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AROMATIC ELECTROPHILIC SUBSTITUTIONS ON VINDOLINE

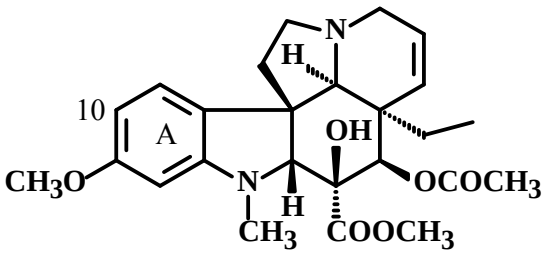
Álmos Gorka-Kereskényi,[1] Lajos Szabó,[1] László Hazai,[2] Miklós Lengyel,[1] Csaba Szántay, Jr.,[3] Zsuzsanna Sánta,[3] György Kalaus,[1] and Csaba Szántay[1,2]*

[1]Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1111 Budapest, Gellért tér 4. Hungary
[2]Research Group for Alkaloid Chemistry of the Hungarian Academy of Sciences, H-1111 Budapest, Gellért tér 4. Hungary, E-mail: szantay@mail.bme.hu
[3]Spectroscopic Research Division, Gedeon Richter Ltd., H-1475 Budapest 10, P. O. Box 27, Hungary

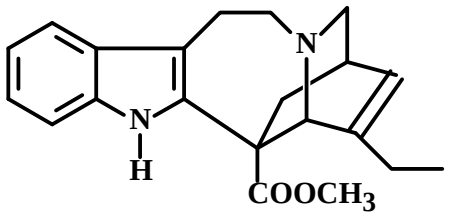
Abstract – Aromatic electrophilic substitution reactions of the monomer alkaloid vindoline resulted in new derivatives substituted on ring A. Halogene-, nitro-, amino- and acylamino derivatives of vindoline were prepared.

INTRODUCTION

Vindoline (**1**), catharanthine (**2**) and their derivatives are the major components of important bis-indole alkaloids, of which vinblastine and vincristine have been used in anticancer therapy.



vindoline (**1**)

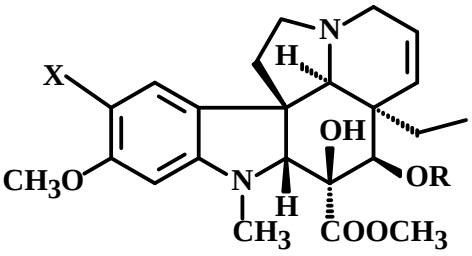


catharantine (**2**)

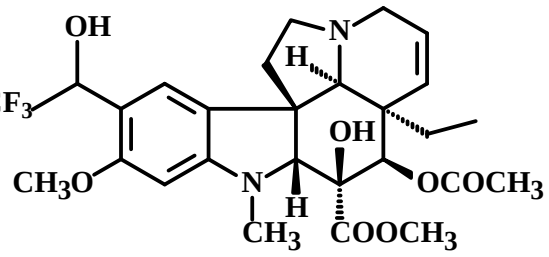
The chemistry of vinblastine and vincristine represents one of the most exciting fields in alkaloid research. However, regarding simple aromatic electrophilic substitutions (nitration, halogenation, *etc*.) accomplished on ring A of the monomer alkaloid vindoline only few data can be found in the literature. Since the nitro derivatives of vincristine[1,2] proved to have potential biological significance, investigations of S_EAr reactions of vindoline (**1**), primarily nitration became important.

10-Iodovindoline (**3a**) was recently prepared in our Department.[3] The 10-chloro-17-des-acetyl derivative (**3b**) was synthesized by Kutney and coworkers.[4] Fluoroalcohol (**4**) formed as a by-product in the course

of a coupling reaction between vindoline (**1**) and catharantine (**2**) carried out in trifluoroacetic anhydride.[5,6] The initial product was the corresponding trifluoroacetyl derivative and sodium borohydride reduction provided the compound **4**.



