59. Total Synthesis of Indole and Dihydroindole Alkaloids. XIII[1]). Further Chemistry of Catharanthine

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Summary

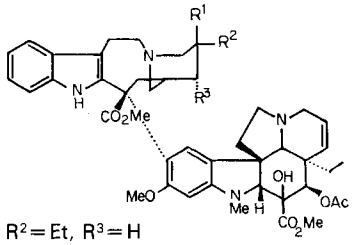
Further investigations on the chemistry of catharanthine have provided information, valuable in the estimation of reactivity and steric requirements of the skeleton. Specific hydroxylations at C(3), C(4) and C(18) have allowed the preparation of several derivatives including (3*R*,4*R*)-3-hydroxy-3,4-dihydrocatharanthine (**7**); (3*R*,4*R*)-3,4-dihydroxycatharanthinic acid lactone (**15**); 18-decarbomethoxy-18-hydroxycatharanthine (**40**).

As part of a continuing effort towards functionalised derivatives of the alkaloid vinblastine (**1**), two strategies have been employed. Elaboration of 3′,4′-dehydrovinblastine (**2**) [1–6], readily available *via* modified *Polonovski* coupling [7–10] between catharanthine (**3**) and vindoline, provided several of the natural products of the vinblastine-vincristine family together with many derivatives. Alternatively selective functionalisation of catharanthine and subsequent *Polonovski* coupling has made available a further series of derivatives [6] [8] [11–19]. The latter route, although often less efficient, has provided unambiguous stereochemical assignment of groups in the 'dimer' molecules.

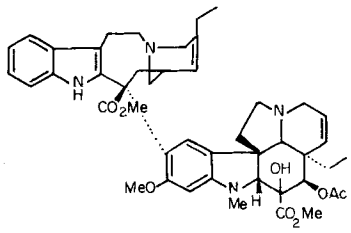
The vinblastine-type alkaloids usually display oxygenation at C(3′) and/or C(4′), thus analogous functions in the catharanthine system were of interest. Several efforts in this area have appeared [4] [6] [11–13] [16–19] and this report describes further investigations of the chemistry of catharanthine.

The glycol **4** and the epoxide **5** have been prepared [16] from catharanthine, and the epoxide converted to the natural product leurosine (**6**) [17]. Alternatively, reaction of catharanthine with borane-methyl sulfide complex in refluxing benzene gave, after oxidation and subsequent equilibration with triethylamine, a secondary alcohol tentatively assigned the structure **7** on mechanistic and steric grounds. The product was readily acetylated to **8** and a triplet at δ 4.64 ppm ($J = 3.5$ Hz), in the ^{1}H-NMR. spectrum, assigned to C(3)–H was consistent with the proposed structure.

[1]) Part XII, [1].



1 R^1=OH, R^2=Et, R^3=H
6 R^1=Et, R^2R^3=–O–
16 R^1=R^3=OH, R^2=Et
19 R^1=Et, R^2=OH, R^3=H



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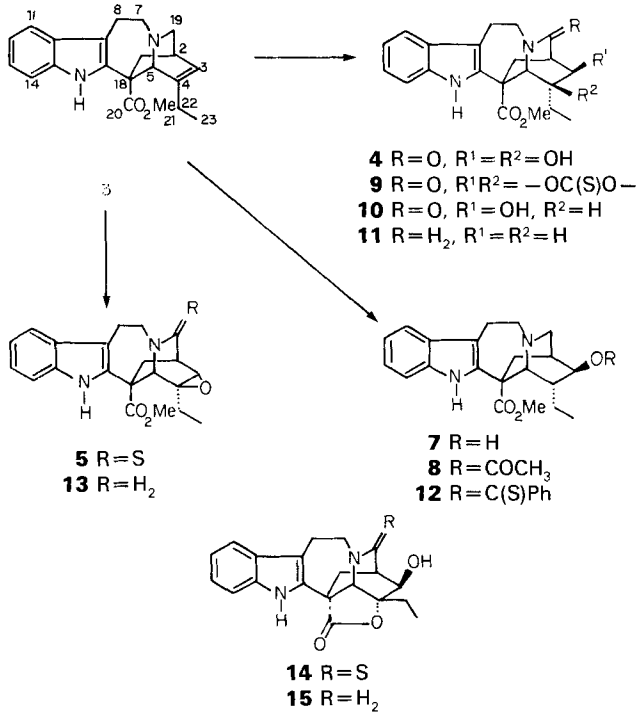
In contrast, treatment of catharanthine with borane-tetrahydrofuran solution at ambient temperature gave no reaction other than amino-borane formation.

Correlation of **7** with the glycol **4** was also possible *(Scheme 1)*. The thionocarbonate **9** was prepared [20], in high yield, from **4**. Adaptation of *Barton*'s [21] [22] deoxygenation procedure readily generated **10** in 65% yield *via* the tertiary radical. Only one of the two possible C(4)-epimers was isolated, and was tentatively assigned the (4*R*)-configuration on steric grounds. Hydrogen atom capture by the intermediate from a molecule of tri-*n*-butylstannane would by necessity occur from the '*β*-face' of the quinuclidine system. Further support for this assignment was available from the ^{1}H-NMR. spectrum of **10**. A doublet at

