Synthesis of Vinca Alkaloids and Related Compounds. 64.[1] Total Syntheses of (±)-Pseudovincadifformine and (±)-20-Epipseudovincadifformine

György Kalaus,[†] István Greiner,[‖] Mária Kajtár-Peredy,[§] János Brlik,[‡] Lajos Szabó,[†] and Csaba Szántay*,[†,§]

Department of Organic Chemistry and MS Laboratory of the Institute for General and Analytical Chemistry, Technical University, Budapest, Gellért tér 4, H-1521 Budapest, Hungary, Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest, Pusztaszeri út 59-67, H-1525 Budapest, Hungary, and Chemical Works of Gedeon Richter Ltd., Gyömröi út 19-21, H-1103 Budapest, Hungary

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Using our previously reported convergent synthetic strategy, secondary amine **6** and aldehyde **9** reacted to give tetracyclic esters **10** and **11**, which readily led to pentacyclic lactams **14–16**. Selective reduction of these products gave (±)-pseudovincadifformine (**4**), (±)-20-epipseudovincadifformine (**5**), and (±)-14-epipseudovincadifformine (**20**). Aldehyde **23** was also prepared and could be directly used for synthesizing (±)-20-epipseudovincadifformine (**5**). The introduction of the double bond into ring D of the pseudoaspidospermane skeleton was successfully achieved to obtain 21-oxopseudotabersonine (**30**).

Introduction

We have previously developed[1] a strategy for synthesizing compounds with the Aspidospermane skeleton that made possible the total synthesis of several alkaloids such as (±)-vincadifformine (**1**), (±)-tabersonine (**2**), and (±)-3-oxotabersonine (**3**). In our present work this strategy has been extended to the synthesis of compounds with the pseudoaspidospermane skeleton. Our aims included the synthesis of (±)-pseudovincadifformine (**4**) and (±)-20-epipseudovincadifformine (**5**). Also the tried and tested method of introducing a double bond, in our synthesis of (±)-tabersonine (**2**),[1] was extended to compounds having the pseudoaspidospermane skeleton. Two alkaloids, **4** and **5**, had been prepared earlier by both approaches, i.e. semi-[2] and total synthesis.[3] However, the successful introduction of a double bond into the pseudoaspidospermane skeleton has been reported only quite recently.[4a] A characteristic feature of the pseudoaspidospermane skeleton is that, in contrast to aspidospermane compounds where only *cis* D/E ring fusion is possible, in the pseudoskeleton *trans* fusion is also known.[3c,4a,b]

Results and Discussion

As it is evident from the foregoing discussion, the primary task was the synthesis of an aldehyde component

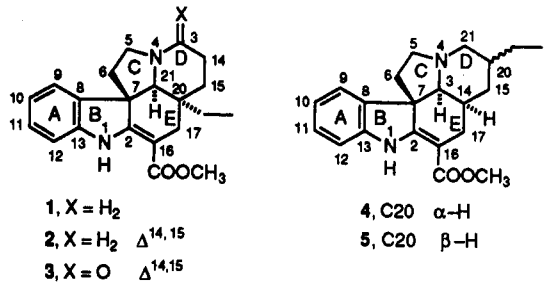

Figure 1.

which would react with the indole skeleton containing secondary amine **6** to give a product that could become the precursor of compounds having the pseudoaspidospermane skeleton. This requirement is satisfied by methyl 2-ethyl-5-oxopentanoate (**9**)[3a] which was prepared as follows: dimethyl ethylmalonate was allowed to react with acrolein in the presence of a base.[5] The resulting aldehyde was treated with trimethyl orthoformate to obtain acetal **7**, and the latter was demethoxycarbonylated in neutral medium.[6] The protecting group of the resulting ester **8** was removed by acid hydrolysis. The formyl group of the product suffered oxidation on standing when exposed to air. Therefore, in later experiments the protective group was not removed until just before further conversion or before recording spectra.

The reaction between secondary amine **6** and aldehyde **9** was effected according to the strategy developed earlier;[1] the product consisted of about a 3:2 mixture of esters **10** and **11** (Figure 3). It was described earlier[3a,4a,b,7] that when the α-carbon atom of the aldehyde component carried two hydrogen atoms, then on forming the *seco*-pseudoaspidospermane skeleton, the hydrogen atoms connected to

† Department of Organic Chemistry, Technical University.
‡ MS Laboratory of the Institute for General and Analytical Chemistry, Technical University.
§ Central Research Institute for Chemistry, Hungarian Academy of Sciences.
‖ Chemical Works of Gedeon Richter Ltd.
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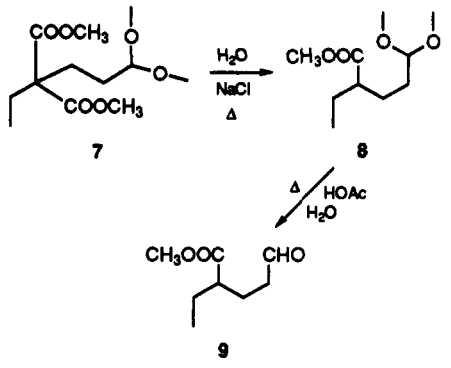

Figure 2.

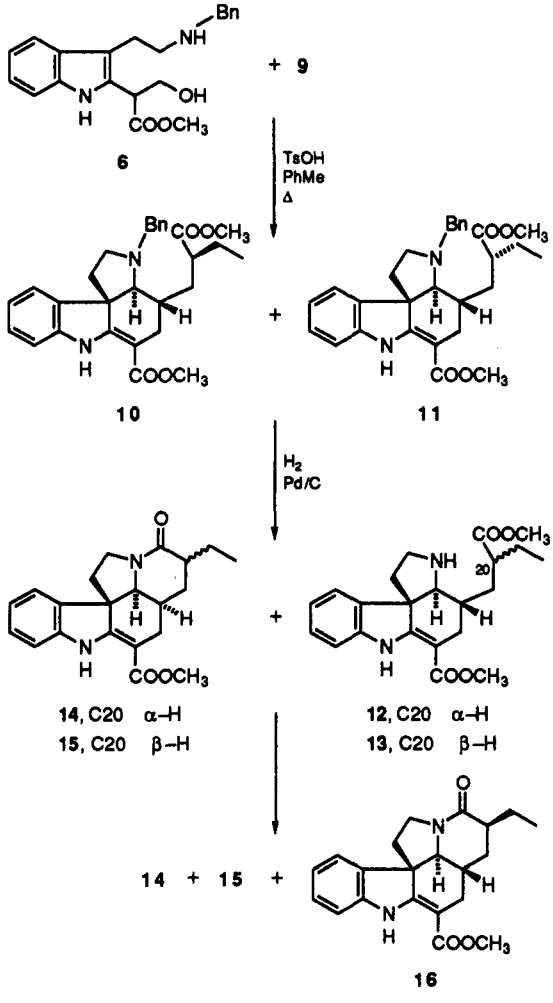

Figure 3.

the carbon atoms in the α- and β-positions relative to the nitrogen always had a *trans* stereochemical arrangement. This result has also been found to hold true in our present case. Therefore, it is reasonable that the reactions described in the literature[3a] and those used by us to prepare these compounds, although starting from substances of different structure, proceed via the same mechanism.

The epimers **10** and **11** were debenzylated without separation, since under the hydrogenolysis conditions in acidic medium, epimerization would have occurred resulting in a mixture of isomers. Workup of the reaction mixtures revealed the presence of four components, **12**, **13**, **14**, and **15**. Thus, the product mixture contained the pentacyclic derivatives, **14**, and **15** with the *cis* geometry of the D/E rings, which, according to earlier experience,[1]

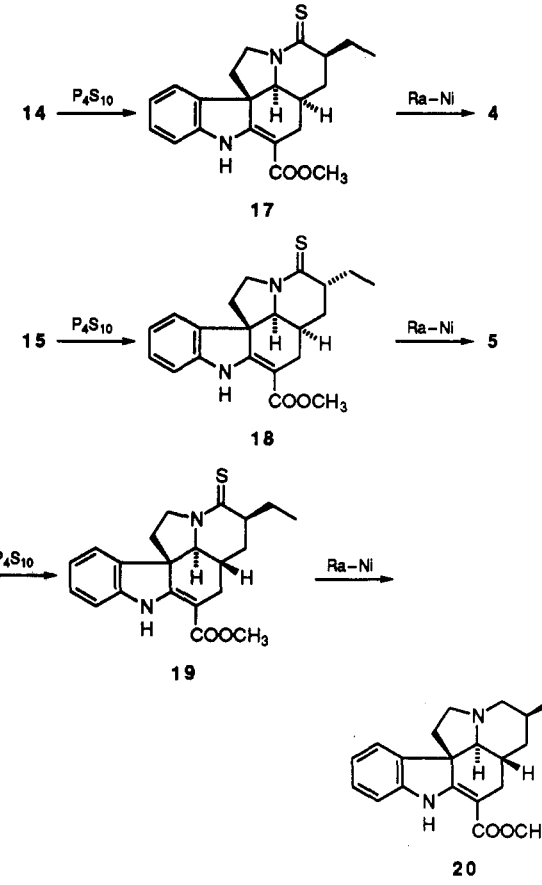

Figure 4.

were formed under the conditions of debenzylation. The two other products, isolated as a mixture, were the secondary amines **12** and **13** having a *trans* configuration of the hydrogen atoms. In these compounds intramolecular acylation is sterically hindered. Components of the mixture were separated only for identification; further conversion was effected using the mixture. The mixture of four compounds (**12**–**15**) was refluxed for 16 h in toluene in the presence of *p*-toluenesulfonic acid giving compounds **14**, **15**, and **16** in a ratio of about 2:3:1. Two of these substances (**14**, **15**) were the above mentioned "*cis*" lactams, while the third compound **16** was the pentacyclic lactam with the *trans* D/E ring fusion. No trace of the fourth possible isomer could be detected in the reaction mixture. It is worthy of note that the *trans* D/E ring fusion present in compound **16** has been found only in some non-natural molecules,[3c,e,4a,b] but the naturally occurring pseudoaspidospermanes all have the *cis* D/E ring fusion.

