Articles

Stereocontrolled Elaboration of Quaternary Carbon Centers through the Asymmetric Michael Reaction Using Chiral Imines: Enantioselective Synthesis of (+)-Aspidospermidine

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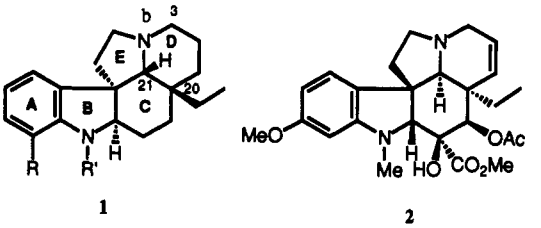
An enantioselective synthesis of (+)-aspidospermidine (**1b**) has been developed. The key strategic element was the stereocontrolled elaboration of quaternary carbon centers through the asymmetric Michael reaction, using chiral imines under neutral conditions. Thus, addition of imine **21**, prepared from 2-ethylcyclohexanone and (*R*)-1-phenylethylamine, to methyl acrylate, led to cyclohexanone (*S*)-**20** with 90% stereoselectivity (Scheme 3). The latter compound was then converted in six steps into dione **19** (Chart 6). Synthesis of [ABC]-type tricyclic carbazolone **18** was next accomplished, starting from this dione, by using the indole synthesis protocol developed by Suzuki. Critical to the success of this approach was the evolution, after extensive experimentation, of an efficient sequence for assembling D ring to carbazolone **18**, having controlled during the events the "natural", *cis* CD ring junction. Thus, treatment of alcohol **57** with trifluoroacetic acid led to tetracycle **58** obtained as a *single* isomer with 94% yield (Chart 10). The intramolecular capture of a putative intermediary iminium ion, as illustrated in **52**, by the carbamate nitrogen atom of **57** has been evoked to rationalize the observed stereoselectivity. The strategy we have adopted for the construction of the fifth E ring of **1b** was in fact the methodology proposed by Magnus, based on an intramolecular Pummerer rearrangement (**17** → **59**). Thus, synthesis of (+)-aspidospermidine (**1b**) has been achieved by a linear sequence of 22 chemical operations, starting with 2-ethylcyclohexanone, with an overall yield of 2.7%.

The *Aspidosperma*-type indole alkaloids comprise a large group of architecturally interesting bases whose presence in certain biologically active molecules (*e.g.*, as components of the antitumor dimeric indole alkaloids) has stimulated worldwide research activity devoted to their synthesis.[1] Among these naturally occurring bases, (-)-aspidospermine (**1a**) and (+)-aspidospermidine[2] (**1b**) have emerged as particularly attractive targets for the development of new synthetic methodologies; thus, various strategies, summarized in Schemes 1 and 2 and Chart 2, have evolved for the total syntheses of these two compounds. The purpose of the present paper is to report a new enantioselective synthesis of natural (+)-aspidospermidine (**1b**). Although the compound in itself is devoid of pharmacological interest, it may be considered as a pertinent model for the approach to more functionalized molecules, exemplified by vindoline **2**, which constitutes the "bottom half" of the aforementioned carcinostatic dimeric alkaloids, such as vincristine and vinblastine.[3]

The pioneering work of Stork in 1963, who succeeded in achieving the first total synthesis of (*rac*)-**1a**, has focused upon the use of the pivotal [CDE]-type tricyclic intermediate **3**, which was converted into **1a** through a Fischer indole synthesis.[4] Several other syntheses of **1a** or **1b** have taken advantage of the preceding findings of Stork,[5] but unfortunately, all suffered undeniably from the modest yields obtained in the critical Fischer indole synthesis step. This vexing drawback was circumvented by Overman a

Chart 1



1 2

a : R = OMe, R' = Ac
b : R = R' = H

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(2) Biemann, K.; Spiteller, G. *J. Am. Chem. Soc.* **1962**, *84*, 4578-4586. Smith, G. F.; Wrobel, J. T. *J. Chem. Soc.* **1960**, 1463-1467. Smith, G. F.; Wahid, M. A. *J. Chem. Soc.* **1963**, 4002-4004. The numbering system due to Le Men and Taylor (Le Men, J.; Taylor, W. I. *Experientia* **1965**, 21, 508-510) was used here.

(3) Antitumor Bisindole Alkaloids from *Catharanthus roseus* (L.). In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990, Vol. 37.

(4) Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872-2873.

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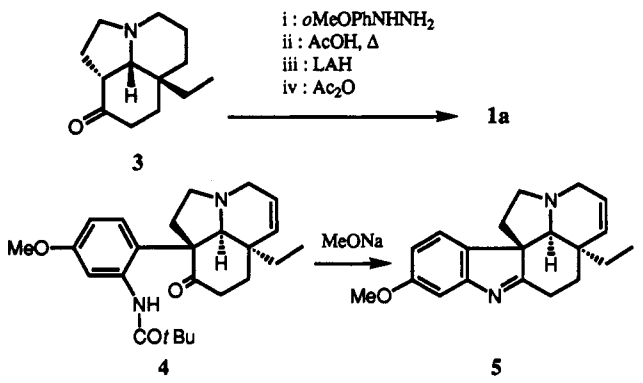
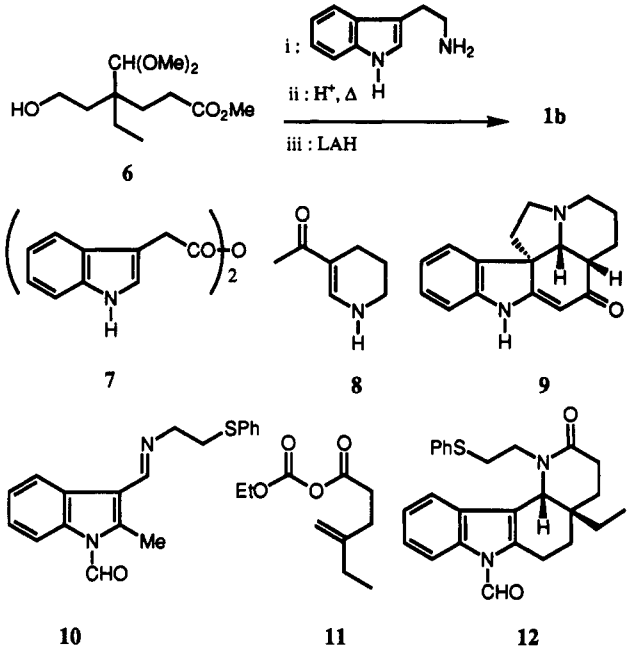
0022-3263/94/1959-2292$04.50/0

Scheme 1



Scheme 2



decade ago, using tricyclic intermediate **4**, in a synthesis of 16-methoxytabersonine, which carried an appropriately functionalized aromatic appendage at the CE ring junction. The construction of the indole moiety (**4** → **5**) was thus achieved with a satisfactory yield.[6]

The acyclic linchpin in the elegant [AB → ABCDE]-type approach to **1b**, due to Harley-Mason, was compound **6**, in which the quaternary carbon atom bore dissimilar alkyl chains at a carbonyl center. The synthesis of aspidospermidine from **6** and tryptamine was then efficiently accomplished in only three steps through the indoloquinolizidine rerrangement.[7] Two enantioselective versions of this methodology have recently been explored.[8] In 1981, Wenkert introduced a short, direct method for the construction of the pentacyclic core of *Aspidosperma* alkaloids, **9**, from anhydride **7** and tetrahydropyridine **8**.[9] The placement of the angular ethyl side chain at the CD ring junction in **9** was achieved by several routes.[10] A concise approach to aspidospermidine **1b** was proposed by Magnus in 1982, in which the [ABCD]-type tetracyclic lactam **12** was prepared by condensation of imine **10** with anhydride **11** through intramolecular Diels-Alder cycloaddition of a transient indoloquinodimethane. Elaboration of the fifth E ring was then accomplished by an intramolecular Pummerer reaction.[11]

Gramain has recently reported a synthesis of **1b** based on the photocyclization of enaminone **13** into an equimolar mixture of stereomers **14**, the latter affording **15** by Michael addition with nitroethylene. Isomer **15** possessing the "natural" stereochemistry (ethyl group *trans* to the nitroethyl chain) was then converted into **1b** in two steps.[12] Of limited synthetic interest, but of particular biogenetic significance, was the observation that the oxidation of (−)-quebrachamine **16** with mercuric acetate led to (+)-aspidospermidine **1b**.[13,14]

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(11) (a) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739–4749. (b) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 4750–4757. (c) Magnus, P. Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212–217. For an enantioselective version, see: (d) Magnus, P. Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217–221. (e) Cardwell, K.; Hewitt, B.; Ladlow, M.; Magnus, P. *J. Am. Chem. Soc.* **1988**, *110*, 2242–2248. For other approaches using pyrido[3,2-c]carbazole, see: (f) Husson, H.-P., Thal, C.; Potier, P.; Wenkert, E. *J. Chem. Soc.,-Chem. Commun.* **1970**, 480–481. (g) Ziegler, F. E.; Spitzner, E. B. *J. Am. Chem. Soc.* **1973**, *95*, 7146–7149. (h) Natsume, M.; Utsunomiya, I. *Heterocycles* **1982**, *17*, 111–115. (i) Wenkert, E.; Hudlicky, T. *J. Org. Chem.* **1988**, *53*, 1953–1957. (j) Hugel, G; Cossy, J.; Lévy, J. *Tetrahedron Lett.* **1987**, *28*, 1773–1776.

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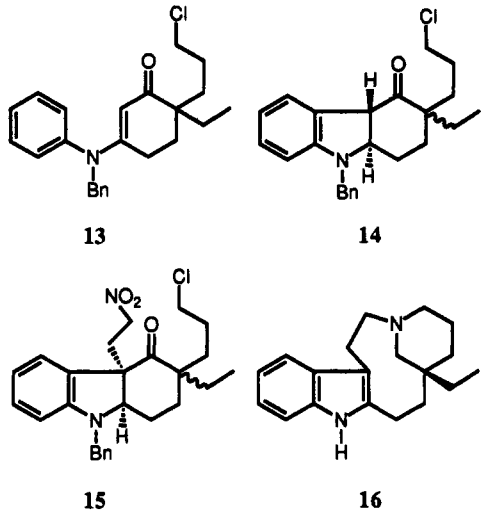
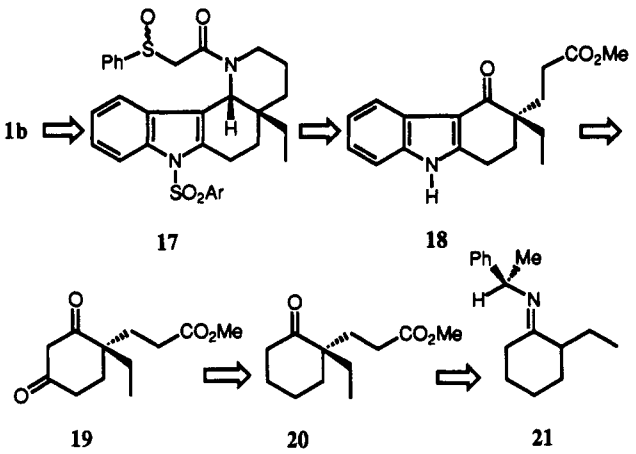
Chart 2



13 14 15 16

Scheme 3



17 18 19 20 21

Results and Discussion

Synthetic Plan. Our own strategy for the synthesis of (+)-aspidospermidine **1b** is outlined in the retrosynthetic pathway depicted in Scheme 3.[15] The basic approach featured a general methodology for the efficient enantioselective elaboration of quaternary carbon as key step in the construction of an [ABC]-type subunit, namely the disubstituted carbazolone **18**. Seeing that all attempts to elaborate this kind of compound from tricyclic imines **24** (*vide infra*) proved to be fruitless, we decided to synthesize this pivotal relay in an indirect manner, by assembling an indole moiety with dione **19**. This intermediate was prepared in its pure chirospecific form by introducing at the proper position an additional carbonyl group onto cyclohexanone **20**, itself resulting from the asymmetric Michael addition between chiral imine **21** and methyl acrylate.[16] Carbazolone **18** was then converted into tetracycle **17**, having established during the events the correct stereochemistry at the CD ring junction. Construction of the fifth E ring of aspidospermidine **1b** was achieved by subjecting tetracyclic derivative **17** to an intramolecular Pummerer rearrangement, a tactic developed by Magnus (*vide supra*).[11a,b]

It was our original hope that a concise, direct route to enantiopure cornerstone carbazolone **18** might require the general methodology for the stereocontrolled construction of quaternary carbon centers we reported a few years ago, based on the Michael-type addition of chiral imines to electrophilic alkenes.[16] This strategy was initially tested on advanced intermediates, namely the model imines **24b** and **24c**, derived from a preformed carbazolone in which the requisite α-ethyl substituent was replaced by a methyl group. These imines were prepared in three steps from 4-methyl-1,3-cyclohexanedione **22**[17] which was first transformed through a Fischer indole synthesis[18] into carbazolone **23a**, a highly regioselective reaction that implicated exclusively the less hindered carbonyl group of starting dione **22**. After specific protection of the nitrogen atom, carbazolone **23a** was converted into the desired imines **24b** and **24c** by means of (*R*)-1-phenylethylamine, in the presence of $TiCl_4$.[19] Unfortunately, these imines proved to be completely inert toward electrophilic alkenes. Thus, no adducts were obtained by exposing **24b** or **24c** to methyl acrylate (neat, 60 °C, 48 h or in THF, 20 °C, 15 kbar, 48 h) or to ethyl α-(phenylselenyl)acrylate[20] (**25**), as a "bis-activated" Michael acceptor (neat, 20 °C, 48 h).