Scheme 1



4 R=O, R^1=R^2=OH
9 R=O, R^1R^2=–OC(S)O–
10 R=O, R^1=OH, R^2=H
11 R=H_2, R^1=R^2=H

5 R=S
13 R=H_2

7 R=H
8 R=$COCH_3$
12 R=C(S)Ph

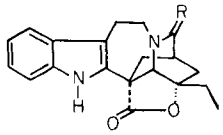
14 R=S
15 R=H_2

δ 4.67 ppm (J=3 Hz), assigned to H–C(5), was consistent with the (4*S*)-configuration of dihydrocatharanthine (**11**) as opposed to that of its 4-epimer, coronaridine. Borane reduction of the lactam **10** provided **7**, identical with that obtained *via* direct hydroboration/oxidation of catharanthine. Alternatively, reaction of (**7**) with the *Vilsmeier* salt from phosgene and *N*,*N*-dimethylbenzamide and *in situ* treatment with hydrogen sulfide gave the relatively unstable thionobenzoate **12** [21]. Radical cleavage with tri-*n*-butylstannane gave dihydrocatharanthine (**11**), identical with an authentic sample. None of the 4-epimer, coronaridine, was detected by thin layer chromatography. Thus the stereochemistry at C(3) and C(4) of the hydroboration product was shown to be as in **7**.

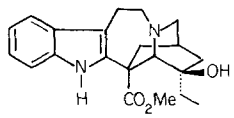
The (3*R*,4*S*)-epoxide **13** has been converted to leurosine (**6**), thus confirming the configuration of the latter [6] [12] [17]. Treatment of **5** with lithium iodide in pyridine effected alkyl-oxygen fission and concomitant lactonisation to yield **14**. Not surprisingly, treatment of **5** with phosphorus pentasulfide in benzene also produced the hydroxylactone **14**. Here phosphorus pentasulfide provided both *Lewis* acid for assisted epoxide opening and a soft *Lewis* base, presumably *via* one of the sulfur atoms, for ester cleavage. Desulfurisation with *Raney*-nickel in ethanol proceeded smoothly to yield the amine **15**. The (3*R*,4*R*)-oxygenation pattern of this product was analogous to that proposed for the dimeric alkaloid vincadioline (**16**) [23].

The potential progenitor **17** for the synthesis of vinblastine (**1**) has been reported [11] [16] [24] [25] and it was of interest to generate the analogous precursor **18** to leurosidine (**19**). The glycol **4**, with the correct configuration at C(4), was an obvious starting material. Both the monotosylate **20** and mesylate **21** were readily prepared from **4**. However, attempts to displace these groups, *e.g.*, with sodium cyanoborohydride in hexamethylphosphoramide, lithium *n*-butylhydridocuprate, lithium bromide in dimethylformamide, and reduction with zinc and sodium iodide in dimethoxyethane, were unsuccessful. Borane reduction of **20** removed only the lactam oxygen to give a mixture of secondary and tertiary tosylates **22** resp. **23**, the latter presumably *via* an intramolecular transesterification. Reduction of **20** with lithium aluminium hydride gave the triol **24**, which was also available by similar reduction of **4**. No 3-deoxy compound was detected. Analogous reduction of the lactone **25** [16] gave the diol **26** and the hemiacetal **27**. Similar treatment of the hydroxyester **28** [16] also yielded **26** and **27**, together with the 18-hydroxy derivative **29**. An attempt to displace the 3-oxygen function of the thionocarbonate **10** using methyl iodide [20] [22] [26] was also unsuccessful, even under forcing conditions.

In view of these and other experiments, the recent report [27] on the preparation of (4*S*)-acetoxy-3,4-dihydrocatharanthine (**30**) seems quite remarkable. In our work, displacement of functions at C(3) or C(4) has proved very difficult. In fact displacement at C(3) by a nucleophile approaching from the 'α-face' of the quinuclidine system has been impossible. On the other hand 4α-functionalisation has been possible only through intramolecular attack by the carboxyl group [16]. An examination of *Dreiding* molecular models showed severe steric crowding on the 'α-face' of the catharanthine skeleton, and in our hands the 'modified *Prévost* reaction' [27] did not transform **3** to **30**.



17 R=H_2
25 R=O



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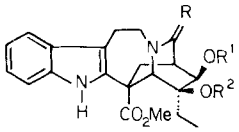
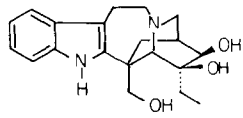


20 R=O, R^1=Ts, R^2=H
21 R=O, R^1=Ms, R^2=H
22 R=H_2, R^1=Ts, R^2=H
23 R=H_2, R^1=H, R^2=Ts



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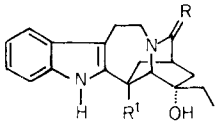
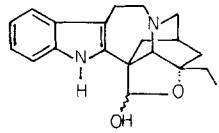


26 R=H_2, R^1=CH_2OH
28 R=O, R^1=CO_2Me
29 R=H_2, R^1=OH



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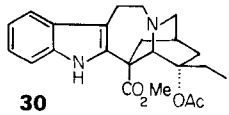

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In connection with other work, a means of radiolabelling catharanthine was sought. To this end, the route outlined in *Scheme 2* was investigated, primarily as a means of introducing ^{14}C at C(20) in the catharanthine skeleton. Here alkaline hydrolysis of **3** followed by an acid-catalysed decarboxylation provided the known [28] decarbomethoxy derivative **31**. Treatment of the corresponding chloroindolenine **32** with potassium cyanide in dimethylacetamide, or with tetra-*n*-butylammonium cyanide in dichloromethane gave low yields of the nitrile **33**. Attempted solvolysis of the nitrile function with methanolic hydrochloric acid gave no observable reaction in accordance with observations by *Büchi et al.* [29] on related systems. Base hydrolysis gave catharanthine (**3**) in only trace amounts but provided 18β-carbomethoxycleavamine (**34**) as the major product. Alternative methods for the radiolabelling of catharanthine were available. The aromatic system could be tritiated using [^3H]-trifluoroacetic acid. The time and temperature for this exchange were quite critical due to the facile acid-catalysed cleavage to **34** *(see Table 1)*. Disproportionation of the intermediate **35** to **34** and the salt **36** accounted for the material balance [30].

