Total synthesis of indole and dihydroindole alkaloids. XVII. The total synthesis of catharine and vinamidine (catharinine)[1–3]

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Oxidation of 16,18-dicarbomethoxycleavamine gave the epoxide (**6**) and the enamide (**9**). Similar oxidation of 3′,4′-dehydrovinblastine (**8**) or leurosine (**7**) gave the natural product catharine (**3**). Potassium permanganate oxidation of **7** or **8** gave 3*R*-hydroxyvinamidine (**19**) whereas similar oxidation of 4′-deoxyleurosidine (**29**) gave the alkaloid vinamidine (**4**).

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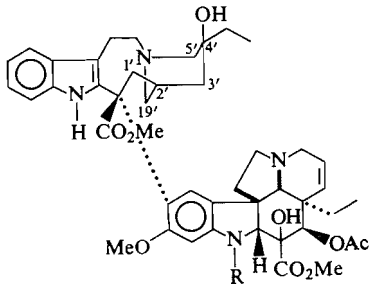
L'oxydation de la dicarbométhoxy-16,18 cléavamine conduit à l'époxyde (**6**) et à l'énamide (**9**). Une oxydation semblable de la déhydro-3′,4′ vinblastine (**8**) ou de la leurosine (**7**) fournit le produit naturel catharine (**3**). L'oxydation de **7** ou **8** par le permanganate de potassium fournit l'hydroxy-3*R* vinamidine (**19**) alors qu'une oxydation semblable de la déoxy-4′ leurosidine (**29**) conduit à l'alcaloïde vinamidine (**4**).

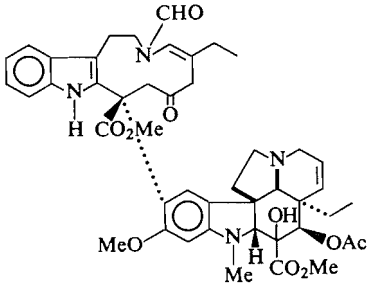
[Traduit par le journal]

The important oncolytic action of many of the members of the vinblastine (**1**) – vincristine (**2**) family initiated innumerable investigations into the chemistry and biochemistry of these 'dimeric' alkaloids. Indeed efforts from several laboratories led to syntheses of some of the natural products as well as many derivatives while more recent work enabled unambiguous structure identification of two interesting ring cleaved compounds catharine (**3**) (4) and vinamidine (catharinine) (**4**) (5, 6). This report describes total syntheses of both **3** and **4**, and several related compounds.

In the early stages of our investigation of totally synthetic routes to 'bisindole' alkaloids, considerable emphasis was placed on selective functionalisation of model systems of the cleavamine type, particularly the protected indole derivative (**5**) (8). In this regard, aerial or hydroperoxide oxidation of (**5**) (7, 8) provided the 3*R*,4*S*-epoxide (**6**) and later adaption of this transformation allowed the first of several syntheses of the natural product leurosine (**7**) from synthetic 3′,4′-dehydrovinblastine (**8**) (7, 8).



1 R = CH_3
2 R = CHO



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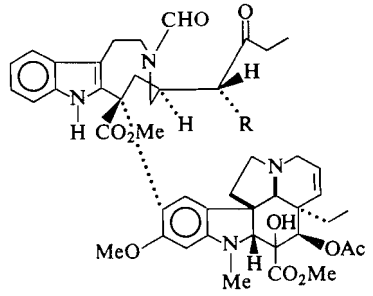

4 R = H **20** R = OAc
19 R = OH **28** R = $OCSC_6H_5$

In an attempt to optimise conditions for the formation of the epoxide **6**, the aerial oxidation of **5** in peroxide-free tetrahydrofuran (THF) containing a small amount of aqueous trifluoroacetic acid (TFA) was studied, the course of the reaction being monitored by thin-layer chromatography (tlc) after 3, 5,

[1]Dedicated to the memory of R. H. F. Manske.
[2]For part XVI, see ref. 1.
[3]For preliminary reports on this work see refs. 2 and 3.

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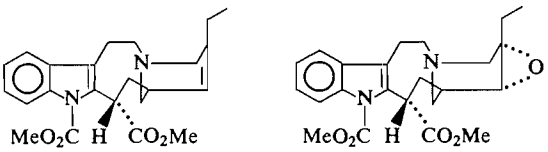
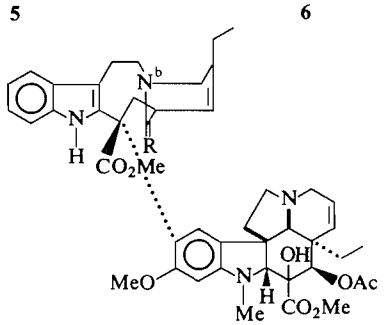
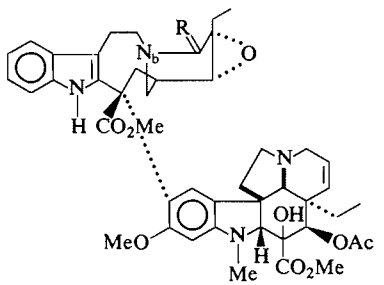
and 8 days. At ambient temperature, no reaction was apparent after 3 days, whereas both **5** and **6** were detected after 5 days. The starting material (**5**) had been consumed after 8 days but the epoxide **6** (isolated in only 10% yield) had undergone further transformation to **9** which was isolated in 52% yield. Based on an assumption that the cleavamine skeleton was intact, this latter product was originally assigned as the 5-oxo derivative **10** (8). The revised assignment (**9**) followed further analysis of spectral properties and results of a chemical transformation. Thus the ^{1}Hmr spectrum of **9** exhibited absorbances at δ 8.13 (N_b-CHO), 5.23 (C5-H), and 1.90 ppm (—CH_2CH_3) in accord with the proposed structure. The duplication of various resonances as observed in this spectrum has also been noted in a number of alkaloids exhibiting rotomers of a formamide group (9). The infrared spectrum showed strong absorbance at 1680 and 1650 cm^{-1} in support of the enamide assignment. The presence of a ketone carbonyl function was substantiated by sodium borohydride reduction to the corresponding secondary alcohol