3a; X=I, R=-$COCH_3$
3b; X=Cl, R=H



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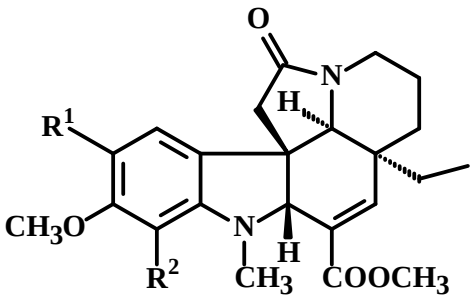


5a; R^1=Br, R^2=H
5b; R^1=R^2=Br
5c; R^1=CHO, R^2=H

Scheme 1

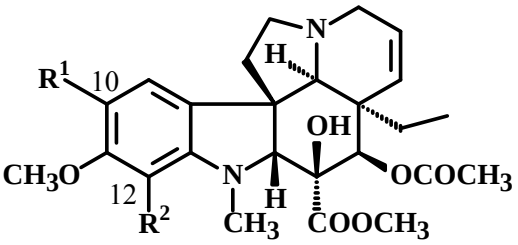
As related compounds, mono- and dibrominated aspidospermidine derivatives (**5a** and **5b**) as well as the Vilsmeier-Haack product (**5c**) are presented (Scheme 1).[4]

RESULTS AND DISCUSSION

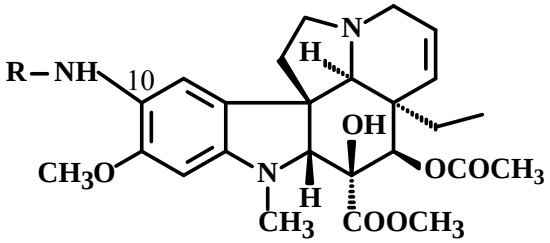
To start with the investigation of the S_EAr reactions of the aromatic ring A of vindoline (**1**), nitration and halogenation reactions were studied (Scheme 2).

In the course of nitration of vindoline (**1**) with a mixture of conc. sulfuric and conc. nitric acid in acetic acid solution at 5 °C, three products were isolated (Scheme 2). 10,12-Dinitrovindoline (**6a**) was obtained in 29% yield as a main product. The position of the two nitro groups in **6a** follows from the fact that in NMR experiments strong homonuclear ^{1}H-^{1}H NOEs were observed from H-9 to H_α-6 and H-21, in accord with the two NO_2 groups being situated on C-10 and C-12. Moreover 10-nitrovindoline (**6b**) and 10-nitrosovindoline (**6c**) were identified after chromatographic separation in 2% and 2.8% yields, respectively. The latter could also be prepared by nitrosation reaction with sodium nitrite in acidic solution.

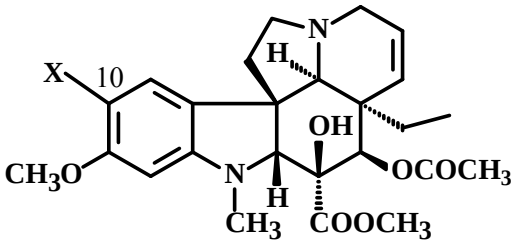
Performing the nitration reaction at 0°C in the 1:1 mixture of acetic acid and dichloromethane yielded 10-nitrovindoline (**6b**) in 54% as the main product.[7] Reduction of the latter nitro derivative **6b** with sodium borohydride in the presence of palladium-on-charcoal catalyst in a methanol-dichloromethane mixture resulted in 10-aminovindoline (**7a**), which was also prepared by the similar reduction of the 10-nitrosovindoline (**6c**). Acylation of 10-aminovindoline (**7a**) with acetic anhydride and methanesulfonyl chloride, respectively, provided the 10-acetylamino- (**7b**) and the 10-methanesulfonylamino (**7c**) derivatives.