Scheme 2

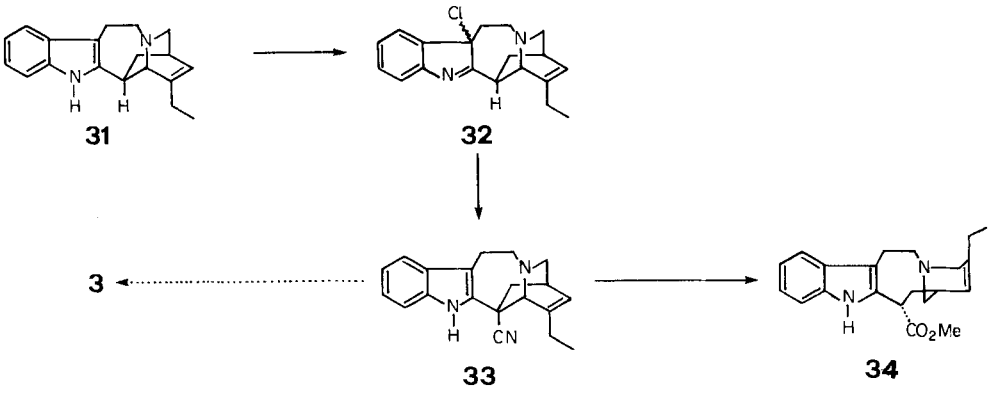


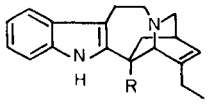
Table. *Reaction of Catharanthine* (3) *with Trifluoroacetic Acid*

Temp. °C	+20	−5	−5	−10	−10	−15	−30
Time (h)	24	24	72	48	50	72	96
% (3)	18	87	40	54	50	49	70
% (34)	41	6	30	-	25	-	-

Direct oxidation of catharanthine (3) with iodine in the presence of sodium hydrogen carbonate gave the known 19-oxo-derivative **37** [16] [31]. The lactam **38** was also isolated, but the mechanism for its formation remains ambiguous.

Reduction of **37** to catharanthine (3) (*e.g.* borane/tetrahydrofuran) provided a potential means of tritiation at C(19). Alternatively, reaction of catharanthinic acid **39**, available in high yield from catharanthine, regenerated **3** with diazomethane in ether thus providing a method of labelling at C(21).

39 R = CO_2H
40 R = OH
41 R = $OCOCH_3$



An attempt to find a more efficient route to the lactone **17** *via* the seleno-lactonisation method [32] was unsuccessful, although the 18-hydroxy derivative **40** was formed in 55% yield, possibly through the intermediacy of the corresponding phenylselenoindolenine. Acetylation of the product gave **41**.

The experiments discussed above have enabled selective hydroxylations at C(3), C(4) and C(18). In addition considerable understanding of the reactivity and steric requirements of the system has been gained.

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 either a *Varian* HA-100 or XL-100 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 done with *Merck* silica gel G (acc. to *Stahl*) containing 2% fluorescent indicator. For preparative layer chromatography, plates of 1 mm thickness were used. Visualisation was effected by viewing under ultraviolet light and/or by colour reaction with ceric sulfate spray reagent. Column chromatography was done with *Merck* silica gel 60 (70–230 mesh) or *Merck* aluminum oxide 90 (neutral).

All reagents and solvents were recrystallized or distilled prior to use.

(*3*R,*4*R)-*3-Hydroxy-3,4-dihydrocatharanthine* (**7**). Catharanthine (**3**) (750 mg) and excess BH_3/Me_2S complex (0.75 ml) were heated in refluxing benzene (60 ml) under N_2 for 24 h. The solution was cooled and concentrated under reduced pressure to a foam, which was dissolved in dry tetrahydrofuran (THF) (60 ml), treated with methanol (5 drops) then 1N NaOH (4.5 ml). A 30% solution of H_2O_2 (3 ml) was added and stirring continued for 2 h. The solution was diluted with water and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4), evaporated and the residue heated in dry THF (30 ml) and triethylamine (30 ml) under reflux for 3 h. Evaporation under reduced pressure and chromatography gave the alcohol **7** (380 mg, 48%). A sample precipitated from ether/petroleum ether had m.p. 120–128°. – UV. (EtOH): 226 (4.40), 277 (3.71), 283 (3.80), 292 (3.71). – IR. ($CHCl_3$): 3600, 3460, 1720, 1465. – NMR. ($CDCl_3$): 7.89 (br. *s*, 1H, NH); 7.1–7.6 (*m*, 4H, arom. H); 3.94 (*d*, J=3.5, 1H, H–C(5)); 3.62 (*s*, 3H, OCH_3); 1.02 (distorted *t*, J=3, 3H, CH_2CH_3). – MS.: 354 (M^+, 100%), 337, 325, 214, 154, 140. – *M:* 354.1949.

