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APPROACHES TO THE SYNTHESIS OF ASPIDOSPERMA ALKALOIDS. PART II. THE SYNTHESIS OF 18,19-DIDEHYDROTABERSONINE.

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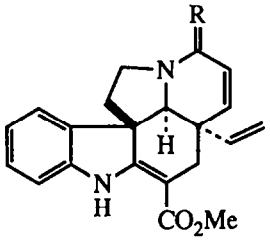
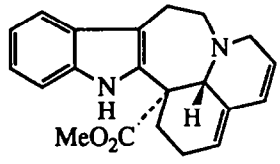
Summary: The total synthesis of 18,19-didehydrotabersonine, via 3-oxo-18,19-didehydrovincadifformine, is described.

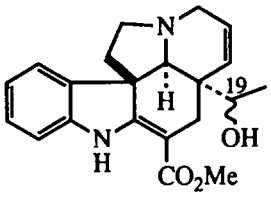
In continuation of our synthetic studies[1] in the vincadifformine sub-group of Aspidosperma alkaloids we next investigated routes to 18,19-didehydrotabersonine (1), a pivotal intermediate from which a number of other alkaloids could in principle be obtained. For example, when heated in methanol at 145°C rearrangement occurs[2] with formation, among other products, of racemic andranginine (2), an alkaloid of Craspidospermum verticillatum.[3] In addition, the alkaloids (3) and (4), which in a formal sense are the result of hydration of the 18,19-double bond in (1), occur in the aerial parts of Catharanthus ovalis;[4] these two alkaloids have already been correlated with kitramine (5) and kitraline (6), which also occur in C. ovalis,[4] with vincoline (7),[4] a constituent of C. lanceus,[5] and with melobaline (8),[6] an alkaloid of Melodinus balansae.[7]



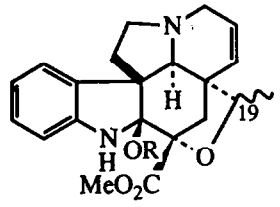
(1) R = H_2
(30) R = O



Andranginine (2)



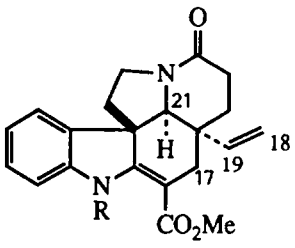
(3) 19R
(4) 19S



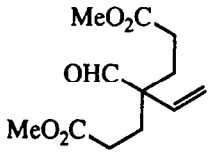
Kitramine (5) R = Me; 19R
Kitraline (6) R = Me; 19S
Vincoline (7) R = H; 19S
Melobaline (8) R = H; 19R

As in our earlier work we initially protected N_b by incorporating it in a lactam function, and since it was considered feasible to introduce the 14,15-double bond at a very late stage in the synthesis our first objective was the pentacyclic lactam ester (9), i.e. 3-oxo-18,19-didehydrovincadifformine. The required starting material was thus either the unsaturated aldehydo-ester (10) or the related phenylthio derivative (11); the use of this latter would in principle provide some flexibility in the exact stage at which the 18,19-double bond was introduced.

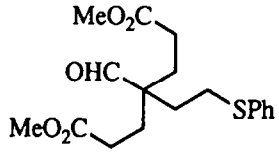
Oxidation of 4-phenylthiobutan-1-ol[8] by Swern's method[9] or by N-chloro-succinimide-dimethyl sulphoxide[10] gave the corresponding aldehyde (12), which was converted into its pyrrolidine enamine and exhaustively alkylated by means of methyl acrylate to give the desired diester (11), together with a small yield of monoalkylated ester (13). Oxidation of (11) by sodium metaperiodate in aqueous methanol gave an almost quantitative yield of the related sulphoxide which, when refluxed in xylene, gave the required unsaturated aldehydo diester (10).



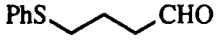
(9) R = H
(22) R = Me
(17) R = H; 18,19-dihydro



(10)



(11)



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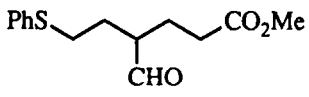
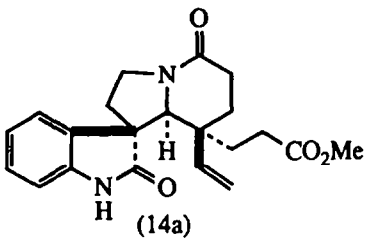
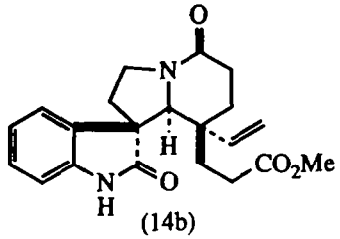


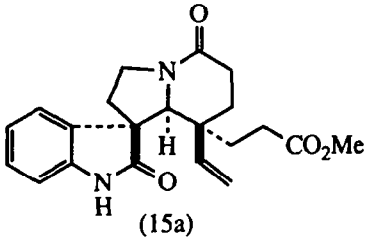
(13)

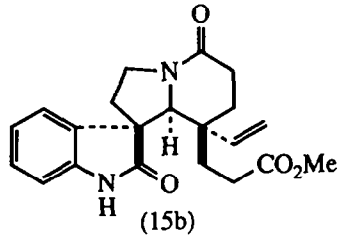
The condensation of the intermediate (10) with 2-hydroxytryptamine, prepared by the method of Savige and Fontana,[11] was examined under a variety of conditions. When 2-hydroxytryptamine hydrochloride, the aldehydo ester (10), and an aqueous ethanolic sodium acetate buffer were used, all four products (14 and 15) were obtained, the proportion of less polar (A) isomers (14a and 14b): more polar (B) isomers (15a and 15b) being approximately 2:3. When the condensation was performed with free 2-hydroxytryptamine base in dry benzene, followed by cyclization with acetic acid, the ratio was 6:1 in favour of the more polar stereoisomers (15a and 15b). Since cyclization of the (B) stereoisomers (15a and 15b) resulted in the desired stereochemistry at the C/D ring junction, and since equilibration of the tetracyclic lactams (14 and 15) was not observed (contrast the well-known interconversion of the related bases in which the C-3 carbonyl group is replaced by a methylene group) these latter conditions for the formation of the tetracyclic lactam esters (14 and 15) were preferred.

In accordance with previous experience in the homologous allyl series[1] the methyl iminoethers of the (A) stereoisomers (14a and 14b) resisted cyclization in the presence of dimsyl sodium in dimethyl sulphoxide, or with sodium hydride in dimethyl formamide, but the (B) stereoisomers (15a and 15b) cyclized smoothly at 65-70°C to give a mixture of the cis-fused pentacyclic lactam ester (9) and its C-20 epimer (16). At 103°C the yield of (9) and (16) was considerably lower,

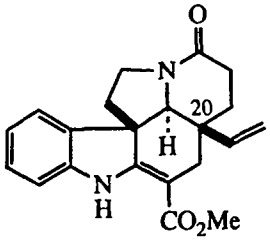

(14a)

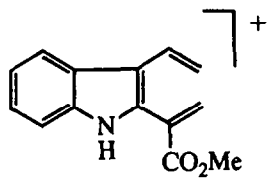

(14b)


(15a)


(15b)

presumably owing to decomposition of the dimsyl sodium at this temperature.[12] However, under none of the conditions used was interconversion of (9) and (16) observed; indeed, the latter was totally unaffected by dimsyl sodium in DMSO at 65°C for 2.5 hours.

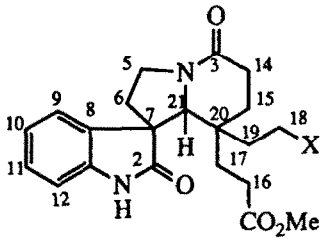

(16)


(18)

Of the two epimers obtained, the more polar one was assigned the stereochemistry shown in (9), with a cis C/D ring junction, since its mass spectrum contained important peaks at m/z 350, 227, and 195, corresponding to those at 352, 227, and 195 in the spectrum of its dihydroderivative, 3-oxovincadifformine (17). As in the mass spectra of (19) and the allyl homologue of (9) (see the preceding paper) the base peak at m/z 227 is due to the ion (18), obtained by reverse Diels-Alder fission of ring C, followed by cleavage of the N_b to C-5 bond, and is diagnostic of a cis C/D ring junction. In contrast, the less polar isomer (16) exhibits a base peak at m/z 264, probably formed by loss of both the vinyl and ester substituents attached to ring C. This conclusion is confirmed by the presence in the proton n.m.r. spectrum of (9) of a small W-coupling ($J_{17\alpha,21}$ = 3 Hz) in the signals at δ 4.03 and 2.72 owing to H-21 and H-17α; no such coupling is observed, and none would be expected, between H-21 (δ 3.77) and either of the C-17 protons (δ 2.25 and 2.975) in trans isomer (16).

In an attempt to develop an improved synthesis of the lactam esters (14 and 15), the tetracyclic system was formed before the vinyl double bond was introduced. Accordingly, the phenylthio aldehydoester (11) was condensed with 2-hydroxytryptamine hydrochloride in buffered aqueous ethanol to give (19) as a mixture of

all four possible racemates from which the different isomers (19a-d) (in order of increasing polarity) were obtained by chromatography.



(19) X = SPh
(20) X = SO_2Ph

The relative stereochemistry at C-7, C-21, and C-20 was determined for all four isomers by a detailed n.m.r. analysis at 400 MHz. For each isomer H-21 was an easily recognisable, slightly broadened singlet at around δ 4 and the two C-5 hydrogens and all of those on aromatic rings could be easily identified. The chemical shift difference between the C-18 hydrogens (α to sulphur) and those on C-14 and C-16 (α to a carbonyl group) was not as pronounced as expected and a definite assignment of the two C-18 protons could only be made for (19a). The remaining aliphatic resonances were assigned to different, isolated four-spin units ($-CH_2CH_2-$) by using the connectivities determined from ^1H-^1H chemical shift correlation (COSY) experiments (see Figure 1).

The C-7/C-21 relative stereochemistry was determined in a straightforward way for all four isomers by nuclear Overhauser effect (n.O.e.) measurements. Irradiation of the H-21 singlet gave an enhancement of the 'doublet' due to H-9 (and vice versa) only for the two most polar isomers (19c and 19d) indicating that in these isomers the 7,8 bond was on the same face of the pyrrolidine ring as H-21, while in (19a) and (19b) it was on the opposite face. This is in agreement with the relationship between stereochemistry at these centres and polarity found for (14) and (15) above.

