Composé **12**. Quantité isolée: 11 mg. F. 200° (déc.). Rf 0,33 (système a); Rf 0,32 (système b); Rf 0,55 (système c); Rf 0,58 (système d); Rf 0,52 (système e).
Dérivé acétylé: F. 194–5° (recristallisé dans EtOH).

$C_{32}H_{32}O_{17}$ (688,57) Calc. C 55,81 H 4,68% Tr. C 55,68 H 4,88%

Composé **13**. Quantité isolée: 2,5 mg. F. 224°. Rf 0,39 (système a); Rf 0,55 (système b); Rf 0,54 (système c); Rf 0,51 (système d); Rf 0,42 (système e).

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155. Total Synthesis of Indole and Dihydroindole Alkaloids. XV[1]). Further Chemistry of Vindoline

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(11.IV.78)

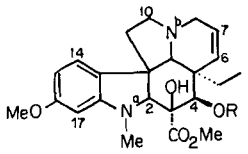
Summary

The general reactivity of various sites in the vindoline series has been investigated. The facility of electrophilic substitution at C(15) and the effect of steric crowding on reactions at C(4) are discussed. At the basic nitrogen sites, oxidations with mercuric acetate and potassium permanganate are also discussed.

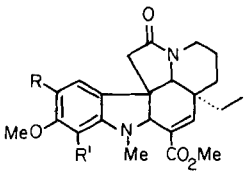
Selective functionalisations of 3′,4′-dehydrovinblastine led to a series of derivatives of the alkaloid vinblastine [2–7]. Alternatively, elaboration of catharanthine and subsequent modified *Polonovski* coupling with vindoline (**1**) provided further examples of the 'dimer' molecules [7–20]. As part of a continuing effort in this area of antineoplastic agents, it was of interest to investigate further

[1]) Part XIV, [1].

the chemistry of vindoline with particular reference to the preparation of derivatives suitable for coupling with catharanthine. The present work describes some transformations within the vindoline skeleton providing insight into the stereochemical requirements of the system and a supplement to the chemistry required for a total synthesis of **1** [1].



1 R = Ac
27 R = H



2 R = R' = H
3 R = Br, R' = H
4 R = R' = Br
5 R = CHO, R' = H

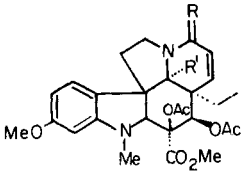
In view of the biological importance of bisindole alkaloids bearing a N_a–CHO group in the vindoline unit (*e.g.* vincristine), we undertook a study of methods for demethylation or oxidation at this position in vindoline derivatives. Direct demethylation of aryl methylamines usually requires forcing reaction conditions and, not surprisingly, *von Braun* reaction of the lactam **2** (see later) with excess cyanogen bromide failed to yield normal cleavage products. When dioxane was the solvent, the 15-bromo derivative **3** was isolated. Similar reaction in benzene gave the dibromide **4** in 77% yield. The formation of these aryl bromides presumably involved the less favoured polarized form of cyanogen bromide [21]. Modified *von Braun* conditions using phenyl chloroformate [22] in ether, acetonitrile or toluene did not give any observable reaction. Treatment of **2** with phenyl chloroformate at *ca.* 110° was also unsuccessful. The use of dimethylformamide as solvent, however, promoted *Vilsmier-Haack* formylation to give the aldehyde **5** in 67% yield.

Protection of N_b was possible by oxidation to either the γ- or δ-lactam using mercuric acetate. Thus, the readily available 3-*O*-acetyl derivative of vindoline (**6**) gave the 8-oxo-compounds **7** and **8** while the dihydro analogue **9** provided the γ-lactam **10** together with **11** and the vinylogous amide **12**. Formation of the cyclic ether lactam **13** from either vindoline or 6,7-dihydrovindoline, using mercuric acetate in refluxing dioxane, has already been described [1], similarly, **15** gave **2**.

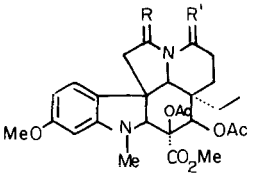
Regeneration of the amines was accomplished by conversion of the amide to the corresponding iminoether followed by reduction of the latter with sodium borohydride, thus **13** gave **14** in 68% yield.

The action of potassium permanganate in acetone solution also promoted oxidation to γ- and δ-lactam derivatives [23–25] with concomitant production of the N_a-formyl function. Here the Δ^3-ester **15** was converted to the lactams **16** and **17**, the former also being available by direct permanganate oxidation of **2**. Similarly the saturated ester **18** afforded **19** and **20**.

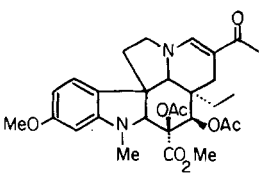
These permanganate oxidations at both N_a and N_b generally proceeded in very poor yield. However in cases where N_b had already been protected as a lactam function, amide formation was quite efficient. In fact **2** gave **16** in 62% yield and the known [1] lactam ether **21** was readily (87%) converted to **22**.



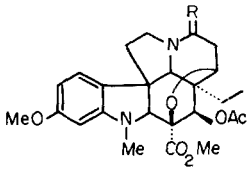
6 R = H_2, R' = H
7 R = O, R' = H
8 R = O, R' = OH



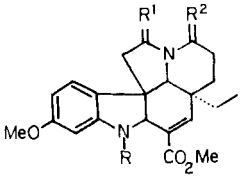
9 R = R' = H_2
10 R = O, R' = H_2
11 R = H_2, R' = O



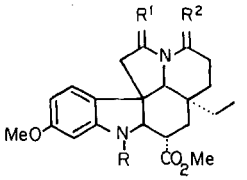
12



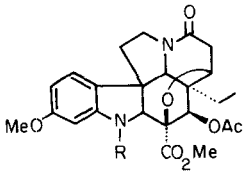
13 R = O
14 R = H_2



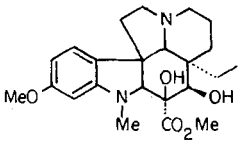
15 R = CH_3, R^1 = R^2 = H_2
16 R = CHO, R^1 = O, R^2 = H_2
17 R = CHO, R^1 = H_2, R^2 = O



18 R = CH_3, R^1 = R^2 = H_2
19 R = CHO, R^1 = O, R^2 = H_2
20 R = CHO, R^1 = H_2, R^2 = O



21 R = CH_3 **22** R = CHO



23

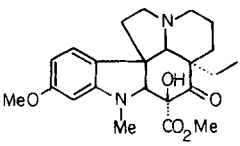
The diacetate **7** failed to react with potassium permanganate under similar conditions probably owing to steric crowding in the region of the N_a nonbonded electrons. On the other hand **6** was oxidized readily at 0° to give a 76% yield of **7**.