$C_{21}H_{26}N_2O_3$ (354.1955) Calc. C 71.60 H 7.39 N 7.90% Found C 71.34 H 7.48 N 7.73%

(*3*R,*4*R)-*3-Acetoxy-3,4-dihydrocatharanthine* (**8**). Acetylation of **7** with acetic anhydride in pyridine at RT. for 3 h gave the acetate **8**; m.p. (ether/petroleum/ether) 176–177°. – UV. (EtOH): 227 (4.36), 277 (3.70), 283 (3.80), 292 (3.70). – IR. ($CHCl_3$): 3450, 1720, 1460. – NMR. ($CDCl_3$): 7.80 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 4H, arom. H); 4.64 (*t*, J=3.5, 1H, H–C(3)); 3.95 (*d*, J=3, 1H, H–C(5)); 3.65 (*s*, 3H, OCH_3); 2.09 (*s*, 3H, $OCOCH_3$); 2.23 (*m*, 2H, CH_2CH_3); 0.93 (distorted *t*, J=7, 3H, CH_2CH_3). – MS.: 396, 336, 229, 228, 168, 154, 138, 135 (100%), 122, 121. – *M:* 396.2037.

$C_{23}H_{28}N_2O_4$ (396.2049) Calc. C 69.67 H 7.12 N 7.07% Found C 69.82 H 7.15 N 7.16%

(*3*R,*4*S)-*Dihydroxy-19-oxo-3,4-dihydrocatharanthine thionocarbonate* (**9**). A solution of the lactam glycol **4** (384 mg) and *N,N'*-thiocarbonyl-diimidazole (712 mg) in butan-2-one (50 ml) was refluxed under N_2 for 18 h. The cooled mixture was partitioned between ethyl acetate and 1N HCl and the

organic phase washed with saturated NaCl solution and saturated $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography gave the thionocarbonate **9** (418 mg, 98%) needles m.p. (methanol) 310–312°. – UV. (MeOH): 223 (4.23), 277 (3.88), 283 (3.93), 292 nm (3.88). – IR. ($CHCl_3$): 3430, 1725. – NMR. ($CDCl_3$ + DMSO-d_6): 10.46 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 4H, arom. H); 4.94 (*s*, 1H, H–C(5)); 4.93 (*d*, *J* = 3, 1H, H–C(3)); 4.4 (*m*, 1H, H–C(2)); 3.68 (*s*, 3H, OCH_3); 1.90 (*q*, *J* = 7, 1H, $CH(H)CH_3$); 1.64 (*q*, *J* = 7, 1H, $CH(H)CH_3$); 1.12 (*t*, *J* = 7, 3H, CH_2CH_3). – MS.: 426 (100%, M^+), 350, 349, 227, 226, 214, 196, 195, 194, 182, 168, 167, 166, 154, 143, 124. – *M*: 426.1248.

$C_{22}H_{22}N_2O_5S.CH_3OH$	Calc.	C 60.25	H 5.72	N 6.11	S 6.99%
(426.1249)	Found	„ 60.07	„ 5.73	„ 5.99	„ 7.25%

(3S,4R)-*3-Hydroxy-19-oxo-3,4-dihydrocatharanthine* (**10**). The thionocarbonate **9** (80 mg) was suspended in refluxing toluene (20 ml) under argon. A solution of excess tributylstannane (0.3 ml) and dibenzoylperoxide (5 mg) in toluene (10 ml) was added very slowly over *ca.* 1 h. After a further 1 h under reflux, the solution was cooled and concentrated under reduced pressure. Chromatography of the residue afforded the alcohol **10** (42 mg, 65%)[2]). Precipitation from ether/petroleum ether gave an amorphous sample m.p. 174–178°. – UV. (EtOH): 222 (4.53), 277 (3.90), 283 (3.94), 292 (3.90). – IR. ($CHCl_3$): 3460, 3150–3500, 1725, 1665, 1465. – NMR. ($CDCl_3$): 8.20 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 4H, arom. H); 4.67 (*d*, *J* = 3, 1H, H–C(5)); 4.4 (*m*, 1H, H–C(2)); 3.58 (*s*, 3H, OCH_3); 0.90 (*t*, *J* = 6, 3H, CH_2CH_3). – MS.: 368 (100%, M^+), 269, 267, 227, 195. – *M*: 368.1720 ($C_{21}H_{24}N_2O_4$: 368.1736).

Borane reduction of **10**. – The lactam **10** (42 mg) and excess 1M BH_3/THF solution (1 ml) were stirred in dry THF (8 ml) under argon for 2 h under reflux. Acetone (1 ml) was added followed by triethylamine (5 ml) and reflux continued for a further 2 h. The mixture was cooled and concentrated i.V., and the residue partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4) and evaporated. Chromatography gave the amine **7** (20 mg, 50%) identical with that prepared earlier.

(3R,4R)-*3-Hydroxy-3,4-dihydrocatharanthine thionobenzoate* (**12**). A solution of the alcohol **7** (35 mg) in dry THF (1 ml) was added to a solution of *N,N*-dimethylphenylchloroimidoyl chloride [prepared [21] from *N,N*-dimethylbenzamide (120 mg) and 12.5% phosgene in benzene solution (1 ml) in dry CH_2Cl_2 (1 ml)] in CH_2Cl_2 (1 ml) and the mixture stirred at RT. for 20 h. CH_2Cl_2 (2 ml) and dry pyridine (0.5 ml) were added. The solution was cooled to 0° and saturated with H_2S for 10 min. The resulting mixture was diluted with CH_2Cl_2, washed with $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated. Chromatography afforded the unstable thionobenzoate **12** (32 mg, 68%). – IR.: 3460, 1720, 1465, 1455. – NMR. ($CDCl_3$): 8.25 (*d* × *d*, *J* = 8 and 2, 2H, arom. H); 7.75 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 7H, arom. H); 5.56 (*t*, *J* = 3.5, 1H, H–C(3)); 4.05 (*d*, *J* = 3, 1H, H–C(5)); 3.67 (*s*, 3H, OCH_3); 1.30 (*m*, 2H, CH_2CH_3); 0.92 (*t*, *J* = 7, 3H). – MS.: 474 (M^+), 472, 336 (100%), 229, 135. – *M*: 474.1978 ($C_{28}H_{30}N_2O_3S$: 474.1978).

