Methods for Indole Alkaloid Synthesis: A Study of the Compatibility of the Indole–2,3-Quinodimethane Strategy for the Synthesis of 16-Methoxy-Substituted Aspidosperma-Type Alkaloids. Synthesis of (+)- and (−)-16-Methoxytabersonine

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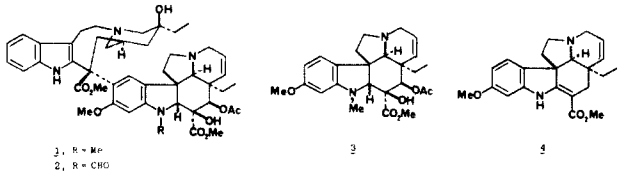
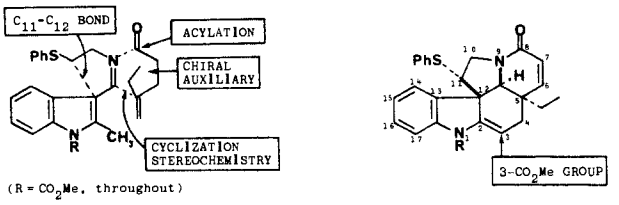
Abstract: 4-Methoxy-2-nitroaniline (**5**) is converted into 1-carbomethoxy-6-methoxy-3-formyl-2-methylindole (**10**) in an overall yield of 28% through five steps. The derived imine from **10** and 2-(phenylthio)ethylamine on treatment with acid chloride (±)-**12** gave hexacyclic adduct **14** (64%). It was converted into sulfoxide **15** and subsequently to heptacyclic adduct **20** by treatment with trifluoroacetic anhydride in toluene containing 2,6-di-*tert*-butyl-4-methylpyridine. In the absence of this hindered Brønsted base, **15** was reduced back to **14**. Thermolysis of **20** gave α,β-unsaturated amide **21**, completing the deethyl series. In the chiral ethyl series the required [2.2.1] chiral auxiliary **22** (X = Cl) was synthesized from **26**, as outlined in Scheme III. Both enantiomers of **22** were prepared. Condensation of imine **11** with (+)-**22** gave hexacycle **31**, which was converted by the Pummerer sequence and retro-Diels–Alder reaction into α,β-unsaturated amide **34**. Desulfurization and concomitant reduction gave **35**, in which the 6,7-double bond was reintroduced by using the thiolactam dehydrogenation procedure to provide **38** (X = S). Removal of the thioamide group and formylation with the Vilsmeier reagent gave the 3-aldehyde **40**, which on oxidation, methylation, and deprotection provided (−)-16-methoxytabersonine (**4**). An identical sequence using (−)-**22** gave the antipode of **4**.

In previous papers in this series we have described in detail the use of the indole–2,3-quinodimethane strategy for the synthesis of Aspidosperma-type indole alkaloids.[1] The most recent advance in this strategy has been the use of a bicyclo[2.2.1]hept-5-ene chiral auxiliary in an enantiospecific version of the indole–2,3-quinodimethane cyclization.[2] Scheme I summarizes the main features of this strategy. The 3-CO_2Me group was introduced through Vilsmeier formylation, followed by oxidation.[3] If this overall strategy is to be valuable for the construction of the more highly functionalized members of the Aspidosperma alkaloids such as 16-methoxytabersonine (**4**)[4] and vindoline (**3**),[5] it is essential that



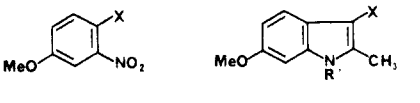
all the previous methodology we have described is compatible with

Scheme I



the presence of a 16-OMe group (*Chemical Abstracts* nomenclature). This requirement is also imperative if the clinically important oncolytic agents vinblastine (**1**) and vincristine (**2**) are to be synthesized by the indole–2,3-quinodimethane strategy. It is important to realize that the 16-OMe substituent is not an innocent bystander to electrophilic chemistry conducted in the C-ring for the construction of vindoline (**3**) or 16-methoxytabersonine (**4**), and this is nowhere better illustrated than in the first synthesis of (±)-vindoline (**3**), executed by Büchi.[5] Consequently, we were acutely aware of the possible unpredictable effects that the 16-OMe substituent might have on the indole–2,3-quinodimethane methodology and subsequent transformations needed to construct 16-methoxytabersonine (**4**).

The first requirement of this work was a convenient way of preparing 6-methoxy-3-formyl-2-methylindole (**9**). 4-Methoxy-2-nitroaniline (**5**) was converted into the corresponding diazonium



5, X = NH_2
6, X = $N_2^+HSO_4^-$
7, X = CH_2COCH_3

8, R = X = H
9, R = H, X = CHO
10, R = CO_2Me, X = CHO

hydrosulfate (**6**) by treatment with *i*-AmONO/H_2SO_4/MeOH (82%). Meerwein arylation using **6** and the recent procedure developed by Raucher[6] gave **7** (55%), which was directly reduced over Raney nickel to give 6-methoxy-2-methylindole (**8**) (≥95%).[7]

(1) Exon, C.; Gallagher, T.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 4739. Gallagher, T.; Magnus, P.; Huffman, J. C. *Ibid.* **1983**, *105*, 4750. Magnus, P.; Gallagher, T.; Brown, P.f Huffman, J. C. *Ibid.* **1984**, *106*, 2105. Magnus, P.; Pappalardo, P. *Ibid.* **1986**, *108*, 212. Magnus, P.; Gallagher, T.; Brown, P.f Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35.

(2) Magnus, P.; Cairns, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 217.

(3) Magnus, P.; Ladlow, M.; Cairns, P. M. *J. Chem. Soc., Chem. Commun.* **1986**, 1756.

(4) Pyuskyulev, B.; Kompis, I.; Oguyanov, I.; Spiteller, G. *Collect. Czech. Chem. Commun.* **1967**, *32*, 1289. Kanfan, C.; Das, B. C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* **1974**, 2839. Baassou, S.; Mehri, H.; Plat, M. *Phytochemistry* **1978**, *17*, 1449. For a synthesis of (±)-16-methoxytabersonine, see: Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685.

(5) Ando, M.; Büchi, G.; Ohnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880. Kutney, J. P.; Buzli-Trepp, U.; Chan, K. K.; de Souza, J. P.; Fujise, Y.; Honda, T.; Katsube, J.; Klein, F. K.; Leutwiler, A.; Morehead, S.; Rohr, M.; Worth, B. R. *Ibid.* **1978**, *100*, 4220. Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *J. Org. Chem.* **1985**, *50*, 961. Takano, S.; Shishido, K.; Sato, M.; Ogasawara, K. *Heterocycles* **1977**, *6*, 1699. Takano, S.; Shishido, K.; Sato, M.; Yuto, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1978**, 943. Ban, Y.; Sekine, Y.; Oishi, T. *Tetrahedron Lett.* **1978**, 151. For an enantiospecific synthesis of (−)-vindoline, see: Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603. Kuehne recently reported the synthesis of (+)-, (−)-, and (±)-vindoline from the corresponding 16-methoxytabersonine using the oxidative methodology described by Danieli:[24] Kuehne, M. E.; Podhorez, D. E.; Mulamba, T.; Bornmann, W. G. *J. Org. Chem.* **1987**, *52*, 347. For a review of the syntheses of vindoline to 1984, see: *Synform* **1984**, *1*, 33.

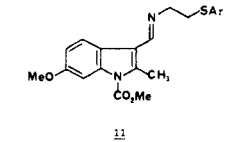
(6) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1983**, *48*, 2066. Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.

(7) Späth, E.; Brunner, O. *Ber.* **1925**, *58*, 518. Kermack, W. O.; Perkin, W. H.; Robinson, R. *J. Chem. Soc.* **1922**, 1872; **1921**, 1602. Blaikie, K.; Perkin, W. H. *Ibid.* **1924**, 296. Hunt, R. R.; Rickard, R. L. *J. Chem. Soc. C* **1966**, 344.

0002-7863/88/1510-2242$01.50/0

Vilsmeier–Haack formylation of **8** using $POCl_3$/DMF/20 °C gave the 3-formyl derivative **9** (84%), and finally N^1-protection ($NaH/ClCO_2Me$/THF) furnished **10** (79%) in an overall yield of 28% through five steps (including diazotization) from commercially available **5**.

[2.2.1]-Deethyl Series. To evaluate the response of the 6-methoxyindole substrate **10** to the indole–2,3-quinodimethane cyclization and subsequent Pummerer reaction sequence to establish the crucial C_{11}–C_{12} bond, we carried out the initial studies in the model deethyl series with the readily available bicyclo-[2.2.1]hept-5-ene-2-carboxylic acid chloride (±)-**12**.[8] The presumed indole–2,3-quinodimethane intermediate (**13**) should not suffer any adverse electronic effects from the MeO substituent, since the N^1-CO_2Me group insulates the diene system. Consequently, we predicted that there should be little or no change in the yields of the cyclized adducts **14** in going from the 6-H series to the 6-MeO series. The 3-formylindole **10** was converted into the derived imines **11** by treatment with $H_2NCH_2CH_2SAr$ (Ar = Ph, C_6H_4-2-CO_2Me, C_6H_4-3-CO_2Me, C_6H_4-2-OMOM, and C_6H_4-3-OMOM) in the presence of 4-Å molecular sieves/CH_2Cl_2. Treatment of **11** with acid chloride (±)-**12** in toluene in the presence of *i*-Pr_2NEt at 110 °C for 1 h gave cyclized adducts **14** in the yields shown in Table 1. The yields are almost identical (within experimental error) with those of the 6-H series. Oxidation of **14** (X = SPh) with MCPBA/CH_2Cl_2/$NaHCO_3$ gave the diastereomeric sulfoxides **15** [X = S(O)Ph] (≥95%).



