Synthesis of Vinca Alkaloids and Related Compounds. 63.[1] A New Synthetic Pathway for Preparing Alkaloids and Related Compounds with the Aspidosperma Skeleton. Total Syntheses of (±)-Vincadifformine, (±)-Tabersonine, and (±)-3-Oxotabersonine

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Compound **3**, which has an indole skeleton containing a masked acryl ester function, was synthesized from the hydrochloride of 2-(ethoxycarbonyl)tryptamine (**2**). The cycloaddition of **3** with methyl 4-formylhexanoate (**21**) or with 5-(benzoyloxy)-2-ethylpentanal (**33**) yielded the starting materials for target compounds (±)-vincadifformine (**4**), (±)-3-oxotabersonine (**42**), and (±)-tabersonine (**43**). The synthesis of vincadifformine (**4**) was achieved in two different ways: via 3-oxovincadifformine (**7**) and via tetracyclic benzoate esters **37** and **38**. The double bond required in tabersonine (**43**) and 3-oxotabersonine (**42**) was introduced by treatment of 3-thioxovincadifformine (**39**) with *p*-toluenesulfinyl chloride.

Introduction

In 1978, Kuehne et al. published the first of a series of papers,[2] entitled *Studies in Biomimetic Alkaloid Syntheses*, dealing with the synthesis of compounds having the aspidosperma skeleton and their analogues. In their approach, the reaction of a suitable aldehyde and a secondary amine having an indoloazepine skeleton afforded the desired end products. Although at that time several methods had been reported in the literature[3] for the preparation of aspidosperma alkaloids, Kuehne et al. were the first to describe a synthesis of the natural products or related compounds by a biomimetic pathway.[4] An unisolated intermediate of general formula **1** (Figure 1) played an important role in the syntheses by Kuehne.

In two earlier publications,[5,6] we also reported the use of a starting material of general formula **1** for the syntheses of target products vincadifformine (**4**), pseudovincadifformine (**5**), and minovine (**6**), as well as 3-oxovincadifformine (**7**) and 3-oxominovine (**8**). The starting compound was, in both cases, the hydrochloride of 2-(ethoxycarbonyl)tryptamine[7] (**2**). The objective of the present work was to develop a convergent synthetic pathway that is suitable for the more convenient and efficient preparation of a number of compounds having the aspidosperma skeleton. The strategy we planned to use was as follows: from indole derivative **2**, we wanted to prepare compound **3**, which, on reaction with suitably substituted aldehydes (**9**), would give—via the unisolated intermediates **1** (R_1 = Bn)—tetracyclic compounds of general formula **10** (Figure 2). Formation of the fifth ring would afford the target compounds. As the aldehyde component could be varied, this strategy would allow the preparation of many analogous compounds; thus, a convenient synthesis of aspidosperma alkaloids and related compounds would become possible. In this article, we report our preparation of key compound **3** and possible uses of this synthetic pathway.

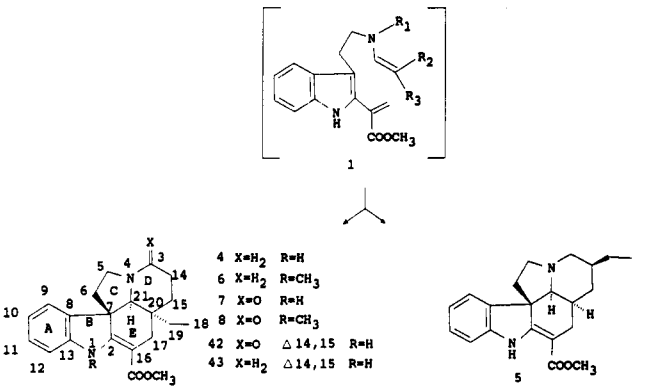

Figure 1.

Results and Discussion

Dibenzyl ester **11** was prepared from the hydrochloride of 2-(ethoxycarbonyl)tryptamine (**2**) as shown in Figure 3. In this reaction sequence, we used the carbon chain extension reaction reported by Kutney et al.[8] at the 2 position of the indole. The extension reaction had also been successfully applied in our work with analogous

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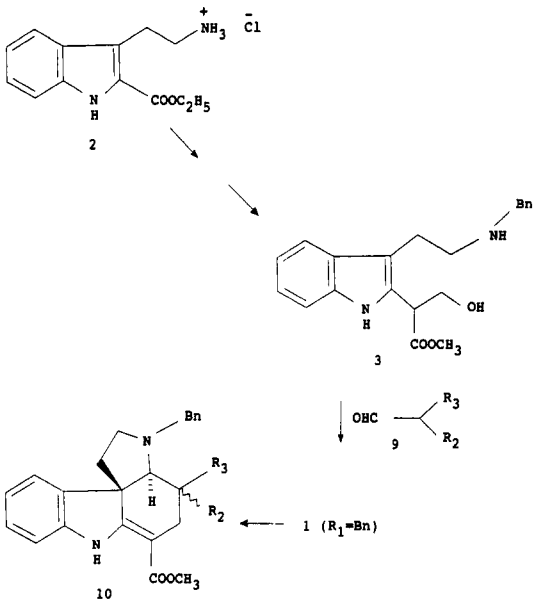

Figure 2.

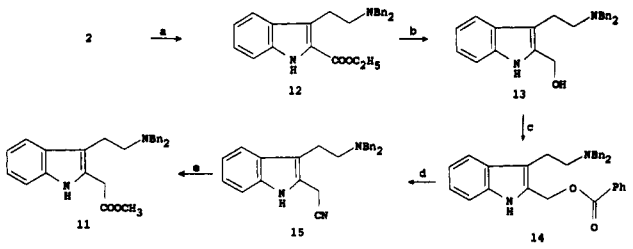

Figure 3. Conditions: (a) BnCl, DMF, rt; (b) $LiAlH_4$, THF, 55 °C; (c) PhCOCl, pyridine, rt; (d) NaCN, DMSO, 70 °C; (e) CH_3OH, HCl (g), Δ.

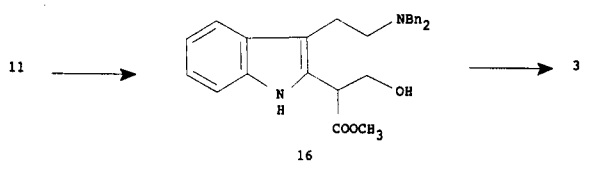

Figure 4.

compounds.[5,6] The overall yield of this reaction sequence was 41% from **2**.

Dibenzyl ester **11** was subjected to Battersby's method[9] for hydroxymethylation to afford compound **16**, from which the required diene structure could be formed by the simple elimination of water. After hydroxymethylation, ester **16** was partially debenzylated to give secondary amine **3**, the structural unit required for the preparation of the enamine function (Figure 4).

The reaction in which the hydroxymethyl group was introduced was thoroughly studied, and some interesting observations were made. The reaction was first effected by the treatment of ester **11** with sodium hydride and methyl formate in benzene. The reaction mixture was then worked up in the usual way, and crude intermediate **17** was dissolved in methanol and reduced with sodium borohydride at −25 °C to afford **16** (62%). If the reaction

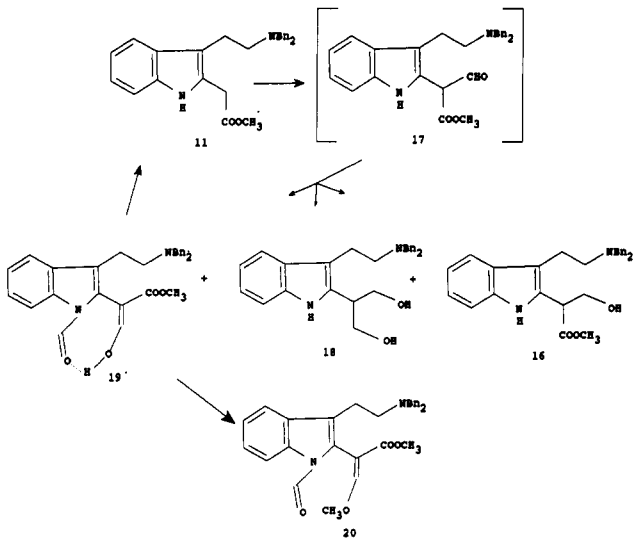

Figure 5.

was done at a higher temperature, a considerable amount of the byproduct, diol **18**, was isolated from the reaction mixture.

Several attempts were made to find a way to eliminate this undesired side reaction. The best result was obtained when the formylation was carried out using methyl formate as the solvent; without further processing, the reaction mixture was diluted with cold methanol, and the resulting solution was reduced with sodium borohydride. These modifications of the procedure eliminated the need for chromatographic purification of the crude product, and a higher yield of crystalline dibenzyl ester **16** was obtained. The reaction mixture, however, still contained two byproducts, diols **18** and **19**. In order to confirm the structure of the latter, enol ether **20** was also prepared by alkylation of **19** with diazomethane. As suggested by the NMR data, the structure of **20** confirmed that compound **19** exists in the enol form stabilized by a hydrogen bridge.

When enol **19** was treated with a saturated solution of hydrogen chloride in methanol, starting ester **11** was recovered. After we determined the structure of byproduct **19**, the surprising fact that in the sodium borohydride reduction the potential formyl group was not converted to the expected alcohol became understandable (Figure 5).