In the next step all three lactams **14**–**16** were selectively reduced to afford the corresponding alkaloids or alkaloid-like molecules (Figure 4) *via* the thiolactams, a synthetic route of proven value in our earlier work. First, the thio derivatives **17**–**19** were prepared by using phosphorus pentasulfide, and these products were desulfurized with Raney nickel to yield the two alkaloids, pseudovincadifformine (**4**) and 20-epipseudovincadifformine (**5**), along with 14-epipseudovincadifformine (**20**)[3e,4a] having the *trans* D/E ring fusion.

A process was also developed for the direct construction of the pentacyclic pseudoaspidospermane skeleton (Figure 5). First, an aldehyde component was synthesized in which the leaving group is the benzoyloxy substituent, found suitable for this purpose earlier.[1] In order to prepare the

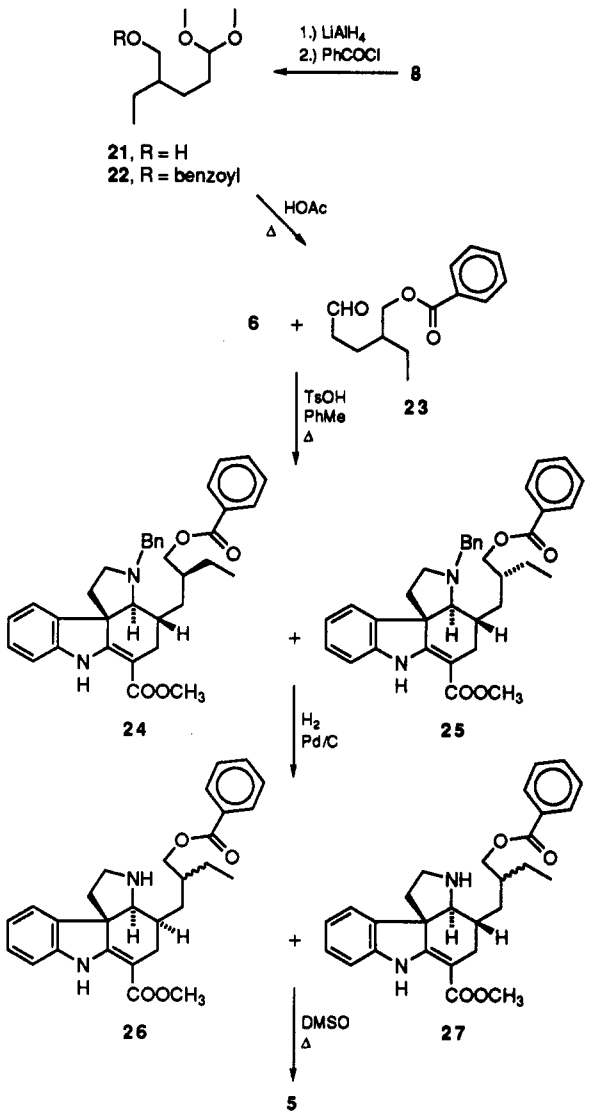

Figure 5.

target compound, the ester group of acetal 8 was initially reduced; the resulting alcohol 21 was benzoylated, and finally the aldehyde function was regenerated. Secondary amine 6 was then allowed to react with aldehyde 23, under the conditions used in earlier analogous reactions. As expected, the reaction gave a mixture of two tetracyclic esters, 24 and 25. On the basis of considerations described above, the isomers were not separated.

The mixture of 24 and 25 was hydrogenated in acetic acid to give a mixture of the secondary amines 26 and 27 (Figure 5). Since epimerization can also occur in the subsequent alkylation step, it was not deemed worthwhile to separate the mixture of isomers. The closure of ring D could only be accomplished in DMSO. Unexpected, the material isolated from the reaction mixture did not consist of the expected mixture of the two alkaloids (i.e. pseudovincadifformine (4) and 20-epipseudovincadifformine (5)) but was only the latter compound.

An attempt was made to introduce an α,β-double bond in ring D of pseudoaspidospermane using methodology which was successful in the case of compounds having an aspidospermane skeleton.[1] A mixture of two epimers 17 and 18 (Figure 6) was treated with *p*-toluenesulfinyl chloride in the presence of *N,N*-diisopropylethylamine. Workup of the reaction mixture gave one product, which

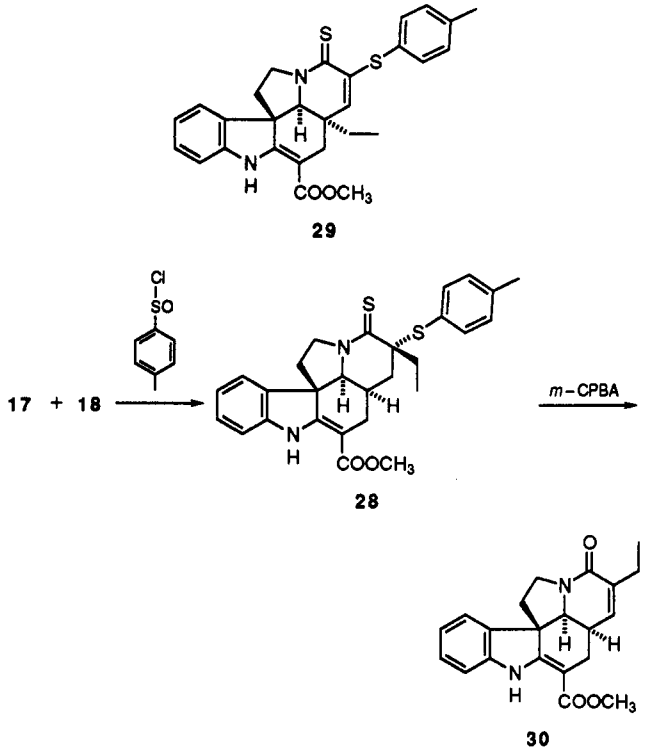

Figure 6.

was not the expected compound but a substance characterized as structure 28. The formation of this compound presumably takes place by analogy with the thioether 29 prepared earlier.[1] It is surprising, however, that the molecule containing a double bond is not formed in the reaction. The required elimination reaction failed in the case of compound 28. Therefore, this compound was further converted to 21-oxopseudotabersonine (30) under oxidative conditions. In this case 30 was obtained as the final product via a multistep reaction sequence.

Experimental Section

Melting points are uncorrected. Chemical shifts (in ppm) are relative to internal Me_4Si. The assignments noted with an asterisk and circle may be interchanged. Thin-layer chromatography separations were 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.

Methyl 2-Ethyl-5-oxo-2-carbomethoxypentanoate. Freshly distilled acrolein (33.4 mL, 28 g, 0.5 mol) was added dropwise at 5–10 °C to a stirred solution of dimethyl ethylmalonate (67 g, 0.42 mol) and 0.2 g (8.7 mmol) of sodium in 250 mL of anhydrous methanol under N_2. The mixture was stirred overnight at rt and 1 mL of acetic acid was added to the solution. The solvent was evaporated in vacuo. The residue was dissolved in 200 mL of ether, washed with 100 mL of brine, and dried. The concentrated solution was distilled to afford methyl 2-ethyl-5-oxo-2-carbomethoxypentanoate (24.0 g, 27%) as a colorless liquid: bp 92–98 °C (20 mbar); $n_D^{20} = 1.4428$; IR (neat) 1720–1750 cm^{-1} (CO); ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.5 Hz; C2-CH_2CH_3), 1.94 (2H, q; C2-CH_2CH_3), 2.20 (2H, m; C3-H_2), 2.45 (2H, m; C4-H_2), 3.72 (6H, s; OCH_3 + OCH_3), 9.75 (1H, t, J = 1.3 Hz; CHO); ^{13}C NMR ($CDCl_3$) δ 8.6 (C2-CH_2CH_3), 24.6 (C3), 26.5 (C2-CH_2CH_3), 39.2 (C4), 52.5 (OCH_3 + OCH_3), 57.3 (C2), 171.7 ($COOCH_3$ + $COOCH_3$), 200.8 (CHO).