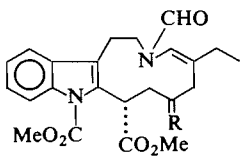
5 **6**



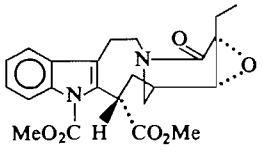
8 R = H_2
16 R = H_2, N_b-oxide
18 R = O



7 R = H_2
15 R = O
17 R = H_2, N_b-oxide



9 R = O
11 R = H, OH



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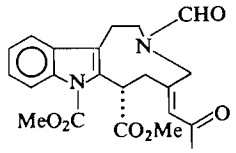

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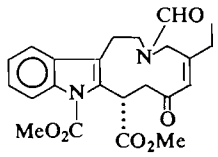

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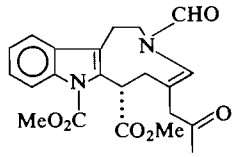

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(**11**), thus ruling out structure **10**. Infrared absorption at 1669 and 1651 cm^{-1} for **11** corroborated the enamide assignment (**9**) and eliminated the alternate cleavage possibilities **12** and **13**. The alternative enamide structure (**14**) was incompatible with the ^{1}Hmr quartet resonance at δ 1.90 ppm due to the methylene of the ethyl group.

Subsequently, the apparent existence of an induction period for the oxidation led to an observation that when THF, which had already undergone some aerial oxidation, was used the alkene **5** was converted to **6** in 4 h and that after 22-h work up afforded **6** (32%) and **9** (25%). Reproducible conditions were found using peroxide-free THF containing a small amount of 1% TFA and added *tert*-butylhydroperoxide. In this manner, a 76% yield of **6** was attained and in fact these conditions were later used for the synthesis of the alkaloid leurosine (**7**). In this regard, similar protection of the indole nitrogen of **8** was neither possible nor necessary and leurosine was obtained directly from **8** without observable oxidation at the β-position of the indole system. Examination of the reaction mixture by tlc indicated that on prolonged treatment leurosine also underwent further oxidation to yield a product readily detected on tlc by its distinct green colouration after spraying with ceric sulphate reagent. Again this product was initially assigned the 5′-oxo structure **15** (8, 10). Later comparison of this product with naturally occurring catharine (**3**)[4], a structure derived

[4]The authors are very grateful to Dr. Gordon Svoboda, Eli Lilly and Company, Indianapolis, IN, for providing samples of catharine and vinamidine.

TABLE 1. Aerial and *tert*-butyl hydroperoxide oxidations

Entry	Substrate	Reaction conditions	Products
1	**8**	*t*BuOOH, THF, 1% TFA(aq), 22 h	**7, 3, 16, 17**
2	**8**	*t*BuOOH, THF, 1% TFA(aq), 5 days	**3, 7, 16, 17**
3	**8**	*t*BuOOH, THF, H_2O, 22 h	**7, 3, 16, 17**
4	**8**	*t*BuOOH, THF, 22 h	**3, 7, 8, 16, 17**, others
5	**8**	*t*BuOOH, THF, 1% TFA(aq), MeOH, 22 h	**8, 7, 16, 17**
6	**8**	*t*BuOOH, THF, 1% TFA(aq), inhibitor*	**8, 16**
7	**16**	*t*BuOOH, THF, 1% TFA(aq), 22 h	No reaction
8	**8**	*t*BuOOH, THF, 5% TFA(aq), 22 h	No reaction
9	**7**	*t*BuOOH, THF, 5% TFA(aq), 22 h	No reaction
10	**7**	*t*BuOOH, THF, 1% TFA(aq), 22 h	**7, 3, 17**
11	**7**	Air, THF, 1% TFA(aq), 11 days	**7, 3**, others
12	**8**	Air, THF, 1% TFA(aq), 11 days	**8, 3**, others
13	**7**	*t*BuOOH, CH_2Cl_2	**3**, others
14	**7**	*t*BuOOH, THF, 1% TFA(aq), dark, inhibitor,* 22 h	**7, 17**
15	**7**	*t*BuOOH, THF, 1% TFA(aq), dark, inhibitor,* 44 h	**17**
16	**17**	*t*BuOOH, THF, 1% TFA(aq), 22 h	No reaction
17	7	Air, CH_2Cl_2, 22 h	No reaction

*The radical inhibitor used was 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulphide.

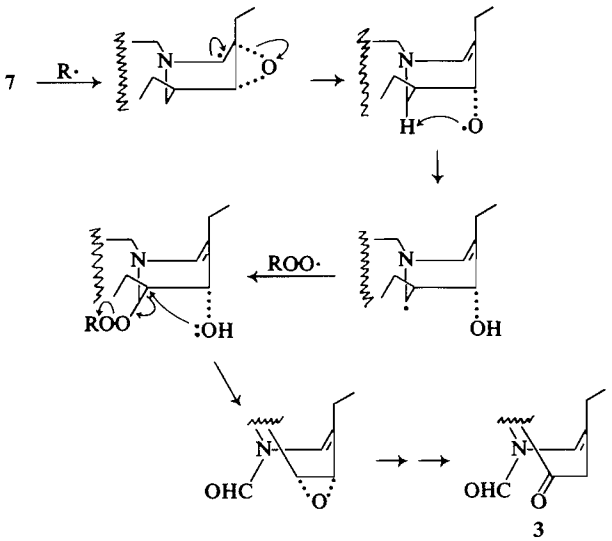
by X-ray analysis (4), showed its identity; mp (acetone) 213–215°C (lit. (4) mp 213–215°C); mp (ethanol) 162–166°C (lit. (11) mp 171–175°C),[5] undepressed on admixture with an authentic sample; $[\alpha]_D$ −49° (*c* 0.7, $CHCl_3$), (lit. (11) $[\alpha]_D$ −51°). Again duplication of ^{1}Hmr signals was consistent with a formamide function (9) and the spectrum of **3** was superimposable on that of authentic catharine.