The first aldehyde to be used in the ring closure reaction was methyl 4-formylhexanoate (**21**).[10] We first attempted to effect the reaction of **3** and **21** by refluxing the components in benzene; however, the isolated products corresponded not to the two expected tetracyclic epimers (**22**, **23**) (cf. Figure 7) but to the esters formed by the elimination of water (**24** and **25**, Figure 6). The former product was a benzylazepine derivative that had been prepared earlier by Kuehne et al.[11]

Compound **25** had been previously synthesized in our laboratory[12] in another way, from secondary amine **26**, which had been prepared by the partial debenzylation of ester **11**. Compound **26** had been allowed to react with formaldehyde in an aqueous acidic medium to afford the hydrochloride of **25**. The ^1H NMR spectrum recorded at

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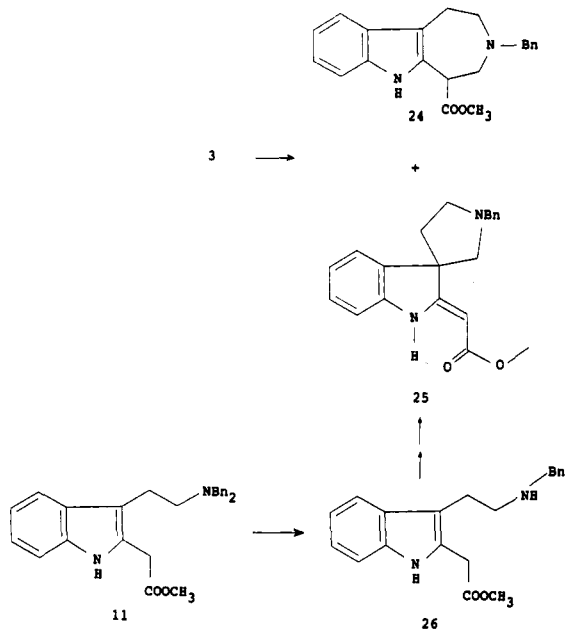

Figure 6.

400 MHz had unequivocally showed that the carbonyl oxygen of the ester group and the hydrogen atom of the indole nitrogen were connected by a hydrogen bridge. We suggest that compound **25** may have been formed from ester **3** by a competing reaction in which the hydroxymethyl group migrated from the carbon to the nitrogen atom to form an α-amino alcohol intermediate and ultimately the spiro compound **25**.

Subjecting **3** and aldehyde **21** to rather vigorous reaction conditions, such as refluxing toluene for 24 h, afforded two products (**22** and **23**) previously reported by Kuehne et al.[13] (Figure 7). By the previously described method,[13] these compounds could be converted to 3-oxovincadifformine (**7**) in one or two steps, in the latter case via secondary amine **27**.

Experiments were also conducted to find out which of the two byproducts (**24** and **25**) (Figure 6) would react with the aldehyde component. Therefore, **24** and **25** were separately caused to react with aldehyde **21**. It was found that azepine ester **24** could be converted into a mixture of the desired end products (**22** and **23**), but spiro compound **25**, after identical treatment, remained unchanged.

Indole derivative **28** (Figure 8), which fits into our strategic plan, was also prepared to test its utility in the cyclization reaction. The synthesis was considerably facilitated by several literature references[14-17] that had reported the addition of pyruvic acid to position 2 of the indole skeleton. Since some of these publications[15,16] also

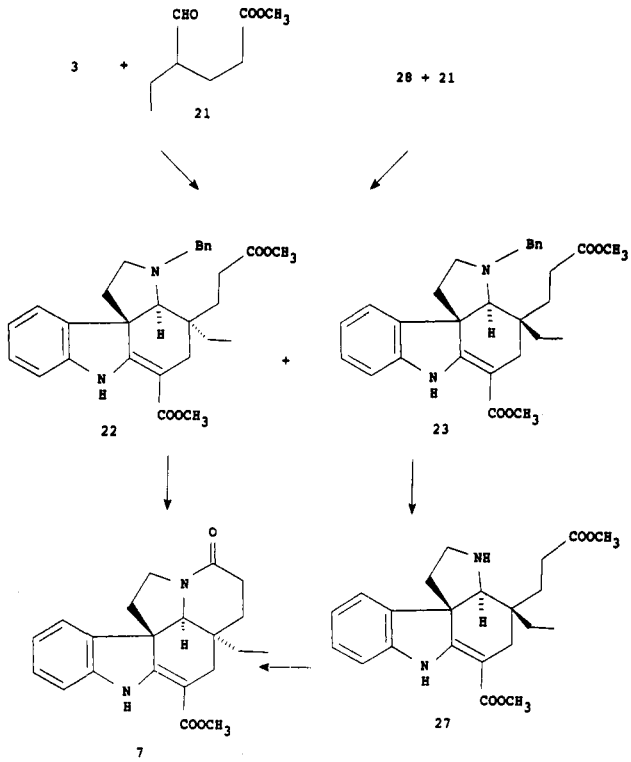

Figure 7.

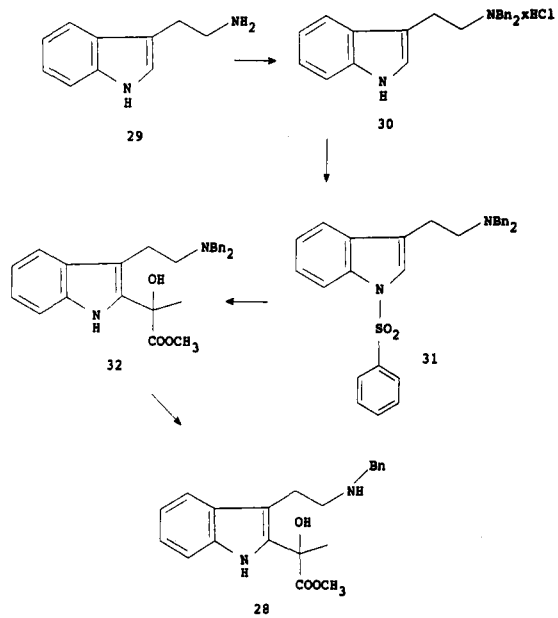

Figure 8.

described the dehydration step, we certainly considered it worthwhile to synthesize this compound. From tryptamine (**29**), the hydrochloride of the N_b-dibenzyl derivative[17] (**30**) was prepared. The N_a nitrogen atom was protected with a benzenesulfonyl group, which was introduced by means of a catalyzed phase-transfer reaction. When the base and methyl pyruvate were used in excess in the addition reaction, this protective group was split off as the sulfonic ester right after the addition.[18] Accordingly, trisubstituted tryptamine derivative **31** was treated with 2.3 molar equiv of *n*-butyllithium, and the resulting dicarbanion was treated with an excess of methyl

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pyruvate. After workup and column chromatographic purification, the expected 2-hydroxypropionic ester (32) was isolated. Ester 32 was subjected to partial debenzylation to give secondary amine 28 in good yield.

A comparison of the overall yields of the two secondary amines (3 and 28) showed that the yield of 3 was 12–15% from 2 and the yield of 28 was 30–35% from tryptamine (29).

The reaction sequence was concluded by effecting the reaction of secondary amine 28 and aldehyde 21 under conditions similar to those used for the reaction of 3 and 21. Since refluxing 28 and 21 in toluene gave only very small quantities of the expected products, the reaction was carried out at a higher temperature, in refluxing xylene. At the higher temperature, intermediates 22 and 23 were isolated in about 20% combined yields (Figure 7).

Comparison of the two alternative synthetic pathways shows that the overall yields of the tetracyclic esters 22 and 23 are almost the same. However, the process starting from tryptamine (29) has an inconvenient step: the formation of the anion by means of *n*-butyllithium and the subsequent addition of the anion to the carbonyl; in addition, the elimination of water from 28 requires much more drastic conditions than the elimination of water from primary alcohol 3. In later experiments, we wanted to allow the indole key compound to react with heat-sensitive aldehydes. For these reasons, the pathway using 3 was used for the remainder of the syntheses.

As a continuation of our work, we attempted to develop a synthetic pathway involving a suitable aldehyde that would allow the preparation of vincadifformine (4) in fewer steps and more directly than before. The first task was to choose an appropriate aldehyde.

The aldehyde had to have a leaving group that would not be so reactive as to take part in the cycloaddition but would, at the required moment and under suitable conditions, be prone to form the fifth ring. We discovered that these conditions were met by the benzoyloxy group. Thus, the first task was the synthesis of aldehyde 33. Compound 34[2] was acylated with benzoyl chloride, and subsequent acid hydrolysis afforded desired aldehyde 33.

Aldehyde 33 and secondary amine 3 were refluxed in toluene, as described previously. A mixture of isomers containing expected tetracyclic esters 35 and 36 was formed in this reaction. The next step of the reaction sequence was effected on the mixture of 35 and 36. The protective benzyl group was removed by hydrogenolysis in glacial acetic acid. The products of the debenzylation were secondary amines 37 and 38, which were separated by preparative thin-layer chromatography.

Next, the internal N-alkylation reaction leading to the formation of ring D was accomplished by refluxing the mixture of 37 and 38 in dimethylformamide for about 1 h. Both isomers afforded vincadifformine (4, Figure 9). The formation of 4 from 38 can be explained in the same way as the formation of 3-oxovincadifformine,[13] i.e., by epimerization at C-21.

The two other alkaloids that were synthesized were tabersonine (43) and 3-oxotabersonine (42). Owing to the presence of a double bond in ring D, we modified our strategy for the synthesis of these compounds. It was deemed impractical to prepare or use an aldehyde partner already containing the double bond required in the product. Since an appropriately masked form could only be prepared with difficulty, we decided to employ the

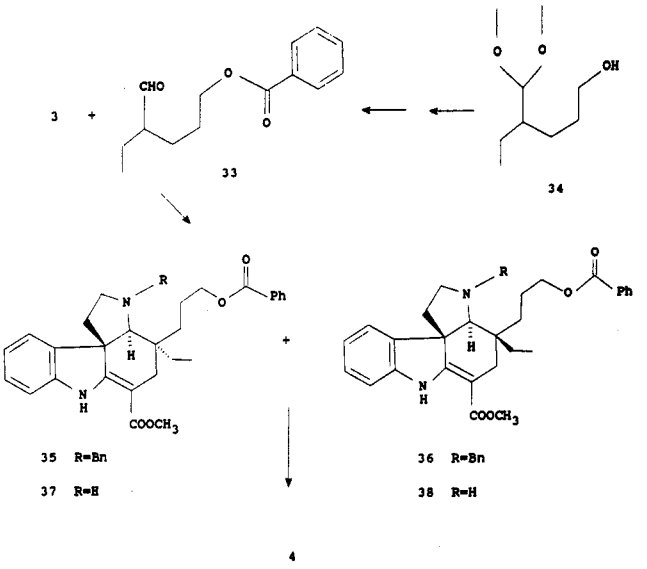

Figure 9.