Dihydrocatharanthine (**11**). – The thiobenzoate **12** (12 mg) was stirred in dry, refluxing toluene (8 ml) under argon. A solution of tributylstannane (0.05 ml) in toluene (2 ml) was added over a 1 h period. After a total of 2 h at reflux, the clear solution was cooled and evaporated under reduced pressure. Chromatography of the residual oil afforded dihydrocatharanthine (**11**) (6.4 mg, 75%) identical with an authentic sample.

(3R,4R)-*3,4-Dihydroxy-19-thiono-3,4-dihydrocatharanthinic acid lactone* (**14**). a) A solution of the epoxide **5** (19 mg) and excess LiI (67 mg) in dry pyridine (2 ml) was heated under reflux for 23 h. The solution was cooled and evaporated under reduced pressure. Chromatography gave the hydroxylactone **14** (12 mg, 65%). – UV. (EtOH): 222 (4.57), 274 (4.25), 278 (4.25), 281 (4.24), 289 (4.16). – IR. ($CHCl_3$): 3600–3100, 3420, 1770, 1475, 1460. – NMR. ($CDCl_3$): 9.40 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 4H, arom. H); 5.2–5.45 (*m*, 1H, H–C(2)); 4.50 (*d*, *J* = 1, 1H, H–C(5)); 4.20 (*d*, *J* = 3.5, 1H, H–C(3)); 1.08 (*t*, *J* = 7, 3H, CH_2CH_3). – MS.: 368 (M^+, 100%). – *M*: 368.1178 ($C_{20}H_{20}N_2O_3S$: 368.1195).

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[2]) In several experiments where the concentration of the reactants was significantly higher than that reported, 19-oxo-catharanthine (**37**) was also isolated in yields of 10–30%.

b) The epoxide **5** (50 mg) and recrystallized phosphorus pentasulfide (25 mg) were heated in refluxing dry benzene (6 ml) under N_2 for 3 h. The cooled mixture was filtered through a short plug of silica gel. The residue from the filtrate was chromatographed to give the lactone **14** (15 mg, 32%) identical with that prepared above.

(3R,4R)-3,4-Dihydroxy-3,4-dihydrocatharanthinic acid lactone (**15**). – The thiolactam **14** (30 mg) and excess *Raney* nickel were stirred in ethanol (8 ml) for 1 h at RT. The mixture was diluted with CH_2Cl_2, filtered, and evaporated. Chromatography of the residue afforded **15** (15 mg, 54%). – UV. (EtOH): 224 (4.49), 275 (3.79), 282 (3.83), 289 (3.79). – IR. ($CHCl_3$): 3600–3100, 3430, 1770. – NMR. ($CDCl_3$): 9.56 (br. *s*, 1H, NH); 7.1–7.6 (*m*, 4 H, arom. H); 4.08 (br. *d*, $J=2$, 1H, H–C(3)); 1.05 (*t*, $J=7$, 3 H, CH_2CH_3). – MS.: 338 (M^+, 100%), 234, 209. – *M*: 338.1628 ($C_{20}H_{22}N_2O_3$: 338.1631).

(3R,4S)-4-Hydroxy-3-tosyloxy-19-oxo-3,4-dihydrocatharanthine (**20**). The lactam glycol **4** (77 mg) and toluenesulfonyl chloride (190 mg) were heated at 70° in pyridine (2 ml) for 3 days. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate washed with 1N HCl then with saturated NaCl, dried (Na_2SO_4) and evaporated. Chromatography of the residue gave the tosylate **20** (102 mg, 95%). Recrystallization from CH_2Cl_2/hexane gave a sample m.p. 288–289° (dec.). – UV. (MeOH): 223 (4.69), 278 (3.95), 284 (3.99), 293 (3.95). – IR. ($CHCl_3$): 3550, 3430, 1720, 1680. – NMR. ($CDCl_3$): 7.82 (br. *s*, 1H, NH); 7.82 (*d*×*d*, $J=8$ and 2, 2 H, arom. H); 7.05–7.55 (*m*, 6 H, arom. H); 4.62 (*d*, $J=4$, 1H, H–C(3)); 4.60 (*s*, 1H, H–C(5)); 4.3–4.6 (*m*, 1H, H–C(2)); 3.64 (*s*, 3 H, OCH_3); 2.42 (*s*, 3 H, CH_3); 0.98 (*t*, $J=7$, 3 H, CH_2CH_3). – MS.: 538 (M^+, 100%), 383, 366, 228, 227, 214, 195, 168, 167, 155, 154, 144, 143. – *M*: 538.1749 ($C_{28}H_{30}N_2O_7S$: 538.1773).

