Total synthesis of indole and dihydroindole alkaloids. XVI.[1,2] Derivatives of vinblastine and vincristine: change of functionality in the vindoline unit

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Studies describing the preparation of various derivatives of vinblastine and vincristine are presented. Vindoline (**3**) is transformed into a series of derivatives and the latter via Polonovski-type coupling with catharanthine (**2**) provide the bisindole alkaloid derivatives of the vinblastine series. Selective Jones' oxidation transforms the vinblastine family into the corresponding vincristine derivatives.

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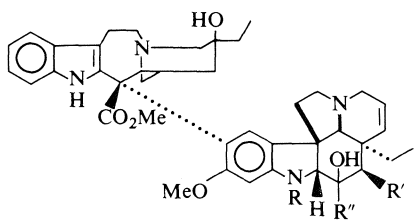
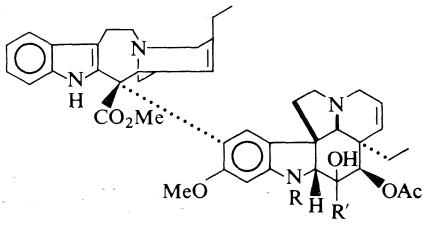
On présente des études décrivant la préparation de divers dérivés de la vinblastine et de la vincristine. On transforme la vindoline (**3**) en une série de dérivés et ces derniers par l'intermédiaire d'un couplage de type Polonovski avec la catharanthine (**2**) fournissent les dérivés de l'alcaloïde bisindole de la série de la vinblastine. Une oxydation sélective de Jones transforme les composés de la famille de la vinblastine en dérivés correspondants de la vincristine.

[Traduit par le journal]

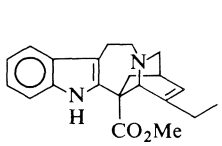
Earlier reports from these (see ref. 5 for earlier parts of this series) and other (6–8) laboratories have discussed syntheses of various derivatives of the antitumour agent, vinblastine (**1**). The two strategies generally employed; functionalisation of catharanthine (**2**) followed by coupling with vindoline (**3**), or direct coupling of (**2**) and (**3**) with subsequent elaboration of the so formed 3′,4′-dehydrovinblastine (**4**); have provided derivatives with various functionality in the indole (cleavamine) unit. The present work describes the preparation of vinblastine–vincristine derivatives bearing different functions in the vindoline unit of the molecule. To this end both the coupling of vindoline derivatives with catharanthine via the modified Polonovski reaction (6,9) and elaboration of 'dimeric' substrates have been utilized.



1 R = Me, R′ = OAc, R″ = CO_2Me
14 R = Me, R′ = H, R″ = CO_2Me
22 R = Me, R′ = OH, R″ = $CONH_2$
23 R = CHO, R′ = OAc, R″ = CO_2Me



4 R = Me, R′ = CO_2Me
25 R = CHO, R′ = CO_2Me
26 R = Me, R′ = CONHMe
27 R = CHO, R′ = CONHMe



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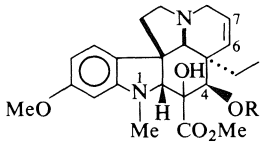
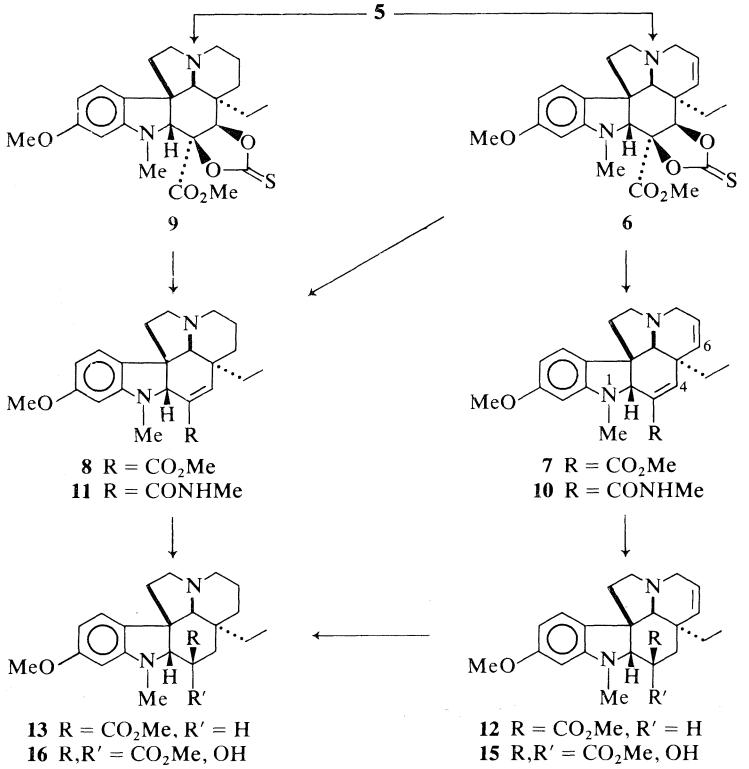


3 R = Ac
5 R = H

Vindoline, a readily available alkaloid from *Catharanthus roseus* G. Don (*Vinca rosea* L.), for which both total (10, 11) and partial (12, 13) syntheses have appeared, was subjected to the transformations depicted in Scheme 1. Reaction of desacetylvindoline (**5**) with *N*,*N*′-thiocarbonyldiimidazole gave a high yield of the thionocarbonate **6** which on treatment with Raney nickel led efficiently to the unsaturated ester **7**. Prolonged reaction of **6** afforded the ring E saturated derivative **8** which was also available from desacetyldihydrovindoline via **9** (14) using a similar reaction sequence. Both esters **7** and **8** were readily converted to the corresponding

[1]For Part XV, see ref. 1.