Methyl 2-Ethyl-2-carbomethoxy-5,5-dimethoxypentanoate (7). Methyl 2-ethyl-5-oxo-2-carbomethoxypentanoate (24.0 g, 0.11 mol), trimethyl orthoformate (14 g, 0.132 mol, 14.4 mL), and *p*-toluenesulfonic acid monohydrate (0.5 g, 2.5 mmol) were dissolved in 100 mL of cold anhydrous methanol and stirred for

1 d. The solution was then neutralized with 1 N methanolic NaOMe and the solvent was removed in vacuo. The residue was dissolved in 200 mL of ether, washed with 50 mL of brine, and dried. The concentrated solution was distilled to afford **7** (24.3 g, 84%) as a colorless liquid: bp 110–115 °C (40 mbar); n_D^{20} = 1.4360; IR (neat) 1720 cm^{-1} (CO); 1050–1080 cm^{-1} [C(OC)$_2$]; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.5 Hz; C2-CH_2CH_3), 1.91 (2H, m; C3-H_2), 1.94 (2H, q; C2-CH_2CH_3), 2.04 (2H, m; C4-H_2), 3.31 (6H, s; OCH_3 + OCH_3), 3.72 (6H, s; $COOCH_3$ + $COOCH_3$), 4.33 (1H, t, J = 5.4 Hz; C5-H); ^{13}C NMR ($CDCl_3$) δ 8.6 (C2-CH_2CH_3), 25.9 (C3), 27.2 (C2-CH_2CH_3), 27.4 (C4), 52.3* (OCH_3 + OCH_3), 52.7* ($COOCH_3$ + $COOCH_3$), 57.7 (C2), 104.3 (C5), 172.0 ($COOCH_3$ + $COOCH_3$).

Methyl 2-Ethyl-5,5-dimethoxypentanoate (8). A mixture of acetal **7** (59.5 g, 0.227 mol), NaCl (13.3 g, 0.227 mol), and water (8.2 mL, 0.454 mol) was refluxed in 200 mL of DMF under N_2 for 130 h. The cooled reaction mixture was diluted with 500 mL of water and extracted three times with 200 mL of ligroin (50–70 °C). The combined organic layers were washed with 100 mL of brine and dried. Removal of the solvent and distillation yielded **8** (37.5 g, 81%) as a colorless liquid: bp 72–88 °C (40 mbar); IR (neat) 1720 (CO), 1050–1080 cm^{-1} [C(OC)$_2$]; ^{1}H NMR ($CDCl_3$) δ 0.90 (3H, t, J = 7.4 Hz; CH_2CH_3), 1.4–1.8 (6H, m; C3-H_2 + C4-H_2 + CH_2CH_3), 2.28 (1H, m; C2-H), 3.30 + 3.31 (2 × 3H, 2 × s; OCH_3 + OCH_3), 3.68 (3H, s; $COOCH_3$), 4.34 (1H, m; C5-H); ^{13}C NMR ($CDCl_3$) δ 11.8 (CH_2CH_3), 25.5 (C3), 26.9 (CH_2CH_3), 30.4 (C4), 46.9 (C2), 51.3 + 52.4 + 52.9 (OCH_3 + OCH_3 + $COOCH_3$), 104.2 (C5), 176.4 ($COOCH_3$).

Methyl 2-Ethyl-5-oxopentanoate (9). A mixture of 34 g (0.167 mol) of acetal **8**, 50 mL of water, and 15 mL of acetic acid was refluxed under N_2 for 1.5 h. The pH of the cooled solution was adjusted to 9 by adding 5% aqueous $NaHCO_3$. The mixture was extracted three times with 100 mL of ether, the combined organic layers were washed with 50 mL of brine and dried, and the solvent was evaporated in vacuo to yield **9** (20.1 g, 76%) as a colorless liquid: IR (neat) 1700–1750 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 7.4 Hz; CH_2CH_3), 1.4–2.6 (7H, m; CH_2CH_3 + C2-H + C3-H_2 + C4-H_2), 3.70 (3H, s; $COOCH_3$), 9.79 (1H, t, J = 1.3 Hz; CHO); ^{13}C NMR ($CDCl_3$) δ 11.7 (CH_2CH_3), 24.1 (C3), 25.5 (CH_2CH_3), 41.7 (C4), 46.3 (C2), 51.4 ($COOCH_3$), 175.8 ($COOCH_3$), 201.3 (CHO).

2,16-Didehydro-16,20-bis(methoxycarbonyl)-21-phenyl-20,21-*seco*-pseudoaspidospermidine (3α,14β,20$\alpha\beta$) (10, 11). A solution of 550 mg (1.56 mmol) of **6**, 550 mg (1.56 mmol) of **9**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of anhydrous toluene was refluxed under argon for 48 h. The reaction mixture was extracted twice with brine (20 mL), and the combined aqueous layers were extracted twice with CH_2Cl_2 (20 mL), dried, and evaporated in vacuo. The residue was purified by preparative TLC eluting with ether–hexane (1:1) to yield an epimeric mixture of **10** and **11** (R_f 0.52) (240 mg, 32%) as a yellow oil: IR (neat) 3320 (indole NH), 1722 (CO), 1670 (conjugated CO), 1603 cm^{-1} (C=C); MS m/z (rel inten) 474 (17.3), 342 (44.6), 261 (14.2), 260 (100.0), 228 (6.9), 91 (74.0); ^{1}H NMR ($CDCl_3$) δ 0.6–3.1 (16H, m; C3-H + C5-H_2 + C6-H_2 + C14-H + C15-H_2 + C17-H_2 + C20-H + CH_2CH_3), 3.60 + 3.61 (3H, s + s; C20-$COOCH_3$), 3.78 (3H, s; C16-$COOCH_3$), 3.55–3.85 (1H, N4-C$H_A$$H_B$Ph), 4.12 (1H, br d, J_{gem} = −13.2 Hz; N4-C$H_A$$H_B$Ph), 6.7–7.5 (9H, m; aromatic H), 8.95 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 11.6 + 11.8 (C18), 21.7 + 23.2 (C17), 26.3 + 25.0 (C19), 33.2 (C15), 37.1 + 37.0 (C14), 42.11 + 42.06 (C6), 44.9 + 44.5 (C20), 50.5 + 50.2 (C5), 50.9 (C16-$COOCH_3$), 51.3 (C20-$COOCH_3$), 55.1 + 55.0 (C7), 57.9 + 57.8 (N4-CH_2Ph), 72.0 + 71.2 (C3), 90.6 + 90.4 (C16), 109.3 (C12), 120.5 (C10), 122.1 (C9), 127.2 (C4′), 127.9 (C11), 128.4 (C3′ + C5′), 129.0 (C2′ + C6′), 137.7 (C8), 138.6 (C1′), 143.01 + 142.98 (C13), 164.9 (C2), 168.95 + 168.93 (C16-$COOCH_3$), 176.5 + 176.6 (C21). The prepared mixture was identical by HPLC to the epimeric mixture synthesized as described in the literature.[3e]

2,16-Didehydro-21-methoxy-16-(methoxycarbonyl)-21-oxo-4,21-*seco*-pseudoaspidospermidine (3α,14β,20$\alpha\beta$) (12, 13), 21-Oxopseudovincadifformine (14), 21-Oxo-20-epi-pseudovincadifformine (15), and 21-Oxo-14-epi-pseudovincadifformine (16). A mixture of 500 mg of an epimeric mixture of **10** and **11** (1.05 mmol), and 0.5 g of 10% Pd/C 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. Two variations were used subsequently: (a) The residue was purified by preparative TLC eluting with $CHCl_3$–methanol (9:1) to yield an epimeric mixture of **12** and **13** (250 mg, 62%) as a yellow oil (R_f 0.38): IR (neat) 3320 (indole NH), 1722 (CO), 1670 (conjugated CO), 1605 cm^{-1} (C=C); MS (m/z rel inten) 384 (46.4), 353 (16.6), 352 (17.1), 342 (21.7), 283 (36.0), 215 (83.9), 195 (12.8), 170 (100.0), 154 (19.4), 138 (14.3), 110 (40.6), 91 (12.3); ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, t, J = 7.3 Hz; CH_2CH_3), 0.8–2.7 (10H, m; C6-H_2 + C14-H + C15-H_2 + C17-H_2 + C20-H + CH_2CH_3), 2.64 (1H, br s; N4-H), 3.05–3.25 (2H, m; C5-H_2), 3.43 + 3.51 (1H, br s + br s; C3-H), 3.63 (3H, s; C20-$COOCH_3$), 3.78 (3H, s; C16-$COOCH_3$), 6.8–7.4 (4H, m; aromatic H), 9.07 (1H, br s; N1-H); ^{13}C NMR ($CDCl_3$) δ 11.8 + 11.6 (C18), 21.4 + 23.0 (C17), 26.1 + 24.9 (C19), 33.6 + 33.7 (C15), 39.2 + 39.1 (C14), 43.97 + 43.95 (C6), 44.7 + 44.5 (C20), 44.98 + 45.01 (C5), 50.9 (C16-$COOCH_3$), 51.4 (C20-$COOCH_3$), 55.6 (C7), 66.9 + 66.0 (C3), 89.8 + 90.1 (C16), 109.3 (C12), 120.8 (C10), 121.9 (C9), 128.0 (C11), 137.5 + 137.4 (C8), 143.13 + 143.17 (C13), 165.1 + 164.9 (C2), 168.8 (C16-$COOCH_3$), 176.4 (C21). Compounds **14** and **15** could be detected by TLC in the reaction mixture along with the epimeric mixture of **12** and **13**.

