35. Total Synthesis of Indole and Dihydroindole Alkaloids. XVIII[1]). Isomers and Analogues of Vinblastine

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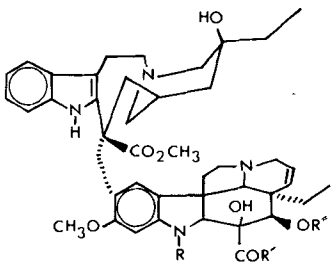
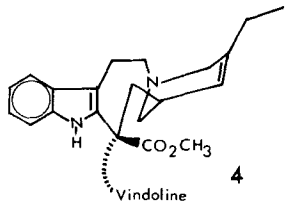
Summary

The synthesis and conformational analysis of (3′*R*)-3-hydroxyleurosidine (**5**), (3′*S*)-3-hydroxyleurosidine (**10**), (3′*S*)-3-acetoxy-4′-deoxyleurosidine (**15**), (3′*R*)-3-acetoxy-4′-deoxyleurosidine (**23**), (3′*R*)-3-acetoxy-4′-deoxyvinblastine (**16**), (3′*S*)-3-acetoxy-4′-deoxyvinblastine (**28**) is discussed.

The *Catharanthus* alkaloids vinblastine (**1**) and vincristine (**2**) are well established as clinically important drugs in the treatment of various cancers in humans. The toxic effects which limit their usage are also well known [2]. Considerable effort, from several laboratories, has been expended towards new agents with superior clinical utility. To this end, vindesine (**3**) [3], a vinblastine amide derivative, has already reached clinical trials while others are at present in preclinical stages. The present work describes the preparation and properties of some isomers and analogues of **1**, characterized by oxygenation of the piperidine ring.



1 R = CH_3, R′ = OCH_3, R″ = A_c
2 R = CHO, R′ = OCH_3, R″ = A_c
3 R = CH_3, R′ = NH_2, R″ = H



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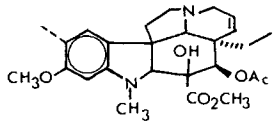

Vindoline

[1]) Part XVII: [1].

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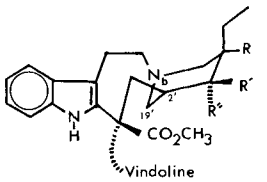
The synthetic olefin (**4**) [4] [5] provided entry into a series of alcohols and glycols at C(3′)/C(4′). Initially, osmylation gave the *cis*-glycol, (3′*R*)-3-hydroxyleurosidine (**5**). Optimisation of the earlier procedure [6] gave a 60% yield of **5**, exemplifying characteristic least hindered approach to the piperidine ring (*cf.* epoxidation to leurosine (**6**) [6]). It seemed likely that the corresponding 3′-thioxobenzoate [7] might be deoxygenated to yield leurosidine (**7**) [8], however reaction of **5** with *N,N*-dimethylphenylchloroimidoyl chloride and subsequent treatment with hydrogen sulfide gave the benzoate **8**, presumably *via* participation of the hydroxyl at C(4′). *Moffatt* oxidation of **5** gave the corresponding ketol **9** which on reduction with sodium borohydride gave the *trans*-glycol, (3′*S*)-3-hydroxyleurosidine (**10**). Attempts, as above, to prepare the corresponding thioxobenzoate were again unsuccessful, however reaction of **10** with thioxobenzoyl chloride [9] in dry pyridine gave the required derivative **11**. Similarly the *cis*-glycol **5** afforded **12**.

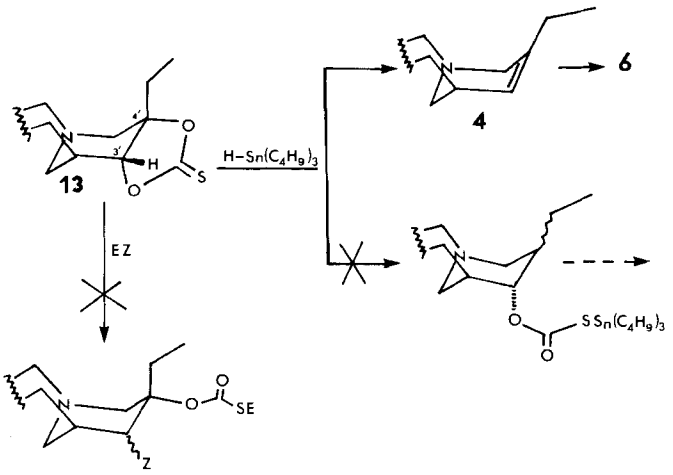


Vindoline

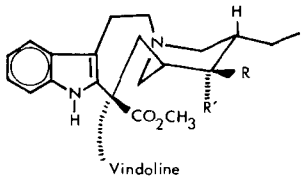
5 R = R″ = OH, R′ = H
6 R,R″ = –O–, R′ = H
7 R = OH, R′ = R″ = H
8 R = OH, R′ = H, R″ = $OCOC_6H_5$
9 R = OH, R′R″ = O
10 R = R′ = OH, R″ = H
11 R = OH, R′ = $OCSC_6H_5$, R″ = H
12 R = OH, R′ = H, R″ = $OCSC_6H_5$
13 R,R″ = –OCSO–, R′ = H
14 R = R′ = H, R″ = OH
15 R = R′ = H, R″ = OA_c
17 R = R′ = H, R″ = $OCSC_6H_5$
18 R = R′ = R″ = H
20 R = H, R′R″ = O
21 R = R′ = H, R″ = $OCOCOC_6H_5$
22 R = R″ = H, R′ = OH
23 R = R″ = H, R′ = OA_c