[2]For preliminary reports on portions of this work see refs. 2–4.



SCHEME 1

TABLE 1. Coupling of vindoline derivatives with the N_b oxide of catharanthine (**2**)

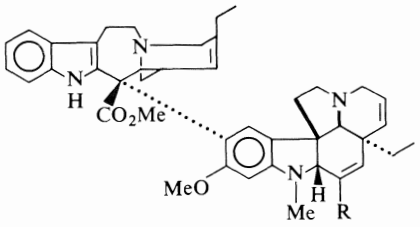
Substrate	Product	Yield (%)
7	**17**	45
8	**18**	30
10	**19**	36
11	**20**	22
15	**21**	32

N-methyl amides **10** and **11** respectively, by the direct action of methylamine. Alternatively, reaction of **7** and **8** with sodium amalgam in methanol solution provided the more favoured 3(*R*)-esters **12** and **13** (11) in high yields. The uncomplicated nature of these reductions may be attributed to severe steric crowding at C4 thus preventing coupling of the presumed radical intermediates.

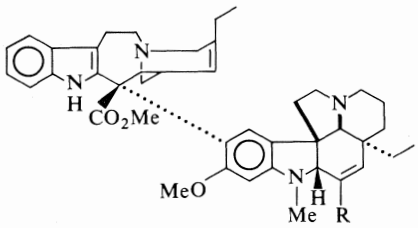
In view of the recent interest in 4-desacetoxyvinblastine (**14**), isolated from *C. roseus* by the Lilly group (15), it seemed appropriate to synthesize derivatives of this type. Here, α-hydroxylation of the esters **12** and **13** with molybdenum peroxide HMPA pyridine complex (16–18) provided the respective hydroxyesters **15** and **16**. The latter was also available by reaction of **13** with hydrogen peroxide in the presence of potassium *tert*-butoxide. In addition, hydrogenation of **15** gave **16**, demonstrating identical configuration at C3. The data available did not enable unambiguous absolute configurational assignment for these hydroxyesters.

The modified Polonovski reaction has found wide application in the preparation of bisindole derivatives of the vinblastine type. Further exploitation of this method enabled the preparation of 'dimeric' compounds from the vindoline derivatives discussed above. Table 1 summarizes these results. The amide derivatives **19** and **20** and the hydroxyester **21** are of particular interest owing to their similarity to vinblastine amide **22** (19) and 4-desacetoxyvinblastine **14** reported by the Lilly group (15). Notably the efficiency of this coupling reaction is retained with substrates of this type which themselves remain highly nucleophilic at the 15-position, while a report has appeared on the failure of N_a-formyl substrates to react (6). The success of the coupling seems also dependent on the ability of the catharanthine derivative to stabilise the reaction intermediate from C5—C18 cleavage (6, 9).

The interesting biological activity of several 22-oxo-'dimeric' alkaloids and derivatives, e.g., vincristine (**23**), 22-oxoleurosine (**24**) (20), and 3′,4′-dehydrovincristine (**25**) (21), prompted the preparation of a series of synthetic derivatives of this type to complement the biological data already available from the parent amines. Indeed a procedure for the



17 R = CO_2Me
19 R = CONHMe



18 R = CO_2Me
20 R = CONHMe

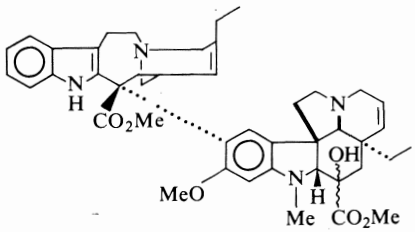


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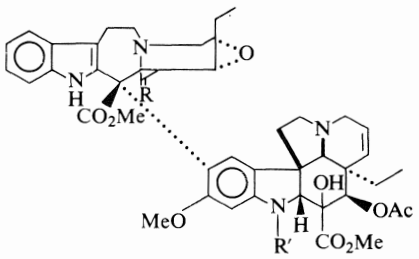
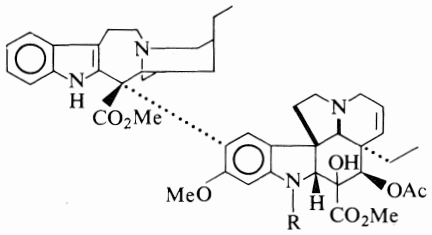
TABLE 2. 22-Oxo derivatives via Jones' oxidation

Substrate	Product	Yield (%)
4	**25**	80
26	**27**	53
28	**29**	68
30	**31**	48
32	**33**	63
34	**24**	75
35	**36**	30
	37	17
39	**38**	72

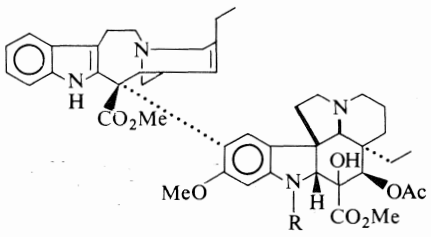
'chromic acid' (CrO_3) oxidation of vinblastine (**1**) to **23** had appeared (22). Although this method was found ineffectual in promoting oxidation of 3′,4′-dehydrovinblastine (**4**), modification of the procedure did enable specific oxidation of the various 'bisindole' derivatives listed in Table 2. Generally, low temperature oxidation with Jones' reagent gave reproducibly high yields of the N_a-formyl compounds. The ease of specific oxidation within these complex molecules is quite remarkable. Oxidations of leurosine (**34**) serve to illustrate this point. Here, treatment of **34** with Jones' reagent at low temperature provided 22-oxoleurosine (**24**) which is presently in clinical use in