It is interesting to compare these results with the facile and selective, analogous chromate oxidations of bisindole derivatives [6].

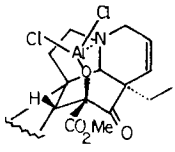
Moffatt oxidation of desacetyldihydrovindoline (**23**) gave the 4-oxo-derivative **24**. The yield of this oxidation was generally *ca.* 55%, but in isolated cases up to 78% of pure **24** could be obtained. Reduction of **24** to **23** was a key step in a total synthesis of vindoline and thus was investigated in some detail. *Büchi et al.* [26] had utilized an aluminium complex **25** to direct hydride reduction of **26** to desacetylvindoline (**27**) (56%). Application of this method to **24**, however did not provide the expected selective attack from the '*a* face' of ring C and gave **23** in only 5% yield. Thus it seems possible that the complex with aluminium chloride[2]) involved bonding with the Δ^6 unsaturation with the N_b lone pair oriented away from the hydroxyl at C(3) as in **28**. Complexation of the latter type is obviously not possible in **24** and as mentioned above no stereoselectivity in hydride reduction was

[2]) It should be noted that *Büchi et al.* [26] offer IR. absorption at 3200–3400 cm^{-1} as evidence for internal hydrogen bonding in **26** thus supporting their assignment **25**. Similar absorption was present in the IR. spectrum of **24**, however molecular models show that this may be due to hydrogen bonding with the carbonyl group at C(4) when ring C is in the chair conformation.

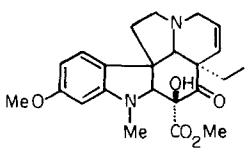
observed. The results obtained from reduction of **24** with several systems are given in *Table 1*.



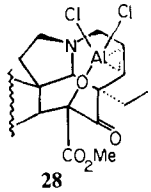
24



25



26



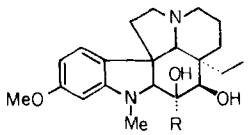
28

Table 1. *Reductions of the ketone* **24**

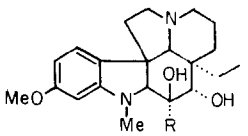
Conditions[a])	% **23**	% **29**	% **30**	% **31**
A	5	–	–	–
B	< 3	14	18	37
C	4	13	–	–
D	9	34	3	3

[a]) Reduction of the complex with $AlCl_3$ using A: sodium bis(2-methoxyethoxy)aluminum hydride [1] [26]; B: $NaBH_4$/THF; C: $Li(OtBu)_3AlH$/THF; D: $LiAlH_4$/THF.

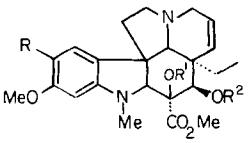
In view of the interest in 'dimer' molecules, of the vinblastine series, with various functionality in ring C of the vindoline unit, transformations of this type within the vindoline skeleton were also studied. Attempted chlorination at C(4) of desacetylvindoline (**27**) using for example thionyl chloride, gave, under a variety of conditions, only the 15-chloro derivative **32**. Reaction of **27** with methanesulfonyl chloride in dichloromethane and triethylamine gave **33** together with a small amount of the di-*O*-methansulfonate **34**. Similar reaction in pyridine gave mainly **35**. Attempted reduction of **35** with sodium iodide/zinc dust in 1,2-dimethoxyethane [27] gave the epoxide **36** presumably *via* the corresponding *trans*-iodohydrin. In fact reaction of **35** with sodium iodide in acetone also afforded **36**. Attack at C(4) by iodide ion is a little surprising in view of the steric crowding at this centre.



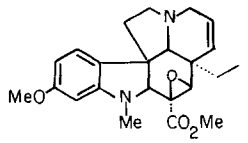
23 R = CO_2Me
30 R = CH_2OH



29 R = CO_2Me
31 R = CH_2OH

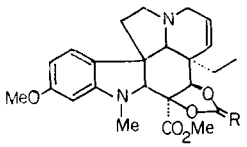


32 R = Cl, $R^1 = R^2 = H$
33 R = H, R^1 = Ms, R^2 = H
34 R = H, $R^1 = R^2$ = Ms
35 R = H, R^1 = H, R^2 = Ms

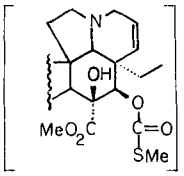


36

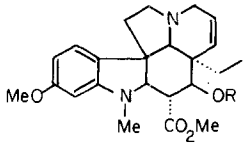
Even more unexpected was the formation of **36** on treatment of the mesylate **35** with lithium *n*-butylhydridocuprate [28] in tetrahydrofuran at 0°. However, here residual iodide ion from the formation of the reagent may have led to the observed product. It was expected that the salt formed from the thioxocarbonate **37** [1] and methyl iodide might undergo displacement at C(4) by iodide but only the carbonate **38** was isolated possibly owing to the intermediacy of the thio-s-carbonate **39** during work-up. Reduction of **37** with tri-*n*-butylstannane [29] gave the expected 3-desoxy derivative **40** which readily formed an acetate and a methanesulfonate. Several attempts to reduce the methanesulfonate **42**, *e.g.* reduction with Zn/NaI, $NaCNBH_3$/HMPA, Li(*n*-BuCuH)/THF, were unsuccessful. In each case the sole product was the α,β-unsaturated ester **43**.



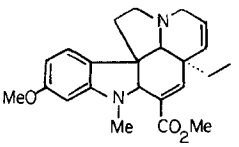
37 R = S
38 R = O



39



40 R = H
41 R = Ac
42 R = Ms



43

These experiments have confirmed the facility of electrophilic attack at C(15) of vindoline derivatives and demonstrated the conformational dependence of ease of reaction in ring C, particularly at C(4), of the vindoline skeleton. Oxidations with mercuric acetate enabled protection of N_b as either a γ- or δ-lactam, whereas with potassium permanganate, oxidation at both N_a and N_b was possible. Application of these results to the preparation of functionalised bisindole compounds will be reported later.

Financial aid from the *National Research Council of Canada* and from Contract N01-CM-23223, *National Cancer Institute, National Institutes of Health*, Bethesda, Maryland, is gratefully acknowledged. We are also grateful to the *Lilly* Research Laboratories for generous gifts of vindoline.

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 (according to *Stahl*) 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 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.