The thiocarbonyl compound **11** proved quite resistant to normal reducing conditions (*e.g.* tributylstannane, chromous ion, *Raney*-nickel) while under forcing conditions (*i.e.* elevated temperatures, prolonged reaction times) decomposition was apparent. On the other hand reaction of **12** with either tributylstannane in refluxing toluene, or *Raney*-nickel in ethanol gave the starting olefin **4** and/or leurosine **6**, the latter presumably by aerial oxidation of **4** during work-up. Leurosidine **7** was not detected in any of these attempted deoxygenations. The *cis*-glycol **5** readily formed a thioxocarbonate **13** which also reacted with tributylstannane to give a mixture of **4** and **6**. The expected secondary alcohol(s) arising from C(4′),O-cleavage and radical capture by a H-atom was not observed. Attempts to displace the oxygen substituent from C(3′) using various *Lewis* acid-base pairs (*e.g.* CH_3I, $HgCl_2$, $(C_2H_5)_3SiH$, $(C_2H_5)_3SiH/CH_3OCOF$, HCO_2H, $ClCO_2CH_3$) were unsuccessful, in fact the thioxocarbonate seemed remarkably stable.

Alternatively, hydroboration/oxidation of **4** gave a secondary alcohol **14** which readily formed an acetate **15**. This product was originally assigned structure **16** [10] on the basis of its ^{1}H-NMR. spectrum where C(3′)–H resonated as a doublet at δ 4.26 with $J = 9$ Hz. Although this structure was consistent with the spectral data it did necessitate sterically unfavoured approach of the reagent to **4** during hydro-

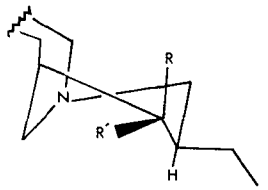


boration. Structure **14**, on the other hand, would arise *via* favoured steric approach by borane. Unambiguous confirmation of the structure as **14** was available by deoxygenation *via* the derived thioxobenzoate **17**. Thus reaction of **17** with tributylstannane in refluxing toluene gave 4′-deoxyleurosidine (**18**) identical with an authentic sample of the natural product. The epimer, 4-deoxyvinblastine (**19**) was not detected.



16 R = OA_c, R′ = H
19 R = R′ = H
24 R, R′ = O
25 R = OH, R′ = H
28 R = H, R′ = OA_c

Hydroboration/oxidation of **4** to give (3′*S*)-4′-deoxy-3′-hydroxyleurosidine (**14**) was consistent with the steric control of the system but still not readily justified from the spectral data of the derived acetate **15**. Examination of a *Dreiding* model of **15** showed very severe 1,3-diaxial steric crowding between the axial substituents at C(2′), C(4′) and Nb in the chair conformation and that the necessary, torsional, strain at C(2′), C(19′) and Nb would probably prevent formation of the alternative chair. The twist boat conformation **15a** however, seems relatively free of steric encumbrance and quite readily formed. Furthermore the ^{1}H-NMR. spectrum was consistent with a conformation **15a** where C(3′)–H is *trans*-diaxial to C(4′)–H and disposed to C(2′)–H with a dihedral angle of *ca.* 90°.



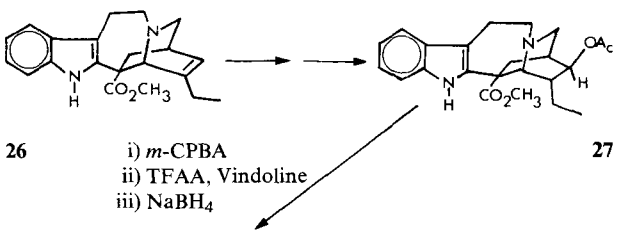
15a R = H, R' = OA_c
23a R = OA_c, R' = H

The observed chemical shift (δ 4.26) for H–C(3') is also consistent with a pseudo-axial proton. Similar conformational arguments may be applied to the glycols **5** and **10**, their derivatives, and predicted for other compounds in this series where the ethyl group at C(4') is oriented β to the piperidine ring. This argument was further investigated by preparing the complete series of C(3')-acetates, with the alternative orientations of the C(4')-ethyl group.

Moffatt oxidation of **14** gave the corresponding ketone **20**, whereas the phenylglyoxylate **21** (^{1}H-NMR. doublet absorption for H–C(3') was observed at δ 4.56 with J = 9 Hz) could not be induced to give **20**. Reduction of the ketone **20** with sodium borohydride gave the epimeric alcohol, (3'*R*)-4'-deoxy-3'-hydroxyleurosidine (**22**) which readily formed an acetate **23** but not a thioxobenzoate. The ^{1}H-NMR. spectrum of **23** showed resonance for H–C(3') as a broad signal at δ 5.10 ($W_{1/2}$ *ca.* 15 Hz) compatible with the conformation **23a**.

Attempts to epimerise **20**, at C(4'), using acid (*e.g. p*-toluenesulfonic acid, acetic acid) or base (pyridine, triethylamine) were unsuccessful as were efforts to form an enol acetate. Reaction of **20** with dimethylamine [11] in a sealed tube gave approximately equal amounts of **20** and the epimer **24**. The two ketones were separated by reverse phase high performance liquid chromatography (HPLC.).