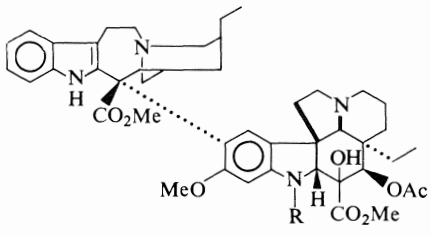
24 R = H_2, R′ = CHO
34 R = H_2, R′ = Me
35 R = O, R′ = Me
36 R = O, R′ = CHO
37 R = O, R′ = H



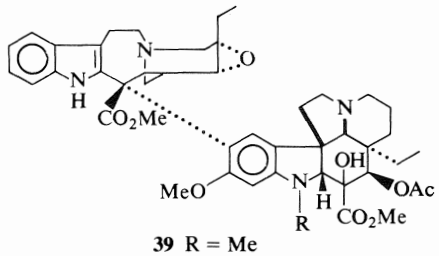
28 R = Me
29 R = CHO



30 R = Me
31 R = CHO



32 R = Me
33 R = CHO



39 R = Me
38 R = CHO

Hungary (20). Further oxidation with iodine in the presence of sodium bicarbonate afforded the 19′-oxidation product **36**. Alternatively, iodine–bicarbonate oxidation of leurosine and subsequent Jones' oxidation of the product **35**, gave **36** together with the secondary amine **37**. The dihydro derivative **38** was also available from 6,7-dihydroleurosine (**39**), prepared by *tert*-butyl hydroperoxide oxidation of **30** or by hydrogenation of leurosine (**34**). In this latter reaction, products of oxiran cleavage were not observed.

The work described here, together with that reported in previous parts of this series, has allowed the preparation of numerous derivatives of vinblastine and vincristine with the potential of extending this number to provide an effective biological screening program. It is hoped that this program will provide valuable information relating to structure–activity relationships for the bisindole alkaloid oncolytic agents.

Experimental

Melting points were determined on a Kofler block and are uncorrected. Ultraviolet (uv) spectra were recorded on a Cary 15 spectrophotometer in ethanol solution. The wavelengths of absorption maxima are reported in nanometers (nm) with log ε values in parentheses. Infrared (ir) spectra were measured on a Perkin Elmer model 710 or 457 spectrophotometer in chloroform solution. The absorption maxima are reported in wavenumbers (cm^{-1}), calibrated with respect to the absorption band of polystyrene at 1601 cm^{-1}. Proton magnetic resonance (^{1}Hmr) spectra were measured in deuteriochloroform ($CDCl_3$) solution at ambient temperature on either a Varian HA-100 or XL-100 spectrometer. Chemical shift values are given in the δ (ppm) scale relative to tetramethylsilane (TMS) used as internal standard. The integrated peak areas, signal multiplicities, and proton assignments are given in parentheses. Low resolution mass spectra (ms) were determined on either an AEI-MS-902 or an Atlas CH-4B spectrometer. High resolution mass spectra were measured on an AEI-MS-902 instrument. Microanalyses were carried out by Mr. P. Borda of the Microanalytical Laboratory, University of British Columbia.

Thin-layer chromatography (tlc) utilized Merck silica gel G (according to Stahl) containing 2% fluorescent indicator. For preparative layer chromatography (plc), plates (20 × 20 or 20 × 60 cm) of 1 mm thickness were used. Visualization was effected by viewing under ultraviolet light and/or by colour reaction with ceric sulphate spray reagent. Column chromatography utilized Merck silica gel 60 (70–230 mesh) or Merck aluminium oxide 90 (neutral).

As a matter of routine, all reagents and solvents were recrystallized or distilled before use.

The Thionocarbonate ***6***

Thiocarbonyl diimidazole (400 mg) was added to a solution of desacetylvindoline (**5**) (230 mg) in butan-2-one (23 ml) and the resulting solution refluxed under a nitrogen atmosphere for 20 h. The mixture was then cooled, diluted with ethyl acetate, washed with 1 *M* sodium carbonate solution, saturated sodium chloride solution, dried (Na_2SO_4), and evaporated *in vacuo*. Recrystallisation of the residue from ethyl acetate afforded the thionocarbonate **6** (210 mg, 83%), mp 184–186°C; uv λ_{max}: 235 (4.28), 300 (3.64); ir ν_{max}: 1740, 1615, 1610, 1315; ^{1}H nmr δ: 7.02 (1H, d, J = 8 Hz, C14-H), 6.43 (1H, dd, J = 8, 2 Hz, C15-H), 6.16 (1H, d, J = 2 Hz, C17-H), 6.00 (1H, m, C7-H), 4.62 (1H, bd, J = 10 Hz, C6-H), 4.78 (1H, d, J = 2 Hz, C4-H), 3.98 (3H, s, —OCH_3), 3.90 (1H, s, C2-H), 3.82 (3H, s, —OCH_3), 2.63 (3H, s, —NCH_3), 0.30 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 456 (M^+), 440, 427, 426, 425, 395, 380, 379 (100%), 349, 295, 188, 174, 135, 121. *Anal.* calcd. for $C_{24}H_{28}SN_2O_5$: C63.13, H6.18, N6.14; found: C63.25, H6.20, N6.42.