Under the conditions employed for the formation of **3**, an acid-catalysed or radical mechanism was possible and a further examination of the reaction was needed to distinguish the pathway involved. Aerial or *tert*-butylhydroperoxide oxidation of **8** in THF containing a small amount of 1% aqueous TFA gave catharine (**3**) (ca. 30% yield) after 11 or 5 days, respectively, and monitoring the course of the reaction by tlc implicated leurosine (**7**) as a precursor of **3**. Accordingly aerial or *tert*-butylhydroperoxide oxidation of leurosine (**7**) also afforded catharine (Table 1, entries 10, 11). Alternatively, reaction of **7** or **8** with *tert*-butylhydroperoxide could be inhibited or the course of reaction changed on addition of a radical inhibitor (entries 6, 14, 15). The role of aqueous acid in the transformation of **8** to **7** was obscure, since although leurosine was formed in small amounts in the absence of acid, the product mixture was very complex. On the other hand, formation of catharine did not require acid or water (entries 4, 13). Indeed optimum conditions for the transformation of **7** to **3** (48% yield) were found using *tert*-butylhydroperoxide in dichloromethane. Finally, the possible intermediacy of the corresponding N_b-oxides **16** and **17** was eliminated since these substrates did not react under the original experimental conditions (entries 7, 16).

[5]In our hands, an authentic sample had mp 164–168°C.

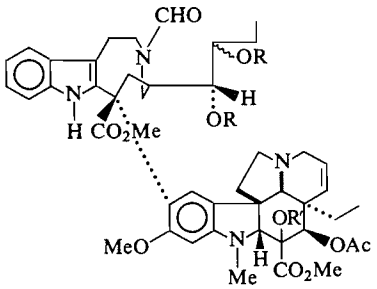
Thus the alkene **8** could be converted to the alkaloid leurosine (**7**), via a radical mechanism. Aqueous acid was necessary for a synthetically useful transformation possibly owing to inhibition of unwanted side reactions at N_b. Catharine (**3**) was in turn formed from leurosine via a radical pathway possibly as shown in Scheme 1. Notably, recent work from these laboratories has shown the biosynthetic intermediacy of leurosine in the natural formation of catharine (12).

Although hydroperoxide oxidation of cleavamine systems led to C19′—C2′ cleavage products, potassium permanganate oxidation allowed an alternative mode of ring cleavage. Here oxidation of **8** with $KMnO_4$ in acetone gave two products (3). The minor component of the mixture was identical with the known 19′-oxo derivative (**18**) (8). The major product

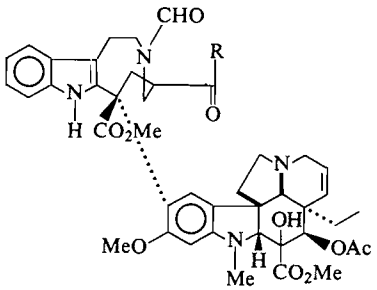


SCHEME 1

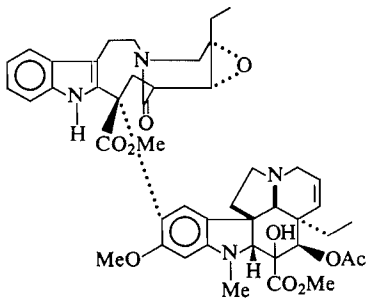
was identified, *ex post facto*, as 3*R*-hydroxyvinamidine (**19**). The identity of this product was established by spectral analysis and by chemical transformations. High resolution mass spectrometry gave the molecular formula $C_{46}H_{56}N_4O_{11}$ while infrared absorbance at 1660 cm^{-1} suggested the presence of an



21 R = R′ = H
22 R = R′ = Ac
23 R = Ac, R′ = H



24 R = $COCH_2CH_3$
26 R = H



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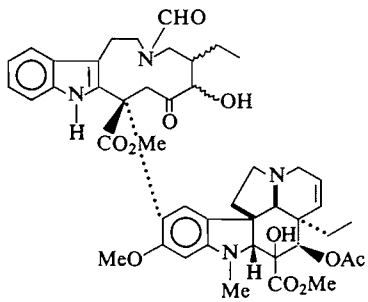

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N_b-formyl function, further evidenced by ^{1}Hmr singlet resonance at δ 7.30 ppm. Acetylation in the usual manner gave the keto acetate **20** with ^{1}Hmr signals at δ 4.80 (bs, C3′-H) and 2.10 (s, —$OCOCH_3$) indicating a secondary alcohol group in **19**. Alternatively reduction of **19** with sodium borohydride gave the triol **21** which on acetylation gave a mixture of the tetraacetate **22** and the triacetate **23**. Oxidation of **19** with cupric acetate (14) in hot methanol gave the α-diketone (ν_{max} 1713 cm^{-1}) **24** thus confirming the α-ketol function in **19**. The possible cleavage structure **25** was eliminated as periodate cleavage of either **19** or **21** gave only the aldehyde **26** exhibiting singlet absorbances at δ 7.61 (N_b-CHO) and 9.20 ppm (—CHO). High resolution mass spectrometry gave the molecular formula $C_{43}H_{50}N_4O_{10}$ thus confirming the loss of a three-carbon fragment. The formation of an aldehyde by periodate cleavage of **19** also supported the ketol orientation as shown. The stereochemistry at C3′ in **19** was assigned *R* on the basis of the permanganate cleavage of leurosine (**7**) to **19** (27% yield) with the assumption that the stereochemical integrity at C3′ had been maintained. The lactam **27** was also isolated from this oxidation.

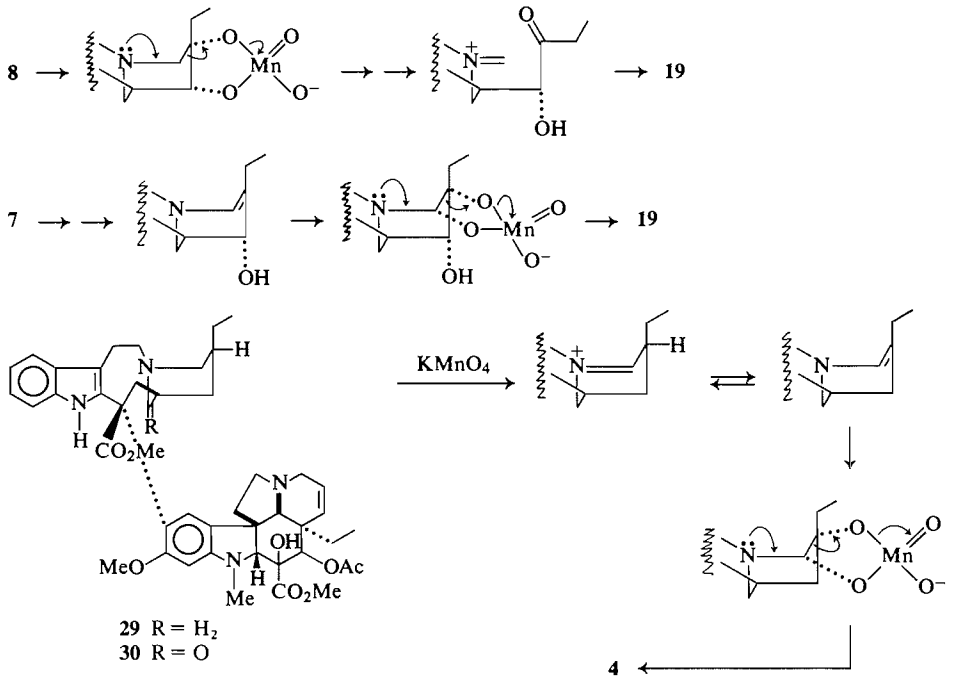
At this time the structure of the alkaloid vinamidine (catharinine) (**4**) was reported (5) and we sought a method to convert the hydroxy derivative **19** to the natural product. However attempted reductive cleavage of the derived acetate **20** was unsuccessful under a variety of conditions as were efforts to form the corresponding thionobenzoate **28**.