(3R,4S)-4-Hydroxy-3-mesyloxy-19-oxo-3,4-dihydrocatharanthine (**21**). The lactam glycol **4** (38 mg) and methanesulfonyl chloride (19 mg) were stirred in pyridine (2 ml) at 5° for 17 h. Work-up as described above for the preparation of **20** gave **21** (27 mg, 50%), m.p. (CH_2Cl_2) 293–294° (dec.). – IR. (nujol): 3330, 1735, 1675. – NMR. ($CDCl_3$): 7.80 (br. *s*, 1H, NH); 7.0–7.6 (*m*, 4 H, arom. H); 4.76 (*d*, $J=4$, 1H, H–C(3)); 4.65 (*s*, 1H, H–C(5)); 4.35–4.65 (*m*, 1H, H–C(2)); 3.66 (*s*, 3 H, OCH_3); 3.13 (*s*, 3 H, CH_3); 1.08 (*t*, $J=7$, 3 H, CH_2CH_3). – MS.: 462 (M^+, 100%), 383, 337, 254, 227, 226, 213, 194, 181, 167, 166, 153, 142. – *M*: 462.1443.

$C_{22}H_{26}N_2O_7S$ (462.1461) Calc. C 57.14 H 5.63 N 6.06% Found C 57.43 H 5.80 N 6.09%

(3R,4S)-3-Tosyloxy-4-hydroxy-3,4-dihydrocatharanthine (**22**) *and (3R,4S)-3-Hydroxy-4-tosyloxy-3,4-dihydrocatharanthine* (**23**). The lactam **20** (13.5 mg) and 1M BH_3/THF solution (0.25 ml) were stirred at RT. in dry THF for 4 h. Acetone (1 ml) was added followed by triethylamine (1 ml). The solution was refluxed for 1.5 h, cooled and concentrated. The residue was dissolved in CH_2Cl_2, washed with dilute ammonium hydroxide solution, dried (Na_2SO_4) and evaporated. Chromatography gave the following:

22 (5.2 mg, 40%). – UV. (MeOH): 223 (4.68), 277 (3.94), 285 (3.99), 292 (3.97). – IR. ($CHCl_3$): 3420, 1710. – NMR. ($CDCl_3$): 9.54 (br. *s*, 1H, OH); 7.74 (br. *s*, 1H, NH); 7.84 (*d*, $J=8$, 2 H, arom. H); 7.0–7.6 (*m*, 6 H, arom. H); 4.14–4.3 (*m*, 2 H, H–C(2), H–C(3)); 3.72 (*s*, 1H, H–C(5)); 3.61 (*s*, 3 H, OCH_3); 2.42 (*s*, 3 H, CH_3); 0.73 (*t*, $J=7$, 3 H, CH_2CH_3). – MS.: 524 (M^+), 494, 369, 368, 365, 354, 353, 352, 339, 295, 294, 293, 228, 227, 214, 197, 196, 195, 194, 187, 186, 182, 180, 172, 171, 170, 169, 168, 167, 165, 157, 156, 155, 154, 144, 143, 130, 115, 91 (100%). – *M*: 524.1987 ($C_{28}H_{32}N_2O_6S$: 524.1981).

23 (6.0 mg, 46%). – UV. (MeOH): 223 (4.74), 277 (3.96), 284 (4.01), 292 (3.98). – IR. ($CHCl_3$): 3260–3520, 3440, 1720. – NMR. ($CDCl_3$): 7.92 (br. *s*, 1H, NH); 7.0–7.9 (*m*, 8 H, arom. H); 4.97 (*s*, 1H, H–C(5)); 4.86 (*s*, 1H, OH); 3.61 (*s*, 3 H, OCH_3); 2.42 (*s*, 3 H, CH_3); 0.92 (*t*, $J=7$, 3 H, CH_2CH_3). – MS.: 524 (M^+), 495, 494, 369, 339, 323, 274, 273, 260, 259, 255, 249, 235, 228, 227, 214, 197, 196, 195, 194, 182, 181, 180, 172, 168, 167, 159, 158, 157, 156, 155, 154, 144, 143, 131, 130, 124, 123, 108, 107, 92, 91 (100%).

(3R,4S)-3,4-Dihydroxy-3,4-dihydrocatharanthinol (**24**). a) The lactam tosylate **20** (30 mg) and $LiAlH_4$ (20 mg) were stirred in dry THF (2 ml) at RT. for 18 h. Water (3 drops) was added and the

mixture was filtered and evaporated. Chromatography gave the triol **24** (8 mg, 42%). – UV. (MeOH): 224 (4.56), 275 (3.89), 282 (3.91), 290 (3.86). – IR. ($CHCl_3$): 3525, 3430. – NMR. ($CDCl_3$): 8.53 (br. *s*, 1H, NH); 7.05–7.55 (*m*, 4H, arom. H); 3.88 ($AB \times qa$, $J_{AB}=10$, $\Delta\nu_{AB}=18$, 2H, CH_2OH); 1.08 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 342 (M^+, 100%), 325, 313, 311, 293, 254, 212, 200, 186, 184, 183, 182, 180, 170, 168, 167, 157, 156, 154, 144, 143, 137, 130. – *M*: 342.1961 ($C_{20}H_{26}N_2O_3$: 342.1944).

b) Reduction of the lactam glycol **4** gave the triol **24** (28%) identical with that obtained above.

(4S)-Hydroxy-3,4-dihydrocatharanthinol (**26**) *and (4S)-4,18-Dihydroxy-18-decarbomethoxy-3,4-dihydrocatharanthine* (**29**). a) Reduction of the hydroxy ester **28** (28 mg) with $LiAlH_4$ as described above gave: 1) the diol **29** (4.3 mg, 18%). – UV. (MeOH): 278 (3.87), 283 (3.90), 290 (3.86). – IR. ($CHCl_3$): 3575, 3430. – NMR. ($CDCl_3$): 8.68 (br. *s*, 1H, NH); 7.0–7.55 (*m*, 4H, arom. H); 2.90 (*s*, 1H, H–C(5)); 0.94 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 312 (M^+), 294, 209, 187, 172, 156, 147, 144, 143, 140, 136, 135 (100%). – *M*: 312.1824 ($C_{19}H_{24}N_2O_2$: 312.1838).