The Unsaturated Ester ***7***

The thionocarbonate **6** (200 mg) in dry THF (10 ml) was added to a suspension of Raney nickel (5 g) in dry THF (50 ml). The mixture was refluxed for 1 h and then filtered. The filtrate was evaporated *in vacuo* and the residue chromatographed on silica gel to give **7** (140 mg, 84%) as a colourless foam; uv λ_{max}: 252 (3.91), 307 (3.74); ir ν_{max}: 1705, 1615; ^{1}H nmr δ: 7.26 (1H, s, C4-H), 7.03 (1H, d, J = 8 Hz, C14-H), 6.28 (1H, dd, J = 8, 2 Hz, C15-H), 6.01 (1H, d, J = 2 Hz, C17-H), 5.65–6.00 (2H, m, C6-H and C7-H), 4.26 (1H, s, C2-H), 3.80 (6H, s, 2 × —OCH_3), 2.74 (3H, s, —NCH_3), 1.42 (2H, q, J = 7.5 Hz, —CH_2CH_3), 0.63 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e*: 380 (M^+), 350, 321, 297, 282, 244, 220, 208, 205, 188, 174, 149. *Mol. wt.* calcd. for $C_{23}H_{28}N_2O_3$: 380.2100; found (high resolution ms): 380.2092.

The Ester ***8***

Reaction of the thionocarbonate (**6**) with Raney nickel in refluxing THF for 20 h gave an almost quantitative yield of the unsaturated ester (11).

The Amide ***10***

The ester **7** (300 mg) in methylamine (10 ml) was heated at 60°C in a sealed tube for 72 h. The solvent was removed *in vacuo*. The residue was dissolved in dichloromethane, washed with water, and dried (Na_2SO_4). Evaporation of the solvent and crystallisation from ethyl acetate – petroleum ether gave the amide **10** (270 mg, 90%), mp 196–198°C; uv λ_{max}: 250 (3.95), 305 (3.73); ir ν_{max}: 3500, 1650, 1620; ^{1}H nmr δ: 7.00 (1H, d, J = 8 Hz, C14-H), 6.48 (1H, s, C4-H), 6.25 (1H, dd, J = 8, 2 Hz, C15-H), 5.98 (1H, d, J = 2 Hz, C17-H), 5.60–6.00 (2H, m, C6-H and C7-H), 4.24 (1H, s, C2-H), 3.77 (3H, s, —OCH_3), 2.87 (3H, d, J = 5 Hz, —$NHCH_3$), 2.76 (3H, s, —NCH_3), 1.40 (2H, q, J = 7.5 Hz, —CH_2CH_3), 0.60 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e*: 379 (M^+), 321, 188, 174, 149. *Mol. wt.* calcd. for $C_{23}H_{29}N_3O_2$: 379.2260; found (high resolution ms): 379.2262. *Anal.* calcd.: C72.79, H7.70, N11.07; found: C72.64, H7.67, N11.00.

The Amide ***11***

Reaction of the ester **8** with methylamine as described above gave the amide **11** (88%) as a colourless foam; ir ν_{max}: 3500, 1660, 1605; ^{1}H nmr δ: 6.34 (1H, s, C4-H), 4.24 (1H, s, C2-H), 3.72 (3H, s, —OCH_3), 2.88 (3H, d, J = 4 Hz, —$NHCH_3$), 2.74 (3H, s, —NCH_3), 0.60 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 381 (M^+), 366, 351, 336, 322, 320, 246, 217, 208, 174, 144, 124 (100%). *Mol. wt.* calcd. for $C_{23}H_{31}N_3O_2$: 381.2416; found (high resolution ms): 381.2412.

The Ester ***12***

An excess of 10% sodium amalgam was added in portions to a solution of the unsaturated ester **7** (100 mg) in methanol (10 ml) at ambient temperature. Stirring was continued for a total of 6 h, the mixture was filtered, and the filtrate concentrated *in vacuo*. Chromatography on silica gel afforded the 3(*R*)-ester **12** (78 mg, 78%); mp (methanol – petroleum ether) 186–188°C; uv λ_{max}: 252 (3.71), 304 (3.55); ir ν_{max}: 1725; ^{1}H nmr δ: 6.90 (1H, d, J = 8 Hz, C14-H), 6.16 (1H, dd, J = 8, 2 Hz, C15-H), 5.95 (1H, d, J = 2 Hz, C17-H), 5.71

(1H, dd, J = 10, 2 Hz, C7-H), 5.84 (1H, bd, J = 10 Hz, C6-H), 3.87 (1H, d, J = 10 Hz, C2-H), 3.76 (3H, s, —OCH_3), 3.67 (3H, s, —OCH_3), 2.73 (3H, s, —NCH_3), 0.77 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 382 (M^+, 100%), 380, 351, 208, 189, 188, 187, 174, 161, 135, 122, 121, 107, 93. *Mol. wt.* calcd. for $C_{23}H_{30}N_2O_3$: 382.2257; found (high resolution ms): 382.2271. *Anal.* calcd. for $C_{23}H_{30}N_2O_3 \cdot \frac{1}{2}H_2O$: C71.89, H7.91, N7.29; found: C71.80, H8.20, N7.01.

The Ester ***13***

Reduction of the ester **8** with 10% sodium amalgam as described above gave the 3(*R*)-ester **13** (82%) identical with an authentic sample (11).