This disappointing lack of reactivity should clearly be attributed to the strong destabilizing *peri*-type interaction between the chiral moiety and an aromatic hydrogen in secondary enamines **26**, the tautomeric forms of imines **24**, which would constitute the nucleophilic species in the expected Michael addition reaction (since the success of this conjugate addition requires imperatively that the NH proton of the secondary enamine should be transferred to the α-vinylic center of the electrophilic alkene, *concertedly* to the creation of the C–C bond, enamines **26** have been intentionally designed in their putative reactive conformers, namely the NH *syn* to the enamine double bond).[16] The absence of tautomeric equilibrium between imines **24** and enamines **26** was confirmed by stirring the former compounds in CD_3OD: there was no incorporation of deuterium atoms after 1 week at 20 °C.[21] In relation with this observation was the fact that imine **24b** was found to be resistant to deprotonation with strong bases; thus, its sequential treatment with LDA (THF, 0 °C) and MeI returned only unreacted starting material. Likewise, the complete lack of reactivity of imine **27**, derived from 2-methyl-1-tetralone, toward electrophilic alkenes, paralleled the preceding findings.[16]

In view of the above results, an alternative plan was devised, in which the order of reactions was inverted, so that the quaternary carbon center of subgoal carbazolone **18** would be created on the future C ring, prior to the construction of the indole moiety. The first strategy we have explored has focused upon the use of chiral imine **29**, derived from monoprotected dione **28**, which was prepared in a highly regioselective manner by treating 4-ethyl-1,3-cyclohexanedione[17] successively with oxalyl chloride[22] and 1,2-ethanedithiol. Surprisingly, imine **29** exhibited a completely unexpected behavior when exposed to Michael acceptors. Thus, for example, the only adduct observed

(15) For a preliminary communication of this work and synthesis of (–)-19-noraspidospermidine, see: Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1990**, *31*, 879–882. d'Angelo, J.; Desmaële, D. *Ibid.* **1990**, *31*, 883–886.

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(17) Kende, A. S.; Fludzinski, P. *Org. Synth.* **1986**, *64*, 68–72.

(18) Clemo, G. R.; Felton, D. G. I. *J. Chem. Soc.* **1951**, 700–703.

(19) Weingarten, H.; Chupp, J. P.; White, W. A. *J. Org. Chem.* **1967**, *32*, 3246–3249.

(20) Compound **25** was prepared according to the procedure of Takaki, having replaced PhSCl by PhSeCl: Takaki, K.; Okada, M.; Yamada, M.; Negoro, K. *J. Org. Chem.* **1982**, *47*, 1200–1205.

(21) Pfau, M.; Ribière, C. *Bull. Soc. Chim. Fr.* **1971**, 2584–2590.

(22) Mewshaw, R. E. *Tetrahedron Lett.* **1989**, *30*, 3753–3756.

Chart 3

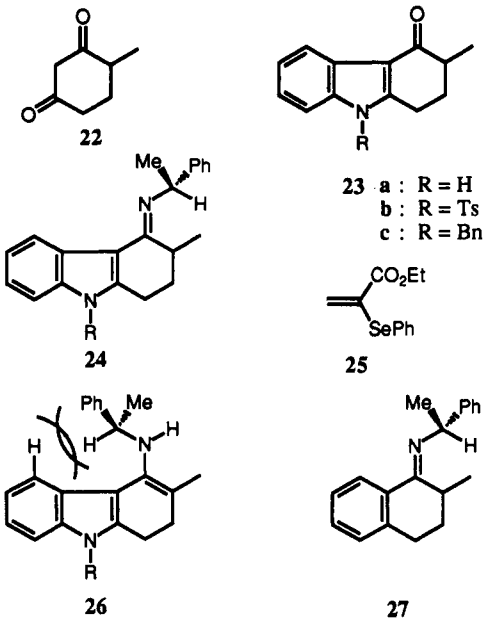
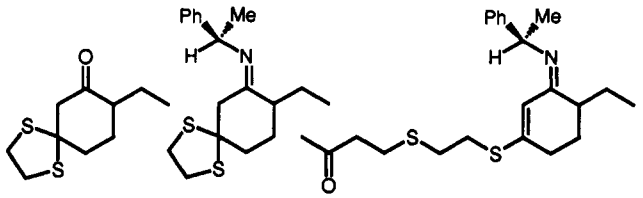


Chart 4



with methyl vinyl ketone was **30**, resulting from the thioketal ring opening, followed by a *S*-hetero-Michael addition. However, adduct **30** proved to be too unstable to be purified and fully characterized, since regenerating thioketal **28** under mild hydrolytic conditions.

At this stage it became apparent that 4-ethyl-1,3-cyclohexanedione did not constitute an adequate starting material for the preparation of tricycle **18**. We therefore turned to an other tactic which would utilize as the C ring subunit a cyclohexanone bearing the already controlled crucial quaternary carbon center at the α-position to the carbonyl group. Two strategies have been evolved for the subsequent elaboration of the indole moiety. In one of these approaches, which has not been more successful thus far, we decided to bind first an appropriately *ortho*-functionalized aromatic ring to the α-vinylic center of a cyclohexenone and to finish the indole synthesis by an intramolecular Michael-type *N*-heterocyclization. For this purpose, model bromo enone **34** (in which the requisite ethyl appendage was replaced by a methyl group) was conveniently prepared in three steps, starting with cyclohexanone **31**.[16] This was first converted into silyl enol ether **32** which, upon oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone,[23] led to enone **33**.[15] Bromination of the latter compound, followed by dehydrobromination with Et_3N,[24] afforded the desired bromo enone **34**. Coupling of this substance with an aromatic moiety was

(23) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736–738. For a mechanistic study of this reaction, see: Bhattacharya, A; DiMichele, L. M.; Dolling, U.-H.; Grabowski, E. J. J.; Grenda, V. J. *J. Org. Chem.* **1989**, *54*, 6118–6120.

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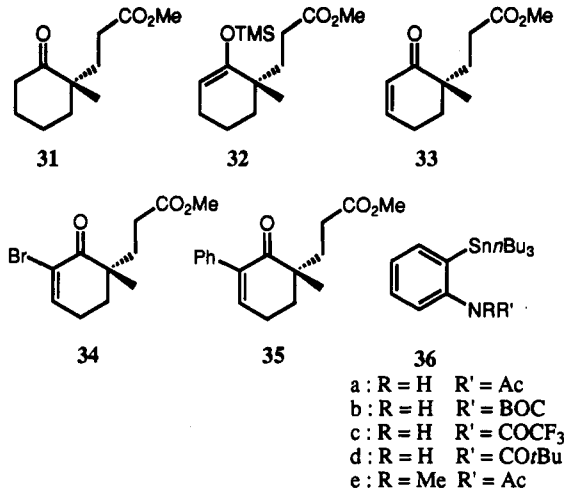
Chart 5



next attempted. Disappointingly, although condensation of phenyltributyltin in the presence of $Pd(PPh_3)_4$ was fruitful, giving the expected compound **35** with a 69% yield, all efforts to link **34** with tin derivatives **36**[25] having nitrogen functionality at the *ortho*-position, employing a variety of *N*-protecting groups, were uniformly unsuccessful.[26]

The strategy that was ultimately adopted has taken advantage of an indole synthesis originally reported by Suzuki, based on the copper(I) iodide-promoted arylation of enolates of β-dicarbonyl compounds with 2-iodoaniline.[27] The first stage in this strategy required the preparation of dione **19** by functionalization at the proper position of cyclohexanone **20**. The latter compound was elaborated with an overall yield of 83% in its desired *S* chirospecific form by asymmetric Michael addition of imine **21**, itself prepared from 2-ethylcyclohexanone[28] and (*R*)-1-phenylethylamine (of 96% ee), to methyl acrylate.[16] Since the ee obtained in this reaction was 86% (90% stereoselectivity), efforts to upgrade the optical purity of the synthetic intermediates were undertaken. This was efficiently achieved by using the semicarbazone derivative of cyclohexanone **20**, or at the level of dione **19**, both having been obtained in their pure enantiomeric forms by crystallization.

In the synthesis of dione **19** from cyclohexanone **20** involving the introduction of an additional β-carbonyl group, functionalization of the related sp^3 carbon center was accomplished by oxidizing ketone **20** into enone **38**,

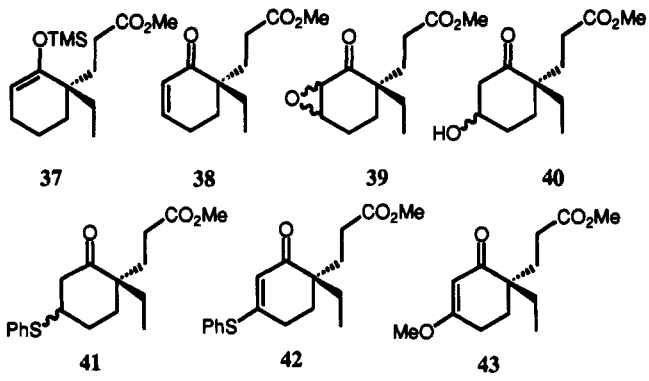
(25) Compounds **36a**, **36d**, and **36e** were prepared by treatment of the corresponding bromides with $(nBu_3Sn)_2$ in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ in DMF at 60 °C. Azarian, D.; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1975**, *117*, C55-C57. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478–5486. Compounds **36b** and **36c** were prepared by metal–halogen exchange by using *t*BuLi, followed by treatment of the resulting lithio derivatives with nBu_3SnCl.

(26) For some related couplings: Negishi, E.-I.; Owczarczyk, Z., R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453–4456. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919–922. Farina, V.; Roth, G., P. *Tetrahedron Lett.* **1991**, *34*, 4243–4246.

(27) Suzuki, H.; Thiruvikraman, S. V.; Osuka, A. *Synthesis* **1984**, 616–617. Osuka, A.; Mori, Y.; Suzuki, H. *Chem. Lett.* **1982**, 2031–2034. For related carbazolone synthesis, see: Okamoto, T.; Shudo, K. *Tetrahedron Lett.* **1973**, 4533–4535. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Chem. Soc., Chem Commun.* **1978**, 766–767. Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem.* **1980**, *45*, 2938–2942. Wender, P. A.; White, A. *Tetrahedron* **1983**, *39*, 3767–3776. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215–218. Uozumi, Y.; Mori, M.; Shibasaki, M. *J. Chem. Soc., Chem Commun.* **1991**, 81–83.

(28) Nedenskov, P.; Taub, W.; Ginsburg, D. *Acta Chem. Scand.* **1958**, *12*, 1405–1410.