(b) A solution of the above residue and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 50 mL of anhydrous toluene was refluxed under argon for 16 h and the cooled reaction mixture was extracted twice with brine (20 mL). The combined brine extracts were then extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried and evaporated in vacuo. The three main components (R_f 0.23, R_f 0.49, and R_f 0.67) were separated by column chromatography (eluent: hexane–ethyl acetate, 3:2). The less-polar compound **16** was obtained as white crystals after crystallization from methanol (37 mg, 10%): mp 206–209 °C; IR (KBr) 3310 (indole NH), 1670 (conjugated CO), 1620 cm^{-1} (amide CO and C=C); MS m/z (rel inten) 352 (100.0), 351 (32.0), 324 (7.9), 321 (18.5), 320 (59.7), 292 (12.6), 180 (17.1), 167 (15.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.42 (1H, dqd, J_{gem} = −13.6, $J_{19A,20\alpha}$ = 7.2 Hz; C19-H_A), 1.66 (1H, m; C15-H_A), 1.83 (1H, ddd, J_{gem} = −12.0, $J_{5\alpha,6\alpha}$ = 6.2, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 1.85 (1H, m; C15-H_B), 1.86 (1H, m; C14-Hβ), 1.99 (1H, dqd, $J_{19B,20\alpha}$ = 6.4 Hz; C19-H_B), 2.15 (1H, dd, J_{gem} = −16.5, $J_{17\alpha,14\beta}$ = 10.7 Hz; C17-Hα), 2.28 (1H, ddd, $J_{5\alpha,6\beta}$ = 11.8, $J_{5\beta,6\beta}$ = 8.3 Hz; C6-Hβ), 2.42 (1H, dddd, $J_{15,20\alpha}$ = 9.1; s 9.5 Hz; C20-Hα), 2.80 (1H, dd, $J_{14\beta,17\beta}$ = 5.4 Hz; C17-Hβ), 3.50 (1H, ddd, J_{gem} = 12.0 Hz; C5-Hα), 3.55 (1H, d, $J_{3\alpha,14\beta}$ = 10.0 Hz; C3-Hα), 3.76 (3H, s; $COOCH_3$), 4.20 (1H, ddd; C5-Hβ), 6.83 (1H, d; C12-H), 6.86 (1H, dd; C10-H), 7.17 (1H, d; C9-H), 7.18 (1H, dd; C11-H), 9.00 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1 (C18), 23.3 (C19), 30.0 (C17), 32.2 (C15), 36.6 (C14), 38.9 (C6), 41.3 (C20), 43.6 (C5), 51.3 ($COOCH_3$), 55.5 (C7), 60.3 (C3), 95.4 (C16), 109.8 (C12), 120.6 (C10), 121.6 (C9), 128.6 (C11), 135.0 (C8), 144.5 (C13), 162.0 (C2), 168.4 ($COOCH_3$), 175.7 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.40; H, 6.72; N, 7.76.

The medium-polarity compound **14** was obtained as white crystals after crystallization from methanol (100 mg, 27%): mp 238–240 °C; IR (KBr) 3300 (indole NH), 1660 (conjugated CO), 1650 (amide CO), 1600 cm^{-1} (C=C); MS m/z (rel inten) 352 (60.0), 320 (3.0), 227 (100.0), 214 (42.0), 195 (35.0), 168 (11.6), 167 (16.8), 154 (15.7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (1H, ddd, J_{gem} = −13.2, $J_{14\alpha,15\beta}$ = 7.0, $J_{15\beta,20\alpha}$ = 12.9 Hz; C15-Hβ), 1.03 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.37 (1H, dqd, J_{gem} = −13.5, $J_{19A,20\alpha}$ = 7.0 Hz; C19-H_A), 1.83 (1H, dd, J_{gem} = −14.0, $J_{14\alpha,17\beta}$ = 12.0 Hz; C17-Hβ), 1.86 (1H, ddd, J_{gem} = −12.6, $J_{5\alpha,6\alpha}$ = 5.9, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 1.87 (1H, m; C14-Hα), 2.00 (1H, dqd, $J_{19B,20\alpha}$ = 5.8 Hz; C19-H_B), 2.02 (1H, ddd, $J_{5\alpha,6\beta}$ = 12.0, $J_{5\beta,6\beta}$ = 7.8 Hz; C6-Hβ), 2.14 (1H, dddd, $J_{15\alpha,20\alpha}$ = 4.8 Hz; C20-Hα), 2.31 (1H, ddd, $J_{14\alpha,15\alpha}$ = 9.0 Hz; C15-Hα), 2.72 (1H, ddd, $J_{14\alpha,17\alpha}$ = 3.0, $J_{3\alpha,17\alpha}$ ~ 1 Hz; C17-Hα), 3.47 (1H, ddd, J_{gem} = −11.7 Hz; C5-Hα), 3.78 (3H, s; $COOCH_3$), 3.97 (1H, br, $J_{3\alpha,14\alpha}$ = 6.4 Hz; C3-Hα), 4.16 (1H, ddd; C5-Hβ), 6.88 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ = 1 Hz; C12-H), 6.93 (1H, ddd, $J_{9,10}$ = 7.5, $J_{10,11}$ = 7.5 Hz; C10-H), 7.21 (1H, m; C9-H), 7.22 (1H, m; C11-H), 8.99 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2 (C18), 22.5 (C19), 27.0 (C17), 31.0 (C15), 34.9 (C14), 39.3 (C6),

42.5 (C20), 42.9 (C5), 51.1 ($COOCH_3$), 56.9 (C7), 60.9 (C3), 94.0 (C16), 109.6 (C12), 121.1 (C10), 121.8 (C9), 128.6 (C11), 135.5 (C8), 143.3 (C13), 162.8 (C2), 168.1 ($COOCH_3$), 173.3 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.43; H, 6.71; N, 7.82.

The most-polar compound **15** was obtained as white crystals after crystallization from methanol (79 mg, 21%): mp 186–189 °C; IR (KBr) 3320 (indole NH), 1655 (conjugated CO), 1625 (amide CO), 1600 cm^{-1} (C=C); MS *m/z* (rel inten) 352 (100.0), 320 (46.6), 227 (72.5), 214 (28.5), 195 (28.8), 180 (13.6), 168 (10.1), 167 (15.7), 154 (13.6); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.59 (1H, dqd, J_{gem} = −13.5, $J_{19A,20\beta}$ = 8.5 Hz; C19-H_A), 1.78 (1H, ddd, J_{gem} = −12.3, $J_{5\alpha,6\beta}$ = 12.1, $J_{5\beta,6\beta}$ = 7.0 Hz; C6-Hβ), 1.79 (1H, m; C14-Hα), 1.83 (1H, ddd, $J_{5\alpha,6\alpha}$ = 5.5, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 1.89 (1H, m; C15-H_A), 1.93 (1H, m; C15-H_B), 1.95 (1H, dqd, $J_{19B,20\beta}$ = 4.8 Hz; C19-H_B), 2.00 (1H, dd, J_{gem} = −15.0, $J_{14\alpha,17\beta}$ = 12.0 Hz; C17-Hβ), 2.39 (1H, dddd, $J_{15,20\beta}$ = 7.0; s 8.8 Hz; C20-Hβ), 2.58 (1H, ddd, $J_{14\alpha,17\alpha}$ = 3.3, $J_{3\alpha,17\alpha}$ = 1.3 Hz; C17-Hα), 3.28 (1H, ddd, J_{gem} = −12.0 Hz; C5-Hα), 3.78 (3H, s; $COOCH_3$), 4.16 (1H, dd, $J_{3\alpha,14\alpha}$ = 5.2 Hz; C3-Hα), 4.49 (1H, ddd; C5-Hβ), 6.87 (1H, br d, $J_{11,12}$ = 7.8 Hz; C12-H), 6.94 (1H, ddd, $J_{9,10}$ = 7.7, $J_{10,11}$ = 7.2, $J_{10,12}$ ~ 1 Hz; C10-H), 7.22 (1H, ddd, $J_{9,11}$ ~ 1 Hz; C11-H), 7.27 (1H, dd; C9-H), 8.93 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (C18), 23.8 (C17), 25.0 (C19), 30.0 (C15), 34.6 (C14), 39.9 (C20), 41.8 (C6), 43.7 (C5), 51.1 ($COOCH_3$), 57.7 (C7), 62.1 (C3), 95.1 (C16), 109.7 (C12), 121.0 (C10), 121.4 (C9), 128.6 (C11), 135.4 (C8), 143.3 (C13), 164.3 (C2), 168.1 ($COOCH_3$), 171.5 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.65; H, 6.91; N, 7.86.