Therefore an alternative route to **4** was considered. The plausible mechanism (outlined in Scheme 2) for the oxidative cleavage of **7** or **8** to give **19** suggested that a substrate of lower oxidation state might similarly lead to vinamidine (**4**). In the event oxidation of 4′-deoxyleurosidine (**29**) with $KMnO_4$ in acetone gave the lactam **30** together with vinamidine (**4**). The cleavage product was identical with an authentic sample[4] of the alkaloid and the specific rotation of the sodium borohydride reduction product was in agreement with the literature value (5).

Thus propitious use of potassium permanganate oxidant enabled preparation of several unusual seco-4′,5′ derivatives including the natural product vinamidine (catharinine) (**4**). Alternatively, hydroperoxide oxidation of leurosine **7** or **8** afforded the seco-2′,19′ compound catharine (**3**).

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



SCHEME 2

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 aluminum oxide 90 (neutral).

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

Autoxidation of 16,18-Dicarbomethoxycleavamine

A solution of 16,18-dicarbomethoxycleavamine (**5**) (400 mg, 1 mmol) in peroxide-free tetrahydrofuran (10 mL) containing aqueous 1% trifluoroacetic acid (1 mL) was stirred at ambient temperature in the presence of air for a period of 8 days. After drying (K_2CO_3), the solvent was removed *in vacuo*. Chromatography of the residue on alumina (activity III, benzene) afforded the epoxide **6** (40 mg, 10%) and the keto enamide **9** (230 mg, 54%).

16,18-Dicarbomethoxy-3*R*,4*S*-epoxydihydrocleavamine **6**, mp 131–132°C (ether); uv λ_{max}: 294 (3.66), 283 sh (3.76), 268 (4.08), 262 (4.09), 227 (4.32); ir ν_{max}: 1728; ^{1}Hmr δ: 8.1 (1H, m, C14-H), 7.3 (3H, m, C11–C13-H's), 5.84 (1H, d, J = 6 Hz, C18-H), 3.91 (3H, s, —OCH_3), 3.57 (3H, s, —OCH_3), 1.00 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e*: 412 (M^+), 224 (base peak), 152, 138; ^{13}Cmr δ: 173.4 (—CO_2CH_3), 152.0 (—CO_2CH_3), 137.1 (C17), 136.0 (C15), 129.8 (C10), 124.5 (C12), 122.9 (C11), 119.5 (C9), 118.2 (C13), 115.9 (C14), 62.7 (C4), 60.6 (C3), 53.4 (C7 and —OCH_3), 52.7 (C5), 51.9 (—OCH_3), 50.6 (C19), 39.5 (C18), 33.6 (C8 and C2), 30.0 (—CH_2CH_3), 26.3 (C1), 8.9 (—CH_2CH_3). *Mol. Wt.* calcd. for $C_{23}H_{28}N_2O_5$: 412.1997; found (high resolution ms): 412.2027. *Anal.* calcd. for $C_{23}H_{28}N_2O_5$: C 66.97, H 6.84, N 6.79; found: C 66.81, H 6.87, N 6.71.

Keto enamide **9** (as a foam); uv λ_{max}: 293 (3.67), 281 sh (3.78), 265 (4.05), 259 (4.06), 227 (4.38); ir ν_{max}: 1732, 1680, 1650; ^{1}Hmr δ: 8.13 (1H, s, N_b-C*H*O), 8.10 (1H, m, C14-H), 7.3 (3H, m, C11–C13-H's), 5.23 (1H, bs, C5-H), 4.00 (3H, bs, —OCH_3), 3.66 (3H, s, —OCH_3), 1.90 (2H, q, J = 7 Hz, —CH_2CH$_3$), 0.79 (3H, t, J = 7 Hz, —CH$_2$CH_3); ms *m/e*: 426 (M^+, base peak), 394, 228; ^{13}Cmr δ: 188.8 (N_b-*C*HO), 163.0 (—*C*O_2CH_3), 160.7 (—*C*O_2CH_3), 135.9 (C17), 132.3 (C15), 128.8 (C10), 126.9 (C5), 125.1 (C12), 123.3 (C11), 122.7 (C4), 119.9 (C9), 118.9 (C13), 116.0 (C14), 53.6 (—O*C*H$_3$), 52.5 (—O*C*H$_3$), 48.7 (C7), 44.9 (C3), 44.3 (C2), 40.0 (C18), 30.3 (C8), 24.5 (—*C*H$_2$CH$_3$), 12.3 (—CH$_2$*C*H$_3$). *Mol. Wt.* calcd. for $C_{23}H_{26}N_2O_6$: 426.1791; found (high resolution ms): 426.1795. *Anal.* calcd. for $C_{23}H_{26}N_2O_6 \cdot \frac{1}{2}CH_3OH$: C 63.80, H 6.33, N 6.33; found: C 64.08, H 6.11, N 6.31.