6a; $R^1=R^2=NO_2$
6b; $R^1=NO_2$, $R^2=H$
6c; $R^1=NO$



7a; R=H
7b; R=-$COCH_3$
7c; R=-SO_2CH_3



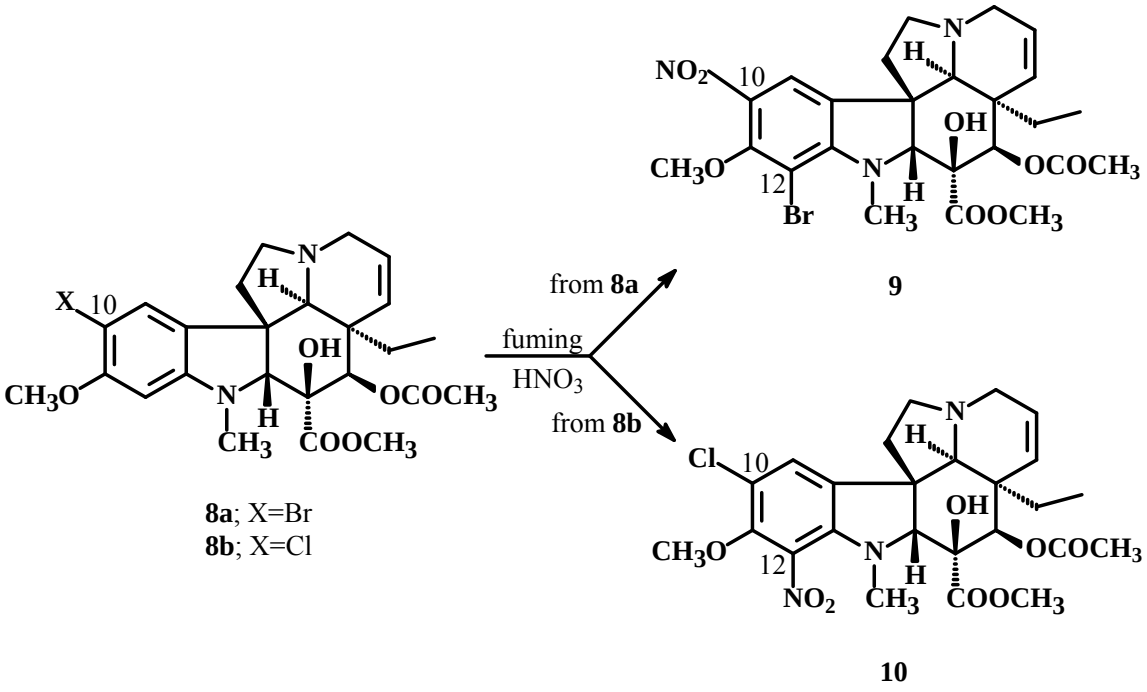
1; X=H
8a; X=Br
8b; X=Cl

Scheme 2

Halogenation reaction of vindoline (**1**) was carried out by reaction with *N*-bromo- and *N*-chlorosuccinimide. 10-Bromovindoline (**8a**) and 10-chlorovindoline (**8b**) were prepared in very good yields, 92% and 89%, respectively.

Vindolines, halogenated in the position 10 **(8a** and **8b**), provided the possibility to introduce the nitro group selectively in position 12 (Scheme 3). Nitration of the 10-bromo derivative **8a** was achieved with fuming nitric acid in chloroform/acetic acid mixture (1:1) between -15°C and -18°C. After chromatographic separation an unexpected anomalous product, the 12-bromo-10-nitrovindoline (**9**) was obtained in 69% yield and 7% of 10-nitrovindoline (**6b**) was also isolated as a product of *ipso*-substitution.[8] This reaction appears to be a further example of the rearrangement discovered by Reverdin.[9] The replacement of halogene by a nitro group or the migration of the halogen to another position of the aromatic ring in the

course of nitration of halogenated phenols and phenol ethers is a common occurence[10] and takes place also in the aromatic ring of other heterocycles.[11] Nitration of the chloro derivative (**8b**), however, resulted in the expected 10-chloro-12-nitrovindoline (**10**). This observation may be attributed to the difference in the homolytic bond dissociation energy for chlorine and bromine carbon bonds (*ca*. 12 kcal/mol) and suggests a radical reaction mechanism.[12]