Reduction of 4'-deoxy-3'-oxovinblastine (**24**) with sodium borohydride gave, as the major product, (3'*R*)-4'-deoxy-3'-hydroxyvinblastine (**25**), characterized as its acetate **16** [12]. The expected chair conformation for this product was confirmed by the ^{1}H-NMR. spectrum. Here H–C(3') resonated as a double doublet at δ 4.39 with J = 11 and 5 Hz [12], compatible with an axial proton, *trans*-diaxial to H–C(4') and disposed to H–C(2') with a dihedral angle of *ca.* 60°.



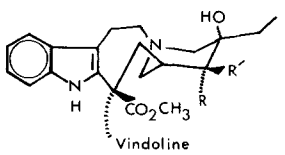
26 **27**

i) *m*-CPBA
ii) TFAA, Vindoline
iii) $NaBH_4$

28 and other products

Three of the four possible 3′-acetoxy compounds were now in hand and the fourth was prepared as shown below. Hydroboration/oxidation and subsequent acetylation of catharanthine (**26**) yielded the necessary precursor **27** [13]. Modified *Polonovski* coupling with vindoline gave a low yield (11%) of the (3′*S*)-acetate **28**, identical with that obtained by acetylation of the minor product (*ca.* 5%) from the reduction of the ketone **24**. The ^{1}H-NMR. spectrum of **28** was again compatible with the chair conformation shown. H–C(3′) absorbed as a broad singlet at δ 4.73, consistent with an equatorial proton disposed at *ca.* 60° to H–C(4′) and at 60° to H–C(2′). The four 3′-acetoxy compounds **15**, **16**, **23** and **28** now available could be distinguished by HPLC.

The two glycols **5** and **10** now supplement the naturally occurring vincadiolines (**29**) and (**30**) and, together with vinblastine (**1**), leurosidine (**7**) and the compounds prepared here provide all of the possible alcohols and glycols at C(3′)/C(4′) for meaningful structure/activity determinations. The conformational effects discussed above may also be responsible, at least in part, for the differences in activity between the alkaloids: vinblastine (**1**), leurosidine (**7**), leurosine (**6**), 4′-deoxyleurosidine (**18**) and 4′-deoxyvinblastine (**19**).



29 R = OH, R′ = H
30 R = H, R′ = OH

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Experimental Part

M.p. (uncorrected) were determined on a *Kofler* block. UV. spectra were recorded on a *Cary* 15 spectrophotometer (λ_{max}: nm ($\log \varepsilon$)). IR. spectra were measured on a *Perkin-Elmer* model 710 or 457 spectrophotometer. The absorption maxima (cm^{-1}) were calibrated with respect to the absorption band of polystyrene at 1610 cm^{-1}. ^{1}H-NMR. spectra were measured at RT. on a *Varian* HA-100 or XL-100 or on a 270 MHz or 400 MHz spectrometer. Chemical shift values δ (ppm) are relative to tetramethylsilane used as internal reference (coupling constants: *J* Hz). Low resolution MS. were determined on either an *AEI* MS-902 or an *Atlas* CH-4B spectrometer. High resolution MS. (M) 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 was carried out using *Merck* silica gel G plates containing 2% fluorescent indicator. For preparative layer chromatography, plates of 1 mm thickness were used. Visualisation was effected by viewing under UV. light and/or by colour reaction with ceric sulfate

spray reagent. Column chromatography utilised *Merck* silica gel 60 (70–230 mesh) of *Merck* aluminium oxide 90 (neutral). High pressure liquid chromatography was carried out using *Waters Associates LC.* equipment on a μ Bondapak C_{18} column.

Reagents and solvents were recrystallized or distilled prior to use. *3'-oxoleurosidine* (**9**). The glycol **5** (82 mg) was dissolved in a mixture of anhydrous DMSO (0.3 ml), benzene (0.3 ml), pyridine (16 mg) and trifluoroacetic acid (TFA) (11.4 mg). *N,N*-Dicyclohexylcarbodiimide (DCC) (62 mg) was added and the mixture stirred at RT. for 20 h. The mixture was diluted with ethyl acetate, filtered, washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel gave the ketol **9** (44 mg, 54%). – UV. (MeOH): 269 (4.10), 286 (4.04), 295 (4.01), 312 (sh. 3.75). – IR. ($CHCl_3$): 3500, 1740, 1690, 1660, 1620. – ^{1}H-NMR. ($CDCl_3$): 8.08 (*s*, 1H, NH); 7.57 (*m*, 1H, H–C(14')); 6.57 (*s*, 1H, H–C(14)); 6.16 (*s*, 1H, H–C(17)); 5.88 (*d*×*d*, *J*=10 and 4, H–C(7)); 5.50 (*s*, 1H, H–C(4)); 5.33 (*d*, *J*=10, 1H, H–C(6)); 4.15 (br. *s*, 1H, H–C(2')); 3.84 (*s*, 6H, 2 OCH_3); 3.82 (*s*, 1H, H–C(2)); 3.62 (*s*, 3H, OCH_3); 2.74 (*s*, 3H, NCH_3); 2.11 (*s*, 3H, $OCOCH_3$); 0.92 (*t*, *J*=7.5, 3H, CH_2CH_3); 0.82 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 824 (M^+), 806, 795, 780, 766, 748, 747, 647, 645, 610, 538, 510, 509, 480, 478, 469. – Mol-wt.: 824.4014, $C_{46}H_{56}N_4O_{10}$ (824.3995).