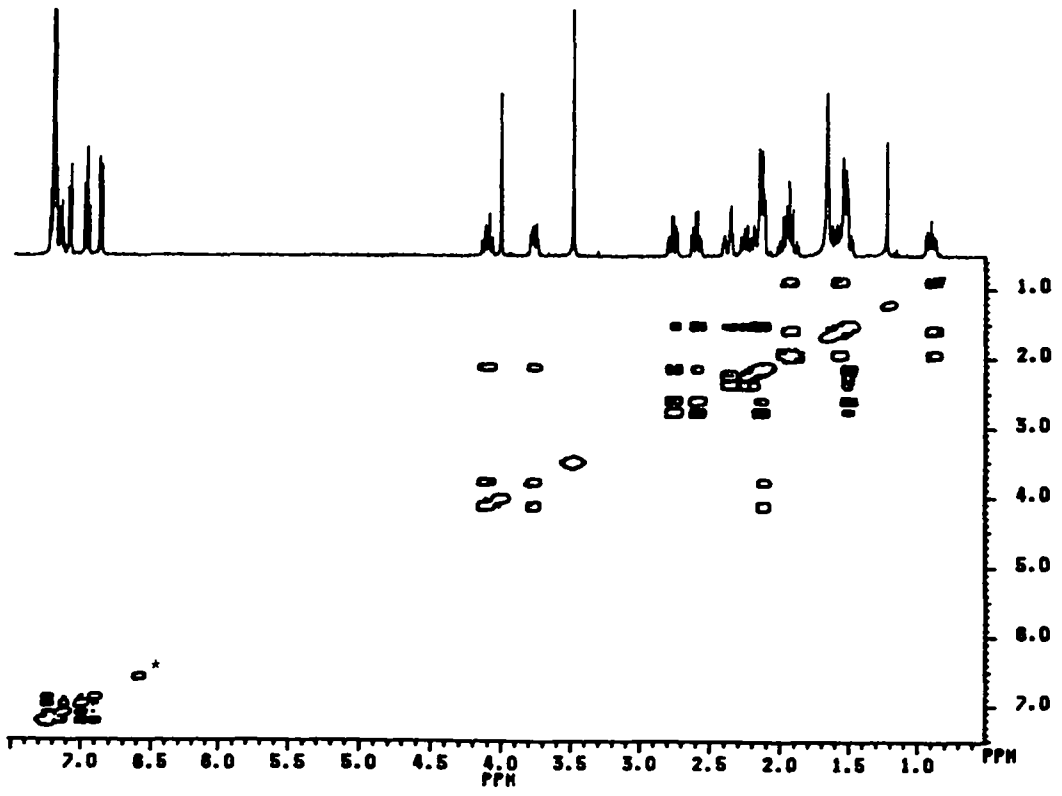
Before the stereochemistry at C-20 could be determined it was necessary to assign unambiguously the resonances of at least one side-chain for each isomer. This was achieved by oxidising each isomer on an n.m.r. scale with two equivalents of mCPBA to give the corresponding sulphones (20a-d). This oxidation resulted in a downfield shift of the methylene protons α to sulphur and permitted their unambiguous assignment. Irradiating H-21 gave n.O.e. enhancements for these C-18 hydrogens for the (a) and (d) isomers and enhanced the resonances of hydrogens α to a carbonyl for the (b) and (c) isomers. Consideration of models showed that H-21 is relatively close to the second methylene of the chain on the same side of the six-membered ring and much further away from the trans side-chain. From the COSY spectra of these oxidised compounds and by comparing the pattern of n.O.e. enhancements on irradiating H-9 and H-21 for each sulphide/sulphone pair it was possible to assign all of the proton resonances of all eight compounds and to confirm their relative stereochemistry as shown. The chemical shift assignments are given in entries 1-8 in Table 1. Additional confirmation of the assignments came from the observation of n.O.e. enhancement of the resonance of H-15β on

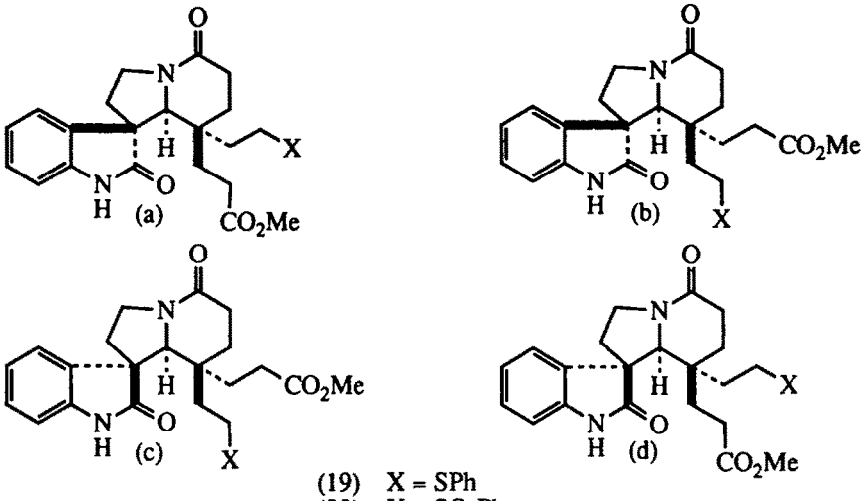
TABLE 1. ^{1}H Chemical shift assignments. All stereochemistry is relative to H-21α.

Compound	5-H	6-H	9-H	10-H	11-H	12-H	14-H	15-H	16-H	17-H	18-H	19-H	21-H	OMe
19a	3.95β 3.87α	2.40α 1.90β	7.09	6.99	7.23	6.87	2.45 2.27	1.65 1.45	1.93 1.93	1.52 0.82	3.00 2.74	1.65 1.42	4.13	3.50
19b	3.94β 3.87α	2.36α 1.86β	6.99	6.92	7.17	6.84	2.41 2.27	1.58α 1.50β	2.46 2.21	1.76 1.45	2.59 2.52	1.53 0.79	4.06	3.61
19c	4.15 3.80	2.17 2.17	7.12	6.99	7.24	6.89	2.39 2.27	1.55 1.55	1.97 1.94	1.61 0.90	2.79 2.61	2.19 1.53	4.05	3.52
19d	4.14 3.81	2.17 2.17	7.13	7.00	7.26	6.93	2.42 2.31	1.68α 1.54β	2.10 2.08	1.64 1.64	2.58 2.52	1.41 1.03	4.12	3.53
20a	3.96α 3.96β	2.37 1.91	7.15	7.05	7.29	6.99	2.49 2.33	1.49α 1.46β	1.99 1.99	1.63 0.80	3.41 2.87	1.88 1.59	4.01	3.52
20b	3.99 3.93	2.38 1.88	7.13	7.12	7.36	7.04	2.36 2.16	1.55 1.39	2.49 2.21	1.55 1.39	2.85 2.79	1.67 0.92	4.12	3.58
20c	4.08 3.80	2.16 2.16	7.12	7.01	7.26	6.99	2.38 1.86	1.52α 1.36β	1.93 1.90	1.43 0.88	3.00 2.86	2.12 1.71	4.07	3.50
20d	4.12 3.82	2.15 2.15	7.11	7.05	7.26	6.88	2.48 2.33	1.53 1.53	2.10 2.04	1.62 1.62	2.71 2.54	1.49 1.21	3.93	3.56
24	4.16 3.90	2.23 2.23	7.20	7.07	7.25	6.84	2.54* 2.48	1.92* 1.75	2.37* 2.32	2.11* 2.05	5.42	6.06	4.18	-

*For (24) the assignments of (H-14, H-15) and H-16, H-17) may be reversed.

FIGURE 1. 400 MHz ^{1}H spectrum and ^{1}H-^{1}H COSY spectrum of (19c).
The peak marked * is the NH which is folded.

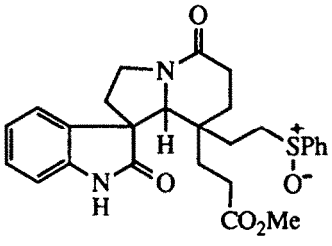




(19) X = SPh
(20) X = SO_2Ph

irradiating H-21. It can also be seen that one of the protons of the first methylene of the side-chain cis to the aromatic ring of the oxindole moiety [C-17 for the (a) and (c) isomers and C-19 for the (b) and (d) isomers] is shifted to much higher field, presumably due to a ring-current effect.

Preliminary experiments aimed at the introduction of the vinyl double bond were attempted on the mixture of phenylthio lactams (19). However, the elimination of phenylsulphinic acid from the thiophenoxide mixture (21) derived from (19) did not give an improved yield of the unsaturated lactam esters (14) and (15), and this approach was not further pursued.



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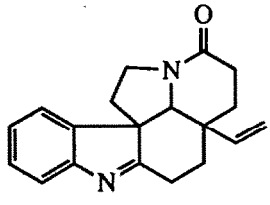

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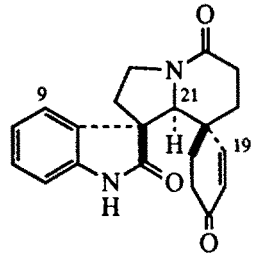
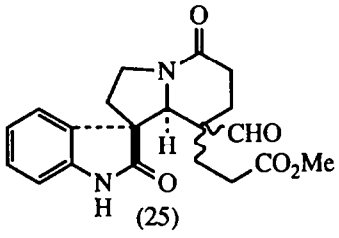


(24)

Initial experiments on the pentacyclic lactam ester (9) were conducted with the aim of preparing a range of anilinoacrylate alkaloids, as outlined above. However, the 18,19 double bond, adjacent to a fully substituted carbon atom, is not readily accessible to most reagents, and little success was achieved, particularly with oxidising agents, which affected the sensitive anilinoacrylate function. Thus, attempted hydration of the 18,19 double bond in (9) or its N_a-methyl derivative (22) by means of mercuric acetate or mercuric trifluoroacetate, followed by sodium borohydride reduction, failed, as did an attempt to convert (9) into the corresponding methyl ketone (3-oxominovincine) by the method of Rodeheaver and Hunt.[13] Oxidative cleavage with osmium tetroxide-sodium paraperiodate and selective ozonolysis also failed. Similarly, it proved impossible

to functionalise preferentially the 18,19 double bond in the 1,2-dehydro-aspidospermidine derivative (23), prepared by acid hydrolysis and decarboxylation of (9). A possible alternative route to (23), which has been applied in the 1,2-dehydroaspidospermidine series,[14] involves the direct cyclization of the tetracyclic oxindole esters (14) and (15). However, when the mixture of (14) and (15) was heated with polyphosphoric acid at 120-130°C the only product obtained proved to be a single diastereoisomer of the spirocyclic cyclohexenone derivative (24). The existence of n.O.e.'s between H-9 and H-21 and vice versa, and between H-19 and H-21 and vice versa, confirmed that the stereochemistry is as shown. The COSY spectrum of (24) again allowed the different four-spin systems to be identified (see entry 9 in Table 1); however, in this case it did not prove possible to distinguish unambiguously the hydrogens on C-14 and C-15 from those on C-16 and C-17.