The bromide **3**. A solution of the lactam **2** (24 mg) in dioxane (0.5 ml) was added to cyanogen bromide (96 mg) in dioxane (1.1 ml) at *ca.* 10°, and the mixture stirred at RT. for 22 h, then at 45° for 16 h. The mixture was cooled, poured into dil. NH_4OH-solution and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated. Chromatography of the residue (22 mg) on silica gel gave starting material **2** (4 mg) and the bromide **3** (12.5 mg, 44%) as a colourless oil. – UV. (MeOH): 208, 258, 317. – IR. ($CHCl_3$): 1710, 1680, 1610, 1590. – NMR. ($CDCl_3$): 7.20 (*s*, 1H, H–C(14)); 7.02 (*s*, 1H, H–C(4)), 6.00 (*s*, 1H, H–C(17)), 4.34 (*s*, 1H, H–C(2)), 4.7–4.3 (*m*, 2H, 2H–C(8)), 3.86 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 3.52 (*d*, J=1, 1H, H–C(19)), 2.93 (*d*×*d*, J=18 and 1, H–C(11)), 2.50 (*d*, J=18, 1H, H–C(11)), 2.76 (*s*, 3H, NCH_3), 0.68 (*t*, J=7, 3H, CH_2CH_3). – MS.: 476 (M^+), 474 (M^+), 461, 459, 447, 445, 395, 338, 336, 254, 252, 43.

The dibromide **4**. Cyanogen bromide (57 mg) and the lactam **2** (7 mg) were heated in dry benzene (0.2 ml) at *ca.* 45° for 4 h, then stirred at RT. for 80 h. The mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and filtered through a short plug of silica gel. Evaporation of the filtrate gave **4** (7.5 mg, 77%) as a clear oil. – UV. (MeOH): 267, 317. – IR. ($CHCl_3$): 1710, 1685. – NMR. ($CDCl_3$): 7.20 (*s*, 1H, H–C(14)), 6.88 (br. *s*, 1H, H–C(4)), 4.31 (*s*, 1H, H–C(2)), 4.0–4.25 (*m*, 2H, 2H–C(8)), 3.86 (*s*, 3H, OCH_3), 3.83 (*s*, 3H, OCH_3), 3.54 (br. *s*, 1H, H–C(19)), 3.22 (*s*, 3H, NCH_3), 2.72 (*q*, J=11, 2H, 2H–C(11)), 0.71 (*t*, J=7, 3H, CH_2CH_3). – MS.: 556 (M^+), 554 (M^+), 552 (M^+), 541, 539, 537, 527, 525, 523, 497, 495, 493, 476, 474, 418, 416, 414, 334, 332, 330, 227, 205, 199, 163, 149, 125, 86, 84, 57.

The aldehyde **5**. The lactam **2** (7 mg) and phenyl chloroformate (32 mg) were stirred in dry DMF (0.2 ml) at RT. for 15 min. The mixture was poured into $NaHCO_3$-solution and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave the aldehyde **5** (5 mg, 67%) as an oil. – UV. (MeOH): 212, 262, 310, 358. – IR. ($CHCl_3$): 1720, 1650, 1605. – NMR. ($CDCl_3$): 10.1 (*s*, 1H, CHO), 7.64 (*s*, 1H, H–C(14)), 7.05 (br. *s*, 1H, H–C(4)), 5.80 (*s*, 1H, H–C(17)), 4.57 (*s*, 1H, H–C(2)), 4.15–4.0 (*m*, 2H, 2H–C(8)), 3.88 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 3.57 (br. *s*, 1H, H–C(19)), 2.85 (*s*, 3H, NCH_3), 2.97 (*d*, J=17, 1H, H–C(11)), 2.50 (*d*, J=17, 1H, H–C(11)), 0.66 (*t*, J=8, 3H, CH_2CH_3). – MS.: 424 (M^+), 409, 396, 395, 393, 368, 367, 365, 363, 324, 286, 202.

The acetate **6**. Reaction of vindoline (**1**) with acetic anhydride in pyridine and subsequent chromatography on alumina, gave **6** (90%), m.p. 134–135°. – UV. (EtOH): 212 (4.52), 249 (3.80), 303 (3.68). – IR. (CH_2Cl_2): 1745, 1621, 1616, 1601. – NMR. ($CDCl_3$): 6.92 (*d*, J=8, 1H, H–C(14)), 6.31 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.08 (*d*, J=2, 1H, H–C(17)), 5.85 (*d*×*d*×*d*, J=10, 5 and 2, 1H, H–C(7)), 5.48 (*s*, 1H, H–C(4)), 5.23 (*d*×*t*, J=10 and 2, 1H, H–C(6)), 3.94 (*s*, 1H, H–C(2)), 3.75 (*s*, 3H, OCH_3), 3.72 (*s*, 3H, OCH_3), 2.71 (*s*, 3H, NCH_3), 1.96 (*s*, 6H, 2 $OCOCH_3$), 0.50 (*t*, J=7, 3H, CH_2CH_3). – MS.: 498 (M^+), 469, 468, 467, 456, 455, 439, 397, 380, 379, 324, 296, 266, 214, 189, 188, 174, 161, 136, 135, 122, 121, 107, 43. – Mol-wt.: 498.2243.

$C_{27}H_{34}N_2O_7$ (498.2365) Calc. C 65.04 H 6.87 N 5.62% Found C 65.00 H 6.89 N 5.42%

The δ-lactams **7** *and* **8**. a) The diacetate **6** (220 mg) and mercuric acetate (705 mg) were heated at reflux in dioxane (5 ml) for 4.5 h. The mixture was cooled, diluted with methanol (50 ml) and treated with H_2S for 15 min, followed by N_2 for 10 min. The mixture was further diluted with 4N NH_4OH, filtered and evaporated. The residue was partitioned between 2N NH_4OH and CH_2Cl_2. The organic phase was washed with NH_4Cl-solution, dried (Na_2SO_4) and concentrated in vacuum. Chromatography on silica gel gave:

– the lactam **7** (43 mg, 19%), m.p. >250°. – UV. (EtOH): 214 (4.66), 251 (3.95), 302 (3.76). – IR. (CH_2Cl_2): 1760, 1668, 1612. – NMR. ($CDCl_3$): 6.87 (*d*, J=8, 1H, H–C(14)), 6.36 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.18 (*d*, J=2, 1H, H–C(17)), 6.01 (*d*, J=10, 1H, H–C(7)), 5.91 (*d*, J=10, 1H, H–C(6)),

5.29 (*s*, 1H, H–C(4)), 4.23 (*s*, 1H, H–C(2)), 3.79 (*s*, 3H, OCH_3), 3.73 (*s*, 3H, OCH_3), 3.63 (*s*, 1H, H–C(19)), 2.84 (*s*, 3H, NCH_3), 2.02 (*s*, 3H, $OCOCH_3$), 2.00 (*s*, 3H, $OCOCH_3$), 0.73 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 512 (M^+), 483, 482, 470, 453, 411, 395, 394, 393, 379, 377, 329, 309, 215, 203, 189, 188, 187, 174, 172, 159, 144, 43. – Mol-wt.: 512.2094, $C_{27}H_{32}N_2O_8$ (512.2157).