(3'S)-3-hydroxyleurosidine (**10**). Sodium borohydride (10 mg) was added to a solution of the ketol **9** (20 mg) in $CHCl_3$ (2 ml) and methanol (2 ml) at 0°. After 30 min, the solvents were removed *in vacuo* and the residue extracted with $CHCl_3$. The solution was dried (Na_2SO_4), filtered and evaporated. Chromatography on silica gel gave the *trans*-glycol **10** (18 mg, 90%). – UV. (MeOH): 257 (4.07), 285 (4.00), 294 (3.96), 305 (sh. 3.81). – IR. ($CHCl_3$): 3650, 3520, 1745, 1665, 1620. – ^{1}H-NMR. ($CDCl_3$): 8.11 (*s*, 1H, NH); 6.51 (*s*, 1H, H–C(14)); 6.15 (*s*, 1H, H–C(17)); 5.88 (*d*×*d*, *J*=10 and 4, 1H, H–C(7)); 5.48 (*s*, 1H, H–C(4)); 5.32 (*d*, *J*=10, 1H, H–C(6)); 3.83 (*s*, 3H, OCH_3); 3.81 (*s*, 3H, OCH_3); 3.77 (*s*, 1H, H–C(2)); 3.65 (*s*, 3H, OCH_3); 2.74 (*s*, 3H, NCH_3); 2.11 (*s*, 3H, $OCOCH_3$); 1.01 (*t*, *J*=7.5, 3H, CH_2CH_3); 0.80 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 826 (M^+), 807, 767, 766, 749, 748, 747, 647, 645, 612, 610, 511, 510. – Mol-wt.: 826.4183, $C_{46}H_{58}N_4O_{10}$ (826.4152).

Thioxobenzoate **11**. The glycol **10** (50 mg) and thiobenzoyl chloride (60 mg) were stirred in dry pyridine (3 ml) at RT. for 20 h. The mixture was diluted with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel gave **11** (32 mg, 56%). – UV. (MeOH): 259 (4.11), 288 (4.05), 295 (4.03), 310 (sh. 3.83). – IR. ($CHCl_3$): 3525, 1730, 1620. – ^{1}H-NMR. ($CDCl_3$): 8.30 (*s*, 1H, NH); 8.1–8.2 (*m*, 2H, ar. H); 7.4–7.6 (*m*, 4H, ar. H); 6.56 (*s*, 1H, H–C(14)); 6.18 (*s*, 1H, H–C(17)); 5.58 (*s*, 1H, H–C(4)); 5.56 (br. *d*, *J*=10, H–C(7)); 5.27 (*d*, *J*=10, 1H, H–C(6)); 4.08 (*s*, 1H, H–C(3')); 3.84 (*s*, 3H, OCH_3); 3.78 (*s*, 3H, OCH_3); 3.66 (*s*, 3H, OCH_3); 2.90 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 0.98 (*t*, *J*=7, 3H, CH_2CH_3); 0.64 (*t*, *J*=7.5, 3H, CH_2CH_3). – MS.: 946 (M^+), 944, 930, 928, 912, 911, 910, 899, 853, 851, 773, 730, 715, 714, 672, 671, 615, 614, 573. – Mol-wt.: 946.4163, $C_{53}H_{62}N_4O_{10}S$ (946.4186).

Thioxobenzoate **12**. In a similar fashion, the *cis*-glycol **5** gave a 59% yield of **12**. – UV. (MeOH): 262 (4.23), 285 (4.17), 295 (4.12), 308 (3.89). – IR. ($CHCl_3$): 3500, 1725, 1615. – ^{1}H-NMR. ($CDCl_3$): 8.18 (*s*, 1H, NH); 8.0–8.1 (*m*, 2H, ar. H); 7.4–7.6 (*m*, 4H, ar. H); 6.46 (*s*, 1H, H–C(14)); 6.08 (*s*, 1H, H–C(17)); 5.50 (*s*, 1H, H–C(4)); 5.47 (br. *d*, *J*=10, 1H, H–C(7)); 5.21 (*d*, *J*=10, 1H, H–C(6)); 4.08 (*s*, 1H, H–C(3')); 3.76 (*s*, 3H, OCH_3); 3.70 (*s*, 3H, OCH_3); 3.63 (*s*, 1H, H–C(2)); 3.56 (*s*, 3H, OCH_3); 2.84 (*s*, 3H, NCH_3); 2.06 (*s*, 3H, $OCOCH_3$); 0.93 (*t*, *J*=7, 3H, CH_2CH_3); 0.54 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 946 (M^+), 945, 944, 928, 926, 887, 886, 834, 833, 832, 748, 747, 746, 648, 647, 634, 631, 589, 588. – Mol-wt.: 946.4212, $C_{53}H_{62}N_4O_{10}S$ (946.4186).