In a parallel series of experiments an attempt was made to functionalise the future 18,19 double bond at an earlier stage in the synthesis. Thus, the more polar mixture of tetracyclic oxindole esters (15a and 15b) was subjected to ozonolysis, which furnished the aldehyde (25) in high yield. Reaction with Meerwein's reagent then gave the iminoether (26) smoothly, but this could not be cyclized with dimsyl sodium to the desired pentacyclic ester; instead, a complex, inseparable mixture of products was obtained. Protection of the aldehyde function as its dimethyl acetal was also achieved, but this failed to give the desired iminoether with Meerwein's reagent.



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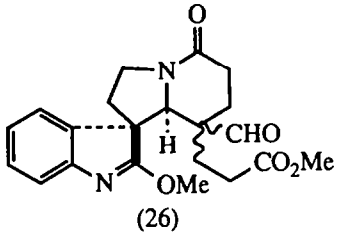

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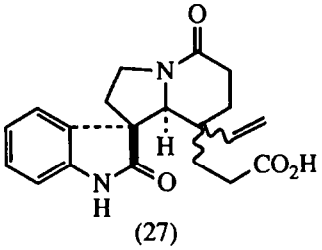

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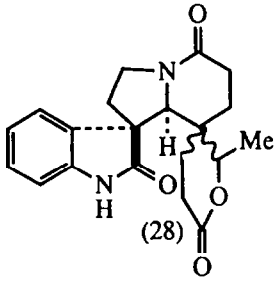


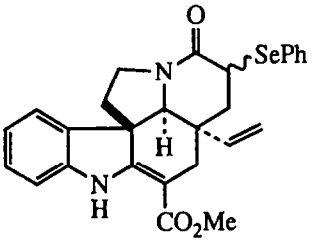
(28)

Yet another intermediate that could, in principle, be used in the synthesis of alkaloids containing oxygen at C-19 was the lactone (28), which could be prepared via the acid (27). Reaction of (27) with iodine and sodium bicarbonate solution gave the desired iodolactone, which was reduced by tributyl tin iodide to the lactone (28). However, the overall yield was poor, and it was therefore not considered that this was a viable route to the C-19 oxygenated alkaloids.

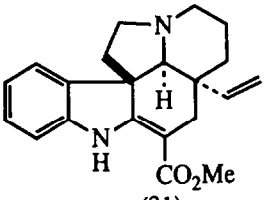
An obvious target from the intermediate (9) is 18,19-didehydrotabersonine (1). Accordingly, 3-oxo-18,19-didehydrovincadifformine (9) was treated with lithium di-isopropylamide and phenylselenyl chloride; in the presence of two

equivalents of base the monoselenenylated lactam (29) was obtained. This contrasts with the experience of Lévy et al.,[15] who obtained only the bis-selenenylated lactam from 3-oxo-vincadifformine in the presence of a large excess of reagent and only one equivalent of base.

The preparation of (29), rather than the bis-selenenylated analogue, afforded a much more elegant method for the introduction of the 14,15 double bond. Oxidation of (29) by means of m-chloroperbenzoic acid followed by elimination gave an almost quantitative yield of 3-oxo-18,19-didehydrotabersonine (30).



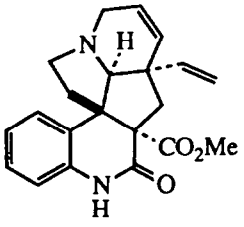
(29)



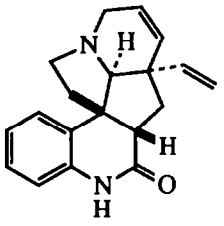
(31)

There remained only the removal of the oxygen atom at position 3. However, controlled reduction of (30) by means of lithium aluminium hydride, as used by Lévy and his collaborators, was unsuccessful, and we therefore turned our attention to the Borch method.[16] In a model experiment 3-oxo-18,19-didehydrovincadifformine (9) was treated with Meerwein's reagent, and the salt produced was reduced with sodium borohydride to give 18,19-didehydrovincadifformine (31). In analogous fashion 3-oxo-18,19-didehydrotabersonine (30) gave 18,19-didehydrotabersonine (1), which exhibited the same R_F values as authentic material[17] in two solvent systems, and the same principal peaks in its mass spectrum.

This synthesis of 18,19-didehydrotabersonine (1) constitutes also a formal synthesis of andranginine (2) which, as noted above, can be obtained[2] by thermal rearrangements of (1) at 145°C, and also the biogenetically related quinolone alkaloids, scandine (32) and meloscine (33), which have recently been obtained from 18,19-didehydrotabersonine by partial synthesis.[18]



(32)



(33)

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage apparatus and are uncorrected. Ultraviolet absorption spectra were measured on a Unicam SP 800A spectrometer with ethanol as solvent. Infrared spectra were measured on Perkin-Elmer 297 spectrometers with chloroform as solvent unless otherwise stated. Proton nuclear magnetic resonance spectra were recorded at 90 MHz on Perkin-Elmer R32 and Jeol FX90Q spectrometers and at 400.13 MHz on a Brüker AM400 spectrometer. Magnitude mode ^1H-^1H COSY spectra were obtained on the AM400, using 128 t_1 increments and a final data set size of 1K by 512W after sine-bell multiplication in both dimensions, zero-filling in the F1 dimension and Fourier transformation. The final digital resolution was approximately 6 Hz/pt. The 90 deg. ^1H pulse length was 13.0 μs. Nuclear Overhauser effect data were recorded on degassed samples with a recycle delay of 8.5 seconds (>>5 T_1). Carbon-13 n.m.r. spectra were recorded at 100.6 MHz on a Brüker WH400 spectrometer. All n.m.r. spectra were recorded on solutions in $CDCl_3$ and chemical shifts are reported in p.p.m. downfield from tetramethylsilane. Mass spectra were measured on either a Kratos MS25 instrument (low resolution spectra) or an Associated Electrical Industries MS950 double focussing instrument (accurate mass measurement).

4-Phenylthiobutanal (12). — Thiophenol (22.0 g, 0.20 mol) was added dropwise to a vigorously stirred, ice-cold ethanolic solution of sodium ethoxide, prepared from sodium (4.6 g, 0.20 mol) and ethanol (100 ml). The mixture was then stirred for a further 15 min, then 4-chlorobutyl acetate[19] (30.1 g, 0.20 mol) was added dropwise over a 30 min period. The resulting solution was then heated under reflux for 4 h and stirred at room temperature for a further 10 h. Potassium hydroxide pellets (11.2 g, 0.20 mol) were added and the suspension was heated under reflux for 2 h, then cooled and poured into water (300 ml). The solution was extracted with ether (3 x 250 ml) and the combined ether extracts were washed with dilute potassium hydroxide solution (2 x 250 ml) and water (2 x 250 ml), then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a yellow liquid which was fractionally distilled to give 4-phenylthiobutan-1-ol (29.4 g, 0.16 mol, 81%) as an almost colourless oil, b.p. 152-154°C/0.1 mmHg.

Dimethyl sulphide (23.2 g, 0.37 mol) was added dropwise to a stirred solution of N-chlorosuccinimide (35.8 g, 0.29 mol) in toluene (800 ml) at 0°C, under an atmosphere of dry nitrogen. The resulting suspension was then cooled in a dry-ice/carbon tetrachloride bath to -25°C and 4-phenylthiobutan-1-ol (32.8 g, 0.18 mol) added dropwise to the stirred solution. Stirring was continued at -25°C for a further 2 h and then triethylamine (25.8 ml) in a small amount of toluene was added dropwise. The cooling bath was removed after 5 min and ether (500 ml) added. The organic layer was washed with 1% aqueous hydrochloric acid (2 x 500 ml) and water (2 x 500 ml), then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a yellow/green oil which was fractionally distilled to give 4-phenylthiobutanal (25.03 g, 77%), b.p. 139-141°C/0.3 mmHg (Found: C, 66.30; H, 6.75; S, 17.07; M^+, 180.06123. $C_{10}H_{12}OS$ requires C, 66.67; H, 6.67; S,

17.8%; M. 180.060883); $\nu_{max.}$ (film) 2861, 2720, 1725, 1586 cm^{-1}; δ ($CDCl_3$) 2.15-1.70 (2H, m, $-CH_2\underline{CH_2}-CH_2-$), 2.60 (2H, dt, J 1, 7 Hz, $-\underline{CH_2}-CHO$), 2.95 (2H, t, J 7 Hz, $-\underline{CH_2}-SPh$), 7.10-7.45 (5H, m, aromatic C-H), 9.73 (1H, t, J 1 Hz, $-\underline{CH}O$); m/z (%) 180 (95), 152 (30), 136 (30), 135 (20), 123 (70), 110 (100), 109 (27), 71 (30), 45 (30).

Pyrrolidine Enamine of 4-Phenylthiobutanal. — 4-Phenylthiobutanal (23.1 g, 0.13 mol) in toluene (100 ml) was added to a stirred suspension of anhydrous potassium carbonate (12 g) in pyrrolidine (18.2 g, 0.26 mol) and dry ether (50 ml) at 0°C. The mixture was stirred at 0°C for 1 h and then at room temperature for a further 3 h. The suspension was filtered through a sintered glass funnel and the solid residue washed well with dry ether. Removal of the solvents under reduced pressure gave the crude pyrrolidine enamine of 4-phenylthiobutanal (28.9 g, 0.12 mol, 97%); $\nu_{max.}$ (film) 1650, 1585 cm^{-1}; δ ($CDCl_3$) 1.42-2.00 (4H, m), 2.01-2.26 (2H, m, $-CH_2-\underline{CH_2}-CH=$), 2.60-3.06 (6H, m), 4.07 (1H, dt, J 7, 14 Hz, $-N-CH=\underline{CH}-CH_2$), 6.23 (1H, d, J 14 Hz, $-N-\underline{CH}=CH-$), 6.90-7.41 (5H, m, aromatic C-H).

Dimethyl 4-Formyl-4-(2-phenylthioethyl)-heptan-1,7-dioate (11). — A solution of the pyrrolidine enamine of 4-phenylthiobutanal (23.0 g, 98.8 mmol) in dry methanol (60 ml) was stirred at 0°C under nitrogen and methyl acrylate (40.0 g, 0.46 mol) added dropwise over 0.5 h. The mixture was stirred at 0°C for 4 h and then at room temperature for 15 h. The solution was then refluxed for 48 h, cooled, acetic acid (20 ml) and water (40 ml) were added, and the mixture was refluxed for a further 8 h. Removal of the solvents under reduced pressure gave a brown oil which was partitioned between dichloromethane and water. The organic layer was separated and washed with dilute hydrochloric acid (2 x 100 ml), dilute sodium carbonate solution (2 x 100 ml) and water (100 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow/brown oil. The majority of the crude mixture was carried straight through to the next stage, but a small amount (1.05 g) was chromatographed on Kieselgel G (50 g), with 15% ethyl acetate in benzene as the eluting agent, to give two main fractions.