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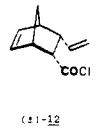
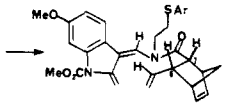


(±)-12



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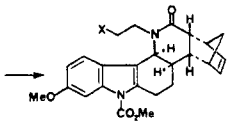
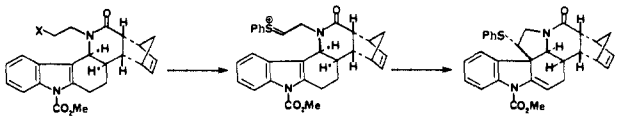


14, X = SAr
15, X = S(O)Ar

TABLE 1

14, X = SAr	% yield
Ar = Ph	64%
Ar = C_6H_4-2-CO_2Me	67%
Ar = C_6H_4-3-CO_2Me	73%
Ar = C_6H_4-3-OMOM	60%
Ar = C_6H_4-3-OMOM	65%

The general method we have used to form the C_{11}–C_{12} bond uses an intramolecular Pummerer reaction, as shown below for the 16-H series. Treatment of sulfoxide **16** [X = S(O)Ph] with trifluoroacetic anhydride at 0 °C in toluene, followed by heating to reflux, gave (**18**) (80%). Presumably, the reaction proceeds through the intermediacy of sulfonium ion **17**, which aligns the C=S$^+$Ph bond antiperiplanar to the indole 2,3-bond, thus leading in a stereospecific manner to **18**, after proton loss. This method has proven extremely reliable. Consequently, we were surprised to find that when the 16-MeO-substituted analogue **15** [X = S(O)Ph] was exposed to trifluoroacetic anhydride in toluene at 0 °C and then rapidly heated to reflux, two products were isolated: the reduced sulfide **14** (X = SPh) (58%), and the vinyl sulfide **19** (26%). *None* of the expected product **20** could be isolated. This unusual result minimally implies that the methoxyindole portion of **15** does not effectively trap the derived sulfonium ion **15a**, even though it is more electron rich. Since trifluoroacetic anhydride is usually contaminated with trifluoroacetic acid (TFA) and TFA is generated in the Pummerer reaction, the possibility exists that the methoxyindole moiety is protonated, and thus its nucleophilicity is drastically reduced. It was decided to run the Pummerer reaction in the presence of a specific Brønsted base,



16, X = SPh
X = S(O)Ph

17

18

(8) For the synthesis of (±)-**12**, see ref 2 and: Andreev, V. M.; Usova, A. V. *Izvn. Akad. Nauk USSR, Ser. Khim.* **1966**, 1404.

Scheme II

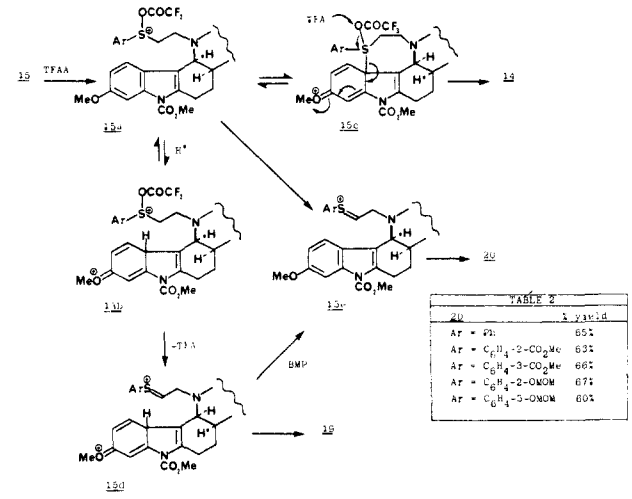
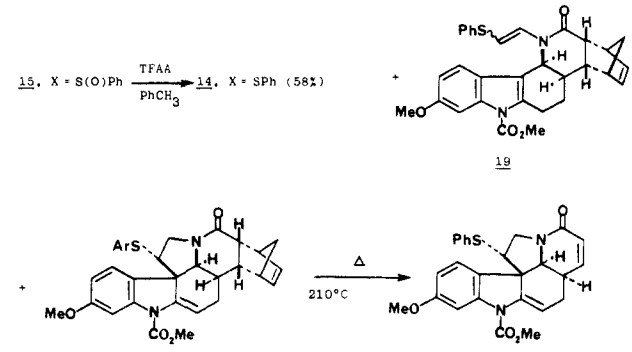


TABLE 2

20	% yield
Ar = Ph	65%
Ar = C_6H_4-2-CO_2Me	63%
Ar = C_6H_4-3-CO_2Me	66%
Ar = C_6H_4-2-OMOM	67%
Ar = C_6H_4-3-OMOM	60%

2,6-di-*tert*-butyl-4-methylpyridine (BMP).[9] In the event, treatment of **15** [X = S(O)Ph] with TFAA/BMP (1.1 equiv)/$PhCH_3$/0–110 °C gave **20** (65%), with no reduction to **14** (X = SPh) or formation of **19**.



Application of this modified procedure to the aryl-substituted sulfoxides **15** (Ar = C_6H_4-2-CO_2Me,[10] C_6H_4-3-CO_2Me, C_6H_4-2-OMOM, and C_6H_4-3-OMOM) worked equally well and gave the required materials **20** in the yields shown in Table 2. A plausible mechanism that rationalizes these observations is shown in Scheme II. Trifluoroacetylation of **15** should produce **15a** with concomitant production of TFA. Two equilibria from **15a** are possible: Protonation at C-13, resulting in **15b** (rendering the indole moiety nonnucleophilic), and sulfurane formation (**15c**).[11] In the former case, **15b** should lead to the sulfonium ion **15d**, which after proton loss results in the vinyl sulfide **19**. The sulfurane intermediate **15c** can undergo nucleophilic attack by TFA at the now electrophilic oxygen site (see **15c**) to give **14**. The presence of the nonnucleophilic base BMP should sequester the protonation step (**15a** ⇌ **15b** etc.) and siphon the sulfonium ion **15e** from unproductive equilibria (**15a** ⇌ **15c**; **15a** ⇌ **15b**) to give the required product **20**. The structure of **20** followed directly from its ^{1}H NMR spectrum, exhibiting diagnostic signals at δ 4.04 (1 H, d, J = 4.9 Hz) and 6.15 (1 H, m). It should be noted that the particular 2- and 3-substituted SAr derivatives of **20** were chosen in order to have functional handles for eventual substitution of C-15 in an intramolecular fashion.[12]

19

20

21

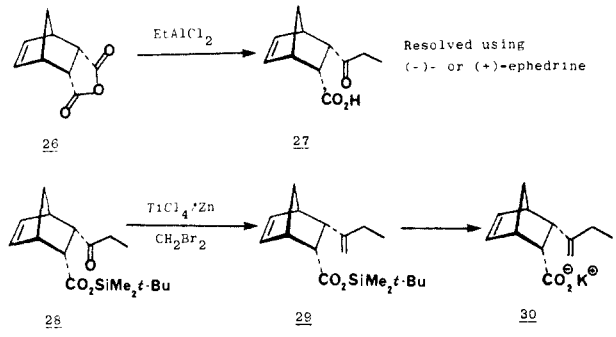
(9) Anderson, A. G.; Stang, P. J. *J. Org. Chem.* **1976**, *41*, 3034. A preliminary account of the abnormal Pummerer process has been published: Cardwell, K.; Hewitt, B.; Magnus, P. *Tetrahedron Lett.* **1987**, 3303.

(10) Sulfoxides ortho to esters are known to undergo oxygen exchange: Landini, D.; Rolla, F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1317. Numata, T.; Sakai, K.; Kise, M.; Kunieda, N.; Oae, S. *Int. J. Sulfur Chem.* **1971**, *1*, 1. Stridsberg, G.; Allenmark, S. *Acta Chem. Scand.* **1974**, *28*, 591.

(11) Martin, J. C.; Perozzi, E. F. *Science (Washington, D.C.)* **1976**, *191*, 154. Numata, T.; Oae, S. *Chem. Ind. (London)* **1973**, 277.

(12) The outline of this strategy was described in: *Stud. Org. Chem. (Amsterdam)* **1986**, *25*, 203.

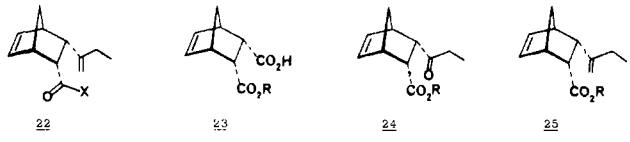
Scheme III



26 27 28 29 30

In an attempt to convert sulfide **14** (X = SPh) directly into the heptacyclic Pummerer product **20** (Ar = Ph), we treated the demethoxy derivative **16** (X = SPh) with $PhI(OCOCF_3)_2$[13]/$PhCH_3$/TFAA/heated to reflux and obtained **18** (74%) without having to isolate the intermediate sulfoxide **16** [X = S(O)Ph]. Application of this procedure to the 16-MeO system **14** (X = SPh) in the presence of BMP, unfortunately, gave mainly the sulfoxide **15** [X = S(O)Ph]. To complete the model study (deethyl series), **20** (Ar = Ph) was heated at 210 °C/$PhCH_3$/56 h in a sealed tube to give the α,β-unsaturated amide **21** (89%). The distinctive ^1H NMR signals δ 6.0 (d, J = 9.9 Hz) and 6.55 (dd, J = 9.9 and 5.8 Hz) for the α,β-unsaturated amide olefinic signals and the loss of the norbornyl moiety readily allow the structural assignment.[14]

[2.2.1]-Ethyl Series. In order to use the bicyclo[2.2.1]hept-5-ene stystems for the synthesis of (−)- and (+)-16-methoxytabersonine (**4**), we required a convenient way of making chiral **22** and its