2) the diol **26** (2.2 mg, 9%). – UV. (MeOH): 226 (4.51), 278 (3.86), 283 (3.88), 290 (3.84). – IR. ($CHCl_3$): 3600, 3430. – NMR. ($CDCl_3$): 8.52 (br. *s*, 1H, NH); 7.05–7.55 (*m*, 4H, arom. H); 4.07 ($J_{AB}=12$, $\Delta\nu_{AB}=34$, 2H, CH_2OH); 3.50 (*s*, 1H, H–C(5)); 0.94 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 326 (M^+, 100%), 309, 308, 295, 279, 254, 209, 196, 194, 186, 184, 182, 168, 167, 163, 154, 144, 143, 141, 140, 137, 130, 124, 123, 122. – *M*: 326.1994 ($C_{20}H_{26}N_2O_2$: 326.1994).

3) the known hemiacetal **27** (2.5 mg, 10%) identical with an authentic sample.

b) Reduction of the lactam lactone **25** as described above gave the diol **26** (21%) and the hemiacetal **27** (7%).

18-Decarbomethoxycatharanthine (**31**). – Catharanthine (**3**) (810 mg) was heated in NaOH solution (40 ml, 12% *w/v*) and ethanol (40 ml) at reflux for 3.5 h under N_2. At *ca.* 65° conc. hydrochloric acid was added slowly to pH 1. The mixture was cooled and extracted with $CHCl_3$. The extract was dried, concentrated, and chromatographed to give **31** (480 mg, 72%) as colourless needles from methanol; m.p. 92° (lit. [28] m.p. 92–94°). – UV. (EtOH): 226, 275 (3.81), 283 (3.87), 290 (3.85). – IR. ($CHCl_3$): 3475, 2940, 2890, 1470. – NMR. ($CDCl_3$): 7.74 (*s*, 1H, NH); 7.4–7.58 (*m*, 1H, arom. H); 7.00–7.34 (*m*, 3H, arom. H); 5.90 (*d*×*d*, $J=6$ and 2, 1H, H–C(3)); 3.54 (*s*, 1H, H–C(5)); 2.08–2.42 (*m*, 2H, CH_2CH_3); 1.82–2.08 (*m*, 1H, H–C(1)); 1.52–1.78 (*m*, 1H, H–C(1)); 1.08 (*t*, $J=8$, 3H, CH_2CH_3). – MS.: 278 (M^+), 171, 170, 135, 122. – *M*: 278.1774.

$C_{19}H_{22}N_2$ (278.1782) Calc. C 82.01 H 7.91 N 10.07% Found C 81.79 H 8.10 N 9.97%

18-Decarbomethoxycatharanthine chloroindolenine (**32**). – A solution of *N*-chlorobenzotriazole (44.4 mg) in dry benzene (2 ml) was added to **31** (80 mg) in benzene (3 ml). After 30 min at RT. the solution was washed with 10% $NaHCO_3$ solution, dried (Na_2SO_4), concentrated and chromatographed to give **32** (78 mg, 87%). – UV. (MeOH): 227 (4.42), 276 (3.88). – IR. (CH_2Cl_2): 3460, 2960, 2880, 1520. – NMR. ($CDCl_3$): 7.66 (*m*, 1H, arom. H); 6.86–7.32 (*m*, 3H, arom. H); 5.70 (*d*, $J=7$, 1H, H–C(3)); 4.40 (*s*, 1H, H–C(5)); 3.6–3.92 (5 lines *m*, 1H); 2.36–1.96 (*m*, 2H, CH_2CH_3); 0.98 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 314 (M^+), 312 (M^+), 278, 277, 170, 135, 121. – *M*: 312.1410 ($C_{19}H_{21}N_2Cl$: 312.1393).

18-Cyano-18-decarbomethoxycatharanthine (**33**). – a) KCN (104 mg) and **32** (50 mg) were stirred in anhydrous dimethylacetamide (3 ml) at RT. for 30 h. The solution was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated under reduced pressure. Chromatography gave **33** (11 mg, 23%). – UV. (EtOH): 222 (4.47), 275 (3.86), 280 (3.89), 288 (3.86). – IR. ($CHCl_3$): 3740, 2940, 2880, 2230, 1450. – NMR. ($CDCl_3$): 7.88 (*s*, 1H, NH); 7.46–7.58 (*m*, 1H, arom. H); 7.10–7.44 (*m*, 3H, arom. H); 5.94 (*d*×*d*, $J=6$ and 2, 1H, H–C(3)); 1.88–2.82 (complex, 2H, CH_2CH_3); 1.08 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 303 (M^+), 160, 122. – *M*: 303.1731 ($C_{20}H_{21}N_3$: 303.1735).

b) Similarly reaction of **32** with tetrabutylammonium cyanide gave **33** in 20% yield.

Reaction of catharanthine with trifluoroacetic acid. Catharanthine (**3**) was stirred in trifluoroacetic acid at −5° for 72 h. The solution was diluted with CH_2Cl_2, washed with $NaHCO_3$ solution, dried

(Na_2SO_4) and evaporated. Chromatography on silica gel gave catharanthine (**3**) (40%) and 18β-carbomethoxycleavamine (**34**) (30%) identical with authentic samples.