Oxidation of 16,18-Dicarbomethoxycleavamine (5) in 'Preoxidized' Tetrahydrofuran[6]

A solution of **5** (900 mg, 2.27 mmol) in 'preoxidized' tetrahydrofuran (20 mL) containing aqueous 1% trifluoroacetic acid (2 mL) was stirred at ambient temperature for 20 h. The

[6]'Preoxidized' tetrahydrofuran refers to tetrahydrofuran which had undergone aerial oxidation and contained an unspecified amount of peroxides.

reaction mixture was poured into a saturated solution of sodium bicarbonate (20 mL) and extracted with ethyl acetate (2 × 40 mL). The combined organic portion was washed with water (3 × 15 mL) and brine (1 × 20 mL). After drying (Na_2SO_4) the solvent was removed *in vacuo* and the residue was chromatographed on alumina (activity III, benzene) to afford the epoxide **6** (306 mg, 33%) and the keto enamide **9** (250 mg, 26%). These compounds were identical with the respective products obtained above.

Oxidation of 16,18-Dicarbomethoxycleavamine (5) using tert-*Butyl Hydroperoxide*

A solution of **5** (1.76 g, 4.4 mmol) in freshly distilled tetrahydrofuran (50 mL) containing aqueous 1% trifluoroacetic acid (10 mL) and *tert*-butyl hydroperoxide (9 mL) was stirred at ambient temperature for 21 h. The reaction mixture was poured into a saturated solution of sodium bicarbonate (40 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic portion was washed with 5% sodium hydroxide solution (1 × 20 mL), water (1 × 20 mL), and brine (1 × 20 mL). After drying (Na_2SO_4) the solvent was removed *in vacuo* to give a viscous oil. Chromatography on alumina (activity III, benzene) afforded the epoxide **6** (1.22 g, 67%) identical with that obtained above.

Hydroxy Enamide (11)

A solution of the keto enamide (**9**) (10 mg, 0.023 mmol) in 95% ethanol (2 mL) was treated with sodium borohydride (4 mg, 0.1 mmol). The reaction mixture was stirred at ambient temperature for 20 min, taken up in water (10 mL), and extracted with methylene chloride (3 × 5 mL). After drying (Na_2SO_4), the solvent was removed *in vacuo* and the residue chromatographed on silica gel (ether) to afford the hydroxy enamide **11** (6 mg, 60%) as a film; uv λ_{max}: 293 (3.50), 281 sh (3.68), 262 (4.03), 224 (4.32); ir ν_{max}: 3530, 3420, 1730, 1669, 1651; ^{1}Hmr δ: 8.05 (1H, m, C14-H), 8.02 (1H, s, N_b-C*H*O), 7.6–7.2 (3H, m, C11–C13-H's), 5.48 (1H, bs, C5-H), 4.00 (3H, s, —OCH_3), 3.66 (3H, s, —OCH_3), 0.98 (3H, t, J = 7.5 Hz, —CH_2CH_3); ms *m/e*: 428 (M^+), 315, 201, 126 (base peak). *Mol. Wt.* calcd. for $C_{23}H_{28}N_2O_6$: 428.1947; found (high resolution ms): 428.1928.

Leurosine (7)

This compound was prepared as described earlier (8).

Catharine (3)

(*A*) A solution of leurosine (7) (30 mg, 0.037 mmol) in tetrahydrofuran (2 mL) containing aqueous 1% trifluoroacetic acid (0.2 mL) was stirred in the presence of air for 11 days. The reaction mixture was diluted with a saturated solution of sodium bicarbonate (5 mL) and extracted with methylene chloride (3 × 5 mL). The combined organic portion was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (ethyl acetate – 12% methanol) afforded leurosine (7) (4 mg) and catharine (**3**) (4 mg, 15%). The synthetic catharine had mp 213–215°C (acetone) (lit. (4) mp 213–215°C); mp 162–166°C (ethanol) (lit. (11) mp 171–175°C),[5] undepressed on admixture with an authentic sample; $[\alpha]_D$ −49° (*c* 0.7, $CHCl_3$) (lit. (11) $[\alpha]_D$ −51°). The ^{1}Hmr, uv, ir, and mass spectra were superimposable with those of authentic material.

(*B*) Oxidation of 3′,4′-dehydrovinblastine (**8**) as above afforded catharine in 34% yield.

(*C*) A solution of leurosine (**7**) (45 mg, 0.56 mmol) in methylene chloride containing *tert*-butyl hydroperoxide (0.06 mL) was stirred at ambient temperature for 24 h. The solvent was removed *in vacuo* and the residue chromatographed on silica gel (methylene chloride – 5% methanol) to afford catharine (22 mg, 48%).

Comparative Oxidations of 3′,4′-Dehydrovinblastine (8), Leurosine (7), and Derivatives, Utilizing tert-*Butyl Hydroperoxide*

All reactions were carried out utilizing 10 mg of substrate dissolved in 0.5 mL tetrahydrofuran containing 0.05 mL of *tert*-butyl hydroperoxide. To these solutions were added any further reagents used. The product composition of the reactions was ascertained via tlc. Authentic samples of 3′,4′-dehydrovinblastine (**8**), leurosine (**7**), catharine (**3**), pleurosine (**17**) (14), and 3′,4′-dehydrovinblastine N_b-oxide (**16**) (8) were used for comparison purposes. The solvent systems used for the chromatographic analysis were ethyl acetate – 20% methanol and methylene chloride – 6% methanol. Visualization was achieved by spraying with ceric sulfate spray reagent and heating at 100°C for 1 h. The relative amounts of products formed were *estimated* from the visualized chromatograms.

Reaction of 3′,4′-Dehydrovinblastine (8) with Potassium Permanganate

A solution of 3′,4′-dehydrovinblastine (**8**) (250 mg, 0.316 mmol) in methylene chloride (2 mL) and acetone (5 mL) was treated at 0°C with a solution of potassium permanganate (105 mg, 0.665 mmol) in acetone (5 mL). The reaction mixture was stirred at 0°C for 5 min and the solvent was removed *in vacuo*. The residue was triturated with methylene chloride (5 mL) and filtered through silica gel (ethyl acetate – 25% methanol). Removal of the solvent *in vacuo* followed by chromatography of the residue on silica gel (ethyl acetate – 15% methanol) afforded the ketol **19** (111 mg, 42%) as the major product (R_f 0.4). 19′-Oxo-3′,4′-dehydrovinblastine (**18**) (25 mg, 9.8%) identical with an authentic sample (8) (tlc, ms, ^{1}Hmr) was obtained as the minor product (R_f 0.75).