The Hydroxyester ***15***

Diisopropylamine (0.5 ml) and *n*-butyllithium (0.5 ml of a 20% solution in heptane) were stirred at 0°C in dry THF (5 ml) for 15 min. A solution of the ester (**12**) (60 mg) in dry THF (5 ml) was added and the solution stirred at 0°C for 30 min and then at ambient temperature for 1 h. The solution was cooled to 0°C and $MoO_5 \cdot Py \cdot HMPA$ complex (16–18), (80 mg) added. The mixture was stirred at 0°C for 1 h, diluted with water, and extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried (Na_2SO_4), and evaporated. Chromatography on silica gel gave the hydroxyester **15** (22 mg, 35%) as a colourless foam; uv λ_{max}: 252 (3.83), 306 (3.77); ir ν_{max}: 3520, 1720, 1615–1610; ^{1}H nmr δ: 6.88 (1H, d, J = 8 Hz, C14-H), 6.17 (1H, dd, J = 8, 2 Hz, C15-H), 5.98 (1H, d, J = 2 Hz, C17-H), 5.70 (1H, bdd, J = 11, 4 Hz, C7-H), 5.52 (1H, bd, J = 11 Hz, C6-H), 3.92 (1H, s, C2-H), 3.82 (3H, s, —OCH_3), 3.78 (3H, s, —OCH_3), 2.78 (3H, s, —NCH_3), 0.79 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 398 (M^+), 382, 338, 296, 224, 189, 136, 135, 121. *Mol. wt.* calcd. for $C_{23}H_{30}N_2O_4$: 398.2205; found (high resolution ms): 398.2183.

The Hydroxyester ***16***

(*a*) Hydroxylation of the ester **13** as described above for the preparation of **15**, gave **16** (32%); uv λ_{max}: 252 (3.73), 305 (3.64); ir ν_{max}: 3550 (br), 1725; ^{1}H nmr δ: 6.85 (1H, d, J = 8 Hz, C14-H), 6.18 (1H, dd, J = 8, 2 Hz, C15-H), 5.98 (1H, d, J = 2 Hz, C17-H), 3.87 (1H, s, C2-H), 3.84 (3H, s, —OCH_3), 3.78 (3H, s, —OCH_3), 2.78 (3H, s, —NCH_3), 0.68 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 400 (M^+), 298, 188, 174, 124. *Mol. wt.* calcd. for $C_{23}H_{32}N_2O_4$: 400.236; found (high resolution ms): 400.235.

(*b*) Oxygen gas was passed through a solution of the anion, prepared as in *a* above, for 18 h at ambient temperature. Work-up as before gave the hydroxyester **16** in 30% yield.

(*c*) The unsaturated derivative **15** was hydrogenated over 10% palladium-on-carbon catalyst in ethanol to give (80%) the ester **16** identical with that prepared above.

The 'Dimer' ***17***

Catharanthine **2** (88 mg) and *m*-CPBA (42 mg) were stirred in dry dichloromethane (1.5 ml) at −10 to −15°C for 30 min. The vindoline derivative **7** (50 mg) was added and the solution cooled to −50°C. Trifluoroacetic anhydride (0.13 ml) was added and the mixture stirred at −50°C for 4 h, poured into a cold solution of sodium borohydride in methanol, and extracted with dichloromethane. The extract was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel gave **17** (35 mg, 45%) as a colourless foam, uv λ_{max}: 263 (4.40), 287 (4.27), 295 (4.24), 311 (3.98); cd: 208 (−22.0), 221.5 (+12.2); ir ν_{max}: 1720, 1700; ^{1}H nmr δ: 8.07 (1H, s, —NH), 7.20 (4H, m, C4-H and indole aromatic —H), 6.54 (1H, s, C14-H), 6.02 (1H, s, C17-H), 5.6–6.0 (3H, m, C3′-H, C6-H, C7-H), 4.24 (1H, s, C2-H), 3.78 (6H, s, 2 × —OCH_3), 3.62 (3H, s, —OCH_3), 2.83 (3H, s, —NCH_3), 1.04 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.80 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e*: 716 (M^+), 657, 536, 534, 464, 451, 393, 380, 353, 336, 277, 237. *Mol. wt.* calcd. for $C_{44}H_{52}N_4O_5$: 716.3937; found (high resolution ms): 716.3948.

The Dimer ***18***

Similarly the ester **8** reacted with catharanthine *N*-oxide to give **18** in 30% yield; uv λ_{max}: 268 (4.31), 284 (4.21), 292 (4.14), 313 (3.87); cd: 207 (−17.4), 222 (+14.0); ir ν_{max}: 1720; ^{1}H nmr δ: 8.04 (1H, s, —NH), 7.10–7.20 (4H, m, C4-H, aromatic —H), 6.60 (1H, s, C14-H), 6.00 (1H, s, C17-H), 5.52 (1H, d, J = 6 Hz, C3-H), 4.24 (1H, s, C2-H), 3.80 (3H, s, —OCH_3), 3.77 (3H, s, —OCH_3), 3.58 (3H, s, —OCH_3), 2.86 (3H, s, —NCH_3), 1.00 (3H, t, J = 7 Hz, —CH_2CH_3), 0.82 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 718 (M^+), 704, 659, 593, 534, 464, 451, 393. *Mol. wt.* calcd. for $C_{44}H_{54}N_4O_5$: 718.4094; found (high resolution ms): 718.4109.

The 'Dimer' ***19***

Similarly, the amide **10** was reacted with catharanthine *N*-oxide to give **19** (36%); uv λ_{max}: 267 (4.38), 287 (4.26), 296 (4.17), 312 (3.96); cd: 207.5 (−28.2), 222 (+14.1); ir ν_{max}: 1720, 1660; ^{1}H nmr δ: 8.07 (1H, s, —NH), 6.62 (1H, s, C14-H), 6.36 (1H, s, C4-H), 6.03 (1H, s, C17-H), 5.5–6.0 (3H, m, C3′-H, C6-H, C7-H), 4.24 (1H, s, C2-H), 2.90 (3H, d, J = 6 Hz, —NHCH_3), 2.88 (3H, s, —NCH_3), 1.02 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.83 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 715 (M^+), 686, 656, 624, 534, 533, 393, 336. *Mol. wt.* calcd. for $C_{44}H_{53}N_5O_4$: 715.4096; found (high resolution ms): 715.4053.