21-Thioxopseudovincadifformine (17). To the solution of 200 mg (0.57 mmol) of 21-oxopseudovincadifformine (**14**) in 40 mL of anhydrous THF was added 400 mg (0.86 mmol) of P_4S_{10}. The reaction mixture was allowed to stir for 1 d at rt and was diluted with 60 mL of CH_2Cl_2. The solution was extracted with 50 mL of brine, and the brine was extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried and evaporated in vacuo. The residue was purified by column chromatography (eluent: ether–hexane 1:1) to yield a yellow oil (R_f 0.57), which was crystallized from ether–hexane to afford **17** (160 mg, 76%) as yellow crystals: mp 206–209 °C; IR (KBr) 3350 (indole NH), 1665 (conjugated CO), 1610 (C=C), 1470 cm^{-1} (N—C=S); MS *m/z* (rel inten) 368 (57.9), 335 (21.3), 240 (46.6), 239 (100.0), 228 (37.1), 196 (21.9), 180 (32.8), 169 (16.8), 167 (19.3); ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (1H, ddd, J_{gem} = −13.2, $J_{14\alpha,15\beta}$ = 8.0, $J_{15\beta,20\alpha}$ = 12.5 Hz; C15-Hβ), 1.05 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.51 (1H, dqd, J_{gem} = −14.0, $J_{19A,20\alpha}$ = 4.5 Hz; C19-H_A), 1.79 (1H, dd, J_{gem} = −15.3, $J_{14\alpha,17\beta}$ = 11.7 Hz; C17-Hβ), 2.00 (1H, ddd, J_{gem} = −12.5, $J_{5\alpha,6\alpha}$ = 6.1, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 2.02 (1H, ddddd, $J_{14\alpha,15\alpha}$ = 9.5, $J_{14\alpha,17\alpha}$ = 4.0, $J_{3\alpha,14\alpha}$ = 7.2 Hz; C14-Hα), 2.13 (1H, ddd, $J_{5\alpha,6\beta}$ = 12.5, $J_{5\beta,6\beta}$ = 8.0 Hz; C6-Hβ), 2.22 (1H, dddd, $J_{15\alpha,20\alpha}$ = 4.3, $J_{19B,20\alpha}$ = 7.6 Hz; C20-Hα), 2.37 (1H, ddd; C15-Hα), 2.41 (1H, dqd; C19-H_B), 2.79 (1H, ddd, $J_{3\alpha,17\alpha}$ = 1.2 Hz; C17-Hα), 3.78 (3H, s; $COOCH_3$), 3.79 (1H, ddd, J_{gem} = −13.0 Hz; C5-Hα), 4.00 (1H, br d; C3-Hα), 4.74 (1H, ddd; C5-Hβ), 6.89 (1H, dd, $J_{11,12}$ = 8.0, $J_{10,12}$ = 1 Hz; C12-H), 6.94 (1H, ddd, $J_{9,10}$ = 7.5, $J_{10,11}$ = 7.5 Hz; C10-H), 7.21–7.26 (2H, m; C9-H + C11-H), 9.00 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3 (C18), 25.8 (C19), 27.0 (C17), 30.7 (C15), 35.3 (C14), 38.5 (C6), 48.9 (C20), 50.2 (C5), 51.2 ($COOCH_3$), 56.7 (C7), 63.3 (C3), 94.1 (C16), 109.7 (C12), 121.2 (C10), 121.7 (C9), 128.9 (C11), 134.9 (C8), 143.2 (C13), 162.2 (C2), 168.0 ($COOCH_3$), 204.3 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.54; H, 6.72; N, 7.86.

21-Thioxo-20-epipseudovincadifformine (18). The reaction was carried out as in the case of **17** starting from 200 mg (0.57 mmol) of 21-oxo-20-epipseudovincadifformine (**15**) and 400 mg (0.86 mmol) of P_4S_{10}. After evaporation of the combined organic layers, the residue was purified by column chromatography (eluent: ether–hexane 1:1) to yield a yellow oil (R_f 0.57), which was crystallized from ether–hexane to give **18** (170 mg, 81%) as yellow crystals: mp 185–188 °C; IR (KBr) 3300 (indole NH), 1660 (conjugated CO), 1600 (C=C), 1460 cm^{-1} (N—C=S); MS *m/z* (rel inten) 368 (54.2), 335 (20.6), 240 (43.7), 239 (100.0), 228 (37.6), 196 (23.9), 180 (35.1), 169 (27.1), 167 (11.5); ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.42 (1H, ddd, J_{gem} = −14.0, $J_{14\alpha,15\beta}$ = 6.8, $J_{15\beta,20\beta}$ = 5.4 Hz; C15-Hβ), 1.55 (1H, dqd, J_{gem} = −13.5, $J_{19A,20\beta}$ = 9.3 Hz; C19-H_A), 1.83 (1H, dd, J_{gem} = −15.0, $J_{14\alpha,17\beta}$ = 11.7 Hz; C17-Hβ), 1.85 (1H, dqd, $J_{19B,20\beta}$ = 6.0 Hz; C19-H_B), 1.95 (1H, ddddd, $J_{3\alpha,14\alpha}$ = 6.9, $J_{14\alpha,15\alpha}$ = 8.8, $J_{14\alpha,17\alpha}$ = 4.0 Hz; C14-Hα), 1.96 (1H, ddd, J_{gem} = −12.5, $J_{5\alpha,6\alpha}$ = 6.2, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 2.00 (1H, ddd, $J_{5\alpha,6\beta}$ = 12.5, $J_{5\beta,6\beta}$ = 7.1 Hz; C6-Hβ), 2.19 (1H, ddd, $J_{15\alpha,20\beta}$ = 2.7 Hz; C15-Hα), 2.80 (1H, ddd, $J_{3\alpha,17\alpha}$ = 1.3 Hz; C17-Hα), 3.14 (1H, dddd; C20-Hβ), 3.78 (1H, ddd, J_{gem} = −13.0 Hz; C5-Hα), 3.79 (3H, s; $COOCH_3$), 4.08 (1H, br d; C3-Hα), 4.79 (1H, ddd; C5-Hβ), 6.89 (1H, dd, $J_{11,12}$ = 8.0, $J_{10,12}$ = ~1 Hz; C12-H), 6.95 (1H, ddd, $J_{9,10}$ = 7.5, $J_{10,11}$ = 7.5 Hz; C10-H), 7.22–7.26 (2H, m; C9-H + C11-H), 8.99 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (C18), 24.2* (C17), 27.2* (C19), 27.9* (C15), 33.3 (C14), 38.1 (C6), 50.7 (C5), 51.2 ($COOCH_3$), 53.2 (C20), 57.2 (C7), 61.9 (C3), 94.6 (C16), 109.8 (C12), 121.2 (C10), 121.6 (C9), 129.0 (C11), 134.9 (C8), 143.3 (C13), 164.2 (C2), 167.9 ($COOCH_3$), 203.5 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.30; H, 6.43; N, 7.40.

21-Thioxo-14-epipseudovincadifformine (19). The reaction was carried out as in the case of **17** starting from a solution of 100 mg (0.28 mmol) of 21-oxo-14-epipseudovincadifformine (**16**) and 200 mg (0.43 mmol) of P_4S_{10} in 20 mL of anhydrous THF. After evaporation of the combined organic layers, the residue was purified by column chromatography (eluent: ether–hexane 1:1) to yield a yellow oil (R_f 0.57), which was crystallized from hexane to yield **19** (75 mg, 71%) as yellow crystals: mp 194–197 °C; IR (KBr) 3300 (indole NH), 1660 (conjugated CO), 1600 (C=C), 1420 cm^{-1} (NC=S); MS *m/z* (rel inten) 368 (51.3), 340 (8.6), 335 (11.7), 240 (50.0), 239 (100.0), 180 (44.1), 167 (17.8); ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.58 (1H, dqd, J_{gem} = −13.6, $J_{19A,20\alpha}$ = 7.6 Hz; C19-H_A), 1.59 (1H, m; C15-H_A), 1.87 (1H, m; C14-Hβ), 1.88 (1H, m; C15-H_B), 1.95 (1H, ddd, J_{gem} = −12.2, $J_{5\alpha,6\alpha}$ = 6.5, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 2.21 (1H, dd, J_{gem} = −16.5, $J_{14\beta,17\alpha}$ = 10.8 Hz; C17-Hα), 2.35 (1H, dqd, $J_{19B,20\alpha}$ = 5.3 Hz; C19-H_B), 2.38 (1H, ddd, $J_{5\alpha,6\beta}$ = 12.0, $J_{5\beta,6\beta}$ = 8.1 Hz; C6-Hβ), 2.51 (1H, dddd, $J_{15,20\alpha}$ ~9 Hz; C20-Hα), 2.84 (1H, dd, $J_{14\beta,17\beta}$ = 5.5 Hz; C17-Hβ), 3.71 (1H, br d, $J_{3\alpha,14\beta}$ = 10.4 Hz; C3-Hα), 3.77 (3H, s; $COOCH_3$), 3.86 (1H, ddd, J_{gem} = −13.0 Hz; C5-Hα), 4.86 (1H, ddd; C5-Hβ), 6.84 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ ~ 1 Hz; C12-H), 6.87 (1H, ddd, $J_{9,10}$ ~ 7.5, $J_{10,11}$ ~ 7.5 Hz; C10-H), 7.16 (1H, dd, $J_{9,11}$ = 1.3 Hz; C9-H), 7.19 (1H, ddd; C11-H), 9.02 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3 (C18), 26.8 (C19), 30.0 (C17), 32.3 (C15), 36.0 (C14), 38.6 (C6), 48.0 (C20), 50.8 (C5), 51.4 ($COOCH_3$), 55.2 (C7), 62.5 (C3), 95.8 (C16), 110.0 (C12), 120.6 (C10), 121.4 (C9), 128.8 (C11), 134.5 (C8), 144.5 (C13), 161.5 (C2), 168.2 ($COOCH_3$), 205.2 (C21). Anal. Calcd for $C_{21}H_{24}N_2O_2S$: C, 68.45; H, 6.56; N, 7.60. Found: C, 68.28; H, 6.69; N, 7.80.