Ketol **19**, mp 198–202°C (ethanol); uv λ_{max}: 310 (3.80), 294 (4.08), 284 (4.14), 268 (4.19), 212 (4.72); ir ν_{max}: 3475, 1734, 1660, 1612; ^{1}Hmr δ: 7.88 (1H, bs, N*H*), 7.51 (1H, m, C14′-H), 7.32 (1H, s, NC*H*O), 7.14 (3H, m, C11′–C13′-H's), 6.71 (1H, s, C14-H), 6.00 (1H, s, C17-H), 5.86 (1H, dd, J = 10 and 4 Hz, C7-H), 5.49 (1H, s, C4-H), 5.30 (1H, d, J = 10 Hz, C6-H), 3.97 (1H, bs, C3′-H), 3.79 (3H, s, —OCH_3), 3.73 (3H, s, —OCH_3), 3.51 (3H, s, —OCH_3), 2.69 (3H, s, —NCH_3), 2.12 (3H, s, —OCOCH_3), 0.79 (3H, t, J = 7 Hz, —CH_2CH_3), 0.70 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 840 (M^+), 781, 680, 573, 135 (base peak). *Mol. Wt.* calcd. for $C_{46}H_{56}N_4O_{11}$: 840.3945; found (high resolution ms): 840.3966.

Reaction of Leurosine (7) with Potassium Permanganate

A solution of leurosine (**7**) (105 mg, 0.13 mmol) in acetone (1 mL) and methylene chloride (0.5 mL) was treated with a solution of potassium permanganate (40 mg, 0.25 mmol) in acetone (4 mL). The reaction mixture was stirred at ambient temperature for 3 min and the solvent was removed *in vacuo*. The residue was treated as above to afford the ketol **19** (30 mg, 27%), identical with that obtained above, and 19′-oxoleurosine (**27**) (20 mg, 19%) as a colorless film.

19′-Oxoleurosine (**27**); uv λ_{max}: 309 sh (3.74), 294 (4.00), 284 (4.05), 262 (4.13), 214 (4.66); ir ν_{max}: 3470, 1738, 1644; ^{1}Hmr δ: 8.06 (1H, bs, N*H*), 7.57 (1H, m, C14′-H), 7.18 (3H, m, C11′–C13′-H's), 6.65 (1H, s, C14-H), 6.19 (1H, s, C17-H), 5.90 (1H, dd, J = 10.5 and 3.5 Hz, C7-H), 5.51 (1H, s, C4-H), 5.33 (1H, d, J = 10.5 Hz, C6-H), 4.76 (1H, m, C2′-H), 3.85 (3H, s, —OCH_3), 3.83 (3H, s, —OCH_3), 3,63 (3H, s, —OCH_3), 2.76 (3H, s, NCH_3), 2.12 (3H, s, —OCOCH_3), 1.01 (3H, t, J = 7.5 Hz, —CH_2CH_3), 0.84 (3H, t, J = 7 Hz, —CH_2CH_3); ms *m/e*: 822 (M^+), 763, 282, 135 (base peak); ^{13}Cmr δ: 163.0 (C19′), 61.6 (C3′), 59.8 (C4′), 8.9 (—CH_2CH_3), 8.5 (—CH_2CH_3). *Mol. Wt.* calcd. for $C_{46}H_{54}N_4O_{10}$: 822.3839; found (high resolution ms): 822.3806.

TABLE 2. Comparative oxidations of 3′,4′-dehydrovinblastine (**8**), leurosine (**7**), and derivatives using *tert*-butyl hydroperoxide

Reaction conditions			Products (%, approximate)				
Substrate	Time	Additive	**3**	**7**	**8**	**16** or **17**	Others
8	22 h	0.05 mL 1% trifluoroacetic acid	5	95	—	5	—
8	5 days	0.05 mL 1% trifluoroacetic acid	40	25	—	5	30
8	22 h	0.05 mL water	5	30	—	5	60
8	22 h	—	30	10	5	10	45
8	22 h	0.05 mL 1% trifluoroacetic acid 0.1 mL methanol	—	50	45	5	—
8	22 h	0.05 mL 1% trifluoroacetic acid 5 mg radical inhibitor*	—	25	70	5	—
16	22 h	0.05 mL 1% trifluoroacetic acid	—	—	—	100	—
8	22 h	0.05 mL 5% trifluoroacetic acid	—	—	100	—	—
7	22 h	0.05 mL 5% trifluoroacetic acid	—	100	—	—	—
7	22 h	0.05 mL 1% trifluoroacetic acid	20	65	—	15	—
7	22 h	0.05 mL 1% trifluoroacetic acid 5 mg radical inhibitor*	5	90	—	5	—
7	44 h	0.05 mL 1% trifluoroacetic acid 10 mg radical inhibitor*	—	—	—	100	—
17	22 h	0.05 mL 1% trifluoroacetic acid	—	—	—	100	—

*3-*tert*-Butyl-4-hydroxy-5-methylphenyl sulphide.

*Keto Acetate **20***

A solution of the ketol **19** (22 mg, 0.026 mmol) in pyridine (2 mL) at ambient temperature under a nitrogen atmosphere was treated with acetic anhydride (4 drops). The reaction mixture was stirred for 30 h. Methanol (1 mL) and toluene (10 mL) were added and the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (ethyl acetate – 10% methanol) afforded the keto acetate **20** (15 mg, 65%) as a white amorphous solid; uv λ_{max}: 310 (3.81), 294 (4.10), 285 (4.17), 270 (4.21), 213 (4.73); ir ν_{max}: 3470, 1738, 1660, 1612; ^{1}Hmr δ: 7.90 (1H, bs, N*H*), 7.51 (1H, m, C14′-H), 7.32 (1H, s, NC*H*O), 7.12 (3H, m, C11′–C13′-H's), 6.64 (1H, s, C14-H), 6.00 (1H, s, C17-H), 5.86 (1H, dd, J = 10 and 4 Hz, C7-H), 5.48 (1H, s, C4-H), 5.31 (1H, d, J = 10 Hz, C6-H), 4.80 (1H, bs, C3′-H), 3.79 (3H, s, —OC*H*$_3$), 3.76 (3H, s, —OC*H*$_3$), 3.72 (1H, s, C2-H), 3.62 (3H, s, —OC*H*$_3$), 2.69 (3H, s, NC*H*$_3$), 2.14 (3H, s, —OCOC*H*$_3$), 2.10 (3H, s, —OCOC*H*$_3$), 0.77 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$), 0.70 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 882 (M^+), 822, 762, 720, 613, 555, 354, 181, 169, 135, 131, 119 (base peak). *Mol. Wt.* calcd. for $C_{48}H_{58}N_4O_{12}$: 882.4050; found (high resolution ms): 882.4046.