Chart 6



37 38 39 40

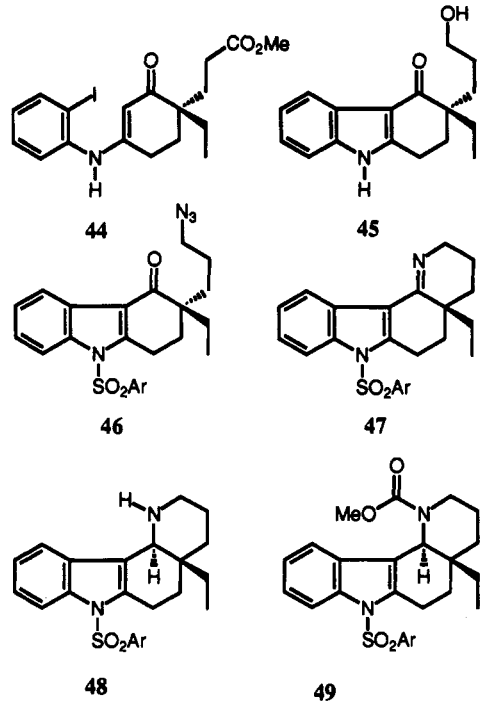
41 42 43

through silyl enol ether **37**, by a procedure in all points identical with the conversion **31** → **33**. Of the three routes attempted to oxidize enone **38** into dione **19**, two proved to be unsuccessful. Thus, treatment of **38** with Na_2PdCl_4 in the presence of *t*BuOOH, according to Tsuji protocol,[29] returned only unreacted starting material. Likewise, dione **19** was not formed when epoxide **39** (synthesized as a mixture of diastereomers by oxidation of enone **38** with H_2O_2 in the presence of NaOH) was subjected to the Noyori isomerization procedure,[30] using palladium 1,2-bis(diphenylphosphinoethane). Although the alternative treatment of epoxide **39** with $PhSeB(OEt)_3Na$[31] led quantitatively to ketol **40**, all attempts at oxidizing the latter derivative into desired dione **19** were once again unsuccessful.

Having thus been forcibly diverted from the direct oxidation of enone **38** into dione **19**, efforts were refocused upon the development of an indirect route, based on the conjugate addition of thiophenol to **38**, giving **41**, followed by oxidation of the latter compound with *N*-chlorosuccinimide[32] into thioether **42**. In view of the fact that the sp^2 carbon center in the β-position to the carbonyl group in **42** now exhibited the same oxidation state that in target dione **19**, hydrolysis of **42** would conclude the synthetic sequence.[33] However, attempted direct hydrolysis of **42**, by using a variety of operating conditions ($HgCl_2/H_2O$; $TiCl_4$/AcOH; $Hg(NO_2)_2$/MeCN/H_2O), was ineffective. Finally, it was discovered that the most efficient protocol to hydrolyze **42** into **19** was its methanolysis, by means of sodium methoxide, into intermediary enol ether **43**, followed by treatment with 1 *N* HCl. Conversion of cyclohexanone **20** into key dione **19** was thus accomplished in six steps, with an overall yield of 35%.

With the necessary dione **19** on hand, the synthesis of target tricyclic carbazolone **18** was next achieved with an overall yield of 79% by condensing **19** with 2-iodoaniline, followed by cyclization of the resulting enaminone **44** (NaH then CuI).[27] The principal issue at this juncture was the construction of the fourth D ring, bearing in mind that the crucial *cis* relationship at the CD ring junction should be established during this course. After we chose to create the D ring by heterocyclization between nitrogen atom

Chart 7



44 45

46 47

48 49

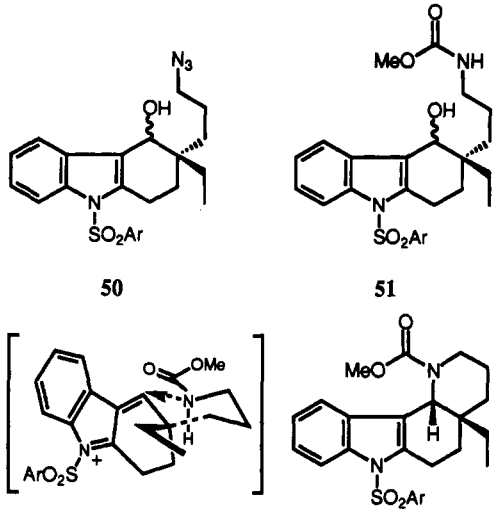
(Ar = *p*-methoxyphenyl)

N-b and C-21 center (*Aspidosperma* alkaloid numbering system, see formula **1**), an azido group, precursor of the future amine function at C-3, was introduced at the extremity of the three-carbon appendage of carbazolone **18**. To attain this end, compound **18** was first reduced with lithium triethylborohydride into alcohol **45**. As anticipated, this reduction was found to be highly chemoselective, since the concomitant generation of the *N*-lithio derivative of carbazolone **18** ensured the internal protection of the vinylogous amide carbonyl function on C ring. Alcohol **45** was then transformed into azide **46** by a three-step sequence involving mesylation, displacement of mesylate with sodium azide, and protection of the indolic nitrogen atom as the (4-methoxyphenyl)sulfonamide derivative under phase-transfer conditions.[34] Conversion **18** → **46** was thus achieved with an overall yield of 65%.

We next examined the possibility of constructing the D ring by an intramolecular aza-Wittig condensation. For this purpose, azide **46** was treated with PPh_3, leading to tetracyclic imine **47**. Reduction of this imine was then undertaken. However, attempts to reduce **47** under a variety of standard conditions led either to unreacted starting material (DIBAL-H, THF, 20 °C), to the *N*-deprotected starting material (LAH in refluxing THF; red-Al in toluene at 20 °C), or to amine **48** exhibiting the "unnatural", *trans* CD ring junction ($NaBH_3CN$, AcOH, 20 °C; H_2, Pd/C, MeOH; BH_3–Me_2S complex, THF, 20 °C; $NaBH_4$, $CeCl_3$, EtOH, 20 °C). The *trans* stereochemical assignment in compound **48** was deduced at the level of the corresponding carbamate derivative **49**, since comparison of the latter derivative with *cis* isomer **53**, previously reported by Magnus,[11b] has revealed several marked discrepancies. Thus, not surprisingly, the reduction of **47** invariably took place from the less congested imine π-face, *anti* to the angular ethyl group.

(29) Tsuji, J.; Hideo, N. Kimihiko, H. *Chem. Lett.* **1980**, 257–260.
(30) Suzuki, M.; Watanabe, A.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 2095–2096.
(31) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697–2699. Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1989**, *111*, 3728–3734.
(32) Bakuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235–239. For an alternative procedure, see: Lee, P. H.; Kim, S. *Bull. Kor. Chem. Soc.* **1992**, *13*, 580–581.
(33) Attempts to add directly 2-iodoaniline either to thioether **42**, or to the corresponding sulfone, were both unsuccessful.
(34) Götz, P. H.; Bats, J. W.; Fritz, H. *Liebigs Ann. Chem.* **1986**, 2065–2080.

Chart 8



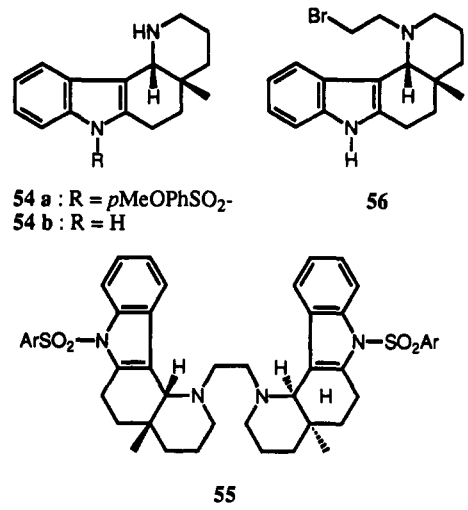
50 51 52 53

(Ar = *p*-methoxyphenyl-)

At this point the direct reduction of imine **47** was abandoned in favor of an alternative strategy, based on the intramolecular capture of an intermediary iminium ion by a carbamate (or amide) nitrogen atom,[35] as illustrated in **52**. Indeed, we reasoned that, according to such a process, the closure of the D ring should necessarily take place from the α-side of the molecule, *anti* to the angular ethyl chain, thereby delivering the "natural", *cis* stereochemistry at the CD ring junction. Alcohol **51**, precursor of iminium ion **52**, was prepared by a three-step sequence, starting from azide **46**. This was first reduced with $NaBH_4$ into alcohol **50**, obtained as an equimolar mixture of diastereomers.[36] Reduction of this compound with PPh_3[37] then furnished an amino alcohol, not isolated, which was selectively *N*-acylated into carbamate–alcohol **51**, by means of methyl chloroformate, using the Schotten–Baumann protocol. To our delight, by subjecting alcohol **51** to acidic treatment under mild conditions (trifluoroacetic acid (TFA), 0 °C, 5 min), the tetracyclic carbamate **53**, exhibiting the desired *cis* stereochemistry, was obtained as a *single* isomer with a 92% yield.[38] Considering the ease of the present ring closure, it appeared manifest that the departure of the hydroxyl group in alcohol **51** was assisted by the indolic nitrogen atom, leading to the putative intermediary iminium ion **52**. The *cis* stereochemical assignment in carbamate **53** was unambiguously established, this molecule proving to be identical in all respects, with the exception of the optical rotation, with the same compound, described in its racemic form by Magnus.[11b]

Having thus efficiently solved the crucial problem of the control of the stereochemistry at the CD ring junction, we stood ready to complete the total synthesis of (+)-aspidospermidine **1b** by constructing the fifth E ring. Our initial investigation was based on the use of 1,2-dibromoethane, which would provide the two missing carbon atoms by an annulation reaction. This strategy was preliminarily tested on model compounds **54a** and **54b**, elaborated in a fashion analogous to the preparation of compound **53**. However, surprisingly, condensation of tetracycle **54a** with 1,2-dibromoethane in the presence of 2,6-di-*tert*-butylpyridine under high pressure-mediated conditions (12 kbar, 50 °C, 72 h) has furnished adduct **55**, a structure unequivocally established by mass spectroscopy, resulting from the coupling of two molecules of **54a** with dibromoethane. Thus, the *intermolecular* displacement of the bromine atom in the primary adduct of this reaction by a second molecule of **54a** took precedence over the *intramolecular* process, which would lead to the expected pentacyclic derivative. This drawback has been attributed to the low nucleophilicity of the indole moiety of **54a**, in which the nitrogen atom was protected as arylsulfonamide derivative, and the preceding experiment was repeated, with the starting material **54a** replaced by the "*N*-deprotected" parent compound **54b**. Unfortunately, although the primary adduct **56** was actually formed in this condensation, all efforts at cyclopentannulation of this adduct failed, in contrast with previous reports.[11f-h]

Chart 9



54 a : R = *p*MeOPhSO$_2$-
54 b : R = H

56

55

The definitive strategy we have adopted for the construction of the E ring of **1b** was in fact the methodology developed by Magnus, based on an intramolecular Pummerer rearrangement.[11a,b] For this purpose amide **57** was prepared with an overall yield of 57% from azide **50**, in close analogy with the conversion **50** → **51**, but by using in the acylation step (phenylthio)acetyl chloride as progenitor of the two missing carbon atoms of the future E ring. By subjecting compound **57** to acidic treatment (TFA, 0 °C, 15 min), the tetracycle **58** was obtained as a single *cis* isomer with a 94% yield. The latter derivative was then oxidized with sodium *m*-periodate into a diastereomeric mixture of sulfoxides **17**, which, by Pummerer rearrangement (trifluoroacetic anhydride, then refluxing chlorobenzene, 30 min), afforded the desired pentacyclic derivative **59** (89% yield from **58**). Desulfurization of **59** with Raney nickel led to **60** which was converted into our goal (+)-aspidospermidine (**1b**), upon treatment with a large excess of lithium aluminum hydride (THF, 20 °C, 48 h, 43% yield from **59**). All data of synthetic (+)-**1b**, including melting point, optical rotation, IR spectrum, ^1H and ^{13}C NMR spectra, and high-resolution mass spectrum,

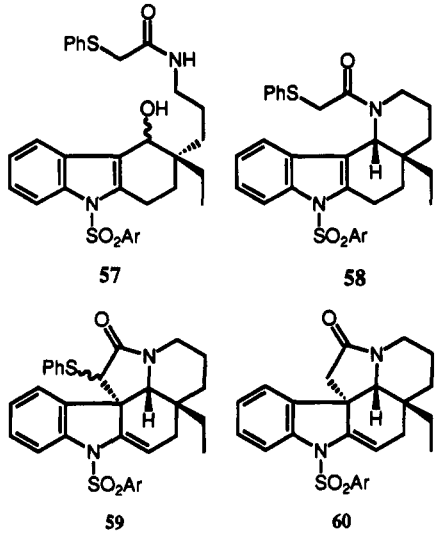
(35) For the reactivity of such indolic Mannich bases, see: Albright, J. D.; Snyder, H. R. *J. Am. Chem. Soc.* **1959**, *81*, 2239–2245. Leete, E. *J. Am. Chem. Soc.* **1959**, *81*, 6023–6025.

(36) Vogel, T.; Huth, H.-U.; Fritz, H. *Liebigs Ann. Chem.* **1982**, 739–744.

(37) Lambert, P. H.; Vaultier, M.; Carrié, R. *J. Chem. Soc., Chem. Comm.* **1982**, 1224–1225. For a recent review, see: Gololobov, Y. G., Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406.