– the lactam **8** (79 mg, 34%). – UV. (EtOH): 214 (4.64), 249 (3.94), 300 (3.70). – IR. (CH_2Cl_2): 3850, 3300, 1760, 1669, 1601. – NMR. ($CDCl_3$): 7.60 (*d*, $J=8$, 1H, H–C(14)), 6.32 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.13 (*d*, $J=10$, 1H, H–C(7)), 6.11 (*d*, $J=2$, 1H, H–C(17)), 5.89 (*d*, $J=10$, 1H, H–C(6)), 5.39 (*s*, 1H, H–C(4)), 4.95 (*s*, 1H, OH), 3.73 (*s*, 3H, OCH_3), 3.65 (*s*, 3H, OCH_3), 3.41 (*s*, 1H, H–C(2)), 2.79 (*s*, 3H, NCH_3), 1.97 (*s*, 3H, $OCOCH_3$), 1.91 (*s*, 3H, $OCOCH_3$), 0.94 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 528 (M^+), 513, 512, 498, 497, 486, 485, 469, 468, 427, 410, 409, 397, 377, 349, 326, 325, 309, 228, 214, 188, 187, 174, 173, 172, 159, 157, 43. – Mol-wt.: 528.1996, $C_{27}H_{32}N_2O_9$ (528.2106).

b) Potassium permanganate (189 mg) was added, over 30 min, to a solution of the diacetate **6** (300 mg) in acetone (18 ml) at 0°. After a total of 50 min, methanol (1 ml) was added, and the mixture filtered through *Celite*. Evaporation of the filtrate gave a residue (370 mg) which after chromatography on silica gel gave **7** (235 mg, 76%) and **8** (15 mg, 5%) identical with respective authentic samples.

The diacetate **9**. Acetylation of dihydrovindoline in the usual manner gave **9** (96%), m.p. 172–173°. – UV. (EtOH): 211 (4.59), 247 (3.87), 301 (3.75). – IR. (CH_2Cl_2): 1752, 1618, 1600. – NMR. ($CDCl_3$): 7.00 (*d*, $J=8$, 1H, H–C(14)), 6.36 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.09 (*d*, $J=2$, 1H, H–C(17)), 5.95 (*s*, 1H, H–C(4)), 3.78 (*s*, 6H, 2 OCH_3), 3.69 (*s*, 1H, H–C(2)), 2.63 (*s*, 3H, NCH_3), 2.05 (*s*, 3H, $OCOCH_3$), 1.98 (*s*, 3H, $OCOCH_3$), 0.51 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 500 (M^+), 470, 469, 458, 457, 441, 427, 399, 382, 367, 326, 299, 298, 188, 174, 124 (100%), 43. – Mol-wt.: 500.2523.

$C_{27}H_{36}N_2O_7$ (500.2522) Calc. C 64.78 H 7.25 N 5.60% Found C 64.53 H 6.97 N 5.33%

The lactams **10** *and* **11** *and the vinylogous amide* **12**. Mercuric acetate (797 mg) and the diacetate **9** (250 mg) were heated in dry dioxane (5 ml) under reflux in an atmosphere of N_2 for 24 h. Work-up as described above gave:

– starting material **9** (22 mg); – the γ-lactam **10** (69 mg, 29%), m.p. (ethyl acetate/ether) 227–228.5°. – UV. (EtOH): 212 (4.64), 247 (3.87), 300 (3.72). – IR. (CH_2Cl_2): 1755, 1679, 1618, 1603. – NMR. ($CDCl_3$): 6.96 (*d*, $J=8$, 1H, H–C(14)), 6.36 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.08 (*d*, $J=2$, 1H, H–C(17)), 5.67 (*s*, 1H, H–C(4)), 4.16 (br. *d*, $J=13$, 1H, H–C(8)), 3.74 (*s*, 6H, 2 OCH_3), 3.69 (*s*, 1H, H–C(2)), 3.45 (*s*, 1H, H–C(19)), 3.07 (br. *d*, $J=17$, 1H, H–C(11)), 2.65 (*d*, $J=17$, 1H, H–C(11)), 2.61 (*s*, 3H, NCH_3), 2.08 (*s*, 3H, $OCOCH_3$), 1.97 (*s*, 3H, $OCOCH_3$), 0.53 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 514 (M^+), 484, 483, 472, 471, 455, 454, 413, 396, 395, 381, 312, 270, 254, 214, 212, 201, 188, 175, 174, 159, 111, 110, 43. – Mol-wt.: 514.2312.

$C_{27}H_{34}N_2O_8$ (514.2313) Calc. C 63.02 H 6.66 N 5.44% Found C 62.74 H 6.44 N 5.39%

– the δ-lactam **11** (53 mg, 22%), m.p. (ethyl acetate/ether) 174–175.5°. – UV. (EtOH): 213 (4.57), 250 (3.81), 304 (3.79). – IR. (CH_2Cl_2): 1758, 1643, 1618, 1600. – NMR. ($CDCl_3$): 6.85 (*d*, $J=8$, 1H, H–C(14)), 6.32 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.12 (*d*, $J=2$, 1H, H–C(17)), 5.30 (*s*, 1H, H–C(4)), 3.94 (*s*, 1H, H–C(2)), 3.75 (*s*, 3H, OCH_3), 3.71 (*s*, 3H, OCH_3), 3.58 (*s*, 1H, H–C(19)), 2.76 (*s*, 3H, NCH_3), 2.07 (*s*, 3H, $OCOCH_3$), 1.99 (*s*, 3H, $OCOCH_3$), 0.76 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 514 (M^+), 484, 483, 471, 455, 454, 413, 396, 395, 381, 336, 312, 263, 215, 213, 188, 187, 174, 173, 172, 157, 149, 43. – Mol-wt.: 514.2253, $C_{27}H_{34}N_2O_8$ (514.2313).

– the vinylogous amide **12** (65 mg, 26%), m.p. (ethyl acetate/ether) 243–244°. – UV. (EtOH): 212 (4.45), 246 (3.72), 316 (4.36). – IR. (CH_2Cl_2): 1755, 1736, 1627, 1615, 1595. – NMR. ($CDCl_3$): 7.35 (br. *s*, 1H, H–C(8)), 6.92 (*d*, $J=8$, 1H, H–C(14)), 6.35 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.09 (*d*, $J=2$, 1H, H–C(17)), 5.73 (*s*, 1H, H–C(4)), 3.75 (*s*, 3H, OCH_3), 3.71 (*s*, 3H, OCH_3), 3.64 (*s*, 1H, H–C(2)), 3.43 (*s*, 1H, H–C(19)), 2.67 (*s*, 3H, NCH_3), 2.10 (*s*, 3H, $OCOCH_3$), 2.05 (*s*, 3H, $OCOCH_3$), 1.83 (*s*, 3H, $COCH_3$), 0.59 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 540 (M^+), 526, 525, 511, 510, 509, 498, 497, 481, 480, 442, 423, 422, 421, 366, 388, 308, 189, 188, 177, 174, 164, 161, 125, 122, 110, 43. – Mol-wt.: 540.2443, $C_{29}H_{36}N_2O_8$ (540.2472).