*Triol **21***

A solution of the ketol **19** (50 mg, 0.06 mmol) in 95% ethanol (3 mL) was treated with sodium borohydride (6 mg, 0.16 mmol). The reaction mixture was stirred at ambient temperature for 30 min and treated with acetone (1 mL). The solvent was removed *in vacuo* and the residue was triturated with methylene chloride (20 mL) and filtered through Celite. Removal of the solvent *in vacuo* followed by chromatography of the residue on silica gel (methylene chloride – 5% methanol) afforded the triol **21** (33 mg, 66%) as a colorless film; uv λ_{max}: 310 (3.65), 295 (4.00), 284 (4.06), 267 (4.11), 212 (4.65); ir ν_{max}: 3585, 3472, 1738, 1660, 1613; ^{1}Hmr δ: 7.98 (1H, s, N*H*), 7.53 (1H, m, C14′-H), 7.45 (1H, s, NC*H*O), 7.15 (3H, m, C11′–C13′-H's), 6.76 (1H, s, C14-H), 6.12 (1H, s, C17-H), 5.90 (1H, dd, J = 10 and 4 Hz, C7-H), 5.46 (1H, s, C4-H), 5.35 (1H, d, J = 10 Hz, C6-H), 3.82 (3H, s, —OC*H*$_3$), 3.80 (3H, s, —OC*H*$_3$), 3.76 (1H, s, C2-H), 3.55 (3H, s, —OC*H*$_3$), 2.71 (3H, s, NC*H*$_3$), 2.10 (3H, s, —OCOC*H*$_3$), 0.84 (3H, t, J = 7.5 Hz, —CH$_2$CH$_3$), 0.79 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 842 (M^+), 783, 681, 574, 516, 135 (base peak). *Mol. Wt.* calcd. for $C_{46}H_{58}N_4O_{11}$: 842.4102; found (high resolution ms): 842.4060.

*Acetylation of Triol **21***

A solution of the triol **21** (32 mg, 0.38 mmol) in pyridine (2 mL) at ambient temperature under a nitrogen atmosphere

was treated with acetic anhydride (0.1 mL). The reaction mixture was stirred for 22 h at which point methanol (0.5 mL) and toluene (10 mL) were added. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (methylene chloride – 5% methanol) to yield the tetraacetate **22** (9 mg, 24%, R_f 0.4) and the triacetate **23** (9 mg, 26%, R_f 0.35). Both compounds were obtained as colorless films.

Tetraacetate **22**; uv λ_{max}: 310 (3.73), 294 (4.06), 284 (4.11), 267 (4.15), 212 (4.70); ir ν_{max}: 3468, 1732, 1666, 1618; ^{1}Hmr δ: 8.06 (1H, bs, N*H*), 7.50 (H, m, C14′-H), 7.36 (1H, s, NC*H*O), 7.14 (3H, m, C11′–C13′-H's), 6.53 (1H, s, C14-H), 6.13 (1H, s, C17-H), 5.89 (1H, dd, J = 10 and 5 Hz, C7-H), 5.52 (1H, s, C4-H), 5.30 (1H, d, J = 10 Hz, C6-H), 4.90 (1H, m, C4′-H), 4.54 (1H, t, J = 6 Hz, C3′-H), 4.03 (1H, s, C2-H), 4.82 (3H, s, —OC*H*$_3$), 4.77 (3H, s, —OC*H*$_3$), 4.59 (3H, s, —OC*H*$_3$), 2.85 (3H, s, NC*H*$_3$), 2.08 (6H, s, 2 × —OCOC*H*$_3$), 1.98 (6H, s, 2 × —OCOC*H*$_3$), 0.75 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$), 0.48 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 968 (M$^+$), 765, 659, 600, 135 (base peak). *Mol. Wt.* calcd. for $C_{52}H_{64}N_4O_{14}$: 968.4419; found (high resolution ms): 968.4395.

Triacetate **23**; uv λ_{max}: 309 (3.70), 294 (4.03), 284 (4.08), 269 (4.10), 212 (4.67); ir ν_{max}: 3480, 1732, 1664, 1617; ^{1}Hmr δ: 7.95 (1H, bs, N*H*), 7.54 (1H, m, C14′-H), 7.38 (1H, s, NC*H*O), 7.15 (3H, m, C11′–C13′-H's), 6.54 (1H, s, C14-H), 6.17 (1H, s, C17-H), 5.88 (1H, dd, J = 10 and 4 Hz, C7-H), 5.55 (1H, s, C4-H), 5.30 (1H, d, J = 10 Hz, C6-H), 4.89 (1H, m, C4′-H), 4.41 (1H, t, J = 6 Hz, C3′-H), 3.84 (3H, s, —OC*H*$_3$), 3.82 (3H, s, —OC*H*$_3$), 3.75 (1H, s, C2-H), 3.58 (3H, s, —OC*H*$_3$), 2.73 (3H, s, NC*H*$_3$), 2.12 (3H, s, —OCOC*H*$_3$), 2.08 (3H, s, —OCOC*H*$_3$), 1.97 (3H, s, —OCOC*H*$_3$), 0.76 (6H, t, J = 7 Hz, 2 × —CH$_2$C*H*$_3$); ms *m/e*: 926 (M$^+$), 867, 765, 659, 600, 135 (base peak). *Mol. Wt.* calcd. for $C_{50}H_{62}N_4O_{13}$: 926.4313; found (high resolution ms): 926.4331.