Pseudovincadifformine (4). To a solution of 100 mg (0.27 mmol) of 21-thioxopseudovincadifformine (**17**) in 20 mL of anhydrous THF was added ~1 g of water, methanol, and anhydrous THF-washed Raney-Ni. The suspension was stirred overnight and filtered. The Raney-Ni was washed with 10 mL of anhydrous THF and the combined filtrate was evaporated in vacuo. The residue was purified by column chromatography (eluent: ether–hexane 1:1) to yield a yellow oil (R_f 0.69), which was crystallized from ether–hexane to yield **4** (73 mg, 80%) as white crystals: mp 109–111 °C; IR (KBr) 3300 (indole NH), 1670 (conjugated CO), 1610 cm^{-1} (C=C); MS *m/z* (rel inten) 338 (40.1), 293 (3.4), 167 (8.6), 124 (100.0), 57 (9.4), 55 (11.1), 43 (9.7), 41 (15.7); ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.3–1.55 (3H, m; C15-H_A + C19-H_A + C14-Hα), 1.49 (1H, dqd, J_{gem} = −13.0, $J_{20\alpha,19B}$ = 7.4 Hz; C19-H_B), 1.65 (1H, br m; C20-Hα), 1.73–1.85 (2H, br m; C6-H_A + C15-H_B), 2.02 (1H, ddd, J_{gem} = −11.5, $J_{5,6B}$ = 11.0; s 6.2 Hz; C6-H_B), 2.29 (1H, dd, J_{gem} = −14.6, $J_{14\alpha,17\beta}$ = 11.2 Hz; C17-Hβ), 2.54 (1H, ddd, $J_{14\alpha,17\alpha}$ = 3.7, $J_{3\alpha,17\alpha}$ ~ 1 Hz; C17-Hα), 2.71 (1H, br m; C5-H_A), 2.83 (2H, d, $J_{20,21}$ = 5.6 Hz; C21-H_2), 2.91 (1H, br dd, J_{gem} = −8.5, J_{vic} = 6.0 Hz; C5-H_B), 3.01 (1H, r d, $J_{3\alpha,14\alpha}$ = 4 Hz; C3-Hα), 3.76 (3H, s; $COOCH_3$), 6.80 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ = 1.0 Hz; C12-H), 6.87 (1H, ddd, $J_{9,10}$ = 7.5, $J_{10,11}$ = 7.3 Hz; C10-H), 7.14 (1H, ddd, $J_{9,11}$ = 1.3 Hz; C11-H), 7.25 (1H, br d; C9-H), 8.94 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (C18), 26.5 (C17), 28.7 (C19), 32.4 (C15), 35.5 (C20), 36.1 (C14), 44.2 (C6), 51.0 ($COOCH_3$), 51.5 (C5), 54.9 (C21), 55.2 (C7), 66.0 (C3), 96.1 (C16), 109.2 (C12), 120.4 (C10), 121.8 (C9), 127.6 (C11), 137.9 (C8), 143.5 (C13), 165.8 (C2), 168.6 ($COOCH_3$).

20-Epipseudovincadifformine (5). Method a. The reaction was carried out as in the case of **4** starting from 100 mg (0.27 mmol) of 21-thioxo-20-epipseudovincadifformine (**18**). For purification, TLC eluting with ether–hexane (1:1) was used to yield a yellow oil (R_f 0.69), which was crystallized from ether–hexane to yield **5** (69 mg, 75%) as white crystals: mp 118–120 °C; IR (KBr) 3300 (indole NH), 1660 (conjugated CO), 1600 cm^{-1} (C=C); MS *m/z* (rel inten) 338 (35.7), 293 (5.5), 239 (2.9), 167 (8.6), 124 (100.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 1.15–1.3 (3H, m; C15-Hα + C19-H_2), 1.46 (1H, m; C14-Hα), 1.74 (1H, m; C20-Hβ), 1.81 (1H, ddd, J_{gem} = −11.5, $J_{5\alpha,6\alpha}$ = 5.0, $J_{5\beta,6\alpha}$ = 2.0 Hz; C6-Hα), 1.89 (1H, dddd, J_{gem} = −13.5, J_{vic} = 4.2; s 2.1, $J_{15\beta,21\beta}$ = 1.5 Hz; C15-Hβ), 2.02 (1H, ddd, $J_{5\alpha,6\beta}$ = 10.0, $J_{5\beta,6\beta}$ = 6.5 Hz; C6-Hβ), 2.15 (1H, dd, J_{gem} = −10.6, $J_{20\beta,21\alpha}$ = 10.9 Hz; C21-Hα), 2.37 (1H, ddd, J_{gem} = −14.6, $J_{14\alpha,17\alpha}$ = 3.5, $J_{3\alpha,17\alpha}$ = 1.5 Hz; C17-Hα), 2.59 (1H, dd, $J_{14\alpha,17\beta}$ = 11.6 Hz; C17-Hβ), 2.67 (1H, ddd, J_{gem} = −8.5 Hz; C5-Hα), 2.89 (1H, br d, $J_{3\alpha,14\alpha}$ = 3 Hz; C3-Hα), 2.93 (1H, ddd; C5-Hβ), 3.20 (1H, ddd, $J_{20\beta,21\beta}$ = 4.3 Hz; C21-Hβ), 3.76 (3H, s; $COOCH_3$), 6.79 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ = 1.0 Hz; C12-H), 6.87 (1H, ddd, $J_{9,10}$ = 7.4, $J_{10,11}$ = 7.4 Hz; C10-H), 7.13 (1H, ddd, $J_{9,11}$ = 1.3 Hz; C11-H), 7.26 (1H, br d; C9-H), 8.90 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (C18), 24.9 (C17), 27.3 (C19), 33.3 (C20), 35.6 (C15), 36.3 (C14), 45.7 (C6), 51.0 ($COOCH_3$), 51.6 (C5), 55.9 (C7), 56.3 (C21), 67.4 (C3), 96.6 (C16), 109.2 (C12), 120.5 (C10), 121.3 (C9), 127.6 (C11), 137.4 (C8), 143.7 (C13), 166.8 (C2), 168.8 ($COOCH_3$).

Method b. A solution of 200 mg (0.43 mmol) of an epimeric mixture of **26** and **27**, and 50 mg (0.3 mmol) of KI in 20 mL of anhydrous DMSO, was stirred at 145 °C for 3.5 h. Then the solvent was evaporated in vacuo and the residue was dissolved in 100 mL of CH_2Cl_2 and extracted with 50 mL of water. The organic layer was dried and evaporated in vacuo. The residue was puriied by TLC, eluting with ether–hexane (1:1) to yield **5** (32 mg, 22%, R_f 0.69) as a yellow oil which was identical spectroscopically to the material prepared by method a.

14-Epipseudovincadifformine (20). The reaction was carried out as in the case of **4** starting from 50 mg (0.14 mmol) of 21-thioxo-14-epipseudovincadifformine (**19**). For purification, TLC eluting with benzene–methanol (10:1) was used to yield **20** (20 mg, 43%) as a white oil (R_f 0.32): IR (neat) 3350 (indole NH), 1670 (conjugated CO), 1600 cm^{-1} (C=C); MS *m/z* (rel inten) 338 (41.0), 124 (100.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (3H, t, $J_{18,19}$ = 7.3 Hz; C18-H_3), 1.45–1.65 (2H, m; C15-H_2), 1.55 (2H, m; C19-H_2), 1.70 (1H, m; C20-Hα), 1.77 (1H, ddd, J_{gem} = −12.0, $J_{5A,6A}$ = 2.0, $J_{5B,6A}$ = 7.8 Hz; C6-H_A), 1.98 (1H, dd, J_{gem} = −15.0, $J_{14\beta,17\alpha}$ = 11.5 Hz; C17-Hα), 2.04 (1H, m; C14-Hβ), 2.49 (1H, ddd, $J_{5A,6B}$ = 9.7, $J_{5B,6B}$ = 9.7 Hz; C6-H_B), 2.57 (1H, dd, $J_{14\beta,17\beta}$ = 4.5 Hz; C17-Hβ), 2.88 (1H, dd, J_{gem} = −13.0, $J_{20\alpha,21A}$ = 5.0 Hz; C21-H_A), 2.98 (1H, br d, $J_{3\alpha,14\beta}$ = 10.0 Hz; C3-Hα), 3.09 (1H, ddd, J_{gem} = −10.0 Hz; C5-H_A), 3.28 (1H, dd, $J_{20\alpha,21B}$ = 3.7 Hz; C21-H_B), 3.45 (1H, ddd; C5-H_B), 3.74 (3H, s; $COOCH_3$), 6.76 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ ~ 1 Hz; C12-H), 6.84 (1H, ddd, $J_{9,10}$ = 7.5, $J_{10,11}$ = 7.4 Hz; C10-H), 7.10 (1H, ddd, $J_{9,11}$ = 1.3 Hz; C11-H), 7.48 (1H, br d; C9-H), 9.02 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (C18), 27.9 (C19), 28.2 (C14), 30.7 (C17), 33.9 (C15), 35.7 (C20), 40.9 (C6), 50.3 (C5), 51.2 ($COOCH_3$), 52.4 (C21), 55.2 (C7), 64.8 (C3), 94.3 (C16), 109.3 (C12), 120.8 (C10), 123.0 (C9), 128.0 (C11), 136.8 (C8), 144.1 (C13), 163.9 (C2), 169.0 ($COOCH_3$).