Reduction of the thioxobenzoate **12**. a) A mixture of **12** (50 mg) and *Raney*-Ni (500 mg of ethanol slurry) was heated in refluxing ethanol for 4 h. The mixture was cooled, filtered and concentrated *in vacuo*. Chromatography on silica gel gave leurosine (**6**) (6 mg) and **4** (4 mg), identical with authentic samples.

b) A solution of tributylstannane (100 mg) in toluene (2 ml) was added, slowly, to a solution of **12** (50 mg) in toluene (2 ml) at 100°. The solution was maintained at this temperature, under N_2 for 5 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel to give leurosine (**6**) (7 mg) and **4** (11 mg), identical with authentic samples.

Thioxocarbonate **13**. The glycol **5** (83 mg) and *N,N'*-thiocarbonyldiimidazole (89 mg) were heated in refluxing 2-butanone (5 ml) for 5 h. The solution was cooled, diluted with ethyl acetate, washed with 5% Na_2CO_3-solution, dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave **13** (74 mg, 85%), m.p. 219–220°. – UV. (MeOH): 260 (4.23), 286 (4.14), 295 (4.08), 312 (sh. 3.68). – IR.

($CHCl_3$): 3450, 1720, 1650. – ^{1}H-NMR. ($CDCl_3$): 8.06 (*s*, 1H, NH); 6.62 (*s*, 1H, H–C(14)); 6.14 (*s*, 1H, H–C(17)); 5.89 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.52 (*s*, 1H, H–C(4)); 5.33 (*d*, *J*= 10, 1H, H–C(6)); 4.17 (br. *s*, 1H, H–C(3′)); 3.84 (*s*, 6H, 2 OCH_3); 3.62 (*s*, 3H, OCH_3); 2.78 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 1.14 (*t*, *J*= 7.5, 3H, CH_2CH_3); 0.85 (*t*, *J*= 7.5, 3H, CH_2CH_3). – MS.: 868 (M^+), 809, 792, 709, 708, 707, 671, 631, 601, 277. – Mol-wt.: 868.3740, $C_{47}H_{56}N_4O_{10}S$ (868.3717).

$C_{47}H_{56}N_4O_{10}S \cdot CH_3OH$	Calc.	C 63.98	H 6.71	N 6.22 S 3.56%
	Found	„ 64.12	„ 6.70	„ 6.08 „ 3.38%

(3′S)-4′-deoxy-3′-hydroxyleurosidine (**14**). A 1M solution of diborane in THF (3.5 ml) was added over 5 min to a solution of 3′,4′-dehydrovinblastine (**4**) (400 mg) in dry, freshly distilled THF at 0°, and then stirred at RT. under N_2 for 1.5 h. The mixture was cooled to 0°, followed by the addition of methanol (4 ml), 1M NaOH (1.2 ml), and 30% hydrogen peroxide (0.8 ml). This mixture was stirred at RT., under N_2, for about 1.5 h. The solvents were removed in vacuum, and the residue partitioned between water and CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. The residue, dissolved in THF (20 ml, containing 3 drops of triethylamine), was treated with Amberlyst A21 resin (4 g), and heated at reflux under N_2 for about 0.5 h. The mixture was cooled, filtered, the resin washed with CH_2Cl_2, and the combined filtrates evaporated. Column chromatography on silica gel gave **14** (191 mg, 47%) as an amorphous solid. – UV. (EtOH): 214, 259, 285, 294. – IR. ($CHCl_3$): 3490, 1738, 1619, 1236. – ^{1}H-NMR. ($CDCl_3$): 7.90 (br. *s*, 1H, NH); 7.48 (*m*, 1H, H–C(14′)); 7.22 (*m*, 3H, H–C(11′,12′,13′)); 6.47 (*s*, 1H, H–C(17)); 6.04 (*s*, 1H, H–C(14)); 5.82 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.40 (*s*, 1H, H–C(4)); 5.26 (*d*, *J*= 10, 1H, H–C(6)); 3.74 (*s*, 3H, OCH_3); 3.72 (*s*, 3H, OCH_3); 3.69 (*s*, 1H, H–C(2)); 3.53 (*s*, 3H, OCH_3); 2.64 (*s*, 3H, NCH_3); 2.02 (*s*, 3H, $OCOCH_3$); 0.90 (*t*, *J*= 7.5, 3H, CH_2CH_3); 0.74 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 810 (M^+), 792, 779, 751, 733, 651, 633, 571, 543, 512, 510, 469, 403, 381, 355, 354, 282, 225, 154, 135, 121. – Mol-wt.: 810.4234, $C_{46}H_{58}N_4O_9$ (810.4189).

(3′S)-3-acetoxy-4′-deoxyleurosidine (**15**). Acetylation of **14** with acetic anhydride and pyridine at –10° for 12 h gave (79%) the acetate **15**. – UV. (MeOH): 214, 259, 285, 294. – IR. ($CHCl_3$): 3460, 1730, 1610. – ^{1}H-NMR. ($CDCl_3$): 8.06 (br. *s*, 1H, NH); 6.52 (*s*, 1H, H–C(17)); 6.14 (*s*, 1H, H–C(14)); 5.90 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.45 (*s*, 1H, H–C(4)); 5.35 (*d*, *J*= 10, 1H, H–C(6)); 4.26 (*d*, *J*= 9, 1H, H–C(3′)); 3.89 (*s*, 3H, OCH_3); 3.80 (*s*, 3H, OCH_3); 3.65 (*s*, 3H, OCH_3); 2.70 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 1.80 (*s*, 3H, $OCOCH_3$); 0.92 (*t*, *J*= 7, 3H, CH_2CH_3); 0.82 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 852 (M^+), 821, 793, 792, 733, 693, 692, 633, 585, 420. – Mol-wt.: 852.4326, $C_{48}H_{60}N_4O_{10}$ (852.4304).