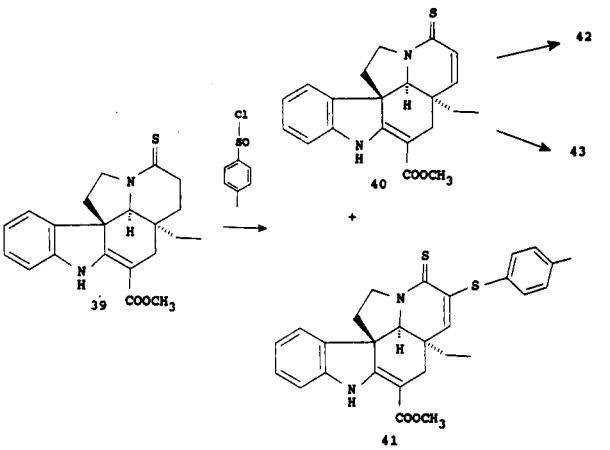

Figure 10.

literature method[19] for forming the double bond via the thiolactam.

The synthesis of the target compounds was simply achieved by starting from 3-thioxovincadifformine[20] (39), which was readily prepared from 3-oxovincadifformine (7) without protection of the indole nitrogen. Accordingly, 3-thioxovincadifformine (39) was made to react with *p*-toluenesulfonyl chloride, in the presence of diisopropylethylamine, by refluxing the mixture in dichloromethane. The isolated main product was unsaturated thiolactam 40, which appeared to be suitable for the preparation of both target compounds. A byproduct characterized by formula 41 was also isolated from the reaction mixture (Figure 10).

A general method was used to prepare tabersonine (43) from thiolactam 40. The thio compound was first refluxed in methyl iodide. Then the excess reagent was removed by distillation, and the residue was dissolved in methanol and reduced with sodium borohydride. Finally, preparative thin-layer chromatography led to the isolation of pure tabersonine (43).[2]

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In the preparation 3-oxotabersonine (42), the sulfur-oxygen exchange was effected with 3-chloroperoxybenzoic acid (*m*-CPBA).[21] When compound 40 was allowed to react with 1.2 equiv of *m*-CPBA at −24 °C in dichloromethane, the alkaloid 3-oxotabersonine (42)[22] was obtained (Figure 10).

The alkaloids synthesized in this work were in all cases compared with authentic natural or semisynthetic products and were found to have identical properties, except for optical rotation.

We intend to use the strategy outlined here for the synthesis of some compounds with pseudoaspidosperma skeleton, thus extending the scope of the method.

Experimental Section

Melting points are uncorrected. Chemical shifts (in parts per million) are relative to internal Me_4Si. The assignments noted with * and ° may be interchanged. Thin-layer chromatography was carried out on silica gel (Kieselgel 60 $PF_{254+366}$). Kieselgel 60 silica gel was used for column chromatography. The organic layers were dried over Na_2SO_4.

N_b,N_b-Dibenzyl-2-(ethoxycarbonyl)tryptamine (12). To a solution of 20 g (74.5 mmol) of 2-(ethoxycarbonyl)tryptamine hydrochloride (2) in anhyd DMF (100 mL) were added 40 g of anhyd K_2CO_3 (290 mmol), 0.2 g (1.2 mmol) of KI, and 25 g (22.7 mL, 17.6 mmol) of benzyl chloride. The mixture was stirred for 4 h at rt and then poured into 1 L of H_2O. The suspension was stirred overnight at rt and then filtered. The product was washed twice with H_2O and recrystallized from methanol to yield 20.7 g (75%) of 12 as white solid: mp 117–118 °C; IR (KBr) 3300 (indole NH), 1680 cm^{-1} (C=O); MS *m/z* (relative intensity) 412 (1.2), 366 (1.0), 306 (1.0), 210 (92.2), 156 (9.0), 128 (9.5), 91 (100.0); ^1H NMR ($CDCl_3$) δ 1.31 (3 H, t, *J* = 7.0 Hz; C2-$COOCH_2CH_3$), 2.80 (2 H, m; C3-CH_2CH_2–), 3.33 (2 H, m; C3-CH_2CH_2–), 3.71 [4 H, s; –$N(CH_2Ph)_2$], 4.29 (2 H, q; C2-$COOCH_2CH_3$), 6.9–7.5 (14 H, m; aromatic H), 9.44 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 14.41 (C2-$COOCH_2CH_3$), 22.66 (C3-CH_2CH_2–), 53.99 (C3-CH_2CH_2–), 58.16 [–$N(CH_2Ph)_2$], 60.43 (C2-$COOCH_2CH_3$), 112.01 (C7), 119.63* (C4), 120.55* (C6), 122.10 (C3), 123.52 (C2), 125.09 (C5), 126.64 (C4′ + C4″), 127.94 (C3a), 128.04 (C3′ + C5′ + C3″ + C5″), 128.58 (C2′ + C6′ + C2″ + C6″), 136.26 (C7a), 139.95 (C1′ + C1″), 162.45 (C2-$COOC_2H5$). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.42; H, 6.88; N, 6.89.

N_b,N_b-Dibenzyl-2-(hydroxymethyl)tryptamine (13). A solution of 20.0 g (48.5 mmol) of 12 in anhyd THF (120 mL) was slowly added from a dropping funnel to an ice-cooled suspension of 3.5 g of $LiAlH_4$ in anhyd THF (200 mL). During the addition, the reaction temperature was kept below 40 °C. The reaction mixture was then warmed to 50–55 °C, allowed to stir for 3.5 h, and then cooled below 20 °C. To the suspension were added dropwise 20 mL of 2 M NaOH and 30 mL of H_2O. The reaction mixture was filtered, the white salts were washed twice with 100 mL of CH_2Cl_2, and the combined filtrate was evaporated in vacuo. To the residue were added 300 mL of CH_2Cl_2 and 300 mL of H_2O. After separation of the two phases, the aqueous layer was extracted twice with 60 mL of CH_2Cl_2, and the combined organic layers were dried and evaporated in vacuo to yield 17.5 g (97%) of 13 as a light yellow oil: IR (neat) 3400–3200 cm^{-1} (indole NH, OH); MS *m/z* (relative intensity) 370 (9.0), 210 (100.0), 160 (1.5), 143 (4.0), 130 (1.9), 91 (83.3); ^1H NMR ($CDCl_3$) δ 2.1 (1 H, br s; C2-CH_2OH), 2.55–2.95 (4 H, m; C3-CH_2CH_2– + C3-CH_2CH_2–), 3.67 [4 H, s; –$N(CH_2Ph)_2$], 4.59 (2 H, s; C2-CH_2OH), 6.9–7.4 (14 H, m; aromatic H), 8.06 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.20 (C3-CH_2CH_2–) 53.66 (C3-CH_2CH_2–), 53.83 (C2-CH_2OH), 58.83 [–$N(CH_2Ph)_2$], 110.97 (C7), 111.32 (C3), 118.61 (C4), 119.12 (C8), 121.92 (C5), 126.95 (C4′ + C4″), 128.03 (C3a), 128.13 (C3′ + C5′ + C3″ + C5″), 129.12 (C2′ + C6′ + C2″ + C6″), 134.09 (C2), 135.55 (C7a), 138.62 (C1′ + C1″).

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N_b,N_b-Dibenzyl-2-[(benzoyloxy)methyl]tryptamine (14). To an ice-cooled solution of 20.0 g (54.0 mmol) of 13 and 0.40 g (2.7 mmol) of DMAP in anhyd pyridine (120 mL) was added dropwise 6.9 mL (59.8 mmol) of benzoyl chloride. The reaction mixture was allowed to stir for 4.5 h at rt and then poured into 1 L of H_2O. The product solidified after about 2 h. It was filtered, washed twice with H_2O, powdered in a mortar, washed again with 500 mL of H_2O, and dried in the air to yield 23.8 g (93%) of 14 as a white solid: mp 96–97 °C; IR (KBr) 3350 (indole NH); 1710 cm^{-1} (CO); MS *m/z* (relative intensity) 474 (1.4), 384 (1.4), 352 (1.4), 262 (3.8), 210 (55.5), 143 (25.0), 122 (88.4), 105 (100.0), 91 (66.6), 77 (92.2), 51 (44.0) ^1H NMR ($CDCl_3$) δ 2.65–3.15 (4 H, m; C3-CH_2CH_2– + C3-CH_2CH_2–), 3.76 (4 H, s; $N(CH_2Ph)_2$), 5.32 (2 H, s; C2-CH_2O–), 6.9–8.05 (19 H, m; aromatic H), 8.46 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.22 (C3-CH_2), 54.57 (C3-CH_2CH_2), 57.93 (C2-CH_2O), 58.70 ($N(CH_2Ph)_2$), 111.05 (C8), 114.63 (C3), 119.27* (C5), 119.30* (C7), 122.76 (C6), 126.88 (C4′ + C4″), 127.58 (C4), 128.23 (C3′ + C5′ + C3″ + C5″), 128.36 (C3‴ + C5‴), 128.79 (C2′ + C6′ + C2″ + C6″), 129.14 (C2), 129.76 (C2‴ + C6‴), 129.83 (C1‴), 133.18 (C4‴), 135.89 (C9), 139.83 (C1′ + C1″), 167.54 (OCOPh). Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.87; H, 6.42; N, 5.83.