The first fraction contained methyl 4-formyl-6-phenylthiohexanoate (13) (95 mg) as a colourless oil (Found: M^+, 266.09813. $C_{14}H_{18}O_2S$ requires M, 266.097659); $\nu_{max.}$ (film) 2850, 2720, 1735 br, 1585 cm^{-1}; δ ($CDCl_3$) 1.6-2.7 (7H, m), 2.98 (2H, t, J 7 Hz, $PhS-\underline{CH_2}-$), 3.67 (3H, s, $-CO_2Me$), 7.10-7.45 (5H, m, aromatic), 9.40 (1H, s, $\underline{CH}O$); m/z (%) 266 (28), 136 (60), 123 (52), 110 (100), 109 (20), 97 (29), 83 (37), 69 (34), 45 (40), 41 (42).

The second fraction contained dimethyl 4-formyl-4-(2-phenylthioethyl)-

heptan-1,7-dioate (805 mg) as a pale yellow oil (Found: M^+, 352.134436. $C_{18}H_{24}O_5S$ requires M, 352.134435); $\nu_{max.}$ (film) 2850, 2710, 1740 br, 1585 cm^{-1}; δ ($CDCl_3$) 1.60-2.40 (10H, m), 2.88 (2H, t, J 7 Hz, PhS-CH_2), 3.65 (6H, s, 2 x $-CO_2Me$), 7.10-7.40 (5H, m, aromatic), 9.40 (1H, s, -CHO); m/z (%) 352 (29), 324 (60), 321 (22), 216 (28), 183 (62), 151 (39), 141 (19), 136 (39), 123 (100), 110 (86), 109 (30), 55 (39), 45 (27).

Dimethyl 4-Formyl-4-vinylheptan-1,7-dioate (10). — The crude mixture of mono- and dialkylated thioetheraldehydes (19.2 g, 0.55 mol) was dissolved in methanol (240 ml) and water (48) ml), and sodium metaperiodate (11.66 g, 0.055 mol) was added in small portions to the stirred solution over a period of 1 h. The solution was then stirred for a further 2 h (i.e. until t.l.c. analysis showed the complete absence of starting material). The solution was then filtered through sintered glass and the solid washed several times with methanol. The solvent was then removed under reduced pressure to give an orange oil which was partitioned between chloroform and water. The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a yellow gum. The i.r. spectrum of this material showed a band at 1040 cm^{-1} corresponding to the sulphoxide group of dimethyl 2-formyl-(phenylsulphinylethyl)-heptan-1,7-dioate. The gum was dissolved in dry xylene (150 ml) and a small quantity of calcium carbonate (≈ 0.5 g) added; the mixture was then heated under reflux for 18 h under an atmosphere of dry nitrogen. The mixture was then cooled, filtered through sintered glass, washed with dilute sodium bicarbonate solution (150 ml) and water (150 ml), and dried ($MgSO_4$). The xylene was removed by distillation under reduced pressure, the resulting yellow/orange oil was transferred to a smaller vessel and subjected to short-path distillation to yield two major fractions.

The first fraction contained methyl 4-formylhex-4-enoate (1.8 g) as a pale yellow oil, b.p. 78-82°C/0.5 mmHg; $\nu_{max.}$ (film) 2830, 2720, 1740, 1685, 1645 cm^{-1}; δ ($CDCl_3$) 2.06 (3H, d, J 7 Hz, $H_3C.CH=C$), 2.3-2.7 (4H, m), 3.67 (3H, s, CO_2Me), 6.69 (1H, q, J 7 Hz, $MeCH=C$), 9.39 (1H, s, CHO). The aldehyde was characterised as its 2,4-dinitrophenylhydrazone, m.p. 157-159°C, recrystallised from glacial acetic acid (Found: C, 50.1; H, 5.05; N, 16.4. $C_{14}H_{16}N_4O_6$ requires C, 50.0; H, 4.8; N, 16.7%).

The second fraction contained dimethyl 4-formyl-4-vinylheptan-1,7-dioate (0.5 g, 43.4 mmol) as a colourless oil, b.p. 127-129 °C/0.3 mmHg (Found: C, 59.50; H, 7.45; M^+, 242.11518. $C_{21}H_{18}O_5$ requires C, 59.49; H, 7.49%; M, 242.115414); $\nu_{max.}$ (film) 2850, 2720, 1730 br, 1640 cm^{-1}; δ ($CDCl_3$) 1.88-2.40

(8H, m), 3.65 (6H, s, 2 x CO_2Me), 5.1-5.92 (3H, m, $C\underline{H}=CH_2$), 9.40 (1H, s, $C\underline{H}O$); m/z (%) 242 (3), 211 (16), 182 (100), 154 (64), 150 (82), 122 (65), 109 (35), 98 (15).

3-Oxo-1-demethyl-18,19-didehydrovincatine (14 and 15). — (a) Dimethyl 4-formyl-4-vinylheptan-1,7-dioate (3.19 g, 13 mmol) and 2-hydroxytryptamine hydrochloride[11] (2.49 g, 11 mmol) were dissolved in ethanol (175 ml) containing water (23 ml) and sodium acetate (3.33 g) added. The mixture was heated under reflux in an atmosphere of nitrogen for 18 h, the solvents were removed under reduced pressure and the residue was partitioned between chloroform and water. The organic layer was separated, dried ($MgSO_4$), and the solvent removed under reduced pressure leaving a yellow oil. The residue was chromatographed on Kieselgel G (200 g) with 3% methanol in chloroform as eluent, to give four main fractions.

The first fraction contained unreacted aldehyde (300 mg), as verified by its i.r. and n.m.r. spectra, and t.l.c. behaviour.

The second fraction contained a stereoisomeric mixture of the less polar (A) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (14a and 14b) (1.17 g, 29%) as a white solid which on recrystallisation from methanol gave white needles, m.p. 197-229°C (Found: C, 68.35; H, 6.70; N, 7.85; $\underline{M}^+$, 368.17410. $C_{21}H_{24}N_2O_4$ requires C, 68.46; H, 6.57; N, 7.60%; $\underline{M}$, 368.17359); $\lambda_{max.}$ 225, 254, 271 infl., 279 infl. nm; $\nu_{max.}$ (Nujol) 3150, 1725 br, 1630 br, cm^{-1}; δ ($CDCl_3$) 1.20-2.90 (10H, m), 3.61 (3H, s, CO_2Me), 3.75-4.40 (3H, m, -N-C$\underline{H}$, N-C$\underline{H}_2$), 4.40-4.95 (2H, m, CH=C$\underline{H}_2$), 5.05-5.70 (1H, m, -C$\underline{H}$=CH_2), 6.85-7.40 (4H, m, aromatic), 9.50 (1H, s, exchanges with D_2O, N-H); m/z (%) 368 (4), 187 (10), 159 (16), 136 (25), 130 (11), 108 (11), 94 (11).

The third fraction contained a mixture of all the stereoisomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (0.3 g, 7%).

The fourth fraction contained a stereoisomeric mixture of the more polar (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (15a and 15b) (1.74 g, 43%) as a yellow solid which on recrystallisation from methanol gave heavy white rods, m.p. 186-198°C (Found: C, 68.45; H, 6.65; N, 7.50; $\underline{M}^+$, 368.17369. $C_{21}H_{24}N_2O_4$ requires C, 68.46; H, 6.57; N, 7.60%; $\underline{M}$, 368.17359); $\lambda_{max.}$ 224, 254, 272 infl., 278 infl. nm; $\nu_{max.}$ (Nujol) 3360, 1720, 1695, 1645, 1620 cm^{-1}; δ ($CDCl_3$) 1.25-2.7 (10H, m), 3.55 (3H, s, -CO_2Me), 3.70-4.30 (3H, m, -N-C$\underline{H}$, -N-C$\underline{H}_2$), 4.40-5.15 (2H, m, CH=C$\underline{H}_2$), 5.60-6.05 (1H, m, -C$\underline{H}$=CH_2), 6.85-7.45 (4H, m, aromatic), 9.85 (1H, s, exchanges with D_2O, N-H); m/z (%) 368 (67), 187 (65), 160 (23), 159 (97), 150 (34), 144 (27), 136 (93), 130 (37), 117 (19), 108 (22), 94 (26).

(b) Dimethyl 4-formyl-4-vinylheptan-1,7-dioate (3.91 g, 16.4 mmol) and

2-hydroxytryptamine (2.32 g, 13.16 mmol) were dissolved in dry benzene and the resulting solution was heated under reflux for 4 h in a Dean-Stark apparatus with removal of the azeotropic benzene/water. The solution was allowed to cool before removal of the solvents under reduced pressure. Glacial acetic acid (30 ml) was then added and the mixture heated under reflux for 1.5 h. The solvent was removed under reduced pressure and water (100 ml) added before extraction with chloroform (3 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed to yield a yellow oil which was chromatographed on Kieselgel G (300 g) with 3% methanol in chloroform as eluent, to give four main fractions.

The first fraction contained unreacted aldehyde (403 mg) as verified by i.r. and n.m.r. spectra, and chromatographic behaviour.

The second fraction contained a stereoisomeric mixture of the less polar (A) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (14a and 14b) (0.49 g, 10%) as a white solid which on recrystallisation from methanol gave white pillars, m.p. 195-222°C (Found: $\underline{M}^+$, 368.1739. $C_{21}H_{24}N_2O_4$ requires $\underline{M}$, 368.17359).

The third fraction contained a mixture of all the stereoisomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (0.25 g. 5.2%).

The fourth fraction contained a stereoisomeric mixture of the more polar (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (15a and 15b) (3.05 g, 63%) as a white solid which on recrystallisation from methanol gave white needles, m.p. 182-199°C (Found: $\underline{M}^+$, 368.1742. $C_{21}H_{24}N_2O_4$ requires $\underline{M}$, 368.17359).

3-Oxo-1-demethyl-18-phenylthiovincatine (19). — Dimethyl 4-formyl-4-(2-phenylthioethyl)-heptan-1,7-dioate (3.95 g, 11 mmol) and 2-hydroxytraptamine hydrochloride (2.13 g, 10 mmol) were dissolved in ethanol (150 ml) containing water (20 ml), and sodium acetate (2.84 g) was added. The resulting mixture was then heated under reflux for 18 h, cooled and the solvent removed under reduced pressure. The residue was partitioned between chloroform and water and the organic layer separated and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a yellow foam which was chromatographed on Kieselgel G (500 g) with 2% methanol in chloroform as eluent to give five main fractions.

The first fraction contained unreacted aldehyde (205 mg), as verified by i.r. and n.m.r. spectra, and chromatographic behaviour.