8a; X=Br
8b; X=Cl

Scheme 3

In both **9** and **10** the position of the nitro group and halogen atom is initially not evident if a possible halogen shift during nitration is taken into account. Both compounds exhibit a single singlet aromatic ^{1}H NMR resonance which gives homonuclear NOEs into H_{α}-6 and H-21 (and no NOE into the NMe group), showing that this resonance is due to H-9. Given the positions of the 11-OMe group and H-9, we thus had to clarify only the position of the nitro group in ring A. To that end, ^{1}H-^{15}N-HMBC NMR measurements were carried out in both **9** and **10**. In the case of **9**, a strong ^{1}H-^{15}N correlation can be observed between H-9 and the nitro group, while such a correlation is absent in the spectrum of **10**. These observations show that in **9** the nitro group is in C(10) (giving a strong ^{3}J coupling between H-9 and the $^{15}NO_2$), while in **10** the nitro group is in C(12) (with no detectable ^{5}J correlation between H-9 and the $^{15}NO_2$). Interestingly, in the ^{1}H-^{15}N-HMBC spectrum of both molecules a through-space *J*-coupling correlation can also be observed between the 16-OH and N-4. This occurs because of a hydrogen bond existing between these two functional groups, as allowed by the free electron pair of N-4 being in the β-position. This feature of the vindoline geometry was pointed out earlier on the basis of ^{1}H NMR chemical shift considerations[13] and ^{1}H-^{1}H NOEs[14]; the presently reported ^{1}H-^{15}N-HMBC experiments provide an independent and elegant piece of evidence in that regard.

EXPERIMENTAL

General

Melting points are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. NMR spectra were recorded on a Varian INOVA 300, Varian INOVA 500 or a Varian VNMRS-500 spectrometer. Chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard (0.00 ppm). 2D NMR experiments (COSY, HSQC, HMBC, DPFG-NOE) were recorded by using the standard spectrometer software package; 0.5 s mixing time was used in the NOE experiments. Mass spectrometric measurements were performed on VG-Trio-2 and a Finnigan MAT 95SQ mass spectrometers using EI (70 eV, 220°C source temperature) and FIB (Cs^+, glycerol matrix, 20 kV) ionization methods. High-resolution MS measurements were carried out on a Finnigan MAT 95SQ mass spectrometer; perfluorotributylamine was the reference compound using EI ionization technique. TLC was carried out using Kieselgel $60F_{254}$ (Merck) glass plates.

10,12-Dinitrovindoline (6a)

Vindoline (**1**) (200 mg, 0.44 mmol) was dissolved in 2 mL of AcOH and 0.1 mL of conc. H_2SO_4 was added with ice cooling. The solution was treated with a mixture of 0.1 mL of conc. H_2SO_4 and 0.1 mL of conc. HNO_3. Then the dark and thick reaction mixture was stirred for 30 min at 5 °C, poured into ice, made alkaline with conc. NH_4OH and extracted with CH_2Cl_2. After drying with $MgSO_4$ the organic layer was evaporated and the residue was subjected to preparative layer chromatography on silica gel. Elution with mixture of CH_2Cl_2-MeOH 9:1 gave 70 mg of product **6a** in 29% yield, mp 216-218 °C. TLC CH_2Cl_2-MeOH 9:1 R_f 0.75. IR(KBr) 1740, 1615, 1525, 1500, 1370, 1320, 1255, 1230 cm^{-1}. $[\alpha]_D^{26}$ -266 ° (c 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): 0.64 (3H, t, H_3-18); 1.12 (1H, dq, H_x-19); 1.72 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.21 (1H, m, H_α-6); 2.41 (1H, m, H_β-6); 2.69 (1H, m, H_α-5); 2.75 (3H, s, NMe); 2.91 (1H, s, H-21); 2.93 (1H, dm, H_α-3); 3.45-3.54 (2H, m, H_β-3+H_β-5); 3.79 (3H, s, OMe); 4.05 (3H, s, OMe); 4.10 (1H, s, H-2); 5.28 (1H, s, H-17); 5.33 (1H, dm, H-15); 5.94 (1H, ddd, H-14); 7.84 (1H, s, H-9); 9.05 (1H, brs, OH). MS (EI) *m/z* (%): 546(M^+, 2.1), 487(3.5), 399(12.5), 387(60.4), 369(26.4), 278(29.9), 135(41.7), 122(100). Anal. Calcd for $C_{25}H_{30}N_4O_{10}$: C, 54.94; H, 5.53; N, 10.25. Found: C, 54.38; H, 5.43; N, 9.98.

In the course of the preparative layer chromatography, moreover, 20 mg (2%) of 10-nitrovindoline (**6b**) (R_f 0.66) and 27 mg (2.8%) of 10-nitrosovindoline (**6c**) (R_f 0.5) were isolated. These side products (**6b** and **6c**) were identified by comparison of m.p. TLC, IR and NMR spectra with authentic samples prepared by other procedures.

