (150 μL). The resulting suspension was filtered, and the filtrate chromatographed on a 0.5-mm silica gel plate eluted with 35% MeOH/EtOAc to give **55** (20.0 mg, 76% yield). The overall yield for the two steps from **48** was 33%: IR ($CHCl_3$) 3480 (indole N–H), 3050–2850, 1605, 1470–1420, 1350, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (1 H, d, J = 10.5 Hz), 7.62 (1 H, d, J = 7.5 Hz), 7.32 (1 H, d, J = 7.6 Hz), 7.17 (2 H, qd, J = 6.3, 1.5 Hz), 5.56 (1 H, t, J = 7.3 Hz), 5.15 (1 H, d, J = 9.4 Hz), 4.19 (1 H, dd, J = 12.7, 7.3 Hz), 3.99 (1 H, dd, J = 12.9, 6.3 Hz), 3.88 (1 H, dd, J = 11.9, 9.4 Hz), 3.36 (2 H, d, J = 4.7 Hz), 3.32–3.22 (2 H, m), 3.17–3.13 (1 H, m), 2.88 (1 H, ddd, J = 16.8, 7.6, 2.8 Hz), 2.58 (3 H, s), 2.56–2.45 (1 H, m), 2.14 (1 H, dd, J = 13.6, 9.8 Hz), 1.26 (1 H, br s); EIMS (m/e) 324 (M^+), 306, 293 (base), 263, 220, 205. 194. 168, 156, 138, 130, 120, 107; HRMS m/e calcd for $C_{20}H_{24}N_2O_2$ 324.1839, found 324.1820.

(+)-Koumine (2). Diethyl azodicarboxylate (8.5 μL, 0.053 mmol), triphenylphosphine (13.4 mg, 0.053 mmol), and a catalytic amount of imidazole (2 mg) were dissolved in dry THF (7 mL). At room temperature, compound **55** (17.0 mg, 0.053 mmol) was added followed by sodium hydride (2.5 mg, 0.106 mmol). The reaction mixture was heated to reflux temperature for 3 h and then cooled to room temperature. The reaction was partitioned between CH_2Cl_2 (20 mL) and water (10 mL), and the organic layer was dried with Na_2SO_4 and concentrated. Chromatography on a 0.25-mm silica gel plate (60% MeOH/EtOAc eluant) gave (+)-koumine (**2**) (6.5 mg, 40%) along with recovered starting material (7.4 mg, 43%). The yield based on starting material reacted was 72%. Alternatively the *E* olefinic isomer **53** could also be converted to (+)-koumine (**2**) in 34% yield by using the identical procedure, except

the conversion was much slower (20 h) and other unidentified products were formed. TLC comparison with an authentic sample of (-)-koumine showed an identical R_f; $[\alpha]_D^{24}$ +218° (c 0.200, EtOH); IR ($CHCl_3$) 3050-2850, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (1 H, d, J = 7.6 Hz), 7.57 (1 H, d, J = 7.4 Hz), 7.38 (1 H, td, J = 7.6, 1.2 Hz), 7.27 (1 H, td, J = 7.4, 1.1 Hz), 5.04 (1 H, ddd, J = 3.6, 2.4, 1.1 Hz), 4.85 (1 H, dd, J = 17.5, 1.2 Hz), 4.81 (1 H, dd, J = 11.2, 1.2 Hz), 4.70 (1 H, dd, J = 17.5, 11.2 Hz), 4.28 (1 H, dd, J = 12.0, 4.4 Hz), 3.64 (1 H, d, J = 12.0 Hz), 3.19 (1 H, d, J = 11.4 Hz), 3.12 (1 H, d, J = 11.4 Hz), 2.84-2.81 (2 H, m), 2.63 (3 H, s), 2.63 (1 H, dt, J = 14.7, 3.8 Hz), 2.42 (1 H, dt, J = 14.3, 1.9 Hz), 2.38 (1 H, dd, J = 14.3, 3.3 Hz), 2.36 (br d, J = 11.7 Hz), 1.90 (1 H, dt, J = 14.7, 2.1 Hz); EIMS (m/e) 306 (M^+, base), 293, 281, 243, 231, 219, 193, 181, 169, 163, 192, 151, 143, 131, 119, 113, 100, 93, 69; HRMS m/e calcd for $C_{20}H_{22}N_2O$ 306.1734, found 306.1734.