The ether **14**. A solution of the lactam ether **13** (47 mg) in dry CH_2Cl_2 (2 ml) was added to a suspension of trimethyloxonium tetrafluoroborate (59 mg) in CH_2Cl_2 (2 ml). The mixture was stirred at RT. for 22 h, evaporated and the residue dissolved in dry ethanol (2 ml). This solution was cooled to 0° and treated with $NaBH_4$ (15 mg). After 20 h at RT., a few drops of water were added, and the solvents removed in vacuum. Chromatography on silica gel gave:

– starting material (15 mg); – the ether **14** (21 mg, 68%). – UV. (EtOH): 214 (4.44), 257 (3.81), 308 (3.66). – IR. (CH_2Cl_2): 1745, 1613, 1598. – NMR. ($CDCl_3$): 6.91 (*d*, $J=8$, 1H, H–C(14)), 6.25 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.03 (*d*, $J=2$, 1H, H–C(17)), 5.40 (*s*, 1H, H–C(4)), 4.08 (*m*, 1H, H–C(6)), 3.80 (*s*, 3H, OCH_3), 3.77 (*s*, 3H, OCH_3), 3.69 (*s*, 1H, H–C(2)), 3.59 (*s*, 1H, H–C(19)), 2.79 (*s*, 3H, NCH_3), 1.95 (*s*, 3H, $OCOCH_3$), 0.82 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 456 (M^+), 442, 426, 425, 413, 411, 397, 369, 311, 297, 282, 267, 202, 188, 174, 173, 158, 124, 123, 122, 121, 108. – Mol-wt.: 456.2272, $C_{25}H_{32}N_2O_6$ (456.2259).

The N*-formyl derivatives* **16** *and* **17**. a) Magnesium sulfate (35 mg) and $KMnO_4$ (8 mg) were added to a solution of the lactam **2** (7 mg) in acetone (0.5 ml) and the mixture stirred at RT. Excess $KMnO_4$ (12 mg) was added in 3 portions over a total of 6 h. Methanol (3 drops) was added and the mixture filtered. Chromatography on silica gel gave the amide **16** (4.5 mg, 62%). – UV. (MeOH): 203, 218, 248, 298. – IR. ($CHCl_3$): 1720, 1665, 1595. – NMR. ($CDCl_3$): 8.63 (br. *s*, 1H, NCHO), 7.75 (br. *s*, 1H, H–C(17)), 7.18 (*d*, $J=8$, 1H, H–C(14)), 7.03 (br. *s*, 1H, H–C(4)), 6.72 (*d*×*d*, $J=8$ and 2.5, 1H, H–C(15)), 5.14 (*s*, 1H, H–C(2)), 3.85 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 3.63 (*s*, 1H, H–C(19)), 2.84 (br. *d*, $J=18$, 1H, H–C(11)), 2.75 (*d*, $J=18$, 1H, H–C(11)), 0.68 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 410 (M^+), 382, 357, 356 (m*), 321, 160, 78.

b) Oxidation of **15** with $KMnO_4$ as described above gave:

– the *γ*-lactam **16** (12%); – the *δ*-lactam **17** (2%). – UV. (MeOH): 215, 248, 293. – IR. ($CHCl_3$): 1715, 1675, 1630, 1600. – NMR. ($CDCl_3$): 8.85 (br. *s*, 1H, NCHO), 7.65 (br. *s*, 1H, H–C(17)), 7.08 (*d*, $J=8$, 1H, H–C(14)), 6.89 (*s*, 1H, H–C(4)), 6.69 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 4.85 (br. *s*, 1H, H–C(2)), 3.83 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 0.77 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 410 (M^+), 382, 367, 321, 283, 251, 173, 160.

The N*-formyl derivatives* **19** *and* **20**. Oxidation of the ester **18** with $KMnO_4$, as described above, gave:

– the *γ*-lactam **19** (7%). – UV. (MeOH): 218, 248, 298. – IR. ($CHCl_3$): 1730, 1680, 1620, 1600. – NMR. ($CDCl_3$): 7.12 (*d*, $J=9$, 1H, H–C(14)), 6.67 (*d*×*d*, $J=9$ and 2.5, 1H, H–C(15)), 4.68 (*d*, $J=3$, 1H, H–C(2)), 3.82 (*s*, 3H, OCH_3), 3.76 (*s*, 3H, OCH_3), 3.40 (*s*, 1H, H–C(19)), 2.84 (*d*, $J=17$, 1H, H–C(11)), 2.59 (*d*, $J=17$, 1H, H–C(11)), 0.60 (distorted *t*, 3H, CH_2CH_3). – MS.: 412 (M^+), 398, 384, 358 (m*), 323, 262, 160, 145, 117, 111.

– the *δ*-lactam **20** (4%). – UV. (MeOH): 215, 248, 295. – IR. ($CHCl_3$): 1730, 1680, 1650, 1600. – NMR. ($CDCl_3$): 7.04 (*d*, $J=8$, 1H, H–C(14)), 6.67 (*d*×*d*, $J=8$ and 2.5, 1H, H–C(15)), 4.77 (*m*, 1H, H–C(2)), 3.85 (*s*, 3H, OCH_3), 3.74 (*s*, 3H, OCH_3), 3.60 (*s*, 1H, H–C(19)), 0.75 (distorted *t*, 3H, CH_2CH_3). – MS.: 412 (M^+), 398, 384, 358 (m*), 351, 323, 201, 174, 173, 160, 138, 110.

The amide **22**. Oxidation of the lactam ether **21** with $KMnO_4$, as described above, gave the amide **22** (87%). – UV. (MeOH): 219 (4.41), 248 (3.94), 297 (3.79). – IR. ($CHCl_3$): 1755, 1680–1650, 1595. – NMR. ($CDCl_3$): 8.74 (*s*, 1H, NCHO), 6.77 (*s*, 1H, H–C(17)), 6.72 (*d*×*d*, $J=8$ and 2.5, 1H, H–C(15)), 7.12 (*d*, $J=8$, 1H, H–C(14)), 5.59 (*s*, 1H, H–C(4)), 4.63 (*s*, 1H, H–C(2)), 4.12 (*s*, 1H, H–C(19)), 3.80 (*s*, 3H, OCH_3), 3.69 (*s*, 3H, OCH_3), 1.90 (*s*, 3H, $OCOCH_3$), 0.88 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 484 (M^+), 456, 432 (m*), 426, 397, 202, 201, 174, 173, 78.