The Dimer ***20***

Similarly the amide **11** gave **20** in 22% yield; uv λ_{max}: 261 (4.25), 287 (4.11), 296 (4.07), 312 (3.93); ir ν_{max}: 1720, 1660; ^{1}H nmr δ: 8.02 (1H, s, —NH), 6.60 (1H, s, C14-H), 6.20 (1H, s, C4-H), 5.98 (1H, s, C17-H), 5.50 (1H, m, C3-H), 4.27 (1H, s, C2-H), 3.76 (3H, s, —OCH_3), 3.57 (3H, s, —OCH_3), 2.90 (3H, d, J = 6 Hz, —NHCH_3), 2.87 (3H, s, —NCH_3), 0.99 (3H, t, J = 7 Hz, —CH_2CH_3), 0.86 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 717 (M^+), 688, 685, 660, 659, 658, 626, 594, 536, 535, 455, 394, 337, 278. *Mol. wt.* calcd. for $C_{44}H_{55}N_5O_4$: 717.4253; found (high resolution ms): 717.4209.

The Dimer ***21***

Similarly the hydroxyester **15** gave a 32% yield of **21**; uv λ_{max}: 272 (4.27), 286 (4.18), 295 (4.07), 317 (3.80); cd: 208 (−24.3), 222 (+27.7); ir ν_{max}: 3470, 1725; ^{1}H nmr δ: 8.14 (1H, s, —NH), 6.58 (1H, s, C14-H), 6.03 (1H, s, C17-H), 5.54 (3H, bs, C3-H, C6-H, C7-H), 3.84 (3H, s, —OCH_3), 3.80 (3H, s, —OCH_3), 3.58 (3H, s, —OCH_3), 2.81 (3H, s, —NCH_3), 0.88–1.08 (6H, m, 2 × —CH_2CH_3); ms *m/e*: 734 (M^+), 676, 675, 674, 616, 615, 495, 494. *Mol. wt.* calcd. for $C_{44}H_{54}N_4O_6$: 734.4042; found (high resolution ms): 734.4009.

The Dimer ***24***

Jones' reagent (0.5 ml) was added, at −78°C under an atmosphere of dry nitrogen, to a solution of leurosine (**34**) (50 mg) in acetic anhydride (1 ml) and acetone (6 ml). The mixture was stirred at this temperature for 1 h, diluted with concentrated ammonium hydroxide (10 ml), and allowed to warm to ca. 0°C. The mixture was partitioned between 5% sodium bisulphite solution and dichloromethane, the organic layer dried (Na_2SO_4), and concentrated *in vacuo*. Chromatography on silica gel gave 22-oxoleurosine (**24**) (38 mg, 75%), mp (methanol) 212–216°C; uv λ_{max}: 219 (4.68), 253 (4.20), 262 (4.15), 289 (4.18), 296 (4.22); ir ν_{max}: 3470, 1738, 1688; ^{1}H nmr δ: 8.80 and 8.20 (1H, 2 × bs, —NCHO), 8.01

(1H, bs —N*H*), 6.88 (2H, bs, C14-H, C17-H), 5.94 (1H, dd, J = 10, 4 Hz, C7-H), 5.44 (1H, d, J = 10 Hz, C6-H), 5.26 (1H, s, C4-H), 4.66 (1H, m, C2-H), 3.92 (3H, s, —OCH_3), 3.75 (3H, bs, —OCH_3), 3.71 (3H, s, —OCH_3), 2.09 (3H, s, —$OCOCH_3$), 1.62 (2H, q, J = 7.5 Hz, —CH_2CH_3), 0.97 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.84 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 822 (M^+), 820, 683, 588, 121 (100%), 106. *Mol. wt.* calcd. for $C_{46}H_{54}N_4O_{10}$: 822.3839; found (high resolution ms): 822.3806.

The Dimer ***25***

Similarly, 3′,4′-dehydrovinblastine (**4**) gave **25** in 80% yield; uv λ_{max}: 218 (4.69), 255 (4.20), 296 (4.20); ir ν_{max}: 3460, 1740, 1680; ^{1}H nmr δ: 8.80 (1H, bs, —NCHO), 8.10 (1H, bs, —NH), 6.90 (1H, s, C14-H), 5.93 (1H, m, C7-H), 5.25 (1H, s, C4-H), 5.36–5.58 (2H, m, C3′-H, C6-H), 3.91 (3H, s, —OCH_3), 3.76 (3H, s, —OCH_3), 3.68 (3H, s, —OCH_3), 2.06 (3H, s, —$OCOCH_3$), 1.00 (3H, t, J = 7 Hz, —CH_2CH_3), 0.82 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 806 (M^+), 355, 354, 169, 168, 150, 149, 136, 122, 121, 106, 77, 44, 43. *Mol. wt.* calcd. for $C_{46}H_{54}N_4O_9$: 806.3890; found (high resolution ms): 806.3931.