N_b,N_b-Dibenzyl-2-(cyanomethyl)tryptamine (15). To a solution of 20.0 g (42.2 mmol) of 14 in 200 mL of anhyd DMSO were added 4.0 g (61.4 mmol) of KCN, and the reaction mixture was stirred for 1 h at rt and 1 h at 70–73 °C. After the mixture cooled, it was poured into 1.5 L of 5% $NaHCO_3$ solution and extracted three times with 300 mL of CH_2Cl_2. The combined organic layers were extracted twice with 10% aqueous NaCl, dried, and evaporated in vacuo. The residue was dissolved in 80 mL of methanol, left in the refrigerator overnight, filtered, washed with 20 mL of cold methanol, and dried to yield 11.8 g (74%) of 15 as a light brown solid: mp 104–106 °C; IR (KBr) 3300 (indole NH); 2280 cm^{-1} (nitrile); MS *m/z* (relative intensity) 379 (3.9), 210 (83.1), 169 (5.5), 115 (3.9), 91 (100.0), 65 (7.8); ^1H NMR ($CDCl_3$) δ 2.5–3.0 (4 H, m; C3-CH_2CH_2– + C3-CH_2CH_2–), 3.53 (2 H, s; C2-CH_2CN), 3.71 [4 H, s; –$N(CH_2Ph)_2$], 6.9–7.4 (14 H, m; aromatic H), 7.95 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 15.04 (C2-CH_2CN), 22.35 (C3-CH_2CH_2–), 53.57 (C3-CH_2CH_2–), 58.91 [–$N(CH_2Ph)_2$], 110.92 (C7), 112.74 (C3), 116.61 (CN), 118.75 (C4), 119.73 (C6), 121.69 (C2), 122.51 (C5), 126.99 (C4′ + C4″), 127.95 (C3a), 128.26 (C3′ + C5′ + C3″ + C5″), 128.84 (C2′ + C6′ + C2″ + C6″), 135.71 (C7a), 139.65 (C1′ + C1″). Anal. Calcd for $C_{26}H_{25}N_3$: C, 82.28; H, 6.64; N, 11.07. Found: C, 82.10; H, 6.49; N, 11.34.

N_b,N_b-Dibenzyl-2-[(methoxycarbonyl)methyl]tryptamine (11). a. Into a refluxing solution of 5.0 g (13.2 mmol) of 15 in anhyd methanol (70 mL) was bubbled dry HCl gas continuously for 2 h. The cold reaction mixture was poured onto crushed ice (100 g), saturated Na_2CO_3 solution was added until the pH value of the aqueous solution rose to between 8 and 9, and the mixture was extracted three times with CH_2Cl_2 (300 mL). The combined organic phases were dried and evaporated in vacuo. The brown oil was crystallized from methanol, and filtration yielded 4.5 g (82%) of 11 as a light brown solid: mp 80–82 °C; IR (KBr) 3350 cm^{-1} (indole NH); 1730 cm^{-1} (CO); MS *m/z* (relative intensity) 412 (9.1), 210 (100.0), 91 (74.3); ^1H NMR ($CDCl_3$) δ 2.5–3.0 (4 H, m; C3-CH_2CH_2– + C3-CH_2CH_2–), 3.58 (2 H, s; C2-CH_2), 3.61 (3 H, s; $COOCH_3$), 3.71 [4 H, s; –$N(CH_2Ph)_2$], 6.85–7.5 (14 H, m; aromatic H), 8.36 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.20 (C3-CH_2CH_2–), 31.44 (C2-CH_2–), 52.15 ($COOCH_3$), 53.88 (C3-CH_2CH_2–), 58.62 [–$N(CH_2Ph)_2$], 110.64 (C7), 111.76 (C3), 118.50 (C4), 119.16 (C5), 121.66 (C6), 126.44 (C2), 126.81 (C4′ + C4″), 128.18 (C3a + C3′ + C5′ + C3″ + C5″), 128.75 (C2′ + C6′ + C2″ + C6″), 133.75 (C7a), 139.87 (C1′ + C1″), 170.97 ($COOCH_3$). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.40; H, 6.90; N, 6.96.

b. A solution of 100 mg (0.23 mmol) of 19 in 10 mL of anhyd methanol saturated with HCl was stirred at rt for 24 h. The reaction mixture was poured into 10% Na_2CO_3 aqueous solution (50 mL) and extracted twice with CH_2Cl_2 (30 mL); the combined organic layers were dried and evaporated in vacuo. The residue was crystallized from methanol to yield 50 mg (54%) of 11 as a light brown solid, which was identical to 11 prepared by method a.

Hydroxymethylation of 11. To a solution of 3 g (7.3 mmol)

of 11 in anhyd methyl formate (60 mL) was added 1 g of NaH (60% dispersion in mineral oil, 25 mmol), and the reaction mixture was refluxed for 1.5 h. The mixture was cooled to below −20 °C, and at this temperature anhyd methanol (90 mL) and glacial acetic acid (3 mL) were added. With the temperature below −20 °C, 3 g of sodium borohydride (79.3 mmol) was added, and the reaction mixture was stirred for 1 h at this temperature. To the cold solution was added hydrochloric acid (5 M, 5 mL), and the mixture was allowed to warm to rt and neutralized with saturated Na_2CO_3 solution (vigorous foaming). The mixture was extracted twice with CH_2Cl_2 (100 mL), and the combined organic layers were dried and evaporated in vacuo. The brown residue was treated twice with petroleum ether (bp 35–60 °C) and evaporated again. The residue was recrystallized from methanol to yield 2.0 g (62%) of **16** as a light brown solid: mp 113–114 °C; IR (KBr) 3500–3200 (indole NH, OH); 1743 cm^{-1} (CO); MS *m/z* (relative intensity) 442 (6.1), 210 (100.0), 91 (61.1); ^1H NMR ($CDCl_3$) δ 2.1 (1 H, br s; OH), 2.55–3.0 (4 H, m; C3-CH_2CH$_2$– + C3-CH$_2$CH_2–), 3.61 (3 H, s; COOCH_3), 3.73 [4 H, s; –N(CH$_2$Ph)$_2$], 3.87 (3 H, s; C2-CHCH$_2$OH), 6.9–7.5 (14 H, m; aromatic H), 8.66 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.18 (C3-CH$_2$CH$_2$–), 44.50 (C2-CH), 52.34 (COOCH$_3$), 54.05 (C3-CH$_2$CH$_2$–), 58.72 [–N(CH$_2$Ph)$_2$], 63.90 (CH$_2$OH), 110.92 (C7), 112.24 (C3), 118.66 (C4), 119.24 (C5), 121.98 (C6), 126.89 (C4′ + C4″), 127.79 (C3a), 128.22 (C3′ + C5′ + C3″ C5″), 128.71 (C2), 128.88 (C2′ + C6′ + C2″ + C6″), 135.70 (C7a), 139.74 (C1′ + C1″), 173.04 (COOCH$_3$). Anal. Calcd for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 76.08; H, 6.72; N, 6.20.

The filtrate was evaporated in vacuo, and the two main components of the residue were separated by preparative thin-layer chromatography with chloroform–methanol (9:1). The more polar compound (**18**) (R_f = 0.44) was obtained as a yellow oil (200 mg, 6.7%): IR (neat) 3500–3100 cm^{-1} (indole NH, OH); MS *m/z* (relative intensity) 414 (3.0), 210 (100.0), 91 (66.3) ^1H NMR ($CDCl_3$) δ 2.56 (2 H, br s; OH) 2.5–3.0 (5 H, m; C2-CH + C3-CH_2CH$_2$– + C3-CH$_2$CH_2–), 3.72 [4 H, s; –N(CH$_2$Ph)$_2$], 3.5–4.0 [4 H, m; C2-CH(CH_2OH)$_2$], 6.85–7.5 (14 H, m; aromatic H), 8.80 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.10 (C3-CH$_2$CH$_2$–), 40.09 (C2-CH), 54.08 (C3-CH$_2$CH$_2$–), 58.62 [–N(CH$_2$Ph)$_2$], 63.50 [CH(CH$_2$OH)$_2$], 110.08 (C3), 110.82 (C7), 118.16 (C4), 118.97 (C5), 121.29 (C6), 127.19 (C4′ + C4″), 127.76 (C3a), 128.30 (C3′ + C5′ + C3″ + C5″), 129.15 (C2′ + C6′ + C2″ + C6″), 134.57 (C2), 135.55 (C7a), 138.60 (C1′ + C1″).

Crystallization of the less polar compound (**19**) (R_f = 0.7) from methanol afforded white crystals (300 mg, 9.5%): mp 135–137 °C; IR (KBr) 3500–3300 (OH); 1690 (CO); 1650 (amide CO); 1600 cm^{-1} (C=C); ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.5–3.3 [4 H, m; C3-(CH$_2$)$_2$N], 3.60 (3 H, s; COOCH$_3$), 3.6–4.1 [4 H, m; N(CH$_2$Ph)$_2$], 6.8–7.6 (13 H, m; aromatic H), 8.33 (1 H, d, *J* = 7.6 Hz; C7-H), 8.76 (1 H, s; NCHO), 8.98 (1 H, s; C=CHOH); ^{13}C NMR ($CDCl_3$ + DMSO-d_6) δ 22.01 (C3-CH$_2$CH$_2$–), 50.89 (OCH$_3$), 50.96 (C3-CH$_2$CH$_2$–), 58.49 [–N(CH$_2$Ph)$_2$], 94.74 (C2-C=), 115.46 (C7), 118.15 (C4), 118.63 (C3), 123.50 (C5), 124.28 (C6), 127.71 (C4′ + C4″), 128.23 (C3′ + C5′ + C3″ + C5″), 128.57 (C3a), 129.49 (C2′ + C6′ + C2″ + C6″), 130.00 (C2), 134.69 (C7a), 135.68 (C1′ + C1″), 160.07 (NCHO), 166.88 (=CHOH), 168.20 (COOCH$_3$). Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.12; H, 5.95; N, 6.15.