2-Ethyl-5,5-dimethoxypentan-1-ol (21). To an ice-cooled suspension of 2.0 g (52.7 mmol) of $LiAlH_4$ in anhydrous THF (40 mL) was slowly added a solution of 9.8 g (48 mmol) of **8** in anhydrous THF (40 mL) from a dropping funnel keeping the temperature below 20 °C. The reaction mixture was allowed to stir for 0.5 h at rt and cooled to 10 °C. To the suspension were added dropwise 12 mL of 2 M aqueous NaOH and 18 mL of water keeping the temperature below 20 °C. The reaction mixture was filtered, the white salts were washed twice with 100 mL of CH_2Cl_2, and the combined filtrates were evaporated in vacuo. The residue was dissolved in 100 mL of CH_2Cl_2 and washed with 100 mL of water. The aqueous layer was washed twice with 40 mL of CH_2Cl_2 and the combined organic layers were dried and evaporated in vacuo to yield **21** (7.2 g, 85%) as a colorless liquid: IR (neat) 3300–3450 (OH); 1010–1090 cm^{-1} [C(OC)$_2$]; ^{1}H NMR ($CDCl_3$) δ 0.91 (3H, t, J = 6.8 Hz; CH_2CH_3), 1.15–1.75 (8H, m; CH_2CH_3 + C2-H + C3-H_2 + C4-H_2 + OH), 3.32 (6H, s; OCH_3 + OCH_3), 3.55 (2H, br; C1-H_2), 4.35 (1H, t, J = 5.3 Hz; C5-H); ^{13}C NMR ($CDCl_3$) δ 11.2 (CH_2CH_3), 23.4 (C3), 25.3 (CH_2CH_3), 29.8 (C4), 41.9 (C2), 52.6 + 52.7 (OCH_3 + OCH_3), 64.6 (C1), 105.0 (C5).

1-(Benzoyloxy)-2-ethyl-5,5-dimethoxypentane (22). To a solution of 7 g (40 mmol) of **21** in 70 mL of CH_2Cl_2 was added 5.0 g (7.0 mL, 50.3 mmol) of triethylamine and the mixture was cooled to 0 °C. Benzoyl chloride (6.2 g, 5.1 mL, 44.1 mmol) was added dropwise keeping the temperature below 0 °C. The mixture was allowed to warm to rt and was stirred overnight at this temperature. The suspension was extracted with 50 mL of saturated aqueous Na_2CO_3 solution, and the organic layer was dried and evaporated in vacuo. The residue was distilled to afford **22** (9.2 g, 83%) as a colorless liquid: bp 130–136 °C (7 mbar); IR (neat) 1720 (CO); 1020–1070 cm^{-1} [C(OC)$_2$]; ^{1}H NMR ($CDCl_3$) δ 0.96 (3H, t, J = 7.0 Hz; CH_2CH_3), 1.3–1.9 (7H, m; CH_2CH_3 + C2-H + C3-H_2 + C4-H_2), 3.31 (6H, s; OCH_3 + OCH_3), 4.27 (2H, d, J = 5.6 Hz; C1-H_2), 4.36 (1H, t, J = 5.0 Hz; C5-H), 7.3–8.2 (5H, m; aromatic H); ^{13}C NMR ($CDCl_3$) δ 11.1 (CH_2CH_3), 24.0* (C3), 25.8* (CH_2CH_3), 29.8 (C4), 38.9 (C2), 52.6 + 52.7 (OCH_3 + OCH_3), 67.0 (C1), 104.6 (C5), 128.4 (C3′ + C5′), 129.5 (C2′ + C6′), 130.5 (C1′), 132.8 (C4′), 166.5 (OCOPh).

5-(Benzoyloxy)-4-ethylpentanal (23). A solution of 7.0 g (25 mmol) of **22** in 20 mL of glacial acetic acid and 5 mL of water were refluxed for 30 min and allowed to cool to rt. To the reaction mixture was added 100 mL of ether and 50 mL of water. The pH of the aqueous layer was adjusted to 9 with saturated aqueous Na_2CO_3 solution. The aqueous layer was extracted twice with 50 mL of ether, and the combined organic layers were dried and evaporated in vacuo to yield **23** (5.2 g, 89%) as a colorless liquid: IR (neat) 1720–1740 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7.0 Hz; CH_2CH_3), 1.3–1.9 (5H, m; CH_2CH_3 + C4-H + C3-H_2), 2.52 (2H, td, J_{vic} = 7.0 and 1.3 Hz; C2-H_2), 4.27 (2H, m; C5-H_2), 7.3–8.1 (5H, m; aromatic H), 9.81 (1H, t, J = 1.3 Hz; CHO); ^{13}C NMR ($CDCl_3$) δ 11.1 (CH_2CH_3), 23.2* (C3), 23.9* (CH_2CH_3), 38.6 (C4), 41.3 (C2), 66.5 (C5), 128.4 (C3′ + C5′), 129.5 (C2′ + C6′), 130.3 (C1′), 133.0 (C4′), 166.5 (OCOPh), 202.0 (CHO).

Preparation of an Epimeric Mixture of 24 and 25. A solution of 0.7 g (2 mmol) of **6**, 1.0 g (4.4 mmol) of **23**, and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 40 mL of anhydrous toluene was refluxed under argon for 24 h and the reaction mixture was extracted twice with brine (20 mL). The combined brine extracts were extracted twice with CH_2Cl_2 (20 mL). The combined organic layers were dried and evaporated in vacuo. The residue was purified by preparative TLC, eluting with ether–hexane (1:1) to yield an epimeric mixture of **24** and **25** (410 mg, 38%) as a yellow oil (R_f 0.73): IR (neat) 3300 (indole NH), 1710 (CO), 1670 (conjugated CO), 1600 cm^{-1} (C=C); MS *m/z* (rel inten) 550 (23.0), 417 (40.6), 337 (23.8), 336 (98.0), 214 (13.1), 105 (65.7), 91 (100.0), 77 (25.7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 + 0.80 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 0.75–1.1 (2H, m; C15-H_2), 1.20 (1H, m; C19-H_A), 1.38 (1H, m; C19-H_B), 1.6–1.7 (2H, m; C6-H_A + C20-H), 1.95–2.10 (2H, m; C6-H_B + C14-H), 2.5–2.8 (3H, m; C17-H_2 + C5-H_A), 2.85–3.0 (2H, m; C5-H_B + C3-H), 3.77 + 3.72 (3H, s; $COOCH_3$), 3.9–4.25 (4H, m; C21-H_2 + N-CH_2-Ph), 6.7–8.0 (14H, m; aromatic H), 9.00 + 8.89 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 + 10.8 (C18), 22.0 + 22.1 (C17), 25.0 + 22.9 (C19), 32.3 + 31.1 (C15), 36.3 + 36.1 (C14), 36.5 + 36.1 (C20), 42.1 + 42.3 (C6), 50.6 + 50.9 (C5), 50.91 + 50.94 ($COOCH_3$), 55.2 (C7), 58.1 + 58.5 (N-CH_2Ph), 67.1 + 67.6 (C21), 72.3 + 72.5 (C3), 90.35 + 90.40 (C16), 109.2 (C12), 120.54 + 120.49 (C10), 122.2 (C9), 127.1 (C4′), 127.8 (C11), 128.4 + 128.3 (C3″ + C5″), 128.3 (C3′ + C5′), 129.0 (C2′ + C6′), 129.44 + 129.48 (C2″ + C6″), 130.33 + 130.36 (C1″), 132.8 (C4″), 137.9 (C8), 138.7 + 139.0 (C1′), 142.9 (C13), 165.2 (C2), 166.6 + 166.4 (OCOPh), 169.0 + 168.9 ($COOCH_3$).

Preparation of Amines 26 and 27. A mixture of 400 mg of an epimeric mixture of **24** and **25** (0.73 mmol), and 0.3 g of 10% Pd/C in 15 mL of glacial acetic acid, was hydrogenated for 2 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 (10 mL). The combined organic layers were dried and evaporated in vacuo. The residue was purified by preparative TLC, eluting with $CHCl_3$–methanol (9:1) to yield an epimeric mixture of **26** and **27** (the ratio of isomers was about 1:2 based on NMR analysis, 270 mg, 81%) as a yellow oil (R_f 0.38): IR (neat) 3250 (NH), 1700 (CO),

1650 (conjugated CO), 1590 cm^{-1} (C=C); MS *m/z* (rel inten) 461 (32.7), 460 (84.6), 417 (25.2), 391 (17.1), 384 (11.8), 283 (39.5), 274 (18.1), 246 (60.4), 215 (100.0), 168 (19.3), 154 (24.9), 124. (59.7), 105 (71.1), 77 (32.3), 68 (27.4).

Epimer **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 + 0.84 (3H, t, $J_{18,19}$ = 7.4 Hz; C18-H_3), 0.9–1.13 (2H, m; C15-H_2), 1.2–1.45 (2H, m; C19-H_2), 1.6–1.75 (1H, m; C20-H), 1.8–2.05 (3H, m; C6-H_2 + C14-H), 2.38 + 2.36 (1H, dd, J_{gem} = −15.5, $J_{14\beta,17\beta}$ = 3.5 Hz; C17-Hβ), 2.69 + 2.75 (1H, ddd, $J_{14\beta,17\alpha}$ = 3.0, $J_{3\alpha,17\alpha}$ = 1.5 Hz; C17-Hα), 3.05–3.25 (2H, m; C5-H_2), ~3.4 (1H, br s; N4-H), 3.51 + 3.55 (1H, br s; C3-H_α), 3.72 + 3.77 (3H, s; $COOCH_3$), 4.00–4.25 (2H, m; C21-H_2), 6.75–8.05 (9H, m; aromatic H), 8.95 + 8.97 (1H, br s; N1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8 + 11.3 (C18), 21.99 + 22.01 (C17), 22.9 + 24.8 (C19), 32.68 + 32.70 (C15), 36.0 + 36.5 (C20), 37.7 + 38.1 (C14), 44.1 + 44.1 (C6), 45.08 + 45.11 (C5), 50.96 + 51.00 ($COOCH_3$), 55.57 + 55.64 (C7), 66.7 + 67.3 (C21), 67.1 + 67.2 (C3), 89.9 + 90.00 (C16), 109.27 + 109.31 (C12), 120.8 + 120.9 (C10), 121.7 + 121.9 (C9), 128.00 + 128.02 (C11), 128.3 + 128.4 (C3′ + C5′), 129.4 + 129.5 (C2′ + C6′), 130.26 + 130.31 (C1′), 132.78 + 132.79 (C4′), 137.1 + 137.3 (C8), 143.00 + 143.02 (C13), 164.9 + 165.0 (C2), 166.4 + 166.6 (OCOPh), 168.7 + 168.8 ($COOCH_3$).