The Dimer ***27***

Similarly the amide **26** gave **27** (53%); ir ν_{max}: 3440, 1730, 1675; ^{1}H nmr δ: 8.80 and 7.92 (1H, 2 × bs, —NCHO), 8.19 (1H, s, —NH), 8.11 (1H, s, —NH), 6.89 (1H, s, C14-H), 5.96 (1H, m, C7-H), 5.7–5.2 (3H, m, C6-H, C4-H, and C3′-H), 4.60 and 4.22 (1H, 2 × s, C2-H), 3.92 (3H, s, —OCH_3), 3.71 (3H, s, —OCH_3), 2.04 (3H, s, —$OCOCH_3$), 1.04 (3H, t, J = 7 Hz, —CH_2CH_3), 0.76 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 805 (M^+), 749, 654, 595, 524, 466, 395, 393, 265, 149, 136, 135, 122, 121, 120, 108, 107, 106, 93, 92, 91, 79, 77, 69, 67, 65, 60, 57, 55, 51, 45, 44 (100%), 43. *Mol. wt.* calcd. for $C_{46}H_{55}N_5O_8$: 805.4049; found (high resolution ms): 805.4023.

The 'Dimer' ***29***

Similarly 4′-deoxyleurosidine (**28**) gave the formamide **29** (68%); uv λ_{max}: 218 (4.59), 248 (4.05), 294 (4.07); ir ν_{max}: 3420, 1730, 1680; ^{1}H nmr δ: 8.81 (1H, bs, —OH), 8.22 and 7.85 (1H, bs, —NCHO), 8.02 (1H, bs, —NH), 6.67 (1H, s, C14-H), 5.95 (1H, m, C7-H), 5.42 (1H, d, J = 10 Hz, C6-H), 5.24 (1H, s, C4-H), 4.77 and 4.52 (1H, bs, C2-H), 3.93 (3H, s, —OCH_3), 3.70 (3H, s, —OCH_3), 2.10 (3H, s, —$OCOCH_3$), 0.92 (3H, t, J = 7 Hz, —CH_2CH_3), 0.84 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 808 (M^+), 806, 782, 781, 780, 751, 750, 749, 650, 592, 591, 526, 524, 466, 464, 354, 353, 282, 281, 223, 209, 169, 168, 167, 149, 138, 125. *Mol. wt.* calcd. for $C_{46}H_{56}N_4O_9$: 808.4046; found (high resolution ms): 808.4064.

The 'Dimer' ***31***

Similarly, 3′,4′-dehydro-6,7-dihydrovinblastine (**30**) gave **31** (48%), mp 243–246°C; uv λ_{max}: 218 (4.70), 250 (4.21), 292 (4.12); ir ν_{max}: 3460, 1730, 1680; ^{1}H nmr δ: 8.15 (1H, bs, —NH), 6.69 (1H, s, C14-H), 6.15 (1H, m, C3-H), 5.38 (1H, s, C4-H), 3.94 (3H, s, —OCH_3), 3.81 (3H, s, —OCH_3), 3.70 3H, s, —OCH_3), 2.08 (3H, s, —$OCOCH_3$), 1.06 (3H, t, J = 7 Hz, —CH_2CH_3), 0.96 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 808 (M^+), 780, 750, 749, 732, 690, 658, 657, 511, 510, 509, 508, 480, 469, 468, 451, 395, 369, 356, 355, 284, 174, 149, 135, 124, 121, 120. *Mol. wt.* calcd. for $C_{46}H_{56}N_4O_9$: 808.4046; found (high resolution ms): 808.4039.

The 'Dimer' ***33***

Similarly 4′-deoxy-6,7-dihydroleurosidine (**32**) gave **33** in 63% yield; mp 198–201°C; uv λ_{max}: 218 (4.51), 248 (3.96), 292 (4.00); ir ν_{max}: 3480, 1730, 1680; ^{1}H nmr δ: 8.01 (1H, bs, —NH), 6.82 (1H, s, C14-H), 5.38 (1H, s, C4-H), 4.61 (1H, s, C2-H), 3.90 (3H, s, —OCH_3), 3.79 (3H, s, —OCH_3), 3.62 (3H, s, —OCH_3), 2.02 (3H, s, —$OCOCH_3$), 0.92 (6H, t, J = 7 Hz, 2 × —CH_2CH_3); ms *m/e*: 810 (M^+), 809, 808, 747, 732, 649, 524, 395, 394, 380, 353, 336, 256, 254, 252, 223, 185, 149, 135, 124, 122. *Mol. wt.* calcd. for $C_{46}H_{58}N_4O_9$: 810.4383; found (high resolution ms): 810.4371.

The 'Dimers' ***36*** *and* ***37***

(*a*) Similarly, 19′-oxoleurosine **35** gave:

(*i*) The 22-oxo derivative **36** (30%); uv λ_{max}: 217 (4.78), 258 (4.24), 280 (4.17), 288 (4.23), 296 (4.27); ir ν_{max}: 3478, 1740, 1678, 1645, 1600; ^{1}H nmr δ: 8.82 (1H, bs, —NCHO), 8.06 (1H, bs, —NH), 7.16 (1H, s, C17-H), 6.93 (1H, s, C14-H), 5.97 (1H, dd, J = 10, 4 Hz, C7-H), 5.47 (1H, d, J = 10 Hz, C6-H), 5.28 (1H, s, C4-H), 4.74 (2H, m, C2′-H, C2-H), 3.95 (3H, s, —OCH_3), 3.78 (3H, s, —OCH_3), 3.68 (3H, s, —OCH_3), 2.10 (3H, s, —$OCOCH_3$), 1.02 (3H, t, J = 7 Hz, —CH_2CH_3), 0.87 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 836 (M^+), 834, 820, 777, 761, 677, 661, 636, 121. *Mol. wt.* calcd. for $C_{46}H_{52}N_4O_{11}$: 836.3620; found (high resolution ms): 836.3686.