10-Nitrovindoline (6b)

2.23 g (4.46 mmol) of vindoline (**1**) was dissolved in a mixture of 9 mL of CH_2Cl_2 and 9 mL of AcOH and at 0 °C a mixture of 0.3 mL of conc. HNO_3 and 0.18 mL of conc. H_2SO_4 was added. After stirring for

30 min at 0 °C, adding of the mixture of acids was repeated and stirring was continued at rt while the starting material could be detected by TLC. The reaction mixture was then poured into ice-water, alkalined by conc. NH_4OH and extracted with CH_2Cl_2. After drying with $MgSO_4$ the solvent was evaporated and the residue was subjected to column chromatography on silica gel. Elution with a mixture of EtOAc-MeOH 20:1 after evaporation of the solvent and washing the residue with isopropyl ether gave 1.2 g (54%) of product (**6b**), mp 247-248 °C. TLC EtOAc-MeOH 20:1 R_f 0.3. IR(KBr) 1740, 1625, 1515, 1325, 1250 cm^{-1}. $[\alpha]_D^{23}$ -49 ° (c 1.075, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): 0.58 (3H, t, H_3-18); 1.10 (1H, dq, H_x-19); 1.65 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.22-2.41 (2H, m, H_2-6); 2.63 (1H, m, H_α-5); 2.80 (1H, s, H-21); 2.82 (3H, s, NMe); 2.88 (1H, dm, H_α-3); 3.42-3.54 (2H, m, H_β-3+H_β-5); 3.81 (3H, s, OMe); 3.99 (4H, s, OMe + H-2); 5.25 (1H, dm, H-15); 5.32 (1H, s, H-17); 5.92 (1H, ddd, H-14); 5.98 (1H, s, H-12); 7.82 (1H, s, H-9); 9.53 (1H, brs, OH). MS (FIB) *m/z*: 502(MH^+); daughter ion spectrum of *m/z* 502: 485, 442, 341, 233. Anal. Calcd for $C_{25}H_{31}N_3O_8$: C, 59.87; H, 6.23; N, 8.38. Found: C, 59.43; H, 6.14; N, 8.31.

10-Nitrosovindoline (6c)

To the solution of vindoline (**1**) (0.59 g, 1.3 mmol) in a mixture of MeOH (20 mL) and 1N HCl (74 mL) at -12°C under stirring $NaNO_2$ (207 mg, 3.0 mmol) was added and the mixture was allowed to stand at the same temperature for 15 min. The pH of the mixture was adjusted with cold saturated aqueous $NaHCO_3$-solution (75 mL) to 8.5 and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was crystallised from ether containing few drops of methanol to give 0.54 g (85%) of green crystalline product **6c**, mp 204-206 °C. IR(KBr) 3440, 1740, 1730, 1620 cm^{-1}. $[\alpha]_D^{25}$ +44.4 ° (c 0.50, CH_2Cl_2 and 2 drops of MeOH). ^1H NMR (300 MHz, $CDCl_3$): 0.49 (3H, t, H_3-18); 1.04 (1H, dq, H_x-19); 1.57 (1H, dq, H_y-19); 2.06 (3H, s, OCOMe); 2.14 (1H, m, H_α-6); 2.30 (1H, m, H_β-6); 2.60 (1H, m, H_α-5); 2.76 (1H, s, H-21); 2.87 (1H, dm, H_α-3); 2.92 (3H, brs, NMe); 3.38-3.51 (1H, m, H_β-3+H_β-5); 3.82 (3H, s, OMe); 4.04 (1H, s, H-2); 4.22 (3H, s, OMe); 5.24 (1H, s, H-17); 5.26 (1H, dm, H-15); 5.87 (1H, ddd, H-14); 6.04 (1H, s, H-12); 6.49 (1H, s, H-9); 9.44 (1H, brs, OH). MS (FIB) *m/z*: 486(MH^+). Anal. Calcd for $C_{25}H_{31}N_3O_7$: C, 61.84; H, 6.43; N, 8.65. Found: C, 61.72; H, 6.48; N, 8.50.