The second fraction contained 3-oxo-1-demethyl-18-phenylthiovincatine-I (19a) (0.73 g, 15%) as a white solid which on recrystallisation from methanol gave colourless needles, m.p. 133-135°C (Found: C, 67.25; H, 6.35; N, 5.81; $\underline{M}^+$, 478.19224. $C_{27}H_{30}N_2O_4S$ requires C, 67.75; H, 6.32; N, 5.85%; $\underline{M}$, 478.192616);

$\nu_{max.}$ (Nujol) 3050 br, 1720 br, 1615 br cm^{-1}; δ_H ($CDCl_3$) 0.82 (1H, ddd, J 6, 11, 14.5 Hz), 1.42 (1H, m), 1.45 (1H, m) 1.52, (1H, m), 1.65 (2H, m), 1.90 (1H, ddd, J 1.5, 7, 12.5 Hz), 1.93 (2H, m), 2.27 (1H, ddd, J 6, 11.5, 18 Hz), 2.40 (1H, ddd, J 10, 11.5, 12.5 Hz), 2.45 (1H, ddd, J 3.5, 6, 18 Hz), 2.74 (1H, dt, J 4.5, 12 Hz), 3.00 (1H, dt, J 4.5, 12 Hz), 3.50 (3H, s), 3.87 (1H, m), 3.95 (1H, dt, J 7, 11.5 Hz), 4.13 (1H, s), 6.84 (1H, br. d, J 7.5 Hz), 6.92 (1H, dt, J 1, 7.5 Hz), 7.09 (1H, br. d, J 7.5 Hz), 7.25 (6H, m), 7.90 (1H, br. s, NH); δ_C ($CDCl_3$) 27.9 (t), 28.1 (t), 28.20 (t), 28.22 (t), 28.4 (t), 34.8 (t), 35.9 (t), 38.7 (s), 44.0 (t), 51.6 (q), 55.9 (s), 69.5 (d), 110.8 (d), 122.5 (d), 125.4 (d), 126.3 (d), 128.6 (d), 128.9 (d), 130.0 (d), 130.3 (s), 136.0 (s), 139.8 (s), 169.1 (s), 172.9 (s), 177.9 (s); m/z (%) 478 (23), 167 (17), 244 (11), 210 (10), 187 (16), 160 (25), 144 (20), 137 (62), 130 (27), 123 (51), 109 (30).

The third fraction contained 3-oxo-1-demethyl-18-phenylthiovincatine-II (19b) (0.81 g, 15.4%) as a white solid which on recrystallisation from methanol gave colourless needles, m.p. 238-240°C (Found: C, 67.75; H, 6.05; N, 5.75; M^+, 478.19278. $C_{27}H_{30}N_2O_4S$ requires C, 67.75; H, 6.32; N, 5.82%; M, 478.192616); $\nu_{max.}$ (Nujol) 3030 br, 1720 br, 1618 br cm^{-1}; δ_H ($CDCl_3$) 0.79 (1H, ddd, J 4.5, 12, 14 Hz), 1.45 (1H, ddd, J 5, 11.5, 15 Hz), 1.50 (1H, m), 1.53 (1H, m), 1.58 (1H, m), 1.76 (1H, ddd, J 5, 11.5, 15 Hz), 1.86 (1H, ddd, J 1.5, 7, 12 Hz), 2.21 (1H, ddd, J 5, 11.5, 17 Hz), 2.27 (1H, m), 2.36 (1H, ddd, J 9, 11, 12 Hz), 2.41 (1H, m), 2.46 (1H, ddd, J 5, 11.5, 17 Hz), 2.52 (1H, dt, J 5, 12 Hz), 2.59 (1H, dt, J 4.5, 12 Hz), 3.61 (3H, s), 3.87 (1H, m), 3.94 (1H, dt, J 7, 12 Hz), 4.06 (1H, s), 6.84 (1H, br. d, J 7.5 Hz), 6.92 (1H, dt, J 1, 7.5 Hz), 6.99 (1H, br. d, J 7.5 Hz), 7.18 (6H, m), 8.0 (1H, br. s, NH); δ_C 27.9 (t), 28.1 (t), 28.5 (t), 28.7 (t), 30.8 (t), 35.1 (t), 36.0 (t), 38.6 (s), 43.8 (t), 51.7 (q), 55.8 (s), 69.0 (d), 110.7 (d), 122.7 (d), 125.1 (d), 126.4 (d), 128.7 (d), 128.8 (d), 130.1 (d), 130.3 (s), 135.7 (s), 139.8 (s), 169.0 (s), 173.6 (s), 178.0 (s); m/z (%) 478 (27), 267 (13), 244 (18), 210 (15), 160 (19), 137 (40), 130 (26), 123 (21), 109 (20), 94 (24).

The fourth fraction contained 3-oxo-1-demethyl-18-phenylthiovincatine-III (19c) (1.23 g, 23%) as a cream/white solid which on recrystallisation from methanol gave colourless pillars, m.p. 143-144°C (Found: C, 67.75; H, 6.03; N, 5.85; M^+, 478.19217. $C_{27}H_{30}N_2O_4S$ requires C, 67.75; H, 6.32; M, 5.85%; M, 478.192617); $\nu_{max.}$ (Nujol) 3030 br (N-H), 1710 br (ester and oxindolyl carbonyls), 1620 br (lactam and aromatic bonds) cm^{-1}; δ_H ($CDCl_3$) 0.90 (1H, ddd, J 5, 10, 15 Hz), 1.53 (1H, m), 1.55 (2H, m), 1.61 (1H, ddd, J 7, 10, 15 Hz), 1.94 (1H, ddd, J 5, 10, 16 Hz), 1.97 (1H, ddd, J 7, 10, 16 Hz), 2.17 (2H, m), 2.19

(1H, m), 2.27 (1H, m), 2.39 (1H, td, J 4, 17 Hz), 2.61 (1H, dt, J 5, 12 Hz), 2.79 (1H, dt, J 4, 12 Hz), 3.52 (3H, s), 3.80 (1H, m), 4.05 (1H, s), 4.15 (1H, m), 6.89 (1H, br. d, J 7.5 Hz), 6.99 (1H, dt, J 1, 7.5 Hz), 7.12 (1H, br. d, J 7.5 Hz), 7.21 (6H, m), 8.05 (1H, br. s, NH); δ_C ($CDCl_3$) 28.0 (t), 28.2 (t), 28.6 (t), 29.3 (t), 30.3 (t), 34.9 (t), 35.5 (t), 38.6 (t), 44.0 (t), 51.5 (q), 54.7 (s), 70.1 (d), 110.9 (d), 122.1 (d), 122.3 (d), 126.4 (d), 128.8 (d), 128.9 (d), 130.1 (d), 130.2 (s), 136.3 (s), 141.0 (s), 168.5 (s), 172.8 (s), 180.0 (s); m/z (%) 478 (38), 167 (22), 224 (15), 210 (10), 187 (22), 160 (26), 144 (24), 137 (63), 130 (40), 123 (72), 109 (55), 94 (34).

The fifth fraction contained 3-oxo-1-demethyl-18-phenylthiovincatine-IV (19d) (1.19 g, 23%) as a yellow solid which on recrystallisation from methanol gave colourless needles, m.p. 197-198°C (Found: 67.71; H, 6.11; M, 5.62; M^+, 478.19231. $C_{27}H_{30}N_2O_4S$ requires C, 67.75; H, 6.32; N, 5.85%; M, 478.192617); $\nu_{max.}$ (Nujol) 3000 br, 1710 br, 1620 br cm^{-1}; δ_H ($CDCl_3$) 1.03 (1H, ddd, J 5, 12, 14 Hz), 1.41 (1H, ddd, J 5, 12, 14 Hz), 1.54 (1H, ddd, J 2.5, 6, 14 Hz), 1.64 (2H, m), 1.68 (1H, m), 2.08 (1H, m), 2.10 (1H, m), 2.17 (2H, m), 2.31 (1H, ddd, J 6, 12, 18 Hz), 2.42 (1H, ddd, J 2.5, 6, 18 Hz), 2.52 (1H, dt, J 5, 12 Hz), 2.58 (1H, dt, J 5, 12 Hz), 3.53 (3H, s), 3.87 (1H, ddd, J 2.5, 7.5, 11 Hz), 4.12 (1H, s), 4.14 (1H, dt, J 7.5, 11 Hz), 6.93 (1H, br. d, J 7.5 Hz), 7.00 (1H, dt, J 1, 7.5 Hz), 7.15 (6H, m), 7.26 (1H, dt, J 1, 7.5 Hz), 8.35 (1H, br. s, NH); δ_C 26.1 (t), 28.2 (t), 28.3 (t), 28.7 (t), 29.2 (t). 35.27 (t), 35.31 (t), 38.7 (s), 44.0 (t), 51.8 (q), 54.6 (s), 70.8 (d), 110.5 (d), 122.2 (d), 122.9 (d), 126.3 (d), 128.7 (d), 128.9 (d), 129.2 (d), 129.5 (s), 136.0 (s), 140.6 (s), 168.4 (s), 173.4 (s), 179.1 (s); m/z (%) 478 (51), 267 (17), 224 (16), 210 (20), 187 (14), 160 (29), 144 (24), 137 (100), 130 (33), 123 (56), 109 (35).

Small scale oxidation of (19a-d); 3-oxo-1-demethyl-18-phenylsulphonylvincatine (20a-d). — m-Chloroperbenzoic acid (2.3 mg, 13 μmol, 2.1 equiv.) was added to a solution of (19a) (3.0 mg, 6.3 μmol) in $CDCl_3$ (0.3 ml) in an n.m.r. tube. After 15 min ^1H n.m.r. showed that oxidation was complete. Thin-layer chromatography, eluting with 30% ethyl acetate in hexane, gave (20a) (3.0 mg) as a white solid; m/z 510 (M^+); δ_H ($CDCl_3$) 0.80 (1H, ddd, J 6. 10, 15 Hz), 1.46 (1H, m), 1.49 (1H, m). 1.59 (1H, m), 1.63 (1H, m), 1.88 (1H, dt, J 3.5, 13 Hz), 1.91 (1H, m), 1.99 (2H, m), 2.33 (1H, m), 2.49 (1H, ddd, J 3, 6, 18 Hz), 2.87 (1H, dt, J 3.5, 13 Hz), 3.41 (1H, dt, J 3.5, 13 Hz), 3.52 (3H, s), 3.96 (2H, dd, J 4, 11 Hz), 4.01 (1H, s), 6.99 (1H, br. d, J 7.5 Hz), 7.05 (1H, br. t, J 7.5 Hz), 7.15 (1H, br. d, J 7.5 Hz), 7.29 (1H, dt, J 1, 7.5 Hz), 7.4-7.7 (5H, m), 8.5 (1H, br. s, NH).

Similar oxidation of (19b-d) gave (20b-d). (20b): δ_H ($CDCl_3$) 0.92 (1H, ddd,

J 4.5, 12, 14 Hz), 1.39 (2H. m), 1.55 (2H, m), 1.67 (1H, ddd, J 5, 12, 14 Hz), 1.88 (1H, ddd, J 1, 7, 12 Hz), 2.16 (1H, ddd, J 6, 11, 16 Hz), 2.21 (1H, ddd, J 6, 11.5, 18 Hz), 2.36 (1H, m), 2.38 (1H, m), 2.49 (1H, ddd, J 3, 5.5, 18 Hz), 2.79 (1H, dt, J 5, 13 Hz), 2.85 (1H, dt, J 4, 13 Hz), 3.58 (3H, s), 3.93 (1H, m), 3.99 (1H, m), 4.12 (1H, s), 7.04 (1H, br. d, J 7.5 Hz), 7.12 (1H, dt, J 1, 7.5 Hz), 7.13 (1H, br. d, J 7.5 Hz), 7.36 (1H, dt, J 2, 7.5 Hz), 7.65-7.4 (5H, m), 8.31 (1H, br. s, NH).