Epimeric **26**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 + 0.97 (3H, t, $J_{18,19}$ = 7.4 Hz; C_{18}-H_3), 1.4–1.6 (3H, m; C19-H_2 + C14-H), 1.55 + 1.65 (2H, m; C15-H_2), 1.8–2.0 (3H, m; C6-H_2 + C20-H), 2.04 (1H, dd, J_{gem} = −15.0, $J_{14\alpha,17\beta}$ = 11.0 Hz; C17-Hβ), 2.50–2.52 (1H, ddd, $J_{14\alpha,17\alpha}$ = 2.5, $J_{3\alpha,17\alpha}$ = 1.5 Hz; C17-Hα), 3.05–3.25 (2H, m; C5-H_2), ~3.4 (1H, br s; N4-H), 3.75 + 3.76 (3H, s; $COOCH_3$), 3.78 + 3.86 (1H, dd, $J_{3\alpha,14\alpha}$ = 4.5 Hz; C3-H_α), 4.15–4.30 (2H, m; C21-H_2), 6.75–8.05 (9H, m; aromatic H), 9.08 (1H, br s; N1-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0 (C18), 23.9 + 24.1 (C17), 24.4 + 24.7 (C19), 32.5 + 32.8 (C15), 36.5 + 36.6 (C20), 39.2 + 39.3 (C14), 44.9 + 45.0 (C5), 45.50 (C6), 51.0 ($COOCH_3$), 57.26 + 57.30 (C7), 62.3 + 62.5 (C3), 67.4 + 67.7 (C21), 95.12 + 95.13 (C16), 109.28 + 109.29 (C12), 120.6 + 120.7 (C10), 121.9 (C9), 127.98 + 128.00 (C11), 128.28 + 128.33 (C3′ + C5′), 129.45 + 129.47 (C2′ + C6′), 130.2 + 130.3 (C1′), 132.80 + 132.84 (C4′), 137.00 + 137.08 (C8), 143.42 + 143.43 (C13), 162.6 + 165.8 (C2), 166.63 + 166.65 (OCOPh), 168.30 ($COOCH_3$).

Thioether 28. To a solution of 100 mg (0.27 mmol) of an epimeric mixture of **17** and **18** (~3:2), and 0.05 mL (37 mg, 0.29 mmol) of *N,N*-diisopropylethylamine in 50 mL of anhydrous CH_2Cl_2, was added dropwise 0.15 mL (150 mg, 0.65 mmol) of *p*-toluenesulfinyl chloride. The reaction mixture was stirred for 24 h at rt, quenched with 40 mL of 1 M acetic acid solution, and was stirred for 5 min. The aqueous layer was neutralized with 5% aqueous $NaHCO_3$. 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 preparative TLC, eluting with benzene–methanol (40:1) to yield **28** (R_f 0.68) as a yellow oil. The oil was treated with hexane to yield 55 mg (41%) of yellow crystals: IR (KBr) 3300 (indole NH), 1670 (conjugated CO), 1440 cm^{-1} (N—C=S), MS *m/z* (rel inten) 490 (73), 367 (100), 335 (21), 227 (16), 125 (41), 91 (15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (3H, t, $J_{18,19}$ = 7.3 Hz; C18-H_3), 1.39 (1H, dd, J_{gem} = −14.5, $J_{14\alpha,15A}$ = 6.6 Hz; C15-H_A), 1.83 (1H, dd, J_{gem} = −15.0, $J_{14\alpha,17\beta}$ = 11.5 Hz; C17-Hβ), 1.98 (1H, ddd, J_{gem} = −12.5, $J_{5\alpha,6\alpha}$ = 6.0, $J_{5\beta,6\alpha}$ ~ 1 Hz; C6-Hα), 2.04 (1H, ddddd, $J_{3\alpha,14\alpha}$ = 7.2, $J_{14\alpha,15B}$ = 9.5, $J_{14\alpha,17\alpha}$ = 4.0 Hz; C14-Hα), 2.06 (1H, ddd, $J_{5\alpha,6\beta}$ = 12.5, $J_{5\beta,6\beta}$ = 7.3 Hz; C6-Hβ), 2.11 (1H, dq, J_{gem} = −14.4 Hz; C19-H_A), 2.15 (1H, dq; C19-H_B), 2.36 (3H, s; $ArCH_3$), 2.41 (1H, dd; C15-H_B), 2.79 (1H, ddd, $J_{3\alpha,17\alpha}$ = 1.2 Hz; C17-Hα), 3.79 (3H, s; $COOCH_3$), 3.85 (1H, ddd, J_{gem} = −13.0 Hz; C5-Hα), 4.71 (1H, ddd; C5-Hβ), 5.24 (1H, br d; C3-Hα), 6.91 (1H, dd, $J_{11,12}$ = 7.8, $J_{10,12}$ = 1.0 Hz; C12-H), 7.00 (1H, ddd, $J_{9,10}$ = 7.3, $J_{10,11}$ = 7.5 Hz; C10-H), 7.14 + 7.35 (4H; aromatic H), 7.26 (1H, ddd, $J_{9,11}$ = 1.2 Hz; C11-H), 7.31 (1H, dd; C9-H), 8.99 (1H, br s; NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5 (C18), 21.4 ($ArCH_3$), 27.5 (C17), 32.7 (C14), 32.9 (C19), 34.0 (C15), 38.3 (C6), 51.2 ($COOCH_3$), 51.7 (C5), 57.2 (C7), 58.9 (C20), 61.7 (C3), 94.1 (C16), 109.8 (C12), 121.3 (C10), 121.7 (C9), 126.2 (C1′), 128.9 (C11), 129.5 (C3′ + C5′), 135.4 (C8), 137.0 (C2′ + C6′), 139.7 (C4′), 143.3 (C13), 162.5 (C2), 167.9 ($COOCH_3$), 199.7 (C21). Anal. Calcd for $C_{28}H_{30}N_2O_2S_2$: C, 68.53; H, 6.16; N, 5.71. Found: C, 68.73; H, 6.32; N, 5.46.

21-Oxopseudotabersonine (30). To a solution of 50 mg (0.1 mmol) of **28** at −20 °C in 30 mL of anhydrous CH_2Cl_2 was added 45 mg (0.24 mmol) of 85% *m*-CPBA. The reaction mixture was stirred below −20 °C for 30 min and then extracted with 5% aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried, and the solvent was evaporated in vacuo. The residue was purified by TLC eluting with ethyl acetate–hexane (2:3) and the compound isolated (R_f 0.69) was treated with ethyl acetate to yield **30** (21 mg, 59%) as white crystals: mp 160–163 °C; IR (KBr) 3300 (indole NH), 1660 (conjugated CO), 1610 (conjugated amide CO), 1600 cm^{-1} (C=C); MS *m/s* (rel inten) 350 (10.9), 227 (100.0), 195 (73.6), 168 (21.1), 167 (30.9), 154 (12.6); ^{1}H NMR ($CDCl_3$) δ 1.10 (3H, t, $J_{18,19}$ = 7.3 Hz; C18-H_3), 1.8–2.9 (7H, m; C6-H_2 + C17-H_2 + C19-H_2 + C14-Hα), 3.44 (1H, ddd, J_{gem} = −12.0, J_{vic} = 10.0 and 6.0 Hz; C5-Hα), 3.79 (3H, s; $COOCH_3$), 4.34 (1H, ddd, J_{vic} = 7.0 and ~1 Hz; C5-Hβ), 4.38 (1H, br d, $J_{3\alpha,14\alpha}$ = 4.8 Hz; C3-Hα), 6.24 (1H, br d, $J_{14\alpha,15}$ = 5 Hz; C15-H), 6.85–7.35 (4H, m; aromatic H), 9.00 (1H, br s; NH); ^{13}C NMR ($CDCl_3$) δ 12.9 (C18), 23.3* (C17), 23.4* (C19), 36.6 (C14), 43.3 (C6), 43.3 (C5), 51.1 ($COOCH_3$), 57.0 (C7), 61.3 (C3), 94.7 (C16), 109.7 (C12), 121.2 (C10), 121.6 (C9), 128.7 (C11), 132.7 (C15), 135.4 (C8), 137.2 (C20), 143.3 (C13), 162.6 (C2), 164.2 (C21), 168.0 ($COOCH_3$). Anal. Calcd for $C_{21}H_{22}N_2O_3$: C, 71.97; H, 6.33; N, 8.00. Found: C, 71.74; H, 6.52; N, 7.86.

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Supplementary Material Available: Spectroscopic data for compounds **7–9**, **10/11**, **12/13**, **14–19**, **21–23**, **24/25**, **26/27**, **28**, **30**, and for methyl 2-ethyl-5-oxo-2-carbomethoxypentanoate (19 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.