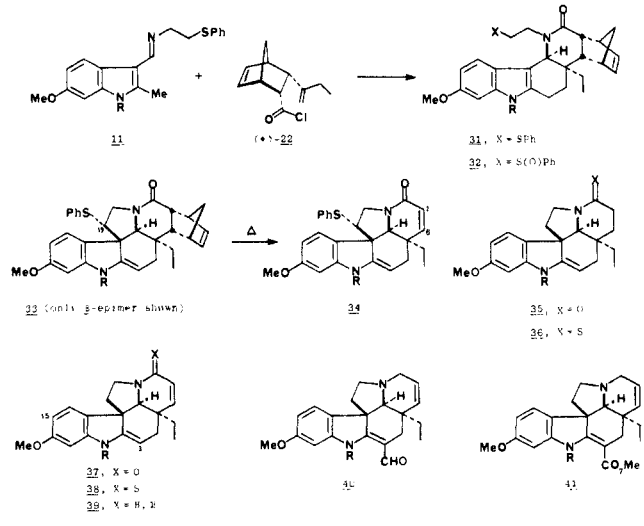


22 23 24 25

antipode. Without going into the extensive details, we quickly found the major problems to be as follows: While compounds such as **23** could be readily resolved via the (*R*)-α-methylbenzylamine salt, they were extensively racemized (≥90%) when converted into the *endo*-ethyl ketone **24** via the derived acid chloride and treatment with $EtAlCl_2$.[15] Methylation of **24** using the Wittig reaction gave only the trans derivative of **25**, and finally, for simple ester derivatives of **25** such as R = Me or Et, hydrolysis was accompanied by substantial amounts of epimerization. The β-chloro ester **25** (R = CH_2CH_2Cl) could be converted into the acid **22** by exposure to $NaEt_2NCS_2$/DMF followed by BF_3·OEt_2/CH_2Cl_2/BMP,[16] but the yield was modest (ca. 60%) and did not scale up satisfactorily. Because of the above difficulites the following route to both enantiomers of **22** was developed (Scheme III).

The Diels–Alder adduct **26** was converted into the *syn*-keto acid **27** (91%) by treatment with $EtAlCl_2/CH_2Cl_2$. Resolution of (±)-**27** was achieved via the (−)-ephedrine salt, a single crystallization giving material of at least 95% ee [determined by NMR in the presence of 2 equiv of CSA (−)-ephedrine]. [The use of (+)-ephedrine gave the antipode of **27**.] The *tert*-butyldimethylsilyl ester **28** was prepared by the Corey[17] procedure, *t*-$BuMe_2SiCl$/imidazole/DMF (87% yield), and treated with the Lombardo reagent,[18] $Zn/CH_2Br_2/TiCl_4$/THF, to give **29** (≥95%). Deprotection of **29** using KF/H_2O/THF gave the potassium salt **30** as a stable, readily purified white powder. The free acid **22** (X = OH) is unstable, slowly lactonizing on storage. The overall yield for the preparation of the enantiomerically pure norbornyl salt is 31%, including the resolution.

(+)- and (−)-16-Methoxytabersonine. The potassium salt **30** was converted into its derived acid chloride **22** (X = Cl) by exposure to oxalyl chloride in the presence of BMP (1.0 equiv) in toluene. When the above acid chloride was treated directly with the imine **11** in toluene and heated at reflux for 2.5 h, the adduct **31** was isolated in 70–75% yield, as an enantiomerically pure compound, $[\alpha]^{20}_D$ +52° (*c* 4.0 in CH_2Cl_2). This single transformation embodies all of the required virtues of the indole–2,3-quinodimethane strategy: It is stereospecific, enantiospecific, and compatible with the 16-MeO substituent, the yields are good (purified material), and it scales up to several grams without any problems.



11 (+)-22 31, X = SPh 32, X = S(O)Ph 33 (only β-epimer shown) 34 35, X = O 36, X = S 37, X = O 38, X = S 39, X = H, H 41 43

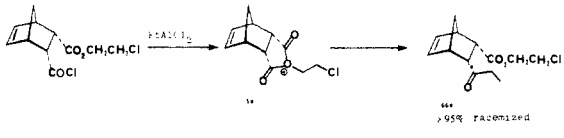
Oxidation of **31** using MCPBA/CH_2Cl_2/aqueous $NaHCO_3$/5 °C to the diastereomeric sulfoxides **32** and exposure of the sulfoxides to TFAA (3.0 equiv)/DBMP(1.1 equiv)/toluene 0–110 °C gave the heptacycle **33** (86%) as a mixture of epimers at C-11 (ca. 9:1/β:α). The Pummerer reaction is, in fact, a reversible reaction, as we have noted in earlier papers.[1] Curiously, it is only in the ethyl series that this manifests itself; here the ratio of β:α epimers at C-11 is a function of the reaction time and acid concentration.

The norbornyl adduct **33** could not be desulfurized with Raney nickel, since the norbornyl double bond was reduced first; this prevents the subsequent retro-Diels–Alder reaction to expose the α,β-unsaturated lactam. Dissolving-metal reduction competitively reduce the 2,3-double bond. Thermolysis of **33** (200 °C in toluene/sealed tube, 30 h) gave the retro-Diels–Alder product **34** (93%). Unfortunately, we could not find conditions that allowed the selective desulfurization of **34** without competitive reduction of the 6,7-double bond. Even the optimized conditions of deactivated Raney nickel/EtOAc/reflux gave **35** (over reduction) and **37** (ca. 1:1). Consequently, to establish a reproducible and efficient sequence, it was decided to deliberately reduce **34** to **35** and reintroduce the 6,7-double bond via the thiolactam dehydrogenation procedure. This protocol introduces one extra step. Freshly

(13) Spyroudis, S.; Varvoglis, A. *J. Chem. Soc., Chem. Commun.* **1979**, 615. Radhakrishna, A. S.; Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 1746.

(14) All of the structures in the deethyl series refer to racemic nonchiral compounds derived from (±)-**12**.

(15) When chiral acid chloride i was treated with $EtAlCl_2$, ketone iii was formed in excellent yield, but it was almost completely racemized. Presumably, the intervention of symmetrical oxonium ion ii is responsible for the undesired problem.



i ii iii >95% racemized

(16) Ho. T.-L. *Synthesis* **1974**, 715. Ho, T.-L. *Synth. Commun.* **1978**, *8*(5), 301. We found that treatment of **25** (R = CH_2CH_2Cl) with $Et_2NCS_2^-Na^+$ followed by BF_3·OEt BMP gave **22** (X = OH) in some 60% yield, but with about 5% epimerization to the trans isomer. This was not acceptable in the subsequent cyclization step.

(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(18) Lombardo, L. *Tetrahedron Lett.* **1982**, 4293. *Org. Synth.* **1987**, *65*, 81. Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417.

activated W-2 Raney nickel in ethyl acetate gave **35** (95%). The amide **35** was converted into its derived thioamide **36** (89%) by using Belleau's reagent[19]/THF/0–20 °C and treated with p-$CH_3C_6H_4S(O)Cl$/*i*-Pr_2NEt/toluene at 110 °C to give the α,β-unsaturated thioamide **38** (85%).[20] The characteristic protons at δ 6.14 (1 H, d, J = 9.7 Hz) and 6.46 (1 H, d, J = 9.7 Hz) substantiate the structural assignment. A single-crystal X-ray crystallographic structure determination was carried out on the thioamide derivative of **34**, which confirmed the relative stereochemistry, although we could not corroborate the absolute configuration at this stage.[21]

The thiocarbonyl group in **38** was reduced by treatment with MeI/reflux, followed by $NaBH_4$/MeOH to give **39** (90%).[22] Exposure of **39** to the Vilsmeier reaction conditions, $POCl_3$/DMF/22 °C, followed by aqueous 2 N NaOH workup, gave **40** (56%), along with 16% of the C-15 formyl derivative of **39** It was not necessary to separate the two aldehydes at this stage, since oxidation of the mixture using $NaClO_2$[23]/H_2O/H_2NSO_3H/acetone–isopropenyl acetate at pH 4, followed by CH_2N_2, gave the methyl ester **41** (65%) with complete destruction of the 15-aldehyde. Finally, treatment of **41** with 1 M NaOMe/MeOH/24 °C gave (−)-16-methoxytabersonine (**4**) (85%), $[\alpha]^{27}_D$ −196° (*c* 0.17, $CHCl_3$). An identical sequence using the antipode of **22** gave (+)-16-methoxytabersonine, the mirror image. Danieli[24] has described an efficient four-step sequence that converts (−)-16-methoxytabersonine (**4**) into (−)-vindoline (**3**) in an overall yield of 55%.

In summary, this research completes our study of the indole–2,3-quinodimethane strategy for the synthesis of Aspidosperma indole alkaloids and illustrates the compatibility of this strategy with the 16-OMe substituent.

Experimental Section

1-(4-Methoxy-2-nitrophenyl)propan-2-one (7). 4-Methoxy-2-nitroaniline (**5**) (70.0 g, 416 mmol) in concentrated sulfuric acid (28 mL) and ethanol (500 mL) was heated at reflux until a blood red solution was formed. The mixture was cooled to −5 °C, and isoamyl nitrite (62.0 mL, 461 mmol) was added dropwise under argon. After 1 h at 0 °C the suspension was filtered, washed with ethanol (50 mL) and ether (100 mL), and dried in vacuo to give the diazonium hydrosulfate **6** (94.8 g, 82%).