(20c): δ_H ($CDCl_3$) 0.88 (1H, ddd, J 5, 10, 15 Hz), 1.36 (1H, ddd, J 1, 6, 13 Hz), 1.43 (1H, ddd, J 7.5, 10, 15 Hz), 1.52 (1H, dt, J 6, 13 Hz), 1.71 (1H, dt, J 4, 13 Hz), 1.86 (1H, m), 1.90 (1H, m), 1.93 (1H, m), 2.12 (1H, dt, J 4, 13 Hz), 2.16 (2H, m), 2.38 (1H, br. dd, J 6, 18 Hz), 2.86 (1H, dt, J 4, 13 Hz), 3.00 (1H, dt, J 4, 13 Hz), 3.50 (3H, s), 3.80 (1H, ddd, J 2, 7, 12 Hz), 4.07 (1H, s), 4.08 (1H, m), 6.99 (1H, br. d, J 7.5 Hz), 7.01 (1H, br. t, J 7.5 Hz), 7.12 (1H, br. d, J 7.5 Hz), 7.26 (1H, dt, J 1, 7.5 Hz), 7.65-7.4 (5H, m), 8.4 (1H, br. s, NH).

(20d): δ_H ($CDCl_3$) 1.21 (1H, m), 1.49 (1H, m), 1.53 (2H, m), 1.62 (2H, m), 2.04 (1H, m), 2.10 (1H, m), 2.15 (2H, m), 2.33 (1H, m), 2.48 (1H, ddd, J 2, 6, 18 Hz), 2.54 (1H, dt, J 3.5, 13 Hz), 2.71 (1H, dt, J 5, 13 Hz), 3.56 (3H, s), 3.82 (1H, ddd, J 2.5, 8, 10 Hz), 3.93 (1H, s), 4.12 (1H, m), 6.88 (1H, br. d, J 7.5 Hz), 7.05 (1H, dt, J 0.5, 7.5 Hz), 7.11 (1H, br. d, J 7.5 Hz), 7.26 (1H, dt, J 1, 7.5 Hz), 7.4-7.65 (5H, m), 8.4 (1H, br. s, NH).

Methyl Iminoether of 3-oxo-1-demethyl-18,19-didehydrovincatine. — (a) To a solution of the more polar isomers (15a and 15b) of 3-oxo-1-demethyl-18,19-didehydrovincatine (1.40 g, 3.8 mmol) in dry dichloromethane (100 ml) was added trimethyloxonium tetrafluoroborate (3.69 g, 24.93 mmol), and the resulting mixture was stirred under nitrogen and at room temperature for 3 days. The suspension was then poured into water (100 ml) and 10% sodium carbonate solution added with vigorous stirring until any traces of brown colour or solid material had been removed. The organic layer was then separated, washed with water, and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a yellow gum which was chromatographed on Kieselgel G (150 g), with 3% methanol in chloroform as eluent to give the methyl iminoether of the (B) isomers of 3-oxo-1-demethyl-18,19 didehydrovincatine (1.22 g, 87%) as a pale yellow solid which was obtained from benzene/petroleum ether as colourless pillars, m.p. 176-179°C (Found: C, 69.15; H, 7.05; N, 7.45; M^+, 382.18943. $C_{22}H_{26}N_2O_4$ requires C, 69.14; H, 6.86; N, 7.33%; M, 382.189245; $\nu_{max.}$ (Nujol) 1730, 1640, 1620, 1579 cm^{-1}; δ ($CDCl_3$) 1.09-2.70 (10H, m), 3.51 (3H, s, CO_2Me), 3.91 (3H, s, N=C-OMe), 3.73-4.14 (3H, m, N-CH, N-CH_2), 4.78-5.16 (2H, m, -CH=CH_2), 5.59-5.90 (1H, m, -CH=CH_2), 7.00-7.40

(4H, m, aromatic); m/z 382 (46), 202 (100), 173 (77), 160 (39), 158 (27), 136 (80), 108 (25), 94 (30).

(b) Treatment of the less polar isomers (14a and 14b) of 3-oxo-1-demethyl-18,19-didehydrovincatine (1.20 g, 3.2 mmol) in a similar manner gave the methyl iminoether of the (A) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (1.01 g, 82%) as a colourless crystalline solid, m.p. 185-189°C (Found: C, 69.05; H, 6.85; N, 7.35; M^+, 382.18909. $C_{22}H_{26}N_2O_4$ requires C, 69.14; H, 6.86; N, 7.33%; M, 382.189245); $\nu_{max.}$ (Nujol) 1730, 1635, 1620, 1585 cm^{-1}; δ ($CDCl_3$) 1.40-2.70 (10H, m), 3.50 (3H, s, CO_2Me), 3.70-4.20 (3H, m, -N-CH, N-CH_2), 4.05 (3H, s, N=C-OMe), 4.62-5.10 (2H, m, -CH=CH_2), 5.40-5.60 (1H, m, -CH=CH_2), 7.00-7.51 (4H, m, aromatic).

3-Oxo-1-demethyl-18-phenylsulphinylvincatine (21). — 3-Oxo-1-demethyl-18-phenylthiovincatine (100 mg, 0.21 mmol) was dissolved in dry dichloromethane (15 ml) and cooled to -78°C. m-Chloroperbenzoic acid (37 mg, 0.22 mmol) in dichloromethane (1 ml) was then added dropwise via a syringe. The mixture was stirred at -78°C for 4 h when t.l.c. analysis showed the absence of any starting material. The reaction mixture was allowed to reach room temperature, and was then partitioned between ether (50 ml) and 10% sodium sulphite solution (50 ml). The organic layer was separated, washed with saturated aqueous sodium bicarbonate solution (2 x 50 ml) and dried ($MgSO_4$). Removal of the solvents under reduced pressure left a colourless gum which crystallised on addition of a small quantity of petroleum ether. The material was recrystallised from benzene/petroleum ether to give 3-oxo-1-demethyl-18-phenylsulphinylvincatine (83 mg, 80%) as colourless pillars, m.p. 118-120°C (Found: C, 65.0; H, 6.0; N, 5.5; M^+, 494.18761. $C_{27}H_{30}N_2O_5S$ requires C, 65.56; H, 6.11; N, 5.66%; M, 494.187531); $\nu_{max.}$ (Nujol) 3200, 1720 br, 1625 br, 1040 cm^{-1}.

3-Oxo-1-demethyl-18,19-didehydrovincatine (14 and 15). — 3-Oxo-1-demethyl-18-phenylsulphinylvincatine (50 mg, 0.10 mmol) was dissolved in toluene (5 ml) and a very small amount of calcium carbonate added. The resulting solution was brought to a temperature just below reflux and stirred overnight when t.l.c. analysis showed the absence of starting material. The reaction mixture was concentrated by evaporation under reduced pressure and the resulting yellow gum chromatographed using Kieselgel G (20 g) with 5% methanol in chloroform as eluent. 3-Oxo-1-demethyl-18,19-didehydrovincatine (11 mg, 30%) was obtained as a colourless, crystalline mixture of diastereoisomers, and was shown to be identical with an authentic sample of (14 and 15) by comparison of i.r. and n.m.r. spectra, and chromatographic behaviour.

3-Oxo-18,19-didehydrovincadifformine (9). — (a) The mixture of iminoethers of the (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (1.0 g, 2.6 mmol), dissolved in dry dimethyl sulphoxide (4 ml), was added dropwise to a stirred solution of dimsyl sodium, prepared from dry dimethyl sulphoxide (12 ml) and sodium hydride (113 mg, 4.70 mmol) under nitrogen at 65°C. The mixture was stirred at this temperature for 2.5 h, then cooled and poured into saturated brine (50 ml). The resulting solution was extracted with dichloromethane (3 x 50 ml) and the combined organic extracts were washed with saturated bring (50 ml) and water (50 ml), then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a yellow oil which was chromatographed using Kieselgel G (100 g), with 5% methanol in chloroform as eluent, to give two fractions.

The first fraction contained the trans isomer, 3-oxo-18,19-didehydro-20-epi-vincadifformine (16) (291 mg, 0.83 mmol, 32%) as a white foam which was recrystallised from methanol to give colourless needles, m.p. 215-217°C (Found: C, 71.8; H, 6.25; N, 7.85; M^+, 350.16285. $C_{21}H_{22}N_2O_3$ requires C, 71.98; H, 6.33; N, 7.99%; M, 350.163032); $\nu_{max.}$ (Nujol) 3280, 1675, 1650, 1630, 1610 cm^{-1}; δ ($CDCl_3$) 1.15-3.20 (8H, m), 3.78 (3H, s, CO_2Me), 3.40-4.10 (3H, m, -N-CH, N-CH_2), 4.95-5.30 (2H, m, -CH=CH_2), 5.76-6.10 (1H, m, -CH=CH_2), 6.70-7.45 (4H, m, aromatic), 8.88 (1H, s, exchanges with D_2O), N-H); m/z (%) 350 (47), 264 (37), 167 (12), 154 (12).

The second fraction contained the cis isomer, 3-oxo-18,19-didehydrovinca-difformine (9) (428 mg, 47%) as a white solid which on recrystallisation from methanol gave colourless needles, m.p. 225-228°C (Found: C, 71.90; H, 6.35; N, 8.05; M^+, 350.16285. $C_{21}H_{22}N_2O_3$ requires C, 71.98; H, 6.33; N, 7.99%; M, 350.163032); $\lambda_{max.}$ 228, 297, 330 nm; $\nu_{max.}$ (Nujol) 3380, 1680, 1650, 1615 cm^{-1}; δ ($CDCl_3$) 1.6-2.9 (8H, m), 3.75 (3H, s, -CO_2Me), 4.05-4.40 (3H, m, -N-CH, -N-CH_2), 4.5-5.8 (3H, m, -CH=CH_2), 6.7-7.4 (4H, m, aromatic), 9.05 (1H, s, exchanges with D_2O); m/z (%) 350 (30), 308 (16), 307 (63), 264 (23), 227 (100), 214 (41), 195 (53), 182 (12), 171 (20), 154 (28).