Thioxobenzoate **17**. A solution of *N*,*N*-dimethylphenylchloroimidoyl chloride (from *N*,*N*-dimethylbenzamide (120 mg) and phosgene (1 ml of 12.5% solution in benzene)) in CH_2Cl_2 (1 ml) was added to a solution of the alcohol **14** (54 mg) in dry THF (1 ml). The mixture was stirred at RT. for 5 h, diluted with CH_2Cl_2 (2 ml) and pyridine (½ ml) and treated, at 0°, with hydrogen sulfide gas for 10 min. The mixture was stirred, at 0–5° for 30 min, further diluted with CH_2Cl_2, washed with saturated $NaHCO_3$-solution, dried (Na_2SO_4) and concentrated *in vacuo*. Chromatography on silica gel gave **17** (35 mg, 56%) as a bright yellow glass. – UV. (EtOH): 214, 247, 287, 295. – IR. ($CHCl_3$): 3460, 1740, 1620. – ^{1}H-NMR. ($CDCl_3$): 6.50 (*s*, 1H, H–C(14)); 6.14 (*s*, 1H, H–C(17)); 5.88 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.40 (*s*, 1H, H–C(4)); 5.36 (*d*, *J*= 10, 1H, H–C(6)); 5.14 (*d*, *J*= 9, 1H, H–C(3′)); 3.94 (*s*, 3H, OCH_3); 3.80 (*s*, 3H, OCH_3); 3.66 (*s*, 3H, OCH_3); 2.60 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 0.96 (*t*, *J*= 7, 3H, CH_2CH_3); 0.82 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 930 (M^+), 792. – Mol-wt.: 930.4269, $C_{53}H_{62}N_4SO_9$ (930.4233).

Reduction of **17**. Tributylstannane (10 µl) was added to a refluxing solution of **17** (40 mg) in toluene (10 ml). After 30 min a further 5 µl of tributylstannane were added and heating continued. One further such addition was made and after a total of 3 h the mixture cooled and concentrated under reduced pressure. Chromatography on silica gel gave 4′-deoxyleurosidine (**18**) (25 mg) identical with an authentic sample.

4′-Deoxy-3′-oxoleurosidine (**20**). The alcohol **14** (337 mg) was treated with a solution of pyridine (135 mg) and TFA (101 mg) in dry benzene (3.3 ml). DMSO (3.3 ml) followed by DCC (421 mg) were added, and the resulting mixture was stirred at RT. under N_2 with the exclusion of light. After 22 h DCC (300 mg) was added, and the mixture stirred for a further 6 h. A solution of oxalic acid (433 mg) in methanol (10 ml) was added, and the mixture stirred under N_2 for 0.5 h, filtered, and then partitioned between saturated Na_2CO_3-solution and CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Column chromatography on silica gel gave **20** (260 mg, 77%) as an amorphous solid. –

UV. (EtOH): 214, 261, 286, 294. – IR. ($CHCl_3$): 3490, 1740, 1620. – ^{1}H-NMR. ($CDCl_3$): 8.05 (br. *s*, 1H, NH); 7.56 (*m*, 1H, H–C(14′)); 7.20 (*m*, 3H, H–C(11′,12′,13′)); 6.55 (*s*, 1H, H–C(17)); 6.16 (*s*, 1H, H–C(14)); 5.89 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.48 (*s*, 1H, H–C(4)); 5.33 (*d*, *J*= 10, 1H, H–C(6)); 3.87 (*s*, 3H, OCH_3); 3.82 (*s*, 3H, OCH_3); 3.76 (*s*, 1H, H–C(2)); 3.64 (*s*, 3H, OCH_3); 2.73 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 0.95 (*t*, *J*= 7, 3H, CH_2CH_3); 0.83 (*t*, *J*= 8, 3H, CH_2CH_3). – MS.: 808 (M^+), 777, 749, 747, 731, 730, 701, 689, 673, 672, 671, 647, 540, 538, 480, 407, 393, 381, 380, 379, 366, 293, 291, 279, 278, 224, 214, 168, 152, 143, 135, 122, 121. – Mol-wt.: 808.4093, $C_{46}H_{56}N_4O_9$ (808.4043).

Phenylglyoxylate (**21**). The alcohol **14** (50 mg) and phenylglyoxalyl chloride (15 µl) were stirred in a mixture of benzene (4 ml) and CH_2Cl_2 (2 ml) at RT. for 4 h. The solvents were removed under reduced pressure and the residue chromatographed on silica gel to give **21** (41 mg, 71%). – IR. ($CHCl_3$): 3460, 1730, 1680, 1610. – ^{1}H-NMR. ($CDCl_3$): 8.06 (br. *s*, 1H, NH); 6.56 (*s*, 1H, H–C(14)); 6.08 (*s*, 1H, H–C(17)); 5.88 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.44 (*s*, 1H, H–C(4)); 5.38 (*d*, *J*= 10, 1H, H–C(6)); 4.56 (*d*, *J*= 9, 1H, H–C(3′)); 3.88 (*s*, 3H, OCH_3); 3.78 (*s*, 3H, OCH_3); 3.65 (*s*, 3H, OCH_3); 2.57 (*s*, 3H, NCH_3); 2.10 (*s*, 3H, $OCOCH_3$); 0.92 (*t*, *J*= 7, 3H, CH_2CH_3); 0.82 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 942 (M^+), 940, 792, 733, 669, 633, 631. – Mol-wt.: 942.4495, $C_{54}H_{62}N_4O_{11}$ (942.4414).