The salt **6** (94.8 g, 342 mmol) was added portionwise to a two-phase solution of isopropenyl acetate (140 mL, 1.27 mol), acetone (900 mL), hydrochloric acid (100 mL, 0.5 M), water (200 mL), cupric chloride (8.0 g, 60 mmol), and lithium chloride (30.0 g) under argon at −5 °C. After complete addition the mixture was warmed to 5 °C and stirred for 3.5 h, keeping the temperature below 10 °C, and then at 20 °C for 4 h. The complete reaction mixture was evaporated in vacuo to approximately 300-mL volume and extracted with ethyl acetate (2 × 500 mL). The dried ($MgSO_4$) extract was evaporated in vacuo to give a red oil, which was purified by flash chromatography, eluting with ether to give **7** (39.5 g, 55%) after recrystallization from ether; mp 53–54 °C; IR ($CHCl_3$) 1730, 1630, 1535 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.21 (3 H, s) 3.70 (3 H, s), 4.0 (2 H, s), 7.13 (2 H, bs), 7.60 (1 H, m). Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.30; H, 5.42; N, 6.66.

6-Methoxy-3-formyl-2-methylindole (9). The ketone **7** (30.0 g, 143 mmol) in ethyl acetate (20 mL) was treated with Raney nickel (30 g), and the suspension was vigorously stirred under a hydrogen atmosphere for 18 h. It was then filtered through a pad of Celite, washing with ethyl acetate, and evaporated in vacuo to give crude **8** (≥95%, mp 95–100 °C, lit. mp 101 °C). ^1H NMR (90 MHz, $CDCl_3$) δ 2.35 (3 H, s), 3.83 (3 H, s), 6.14 (1 H, bs), 6.75 (2 H, m), 7.40 (1 H, d, J = 8.5 Hz). The crude product **8** was dissolved in dimethylformamide (50 mL) and treated at 0 °C with a solution of phosphorus oxychloride (20 mL, 215 mmol) in dimethylformamide (50 mL) (previously prepared by mixing at 0 °C for 20 min and then stirring at 20 °C for 1 h). After 0.5 h at 0 °C the solution was poured onto ice-water (500 g), and a solution of NaOH (50 g) in ice-water (100 g) was added slowly over 10 min. The above aqueous dimethylformamide mixture was heated to a reflux for 15 min to hydrolyze any excess $POCl_3$. The mixture was cooled to room temperature and filtered to give **9** (22.9 g, 84% from **7**, after drying over P_2O_5 in vacuo): mp 223–224 °C (from 2-methoxyethanol); IR ($CHCl_3$) 1660, 1460, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (3 H, s), 3.76 (3 H, s), 6.73 (1 H, dd, J = 8.4 and 2.4 Hz), 6.82 (1 H, d, J = 2.4 Hz), 7.88 (1 H, d, J = 8.4 Hz), 11.80 (1 H, s). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 6.04; N, 7.40. Found: C, 69.92; H, 5.86; N, 7.34.

1-Carbomethoxy-6-methoxy-3-formyl-2-methylindole (10). Sodium hydride (5.50 g, 131 mmol, 57% dispersion) was added to a solution of **9** (20.7 g, 110 mmol) in dry THF (500 mL) at 0 °C under argon. The mixture was heated at reflux for 10 min (dark red solution) and cooled to 0 °C to ensure complete anion formation. Methyl chloroformate (11.0 mL, 142 mmol) was added to the mixture, and it was warmed to room temperature over 15 min. The mixture was filtered through a pad of Celite and evaporated in vacuo, and the residue was chromatographed over silica gel (2 in. × 3 in. column), eluting with dichloromethane to give the crude product, which was recrystallized from dichloromethane/hexane, providing **10** (21.4 g, 79%) as pale yellow needles: mp 119–120 °C; IR ($CHCl_3$) 1760, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.83 (3 H, s), 3.84 (3 H, s), 4.10 (3 H, s), 6.92 (1 H, dd, J = 8.6 and 2.3 Hz), 7.60 (1 H, d, J = 2.3 Hz), 8.15 (1 H, d, J = 8.6 Hz), 10.22 (1 H, s). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.14; H, 5.29; N, 5.66. Found: C, 63.14; H, 5.28; N, 5.65.

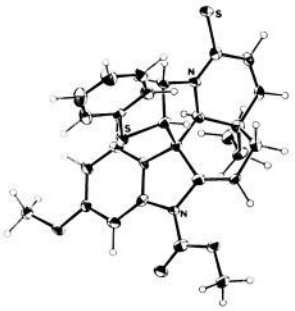
(*E*)-1-Carbomethoxy-2-methyl-6-methoxy-3-[*N*-[2-(phenylthio)ethyl]formimidoyl]indole (11) (Ar = Ph). A solution of the indole **10** (363 mg, 1.47 mmol) and 2-(phenylthio)ethylamine (225 mg, 1.47 mmol) in dry toluene (20 mL) containing 3-Å powdered molecular sieves (1.5 g, freshly activated) was stirred at 20 °C for 23 h. The mixture was filtered through Celite, and the filtrate was evaporated to give the imine **11** (Ar = Ph) in essentially quantitative yield. It was used directly as a solution in toluene (20 mL) in the next stage. ^1H NMR (360 MHz, $CDCl_3$) δ 2.64 (3 H, s), 3.30 (2 H, t, J = 7.7 Hz), 3.83 (2 H, t, J = 7.7 Hz), 3.84 (3 H, s), 4.01 (3 H, s), 6.89 (1 H, dd, J = 7.2 and 2.5 Hz), 7.15 (1 H, t J = 6.6 Hz), 7.26 (2 H, t, J = 6.6 Hz), 7.49 (2 H, t, J = 6.6 Hz), 7.13 (1 H, d, J = 2.5 Hz), 8.25 (1 H, d, J = 7.2 Hz), 8.45 (1 H, s).

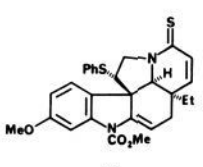
The imines **11** (Ar = C_6H_4-2-CO_2Me, C_6H_4-3-CO_2Me, C_6H_4-2-OMOM, and C_6H_4-3-OMOM) were made from the corresponding 2-(arylthio)ethylamines by the same method as above and used directly in the next step.[25]

(19) Lajoie, G.; Lepine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, 3815.

(20) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212.

(21) The X-ray crystallographic structure determination of the thioamide derivative of **34** was carried out by Dr. John Huffman, Molecular Structure Center, Indiana University, Bloomington, IN 47405. For details, request report 87003.





34a

ORTEP OF THIOAMIDE 34a

(22) Raucher, S.; Klein, P. *Tetrahedron Lett.* **1980**, 4061. Sundberg, R. J.; Walters, C. P.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 3730.

(23) Magnus, P.; Gallagher, T.; Schultz, J.; Or. Y.-S.; Ananthanarayan, T. P. *J. Am. Chem. Soc.* **1987**, *109*, 2706.

(24) Danieli, B.; Lesma, G.; Palmisano, G.; Riva, R. *J. Chem. Soc., Chem. Commun.* **1984**, 909.

(25) $H_2NCH_2CH_2SC_6H_4$-2-CO_2Me was made from thiosalicylic acid by S-alkylation with $BrCH_2CH_2NH_2Br$, followed by esterification with MeOH/HCl. $H_2NCH_2CH_2SC_6H_4$-3-CO_2Me was made from 3-(chlorosulfonyl)benzoic acid by reduction (Zn/HCl) to the disulfide ($HO_2CC_6H_4$-3-$S)_2$ and cleavage (Ph_3P/H_2O) to give HSC_6H_4-3-CO_2H, followed by S-alkylation with $BrCH_2CH_2NH_2Br$ and esterification with MeOH/HCl. $H_2NCH_2CH_2SC_6H_4$-2-OMOM was made from 2-aminophenol by diazotization followed by workup with potassium xanthate and hydrolysis, to give 2-hydroxythiophenol. Oxidation ($FeCl_3$/MeOH) gave the corresponding disulfide, which was converted into its methoxymethyl (MOM) ether derivative and reduced (Ph_3P/H_2O/THF) to give HSC_6H_4-2-OMOM. S-Alkylation using $BrCH_2CH_2NH_2Br$ completed the sequence. $H_2NCH_2CH_2SC_6H_4$-3-OMOM was made by an identical sequence of transformations starting with 3-aminophenol: Watson, E. R.; Dutt, S. *J. Chem. Soc.* **1922**, 2414. Smiles, S.; Stewart, J. *Ibid.* **1921**, 1792. Djerassi, C.; Gorman, M.; Markley, F. X.; Oldenburg, E. B. *J. Am. Chem. Soc.* **1955**, *77*, 568. Wünsch, K.-H.; Ehlers, A.; Beyer, H. *Chem. Ber.* **1969**, *102*, 1618. van Heerden, F. R.; Zyl, J. J.; Rall, G. J. H.; Brandt, E. V.; Roux, D. G. *Tetrahedron Lett.* **1971**, 661. Overman, L. E.; Smoot, J.; Overman, J. D. *Synthesis* **1974**, *59*.

(±)-Hexacyclic Adduct 14 (X = SPh). The imine **11** (Ar = Ph) [prepared from **10** (161 mg, 0.65 mmol)] in dry toluene (5 mL) at 0 °C was treated with diisopropylethylamine (220 μL, 2.0 equiv), followed by the acid chloride (±)-**12** (140 mg, 0.71 mmol). The mixture was allowed to warm to room temperature and then heated at reflux for 1 h. After cooling to room temperature, the solution was diluted with ethyl acetate (20 mL) and washed sequentially with 2 N HCl (20 mL), water (2 × 20 mL), and saturated brine solution (20 mL). The dried ($MgSO_4$) extract was evaporated in vacuo, and the residue was purified by flash chromatography to give **14** (X = SPh) (219 mg, 64%) after recrystallization from EtOAc–hexane: mp 183–184 °C; IR ($CHCl_3$) 1730, 1630, 1440 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.48 (1 H, d, J = 8.5 Hz), 3.84 (3 H, s), 4.02 (3 H, s), 4.45 (1 H, b), 4.72 (1 H, b), 6.14 (1 H, b), 6.31 (1 H, dd, J = 6.0 and 2.7 Hz), 6.80 (1 H, dd, J = 8.7 and 2.2 Hz), 7.15 (1 H, d, J = 8.7 Hz), 7.75 (1 H, d, J = 2.2 Hz) (many signals are broadened because of carbamate resonance; consequently, only the more defined signals are given); UV (95% EtOH) 231, 257, and 270 nm (ε 27 000, 15 800, and 15 800, respectively). Anal. Calcd for $C_{31}H_{32}N_2O_4S$: C, 7/.45; H, 6.06; N, 5.30. Found: C, 69.99; H, 6.05; N, 5.48.