(b) The mixture of iminoethers of the (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (0.5 g, 1.3 mmol), dissolved in dry dimethyl sulphoxide (2 ml), was added dropwise to a stirred solution of dimsyl sodium prepared from dimethyl sulphoxide (6 ml) and sodium hydride (56 mg, 2.35 mmol) under nitrogen at 103°C. The mixture was stirred at this temperature for 2.5 h, cooled and worked up in the manner described above to give a brown gum. Analysis of this reaction mixture by t.l.c. (eluting with 7% methanol in chloroform) showed the presence of a large number of products. Chromatography using Kieselgel G (40 g) gave 3-oxo-18,19-

didehydro-20-epivincadifformine (16) (35 mg, 8%) and 3-oxo-18,19-didehydro-vincadifformine (9) (53 mg, 12%), both of which were recrystallised from methanol and found to be identical to previously prepared samples by comparison of t.l.c. behaviour and i.r. and n.m.r. spectra.

Attempted Isomerisation of 3-oxo-18,19-didehydro-20-epivincadifformine (16). — 3-Oxo-18,19-didehydro-2o-epivincadifformine (50 mg, 0.14 mmol) was added to a stirred solution of dimsyl sodium prepared from sodium hydride (5 mg, 0.21 mmol) and dry dimethyl sulphoxide (3 ml), under nitrogen at 65°C. The mixture was stirred at this temperature for 2.5 h, then poured into saturated brine (15 ml), and extracted with dichloromethane (3 x 20 ml). The organic extracts were combined and washed with saturated brine (20 ml) and water (20 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a yellow gum which crystallised upon addition of a small quantity of petroleum ether. Analysis of this material indicated that it was solely starting material (41 mg) as verified by t.l.c. behaviour, and i.r. and n.m.r. spectra.

N-Methyl-3-oxo-18,19-didehydrovincadifformine (22). — In an atmosphere of nitrogen 3-oxo-18,19-didehydrovincadifformine (9) (150 mg, 0.43 mmol), dissolved in dry dimethylformamide (2 ml), was added to a solution of sodium hydride (10 mg, 0.86 mmol) in dry dimethylformamide (2 ml). The solution was stirred at room temperature for 20 min, then methyl iodide (202 mg, 1.28 mmol) was added and the reaction mixture stirred for 10 min. Water (5 ml) was then added, the solution extracted with ether (3 x 20 ml), and the combined organic extracts were dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil which was chromatographed on Kieselgel G (50 g), with 2% methanol in chloroform as eluent, to give N-methyl-18,19-didehydrovincadifformine (22) (123 mg, 78%) as an amorphous white solid, m.p.237-239°C (Found: C, 72.55; H, 6.98; N, 7.40; M^+, 364.17856. $C_{22}H_{24}N_2O_3$ requires C, 72.51; H, 6.64; N, 7.69%; M, 364.17868); $\lambda_{max.}$ 217, 303, 337 nm; $\nu_{max.}$ (Nujol) 1695, 1640, 1600 cm^{-1}; δ ($CDCl_3$) 1.40-3.05 (8H, m), 3.26 (3H, s, N-CH_3), 3.75 (3H, s, CO_2Me), 4.00-4.50 (3H, m, -N-CH, -N-CH_2), 4.75-6.10 (3H, m, -CH=CH_2), 6.62-7.45 (4H, m, aromatic); m/z (%) 364 (34), 336 (13), 241 (76), 228 (57), 182 (24), 168 (23), 149 (21), 135 (25).

3-Oxo-1,2,18,19-tetradehydroaspidospermidine (23). — 3-Oxo-18,19-didehydro-vincadifformine (9) (200 mg, 0.57 mmol) was dissolved in a mixture of concentrated hydrochloric acid and water (1.1, 10 ml) and the resulting solution heated under reflux for 2 h. The reaction mixture was allowed to cool, then water (6 ml) was added and the solution neutralised with potassium carbonate. The mixture was

extracted with chloroform (3 x 20 ml) and the combined organic extracts were washed with water, then dried ($MgSO_4$). Removal of the solvent under reduced pressure left a colourless oil which was chromatographed on Kieselgel G (40 g), with 3% methanol in chloroform as eluent, to give two main fractions.

The first fraction contained starting material (23 mg) as verified by its t.l.c. behaviour and i.r. spectrum.

The second fraction contained 3-oxo-1,2,18,19-tetradehydroaspidospermidine (21 mg, 0.072 mmol, 13%) as a colourless gum (Found: $\underline{M}^+$, 292.15741. $C_{19}H_{20}N_2O$ requires $\underline{M}$, 292.157555); $\lambda_{max.}$ 225, 243 sh, 270 sh nm; $\nu_{max.}$ 1650 br, 1580 cm^{-1}; δ ($CDCl_3$) 1.10-3.29 (10H, m), 3.81-4.40 (3H, m, N-C$\underline{H}$ and N-C$\underline{H}_2$), 5.10-5.50 (2H, m, -CH=C$\underline{H}_2$), 5.80-6.20 (1H, m, C$\underline{H}$=CH_2), 7.01-7.71 (4H, m, aromatic); m/z (%) 297 (7), 264 (19), 263 (16), 184 (7), 170 (9).

Action of Polyphosphoric acid on 3-oxo-1-demethyl-18,19-didehydrovincatine. — A mixture of 3-oxo-1-demethyl-18,19-didehydrovincatine (427 mg, 1.16 mmol) and polyphosphoric acid (10 ml) was heated, under nitrogen and with mechanical stirring, to 120-130°C for 2 h. The solution was allowed to cool, then water (50 ml) was added and the resulting mixture extracted with chloroform (3 x 30 ml). The combined organic extracts were washed with water, then dried ($MgSO_4$). Removal of the solvents under reduced pressure left an orange oil which was chromatographed on Kieselgel G (60 g), with 5% methanol in chloroform as eluent, to give an unsaturated ketolactam (24), (67 mg, 17%), which was obtained as white pillars, m.p. 267-269°C, from methanol (Found: C, 71.65; H, 6.35; N, 8.0; $\underline{M}^+$, 336.14725. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33%; $\underline{M}$, 336.147383); $\lambda_{max.}$ 216, 240 sh, 263 sh nm; $\nu_{max.}$ (Nujol) 3440, 3200, 1710 br, 1670, 1640, 1620 cm^{-1}; δ_H ($CDCl_3$) 1.75 (1H, dddd, $\underline{J}$ 1.5, 7, 12, 14 Hz), 1.92 (1H, ddd, $\underline{J}$ 2, 6.5, 14 Hz), 2.05 (1H, dddd, $\underline{J}$ 2, 4, 5, 14 Hz), 2.11 (1H, dddd, $\underline{J}$ 1.5, 6, 12, 14 Hz), 2.23 (2H, m), 2.32 (1H, ddd, $\underline{J}$ 5, 12, 17.5 Hz), 2.37 (1H, ddd, $\underline{J}$ 4, 6, 17.5 Hz), 2.48 (1H, ddd, $\underline{J}$ 6.5, 12, 18 Hz), 2.54 (1H, ddd, $\underline{J}$ 2, 7, 18 Hz), 3.90 (1H, m), 4.16 (1H, m), 4.18 (1H, s), 5.42 (1H, d, $\underline{J}$ 10 Hz), 6.06 (1H, dd, $\underline{J}$ 2, 10 Hz), 6.84 (1H, br. d, $\underline{J}$ 7.5 Hz), 7.07 (1H, dt, $\underline{J}$ 1, 7.5 Hz), 7.20 (1H, br. d, $\underline{J}$ 7.5 Hz), 7.25 (1H, dt, $\underline{J}$ 1, 7.5 Hz), 7.75 (1H, br. s, NH); m/z (%) 366 (49), 318 (27), 263 (24), 187 (100), 169 (59), 163 (32), 159 (47), 144 (30), 136 (33), 130 (31), 123 (28), 109 (24), 91 (30).

3-Oxo-1-demethyl-20-desethyl-20-formylvincatine (25). — A solution of the (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (250 mg, 0.68 mmol) in methanol (200 ml) was cooled to -78°C in a dry-ice/acetone bath and ozone gas was bubbled through the mixture until a pale blue colour persisted. The solution was

stirred for a few minutes until all traces of the blue colour had disappeared, then the cooling bath was removed and dimethyl sulphide (2 ml) added. Stirring was continued at room temperature until test with starch-iodide paper was negative. The solvent was then removed under reduced pressure leaving a yellow oil which was partitioned between chloroform and water. The chloroform layer was separated and the aqueous layer extracted again with chloroform, then the combined organic extracts were washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a pale yellow solid which was recrystallised from methanol to give 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (167 mg, 66%) as white pillars, m.p. 256-259°C (Found: C, 64.80; H, 6.30; N, 7.55; M^+, 370.15281. $C_{20}H_{22}N_2O_5$ requires C, 64.85; H, 5.99; N, 7.56%; M, 370.152861); $\nu_{max.}$ (Nujol) 3180, 1725 br, 1620 br cm^{-1}; δ ($CDCl_3$) 1.50-2.60 (10H, m), 3.52 (3H, s, $-CO_2Me$), 3.45-4.05 (3H, m, -N-CH and $-N-CH_2$), 6.70-7.22 (4H, m, aromatic), 8.80 (1H, s, -CHO), 10.56 (1H, s, exchanges with D_2O, N-H); m/z (%) 370 (2), 342 (24), 210 (15), 197 (19), 187 (12), 184 (19), 160 (18), 159 (53), 146 (21), 144 (15), 130 (18), 124 (56), 117 (12), 110 (17), 94 (11).

Methyl iminoether of 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (26). — To a solution of the (B) isomers of 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (1.42 g, 3.84 mmol) in dry dichloromethane (100 ml) was added trimethyloxonium tetrafluoroborate (3.69 g, 24.93 mmol) and the resulting solution stirred at room temperature under nitrogen for 3 days. The solution was then poured into water and 10% sodium carbonate solution added until any traces of brown colour or solid material had been removed. The organic layer was then separated and the aqueous portion extracted with dichloromethane (2 x 50 ml). The combined organic extracts were then washed with water, then dried ($MgSO_4$). Removal of the solvent under reduced pressure left a yellow oil which was chromatographed on Kieselgel G (250 g). Elution with 3% methanol in chloroform gave the methyl iminoether of 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (780 mg, 55%), which was obtained from benzene as white needles, m.p. 126-128°C (Found: C, 65.15; H, 6.35; N, 7.35; M^+, 384.16854. $C_{21}H_{24}N_2O_5$ requires C, 65.61; H, 6.29; N, 7.29%; M, 384.16851); $\nu_{max.}$ (Nujol) 1720, 1630 br, 1572 cm^{-1}; δ ($CDCl_3$) 1.65-2.60 (10H, m), 3.62 (3H, s, CO_2Me), 4.12 (3H, s, -N=C-OMe), 3.75-4.40 (3H, m, -N-CH and $N-CH_2$), 7.01-7.55 (4H, m, aromatic), 8.72 (1H, s, -CHO); m/z (%) 384 (9), 353 (3), 201 (7), 196 (17), 173 (100), 160 (83), 158 (13), 130 (15).