(38) This process clearly reflected a kinetic control, since treatment of *trans*-derivative **49** with TFA returned only unchanged starting material.

Chart 10



(Ar = *p*-methoxyphenyl-)

were found to be identical to those described for the natural compound. This synthesis has thus been completed in 2.7% overall yield from 2-ethylcyclohexanone by a linear sequence of 22 chemical operations. Critical to the success of this synthesis endeavor was the evolution, through extensive experimentation, of an efficient procedure for assembling the D ring onto an [ABC]-type subunit, having controlled during the events the "natural", *cis* CD ring junction. Further extensions of this methodology will be reported in due course.

Experimental Section

General. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. IR spectra were obtained as neat films between NaCl plates or KBr pellets and were recorded on a Perkin-Elmer 297 or a Nicolet FT IR 205 spectrometers. Only Polartronic I polarimeter in a 1-dm cell. ^{1}H NMR spectra were recorded on a Bruker AM 250 (250 MHz) or a Bruker AC 200 P (200 MHz) spectrometer. ^{13}C NMR spectra were recorded on either a 20-MHz, a 50-MHz, or a 62.9-MHz instrument, and the multiplicities were determined using DEPT sequence. $CDCl_3$ with tetramethylsilane (TMS) as internal standard was used as NMR solvent, unless otherwise noted. Mass spectra analyses were recorded by electron impact at 70 eV on a JEOL-JMS-AX500. All liquid chromatography separations were performed using Merck SiO_2 60 (230–400 mesh ASTM). Thin-layer chromatographic analyses were performed on Merck SiO_2 60 F_{254} precoated plates and on Merck Al_2O_3 F $_{254}$ (type E) precoated plates. Ether and tetrahydrofuran (THF) were distilled from Na–benzophenone ketyl. Methanol and ethanol were dried over magnesium and distilled. Toluene, CH_2Cl_2, HMPA, and DMF were distilled from calcium hydride, under nitrogen atmosphere. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware which was flame-dried under a positive nitrogen pressure. Small-scale distillations were performed with a cold finger apparatus. The boiling points refer to oil bath temperatures. Organic layers were dried over anhydrous $MgSO_4$. Materials were obtained from commercial suppliers and used without further purification, unless otherwise noted.

3-Methyl-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (23a). A stirred solution of 4-methyl-1,3-cyclohexanedione (**22**) (10.7 g, 85 mmol) in a mixture of water (80 mL) and ethanol (20 mL) was treated dropwise with phenylhydrazine (9.62 g, 89 mmol). After 30 min the slurry was filtered and the solid dried in vacuo to give the hydrazone (18 g, 98%) as a pale yellow solid. To a stirred solution of concentrated sulfuric acid (78 mL) and water (200 mL) was added portionwise the crude hydrazone (18 g, 83.3 mmol). The resulting mixture was heated for 2 h at 90 °C. After cooling, the reaction mixture was poured into water (800 mL) and allowed to settle at 0 °C overnight. The solid was filtered with suction through a sintered-glass funnel, dried under vacuum over phosphorus pentoxide, and recrystallized from ethanol to give carbazolone **23a** (8.0 g, 47%): mp 228 °C (EtOH); IR (KBr, cm^{-1}) 1660, 1590, 1555; ^{1}H NMR (DMSO-d_6, 200 MHz) δ 11.8 (s, 1H), 7.95 (m, 1H), 7.40 (m, 1H), 7.15 (m, 2H), 3.00 (m, 2H), 2.50 (m, 1H), 2.20 (m, 1H), 1.90 (m, 1H), 1.15 (d, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 195.3 (C), 151.7 (C), 136.1 (C), 124.8 (C), 122.3 (CH), 121.4 (CH), 120.2 (CH), 111.5 (CH), 111.1 (C), 38.3 (CH), 31.4 (CH_2), 22.0 (CH_2), 15.3 (CH_3); MS m/e 199 ($M^{+\cdot}$, 50), 157 (100), 129 (48), 102 (10). Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.57; N, 7.03. Found: C, 78.21; H, 6.69; N, 7.06.

3-Methyl-9-(*p*-toluenesulfonyl)-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (23b). In a two-necked flask equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser was placed sodium hydride (50% in mineral oil, 0.46 g, 10.0 mmol). The solid was washed with hexane under nitrogen (2 × 5 mL) and covered with THF (5 mL). A solution of carbazolone **23a** (1.00 g, 5.02 mmol) in THF (40 mL) was added dropwise with stirring and the resulting mixture refluxed for 2 h. After the mixture was cooled to 0 °C, *p*-toluenesulfonyl chloride (1.43 g, 7.5 mmol) in THF (5 mL) was added and the reaction mixture stirred for 1 h at 20 °C. The solution was poured into water (50 mL), acidified to pH 5–6 with 2 N HCl, extracted with ether (3 × 50 mL), dried, and concentrated in vacuo. Chromatography (hexane–AcOEt, 60:40) gave protected indole **23b** (1.47 g, 82%): mp 166 °C (ether); IR (film, cm^{-1}) 1665, 1600, 1555, 1470; ^{1}H NMR (250 MHz) δ 8.23 (m, 1H), 8.13 (m, 1H), 7.74 (d, J = 8.2 Hz, 2H), 7.32 (m, 2H), 7.23 (d, J = 8.2 Hz, 2H), 3.49 (ddd, J = 18.7, 4.7, 4.5 Hz, 1H), 3.18 (ddd, J = 18.7, 10.3, 5.1 Hz, 1H), 2.55 (m, 1H), 2.33 (s, 3H), 2.27 (m, 1H), 1.92 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz) δ 197.3 (C), 150.2 (C), 145.6 (C), 135.9 (C), 135.3 (C), 130.0 (2CH), 126.4 (2CH), 125.8 (C), 125.0 (CH), 124.6 (CH), 121.6 (CH), 117.2 (C), 113.8 (CH), 41.2 (CH), 31.0 (CH_2), 23.8 (CH_2), 21.4 (CH_3), 14.6 (CH_3). Anal. Calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96; S, 9.07. Found: C, 67.62; H, 5.35; N, 4.09; S, 9.31.

9-(*p*-Toluenesulfonyl)-4-(1-phenylethylimino)-3-methyl-1,2,3,9-tetrahydro-4*H*-carbazole (24b). To a stirred solution of carbazolone **23b** (374 mg, 1.06 mmol) in toluene (10 mL) was added (*R*)-(+)-1-phenylethylamine (384 mg, 3.18 mmol), followed by $TiCl_4$ (115 mg, 0.60 mmol). After 24 h the reaction mixture was poured into dried ether (100 mL) and filtered through a sintered-glass funnel. The solvents were removed under reduced pressure and the residue chromatographed on silica gel (hexane–AcOEt, 60:40, R_f 0.60) to give imine **24b** (415 mg, 86%) as an equimolar mixture of diastereomers: mp 94 °C; IR (film, cm^{-1}) 1620, 1600, 1450; ^{1}H NMR (250 MHz) δ 8.68 and 8.61 (m, 1H), 8.15 (m, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.50 and 7.43 (d, J = 7.2 Hz, 2H), 7.33–7.10 (m, 7H), 4.94 (m, 1H), 3.35–3.00 (m, 3H), 2.30 (s, 3H), 2.08–1.82 (m, 2H), 1.56 and 1.49 (d, J = 6.5 Hz, 3H), 1.12 and 1.49 (d, J = 7.2 Hz, 3H); ^{13}C NMR (62.9 MHz) δ 164.5 (C), 146.7 (C), 145.0 (C), 141.5 (C), 136.6 (C), 136.0 (C), 129.9 (2CH), 128.3 (2CH), 127.9 (C), 126.7 (CH), 126.5 (2CH), 126.4 (2CH), 124.5 (CH), 124.2 (CH), 123.3 (CH), 117.2 (C), 113.8 (CH), 58.6 and 58.1 (CH), 29.2 and 28.8 (CH), 29.0 (CH_2), 26.3 (CH_3), 21.5 (CH_3), 20.3 (CH_2), 16.2 and 15.6 (CH_3). Anal. Calcd for $C_{28}H_{28}N_2O_2S$: C, 73.65; H 6.18; N, 6.13; S, 7.02. Found: C, 73.69; H, 6.23; N, 6.11; S, 7.99.

8-Ethyl-1,4-dithiaspiro[4.5]decan-7-one (28). A stirred solution of 4-ethyl-1,3-cyclohexanedione[17] (3.12 g, 22.3 mmol) and DMF (2.10 g, 29 mmol) in CH_2Cl_2 (25 mL) was cooled to −10 °C and oxalyl chloride (3.11 g, 24.5 mmol) was added over 5 min with concurrent gas evolution. After the solution was stirred for 30 min, no starting material was detected by TLC. The reaction mixture was concentrated in vacuo at room temperature, and the resulting oil was immediately taken in CH_2Cl_2 (10 mL) and added dropwise to an ice-cooled solution of 1,2-ethanedithiol (2.63 g, 28 mmol), triethylamine (3.38 g, 33.5 mmol), and 4-(dimethylamino)pyridine (0.1 g, 0.8 mmol) in 20 mL of CH_2Cl_2. The reaction mixture was warmed to 22 °C and stirred for 5 h. The solvent was removed in vacuo, and the residue was purified by chromatography on silica gel (hexane–AcOEt, 4:1, R_f 0.63) to give thioketal **28** as a yellow oil (2.45 g, 51%): IR (film,

cm^{-1}) 1713, 1681, 1451; ^1H NMR (200 MHz) δ 3.26 (s, 4H), 2.81 (s, 2H), 2.24 (m, 2H), 2.07 (m, 2H), 1.90–1.40 (m, 2H), 1.22 (m, 1H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz) δ 207.6 (C), 68.7 (C), 57.0 (CH_2), 50.3 (CH), 40.5 (CH_2), 39.1 ($2CH_2$), 30.9 (CH_2), 21.8 (CH_2), 11.3 (CH_3). Attempted distillation led to extensive decomposition; however, satisfactory microanalytical data could be obtained from the corresponding semicarbazone. Anal. Calcd for $C_{11}H_{19}N_3OS_2$: C, 48.32; H, 7.00; N, 15.37. Found: C, 48.27; H, 6.98; N, 15.34.

(+)-(*S*)-1-Ethyl-2-oxocyclohexane-1-propanoic Acid Methyl Ester (20). A solution of 2-ethylcyclohexanone[28] (42.2 g, 0.335 mol) in toluene (500 mL) was placed in a 1-L round-bottom flask equipped with a Dean-Stark trap. (*R*)-(+)-1-Phenylethylamine (48.6 g, 0.40 mol, $[\alpha]^{22}_D$ +39.1° (neat), ee 96%) was added, followed by *p*-toluenesulfonic acid (0.5 g, 2.6 mmol). The reaction mixture was refluxed for 12 h with azeotropic removal of water. After cooling, the reaction mixture was concentrated under reduced pressure (0.05 Torr, 40 °C) to give crude imine **21** as a yellow viscous oil. Methyl acrylate (48 g, 0.56 mol) and hydroquinone (0.1 g) were then added, and the stirring mixture was heated at 65 °C for 3 days until all the starting imine was consumed. After the mixture was cooled to 20 °C, 20% aqueous acetic acid (300 mL) and THF (500 mL) were added, and the mixture was stirred for 3 h. The solvents were removed under reduced pressure, and 1 N HCl (100 mL) was added to the residual oil. The mixture was extracted with ether (5 × 250 mL), and the collected organic phases were washed with brine, dried, and concentrated in vacuo. Chromatography on silica gel (hexane–AcOEt, 4:1, R_f 0.39) gave keto ester **20** (59 g, 83%). Distillation afforded an analytical sample: bp 120–130 °C (0.05 Torr); $[\alpha]^{22}_D$ +19.8° (EtOH, c = 10); IR (film, cm^{-1}) 1740 1705, 1442; ^1H NMR (250 MHz) δ 3.57 (s, 3 H), 2.25 (m, 2H), 2.22–1.97 (m, 2H), 1.85–1.55 (m, 8H), 1.46–1.34 (m, 2H), 0.68 (t, 3H, J = 7.5 Hz); ^{13}C NMR (20 MHz) δ 214.2 (C), 174.0 (C), 51.5 (CH_3), 51.0 (C), 39.0 (CH_2), 35.8 (CH_2), 29.1 (CH_2), 28.7 (CH_2), 27.1 ($2CH_2$), 20.8 (CH_2), 7.7 (CH_3). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.46. Found: C, 68.10; H, 9.37.