10-Aminovindoline (7a)

To the solution of 10-nitrosovindoline (**6c**) (0.30 g, 0.63 mmol) 10% Pd/C catalyst (0.30 g) and at 15 °C under 10 min $NaBH_4$ (0.30 g) was added. After filtering off the catalyst the excess of the reagent was destroyed with acetic acid and the solvent was removed in vacuo. The residue was treated with water (8 mL) basified with NH_4OH, extracted with CH_2Cl_2 (3x5 mL). The combine extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. The residual oil was crystallised from Et_2O (3 mL) to yield mild blue crystalls (0.15 g, 52%) mp 219 °C. IR(KBr) 3440, 3360, 1740, 1730, 1250 cm^{-1}. $[\alpha]_D^{22}$ -54 ° (c 1.00,

CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): 0.49 (3H, t, H_3-18); 1.13 (1H, dq, H_x-19); 1.64 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.30-2.36 (2H, m, H_2-6); 2.47 (1H, q, H_α-5); 2.59 (1H, s, H-21); 2.61 (3H, brs, NMe); 2.79 (1H, dm, H_α-3); 3.40 (1H, m, H_β-5); 3.48 (1H, s, H-2); 3.49 (1H, ddd, H_β-3); 3.78 (3H, s, OMe); 3.84 (3H, s, OMe); 5.23 (1H, dm, H-15); 5.49 (1H, s, H-17); 5.83 (1H, ddd, H-14); 6.12 (1H, s, H-12); 6.44 (1H, brs, H-9); 9.40 (1H, brs, OH). MS (EI) *m/z* (%): 471(M^+, 20.0), 412(3.0), 282(10.0), 204(35.0), 189(24.0), 135(100.0), 122(35.0), 107(29.0), 93(18.0). Anal. Calcd for $C_{25}H_{33}N_3O_6$: C, 63.65; H, 7.05; N, 8.91. Found: C, 63.49; H, 6.80; N, 8.77.

10-Acetylaminovindoline (7b)

The solution of 10-aminovindoline (**7a**) (0.50 g, 1.06 mmol) in Ac_2O (5.0 mL) was allowed to stand at rt for 2 days. Thereafter the reaction mixture was poured into ice-water (20 mL), basified with NH_4OH and extracted with CH_2Cl_2 (3x20 mL). The combine extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure and the residue was separated by preparative layer chromatography (silicagel $PF_{254+366}$, CH_2Cl_2-MeOH 20:1, elution 20:4) to give 0.30 g (55%) of the title compound, mp 197-198 °C. IR(KBr) 3440, 1740, 1670, 1620 cm^{-1}. $[\alpha]_D^{22}$ -72 ° (c 1.00, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): 0.53 (3H, t, H_3-18); 1.08 (1H, dq, H_x-19); 1.60 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.16 (3H, s, NHCOMe); 2.22-2.43 (2H, m, H_2-6); 2.56 (1H, q, H_α-5); 2.66 (3H, s, NMe); 2.76 (1H, s, H-21); 2.84 (1H, dm, H_α-3); 3.36-3.52 (2H, m, H_β-5 + H_β-3); 3.47 (1H, s, H-2); 3.78 (3H, s, OMe); 3.87 (3H, s, OMe); 5.23 (1H, dm, H-15); 5.43 (1H, s, H-17); 5.85 (1H, ddd, H-14); 6.11 (1H, s, H-12); 5.53 (1H, s, NH); 8.06 (1H, s, H-9); ~9.20 (1H, br, OH). MS (EI) *m/z* (%): 513(M^+, 4.0), 454(2.0), 354(13.0), 282(15.0), 245(40.0), 135(100.0), 121(33.0), 107(20.0), 93(14.0). Anal. Calcd for $C_{27}H_{35}N_3O_3$: C, 63.14; H, 6.87; N, 8.18. Found: C, 63.03; H, 6.65; N, 8.00.

10-Methanesulfonylaminovindoline (7c)