Similarly, **1** (Ar = C_6H_4-2-CO_2Me) gave **14** (X = SC_6H_4-2-CO_2Me) (67% foam) and **11** (Ar = C_6H_4-3-CO_2Me) gave **14** (X = SC_6H_4-3-CO_2Me) (73%), mp 184–185 °C (from EtOAc–hexane). Anal. Calcd for $C_{33}H_{34}N_2O_6S$: C, 67.58; H, 5.80; N, 4.78. Found: C, 67.65; H, 5.72; N, 4.78. **11** (Ar = C_6H_4-2-OMOM) gave **14** (X = SC_6H_4-2-OMOM) (60%), mp 177–178 °C (from EtOAc–hexane). Anal. Calcd for $C_{33}H_{36}N_2O_6S$: C, 67.34; H, 6.12; N, 4.76. Found: C, 66.96; H, 6.12; N, 4.77. **11** (Ar = C_6H_4-3-OMOM) gave **14** (X = C_6H_4-3-OMOM) (65%), mp 140–144 °C (from EtOAc–hexane). Anal. Calcd for $C_{33}H_{36}N_2O_6S$: C, 67.34; H, 6.12; N, 4.76. Found: C, 67.08; H, 6.14; N, 4.87. In all cases the ^1H NMR spectra showed substantial line broadening due to carbamate resonance.

(±)-Heptacyclic Adduct 11 (Ar = Ph). A solution of *m*-chloroperoxybenzoic acid (37 mg, 0.22 mmol) in dichloromethane (0.5 mL) was added dropwise to a rapidly stirred solution of the hexacyclic sulfide **14** (X = SPh) (100 mg, 0.19 mmol) in dichloromethane (3 mL) and 10% aqueous sodium bicarbonate (3 mL). After 1 h at 0 °C the phases were separated, and the aqueous phase was extracted with dichloromethane (3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give **15** [X = S(O)Ph] (100 mg, 98%) as a foam. TLC and ^1H NMR analysis indicated that the sulfoxides were present as a 1:1 mixture of diastereoisomers. The above foam in dry toluene (3 mL) and 2,6-di-*tert*-butyl-4-methylpyridine (40 mg, 0.20 mmol) at 0 °C were treated with freshly distilled trifluoroacetic anhydride (100 μL, 0.7 mmol), and the mixture was warmed to 20 °C. The solution was heated at reflux for 1 h, cooled, diluted with ethyl acetate (10 mL), and washed with 2 N HCl (10 mL), saturated aqueous sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL). The dried (Na_2SO_4) extract was evaporated in vacuo, and the residue was chromatographed over silica gel, eluting with ether to give **20** (Ar = Ph) (66 mg, 65%) as a glass: IR ($CHCl_3$) 1720, 1620, 1445 cm^{-1}; ^1H NMR δ 1.37 (1 H, d, J = 8.5 Hz), 1.45 (1 H, d, J = 8.5 Hz), 1.75 (1 H, m), 2.05 (2 H, m), 2.45 (1 H, dd, J = 9.1 and 3.2 Hz), 2.91 (1 H, dd, J = 9.1 and 4.2 Hz), 3.00 (1 H, bs), 3.10 (2 H, m), 3.36 (1 H, bs), 3.85 (3 H, s), 3.87 (3 H, s), 4.04 (1 H, d, J = 4.9 Hz), 4.61 (1 H, dd, J = 11.1 and 6.0 Hz), 6.15 (1 H, m), 6.26 (2 H, m), 6.65 (1 H, dd, J = 8.3 and 2.3 Hz), 7.0 (1 H, d, J = 8.3 Hz); MS calcd for $C_{31}H_{30}N_2O_4S$, m/e 526.2004; found, 526.1965. The aryl-substituted examples listed in Table 2 were conducted in the same manner.

(±)-2,3,6,7-Tetrahydro-1-carbomethoxy-11β-(phenylthio)-16-methoxy-20,21-dinoraspidospermidin-8-one (21). A degassed solution of **20** (Ar = Ph) (25 mg, 47 μmol) in dry toluene (5 mL) in a resealable Carius tube was heated to 180–190 °C for 24 h, cooled, and evaporated, and the residue was chromatographed over silica gel, eluting with ether to give **21** (19.0 mg, 88%): mp 171–173 °C (from dichloromethane–hexane); IR ($CHCl_3$) 1715, 1660, 1610, 1450, 1380 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.05 (1 H, m), 2.15 (1 H, m), 2.25 (1 H, m), 3.4 (2 H, m), 3.8 (3 H, s), 3.9 (3 H, s), 4.50 (2 H, m), 6.0 (1 H, d, J = 9.9 Hz), 6.4 (1 H, bs), 6.55 (1 H, dd, J = 9.9 and 5.8 Hz), 6.70 (1 H, dd, J = 8.3 and 2.3 Hz), 7.20 (6 H, m), 7.50 (1 H, bs); MS calcd for $C_{26}H_{26}N_2O_4S$, m/e 460.1449; found, 460.1453.

(±)-(2,3-*endo*)-3-(1-Oxopropyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (27). Ethylaluminum chloride[26] (800 mL, 1.0 M in hexane, 2.05 equiv) was added over 80 min to a suspension of the anhydride **26** (64.0 g, 0.390 mol) in dry dichloromethane (650 mL) stirred at −10 °C under argon. After 1 h at −10 °C the mixture was poured onto ice (ca. 800 g) and concentrated HCl (250 mL). The dichloromethane phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated to low bulk in vacuo (ca. 200 mL), followed by the slow addition of hexane (400 mL) with continued evaporation to give **27** (68.8 g, 91%) as fine white needles, mp 103–105 °C (lit. mp 102–103 °C).[27] (1*R*,2*S*)-(−)-Ephedrine (42.5 g, 0.257 mol) was dissolved in benzene (150 mL) at reflux. The solution was cooled to room temperature and added dropwise to a solution of (±)-**27** (50.0 g, 0.257 mol) in benzene (250 mL). A further portion of benzene (100 mL) was added, and the resulting slurry was stirred for 15 min. Filtration gave (+)-**27**. (−)-Ephedrine (44.5 g, 48%), $[\alpha]^{20}_D$ +5.3° (*c* 4.1 in 95% EtOH). Similarly, (1*S*,2*R*)-(+)-ephedrine gave (−)-**27** (48%): mp 138–139 °C; $[\alpha]^{20}_D$ −7.5 (*c* 1.1 in 95% EtOH).

(+)-(2,3-*endo*)-*tert*-Butyldimethylsilyl 3-(1-Oxopropyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (28). The ephedrine salt of (+)-**27** (22.0 g, 61.2 mmol) was added to a mixture of dichloromethane (150 mL), 2 M hydrochloric acid (75 mL), and ice (25 g), and the suspension was shaken thoroughly. The organic phase was separated, and the aqueous phase was extracted with dichloromethane (2 × 100 mL). The organic phases were combined, dried ($MeSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in dry dimethylformamide (50 mL), and the solution was added via canula to a solution of *tert*-butyldimethylsilyl chloride (10.6 g, 70.3 mmol) and imidazole (12.0 g, 176 mmol) in dry dimethylformamide (100 mL) at 5 °C under argon. The mixture was warmed to 20 °C and stirred for 5 h before evaporation in vacuo to low bulk (ca. 100 mL). The resulting slurry was partitioned between hexane (100 mL) and wate (200 mL). The organic phase was washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated in vacuo to gave (+)-**28** (16.35 g, 87%) as waxy needles: mp 43–44.5 °C; bp 115 °C/0.15 mmHg; IR (CCl_4) 1720 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.24 (6 H, s), 0.88 (9 H, s), 1.03 (3 H, t, J = 7.4 Hz), 1.32 (1 H, d, J = 8.1 Hz), 1.44 (1 H, dt, J = 8.1 and 1.6 Hz), 2.39 (2 H, q, J = 7.4 Hz), 3.10 (1 H, s), 3.14 (1 H, s), 3.26 (1 H, dd, J = 10.6 and 3.2 Hz), 3.40 (1 H, dd, J = 10.6 and 3.2 Hz), 6.14 (1 H, dd, J = 5.5 and 3.0 Hz), 6.23 (2 H, dd, J = 5.5 and 3.3 Hz); MS calcd for $C_{17}H_{28}O_3Si$, m/e 308.1808; found 308.1816; $[\alpha]^{23}_D$ +24.4° (*c* 4.2 in CH_2Cl_2) from (−)-ephedrine and $[\alpha]^{20}_D$ −25.0° (*c* 1.8 in CH_2Cl_2) from (+)-ephedrine; ≥95% ee, by shift reagent study with (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol.