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Synthesis of *N*-(Phenylsulfonyl)-CI, *N*-((*tert*-Butyloxy)carbonyl)-CI, CI-CDPI$_1$, and CI-CDPI$_2$: CC-1065 Functional Analogues Incorporating the Parent 1,2,7,7a-Tetrahydrocycloprop[1,2-*c*]indol-4-one† (CI) Left-Hand Subunit

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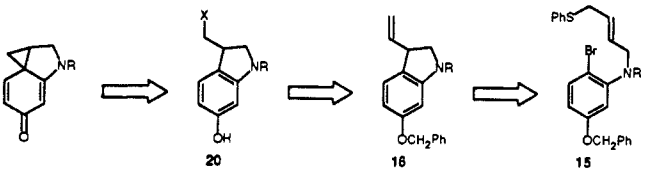
Abstract: Full details of the synthesis of *N*-(phenylsulfonyl)- and *N*-((*tert*-butyloxy)carbonyl)-1,2,7,7a-tetrahydrocycloprop[1,2-*c*]indol-4-one [*N*-(phenylsulfonyl)-CI (**9**) and *N*-BOC-CI (**10**)] constituting stable derivatives of the parent cyclopropylcyclohexadienone ring system of the CC-1065 left-hand subunit are described. The resolution of an immediate CI synthetic precursor, (+)- and (-)-**17b**, and the incorporation of (±)-, (+)-, and (-)-**17b** into the synthesis of racemic and optically active CI-CDPI$_1$ (**7**) and CI-CDPI$_2$ (**8**) are detailed.

(+)-CC-1065 (**1**, NSC-298223), an antitumor-antibiotic isolated from cultures of *Streptomyces zelensis*,[2] possesses exceptionally potent in vitro cytotoxic activity, broad spectrum antimicrobial activity, and confirmed in vivo antitumor activity. In a series of extensive investigations, the site and mechanism of the (+)-CC-1065 antitumor activity have been related to its irreversible, covalent alkylation of sequence-selective B-DNA minor groove sites [5′-d(A/GNTTA)-3′ and 5′-d(AAAAA)-3′] that has been demonstrated to proceed by 3′-adenine *N*-3 alkylation of the electrophilic spiro[2.5]octa-4,7-dien-6-one present in the left-hand segment (CPI) of (+)-CC-1065.[3] In contrast to conclusions drawn from early efforts,[2-4] recent investigations have suggested that the sequence-selective DNA binding properties as well as the intrinsic antitumor activity of (+)-CC-1065 may be embodied in the CPI left-hand segment albeit with substantially reduced potency (ca. 10000×).[5] However, the additional observations of the distinct and indistinguishable cytotoxic potency of the enantiomeric pairs of agents, (+)-CC-1065 (**1**)/*ent*-(-)-CC-1065 (**2**)[6] and (+)-CPI-CDPI$_2$ (**3**)/(-)-CPI-CDPI$_2$ (**4**),[7,8] the contrasting observation of the lack of potent cytotoxic activity exhibited by simplified[4] and aborted[9] agents bearing the enantiomeric CPI left-hand subunit, the demonstrated A-T rich noncovalent DNA binding selectivity of simplified agents including CDPI$_3$ methyl ester,[10] and the recent results of direct comparative footprinting studies of a series of structurally related agents[5,9] have suggested that the CC-1065 central and right-hand segments may simply potentiate[5] *and/or* alter[9] the DNA binding properties of the class of agents bearing the intact CPI left-hand subunit. Consequently, the definition of the structural and functional features of the CC-1065 CPI left-hand subunit that contribute to its sequence-selective B-DNA minor groove binding properties, cytotoxic ac-

Scheme I



† The numbering system used for the parent CI is not that given in the *Ring Systems Handbook*. For consistency with related work, the numbering sequence follows that used for CPI in the *Ring Systems Handbook*.

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