Diketone ***24***

A solution of the ketol **19** (30 mg, 0.036 mmol) and cupric acetate (monohydrate) (20 mg, 0.11 mmol) in methanol (3 mL) was heated at reflux for 25 min. The solvent was removed *in vacuo* and the residue was triturated with methylene chloride (2 mL) and filtered through Celite. Removal of the solvent *in vacuo* followed by chromatography of the residue on silica gel (methylene chloride – 5% methanol) afforded the diketone **24** (16 mg, 53%) as a pale yellow film; uv λ_{max}: 308 (3.70), 293 (4.03), 277 (4.11), 260 (4.20), 207 (4.70); ir ν_{max}: 3450, 1739, 1713, 1662, 1615; ^{1}Hmr δ: 7.94 (2H, bs, N*H*, NC*H*O), 7.52 (1H, m, C14′-H), 7.18 (3H, m, C11′–C13′-H's), 6.77 (1H, s, C14-H), 6.10 (1H, s, C17-H), 5.91 (1H, dd, J = 10 and 4 Hz, C7-H), 5.51 (1H, s, C4-H), 5.34 (1H, d, J = 10 Hz, C6-H), 3.82 (3H, s, —OC*H*$_3$), 3.74 (3H, bs, —OC*H*$_3$), 3.62 (3H, s, —OC*H*$_3$), 2.74 (3H, s, NC*H*$_3$), 2.12 (3H, s, —OCOC*H*$_3$), 1.04 (3H, t, J = 7.5 Hz, —CH$_2$C*H*$_3$), 0.79 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 838 (M$^+$), 779, 678 (base peak), 570, 135. *Mol. Wt.* calcd. for $C_{46}H_{54}N_4O_{11}$: 838.3789; found (high resolution ms): 838.3770.

Periodic Acid Cleavage of ***21***

A solution of **21** (25 mg, 0.030 mmol) in tetrahydrofuran (2 mL) at ambient temperature under a nitrogen atmosphere was treated with a solution of periodic acid (8.5 mg, 0.066 mmol) in tetrahydrofuran (0.5 mL). The reaction mixture was stirred for 2 min and concentrated *in vacuo*. Chromatography of the residue on silica gel (methylene chloride – 5% methanol – 0.1% ammonium hydroxide) afforded the N_b-formyl aldehyde **26** (15 mg, 65%) as a colorless film; uv λ_{max}: 310 (3.67), 294 (4.00), 284 (4.08), 268 (4.15), 213 (4.66); ir ν_{max}: 3464, 1732, 1661, 1612; ^{1}Hmr δ: 9.20 (1H, s, —C*H*O), 7.96 (1H, bs, N*H*), 7.61 (1H, s, NC*H*O), 7.56 (1H, m, C14′-H), 7.18 (3H, m, C11′–C13′-H's), 6.64 (1H, s, C14-H), 6.11 (1H, s, C17-H), 5.88 (1H, dd, J = 10 and 4 Hz, C7-H), 5.49 (1H, s, C4-H), 5.29 (1H, d, J = 10 Hz, C6-H), 3.80 (6H, s, 2 × —OC*H*$_3$), 3.62 (3H, s, —OC*H*$_3$), 3.50 (1H, s, C2-H), 2.71 (3H, s, NC*H*$_3$), 2.11 (3H, s, —OCOC*H*$_3$), 0.74 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 782 (M$^+$), 723, 621, 514, 135 (base peak). *Mol. Wt.* calcd. for $C_{43}H_{50}N_4O_{10}$: 782.3515; found (high resolution ms): 782.3484.

Periodic Acid Cleavage of the Ketol ***19***

A solution of the ketol **19** (40 mg, 0.048 mmol) in tetrahydrofuran (2 mL) at ambient temperature under a nitrogen atmosphere was treated with a solution of periodic acid (15 mg, 0.117 mmol) in tetrahydrofuran (1 mL). The reaction mixture was stirred for 4 h and the solvent was removed *in vacuo*. Chromatography of the residue on silica gel (methylene chloride – 5% methanol – 0.1% ammonium hydroxide) afforded the N_b-formyl aldehyde **26** (20 mg, 54%) identical with that obtained above.

*Reaction of 4′-Deoxyleurosidine (****29****) with Potassium Permanganate*

A solution of 4′-deoxyleurosidine (**29**) (260 mg, 0.33 mmol) in acetone (5 mL) and methylene chloride (2 mL) at ambient temperature under a nitrogen atmosphere was treated with a solution of potassium permanganate (158 mg, 1 mmol) in acetone (3 mL). The reaction mixture was stirred for 20 min and the solvent was removed *in vacuo*. The residue was triturated with methylene chloride (10 mL) and filtered through silica gel (ethyl acetate – 25% methylene chloride – 15% methanol). Removal of the solvent *in vacuo* followed by chromatography of the residue on silica gel (ethyl acetate – 13% methanol) afforded vinamidine (**4**) (60 mg, 22%) and 19′-oxo-4′-deoxyleurosidine (**30**) (30 mg, 11%). The synthetic vinamidine had $[\alpha]_D$ −35° (*c* 1.1, $CHCl_3$) (lit. (5) $[\alpha]_D$ −33°). The ^{1}Hmr and mass spectra as well as the tlc properties of the synthetic material were in accord with those exhibited by an authentic sample.

19′-Oxo-4′-deoxyleurosidine (**30**); uv λ_{max}: 311 (3.92), 294 (4.03), 284 (4.08), 263 (4.13), 212 (4.72); ir ν_{max}: 3476, 1736, 1640, 1615; ^{1}Hmr δ: 8.05 (1H, bs, N*H*), 7.58 (1H, m, C14′-H), 7.17 (3H, m, C11′–C13′-H's), 6.65 (1H, s, C14-H), 6.16 (1H, s, C17-H), 5.88 (1H, dd, J = 10.5 and 4 Hz, C7-H), 5.51 (1H, s, C4-H), 5.31 (1H, d, J = 10 Hz, C6-H), 4.84 (1H, m, C2′-H), 3.82 (6H, s, 2 × —OC*H*$_3$), 3.78 (1H, s, C2-H), 3.61 (3H, s, —OC*H*$_3$), 2.74 (3H, s, NC*H*$_3$), 2.12 (3H, s, —OCOC*H*$_3$), 0.92 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$), 0.84 (3H, t, J = 7 Hz, —CH$_2$C*H*$_3$); ms *m/e*: 808 (M$^+$), 749, 690, 646 (base peak), 589, 540, 135. *Mol. Wt.* calcd. for $C_{46}H_{56}N_4O_9$: 808.4079; found (high resolution ms): 808.4046.

Catharinol

Catharininol was prepared from the synthetic vinamidine (catharinine) via the literature procedure (5). This material had $[\alpha]_D$ −78° (*c* 0.42, $CHCl_3$) (lit. (5) $[\alpha]_D$ −80°).

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