*(3′*R*)-4′-Deoxy-3′-hydroxyleurosidine* (**22**). Sodium borohydride (15 mg) was added to a solution of **20** (22 mg) in methanol/$CHCl_3$ 6:1 (3.5 ml) at – 10°. The mixture was stirred at RT. for 30 min, poured into saturated Na_2CO_3-solution and extracted with CH_2Cl_2. The organic phase was washed with brine, dried (Na_2SO_4) and evaporated to give an almost quantitative yield of **22**. – UV. (EtOH): 259, 285, 294. – IR. ($CHCl_3$): 3480, 1735, 1620, 1235. – ^{1}H-NMR. ($CDCl_3$): 8.15 (*s*, 1H, NH); 6.37 (*s*, 1H, H–C(17)); 6.12 (*s*, 1H, H–C(14)); 5.89 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.43 (*s*, 1H, H–C(4)); 5.32 (*d*, *J*= 10, 1H, H–C(6)); 4.15 (poorly resolved *d*, *J*= *ca.* 6, 1H, H–C(3′)); 3.84 (*s*, 3H, OCH_3); 3.81 (*s*, 3H, OCH_3); 3.78 (*s*, 1H, H–C(2)); 3.68 (*s*, 3H, OCH_3); 2.75 (*s*, 3H, NCH_3); 2.65 (*s*, 1H, H–C(19)); 2.12 (*s*, 3H, $OCOCH_3$); 0.97 (*t*, *J*= 7.5, 3H, CH_2CH_3); 0.79 (*t*, *J*= 7.5, 3H, CH_2CH_3). – Mol.-wt.: 810.4199, $C_{46}H_{58}N_4O_9$ (810.4189).

*(3′*R*)-3-Acetoxy-4′-deoxyleurosidine* (**23**). Acetylation of **22** as described above gave **23**. – IR. ($CHCl_3$): 3460, 1730, 1615. – ^{1}H-NMR. ($CDCl_3$): 8.14 (br. *s*, 1H, NH); 6.46 (*s*, 1H, H–C(14)); 6.12 (*s*, 1H, H–C(17)); 5.92 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.46 (*s*, 1H, H–C(4)); 5.37 (*d*, *J*= 10, 1H, H–C(6)); 5.10 (*m*, 1H, H–C(3′)); 3.84 (*s*, 3H, OCH_3); 3.82 (*s*, 3H, OCH_3); 3.68 (*s*, 3H, OCH_3); 2.79 (*s*, 3H, NCH_3); 2.20 (*s*, 3H, $OCOCH_3$); 2.15 (*s*, 3H, $OCOCH_3$); 0.92 (*t*, *J*= 7, 3H, CH_2CH_3); 0.86 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 852 (M^+), 850, 819, 791, 790, 789, 731, 729, 689. – Mol-wt.: 852.4309, $C_{48}H_{60}N_4O_{10}$ (852.4294).

4′-Deoxy-3′-oxovinblastine (**24**). The ketone **20** (117 mg) in dimethylamine (1 ml) was kept in a sealed tube at RT. for 24 h. The solvent was allowed to evaporate and the residue chromatographed by HPLC. on a reverse phase column using acetonitrile/water 1:1 to give **20** (29 mg) and **24** (20 mg). – UV. (MeOH): 215 (4.17), 260 (3.66), 285 (3.60). – ^{1}H-NMR. ($CDCl_3$): 8.06 (*s*, 1H, NH); 6.59 (*s*, 1H, H–C(14)); 6.14 (*s*, 1H, H–C(17)); 5.88 (*d*×*d*, *J*= 10 and 4, 1H, H–C(7)); 5.48 (*s*, 1H, H–C(4)); 5.30 (*d*, *J*= 10, 1H, H–C(6)); 3.82 (*s*, 6H, 3 OCH_3); 3.77 (*s*, 1H, H–C(2)); 2.74 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 0.95 (*t*, *J*= 7, 3H, CH_2CH_3); 0.82 (*t*, *J*= 7, 3H, CH_2CH_3). – MS.: 808 (M^+), 806, 747, 689, 687, 647, 645, 168, 152, 149, 83, 50, 44. – Mol-wt.: 808.3994, $C_{46}H_{56}N_4O_9$ (808.4045).

A similar reaction for a 3 day period gave a 50% conversion to **24**.