Debenzylation of 16. A mixture of 1.0 g of **16** (2.2 mmol) and 1.0 g of 10% palladium–charcoal in 20 mL of glacial acetic acid was hydrogenated for 1.5 h and then filtered. The filtrate was poured into 60 mL of ice–water and neutralized with saturated Na_2CO_3 solution. The solution was extracted three times with CH_2Cl_2 (30 mL), and the combined organic layers were dried and evaporated in vacuo to yield 0.7 g of **3** (88%) as a yellow oil: IR (neat) 1718 cm^{-1} (CO); MS *m/z* (relative intensity) 352 (6.8), 334 (59.0), 261 (6.6), 233 (43.2), 215 (20.5), 202 (29.0), 156 (17.6), 133 (19.4), 120 (31.5), 91 (100.0), 59 (17.0), 43 (60.1); ^1H NMR ($CDCl_3$) δ 2.96 (4 H, m; C3-CH_2CH$_2$– + C3-CH$_2$CH_2–), 3.07 (2 H, s; O*H* + N*H*), 3.66 (3 H, s; COOCH_3), 3.72 (2 H, s; –NCH_2Ph), 3.95–4.25 (3 H, m; C2-CHCH_2OH), 6.95–7.6 (9 H, m; aromatic H), 8.8 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 24.20 (C3-CH$_2$CH$_2$–), 45.69 (C2-CH), 48.28 (C3-CH$_2$CH$_2$–), 52.28 (COOCH$_3$), 53.32 (–NCH$_2$Ph), 64.02 (CH$_2$OH), 111.16 (C3 + C7), 118.49 (C4), 119.51 (C5), 122.24 (C6), 127.35 (C4′), 127.73 (C3a), 128.36 (C3′ + C5′), 128.48 (C2′ + C6′), 130.40 (C2), 136.07 (C7a), 138.30 (C1′), 172.79 (COOCH$_3$).

2,16-Didehydro-3-phenyl-14,16-bis(methoxycarbonyl)-3,-14-secoaspidospermidine (20α,21α) (22) and 2,16-Didehydro-3-phenyl-14,16-bis(methoxycarbonyl)-3,14-secoaspidospermidine (20β,21α) (23). a. A solution of 550 mg (1.56 mmol) of **3**, 550 mg (1.56 mmol) of **21**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of anhyd toluene was refluxed under argon for 38 h. The reaction mixture was extracted twice with brine (20 mL), and the combined brine washes were extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried and evaporated in vacuo. The two main components of the residue were separated by preparative thin-layer chromatography with benzene–methanol (10:1). The less polar compound (**22**) (R_f = 0.76) was obtained as a yellow oil (115 mg, 16%): IR (neat) 3320 (indole NH); 1722 (CO); 1665 (conj. CO); 1606 cm^{-1} (C=C); MS *m/z* (relative intensity) 474 (23.2), 443 (4.4), 332 (9.4), 261 (26.2), 260 (100.0), 91 (32.2); ^1H NMR ($CDCl_3$) δ 0.55–1.10 (5 H, m; C19-H$_2$ + C18-H$_3$), 3.64 (3 H, s; C14-COOCH_3), 3.77 (3 H, s; C16-COOCH_3), 3.79 (1 H, d, J_{gem} = 13 Hz; N4-CH_AH$_B$-Ph), 4.26 (1 H, d; N4-CH$_A$$H_B$Ph), 6.7–7.6 (9 H, m; aromatic H), 8.96 (1 H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 7.52 (C18), 27.14 (C15), 28.53 (C14 + C17), 29.81 (C19), 41.27 (C6), 42.26 (C20), 50.80 (C16-COOCH_3), 51.43 (C14-COOCH_3), 51.86 (C5), 57.82 (C7), 61.64 (N4-CH_2Ph), 73.51 (C21), 89.84 (C16), 109.27 (C12), 120.54 (C10), 122.63 (C9), 127.03 (C4′), 127.84 (C11), 128.31 (C3′ + C5′), 128.89 (C2′ + C6′), 137.43 (C8), 139.11 (C1′), 143.09 (C13), 165.14 (C2), 168.67 (C16-$COOCH_3$), 174.53 (C3). The more polar compound (**23**) (R_f = 0.64) was obtained as a yellow oil (115 mg, 16%): IR (neat) 3390 (indole NH); 1730 (CO); 1675 (conj. CO); 1620 cm^{-1} (C=C); MS *m/z* (relative intensity) 474 (24.0), 443 (4.3), 332 (9.1), 261 (17.1) 260 (100.0), 91 (32.2); ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, *J* = 7.5 Hz; C18-H$_3$), 3.52 (3 H, s; C14-COOOCH_3), 3.75 (1 H, d, J_{gem} = 13, 2 Hz; N4-CH_AH$_B$Ph), 3.77 (3 H, s; C16-COOCH_3), 4.26 (1 H, d; N4-CH$_A$$H_B$Ph), 6.7–7.6 (9 H, m; aromatic H), 8.91 (1 H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 9.42 (C18), 25.53 (C19), 28.32 (C15), 28.61 (C17), 28.79 (C14), 41.67 (C6), 42.73 (C20), 50.92 (C16-COOCH_3), 51.44 (C14-COOCH_3), 52.00 (C5), 57.91 (C7), 61.44 (N4-CH_2Ph), 73.31 (C21), 89.90 (C16), 109.40 (C12), 120.63 (C10), 122.62 (C9), 127.06 (C4′), 127.94 (C11), 128.41 (C3′ + C5′), 128.59 (C2′ + C6′), 137.45 (C8), 139.47 (C1′), 143.08 (C13), 165.52 (C2), 168.69 (C16-$COOCH_3$), 174.18 (C3).

b. A solution of 550 mg (1.56 mmol) of **28**, 550 mg (1.56 mmol) of **21**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of anhyd xylene was refluxed under argon for 48 h. The reaction mixture was extracted twice with brine (20 mL), and the combined brine washes were extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried and evaporated in vacuo. The two main components of the residue were separated by preparative thin-layer chromatography with benzene–methanol (10:1). The less polar compound (**22**) (R_f = 0.76) was obtained as a yellow oil (73 mg, 9.8%). The more polar compound (**23**) (R_f = 0.64) was also obtained as a yellow oil (73 mg, 9.8%). The compounds were identical to those prepared by method a.

Enol Ether 20. To a solution of 100 mg (0.21 mmol) of **19** in 5 mL of anhyd methanol a solution of diazomethane in diethyl ether was added until the solution turned yellow. The reaction mixture was allowed to stir at rt for 2 h and then carefully evaporated in vacuo. Crystallization of the residue in methanol yielded 90 mg of **20** (87%) as white crystals: mp 132–134 °C; IR (KBr) 1680 (CO); 1640 (amide CO); 1600 cm^{-1} (C=C); MS *m/z* (relative intensity) 482 (2.6), 211 (20.4), 210 (100.0), 91 (86.5); ^1H NMR ($CDCl_3$) δ 2.72 [4 H, br s; C3-(CH$_2$)$_2$N], 3.65 (3 H, s; OCH$_3$), 3.66 (3 H, s; OCH$_3$), 3.72 [4 H, s; N(CH$_2$Ph)$_2$], 7.0–7.55 (13 H, m; aromatic H), 7.65 (1 H, s; C=CHOCH$_3$), 8.35 (1 H, d, *J* = 7.6 Hz; C7-H), 8.89 (1 H, s; NCHO); ^{13}C NMR ($CDCl_3$) δ 22.43 (C3-CH$_2$CH$_2$–), 51.88 (COOCH$_3$), 52.14 (C3-CH$_2$CH$_2$–), 58.48 [–N(CH$_2$Ph)$_2$], 62.31 (=CHOCH$_3$), 99.85 (C2-C=), 115.81 (C7), 118.98 (C4), 121.42 (C3), 123.89 (C5), 125.02 (C6), 125.75 (C3a), 126.92 (C4′ + C4″), 128.26 (C3′ + C5′ + C3″ + C5″), 128.73 (C2′ + C6′ + C2″ + C6″), 30.33 (C2), 134.97 (C7a), 139.73 (C1′ + C1″), 159.12 (NCHO), 164.33 (=CHOCH$_3$), 166.69 (COOCH$_3$). Anal. Calcd

for $C_{30}H_{30}N_2O_4$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.51; H, 6.15; N, 5.71.

Methyl 3-Benzyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (24) and Spiro Compound 25. A solution of 200 mg (0.57 mmol) of **3** in 20 mL of anhyd benzene was refluxed for 2 h. The reaction mixture was evaporated in vacuo, the residue was purified by thin-layer chromatography with benzene–methanol (10:1), and the two main compounds (R_f = 0.82 and R_f = 0.60) were isolated. The less polar compound (**25**) was obtained as a yellow oil (74 mg, 39%): IR (neat) 3300 (indole NH); 1660 (CO); 1600 cm^{-1} (C=C); MS *m/z* (relative intensity) 334 (83.9), 261 (11.4), 243 (10.5), 215 (32.3), 202 (44.1), 183 (16.7), 169 (15.8), 156 (32.1), 154 (12.1), 133 (45.2), 91 (52.6), 42 (100.0); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.18 (1 H, ddd, J_{gem} = −13.0, J_{vic} = 6.3; s 8.0 Hz; C5′-H_A) 2.22 (1 H, ddd, J_{vic} = 6.0; s 7.8 Hz; C5′-H_B), 2.74 (1 H, d, J_{gem} = −9.3 Hz; C2′-H_A), 2.81 (1 H, d; C2′-H_B), 2.85 (2 H, m; C4′-H_2), 3.67 (1 H, d, J_{gem} = −13.1 Hz; NC$H_A$$H_B$-Ph), 3.70 (1 H, d; NC$H_A$$H_B$Ph), 3.72 (3 H, s; OCH_3), 5.20 (1 H, s; C2=CH), 6.78 (1 H, ddd, $J_{6,7}$ = 7.8, $J_{5,7}$ = 1.0, $J_{4,7}$ = 0.6 Hz; C7-H), 6.93 (1 H, ddd, $J_{4,5}$ = 7.5, $J_{5,6}$ = 7.5; C5-H), 7.14 (1 H, ddd, $J_{4,6}$ = 1.3 Hz; C6-H), 7.20–7.38 (5 H, m; aromatic H), 7.39 (1 H, br d; C4-H), 9.71 (1 H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.72 (C5′), 50.59 (OCH_3), 54.16 (C4′), 55.32 (C3), 59.60 (NCH_2Ph), 68.18 (C2′), 80.79 (C2=CH), 108.70 (C7), 121.45 (C5), 123.01 (C4), 126.98 (C4″), 127.90 (C6), 128.27 (C3″ + C5″), 128.47 (C2″ + C6″), 136.95 (C3a), 138.87 (C1″), 142.75 (C7a), 170.70 ($COOCH_3$), 171.60 (C2). The more polar compound (**24**) was obtained as off-white crystals (68 mg, 36%): mp 134–136 °C; IR (KBr) 3300 (indole NH); 1730 cm^{-1} (CO); MS *m/z* (relative intensity) 334 (46.3), 261 (7.2), 243 (7.5), 215 (18.1), 214 (19.8), 202 (21.9), 183 (9.6), 169 (16.2), 156 (24.0), 154 (20.3), 133 (25.0), 91 (84.0), 42 (100.0); ^{1}H NMR ($CDCl_3$) δ 2.7–3.1 (4 H, m; C6-H_2 + C7-H_2), 3.17 (1 H, dd, J_{gem} = −13.0; $J_{3,4A}$ = 3.0 Hz; C4-H_A), 3.40 (1 H, dd, $J_{3,4B}$ = 7.0 Hz; C4-H_B), 3.70 (3 H, s; OCH_3), 3.83 (2 H, s; NCH_2Ph), 4.08 (1 H, dd; C3-H), 6.95–7.55 (9 H, m; aromatic H), 8.30 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 24.27 (C7), 45.69 (C3), 52.18 (OCH_3), 55.54 (C6), 57.60 (C4), 62.42 (NCH_2Ph), 110.71 (C11), 114.06 (C7a), 118.02 (C8), 119.19 (C9), 121.47 (C10), 127.05 (C4′), 128.23 (C3′ + C5′), 128.53 (C7b), 128.85 (C2′ + C6′), 132.19 (C2), 134.84 (C11a), 139.14 (C1′), 172.44 ($COOCH_3$).