(+)-(2,3-*endo*)-*tert*-Butyldimethylsilyl 3-(1-Methenylpropyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (29). A slurry of Lombardo's reagent (ca. 650 mL, 0.274 mol, 5.6 equiv) was added rapidly to a solution of (+)-**28** (15.00 g, 48.6 mmol) in dry dichloromethane (1 L) stirred at 20 °C under argon. After 30 min the slurry was added to a stirred mixture of sodium bicarbonate (500 g), water (500 mL), ice (500 g) and ether (1 L). The ether layer was decanted, and the aqueous slurry was washed with ether (2 × 500 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to (+)-**29** (14.64 g, 99%) as an oil: IR ($CHCl_3$) 2950, 2860, 1715, 1650 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 0.15 (3 H, s), 0.21 (3 H, s), 0.89 (9 H, s), 1.01 (3 H, t, J = 7.4 Hz), 1.34 (1 H, d, J = 8.2 Hz), 1.45 (1 H, dt, J = 8.3 and 1.7 Hz), 1.98 (2 H, q, J = 7.4 Hz), 2.92 (1 H, bs), 3.03 (1 H, dd, J = 10.8 and 3.1 Hz), 3.06 (1 H, bs), 3.25 (1 H, dd, J = 10.8 and 3.3 Hz), 4.39 (1 H, s), 4.66 (1 H, m), 6.15 (1 H, dd, J = 5.3 and 3.0 Hz), 6.35 (1 H, dd, J = 5.3 and 3.0 Hz); MS calcd for $C_{18}H_{30}O_2Si$, m/e 306.2015; found, 306.2045; $[\alpha]^{23}_D$ +13.1° (*c* 4.1 in CH_2Cl_2). The (−)-enantiomer had $[\alpha]^{25}_D$ −12.4° (*c* 3.9 in CH_2Cl_2).

(−)-(2,3-*endo*)-Potassium 3-(-Methenylpropyl)bicyclo[2.2.1]hept-5-ene-2-carboxylate (30). An emulsion of (+)-**29** (14.46 g, 47.2 mmol), KF·$2H_2O$ (4.50 g, 47.8 mmol), THF (150 mL), and water (25 mL) was stirred at 20 °C for 1 h. The mixture was evaporated in vacuo, THF (400 mL) was added, and the slurry was reduced to 50 mL. Hexane (400 mL) was added to the slurry, and the white powder was filtered and washed with hexane (2 × 50 mL) to give (−)-**30** (8.49 g, 78%), mp 219–221 °C dec. The free acid has the following properties: IR (CCl_4) 3600–2400 (b), 3400, 1705, 1645, 900 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 1.00 (3 H, t, J = 7.4 Hz), 1.37 (1 H, d, J = 8.3 Hz), 1.48 (1 H, dt, J = 8.3 and 1.7 Hz), 1.95 (2 H, ABX_3, Δ_ν = 17.6 Hz, J = 15.3 and 7.6 Hz), 2.96 (1 H, bs), 3.09 (1 H, bs), 3.10 (1 H, dd, J = 10.2 and 2.9 Hz), 3.25 (1 H, dd, J = 10.2 and 3.3 Hz), 4.64 (1 H, s), 4.70 (1 H, s), 6.21 (1 H, dd, J = 5.6 and 3.0 Hz), 6.29 (1 H, dd, J = 5.6 and 3.0 Hz). Anal. Calcd for $C_{20}H_{27}O_2N$ (α-methylbenzylamine salt, mp 138–140 °C): C, 76.64; H, 8.68; N, 4.47. Found: C, 76.55; H, 8.65; N, 4.72. (−)-**30** has $[\alpha]^{22}_D$ −17.2° (*c* 4.0 in .5% EtOH); (+)-**30** has $[\alpha]^{29}_D$ +18.5° (*c* 1.23 in MeOH).

(+)-Hexacyclic Adduct (31) (X = SPh). Freshly distilled oxalyl chloride (600 μL, 6.87 mM) was added to a rapidly stirred suspension of (+)-**30** (1.82 g, 8.0 mM) in dry toluene (25 mL) at −10 °C, containing 2,6-di-*tert*-butyl-4-methylpyridine (1.96 g, 9.56 mM). After 1 h at 20 °C the mixture was added dropwise to a solution of the imine **11** (Ar =

(26) Adkins, H.; Scnaley, C. *J. Am. Chem. Soc.* **1951**, *73*, 2854.

(27) Walton, H. M. *J. Org. Chem.* **1957**, *22*, 308, 312.

Ph) [made from **10** (713 mg)] in toluene (40 mL) at −10 °C. the resulting suspension was stirred at 25 °C for 30 min and heated at reflux for 2.5 h, allowed to cool to room temperature, and filtered through Celite. The Celite was washed with ether, and the combined filtrates were evaporated in vacuo to give a brown oil. Chromatography over silica gel, eluting with ether, gave (+)-**31** (X = SPh) (1.13 g, 70.2%) as a colorless foam. In the racemic series, (±)-**31** (X = SPh) was crystalline, mp 170–172 °C (CH_2Cl_2). Anal. Calcd for $C_{33}H_{36}N_2O_4S$: C, 71.19; H, 6.52; N, 5.03. Found: C, 71.28; H, 6.30; N, 4.78. (+)-**31** (X = SPh) has the following: IR ($CHCl_3$) 2960, 1730, 1610, 1440, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3 H, t, J = 7.6 Hz), 1.22 (2 H, m), 1.43 (1 H, d, J = 8.4 Hz), 1.53 (1 H, d, J = 8.4 Hz), 1.75 (1 H, m), 1.96 (1 H, m), 2.38–2.56 (2 H, m), 2.88 (2 H, m), 3.10 (3 H, m), 3.30 (1 H, m), 3.38 (1 H, m), 3.56 (1 H, m), 3.95 (3 H, s), 4.15 (3 H, s), 4.19 (1 H, s), 6.26 (2 H, m), 6.85 (1 H, dd, J = 8.6 and 2.4 Hz), 7.04 (5 H, m), 7.24 (1 H, d, J = 8.6 Hz), m.75 (1 H, d, J = 2.4 Hz); MS calcd for $C_{33}H_{36}N_2O_4S$, m/e 556.2396; found, 556.2390; $[\alpha]^{24}_D$ +52.0° (c 4.5 in CH_2Cl_2); (−)-**31** (X = SPh) has $[\alpha]^{24}_D$ −54.9° (c 4.0 in CH_2Cl_2).

Heptacyclic Adduct (33). *m*-Chloroperoxybenzoic acid (286 mg, 85% 1.4 mM) in dichloromethane (10 mL) was added rapidly to a mixture of (+)-**31** (784 mg, 1.41 mmol) in dichloromethane (15 mL) and saturated aqueous sodium bicarbonate solution (25 mL) at 5 °C. When TLC analysis indicated complete consumption of **31**, the mixture was extracted with dichloromethane (2 × 5 mL), washed with saturated aqueous sodium bicarbonate solution (5 mL), dried ($MgSO_4$), and evaporated to a white foam of the diastereomeric sulfoxides **32**. The sulfoxides **32**, in toluene (35 mL), containing 2,6-di-*tert*-butyl-4-methylpyridine (318 mg, 1.55 mmol) at 0 °C were treated with trifluoroacetic anhydride (597 μL, 4.23 mmol), added dropwise over 5 min. After 15 min at 25 °C the mixture was rapidly heated to 130 °C for 5 min and cooled to 25 °C. The mixture was quenched with saturated aqueous sodium bicarbonate (10 mL), and the organic layer was dried ($MgSO_4$), and evaporated in vacuo to give a residue, which was purified by chromatography over silica gel, eluting with 60% EtOAc–hexane, to give **33** (752 mg, 96%). The product was a mixture of epimers at C-11 (ca. 9:1 by NMR). In the racemic series, (±)-**33** had for one pure epimer (11-β) mp 225–230 °C dec. Anal. Calcd for $C_{33}H_{34}N_2O_4S$: C, 71.45; H, 6.18; N, 5.05. Found: C, 71.02; H, 6.13; N, 5.35. IR ($CHCl_3$) 2970, 1730, 1640, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) major 11β-isomer, δ 0.78 (3 H, t, J = 7.0 Hz), 0.99 (1 H, dq, J = 14.0 and 6.9 Hz), 1.26 (1 H, dq, J = 14.0 and 6.9 Hz), 1.37 (1 H, d, J = 8.6 Hz), 1.50 (1 H, d, J = 8.6 Hz), 1.99 (2 H, d, J = 5.8 Hz), 2.45 (1 H, dd, J = 9.9 and 3.0 Hz), 2.97 (1 H, t, J = 11.7 Hz)8 2.98 (1 H, dd, J = 8.7 and 4.6 Hz), 3.07 (1 H, bs), 3.19 (1 H, dd, J = 11.8 and 6.9 Hz), 3.34 (1 H, bs), 3.58 (1 H, s), 3.85 (3 H, s), 3.87 (3 H, s), 4.68 (1 H, dd, J = 12.0 and 6.9 Hz), 5.95 (1 H, bs), 6.21 (2 H, m), 6.65 (1 H, dd, J = 8.4 and 2.4 Hz), 7.03 (1 H, d, J = 8.4 Hz), 7.18 (5 H, s), 7.48 (1 H, bs); MS calcd for $C_{33}H_{34}N_2O_4S$, m/e 554.2239; found 554.2212. The rotation was not recorded, since a pure 11-epimer could not be isolated in the chiral series.