The optical purity of keto ester **20** (ee 86%) could be upgraded to *ca.* 100% ee by the following procedure. A solution of keto ester **20** (55.2 g, 0.26 mol, $[\alpha]^{22}_D$ +19.8°) in ethanol (100 mL) was treated by a solution of semicarbazide hydrochloride (30.5 g, 0.27 mol) and sodium acetate (24 g, 0.29 mol) in water (300 mL). The reaction mixture was allowed to settle at 0 °C for 18 h. The solid was filtered with suction through a sintered-glass funnel and dried under vacuum to provide 69 g of white crystals (mp 133 °C). One recrystallization from 95% ethanol gave pure semicarbazone (mp 135 °C). This compound was added portionwise to a two-phase mixture of cyclohexane (600 mL) and 2 N HCl (250 mL). The resulting slurry was stirred until all the solid was dissolved. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 250 mL). The combined organic phases were washed with saturated sodium bicarbonate and brine, dried over $MgSO_4$, and concentrated in vacuo. Distillation gave optically pure **20** (45 g, 81%) $[\alpha]^{22}_D$ +23.0° (EtOH, c = 4).

(*S*)-1-Ethyl-2-[(trimethylsilyl)oxy]-2-cyclohexene-1-propanoic Acid Methyl Ester (37). To a solution of keto ester **20** (57.5 g, 0.27 mol, ee 86%) in dry DMF (400 mL) were added triethylamine (144 g, 1.43 mol) and trimethylchlorosilane (89 g, 0.82 mol). The reaction mixture was heated at 100 °C for 48 h until all the starting material had reacted. After being cooled to room temperature, the reaction mixture was diluted with hexane (500 mL), poured into cold water (500 mL), and extracted with hexane (3 × 250 mL). The collected organic phases were dried and concentrated in vacuo to yield crude enol ether **37** (75.4 g, 97.8%) which was used directly in the next step: IR (film, cm^{-1}) 1730, 1645, 1420; ^1H NMR (200 MHz) δ 4.73 (t, J = 3.9 Hz, 1H), 3.65 (s, 3H), 2.30 (m, 2H), 1.90 (m, 2H), 1.85–1.25 (m, 8H), 0.80 (t, J = 7.5 Hz, 3H), 0.01 (s, 9H).

(+)-(*S*)-1-Ethyl-2-oxo-3-cyclohexene-1-propanoic Acid Methyl Ester (38). To a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (80 g, 0.352 mol) and 2,6-lutidine (20 g, 0.187 mol) in dry toluene (1 L) was added dropwise silyl enol ether **37** (75 g, 0.264 mol) in toluene (300 mL). The reaction mixture was stirred vigorously at 20 °C. After 48 h additional portions of DDQ (40 g, 0.17 mol) and 2,6-lutidine (10 g, 0.094 mol) were added, and stirring was continued for 48 h until TLC analysis (hexane–AcOEt, 4:1) revealed the disappearance of starting material (R_f 0.8). The reaction mixture was diluted with hexane (1 L) and filtered through a large pad of silica, and the black solid was repeatedly washed with hexane (2 L). The filtrate was concentrated under vacuum to ca. 800 mL and the residual solution filtered through a new pad of silica. The solid was washed with hexane (1 L) and the filtrate concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–AcOEt, 3:1, R_f 0.45) to give enone **38** as a colorless oil (44.3 g, 80%). Distillation provided an analytical sample: bp 100–105 °C (0.05 Torr); $[\alpha]^{22}_D$ +23.8° (EtOH, c = 7); IR (film, cm^{-1}) 1730, 1660, 1600, 1425; ^1H NMR (250 MHz) δ 6.86 (dt, J = 10.0, 3.9 Hz, 1H), 5.89 (dt, J = 10.0, 2.0 Hz, 1H), 3.65 (s, 3H), 2.40 (m, 2H), 2.30–2.21 (m, 2H), 1.88 (m, 4H), 1.57 (m, 2H), 0,83 (t, J = 7.46 Hz, 3H); ^{13}C NMR (20 MHz) δ 202.8 (C), 174.1 (C), 148.5 (CH), 128.8 (CH), 51.6 (CH_3), 47.0 (C), 30.4 (CH_2), 28.8 (CH_2), 28.6 (CH_2), 26.5 (CH_2), 22.9 (CH_2), 8.1 (CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62. Found: C, 68.39; H, 8.54.

(–)-(*S*)-1-Methyl-2-oxo-3-phenyl-3-cyclohexene-1-propanoic Acid Methyl Ester (35). To a solution of enone **33**[15] (0.5 g, 2.55 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dropwise a solution of bromine (0.42 g, 2.6 mmol) in CH_2Cl_2 (2 mL). After the addition was complete, triethylamine (0.44 g, 4.34 mmol) was added and the stirring was maintained for 2 h at room temperature. The mixture was diluted with ether (50 mL), filtered through a small pad of silica gel, and concentrated in vacuo to give bromo enone **34** (0.65 g, 92%) which was used directly in the next step without further purification: IR (film, cm^{-1}) 1730, 1660, 1435; ^1H NMR (90 MHz) δ 7.35 (t, J = 4.5 Hz, 1H), 3.66 (s, 3H), 2.60–1.70 (m, 8H), 1.16 (s, 3H).

A mixture of bromo enone **34** (307 mg, 1.1 mmol), phenyltributyltin (1.01 g, 2.75 mmol), and $Pd(Ph_3)_4$ (38 mg, 0.033 mmol, 3 mol %) in THF (5 mL) was refluxed for 5 h, after which time another portion of $Pd(Ph_3)_4$ (38 mg) was added and the reflux was maintained for 18 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was directly chromatographed over silica gel (hexane–AcOEt, 1:2, R_f 0.40) to yield enone **35** as a pale yellow oil (210 mg, 69%): $[\alpha]^{22}_D$ –23.3° (EtOH, c = 3.3); IR (film, cm^{-1}) 1735, 1670, 1440; ^1H NMR (300 MHz) δ 7.30 (m, 5H), 6.90 (t, J = 4.12 Hz, 1H), 3.65 (s, 3H), 2.54 (m, 2H), 2.45–2.25 (m, 2H), 2.06–1.82 (m, 4H), 1.17 (s, 3H); ^{13}C NMR (62.9 MHz) δ 201.5 (C), 173.9 (C), 145.7 (CH), 138.7 (C), 136.8 (C), 128.6 (2CH), 127.8 (2CH), 127.4 (CH), 51.5 (CH_3), 44.0 (C), 33.5 (CH_2), 31.4 (CH_2), 29.1 (CH_2), 23.1 (CH_2), 21.7 (CH_3). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.88; H, 7.36.

(1*S*,3*R*,4*R*)-1-Ethyl-2-oxo-3,4-epoxycyclohexane-1-propanoic Acid Methyl Ester and (1*S*,3*S*,4*S*)-1-Ethyl-2-oxo-3,4-epoxycyclohexane-1-propanoic Acid Methyl Ester (39). To a stirred solution of enone **38** (150 mg, 0.71 mmol) in methanol (4 mL) was added at 0 °C 30% hydrogen peroxide (0.5 mL, 4.4 mmol) followed by 20% aqueous NaOH (0.01 mL, 0.05 mmol). After 15 min, the reaction was quenched by addition of one drop of acetic acid. The reaction mixture was poured into brine and extracted with ether (3 × 10 mL). The combined organic layers were washed with sodium bisulfite, dried, and concentrated. The resulting oily residue was chromatographed on silica gel (hexane–AcOEt, 2:1, R_f 0.54) to give keto epoxide **39** as a 3:2 mixture of stereoisomers (153 mg, 95%): IR (film, cm^{-1}) 1740, 1705, 1439,-1198; ^1H NMR (200 MHz) δ 3.62 (s, 3H), 3.52 (m, 1H), 3.14 (d, J = 3.7 Hz, 1H), 2.30–1.20 (m, 10 H), 0.79 (t, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz) (only the major isomer is described) δ 208.1 (C), 173.8 (C), 54.3 (CH), 53.4 (CH), 51.5 (CH_3), 47.7 (C), 29.9 (CH_2), 29.0 (CH_2), 28.2 (CH_2), 22.5 (CH_2), 20.2 (CH_2), 7.6 (CH_3). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 7.90. Found: C, 63.65; H, 7.85.

(1*S*,4*R*)-1-Ethyl-2-oxo-4-hydroxycyclohexane-1-propanoic Acid Methyl Ester and (1*S*,4*S*)-1-Ethyl-2-oxo-4-hydroxycyclohexane-1-propanoic Acid Methyl Ester (40). In a 25- mL round-bottom flask under nitrogen atmosphere was placed diphenyl diselenide (469 mg, 1.50 mmol) in anhydrous EtOH (7 mL). Sodium borohydride (115 mg, 3.0 mmol) was added by portion, the initially yellow color faded out, and the colorless solution obtained was stirred for 5 min. Acetic acid (11 μL) was added followed by epoxy ketone **39** (220 mg, 0.97 mmol) in ethanol (1 mL). The resulting solution was stirred for 3 h at

room temperature. The reaction was quenched by addition of 1 N HCl (10 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were dried, and the solvent was removed under vacuo. Purification was accomplished by chromatography on silica gel (hexane–AcOEt, 1:2, R_f 0.53) to provide β-hydroxy ketone **40** as a 3:2 mixture of stereoisomers (162 mg, 74%). Distillation afforded an analytical sample: bp 120–130 °C (0.5 Torr); IR (film, cm^{-1}) 3450, 1740, 1710; ^1H NMR (200 MHz) δ 4.15 and 4.05 (two m, 1H), 3.62 (s, 3H), 2.82 (broad s, OH), 2.61 (ddd, J = 14.5, 3.6, 3.1 Hz, 1H), 2.47–2.34 (m, 1H), 2.29–1.33 (m, 10H), 0.73 (t, J = 7.5 Hz, 3H), ^{13}C NMR (50 MHz) δ 213.2 and 212.8 (C), 174.2 and 174.1 (C), 69.5 and 69.3 (CH), 51.6 (CH_3), 50.2 and 50.0 (C), 47.5 and 47.1 (CH_2), 29.8 and 29.5 (CH_2), 28.6 ($2CH_2$), 28.3 and 28.2 (CH_2), 26.9 and 26.7 (CH_2), 7.7 and 7.4 (CH_3). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.88. Found: C, 62.94; H, 8.82.

(1*R*,4*R*)-1-Ethyl-2-oxo-4-(phenylthio)cyclohexane-1-propanoic Acid Methyl Ester and (1*R*,4*S*)-1-Ethyl-2-oxo-4-(phenylthio)cyclohexane-1-propanoic Acid Methyl Ester (41). To a solution of enone **38** (44 g, 0.21 mol) in CH_2Cl_2 (100 mL) containing triethylamine (2.2 g, 0.02 mol) was added dropwise, at 0 °C, thiophenol (24.2 g, 0.22 mol). The reaction mixture was stirred for 3 h at 0 °C, and acetic acid (1.2 g, 0.02 mol) was then added. The reaction mixture was concentrated in vacuo and the residue chromatographed on silica gel, eluting with hexane–AcOEt (10:1) to get rid of the excess of thiophenol and then with hexane–AcOEt (4:1) (R_f 0.42) to give sulfide **41** as an equimolar mixture of stereomers (62.5 g, 93%); IR (film, cm^{-1}) 1730, 1700, 1585; ^1H NMR (200 MHz) δ 7.11–6.50 (m, 5H), 3.58 and 3.56 (s, 3H), 3.50–3.10 (m, 1H), 2.65–1.30 (m, 12H), 0.68 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz) δ 211.2 (C), 174.1 and 173.8 (C), 133.4 (C), 133.1 (CH), 133.0 (CH), 129.1 (2CH), 127.7 (CH), 51.6 (CH_3), 50.3 and 50.2 (C), 46.3 and 46.2 (CH), 44.9 and 44.5 (CH_2), 33.1 and 32.6 (CH_2), 29.1 and 28.7 (CH_2), 28.6 (CH_2), 27.2 and 27.1 (CH_2), 26.9 and 26.7 (CH_2), 7.7 (CH_3).