***N*$_b$,*N*$_b$-Dibenzyltryptamine Hydrochloride (30).** To a solution of 20 g (0.13 mol) of tryptamine (**29**) in anhyd DMF (70 mL) were added 30 g of anhyd K_2CO_3 (0.22 mol), 0.2 g (1.2 mmol) of KI, and 33.2 g (30.2 mL, 0.262 mol) of benzyl chloride. The mixture was stirred for 24 h at rt and then poured into 1 L of H_2O. The suspension was extracted three times with CH_2Cl_2 (100 mL), and the combined organic layers were dried and evaporated in vacuo. The residue was dissolved in 200 mL of anhyd methanol, and the pH was adjusted to 1 with an anhyd methanol solution saturated with HCl. The suspension was cooled to 0 °C and filtered. The filtrate was evaporated to half its volume, allowed to stand in a refrigerator overnight, and filtered. The combined solids were dried to yield 40.2 g (85%) of **30** as white crystals: mp 202–204 °C; IR (KBr) 1100 (tert. amine); 1140 (tert. amine); 3300 cm^{-1} (indole NH); MS *m/z* (base, relative intensity) 340 (1.7), 210 (100.0), 130 (7.5), 91 (30.6).

***N*$_b$,*N*$_b$-Dibenzyl-*N*$_a$-(phenylsulfonyl)tryptamine (31).** To a suspension of 5 g (13.1 mmol) of **30** in 50 mL of toluene were added 50 mL of 40% aqueous NaOH and 0.2 g (0.9 mmol) of benzyltriethylammonium chloride. The mixture was allowed to stir for 15 min, and then 2.8 g (2 mL, 15.6 mmol) of benzenesulfonyl chloride was dropped into the emulsion. The mixture was allowed to stir for 4 h at rt. The organic layer was separated, the aqueous layer was extracted twice with 20 mL of CH_2Cl_2, and the combined organic layers were dried and evaporated in vacuo. The residue was treated with methanol to give 5.6 g (88%) **31** as white crystals: mp 105–106 °C; IR (KBr) 1100 (tert. amine); 1140 (tert. amine); 1350 cm^{-1} (Ph-SO_2-N); MS *m/z* (relative intensity) 270 (1.0), 210 (97.7), 91 (100.0), 77 (13.6); ^{1}H NMR ($CDCl_3$) δ 2.80 (4 H, s; C3-CH_2CH_2N), 3.66 [4 H, s; N(CH_2Ph)$_2$], 7.0–8.05 (20 H, m; aromatic H); ^{13}C NMR ($CDCl_3$) δ 22.79 (C3-CH_2), 52.34 (C3-CH_2CH_2N), 58.26 [N(CH_2Ph)$_2$], 113.29 (C7), 119.15 (C4), 121.10 (C3), 122.71* (C2), 122.84* (C5), 124.22 (C6), 126.27° (C2‴ + C6‴), 126.60° (C4′ + C4″), 127.90 (C3′ + C5′ + C3″ + C5″), 128.45 (C2′ + C6′ + C2″ + C6″), 128.75 (C3‴ + C5‴), 130.76 (C3a), 133.19 (C4‴), 134.82 (C7a), 137.95 (C1‴), 139.04 (C1′ + C1″). Anal. Calcd for $C_{30}H_{28}N_2O_2S$: C, 74.97; H, 5.87; N, 5.83. Found: C, 75.26; H, 6.01; N, 6.11.

Alcohol 32. To a cold solution of 4.8 g (10.0 mmol) of **31** in 50 mL of anhyd THF was added a 2.5 M solution of *tert*-butyllithium in pentane (8.8 mL, 0.32 g, 22.2 mmol) dropwise while the temperature of the reaction mixture was kept below 5 °C. The mixture was stirred at this temperature for 30 min and then was added to a −78 °C solution of 6.8 g (6.0 mL, 66.4 mmol) of methyl pyruvate in 50 mL of anhyd THF. During the addition, the temperature was kept below −60 °C. The mixture was stirred at −78 °C for 30 min and then quenched with 5 mL of H_2O. The suspension was allowed to warm to rt, and 100 mL of H_2O and 100 mL of CH_2Cl_2 were added. After being separated, the aqueous layer was extracted twice with 50 mL of CH_2Cl_2, and the combined organic layers were dried and evaporated in vacuo. The residue was purified by column chromatography (eluent: benzene–methanol (10:1)) to yield 2.0 g (54%) of **32** (R_f = 0.52) as a yellow oil: IR (neat) 3300 (indole NH); 1710 cm^{-1} (CO); MS *m/z* (relative intensity) 442 (1.6), 210 (100.0), 167 (12.2), 130 (5.2), 91 (97.5), 77 (8.5), 43 (36.0); ^{1}H NMR ($CDCl_3$) δ 1.75 (3 H, s; C2-CCH_3), 2.65–3.2 (4 H, m; C3-CH_2CH_2N), 3.69 (3 H, s; OCH_3), 3.78 [4 H, s; N(CH_2Ph)$_2$], 4.66 (1 H, br s; OH), 6.85–7.6 (14 H, m; aromatic H), 8.39 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 22.01 (C3-CH_2), 26.66 (C2-CCH_3), 53.01 (OCH_3 + C3-CH_2CH_2N), 58.22 [N(CH_2Ph)$_2$], 73.27 (C2-C^t), 109.39 (C3), 110.83 (C7), 118.12 (C4), 119.01 (C5), 121.85 (C6), 127.24 (C4′ + C4″), 128.07 (C3′ + C5′ + C3″ + C5″), 128.55 (C3a), 129.30 (C2′ + C6′ + C2″ + C6″), 134.09 (C2), 134.30 (C7a), 136.60 (C1′ + C1″), 174.66 ($COOCH_3$).

Debenzylation of 32. A mixture of 1.0 g of **32** (2.2 mmol) and 0.5 g of 10% palladium–charcoal in 20 mL of glacial acetic acid was hydrogenated for 1.5 h and then filtered. The filtrate was poured into 60 mL of ice–water and neutralized with saturated Na_2CO_3 solution. The solution was extracted three times with CH_2Cl_2 (30 mL), and the combined organic layers were dried and evaporated in vacuo to yield 0.7 g (88%) of **28** as a yellow oil: IR (neat) 3300 (indole NH, OH); 1730 cm^{-1} (CO); MS *m/z* (relative intensity) 352 (2.6), 334 (4.5), 293 (3.5), 276 (5.1), 261 (21.5), 233 (99.2), 174 (64.1), 158 (13.1), 134 (60.2), 130 (9.4), 120 (39.8), 91 (100.0); ^{1}H NMR ($CDCl_3$) δ 1.83 (3 H, s; C2-CCH_3), 2.7–3.4 (4 H, m; C3-CH_2CH_2N), 3.59 (3 H, s; OCH_3), 3.70 (2 H, s; NHCH_2Ph), 4.11 (2 H, br s; NH + OH), 6.95–7.55 (9 H, m; aromatic H), 8.48 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 23.98 (C3-CH_2), 27.54 (C2-CCH_3), 47.30 (C3-CH_2CH_2N), 52.51 ($COOCH_3$), 53.76 ($NHCH_2Ph$), 73.73 (C2-C^t), 109.19 (C3), 110.89 (C7), 117.99 (C4), 119.18 (C5), 122.07 (C6), 126.96 (C4′), 128.19 (C3a + C3′ + C5′), 128.26 (C2′ + C6′), 135.07 (C2), 136.31 (C7a), 138.54 (C1′), 175.39 ($COOCH_3$).