2,3,6,7-Tetradehydro-1-carbomethoxy-11β-(phenylthio)-16-methoxyaspidospermidin-8-one (34) (11α- and 11β-Epimers). A solution of **33** (725 mg, 1.31 mmol) in dry toluene (30 mL) was degassed (freeze–thaw, three times) and heated at 200 °C for 24 h in a resealable Carius tube. The solution was evaporated in vacuo, and the residue was chromatographed over silica gel, eluting with 60% EtOAc/hexane, to give **34** (540 mg, 86%) as a mixture of epimers at C-11 (ca. 9:1 β:α). The major (β) epimer had the following: IR ($CHCl_3$) 2950, 1720, 1660, 1600, 1400 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (11β-epimer) δ 0.75 (3 H, t, J = 7.4 Hz), 1.13 (1 H, dq, J = 14.7 and 7.3 Hz), 1.26 (1 H, dq, J = 14.7 and 7.3 Hz), 2.10 (2 H, d, J = 6.0 Hz), 3.27 (1 H, t, J = 11.7 Hz), 3.38 (1 H, dd, J = 11.7 and 5.9 Hz), 3.87 (3 H, s), 3.91 (3 H, s), 4.11 (1 H, s), 4.49 (1 H, dd, J = 17.7 and 6.4 Hz), 5.93 (1 H, d, J = 10.1 Hz), 6.11 (1 H, bs), 6.42 (1 H, d, J = 10.1 Hz), 6.67 (1 H, dd, J = 8.1 and 2.7 Hz), 7.14 (1 H, d, J = 8.0 Hz), 7.24 (5 H, m), 7.52 (1 H, bs); MS calcd for $C_{28}H_{28}N_2O_4S$, m/e 488.1770; found 488.1781. The rotation was not recorded, since a pure 11-epimer could not be isolated in the chiral series. The derived thioamide 11β-isomer has mp 167–168 °C.[21]

(−)-2,3-Didehydro-1-carbomethoxy-16-methoxyaspidospermidin-8-one (35) (X = O). W-2 Raney nickel (ca. 5 g) was added in portions to a solution of **34** (200 mg, 4.10 mM) in ethyl acetate (30 mL) heated at reflux. After 4.5 h the mixture was filtered through Celite, evaporated in vacuo, and filtered through Celite in chloroform. Evaporation of the chloroform solution in vacuo gave (−)-**35** (148 mg, 94.5%) as a white foam: IR ($CHCl_3$) 2960, 1720, 1690, 1445, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.73 (3 H, t, J = 7.3 Hz), 1.02 (1 H, dq, J = 13.2 and 6.7 Hz), 1.15 (1 H, dq, J = 13.2 and 6.7 Hz), 1.37 (1 H, m), 1.78–1.98 (4 H, m), 2.09 (1 H, dd, J = 16.0 and 8.1 Hz), 2.34 (2 H, m), 3.32 (1 H, dt, J = 18.3 and 6.1 Hz), 3.44 (1 H, d, J = 1.4 Hz), 3.82 (3 H, s), 3.95 (3 H, s), 4.06 (1 H, dd, J = 14.7 and 7.4 Hz), 6.05 (1 H, m), 6.60 (1 H, dd, J = 8.2 and 2.4 Hz), 7.04 [1 H, d, J = 8.4 Hz), 7.49 (1 H, bs); MS calcd for $C_{22}H_{26}N_2O_4$, m/e 382.1892; found 382.1896; $[\alpha]^{25}_D$ −7.6 (c 1.6 in CH_2Cl_2). (+)-**35** (X = O) had $[\alpha]^{25}_D$ + 14.8° (c 4.0 in CH_2Cl_2).

(+)-2,3-Didehydro-1-carbomethoxy-16-methoxyaspidospermidine-8-thione (36) (X = S). A solution of **35** (193 mg, 0.51 mmol) in dry THF (15 mL) was treated with Belleau's reagent (133 mg, 0.25 mmol) at 0 °C. After 0.45 h at 20 °C the mixture was evaporated in vacuo, and the residue was chromatographed over silica gel, eluting with 2% Et_2O/CH_2Cl_2, to give **36** (180 mg, 89%): IR ($CHCl_3$) 2960, 1720, 1620, 1490, 1450, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.75 (3 H, t, J = 7.3 Hz), 1.02–1.26 (3 H, m), 1.81 (1 H, dd, J = 15.9 and 3.4 Hz), 2.00 (3 H, m), 2.23 (1 H, dd, J = 16.0 and 8.1 Hz), 2.56 (1 H, dt, J = 7.2 and 3.4 Hz), 3.12 (1 H, dt, J = 14.6 and 3.2 Hz), 3.37 (1 H, s), 3.68 (1 H, m), 3.83 (3 H, s), 3.97 (3 H, s), 4.48 (1 H, dd, J = 14.0 and 7.0 Hz), 6.13 (1 H, m), 6.61 (1 H, dd, J = 8.3 and 2.3 Hz), 7.05 (1 H, d, J = 8.4 Hz), 7.05 (1 H, bs); MS calcd for $C_{22}H_{26}N_2O_3S$, m/e 398.1664; found 398.1628; $[\alpha]^{23}_D$ +140° (c 4.2 in CH_2Cl_2). (−)-**36** (X = S) had $[\alpha]^{25}_D$ −133° (c 3.8 in CH_2Cl_2).

(+)-2,3,6,7-Tetradehydro-1-carbomethoxy-16-methoxyaspidospermidine-8-thione (38). Dry (i-Pr)$_2$NEt (218 μL, 1.26 mmol) was injected into a stirred solution of the thiolactam **36** (100 mg, 251 μM) in dry toluene (10 mL) heated at reflux. To this solution freshly prepared *p*-toluenesulfinyl chloride (87 μL, 627 μM) was added, and after 10 min the mixture was evaporated in vacuo. The residue was dissolved in chloroform (1 mL) and purified by PLC, eluting with 30% EtOAc/hexane, to give **38** (84.1 mg, 84.5%) as a yellow foam: IR ($CHCl_3$) 2980, 1740, 1630, 1490, 1450, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.76 (3 H, t, J = 7.2 Hz), 1.13 (1 H, dq, J = 13.6 and 7.0 Hz), 1.29 (1 H, dq, J = 13.6 and 7.0 Hz), 2.04 (4 H, m), 3.72 (1 H, m), 3.83 (3 H, s), 3.93 (1 H, s), 3.96 (3 H, s), 4.59 (1 H, m), 6.08 (1 H, m), 6.14 (1 H, d, J = 9.7 Hz), 6.46 (1 H, d, J = 9.7 Hz), 6.63 (1 H, dd, J = 8.0 and 2.3 Hz), 7.12 (1 H, d, J = 8.1 Hz), 7.51 (1 H, bs); MS calcd for $C_{22}H_{24}N_2O_3$, m/e 396.1508; found, 396.1515. $[\alpha]^{26}_D$ +82° (c 1.7 in $CHCl_3$). (−)-**38** has $[\alpha]^{20}_D$ −64.7° (c 4.3 in CH_2Cl_2).

(+)-2,3,6,7-Tetradehydro-1-carbomethoxy-16-methoxyaspidospermidine (39). A solution of the thiolactam **38** (100.5 mg, 254 μmol) in dry methyl iodide (5.0 mL) was heated at reflux for 1 h. The mixture was evaporated, and the residue was dissolved in dry methanol (5.0 mL), cooled to 0 °C, and treated with sodium borohydride (excess, added in three portions). After 2 h the mixture was evaporated, and the residue was dissolved in chloroform (5 mL), washed with 0.5 N HCl (2.0 mL), and neutralized with aqueous sodium bicarbonate solution. The pH was adjusted to ca. pH 11 with 2 M NaOH (1 mL), and the solution was extracted with chloroform (3 × 2 mL). The dried ($MgSO_4$) extract was evaporated in vacuo, and the residue was purified by PLC, eluting with 25% EtOAc–hexane to give (+)-**39** (71.1 mg, 76.5%): IR ($CHCl_3$) 2970, 2800, 1720, 1620, 1450, 1360 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 0.68 (3 H, t, J = 7.5 Hz), 1.13 (1 H, dq, J = 14.0 and 7.3 Hz), 1.27 (1 H, dq, J = 14.0 and 7.3 Hz), 1.69 (1 H, dd, J = 11.3 and 4.7 Hz), 1.96 (1 H, m), 2.11 (1 H, m), 2.32 (1 H, m), 2.69 (1 H, s), 2.75 (1 H, t, J = 7.1 Hz), 2.84 (1 H. dd, J = 15.2 and 3.2 Hz), 2.95 (1 H, d, J = 16.0 Hz), 3.29 (1 H, dd, J = 16.0 and 4.3 Hz), 3.44 (3 H, s), 3.45 (3 H, s), 5.65 (2 H, m), 6.17 (1 H, d, J = 8.3 Hz), 6.60 (1 H, dd, J = 8.1 and 2.3 Hz), 7.00 (1 H, d, J = 8.2 Hz), 8.01 (1 H, bs) (considerable line broadening was observed, but it was reduced when the spectrum was run in C_6D_6); MS calcd for $C_{22}H_{26}N_2O_3$, m/e 366.1943; found, 366.1937; $[\alpha]^{27}_D$ +15° (c 0.17 in MeOH).