Using [^{3}H]-trifluoroacetic acid at $-5°$ for 48 h, a 54% yield of [Ar^{3}H]-catharanthine (6.39×10^9 dpm/mmol) was obtained.

19-Oxocatharanthine (**37**) *and 18β-carbomethoxy-5-oxocleavamine* (**38**). Iodine (59 mg) in THF (1 ml) was added to a mixture of catharanthine (**3**) (45 mg) and $NaHCO_3$ (65 mg) in water (1 ml) and THF (1.5 ml) at RT. After 30 min the solution was diluted with water and extracted with CH_2Cl_2. The extract was washed, successively with 0.1M sodium thiosulfate solution, water, 2N H_2SO_4, water, and dried (Na_2SO_4). Evaporation under reduced pressure and chromatography gave:

37 (10.4 mg, 22%), m.p. 231° (lit. [31] 235°). – UV. (MeOH): 222, 276 (3.92), 283 (3.95), 292 (3.89). – IR. ($CHCl_3$): 3460, 1725, 1670, 1655. – NMR. ($CDCl_3$): 8.02 (*s*, 1H, NH); 7.34–7.51 (*m*, 1H, arom. H); 7.05–7.22 (*m*, 3H, arom. H); 6.12 (*d*×*d*, *J*=4 and 2, 1H, H–C(3)); 5.05 (*d*, *J*=2, 1H, H–C(5)); 3.94–4.26 (*m*, 1H, H–C(2)); 3.64 (*s*, 3H, OCH_3); 1.05 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 350 (M^+), 228, 227, 195, 168, 167, 154. – *M:* 350.1627 ($C_{21}H_{22}N_2O_3$: 350.1630).

38 (2.9 mg, 6%). – UV. (EtOH): 223 (4.42), 276 (3.81), 283 (3.83), 291 (3.77). – IR. ($CHCl_3$): 3460, 1745, 1720, 1675, 1460 cm^{-1}. – NMR. ($CDCl_3$): 8.20 (*s*, 1H, NH); 7.10–7.64 (*m*, 4H, arom. H); 6.55 (*d*, *J*=8, 1H, H–C(3)); 3.80 (*s*, 3H, OCH_3); 2.18 (*qa*, *J*=7, 2H, CH_2CH_3); 1.00 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 352 (M^+), 336, 293, 291, 264, 263, 229, 228, 227, 214. – *M:* 352.1787 ($C_{21}H_{24}N_2O_3$: 352.1787).

Catharanthinic acid (**39**). Catharanthine (**3**) (200 mg) was heated in 12% NaOH solution (30 ml) and ethanol (30 ml) under reflux for 3.5 h. The solution was cooled to 0° and Amberlite resin IR-124 added until the pH reached *ca.* 7.0. The mixture was filtered and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated i.V. and chromatographed to give **39** (153 mg, 80%); m.p. 189°. – UV. (EtOH): 224 (4.50), 275 (3.82), 282 (3.85), 291 (3.79). – IR. (KBr): 3400, 3040, 2940, 2620–2240, 1700*w*, 1600. – NMR. (CD_3OD): 7.47–6.93 (*m*, 4H, arom. H); 6.07 (*d*, *J*=5, 1H, H–C(3)); 4.48 (*s*, 1H, H–C(5)); 1.07 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 322 (M^+, 100%), 278, 135. – *M:* 322.1670 ($C_{20}H_{22}N_2O_2$: 322.1681).

18-Decarbomethoxy-18-hydroxycatharanthine (**40**). A solution of phenylselenyl chloride (72 mg) in CH_2Cl_2 (3 ml) was added dropwise to a solution of catharanthinic acid (**39**) (64 mg) and triethylamine (42 mg) in CH_2Cl_2 (5 ml) at RT. under N_2. After 30 min the mixture was diluted with CH_2Cl_2, washed with water, dried (Na_2SO_4) and evaporated. Chromatography gave the alcohol **40** (32 mg, 55%). – UV. (MeOH): 275 (3.79), 282 (3.81), 288 (3.75). – IR. ($CHCl_3$): 3600, 3480. – NMR. ($CDCl_3$): 8.53 (br. *s*, 1H, NH); 7.0–7.5 (*m*, 4H, arom. H); 5.86 (*d*, *J*=7, 1H, H–C(3)); 3.52 (*s*, 1H, H–C(5)); 1.02 (*t*, *J*=8, 3H, CH_2CH_3). – MS.: 294 (M^+), 279, 277, 265, 263, 210, 209 (100%), 184, 183, 168. – *M:* 294.173 ($C_{19}H_{22}N_2O$: 294.169).

18-Acetoxy-18-decarbomethoxycatharanthine (**41**). Acetylation of **40** (50 mg) with acetic anhydride in pyridine gave the acetate **41** (42 mg, 74%), m.p. (methanol/petroleum ether) 181–183°. – UV. (MeOH): 273 (3.77), 280 (3.79), 288 (3.72). – IR. ($CHCl_3$): 3500, 1740. – NMR. ($CDCl_3$): 6.06 (*d*, *J*=6, 1H, H–C(3)); 5.19 (*s*, 1H, H–C(5)); 1.96 (*s*, 3H, $OCOCH_3$); 1.02 (*t*, *J*=7, 3H, CH_2CH_3). – MS.: 336 (M^+), 294, 293 (100%), 278, 277, 276, 247, 235, 234, 209, 205, 204. – *M:* 336.152 ($C_{21}H_{24}N_2O_2$: 336.149).

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