5-(Benzoyloxy)-2-ethylpentanal (33). To a solution of 10 g (56.8 mmol) of 4-(dimethoxymethyl)-1-hexanol (**34**) in 70 mL of CH_2Cl_2 was added 6.5 g (9 mL, 64.3 mmol) of triethylamine. The mixture was cooled to 0 °C, and at this temperature 12.1 g (10 mL, 86.4 mmol) of benzoyl chloride was added dropwise. The mixture was allowed to warm to rt and then stirred for 0.5 h. The suspension was extracted with 200 mL of 5% aqueous $NaHCO_3$, and the organic layer was allowed to stir for 12 h with 70 mL of 2 M aqueous NaOH at rt. The organic layer was separated, dried, and evaporated in vacuo. The residue was diluted with 100 mL of diethyl ether. To the ether solution was added 70 mL of 5 M aqueous HCl, and the mixture was allowed to stir for 12 h at rt. The organic layer was separated, extracted with 100 mL of brine, and dried, and the solvent was evaporated to yield 11.0 g (83%) of a colorless liquid (**33**): IR (neat) 2900 (aldehyde CH); 1720–1690 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 0.94 (3 H, t, J = 7.3 Hz; C6-H_3), 1.2–2.1 (6 H, m; C2-H_2 + C3-H_2 + C5-H_2), 2.27 (1 H, m; C4-H), 4.34 (2 H, t, J = 6 Hz; Cl-H_2), 7.2–7.7 (3 H, m; C3′-H + C4′-H + C5′-H), 7.9–8.2 (2 H, m; C2′-H + C6′-H), 9.67 (1 H, d, J = 2.4 Hz; C4-CHO); ^{13}C NMR ($CDCl_3$) δ 11.32 (C6), 21.78 (C5), 24.67 (C3), 26.30 (C2), 52.78 (C4), 64.68 (C1), 128.41 (C3′ + C5′), 129.57 (C2′ + C6′), 130.56 (C1′), 132.97 (C4′), 166.53 (*C*OPh), 204.83 (C4-*C*HO).

2,16-Didehydro-3-(benzoyloxy)-4-benzyl-16-(methoxycarbonyl)-3,4-secoaspidospermidine (20α,21α) (35) and 2,16-Didehydro-3-(benzoyloxy)-4-benzyl-16-(methoxycarbonyl)-3,4-secoaspidospermidine (20β,21α) (36). A solution of 0.7 g (2.0 mmol) of **3**, 550 mg (1.56 mmol) of **33**, and 10 mg (0.06 mmol)

of *p*-toluenesulfonic acid monohydrate in 40 mL of anhyd toluene was refluxed under argon for 24 h. The reaction mixture was extracted twice with brine (20 mL). The combined brine extracts were extracted twice with 20 mL of CH_2Cl_2. The combined organic layers were dried and evaporated in vacuo. The residue was purified by preparative thin-layer chromatography with ether–hexane (1:1). The 1:1 epimeric mixture of **35** and **36** (R_f = 0.62) was obtained as a yellow oil (280 mg, 26%): IR (neat) 3400 (indole NH); 1720 (CO); 1680 (CO); 1605 cm^{-1} (C=C); MS *m/z* (relative intensity) 550 (3.3), 336 (34.4), 222 (10.5), 214 (37.1), 194 (14.4), 180 (15.7), 168 (21.8), 167 (20.6), 154 (22.2), 105 (72.8), 91 (100.0), 77 (59.5), 65 (16.9); ^1H NMR ($CDCl_3$) δ 0.55–1.3 (5 H, m), 1.3–3.3 (11 H, m), 3.80 (3 H, s; C16-$COOCH_3$), 3.6–4.5 (4 H, m; N4-CH_2Ph + C3-H_2), 6.7–8.2 (14 H, m; aromatic H), 8.89–8.98 (1 H, 2 × br s; N1-H); ^{13}C NMR ($CDCl_3$) δ C20-Hα compound: 7.67 (C18), 24.00 (C14), 26.80 (C15), 28.90 (C17), 29.43 (C19), 41.41 (C6), 42.76 (C20), 50.89 ($COOCH_3$), 52.00 (C5), 57.79 (C7), 61.66 (N4-CH_2Ph), 65.96 (C3), 73.45 (C21), 90.09 (C16), 109.22 (C12), 120.54 (C10), 122.65 (C9), 127.01 (C4′), 127.86 (C11), 128.36 (C3′ + C5′ + C3″ + C5″), 128.56 (C2′ + C6′), 129.54 (C2″ + C6″), 130.45 (C1″), 132.76 (C4″), 137.50 (C8), 139.26 (C1′), 143.05 (C13), 165.45 (C2), 166.63 (OCOPh), 168.92 ($COOCH_3$); C20β compound: 9.45 (C18), 22.52 (C14), 25.48 (C19), 29.06 (C17), 29.96 (C15), 41.77 (C6), 42.59 (C20), 50.91 ($COOCH_3$), 52.00 (C5), 57.87 (C7), 61.42 N4-CH_2Ph), 65.31 (C3), 73.21 (C21), 90.09 (C16), 109.22 (C12), 120.54 (C10), 122.55 (C9), 127.01 (C4′), 127.86 (C11), 128.26 (C3″ + C5″), 128.36 (C3′ + C5′), 128.53 (C2′ + C6′), 129.43 (C2″ + C6″), 130.37 (C1″), 132.67 (C4″), 137.57 (C8), 139.54 (C1′), 142.92 (C13), 165.65 (C2), 166.41 (OCOPh), 168.78 ($COOCH_3$).

2,16-Didehydro-3-(benzoyloxy)-16-(methoxycarbonyl)-3,4-secoaspidospermidine (20α,21α) (37) and 2,16-Didehydro-3-(benzoyloxy)-16-(methoxycarbonyl)-3,4-secoaspidospermidine (20β,21α) (38). A mixture of 0.85 g of **35** + **36** (1.5 mmol) and 0.5 g of 10% palladium–charcoal in 20 mL of glacial acetic acid was hydrogenated for 40 min and then filtered. The filtrate was poured into 60 mL of ice–water and neutralized with saturated Na_2CO_3 solution. The solution was extracted three times with CH_2Cl_2 (30 mL), and the combined organic layers were dried and evaporated in vacuo. The residue was separated by preparative thin-layer chromatography with benzene–methanol (10:1) to yield two compounds. The less polar compound (**37**, R_f = 0.47) was obtained as a yellow oil (110 mg, 15%): IR (neat) 3350 (NH); 1715 (CO); 1675 (CO); 1610 cm^{-1} (C=C); MS *m/z* (relative intensity) 460 (24.4), 246 (60.8), 215 (14.9), 180 (11.5), 160 (21.3), 167 (19.6), 154 (26.1), 124 (100.0), 105 (77.4), 77 (60.5), 55 (16.4), 54 (19.8); ^1H NMR ($CDCl_3$) δ 0.45–1.05 (5 H, m; C19-H_2 + C18-H_3), 1.4–2.6 (9 H, m; C6-H_2 + C14-H_2 + C15-H_2 + C17-H_2 + N4-H), 3.0–3.2 (2 H, m; C5-H_2), 3.35 (1 H, d, J = 1.8 Hz; C21-H), 3.77 (3 H, s; C16-$COOCH_3$), 4.37 (2 H, t, J = 6.0 Hz; C3-H_2), 6.7–8.2 (9 H, m; aromatic H), 9.00 (1 H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 7.06 (C18), 23.69 (C14), 24.93 (C15), 27.52 (C17), 28.98 (C19), 41.87 (C20), 45.03* (C6), 45.18* (C5), 50.88 ($COOCH_3$), 56.65 (C7), 65.61 (C3), 67.48 (C21), 90.36 (C16), 109.28 (C12), 120.59 (C10), 121.69 (C9), 127.80 (C11), 128.36 (C3′ + C5′), 129.53 (C2′ + C6′), 130.43 (C1′), 132.86 (C4′), 137.91 (C8), 143.12 (C13), 166.65 (C2), 167.02 (OCOPh), 168.77 ($COOCH_3$). The more polar compound was treated with methanol to yield **38** as white crystals (200 mg, 28%): mp 147–148 °C; IR (KBr) 3350 (NH); 1712 (CO); 1660 (CO); 1605 cm^{-1} (C=C); MS *m/z* (relative intensity) 460 (24.4), 246 (60.8), 215 (14.9), 180 (11.5), 160 (21.3), 167 (19.6), 154 (26.1), 124 (100.0), 105 (77.4), 77 (60.5), 55 (16.4), 54 (19.8); ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 7 Hz; C18-H_3), 0.7–1.1 (2 H, m; C15-H_2), 1.2–2.5 (9 H, m; C6-H_2 + C14-H_2 + C17-H_2 + C19-H_2 + N4-H), 3.0–3.2 (2 H, m; C5-H_2), 3.34 (1 H, d, J = 1.8 Hz; C21-H), 3.76 (3 H, s; C16-$COOCH_3$), 4.08 (2 H, t, J = 6.2 Hz; C3-H_2), 6.65–8.0 (9 H, m; aromatic H), 8.9 (1 H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 8.70 (C18), 22.13 (C14), 25.63 (C19), 27.94 (C17), 28.09 (C15), 41.88 (C20), 44.96* (C6), 45.21* (C5), 50.95 ($COOCH_3$), 56.61 (C7), 65.18 (C3), 67.11 (C21), 90.38 (C16), 109.28 (C12), 120.62 (C10), 121.69 (C9), 127.79 (C11), 128.24 (C3′ + C5′), 129.46 (C2′ + 6′), 130.39 (C1′), 132.72 (C4′), 137.83 (C8), 142.99 (C13), 166.34 (C2), 167.02 (OCOPh), 168.60 ($COOCH_3$).

Vincadifformine (4). a. A mixture of 110 mg (0.24 mmol) of **37** and 10 mg (0.06 mmol) of KI in 5 mL of DMF was refluxed for 1 h, and the solvent was evaporated in vacuo (0.5 mbar). The residue was purified by preparative thin-layer chromatography with benzene–methanol (10:1), and the resulting oil (R_f = 0.71) was treated with ethanol to yield **4** as white crystals (47 mg, 58%): mp 123–125 °C (lit.[23] mp 124–125 °C); IR (KBr) 3400 (indole NH); 1670 (CO); 1600 cm^{-1} (C=C); MS *m/z* (relative intensity) 338 (31.6), 124 (100.0); ^1H NMR ($CDCl_3$) δ 0.61 (3 H, m; C20-CH_2CH_3), 3.77 (3 H, s; $COOCH_3$), 6.7–7.3 (4 H, m; aromatic H), 8.89 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 7.12 (C18), 22.11 (C14), 25.63 (C17), 29.32 (C19), 32.90 (C15), 38.20 (C20), 45.27 (C6), 50.64 (C5), 50.89 ($COOCH_3$), 51.73 (C3), 55.51 (C7), 72.63 (C21), 92.64 (C16), 109.31 (C12), 120.49 (C10), 121.02 (C9), 127.43 (C11), 137.92 (C8), 143.32 (C13), 167.73 (C2), 169.13 ($COOCH_3$). b. A mixture of 200 mg (0.43 mmol) of **38** and 10 mg (0.06 mmol) of KI in 5 mL of DMF was refluxed for 1 h, and the solvent was evaporated in vacuo (0.5 mbar). The residue was purified by preparative thin-layer chromatography with benzene-methanol 10:1, and the oil (R_f = 0.71) was treated with ethanol to yield white crystalline **4** (89.9 mg, 61%) which was identical to that prepared by method a.