(+)-2,3,6,7-Tetradehydro-1-carbomethoxy-3-formyl-16-methoxyaspidospermidine (40). Freshly distilled $POCl_3$ (966 μL, 10.4 mmol) was added dropwise to a stirred solution of the amine **39** (190 mg, 519 μM) in dry DMF (5.0 mL) at 0 °C. After 10 min at 0 °C the mixture was allowed to warm to room temperature and left for 72 h. The mixture was added to a rapidly stirred ice-cooled mixture of $CHCl_3$ (30 mL) and 2 M NaOH (20 mL). After 30 min the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 15 mL). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, and the residue was purified by column chromatography over silica gel, eluting with 30% EtOAc/hexane, to give **40** and the 15-formyl derivative of **39**, total weight 158 mg, 77% (3.1:1). In this experiment they were not separated, but carried forward into the next step, since the unwanted 15-formyl compound was readily removed. In a separate experiment on a small scale (26.9 mg of **39**) the 3-formyl derivative **40** and the 15-formyl isomer were separated by PLC to give **40**: IR ($CHCl_3$) 3020, 1730, 1670, 1450 cm^{-1}; UV (EtOH) 233 and 275 nm (ε 11 380 and 6700, respectively); ^1H NMR (300 MHz, $CDCl_3$) δ 0.58 (3 H, t, J = 7.8 Hz), 0.89 (2 H, m), 1.76 (1 H, dd, J = 11.5 and 4.9 Hz), 2.16 (1 H, m), 2.34 (1 H, d, J = 14.8 Hz), 2.50 (1 H, m), 2.61 (1 H, s), 2.66 (1 H, d, J = 14.8 Hz), 3.06 (2 H, m), 3.59 (1 H, dd, J = 16.2 and 4.7 Hz), 3.84 (3 H, s), 3.91 (3 H, s), 5.68 (1 H, d, J = 10.5 Hz), 5.80 (1 H, dd, J = 10.5 and 4.0 Hz), 6.64 (1 H, dd, J = 8.2 and 2.4 Hz), 7.12 (1 H, d, J = 8.2

Hz), 7.36 (1 H, J = 2.4 Hz), 9.95 (1 H, s); MS calcd for $C_{23}H_{26}N_2O_4$, m/e 394.1893; found, 394.1917; $[\alpha]^{25}_D$ +58° (c 0.36 in MeOH). (-)-**40** has $[\alpha]^{20}_D$ -51.1° (c 1.1 in CH_2Cl_2). The 15-formyl derivative of **39** has the following: IR ($CHCl_3$) 2940, 1720, 1670, 1600, 1480, 1450, 1380 cm^{-1}; UV (EtOH) 290 and 340 nm (ϵ 6620 and 9930, respectively); ^1H NMR (300 MHz, $CDCl_3$) δ 0.67 (3 H, t, J = 7.3 Hz), 0.96 (1 H, dq, J = 14.0 and 7.3 Hz), 1.09 (1 H, dq, J = 14.0 and 7.3 Hz), 1.70 (1 H, dd, J = 11.5 and 4.7 Hz), 2.04 (2 H, m), 2.53 (2 H, m), 2.67 (1 H, s), 3.02 (1 H, t, J = 6.6 Hz), 3.13 (1 H, d, J = 15.5 Hz), 3.50 (1 H, dd, J = 15.5 and 5.0 Hz), 3.98 (6 H, s), 5.65 (1 H, d, J = 10.1 Hz), 5.82 (1 H, dd, J = 10.1 and 3.9 Hz), 5.92 (1 H, dd, J = 8.6 and 3.0 Hz), 7.68 (1 H, s), 7.69 (1 H, d, J = 1.7 Hz), 10.18 (1 H, s); MS calcd for $C_{23}H_{26}N_2O_4$, m/e 394.1893; found, 394.1906; $[\alpha]^{25}_D$ +26° (c 0.1 in $CHCl_3$).

(-)-1-Carbomethoxy-16-methoxytabersonine (41) and (-)-16-Methoxytabersonine (4). A solution of sodium chlorite (184 μL, 1 M) was added to a mixture of (+)-**40**/(+)-15-formyl derivative (65.9 mg, 167 μM) and amidosulfonic acid (100 mg, 1.03 μM) in acetone (6 mL), isopropenyl acetate (1.8 mL), and 10% NaH_2PO_4-H_2O buffer (1.8 mL) at 0 °C. After 0.5 h ethereal diazomethane was added until a yellow color persisted. The solvent was evaporated to low bulk, and the residue was diluted with saturated aqueous sodium bicarbonate solution (5 mL) and extracted with chloroform (4 × 4 mL). The extract was filtered through $MgSO_4$ and evaporated to leave a yellow gum. On a small scale this was purified by PLC, eluting with 50% EtOAc/hexane, to give **41** (65%): IR ($CHCl_3$) 3010, 2960, 1740, 1600, 1440, 1370 cm^{-1}; UV (EtOH) 213, 238, and 281 nm (ϵ 18 320, 9670, and 3820, respectively); ^1H NMR (300 MHz, $CDCl_3$) δ 0.62 (3 H, t, J = 7.2 Hz), 1.02 (2 H, m), 1.72 (1 H, dd, J = 11.4 and 5.0 Hz), 2.13 (1 H, m), 2.79 (1 H, dd, J = 15.0 and 2.0 Hz), 2.46 (1 H, m), 2.59 (1 H, s), 2.69 (1 H, d, J = 15.0 Hz), 3.05 (2 H, m), 3.48 (1 H, dd, J = 16.0 and 4.7 Hz), 3.74 (3 H, s), 3.81 (6 H, s), 3.83 (3 H, s), 5.63 (1 H, d, J = 10.0 Hz), 5.80 (1 H, dd, J = 10.0 and 5.0 Hz), 6.57 (1 H, dd, J = 8.4 and 2.6 Hz), 7.07 (1 H, d, J = 8.4 Hz), 7.45 (1 H, d, J = 2.7 Hz); MS calcd for $C_{24}H_{28}N_2O_5$, m/e 424.1998; found, 424.1993; $[\alpha]^{27}_D$ -62° (c 0.23 in CH_2Cl_2). (+)-**41** has $[\alpha]^{20}_D$ +56° (c 1.1 in CH_2Cl_2).

The above yellow gum was dissolved in dry methanol (3 mL) at 4 °C and treated with NaOMe in methanol (6 mL, 2 M). After the mixture was stirred at 24 °C for 5 h, it was cooled to 4 °C, and acetic acid (720 μL) was added. The mixture was concentrated to low bulk and diluted with saturated aqueous sodium bicarbonate solution (4 mL) and 2 M aqueous sodium hydroxide (4 mL). The solution was extracted with $CHCl_3$ (4 × 4 mL), and the combined extracts were filtered through $MgSO_4$ and evaporated to leave a yellow gum. Column chromatography over silica gel, eluting with 23% EtOAc-hexane, gave a colorless glass, (-)-**4** (31.0 mg, 75.1% from **40**): IR ($CHCl_3$) 3380, 2960, 2780, 1670, 1620, 1440, 1260 cm^{-1}; UV (EtOH) 244 and 326 nm (ϵ 7250 and 9660, respectively); ^1H NMR (300 MHz, C_6D_6) δ 0.73 (3 H, t, J = 7.1 Hz), 1.02 (1 H, dq, J = 14.5 and 7.2 Hz), 1.18 (1 H, dq, J = 14.5 and 7.2 Hz), 1.72 (1 H, dd, J = 11.7 and 7.6 Hz), 2.19 (1 H, m), 2.48 (1 H, m), 2.72 (2 H, s), 2.90 (2 H, s), 3.01 (1 H, d, J = 14.8 Hz), 3.22 (1 H, dd, J = 14.8 and 7.6 Hz), 3.32 (3 H, s), 3.59 (3 H, s), 5.68 (2 H, m), 5.93 (1 H, d, J = 2.4 Hz), 6.45 (1 H, dd, J = 8.2 and 2.4 Hz), 6.99 (1 H, d, J = 8.2 Hz), 9.40 (1 H, bs); MS calcd for $C_{22}H_{26}N_2O_3$, m/e 366.1943; found, 366.1920; $[\alpha]^{27}_D$ -196° (c 0.17 in $CHCl_3$) [the rotation varies with the age of the sample; in another experiment $[\alpha]^{29}_D$ -253° (c 1.55 in $CHCl_3$)]. (+)-**4** has $[\alpha]^{20}_D$ +253° (c 0.32 in CH_2Cl_2) (lit. values:[4,5] $[\alpha]^{23}_D$ -310 ± 2° (c 0.23 in $CHCl_3$), $[\alpha]^{24}_D$ -211° (c 0.114 in $CHCl_3$). The ^1H NMR spectra of both (+)- and (-)-16-methoxytabersonine were identical with that of (±)-16-methoxytabersonine provided by Professor L. Overman.

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Total Synthesis of (-)-Laurenyne. Use of Acetal-Initiated Cyclizations To Prepare Functionalized Eight-Membered Cyclic Ethers

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Abstract: A highly stereocontrolled and enantioselective synthesis of the title compound **1** is described. The key step is cyclization of mixed acetal **13** to yield oxocene **14**. This step not only forms the eight-membered ring but also introduces the Δ^4-unsaturation and cis-oriented side chains of the marine natural product. This synthesis also demonstrates that the absolute configuration for natural laurenyne must be revised to 2*R*,7*R*,8*R* (i.e., enantiomeric with **1**). Also reported are exploratory studies that help to define the scope and limitations of the acetal cyclization route to eight-membered ring ethers.

A variety of structurally unusual C_{15} nonisoprenoid metabolites have been isolated from red algae as well as the molluscs that feed on them.[2] The vast majority of these are cyclic ethers, which are elaborated in a fascinating variety of ring sizes. Since the pioneering isolation and structure elucidation of laurencin (**2**) by Irie and co-workers,[3] halogenated eight-membered cyclic ethers (oxocanes) and enyne side chains have been shown to be common structural features of many of these natural products, particularly those isolated from the genus *Laurencia*. Three representative examples are depicted in Figure 1.

The structure of laurencin was initially suggested on the basis of extensive spectroscopic evidence[3] and later confirmed by a single-crystal X-ray analysis.[4] The absolute configuration was assigned by application of Prelog's atrolactic acid method[5] to a laurencin degradation product[3] and by X-ray crystallography.[4] The structures of most subsequently isolated members of this group, e.g., laurenyne (**1**)[6] and the pinnatifidenynes (**3**),[7] have

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(2) For reviews, see: Moore, R. E. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1978; Vol. 1, Chapter 2. Erickson, K. K. *Ibid.*, 1983; Vol. 5, p 131. Faulkner, D. J. *Natl. Prod. Rep.* **1984**, 251; **1986**, 1.

(3) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193. Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, 1091.

(4) Cameron, A. F.; Cheung, K. K.; Ferguson, G.; Robertson, J. M. *Chem. Commun.* **1965**, 638.

(5) Prelog, V. *Helv. Chim. Acta* **1953**, *36*, 308.

0002-7863/88/1510-2248$01.50/0