(+)-(*R*)-1-Ethyl-2-oxo-4-(phenylthio)-3-cyclohexene-1-propanoic Acid Methyl Ester (42). To a solution of thiophenol free thioether **41** (52 g, 0.162 mol) in carbon tetrachloride (300 mL) was added in small portions, at 0 °C, *N*-chlorosuccinimide (26 g, 0.194 mol). The reaction mixture was stirred for 5 h at 0 °C, filtered through Celite, and concentrated in vacuo. The crude residue was chromatographed on silica gel (hexane–AcOEt, 4:1, R_f 0.42) to afford thioether **42** (42.5 g, 82%). $[\alpha]^{22}_D$ + 16.2° (EtOH, c = 4.7); IR (film, cm^{-1}) 1740, 1652, 1582, 1475, 1430; ^1H NMR (200 MHz) δ 7.43 (s, 5H), 5.38 (s, 1H), 3.64 (s, 3H), 2.56 (t, J = 6.1 Hz, 2H), 2.20 (m, 2H), 2.10–1.80 (m, 4H), 1.56 (m, 2H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR (20 MHz) δ 199.9 (C), 173.8 (C), 163.9 (C), 135.4 (2CH), 130.0 (CH), 129.8 (2CH), 128.1 (C), 120.1 (CH), 51.4 (CH_3), 46.2 (C), 30.7 (CH_2), 28.8 ($2CH_2$), 26.8 ($2CH_2$), 8.0 (CH_3); MS *m/e* 318 ($M^{\cdot+}$, 8), 290 (18), 232 (38), 176 (100), 147 (60). Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.89; H, 6.96; S,10.06. Found: C, 68.05; H, 6.91; S, 10.13.

(+)-(*S*)-1-Ethyl-2-oxo-4-methoxy-3-cyclohexene-1-propanoic Acid Methyl Ester (43). A solution of thioether **42** (42.3 g, 0.133 mol) in dry methanol (100 mL) was added dropwise with stirring to a solution of sodium methoxide in methanol (from 9.2 g of sodium (0.40 mol) and 300 mL of methanol) and the reaction mixture was refluxed for 2 h. After the mixture was cooled to 0 °C, acetic acid (30 g, 0.5 mol) was added and the mixture concentrated in vacuo. The crude residue was diluted with water (200 mL) and extracted with ether (3 × 200 mL). The combined ether extracts were dried and evaporated to give a yellow oil which was purified by flash chromatography on silica gel. Elution with hexane removed thiophenol, and then further elution (hexane–AcOEt, 2:1, R_f 0.38) gave enone **43** (25.4 g, 80%). Distillation afforded an analytical sample: bp 110 °C (0.05 Torr); $[\alpha]^{22}_D$ +19.4° (EtOH, c = 8); IR (film, cm^{-1}) 1735, 1650, 1610, 1450, 1380; ^1H NMR (200 MHz) δ 5.26 (s, 1H), 3.69 (s, 3H), 3.64 (s, 3 H), 2.46 (t, J = 6.3 Hz, 2H), 2.02 (m, 2H), 1.86 (m, 4H), 1.56 (m, 2H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz) δ 201.8 (C), 176.0 (C), 173.6 (C), 100.8 (CH), 55.2 (CH_3), 51.0 (CH_3), 45.4 (C), 28.7 (CH_2), 28.6 (CH_2), 28.4 (CH_2), 26.6 (CH_2), 25.0 (CH_2), 7.7 CH_3). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.94; H, 8.22.

(+)-(*S*)-1-Ethyl-2,4-dioxocyclohexane-1-propanoic Acid Methyl Ester (19). A mixture of compound **43** (23 g, 96 mmol), 1 N HCl (100 mL), and THF (200 mL) was allowed to stand for 3 h. The reaction mixture was concentrated and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine and dried. Evaporation in vacuo left a yellow solid which was recrystallized from ether to give optically pure dione **19** (16.1 g, 74%) as a white solid: mp 93 °C; $[\alpha]^{20}_D$ +34.1° (EtOH, c = 3.6); IR (KBr, cm^{-1}) 2600, 1730, 1600, 1580, 1500; ^1H NMR (200 MHz) enol form δ 7.8 (br s, 1H), 5.46 (s, 1H), 3.67 (s, 3H), 2.47 (t, J = 6.4 Hz, 2H), 2.30 (m, 2H), 2.0–1.5 (m, 6H), 0.87 (t, J = 7.4 Hz, 3H); diketone form δ 3.66 (s, 3H), 3.48 (d, J = 17.8 Hz, 1H), 3.38 (d, J = 17.8 Hz, 1H), 2.63 (dd, J = 6.5, 7.3 Hz, 2H), 2.30 (m, 2H), 2.0–1.5 (m, 6H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (20 MHz) enol form δ 190.2 (C), 185.8 (C), 174.6 (C), 104.2 (CH), 51.8 (CH_3), 44.3 (C), 29.8 (CH_2), 29.2 ($2CH_2$), 27.9 ($2CH_2$), 8.3 (CH_3); diketone form δ 207.1 (C), 204.3 (C), 173.8(C), 56.4(CH_2), 51.8 (CH_3), 49.8 (C), 29.1 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 7.8 (CH_3). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.94; H, 7.99.

(+)-(*S*)-1-Ethyl-2-oxo-4-[(2-iodophenyl)amino]-3-cyclohexene-1-propanoic Acid Methyl Ester (44). 2-Iodoaniline (13.14 g, 60 mmol) was added to a solution of dione **19** (12.8 g, 56.6 mmol) and *p*-toluenesulfonic acid (0.4 g, 2 mmol) in toluene (250 mL). The reaction mixture was refluxed for 5 h with the use of a Dean-Stark trap. After cooling, the solution was diluted with ether, washed with aqueous sodium carbonate, and dried. Concentration in vacuo afforded a yellow solid (22.7 g, 94%). Recrystallization from ether provided an analytical sample of **44** as white crystals: mp 100 °C; $[\alpha]^{20}_D$ +1.4° (EtOH, c = 4.0); IR (KBr, cm^{-1}) 3200, 1740, 1600, 1585, 1570, 1510; ^1H NMR (250 MHz) δ 7.79 (dd, J = 8.2, 1.1 Hz, 1H), 7.30–7.20 (m, 2H), 6.85 (ddd, J = 8.0, 6.4, 2.6 Hz, 1H), 6.50 (br s, 1H), 5.08 (s, 1H), 3.58 (s, 3H), 2.53 (t, J = 6.3 Hz, 2H), 2.25 (m, 2H), 1.95–1.70 (m, 4H), 1.53 (m, 2H), 0.79 (t, J = 7.4 Hz, 3H); ^{13}C NMR (62.9 MHz) δ 200.9 (C), 174.3 (C), 159.7(C), 139.5 (CH and C), 129.0 (CH), 127.5 (CH), 126.4 (CH), 99.9 (CH), 96.2 (C), 51.3 (CH_3), 45.2 (C), 29.4 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.4 (CH_2), 25.7 (CH_2), 8.1 (CH_3); MS *m / e* 427 ($M^{\cdot+}$, 5), 399 (26), 341 (90), 320 (30), 285 (20), 158 (27), 130 (100). Anal. Calcd for $C_{18}H_{22}NO_3I$: C, 50.59; H, 5.19; N, 3.28; I, 29.70. Found: C, 50.77; H, 5.29; N, 3.16; I, 29.41.

(−)-(*S*)-[3-Ethyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl]propanoic Acid Methyl Ester (18). In a nitrogen-flushed 500-mL two-necked flask equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser was placed sodium hydride (50% in mineral oil, 5.1 g, 0.106 mol). Hexane (20 mL) was added, and the dispersion was stirred for 2 min. The NaH was allowed to settle, and the supernatant liquid was removed with syringe. The washing operation was repeated with an additional 20-mL portion of hexane, and HMPA (50 mL) was added to the reaction flask. A solution of iodoenamine ketone **44** (22.7 g, 53.2 mmol) in HMPA (200 mL) was added dropwise, and stirring was continued until H_2 evolution had ceased. Cuprous iodide (20.2 g, 0.106 mol) was then added in one portion, and the resulting dark mixture was heated at 120 °C for 2 h. After cooling, the reaction mixture was poured into 1 N aqueous HCl and filtered with suction through Celite. The filtrate was extracted with ether (4 × 400 mL), and the combined organic layers were washed with saturated aqueous ammonium chloride, dried, and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane–AcOEt 1:1, R_f 0.72) to give carbazolone **18** as a white solid (13.4 g, 84%), and recrystallization from hexane–AcOEt (2:1) afforded white crystals: mp 125–126 °C; $[\alpha]^{20}_D$ −17.6° (EtOH, c = 4.3); IR (KBr, cm^{-1}) 3200, 1740, 1610, 1580; ^1H NMR (250 MHz) δ 10.46 (s, 1H), 8.28 (m, 1H), 7.45 (m, 1H), 7.25 (m, 2H), 3.64 (s, 3H), 3.08 (t, J = 6.0 Hz, 2H), 2.50–2.35 (m, 2H), 2.25–1.60 (m, 6H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (62.9 MHz) δ 198.2 (C), 174.3 (C), 150.5 (C), 136.5 (C), 125.2 (C), 123.0 (CH), 122.1 (CH), 120.9 (CH), 111.9 (C), 111.4 (CH), 51.4 (CH_3), 47.4 (C), 31.4 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.5 (CH_2), 20.0 (CH_2), 8.4 (CH_3); MS *m/e* 299 ($M^{\cdot+}$, 14), 271 (8), 268 (6), 213 (26), 198 (14), 157 (100), 129 (38). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.13; H, 6.98; N, 4.52.

(−)-(*S*)-3-Ethyl-3-(3-hydroxypropyl)-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (45). A stirred solution of carbazolone **18** (13.6 g, 45.5 mmol) in THF (100 mL) under a nitrogen atmosphere

was cooled to −40 °C, and a solution of 1 N lithium triethylborohydride in THF (150 mL, 0.15 mol) was added dropwise. After 1 h, absolute ethanol (150 mL) was carefully added followed with 6 N aqueous NaOH (75 mL, 0.45 mmol). The mixture was cooled in an ice–water bath, and 30% hydrogen peroxide (46 mL, 0.45 mmol) was added. The resulting solution was stirred at room temperature for 15 h, and saturated aqueous ammonium chloride (200 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 200 mL), and the combined organic extracts were washed with brine, dried, and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–AcOEt, 1:4, R_f 0.55) to give alcohol **45** (10.9 g, 88%) as a white solid. Recrystallization from AcOEt–hexane (1:1) gave an analytical sample: mp 145–146 °C; $[\alpha]^{20}_D$ −23.2° (MeOH, c = 2.5); IR (KBr, cm^{-1}) 3360, 3200, 1610, 1580; ^1H NMR (acetone-d_6, 250 MHz) δ 10.8 (s, 1H), 8.15 (m, 1H), 7.40 (m, 1H), 7.15 (m, 2H), 3.64 (t, J = 5.1 Hz, OH), 3.50 (m, 2H), 3.06 (t, J = 6.4 Hz, 2H), 2.11 (t, J = 6.3 Hz, 2H), 1.85–1.45 (m, 6H), 0.87 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.9 MHz, acetone-d_6) δ 198. 3 (C), 150.9 (C), 137.6 (C), 126.7 (C), 123.3 (CH), 122.2 (CH), 121.8 (CH), 112.6 (C), 112.0 (CH), 63.2 (CH_2), 48.4 (C), 32.3 (CH_2), 31.7 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 20.6 (CH_2), 8.9 (CH_3); MS m/e 271 ($M^{\bullet+}$, 12), 243 (10), 214 (11), 213 (56), 198 (24), 158 (12), 157 (100), 129 (48). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16. Found: C, 75.09; H, 8.25; N, 4.99.