3-Thioxotabersonine (40) and 14-(*p*-Toluenesulfinyl)-3-thioxotabersonine (41). To a solution of 100 mg (0.27 mmol) of 3-thioxovicadifformine (**39**) and 37 mg (0.29 mmol) of *N,N*-diisopropylethylamine in 50 mL of anhyd CH_2Cl_2 was added 150 mg (0.654 mmol) of *p*-toluenesulfinyl chloride dropwise, and the reaction mixture was refluxed for 2 h. To the mixture was added 50 mL of 1 M aqueous acetic acid, and the mixture was neutralized with 5% aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried and evaporated in vacuo. The residue was purified by column chromatography (eluent: benzene–methanol (40:1)) to afford two compounds (R_f = 0.79 and R_f = 0.73). The less polar compound (**41**) was obtained as a yellow oil (10 mg, 7.5%): IR (neat) 3250 (indole NH); 1650 (CO); 1590 (C=C); 1450 cm^{-1} (N-C=S); MS *m/z* (relative intensity) 488 (8.3), 455 (2.9), 261 (9.4), 227 (100.0), 195 (61.7), 168 (19.0), 167 (27.0), 91 (7.6); ^1H NMR ($CDCl_3$) δ 0.45 (3 H, t, J = 7.0 Hz; C18-H_3), 0.90 (2 H, q; C19-H_2), 1.9–2.6 (4 H, m; C6-H_2 + C17-H_2), 2.36 (3 H, s; Ar-CH_3), 3.70 (1 H, m; C5-H_A), 3.74 (3 H, s; $COOCH_3$), 3.97 (1 H, br s; C21-H), 4.92 (1 H, m; C5-H_B), 5.40 (1 H, s; C15-H), 6.8–7.5 (8 H, m; aromatic H), 9.00 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 7.30 (C18), 21.30 (Ar-CH_3), 25.68 (C17), 27.80 (C19), 41.34 (C20), 42.67 (C6), 50.40 (C5), 51.19 ($COOCH_3$), 56.17 (C7), 67.49 (C21), 90.51 (C16), 109.98 (C12), 121.31 (C10), 121.48 (C9), 128.92 (C11 + C15), 129.85 (C1′), 130.42 (C3′ + C5′), 134.91 (C8), 135.45 (C2′ + C6′), 138.75 (C14), 139.19 (C4′), 142.80 (C13), 164.78 (C2), 168.24 ($COOCH_3$), 185.27 (C3). The more polar compound was treated with hexane to yield **40** (39 mg, 40%) as yellow crystals: mp 96–99 °C; IR (KBr) 3330 (indole NH); 1650 (CO); 1600 (C=C); 1460 cm^{-1} (N-C=S); MS *m/z* (relative intensity) 367 (12.8), 227 (100.0), 195 (86.2), 168 (29.1), 167 (50.0), 154 (10.0); ^1H NMR ($CDCl_3$) δ 0.6–1.2 (5 H, m; C20-CH_2CH_3), 1.9–2.15 (2 H, m; C6-H_2), 2.08 (1 H, d, J_{gem} = −15.5 Hz; C17-H_A), 2.62 (1 H, dd, $J_{17,21}$ = 1.5 Hz; C17-H_B), 3.71 (1 H, m; C5-H_A), 3.79 (3 H, s; $COOCH_3$), 3.93 (1 H, br s; C21-H), 4.90 (1 H, m; C5-H_B), 6.16 (1 H, d, $J_{14,15}$ = 9.6 Hz; C14-H), 6.49 (1 H, d; C15-H), 6.85–7.4 (4 H, m; aromatic H), 9.05 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 7.18 (C18), 25.01 (C17), 27.21 (C19), 40.33 (C20), 42.80 (C6), 49.56 (C5), 51.24 ($COOCH_3$), 56.05 (C7), 67.86 (C21), 90.32 (C16), 109.98 (C12), 121.33 (C10), 121.38 (C9), 128.87 (C11), 129.42 (C14), 135.03 (C8), 136.73 (C15), 142.80 (C13), 164.95 (C2), 168.16 ($COOCH_3$), 186.33 (C3). Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.65. Found: C, 69.05; H, 6.28; N, 7.39.

3-Oxotabersonine (42). To a solution of 50 mg (0.136 mmol) of 3-thioxotabersonine (**40**) in 30 mL of anhyd CH_2Cl_2 at −20 °C was added 29 mg (0.164 mmol) of 85% *m*-CPBA. The reaction mixture was stirred at −20 °C for 30 min, and the solvent was evaporated in vacuo. The residue was purified by thin-layer chromatography with benzene–methanol (10:1), and the isolated compound (R_f = 0.61) was treated with ethyl acetate to yield **42** (36 mg, 74%) as white crystals: mp 119–121 °C (lit.[22] mp 151.5–153.0 °C for optically active compound); IR (KBr) 3300 (indole NH); 1650 (CO); 1620 (amide CO); 1600 cm^{-1} (C=C); MS *m/z* (relative intensity) 350 (8.0), 228 (15.6), 227 (100.0), 195 (66.2),

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168 (14.8), 167 (19.1), 154 (8.4); ^{1}H NMR ($CDCl_3$) δ 0.73 (3 H, t, J = 7.0 Hz; C18-H_3), 2.06 (2 H, q; C19-H_2), 1.8–2.1 (2 H, m; C6-H_2), 2.09 (1 H, d, J = −15.5 Hz; C17-H_A), 2.62 (1 H, dd, $J_{17,21}$ = 1.8 Hz; C17-H_B), 3.39 (1 H, m; C_5-H_A), 3.79 (3 H, s; $COOCH_3$), 4.00 (1 H, br d; C21-H), 4.30 (1 H, m; C5-H_B), 5.98 (1 H, d, $J_{14,15}$ = 10.0 Hz; C14-H), 6.44 (1 H, d; C15-H), 6.85–7.3 (4 H, m; aromatic H), 9.04 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 7.32 (C18), 26.00 (C17), 27.08 (C19), 40.42 (C20), 43.26 (C5), 43.42 (C6), 51.11 ($COOCH_3$), 56.70 (C7), 66.44 (C21), 90.08 (C16), 109.88 (C12), 121.19 (C10), 121.43 (C9), 122.82 (C14), 128.63 (C11), 135.50 (C8), 142.94 (C13), 145.17 (C15), 161.32 (C3), 165.19 (C2), 168.11 ($COOCH_3$).

Tabersonine (43). A solution of 50 mg (0.136 mmol) of 3-thioxotabersonine (**40**) in 30 mL of CH_3I was refluxed for 4 h, and then the solvent was evaporated and the residue was dissolved in 30 mL of methanol. Sodium borohydride (50 mg, 1.31 mmol) was added to the solution, and it was allowed to stir for 30 min at rt. The pH of the suspension was adjusted to 1 with 1 M aqueous HCl, and the mixture was neutralized with 5% aqueous $NaHCO_3$. To the solution was added 30 mL of CH_2Cl_2, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were dried and evaporated. The residue was purified by thin-layer chromatography with benzene–methanol (10:1) to yield 24 mg (49%) of **43**[24] (R_f = 0.75) as an unstable light yellow oil: IR (neat) 3300 (indole NH); 1660 (CO); 1600 cm^{-1} (C=C); MS m/z (relative intensity) 336 (50.8), 229 (24.8), 228 (12.8), 214 (8.0), 168 (20.4), 135 (100.0), 122 (30.7), 121 (22.4), 107 (36.3), 93 (18.0); ^{1}H NMR ($CDCl_3$) δ 0.5–1.2 (5 H, m; CH_2CH_3), 1.82 (1 H, ddd, J_{gem} = −11.5, $J_{5A,6A}$ = 5.0, $J_{5B,6A}$ = 1.5 Hz; C6-H_A), 2.08 (1 H, ddd, $J_{5A,6B}$ = 10.2, $J_{5B,6B}$ = 6.5 Hz; C6-H_B), 2.48 (1 H, d, J_{gem} = −15.0 Hz; C17-H_A), 2.55 (1 H, dd, $J_{17B,21}$ = 1.5 Hz; C17-H_B), 2.71 (1 H, br s; C21-H), 2.74 (1 H, ddd, J_{gem} = −8.2; C5-H_A), 3.05 (1 H, ddd; C5-H_B), 3.20 (1 H, br d, J_{gem} = −16.0 Hz; C3-H_A), 3.46 (1 H, dd, J_{vic} = 3.0 Hz; C3-H_B), 3.78 (3 H, s; $COOCH_3$), 5.6–5.9 (2 H, m; C14-H + C15-H), 6.75–7.3 (4 H, m; aromatic H), 9.00 (1 H, br s; indole NH); ^{13}C NMR ($CDCl_3$) δ 7.47 (C18), 26.94 (C19), 28.56 (C17), 41.32 (C20), 44.53 (C6), 50.54 (C5), 50.95 ($COOCH_3$ + C3), 55.15 (C7), 70.01 (C21), 92.14 (C16), 109.30 (C12), 120.58 (C10), 121.46 (C9), 124.85 (C14), 127.65 (C11), 133.08 (C15), 138.09 (C8), 143.23 (C13), 166.76 (C2), 168.96 ($COOCH_3$).

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Supplementary Material Available: Spectroscopic data for compounds **3**, **13**, **18**, **25**, **28**, **32**, **33**, **35–38**, and **41** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.