Dimethyl acetal of 3-oxo-1-demethyl-20-desethyl-20-formylvincatine. — 3-Oxo-

1-demethyl-20-desethyl-20-formylvincatine (200 mg, 0.54 mmol) was dissolved in trimethyl orthoformate (5 ml) and boron trifluoride etherate (3 drops) was added. The mixture was stirred at room temperature under nitrogen for 20 h, then poured into dilute sodium carbonate solution (15 ml) and extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with water (50 ml) and dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a pale yellow/green oil which was found to contain some trimethyl orthoformate. A dichloromethane solution of this oil was filtered through a small pad of basic alumina and the solvent removed under reduced pressure to give the dimethyl acetal of 3-oxo-1-demethyl-20-desethyl-20-formylvincatine (179 mg, 80%) as a yellow gum (Found: M^+, 416.194711. $C_{22}H_{28}N_2O_6$ requires M, 416.194723); $\nu_{max.}$ (film) 3430, 3200, 2831, 1720 br cm^{-1}; δ ($CDCl_3$) 1.4-2.7 (10H, m), 3.11 (6H, s, 2 x OMe), 3.55-4.11 (3H, m, N-CH and N-CH_2), 4.45 [1H, s, $CH(OMe)_2$], 6.80-7.55 (4H, m, aromatic), 9.48 (1H, s, exchanges with D_2O, N-H).

Hydrolysis of 3-oxo-1-demethyl-18,19-didehydrovincatine. — The mixture of (B) isomers of 3-oxo-1-demethyl-18,19-didehydrovincatine (400 mg, 1.09 mmol) was dissolved in methanol (20 ml) and dilute sodium hydroxide solution (150 ml) was added. The resulting mixture was stirred at room temperature for 24 h, then cooled to 0-5°C and extracted with ether (100 ml). The aqueous solution was then acidified with concentrated hydrochloric acid with cooling to maintain the temperature below 10°C. Extraction of the solution with chloroform (3 x 75 ml), drying ($MgSO_4$), and removal of the solvents under reduced pressure gave a yellow solid which was recrystallised from methanol/ether to give the required carboxylic acid (27) (303 mg, 79%) as white needles, m.p. 286-288°C (Found: C, 67.9; H, 6.3; N, 7.90; M^+, 354.15706. $C_{20}H_{22}N_2O_4$ requires C, 67.78; H, 6.26; N, 7.90%; M, 354.157947); $\lambda_{max.}$ 223, 256, 286 nm; $\nu_{max.}$ (Nujol) 3450, 3300 br, 1720, 1690, 1620 cm^{-1}; δ ($CDCl_3$) 1.11-2.80 (11H, m), 3.80-4.50 (3H, m, -N-CH, -N-CH_2), 4.70-5.10 (2H, m, CH=CH_2), 5.69-5.99 (1H, m, -CH=CH_2), 6.70-7.50 (4H, m, aromatic), 10.6 (1H, s, exchanges with D_2O, CO_2H); m/z (%) 354 (61), 196 (12), 187 (84), 186 (11), 160 (20), 159 (100), 150 (26), 144 (34), 136 (93), 130 (48), 117 (24).

Halolactonisation of 3-oxo-1-demethyl-18,19-didehydrovincatinic acid (27). — 3-Oxo-1-demethyl-18,19-didehydrovincatinic acid (27) (70 mg, 0.198 mmol) was dissolved in a tetrahydrofuran:water mixture (1.7:1, 14 ml) with potassium bicarbonate (99 mg, 0.99 mmol), iodine (400 mg, 1.58 mmol) and potassium iodide (260 mg, 1.58 mmol) added. The resulting mixture was allowed to stand at 0-5°C for 3 days with occasional stirring. The reaction solution was then extracted

with chloroform (3 x 20 ml) and the combined organic extracts were washed with sodium thiosulphate (20 ml), then dried ($MgSO_4$). Removal of the solvents under reduced pressure gave a pale yellow solid (35 mg, 0.073 mmol, 37%) which was found to be that of the required 6-iodolactone (Found: M^+, 480.05432. $C_{20}H_{21}O_4N_2I$ requires M. 480.054782).

3-Oxo-1-demethyl-19-hydroxyvincatinic acid lactone (28). — To a cold solution (5°C) of the iodolactone (30 mg, 0.06 mmol) in benzene was added under an atmosphere of nitrogen two drops of tributyl tin hydride. The resulting solution was stirred at room temperature under nitrogen for 24 h and then the solvents were removed under reduced pressure to leave a red solid consisting of the required lactone and tributyl tin hydride. Recrystallisation from methanol/ether gave the lactone (28) (13 mg, 61%) as pale yellow prisms (Found: M^+, 354.15741. $C_{20}H_{22}N_2O_4$ requires M, 354.157947).

3-Oxo-14-phenylselenyl-18,19-didehydrovincadifformine (29). — To a solution of diisopropylamine (58 mg, 0.57 mmol) in tetrahydrofuran (5 ml) and hexamethylphosphoramide (0.035 ml) at 0°C under nitrogen a hexane solution of 1.8M n-butyl lithium (0.37 ml, 0.57 mmol) was added and the resulting solution stirred at 0°C for 10 min. The reaction mixture was then cooled to -78°C in a dry ice/acetone bath and 3-oxo-18,19-didehydrovincadifformine (100 mg, 0.286 mmol) dissolved in tetrahydrofuran (2 ml) was added dropwise over a 5 min period. The solution was stirred at -78°C for 40 min, then phenyl selenyl chloride (60.5 mg, 0.315 mmol) dissolved in tetrahydrofuran (2 ml) was added dropwise. The mixture was then stirred at -78°C for a further 30 min before being warmed to room temperature. The reaction mixture was then poured into water (70 ml) and extracted with chloroform (2 x 50 ml). The combined organic extracts were washed with dilute sodium hydroxide (50 ml), water (50 ml) and dilute hydrochloric acid (50 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave a pale yellow solid which was recrystallised from methanol to give 3-oxo-14-phenylselenyl-18,19-didehydrovincadifformine (91 mg, 0.18 mmol, 63%) as colourless plates, m.p. 218-220°C (Found: C, 64.65; H, 5.25; N, 5.50. $C_{27}H_{26}N_2O_3Se$ requires C, 64.16; H, 5.18; N, 5.54%); $\lambda_{max.}$ 237, 291, 327 nm; $\nu_{max.}$ (Nujol) 3360, 1678, 1641, 1611 cm^{-1}; δ ($CDCl_3$) 1.10-3.10 (7H, m), 3.75 (3H, s, CO_2Me), 3.30-4.20 (3H, m, N-CH and N-CH_2), 4.95-5.40 (2H, m, -CH=CH_2), 5.50-6.25 (1H, m, -CH=CH_2), 6.70-7.85 (9H, m, aromatic H), 8.81 (1H, s, exchanges with D_2O, N-H); m/z (%) 505 (17), 349 (100).

18,19-Didehydro-3-oxotabersonine (30). — 3-Oxo-14-phenylselenyl-18,19-didehydrovincadifformine (46 mg, 0.091 mmol) was dissolved in dichloromethane (5 ml) and the

resulting solution cooled to -78°C in a dry-ice/acetone bath under nitrogen. A solution of m-chloroperbenzoic acid (18 mg, 0.091 mmol) in dichloromethane (2 ml) was then added and the mixture stirred at -78°C under nitrogen for 10 min. The solution was then allowed to warm to room temperature and poured into water (10 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane (8 ml). The combined organic extracts were then washed with dilute sodium bicarbonate solution (10 ml) and water (10 ml), then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 18,19-didehydro-3-oxotabersonine (30 mg, 93%) as a colourless gum; $\lambda_{max.}$ 230, 286, 328 nm; $\nu_{max.}$ ($CHCl_3$) 3400, 1720, 1655, 1603 cm^{-1}; δ ($CDCl_3$) 1.10-3.20 (4H, m), 3.81 (3H, s, CO_2Me), 4.0-4.5 (3H, m, N-CH, $N-CH_2$), 5.10-5.40 (2H, m, $-CH=CH_2$), 5.71-6.10 (1H, m, $-CH=CH_2$), 6.11-6.56 (2H, dd, J 18, 9 Hz, $-CH=CH-CO$), 6.70-7.50 (4H, m, aromatic H); 9.91 (1H, s, N-H); m/z (%) 348 (55), 347 (17), 320 (20), 291 (23), 278 (19), 263 (14), 262 (13), 227 (59), 195 (100), 167 (42), 154 (17).

18,19-Didehydrovincadifformine (31). — 3-Oxo-didehydrovincadifformine (50 mg, 0.143 mmol) was dissolved in dry dichloromethane (5 ml) and trimethyloxonium tetrafluoroborate (23 mg, 0.157 mmol) was added. The resulting solution was stirred at room temperature, under nitrogen, for 20 h, then the solvent was removed under reduced pressure. Ethanol (5 ml) was added, and the reaction mixture was cooled to 0°C in an ice/salt bath. Sodium borohydride (11 mg, 0.286 mmol) was then added and the mixture stirred at room temperature for 16 h. The solution was then poured into water (50 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were then washed with water (50 ml), and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave 18,19-didehydrovincadifformine (32 mg, 66%) as a yellow gum (Found: M^+, 336.18310. $C_{21}H_{24}N_2O_2$ requires M, 336.183768); $\lambda_{max.}$ 258, 298, 332 nm; $\nu_{max.}$ (film) 3400, 1670, 1610 cm^{-1}; δ ($CDCl_3$) 1.40-3.50 (13H, m), 3.72 (3H, s, CO_2Me), 4.50-6.60 (3H, m, $CH=CH_2$), 6.60-7.50 (4H, m, aromatic H), 8.82 (1H, s, exchanges with D_2O, N-H); m/z (%) 336 (8), 292 (3), 147 (14), 122 (100), 115 (2).

18,19-Didehydrotabersonine (1). — 18,19-Didehydro-3-oxotabersonine (8 mg, 0.02 mmol) was dissolved in dry dichloromethane (2 ml) and trimethyloxonium tetrafluoroborate (4.4 mg, 0.03 mmol) was added. The resulting solution was stirred at room temperature under nitrogen for 18 h, then the solvent was removed under reduced pressure. Ethanol (2 ml) was added, and the mixture was then cooled to 0°C in an ice/salt bath. Sodium borohydride (2 mg, 0.04 mmol) was added and the mixture stirred at room temperature for 16 h. The solution was then poured into water (10 ml) and extracted with ether (3 x 20 ml). The combined organic extracts were

washed with water (20 ml), and dried ($NaSO_4$). Removal of the solvents under reduced pressure gave (±)-18,19-didehydrotabersonine (3 mg, 57%) as a pale yellow gum, identical in chromatographic behaviour in two solvent systems (2% methanol in chloroform, and 10% ether in benzene) and in mass spectrum with authentic 18,19-didehydrotabersonine[17] (Found: M^+, 334.16836. $C_{21}H_{22}N_2O_2$ requires M, 334.168118).

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