*(3′*R*)-4′-Deoxy-3′-hydroxyvinblastine* (**25**). The ketone **24** (32 mg) dissolved in ethanol (5 ml) was treated with sodium borohydride (10 mg), and stirred at RT. for 2 h, and then partitioned between water and CH_2Cl_2. The extract was dried (Na_2SO_4) and evaporated. Preparative layer chromatography on silica gel gave the alcohol **25** (15 mg, 47%) as an amorphous solid. – ^{1}H-NMR. ($CDCl_3$): 8.18 (br. *s*, 1H, NH); 7.30 (*m*, 1H, H–C(14′)); 7.10 (*m*, 3H, H–C(11′,12′,13′)); 6.42 (br. *s*, 1H, H–C(17)); 6.14 (*s*, 1H, H–C(14)); 5.88 (*d*×*d*, *J*= 11 and 4, 1H, H–C(7)); 5.41 (*s*, 1H, H–C(4)); 5.31 (*d*, *J*= 11, 1H, H–C(6)); 3.84 (*s*, 3H, OCH_3); 3.82 (*s*, 3H, OCH_3); 3.76 (*s*, 1H, H–C(2)); 3.68 (*s*, 3H, OCH_3); 2.74 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 0.96 and 0.84 (poorly resolved, unsymmetrical *t*, 6H, 2 CH_2CH_3). – MS.: 810 (M^+), 808, 792, 779, 751, 733, 719, 703, 691, 673, 649, 617, 571, 543, 527, 512, 469, 399, 355, 311, 295, 282, 241, 205, 188, 161, 154, 149, 135, 121, 107. – Mol-wt.: 810.4198, $C_{46}H_{58}N_4O_9$ (810.4189).

The remaining minor alkaloid fraction, Rf 0.2–0.6, was acetylated in the usual manner, and compared by HPLC. with the product **28** obtained from coupling vindoline with (3*R*,4*S*)-3-acetoxy-3,4-dihydrocatharanthine (**27**) (described later).

(3'R)-3'-Acetoxy-4'-deoxyvinblastine (**16**). The alcohol **25** (15 mg) was treated with pyridine (0.3 ml), and acetic anhydride (0.15 ml). The mixture was left overnight at $-10°$, and the reactants were removed on a vacuum line. Preparative layer chromatography on silica gel gave the acetate **16** (8 mg, 51%) as an amorphous solid. – UV. (MeOH): 260 (4.12), 286 (4.02), 295 (3.99), 314 (3.72). – ^{1}H-NMR. ($CDCl_3$, 270 MHz): 8.09 (*s*, 1H, NH); 7.55 (poorly resolved *d*, $J=7.5$, 1H, H–C(14')); 7.18 (*m*, 3H, H–C(11',12',13')); 6.62 (*s*, 1H, H–C(17)); 6.09 (*s*, 1H, H–C(14)); 5.89 (*d*×*d*, $J=10$ and 4, 1H, H–C(7)); 5.49 (*s*, 1H, H–C(4)); 5.33 (*d*, $J=10$, 1H, H–C(6)); 4.39 (*d*×*d*, $J=11$ and 5, 1H, H–C(3')); 3.82 (*s*, 3H, OCH_3); 3.80 (*s*, 3H, OCH_3); 3.65 (*s*, 3H, OCH_3); 2.74 (*s*, 3H, NCH_3); 2.12 (*s*, 3H, $OCOCH_3$); 2.05 (*s*, 3H, $OCOCH_3$); 0.90 (poorly resolved unsymmetrical *t*, 3H, CH_2CH_3); 0.81 (*t*, $J=7.5$, 3H, CH_2CH_3). – MS.: 852 (M^+), 850, 821, 793, 733, 691, 633, 613, 585, 524, 469, 446, 397, 337, 297, 282, 251, 222, 214, 196, 188, 168, 149, 138, 136, 135, 124, 122, 121, 107, 93. – Mol-wt.: 852.4271, $C_{48}H_{60}N_4O_{10}$ (852.4294).

(3'S)-3'-Acetoxy-4'-deoxyvinblastine (**28**). *m*-Chloroperbenzoic acid (30 mg) was added to a solution of the acetate **27** (60 mg) in CH_2Cl_2 (1 ml) at $-20°$ under N_2. After stirring for 1 h, vindoline (76 mg) and trifluoroacetic anhydride (0.12 ml) were added at $-50°$. The mixture was kept at this temperature for 5 h, and then slowly added to an excess of sodium borohydride in methanol ($-20°$). The resulting mixture was diluted with water, and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and concentrated in *vacuo*. Repetitive preparative layer chromatography on silica gel gave the acetate **28** (14 mg, 11%) identical (HPLC.) with that derived from the minor product from the reduction of **24**. – UV. (MeOH): 259, 285, 295, 314. – IR. ($CHCl_3$): 3460, 1732, 1612. – ^{1}H-NMR. ($CDCl_3$): 8.10 (br. *s*, 1H, NH); 6.48 (*s*, 1H, H–C(17)); 6.12 (*s*, 1H, H–C(14)); 5.90 (*d*×*d*, $J=10$ and 4, 1H, H–C(7)); 5.40 (*s*, 1H, H–C(4)); 5.30 (*d*, $J=10$, 1H, H–C(6)); 4.72 (br. *s*, 1H, H–C(3')); 3.77 (*s*, 3H, OCH_3); 3.82 (*s*, 3H, OCH_3); 3.70 (*s*, 3H, OCH_3); 2.62 (*s*, 3H, NCH_3); 2.06 (*s*, 3H, $OCOCH_3$); 2.00 (*s*, 3H, $OCOCH_3$); 0.86 (*t*, $J=7.5$, 3H, CH_2CH_3); 0.65 (*t*, $J=7.5$, 3H, CH_2CH_3). – MS.: 852 (M^+), 850, 821, 793, 733, 691, 633, 613. – Mol-wt.: 852.4310, $C_{48}H_{60}N_4O_{10}$ (852.4294).

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