The ketone **24**. Desacetyldihydrovindoline **23** (100 mg), anhydrous H_3PO_4[3]) (0.4 ml of a 1M solution in DMSO) and DCC (262 mg) were stirred in dry DMSO (3 ml) under a N_2 atmosphere at RT. for 23 h. Chromatography on alumina gave the ketone **24** (56 mg, 56%). – UV. (EtOH): 213 (4.49), 248 (3.81), 303 (3.67). – IR. ($CHCl_3$): 3450–2450, 1748, 1712, 1616. – NMR. ($CDCl_3$): 6.96 (*d*, $J=8$, 1H, H–C(14)), 6.36 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.11 (*d*, $J=2$, 1H, H–C(17)), 3.83 (*s*, 3H, OCH_3), 3.75 (*s*, 3H, OCH_3), 2.64 (*s*, 3H, NCH_3), 0.51 (*t*, $J=7$, 3H, CH_2CH_3). – MS.: 414 (M^+), 258, 188, 174, 124. – Mol-wt.: 414.214, $C_{23}H_{30}N_2O_5$ (414.215).

Reduction of **24** *to the alcohols* **23**, **29**, **30** *and* **31**. a) $NaBH_4$ (50 mg) was added to a solution of the ketone **24** (48 mg) in dry THF (10 ml), and the mixture stirred at RT. for 16 h. The mixture was cooled to 0° and treated with 2N HCl (2 drops). Most of the solvent was removed in vacuum, the residue diluted with 4N NH_4OH and extracted with CH_2Cl_2. The extract was washed with water, dried (Na_2SO_4) and concentrated in vacuum. Chromatography on silica gel gave:

– the diol **29** (6.9 mg, 14%). – UV. (EtOH): 213 (4.46), 254 (3.76), 305 (3.63). – IR. (CH_2Cl_2): 3520, 1737, 1718, 1616, 1601. – NMR. ($CDCl_3$): 6.96 (*d*, $J=8$, 1H, H–C(14)), 6.32 (*d*×*d*, $J=8$ and 2, 1H, H–C(15)), 6.10 (*d*, $J=2$, 1H, H–C(17)), 3.86 (*s*, 3H, OCH_3), 3.77 (*s*, 3H, OCH_3), 3.82 (*s*, 1H, H–C(2)),

[3]) P_2O_5 was added to 85% H_3PO_4 until no further reaction was observed and a solid deposit was visible. The supernatant liquid was used as anhydrous H_3PO_4.

2.77 (*s*, 3 H, NCH_3), 0.52 (*t*, $J = 7.5$, 3 H, CH_2CH_3). – MS.: 416 (M^+), 399, 398, 386, 357, 327, 298, 268, 242, 188, 174, 124 (100%). – Mol-wt.: 416.2211, $C_{23}H_{32}N_2O_5$ (416.2310).

– the triol **30** (8 mg, 18%), m.p. (methanol/ether) 174–176°. – UV. (EtOH): 213 (4.52), 251 (3.88), 303 (3.74). – IR. (CH_2Cl_2): 3450, 1617, 1603. – NMR. ($CDCl_3$): 6.85 (*d*, $J = 8$, 1H, H–C(14)), 6.32 (*d*×*d*, $J = 8$ and 2, 1H, H–C(15)), 6.10 (*d*, $J = 2$, 1H, H–C(17)), 3.78 (*s*, 3 H, OCH_3), 2.95 (*s*, 3 H, NCH_3), 0.65 (distorted *t*, 3 H, CH_2CH_3). – MS.: 388 (M^+), 371, 358, 327, 301, 300, 299, 251, 214, 196, 188, 187, 174, 124 (100%). – Mol.-wt.: 388.2333, $C_{22}H_{32}N_2O_4$ (388.2361).

– the triol **31** (16.5 mg, 37%), m.p. (ether) 148.5–149.5°. – UV. (EtOH): 213 (4.44), 250 (3.77), 302 (3.65). – IR. (CH_2Cl_2): 3540, 3450, 1614, 1599. – NMR. ($CDCl_3$): 9.5 (br. *s*, 1H, OH), 6.96 (*d*, $J = 8$, 1H, H–C(14)), 6.40 (*d*×*d*, $J = 8$ and 2, 1H, H–C(15)), 6.17 (*d*, $J = 2$, 1H, H–C(17)), 3.97 (br. *s*, 2 H, CH_2OH), 3.77 (*s*, 3 H, OCH_3), 3.68 (*d*, $J = 1.5$, 1H, H–C(2)), 3.38 (*d*, $J = 1.5$, 1H, H–C(4)), 2.89 (*s*, 3 H, NCH_3), 0.52 (*t*, $J = 7$, 3 H, CH_2CH_3). – MS.: 388 (M^+), 371, 370, 357, 302, 301, 300, 299, 269, 214, 196, 188, 174, 124 (100%). – Mol-wt.: 388.2336.

$C_{22}H_{32}N_2O_4$ (388.2361) Calc. C 68.01 H 8.30 N 7.21% Found C 67.97 H 8.29 N 6.97%

b) Reduction of desacetyldihydrovindoline **23** with excess $LiAlH_4$ in refluxing THF gave (95%) the triol **30** identical with that obtained above.

c) $Li(OtBu)_3AlH$ (204 mg) was added to a solution of the ketone **24** (200 mg) in dry THF (40 ml). The solution was heated at reflux under N_2 for 5.5 h, cooled and diluted with methanol (5 ml) then 4N NH_4OH (5 ml). The mixture was filtered through a *Celite* pad and the filtrate concentrated in vacuum. The residue was partitioned between 4N NH_4OH and CH_2Cl_2. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave: starting material **24** (13.7 mg), the diol **29** (24 mg, 13%), and the diol **23** (8 mg, 4%).

d) $LiAlH_4$ (20 mg) was added to a solution of the ketone **24** (110 mg) in dry THF (20 ml) at −78°. The mixture was stirred at −65 to −75° for 110 h. Excess $LiAlH_4$ was destroyed by the addition of 2 drops of water. The solvent was evaporated in vacuum. Work-up as described above gave: starting material **24** (33 mg), the diol **29** (26 mg, 34%), the diol **23** (7 mg, 9%), the triol **30** (2 mg, 3%), and the triol **31** (2 mg, 3%).