(*ii*) The secondary amine **37** (17%); uv λ_{max}: 212 (4.70), 224 sh (4.58), 252 (4.10), 279 (4.09), 286 (4.11) 294 (4.07), 314 sh (3.75); ir ν_{max}: 3476, 1735, 1645, 1620; ^{1}H nmr δ: 8.02 (1H, bs, —NH), 6.66 (1H, s, C14-H), 6.30 (1H, s, C17-H), 5.89 (1H, dd, J = 10, 3.5 Hz, C7-H), 5.57 (1H, s, C4-H), 5.34 (1H, d, J = 10 Hz, C6-H), 4.78 (2H, m, C2′-H, —NH), 4.19 (1H, bs, C2-H), 3.81 (6H, s, 2 × —OCH_3), 3.62 (3H, s, —OCH_3), 2.14 (3H, s, —$OCOCH_3$), 1.02 (3H, t, J = 7 Hz, —CH_2CH_3), 0.84 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 808 (M^+), 806, 749, 648, 296, 207, 174. *Mol. wt.* calcd. for $C_{45}H_{52}N_4O_{10}$: 808.3593; found (high resolution ms): 808.3618.

(*b*) Iodine (25 mg) was added to a mixture of 22-oxoleurosine (**24**) (34 mg) in THF (5 ml) and sodium bicarbonate (35 mg) in water (2 ml). The mixture was stirred vigorously at ambient temperature for 15 min, poured into saturated sodium bicarbonate solution, and extracted with dichloromethane. The extract was washed with 10% sodium bisulphite solution, dried (Na_2SO_4), and evaporated. Chromatography on silica gel gave **36** (24 mg, 67%).

*3′,4′-Dehydro-6,7-dihydrovinblastine (****30****)*

As described above for the preparation of **17**, dihydrovindoline gave **30** (33%); uv λ_{max}: 213 (4.70), 255 (4.15), 287 (4.10), 295 (4.08), 307 (3.80); cd: 210 (−34.3), 226 (+27.1), 257 (+21.7), 304 (+9.75); ir ν_{max}: 3465, 1735, 1730, 1710, 1610; ^{1}H nmr δ: 7.96 (1H, bs, —NH), 6.52 (1H, s, C14-H), 6.02 (1H, s, C17-H), 5.55 (1H, s, C4-H), 5.41 (1H, bd, J = 8 Hz, C3-H), 3.76 (3H, s, —OCH_3), 3.75 (3H, s, —OCH_3), 3.60 (1H, s, C2-H), 3.52 (3H, s, —OCH_3), 2.58 (3H, s, —NCH_3), 2.02 (3H, s, —$OCOCH_3$), 0.92 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.73 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 794 (M^+), 736, 735, 734, 370, 284, 136, 135, 124, 121 (100%), 120. *Mol. wt.* calcd. for $C_{46}H_{58}N_4O_8$: 794.4254; found (high resolution ms): 794.4275.

*6,7-Dihydroleurosine (****39****)′*

tert-Butyl hydroperoxide (0.3 ml) was added to a solution of **30** (60 mg) in dry THF (3 ml) containing 1% aqueous trifluoroacetic acid (0.3 ml). The solution was stirred at ambient temperature for 9 h, diluted with methanol (1 ml), and partitioned between saturated sodium bicarbonate solution and dichloromethane. The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel gave **39** (25 mg, 41%) as a clear glass; uv λ_{max}: 213 (4.68), 260 (4.12), 284 (4.03), 294 (4.00), 310 (3.75); ir ν_{max}: 3478, 1738, 1612; ^{1}H nmr δ: 8.03 (1H, bs, —NH), 6.57

(1H, s, C14-H), 6.13 (1H, s, C17-H), 5.64 (1H, s, C4-H), 3.84 (3H, s, $-OCH_3$), 3.82 (3H, s, $-OCH_3$), 3.73 (1H, s, C2-H), 3.62 (3H, s, $-OCH_3$), 2.68 (3H, s, $-NCH_3$), 2.12 (3H, s, $-OCOCH_3$), 0.98 (3H, t, $J = 7.5$ Hz, $-CH_2CH_3$), 0.82 (3H, t, $J = 7$ Hz, $-CH_2CH_3$); ms *m/e*: 810 (M^+), 808, 671, 453, 106 (100%). *Mol. wt.* calcd. for $C_{46}H_{58}N_4O_9$: 810.4203; found (high resolution ms): 810.4203.

The 'Dimer' 38

Oxidation of **39**, as described above for the preparation of **24**, gave **38** (72%), mp (methanol) 202–205°C; uv λ_{max}: 218 (4.68), 252 (4.20), 287 (4.18), 296 (4.22); ir ν_{max}: 3478, 1738, 1687; ^{1}H nmr δ: 8.00 (1H, bs, —NH), 6.82 (1H, s, C17-H), 5.40 (1H, s, C4-H), 4.67 (1H, bs, C2-H), 3.92 (3H, s, $-OCH_3$), 3.81 (3H, s, $-OCH_3$), 3.66 (3H, s, $-OCH_3$), 2.08 (3H, s, $-OCOCH_3$), 0.99 (6H, t, $J = 7$ Hz, $2 \times -CH_2CH_3$); ms *m/e*: 824 (M^+), 686, 658, 138, 124 (100%), 106. *Mol. wt.* calcd. for $C_{46}H_{56}N_4O_{10}$: 824.3995; found (high resolution ms): 824.3955.

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