(+)-(*R*)-3-(3-Azidopropyl)-3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-1,2,3,9-tetrahydro-4*H*-carbazol-4-one (46). A mixture of alcohol **45** (10.6 g, 39.1 mmol), triethylamine (5.9 g, 58 mmol), and 4-(dimethylamino)pyridine (0.2 g, 1.6 mmol) in 200 mL of a 5:1 mixture of CH_2Cl_2–THF was cooled to 0 °C. Methanesulfonyl chloride (5.38 g, 47 mmol) was added dropwise via syringe and the resulting solution stirred for 2 h. The reaction mixture was partitioned between 0.5 N HCl and CH_2Cl_2. The aqueous layer was extracted twice with CH_2Cl_2 and successively washed with saturated sodium bicarbonate and brine. The organic extracts were dried and evaporated under reduced pressure leaving 13.5 g (99%) of crude mesylate as a yellow oil. The latter compound was taken up in dry DMF (100 mL), sodium azide (5.2 g, 80 mmol) was added, and the reaction mixture was heated at 80 °C for 2 h. The mixture was poured into water (150 mL) and extracted with ether (4 × 100 mL). The combined organic layers were dried and concentrated in vacuo to give the crude azidoindole (9.84 g, 86%) which was used directly in the next step. A mixture of the above azide (9.84 g, 33.2 mmol), tetrabutylammonium hydrogenosulfate (0.7 g, 2 mmol), and (*p*-methoxyphenyl)sulfonyl chloride (8.25 g, 39.9 mmol) in CH_2Cl_2 (120 mL) was treated with 50% aqueous NaOH (20 mL). The resulting two-phase mixture was stirred for 2 h and poured into water. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extracts were dried and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (hexane–AcOEt, 1:2, R_f 0.65) to afford protected azide **46** as an oil which crystallized upon standing (13.5 g, 74% overall from **45**); mp 96–98 °C (MeOH–AcOEt); $[\alpha]^{20}_D$ +7.2° (EtOH, c = 3.6); IR (KBr, cm^{-1}) 2100, 1655 1590, 1575; ^1H NMR (250 MHz) δ 8.27 (m, 1H), 8.14 (m, 1H), 7.82 (d, J = 9.0 Hz, 2H), 7.32 (m, 2H), 6.90 (d, J = 9.0 Hz, 2H), 3.75 (s, 3H), 3.35 (t, J = 6.0 Hz, 2H), 3.23 (t, J = 6.2 Hz, 2H), 2.09 (t, J = 6.1 Hz, 2H), 1.8–1.5 (m, 6H), 0.85 (t, J = 7.4 Hz, 3H); ^{13}C NMR (62.9 MHz) δ 198.5 (C), 164.1 (C), 148.9(C), 136.0 (C), 129.6 (C), 128.7 (2CH), 126.1 (C), 125.0 (CH), 124.5 (CH), 121.7 (CH), 116.3 (C), 114.6 (2CH), 113.6 (CH), 55.5 (CH_3), 51.7 (CH_2), 47.5 (C), 31.0 (CH_2), 30.7 (CH_2), 26.8 (CH_2), 23.4 (CH_2), 21.4 (CH_2), 8.1 (CH_3). Anal. Calcd for $C_{24}H_{26}N_4O_4S$: C, 61.78; H, 5.61. Found: C, 61.48; H, 5.91.

(*R*)-4a-Ethyl-2,3,4,4a,5,6-hexahydro-7-[(4-methoxyphenyl)sulfonyl]-7*H*-pyrido[3,2-*c*]carbazole (47). Procedure A. A solution of azide **46** (800 mg, 1.71 mmol) and triphenylphosphine (524 mg, 2 mmol) in THF (5 mL) was stirred for 18 h at room temperature. The reaction mixture was next refluxed for 6 h. After cooling, the reaction mixture was concentrated in vacuo and the residue was purified by chromatography on alumina (Al_2O_3, activity II, 70–230 mesh, hexane–AcOEt, 5:1, R_f 0.40) to afford imine **47** as an amorphous white solid (0.50 g, 69%).

Procedure B. Catalytic hydrogenation of **46** (500 mg, 1.07 mmol) using 10% Pd/C (50 mg) and H_2 (5 atm) in EtOH (5 mL) containing AcOH (0.5 mL) at 20 °C for 24 h afforded after chromatography on alumina pure imine **47** (410 mg, 0.91%): $[\alpha]^{20}_D$ +82.8 (MeOH, c = 2.7); IR (film, cm^{-1}) 1629, 1596, 1497; ^1H NMR (C_6D_6, 200 MHz) δ 8.88 (m, 1H), 8.50 (m, 1H), 7.62 (d, J = 8.9 Hz, 2H), 7.23 (m, 2H), 6.21 (d, J = 8.9 Hz, 2H), 3.93 (dd, J = 7.9, 5.2 Hz, 1H), 3.74–3.57 (m, 1H), 3.33–2.95 (m, 2H), 2.93 (s, 3H), 1.67–0.90 (m, 8H), 0.56 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, C_6D_6) δ 167.1 (C), 163.9 (C), 141.1 (C), 137.7 (C), 131.4 (C), 128.6 (2CH), 128.2 (CH), 124.7 (CH), 124.3 (CH), 123.7 (CH), 118.4 (C), 114.4 (2CH), 114.3 (CH), 55.1 (CH_3), 50.0 (CH_2), 36.7 (C), 32.5 (CH_2), 29.1 (CH_2), 24.7 (CH_2), 22.6 (CH_2), 19.2 (CH_2), 7.8 (CH_3); MS m/e 422 ($M^{\bullet+}$, 100), 394 (8), 251 (95), 223 (32), 155 (41); HRMS m/e calcd for $C_{24}H_{26}N_2O_3S$ 422.1664, found 422.1665.

(+)-(4a*R*,11c*S*)-4a-Ethyl-*trans*-2,3,4,4a,5,6,7,11c-octahydro-7-[(4-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole-1-carboxylic Acid Methyl Ester (49). To a stirred solution of imine **47** (210 mg, 0.48 mmol) in methanol (4 mL) containing AcOH (1 mL) was added by portion sodium cyanoborohydride (320 mg, 5.09 mmol). The reaction mixture was stirred for 1 h at 20 h, and aqueous sodium carbonate was added. The solution was extracted with CH_2Cl_2 (3 × 20 mL) and washed with brine. The organic extracts were dried and evaporated under reduced pressure leaving 145 mg (69%) of crude amine **48** as an oil which was taken up in CH_2Cl_2 (20 mL). The solution was cooled to 0 °C, and methyl chloroformate (470 mg, 5.0 mmol) and 1 N NaOH (6 mL, 6 mmol) were added simultaneously with rapid stirring. After 30 min the organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Chromatography on silica gel (hexane–AcOEt, 2:1, R_f 0.39) gave **49** (190 mg, 79%) as a foam: IR (film, cm^{-1}) 1695, 1579, 1471, 1451; $[\alpha]^{20}_D$ +38.4 (EtOH, c = 1.1); ^1H NMR (200 MHz) δ 8.09 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.65–7.10 (m, 3H), 6.81 (d, J = 8.8 Hz, 2H), 4.48 (dd, J = 14.5, 4.6 Hz, 1H), 4.43 (s, 3H), 3.78 (s, 3H), 3.0–2.9 (m, 2H), 2.75 (s, 3H), 1.96–1.16 (m, 8H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz) δ 163.3 (C), 157.2 (C), 136.3 (C), 133.4 (C), 130.7 (C), 130.1(C), 128.7 (2CH), 123.6 (CH), 123.4 (CH), 119.5 (CH), 119.3 (C), 114.5 (CH), 113.8 (2CH), 64.0 (CH_2), 55.4 (CH_3), 51.0 (CH_3), 48.9 (CH_2), 37.5 (C), 33.6 (CH_2), 31.9 (CH_2), 21.5 (CH_2), 21.1 (CH_2), 17.5 (CH_2), 7.2 (CH_3); MS m/e 482 ($M^{\bullet+}$, 22), 383 (12), 310 (60), 279 (100), 250 (35), 207 (40). No satisfactory microanalytical data could be obtained for that uncrystalline material.

(3*R*,4*R*)-3-(3-Azidopropyl)-3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-1*H*-carbazol-4-ol and (3*R*,4*S*)-3-(3-Azidopropyl)-3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-1*H*-carbazol-4-ol (50). To a refluxing solution of carbazolone **46** (2.50 g, 5.36 mmol) in ethanol (50 mL) was added portionwise 2.03 g (53.6 mmol) of sodium borohydride. The mixture was refluxed until all the starting material was consumed (30 min). After being cooled to 20°C, the solution was poured into saturated aqueous ammonium chloride (50 mL) and extracted with AcOEt (3 × 50 mL). The combined organic extracts were dried, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (hexane–AcOEt, 2:1, R_f 0.55) to afford a mixture of epimeric alcohols **50** in a 1:1 ratio as an amorphous white solid (2.30 g, 92%): IR (KBr, cm^{-1}) 3400, 2100, 1590, 1575, 1490; ^1H NMR (200 MHz) δ 8.03 (d, J = 7.8 Hz, 1H), 7.60 (d, J = 8.9 Hz, 2H), 7.47 (m, 1H), 7.15 (m, 2H), 6.73 (d, J = 8.9 Hz, 2H), 4.39 (m, 1H), 3.66 (s, 3H), 3.35–2.90 (m, 3H), 2.80–2.55 (m, 1H), 1.90–0.95 (m, 8H), 0.84 and 0.74 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz) δ 163.7 (C), 136.6 (C), 136.5 (C), 130.4 (C), 129.3 (C), 128.5 (2CH), 124.2 (CH), 123.4 (CH), 119.2 (C), 118.4 (CH), 114.4 (2CH), 67.7 and 67.5 (CH), 55.6 (CH_3), 52.2 and 52.1 (CH_2), 39.1 and 39.0 (C), 29.6 and 27.7 (CH_2), 27.3 and 26.9 (CH_2), 25.2 and 23.3 (CH_2), 23.4 and 23.3 (CH_2), 21.7 (CH_2), 7.9 and 7.2 (CH_3). No satisfactory microanalytical data could be obtained for that uncrystalline material.

(3*S*,4*R*)-*N*-[3-[3-Ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-4-hydroxy-1*H*-carbazol-3-yl]propyl]carbamic Acid Methyl Ester and (3*S*,4*S*)-*N*-[3-[3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-4-hydroxy-1*H*-carbazol-3-yl]propyl]carbamic Acid Methyl Ester (51). A mixture of azide–alcohol **50** (250 mg, 0.53 mmol) and triphenylphosphine (280 mg, 1.07 mmol) in THF (6 mL) was stirred

for 18 h at room temperature. Water (0.25 mL) was added and the solution stirred for a further 12 h. The reaction mixture was concentrated in vacuo, the residue was taken up in CH_2Cl_2 (20 mL), and the solution was cooled to 0 °C. Methyl chloroformate (470 mg, 5.0 mmol) and 1 N NaOH (6 mL, 6 mmol) were added simultaneously with rapid stirring. After 30 min, the organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried and concentrated in vacuo. Chromatography on silica gel (hexane–AcOEt, 1:1, R_f 0.37 and 0.25) gave **51** as a mixture of isomers (174 mg, 65%): IR (film, cm^{-1}) 3428, 1705, 1597, 1532; ^1H NMR (200 MHz) δ 8.04 (d, J = 7.6 Hz, 1H), 7.61 (d, J = 8.8 Hz, 2H), 7.60–7.30 (m, 1H), 7.15 (m, 2H), 6.76 (m, 2H), 5.02 and 4.78 (two br t, NH), 4.40 (m, 1H), 3.67 (s, 3H), 3.61 (m, 2H), 3.52 (br s, 3H), 3.22–2.60 (m, 4H), 2.35 and 2.05 (two m, OH), 1.70–0.80 (m, 6H), 0.82 and 0.72 (two t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz) δ 163.5 (C), 157.1 and 156.9 (C), 136.4 (C), 136.3 (C), 132.0 and 131.8 (CH), 130.2 (C), 129.2 (C), 128.4 (2CH), 124.0 (CH), 123.3 (CH), 119.3 and 119.1 (C), 118.5 and 118.3 (CH), 114.3 (2CH), 67.7 and 66.5 (CH), 55.5 (CH_3), 51.8 (CH_3), 41.5 (CH_2), 38.9 and 38.8 (C), 29.4 and 27.7 (CH_2), 27.2 and 26.8 (CH_2), 25.0 and 24.2 (CH_2), 23.1 and 22.9 (CH_2), 21.8 (CH_2), 7.9 and 7.2 (CH_3). No satisfactory microanalytical data could be obtained for that uncrystalline material.

(+)-(4a*R*,11c*R*)-4a-Ethyl-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7-[(4-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole-1-carboxylic Acid Methyl Ester (53). To a solution of carbamate **51** (158 mg, 0.32 mmol) in anhyd. CH_2Cl_2 (20 mL) at 0 °C was added trifluoroacetic acid (110 mg, 0.96 mmol). After 5 min TLC indicated that both isomers were transformed into a less polar compound. The reaction mixture was poured into saturated $NaHCO_3$ solution (5 mL). The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–AcOEt, 2:1, R_f 0.5) to give **53** (140 mg, 92%) as a pale yellow foam that crystallized upon standing: mp 147–149 °C (ether); $[\alpha]^{20}_D$ +112.3° (EtOH, c = 3); IR (KBr, cm^{-1}) 1695, 1597, 1451; ^1H NMR (200 MHz) due to the presence of amide bond rotamers, two distinct sets of NMR signals in a ratio of 1:1 were observed for certain protons; δ 8.15 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.30–7.10 (m, 3H), 6.84 (d, J = 8.8 Hz, 2H), 5.24 and 5.08 (two br s, 1H), 4.10–3.80 (m, 1H), 3.84 and 3.81 (two s, 3H), 3.79 (s, 3H), 3.15–2.85 (m, 2H), 2.21 (m, 1H), 1.85–1.20 (m, 8H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR (50 MHz) δ 163.4 (C), 156.5 (C), 136.6 (C), 135.9 (C), 130.4 (C), 128.5 (C), 128.2 (2CH), 123.8 (CH), 123.5 (CH), 118.7 (CH), 116.7 and 116.5 (C), 114.2 (3CH), 55.4 (CH_3), 55.5 and 54.2 (CH), 52.6 (CH_3), 39.3 (CH_2), 34.8 (C), 31.2 (CH_2), 27.9 (CH_2), 25.8 (CH_2), 21.2 (CH_2), 20.7 and 20.2 (CH_2), 7.5 (CH_3). Anal. Calcd for $C_{26}H_{30}N_2O_5S$: C, 64.71; H, 6.26; N, 5.80. Found: C, 64.66; H, 6.36; N, 5.76.