The 15-chloro compound **32**. A solution of **27** (30 mg), $SOCl_2$ (45 mg) and pyridine (1 ml) in CH_2Cl_2 (3 ml) was allowed to stand at *ca.* 5° for 24 h. The solution was concentrated in vacuum and the residue dissolved in $CHCl_3$, washed with water and the solution dried (Na_2SO_4), and evaporated. Chromatography on silica gel gave **32** (23 mg, 71%). – IR. ($CHCl_3$): 3650, 1750. – NMR. ($CDCl_3$): 6.92 (*s*, 1 H, H–C(14)), 6.09 (*s*, 1H, H–C(17)), 5.82 (br. *s*, 2 H, H–C(6) and H–C(7)), 4.08 (*s*, 1H, H–C(4)), 3.86 (*s*, 3 H, OCH_3), 3.82 (*s*, 3 H, OCH_3), 3.72 (*s*, 1H, H–C(2)), 2.71 (*s*, 3 H, NCH_3), 2.68 (*s*, 1H, H–C(19)), 0.67 (*t*, $J = 7$, 3 H, CH_2CH_3). – MS.: 450 (M^+), 448 (M^+), 332, 331, 330, 250, 241, 240, 223, 222 (100%), 208, 134, 121, 120. – Mol-wt.: 448.1777, $C_{23}H_{29}N_2O_5Cl$ (448.1765).

The methanesulfonates **33**, **34** *and* **35**. a) Methanesulfonyl chloride (11 mg) was added to a solution of **27** (41 mg) and Et_3N (10 mg) in CH_2Cl_2 (2 ml) at 0°. After stirring at 0° for 2 h, the mixture was poured into ice water and extracted with $CHCl_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. Chromatography of the residue on silica gel gave:

– starting material **27** (25 mg); – the tertiary methanesulfonate **33** (12 mg, 25%), m.p. (MeOH) 135–136°. – UV. (MeOH): 252 (3.84), 304 (3.72). – IR. ($CHCl_3$): 3575, 1735. – NMR. ($CDCl_3$): 6.85 (*d*, $J = 8$, 1H, H–C(14)), 6.23 (*d*×*d*, $J = 8$ and 2, 1H, H–C(15)), 5.99 (*d*, $J = 2$, 1H, H–C(17)), 5.84 (br. *d*×*d*, $J = 10$ and 5, 1H, H–C(7)), 5.61 (br. *d*, $J = 10$, 1H, H–C(6)), 4.12 (*s*, 1H, H–C(4)), 3.94 (*s*, 1H, H–C(2)), 3.74 (*s*, 3 H, OCH_3), 3.70 (*s*, 3 H, OCH_3), 3.14 (*s*, 3 H, OSO_2CH_3), 2.78 (*s*, 3 H, NCH_3).

$C_{24}H_{32}N_2O_7S \cdot H_2O$ (510.59) Calc. C 56.45 H 6.71 N 5.49% Found C 56.44 H 6.28 N 5.33%

– the dimethanesulfonate **34** (4 mg, 8%), m.p. (MeOH) 137–138°. – UV. (MeOH): 242 (3.85), 297 (3.74). – IR. ($CHCl_3$): 1750. – NMR. ($CDCl_3$): 6.94 (*d*, $J = 8$, 1H, H–C(14)), 6.35 (*d*×*d*, $J = 8$ and 2, 1H, H–C(15)), 6.06 (*d*, $J = 2$, 1H, H–C(17)), 5.88 (br. *d*×*d*, $J = 10$ and 4, 1H, H–C(7)), 5.49 (*d*, $J = 10$, 1H, H–C(6)), 5.41 (*s*, 1H, H–C(4)), 3.86 (*s*, 3 H, OCH_3), 382 (*s*, 1H, H–C(2)), 3.72 (*s*, 3 H, OCH_3), 3.09 (*s*, 6 H, 2 OSO_2CH_3), 2.61 (*s*, 3 H, NMe).

$C_{25}H_{34}N_2O_9S_2$ (570.66) Calc. C 52.62 H 6.01 N 4.91% Found C 52.60 H 5.94 N 4.93%

b) A solution of **27** (41 mg) and methanesulfonyl chloride (11 mg) in pyridine (2 ml) was allowed to stand at 0° for 24 h. Work-up as described above gave:

– the starting material **27** (18 mg); – the secondary methanesulfonate **35** (16 mg, 32%), m.p. (MeOH) 151–152°. – UV. (MeOH): 248 (3.86), 302 (3.76). – IR. ($CHCl_3$): 1740. – NMR. ($CDCl_3$): 6.92 (*d*, J=8, 1H, H–C(14)), 6.34 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.11 (*d*, J=2, 1H, H–C(17)), 5.95 (br. *d*×*d*, J=10 and 4, 1H, H–C(7)), 5.67 (br. *d*, J=10, 1H, H–C(6)), 5.22 (*s*, 1H, H–C(4)), 3.85 (*s*, 3H, OCH_3), 3.78 (*s*, 3H, OCH_3), 3.16 (*s*, 3H, OSO_2CH_3), 2.69 (*s*, 3H, NCH_3), 0.54 (*t*, J=7, 3H, CH_2CH_3).

$C_{24}H_{32}N_2O_7S$ (492.57) Calc. C 58.52 H 6.55 N 5.69% Found C 58.99 H 6.58 N 5.46%

The epoxide **36**. a) A mixture of the methanesulfonate **35** (57 mg), NaI (75 mg) and Zn dust (200 mg) was heated in refluxing 1,2-dimethoxyethane (10 ml) for 10 h. The mixture was cooled, filtered and the filtrate evaporated. Chromatography of the residue on silica gel gave the epoxide **36** (28 mg, 61%). – UV. (MeOH): 258 (3.90), 312 (3.62). – IR. ($CHCl_3$): 1725, 1620. – NMR. ($CDCl_3$): 6.92 (*d*, J=8, 1H, H–C(14)), 6.17 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 5.93 (*d*, J=2, 1H, H–C(17)), 5.79 (*d*×*d*, J=10 and 4, 1H, H–C(7)), 5.51 (br. *d*, J=10, 1H, H–C(6)), 4.60 (*s*, 1H, H–C(4)), 3.80 (*s*, 3H, OCH_3), 3.77 (*s*, 3H, OCH_3), 3.62 (*s*, 1H, H–C(2)), 2.79 (*s*, 3H, NCH_3), 0.70 (*t*, J=7, 3H, CH_2CH_3). – MS.: 396 (M^+), 367, 337, 310, 309, 222, 189, 188 (100%), 187, 174, 173, 168, 158, 135, 107. – Mol-wt.: 396.2054, $C_{23}H_{28}N_2O_4$ (396.2049).

b) The methanesulfonate **35** (20 mg) was added to a solution of excess lithium *n*-butylhydrido cuprate [28] in dry THF (4 ml) at −78°. The solution was stirred at −78° to 0° for 2 h, diluted with water and extracted with ethyl acetate. The extract was washed with water, dried (Na_2SO_4) and evaporated. Chromatography on silica gel gave the epoxide **36** (8 mg, 50%).

c) The methanesulfonate **35** (40 mg) and NaI (100 mg) were heated in acetone (5 ml) for 20 h at reflux. Chromatography on silica gel gave the epoxide **36** (29 mg, 88%).

The cyclic carbonate **38**. The thioxocarbonate **37** (50 mg) was heated in CH_3I (5 ml) for 40 h at reflux. The solvent was removed in vacuum and the residue chromatographed on silica gel to give **38** (37 mg, 77%), m.p. (MeOH): 183.5–184°. – UV. (MeOH): 241 (3.77), 297 (3.69). – IR. ($CHCl_3$): 1800, 1740, 1615, 1600. – NMR. ($CDCl_3$): 6.95 (*d*, J=8, 1H, H–C(14)), 6.35 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.07 (*d*, J=2, 1H, H–C(17)), 5.89 (*m*, 1H, H–C(7)), 5.27 (br. *d*, J=10, 1H, H–C(6)), 4.92 (br. *s*, 1H, H–C(4)), 3.87 (*s*, 3H, OCH_3), 3.75 (*s*, 1H, H–C(2)), 3.70 (*s*, 3H, OCH_3), 2.57 (*s*, 3H, NCH_3). – MS.: 440 (M^+), 309, 307, 306, 303, 298, 297, 296, 295, 293, 282, 189, 188, 187, 174, 173, 161, 159, 135, 122, 121, 107 (100%). – Mol-wt.: 440.1939.

$C_{24}H_{28}N_2O_6$ (440.1947) Calc. C 65.44 H 6.41 N 6.36% Found C 65.62 H 6.31 N 6.28%

The alcohol **40**. A solution of tri-*n*-butylstannane (50 mg) and dibenzoyl peroxide (0.5 mg) in toluene (1 ml) was heated at reflux with a solution of **37** (50 mg) in toluene (15 ml). Two further additions of tri-*n*-butylstannane (2×50 mg) were made over a period of 3 h. After a total of 5 h at reflux, the solvent was removed in vacuum and the residue chromatographed on silica gel to give **40** (27 mg, 62%). – UV. (MeOH): 251 (3.84), 302 (3.66). – IR. ($CHCl_3$): 3550, 1720. – NMR. ($CDCl_3$): 6.90 (*d*, J=8, 1H, H–C(14)), 6.26 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.04 (*d*, J=2, 1H, H–C(17)), 5.91 (*d*×*t*, J=12 and 2, 1H, H–C(7)), 5.58 (br. *d*, J=12, 1H, H–C(6)), 3.99 (*d*×*d*, J=12 and 2, 1H, H–C(3)), 3.76 (*s*, 6H, 2 OCH_3), 3.67 (*d*, J=3, 1H, H–C(2)), 2.68 (*s*, 3H, NCH_3), 0.57 (*t*, J=7, 3H, CH_2CH_3). – MS.: 398 (M^+), 381, 380 (100%), 321, 296, 295, 258, 244, 228, 215, 214, 206, 189, 188, 174, 161, 135, 122, 121, 107, 95. – Mol-wt.: 398.2208, $C_{23}H_{30}N_2O_4$ (398.2205).

The acetate **41**. Acetylation of **40** with acetic anhydride/pyridine in the usual manner gave **41**. – UV. (MeOH): 247 (3.94), 300 (3.76). – IR. ($CHCl_3$): 1730, 1615–1600. – NMR. ($CDCl_3$): 6.97 (*d*, J=8, 1H, H–C(14)), 6.29 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.60 (*d*, J=2, 1H, H–C(17)), 5.77 (*d*×*t*, J=10 and 2.4, 1H, H–C(7)), 5.38 (*d*, J=12, 1H, H–C(4)), 5.13 (br. *d*, J=10, 1H, H–C(6)), 3.92 (*d*×*d*, J=12 and 2, 1H, H–C(3)), 3.78 (*s*, 3H, OCH_3), 3.73 (*s*, 3H, OCH_3), 3.58 (*d*, J=2, 1H, H–C(2)), 2.62 (*s*, 3H, NCH_3), 1.98 (*s*, 3H, $OCOCH_3$), 1.51 (*q*, J=7.5, 2H, CH_2CH_3). – MS.: 440 (M^+), 428, 394, 380 (100%), 362, 297, 282, 266, 214, 204, 200, 189, 187, 174, 161, 160, 159, 144, 135, 132, 123, 122, 121. – Mol-wt.: 440.2326, $C_{25}H_{32}N_2O_5$ (440.2311).

The methanesulfonate **42**. Esterification of **40** with methanesulfonyl chloride in pyridine gave **42**. – UV. (MeOH): 250 (3.85), 301 (3.69). – IR. ($CHCl_3$): 1720, 1610, 1595. – NMR. ($CDCl_3$): 7.94 (*d*, J=8, 1H, H–C(14)), 7.30 (*d*×*d*, J=8 and 2, 1H, H–C(15)), 6.07 (*d*, J=2, 1H, H–C(17)), 5.90 (br. *d*×*q*, J=12, 4 and 2, 1H), 5.50 (br. *d*, J=10, 1H, H–C(6)), 5.19 (*d*, J=11, 1H, H–C(4)), 4.14 (*d*×*d*, J=11 and 2, 1H, H–C(3)), 3.78 (*s*, 6H, 2 OCH_3), 3.56 (*d*, J=2, 1H, H–C(2)), 3.03 (*s*, 3H,

SO_2CH_3), 2.66 (*s*, 3 H, NCH_3). – MS.: 476 (M^+), 414, 381, 380 (100%), 350, 349, 321, 244, 208, 206, 188, 187, 174, 135, 121, 107. – Mol-wt.: 476.1956.

$C_{24}H_{32}N_2O_5S$ (476.1981) Calc. C 60.48 H 6.77 N 5.88% Found C 59.93 H 6.60 N 5.72%

The α,β-unsaturated ester **43**. a) A mixture of the methanesulfonate **42** (50 mg), NaI (75 mg) and Zn dust (150 mg) was heated at reflux in 1,2-dimethoxyethane (10 ml) for 10 h. After cooling, the mixture was filtered through *Celite* and the filtrate evaporated. Chromatography on silica gel gave **43** (28 mg, 70%) identical with an authentic sample [13].

b) A mixture of the methanesulfonate **42** (50 mg), $NaCNBH_3$ (30 mg) and HMPA (3 ml) was stirred at 80° for 20 h. The mixture was cooled, diluted with ethyl acetate, washed with water, dried (Na_2SO_4) and concentrated under vacuum. Chromatography afforded **43** (18 mg, 45%).

c) Reaction of **42** with Li *n*BuCuH, as described above for the preparation of **36**, gave **43** in 50% yield.

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