(3*R*,4*R*)-2-(Phenylthio)-*N*-[3-[3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-4-hydroxy-1*H*-carbazol-3-yl]propyl]acetamide and (3*R*,4*S*)-2-(Phenylthio)-*N*-[3-[3-ethyl-9-[(4-methoxyphenyl)sulfonyl]-2,3,4,9-tetrahydro-4-hydroxy-1*H*-carbazol-3-yl]propyl]acetamide (57). A mixture of azide **50** (2.30 g, 4.91 mmol) and triphenylphosphine (2.57 g, 9.82 mmol) in THF (10 mL) was stirred for 18 h at room temperature. Water (0.25 mL) was added and the solution stirred for further 12 h. The reaction mixture was concentrated in vacuo, the residue was taken up in CH_2Cl_2 (30 mL), and the solution cooled to 0 °C. A solution of (phenylthio)acetyl chloride (1.8 g, 9.67 mmol) in CH_2Cl_2 (5 mL) and 1 N NaOH (20 mL, 20 mmol) were added simultaneously with rapid stirring. After 30 min the organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated in vacuo. Chromatography on silica gel (hexane–AcOEt, 1:4, R_f 0.50 and 0.22) gave amide **57** (1.80 g, 62%). Both TLC and ^1H NMR analysis indicated that compound **57** is an equimolar mixture of diastereomers. These derivatives show strong amide resonance giving rise to broad, and in some cases double, NMR signals: IR (neat, cm^{-1}) 3400, 1650, 1590; ^1H NMR (90 MHz) δ 8.18 (m, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.50 (m, 1H), 7.20 (m, 6H), 7.00 (m, 1H), 6.88 (d, J = 8.4 Hz, 2H), 4.42 (m, 1H) 3.75 (s, 3H), 3.57 (s, 2H), 3.40–2.60 (m, 4H), 1.90 (m, 1H), 1.75-0.80 (m, 6H), 0.73 (t, J = 7.3 Hz, 3H). No satisfactory microanalytical data could be obtained for that uncrystalline material, which was used directly in the next stage to give **58**.

(+)-(4a*R*,11c*S*)-4a-Ethyl-1-[(phenylthio)acetyl]-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7-[(4-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (58). To a solution of amide **57** (1.80 g, 3.04 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added trifluoroacetic acid (1.14 g, 10 mmol). After 15 min, TLC indicated that both isomers were transformed into tetracycle **58**. The reaction mixture was poured into saturated $NaHCO_3$ solution (20 mL), the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane–AcOEt, 1:1, R_f 0.68) to give **58** as a pale yellow foam (1.63 g, 93.5%): $[\alpha]^{20}_D$ +42.5° ($CHCl_3$, c = 3); IR (KBr, cm^{-1}) 1640, 1590, 1575, 1500, 1165; ^1H NMR (250 MHz) due to the presence of amide bond rotamers, two distinct sets of NMR signals in a ratio of 4:1 were observed; only the major conformer is described δ 8.14 (d, J = 8.35 Hz, 1H), 7.67 (d, J = 9.8 Hz, 2H), 7.52 (m, 2H), 7.35–7.16 (m, 5H), 7.02 (dt, J = 7.1, 1.0 Hz, 1H), 6.84 (d, J = 9.8 Hz, 2H), 5.67 (br s, 1H), 3.94 (s, 2H), 3.77 (s, 3H), 3.59 (br d, J = 14.1 Hz, 1H), 3.20–2.80 (m, 2H), 2.57 (ddd, J = 12.0, 12.0, 2.0 Hz, 1H), 1.85–1.20 (m, 8H), 0.82 (t, J = 7.40 Hz, 3H); ^{13}C NMR (62.8 MHz) δ 167.8 (C), 163.6 (C), 136.8 (C), 136.4 (C), 135.5 (C), 130.6 (C), 129.4 (2CH), 129.0 (2CH), 128.3 (C and 2CH), 126.6 (CH), 124.0 (CH), 123.5 (CH), 119.2 (CH), 116.5 (C), 114.4 (2CH), 114.3 (CH), 55.5 (CH_3), 51.9 (CH), 42.6 (CH_2), 36.7 (CH_2), 35.3 (C), 31.3 (CH_2), 28.0 (CH_2), 25.4 (CH_2), 21.5 (CH_2), 21.4 (CH_2), 7.56 (CH_3); MS m/e 574 ($M^{\cdot+}$, 13), 465 ($M^{\cdot+}$ – SPh, 54), 403 (100), 295 (48), 253 (85), 223 (28); HRMS m/e calcd for $C_{32}H_{34}N_2O_4S_2$: 574.1960, found 574.1958.

(4a*R*,11c*S*)-4a-Ethyl-1-[(phenylsulfinyl)acetyl]-*cis*-2,3,4,4a,5,6,7,11c-octahydro-7-[(4-methoxyphenyl)sulfonyl]-1*H*-pyrido[3,2-*c*]carbazole (17). To a solution of sulfide **58** (1.34 g, 2.33 mmol) in a mixture of THF (30 mL) and methanol (10 mL) was added a solution of sodium *m*-periodate (1.5 g, 7.0 mmol) in 20 mL of water. After the mixture was stirred for 24 h at room temperature, additional periodate was added (1 g, 4.6 mmol), and stirring was continued until none of the sulfide could be detected by TLC (48 h). The solution was filtered, concentrated in vacuo, and diluted with water. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic extrats were dried. Removal of the solvents and chromatography on silica gel (hexane–AcOEt, 1:4, R_f 0.52 and 0.47) afforded sulfoxide **17** (1.21 g, 88%) as a pale yellow foam: IR (film, cm^{-1}) 3062, 1633, 1596, 1579, 1498, 1446. This product was obtained as a mixture of diastereomers whose NMR spectrum was in addition complicated by the amide resonance. It was used directly in the next stage to give **60**.

(+)-2,3-Didehydro-1-[(4-methoxyphenyl)sulfonyl]aspidospermidin-10-one (60). According to the procedure of Magnus,[11a,b] in a 250-mL two-necked flask equipped with a distillation column was placed an ice-cooled solution of sulfoxide **17** (1.30 g, 2.30 mmol) in anhydrous CH_2Cl_2 (100 mL), and trifluoroacetic anhydride (1.3 g, 6.2 mmol) was added. After the mixture was stirred for 15 min no trace of the sulfoxides was detected by TLC; chlorobenzene (100 mL) was then added, and the reaction mixture was heated at 135 °C over 30 min during which time the CH_2Cl_2 was allowed to distill and heating was maintained for a further 2 h. After cooling, the solvents were removed under vacuum (50 °C, 0.05 Torr), and the residue was purified by chromatography on silica gel (hexane–AcOEt, 1:1) to give lactams **59** as a pale yellow foam (1.12 g, 89%). Spectroscopic data of **59** were fully consistent with those reported by Magnus.

A solution of **59** (1.12 g, 1.96 mmol) in DMF (25 mL) and ethanol (100 mL) was treated with an excess of W-2 Raney nickel . After it was stirred for 20 min, no starting material was detected by TLC. The mixture was filtered through a Celite pad and the solid washed well with ethanol, followed by CH_2Cl_2. Removal of the solvent and purification by chromatography on silica gel (AcOEt, R_f 0.31) gave **60** (0.57 g, 56% overall from **58**) as a colorless foam that crystallized upon standing: mp 132–133 °C; $[\alpha]^{20}_D$ +57.3° (EtOH, c = 4.4); IR (KBr, cm^{-1}) 1689, 1594, 1460, 1362, 1263, 1164; ^1H NMR (250 MHz) δ 7.81 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 9.0 Hz, 2H), 7.24 (dt, J = 7.0, 1.9 Hz, 1H), 7.11–7.02 (m, 2H), 6.82 (d, J = 9.0 Hz, 2H), 6.08 (dd, J = 8.6, 3.2 Hz, 1H), 4.18

(m, 1H), 3.76 (s, 3H), 3.55 (s, 1H), 2.69 (m, 1H), 2.16 (dd, J = 15.9, 3.2 Hz, 1H), 1.85–1.70 (m, 4H), 1.60–1.40 (m, 3H), 1.12 (m, 1H), 0.72 (m, 1H), 0.56 (t, J = 7.1 Hz, 3H); ^{13}C NMR (62.8 MHz) δ 170.0 (C), 163.6 (C), 144.2 (C), 140.0 (C), 137.5 (C), 129.1 (C), 128.9 (2CH), 128.3 (CH), 125.2 (CH), 121.2 (CH), 115.6 (CH), 114.1 (2CH), 110.3 (CH), 68.4 (CH), 55.4 (CH_3), 48.4 (CH_2), 45.2 (C), 39.9 (CH_2), 37.3 (C), 32.9 (CH_2), 29.2 (CH_2), 25.5 (CH_2), 19.7 (CH_2), 6.7 (CH_3); MS m/e 464 ($M^{\bullet+}$, 58), 326 (31), 294 (85), 293 (76), 265 (31), 262 (25), 156 (100); HRMS m/e calcd for $C_{26}H_{28}N_2O_4S$ 464.17698, found 464.17694.

(+)-Aspidospermidine (1b). To an ice-cooled stirred slurry of lithium aluminum hydride (1.2 g, 31.5 mmol) in THF (40 mL) was added a solution of lactam **60** (294 mg, 0.63 mmol) in THF (20 mL). The mixture was allowed to warm to 20 °C and stirred for 48 h. The reaction mixture was cooled to 0 °C and successively treated with water (1.2 mL), 15% aqueous NaOH (1.2 mL), and water (3.6 mL). The solid was removed by filtration and repeatedly washed with THF. The filtrate was concentrated in vacuo to gave a pale yellow oil. Chromatography on silica gel (AcOEt–MeOH, 20:1, R_f 0.30) led to a colorless oil that crystallized upon standing at −20 °C. Sublimation (110 °C, 0.05 Torr) gave (+)-aspidospermidine (**1b**) (122 mg, 68%): mp 117–118 °C; $[\alpha]^{20}_D$ +20.8° (EtOH, c = 2.4) (lit.[13a] mp 119–121 °C; $[\alpha]^{20}_D$ +21°); IR (KBr, cm^{-1}) 3306, 2950, 2795 and 2771 (Wenkert–Bohlmann bands), 1610, 1482, 1468, 1329, 1314, 1260; ^{1}H NMR (acetone-d_6, 200 MHz) δ 6.93 (d, J = 7.2 Hz, 1H), 6.77 (dt, J = 7.6, 1.2 Hz, 1H), 6.50–6.40 (m, 2H), 4.50 (broad s, NH), 3.28 (dd, J = 10.8, 6.2 Hz, 1H), 2.90 (m, 2H), 2.15–2.01 (m, 3H), 1.90–1.80 (m, 2H), 1.70–1.10 (m, 7H), 1.10–0.70 (m, 3H), 0.49 (t, J = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.3 (C), 135.4 (C), 127.1 (CH), 122.7 (CH), 118.9 (CH), 110.3 (CH), 71.2 (CH), 65.4 (CH), 53.8 (CH_2), 53.3 (C), 52.8 (CH_2), 38.6 (C), 35.7 (CH_2), 34.3 (CH_2), 29.9 (CH_2), 28.0 (CH_2), 22.9 (CH_2), 21.5 (CH_2), 6.7 (CH_3); MS m/e 282 ($M^{\bullet+}$, 14), 254 (10), 152 (5), 124 (100); HRMS m/e calcd for $C_{19}H_{26}N_2$ 282.2096, found 282.2097. Anal. Calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.66; H, 9.35; N, 9.98.

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