To the solution of 10-aminovindoline (**7a**) (0.40 g, 0.84 mmol) in CH_2Cl_2 (5 mL) at 0 °C under stirring Et_3N (0.20 mL) and methanesulfonyl-chloride (0.12 g, 1.04 mmol) were added and allowed to stand at rt for 50 min. The solvent was evaporated, the residue was devided between 5% HCl and EtOAc. The acidic phase was basified with NH_4OH, extracted with CH_2Cl_2. After drying, and filtering, the solvent was evaporated. The residue (0.35 g) was separated by preparative layer chromatography (silicagel $PF_{254+366}$, CH_2Cl_2-MeOH 20:2, elution 20:4) to give the product **7c** (0.16 g, 34.3%), mp 142-144 °C (Et_2O). IR(KBr) 3450, 3250, 1740, 1620, 1500, 1230 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): 0.44 (3H, t, H_3-18); 0.95 (1H, dq, H_x-19); 1.48 (1H, dq, H_y-19); 1.94 (3H, s, OCOMe); 2.15-2.28 (2H, m, H_2-6); 2.59 (1H, q, H_α-5); 2.62 (3H, s, SO_2Me); 2.67 (1H, s, H-21); 2.78 (3H, s, NMe); 2.82 (1H, dm, H_α-3); 3.27 (1H, m, H_β-5); 3.40 (1H, dd, H_β-3); 3.58 (1H, s, H-2); 3.66 (3H, s, OMe); 3.81 (3H, s, OMe); 5.09 (1H, dm, H-15); 5.18 (1H, s, H-17); 5.82 (1H, ddd, H-14); 6.38 (1H, s, H-12); 6.99 (1H, s, H-9); 8.53 (1H, s) & 8.81 (1H, s): NH & OH. MS (EI) *m/z* (%): 549(M^+, 6.7), 470(23.2), 390(8.0), 310(49.1), 282(17.9),

203(25.9), 135(100), 121(54.5), 107(31.3), 93(41.1). Anal. Calcd for $C_{26}H_{35}N_3O_8S$: C, 56.81; H, 6.41; N, 7.64. Found: C, 56.75; H, 6.50; N, 7.42.

10-Bromovindoline (8a)

To a solution of vindoline (**1**) (2.0 g, 4.26 mmol) in 40 mL of dry CH_2Cl_2 *N*-bromosuccinimide (816 mg, 4.26 mmol) was added. After standing at rt for 45 min the reaction mixture was washed with 5% aqueous $NaHCO_3$ and then with water. The organic layer was dried with $MgSO_4$ and evaporated. The residue was washed with Et_2O and then with MeOH gave 2.23 g (92.3%) of product (**8a**), mp 276-278 °C. TLC CH_2Cl_2-MeOH 20:1 R_f 0.4. IR(KBr) 2960, 1725, 1715, 1600, 1495, 1250, 1230, 1050, 815 cm^{-1}. $[\alpha]_D^{24}$ -41.1 ° (c 1.04, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): 0.52 (3H, t, H_3-18); 1.11 (1H, dq, H_x-19); 1.66 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.26-2.42 (2H, m, H_2-6); 2.54 (1H, q, H_α-5); 2.66 (1H, s, H-21); 2.69 (3H, s, NMe); 2.84 (1H, dm, H_α-3); 3.40-3.59 (2H, m, H_β-5 + H_β-3); 3.76 (1H, s, H-2); 3.79 (3H, s, OMe); 3.88 (3H, s, OMe); 5.24 (1H, dm, H-15); 5.44 (1H, s, H-17); 5.85 (1H, ddd, H-14); 6.10 (1H, s, H-12); 7.11 (1H, s, H-9); 9.48 (1H, s, OH). ^1H NMR (500 MHz, DMSO-d_6): 0.45 (3H, t, H_3-18); 0.92 (1H, m, H_x-19); 1.50 (1H, m, H_y-19); 1.94 (3H, s, OCOMe); 2.17-2.27 (2H, m, H_2-6); 2.61 (4H, m, NMe, H_α-5); 2.71 (1H, s, H-21); 2.81 (1H, dm, H_α-3); 3.22-3.29 (1H, m, H_β-5); 3.40 (1H, dd, H_β-3); 3.60 (1H, s, H-2); 3.66 (3H, s, COOMe); 3.81 (3H, s, ArOMe); 5.09 (1H, dm, H-15); 5.18 (1H, s, H-17); 5.83 (1H, ddd, H-14); 6.42 (1H, s, H-12); 7.38 (1H, s, H-9); 8.84 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): 7.5 (C-18); 20.7 (OCO*Me*); 30.6 (C-19); 38.0 (NMe); 42.4 (C-20); 43.6 (C-6); 50.4 (C-3); 50.9 (C-5); 51.8 (COOMe); 52.1 (C-7); 56.2 (ArOMe); 66.0 (C-21); 75.8 (C-17); 78.6 (C-16); 82.8 (C-2); 94.8 (C-12); 98.8 (C-10); 124.6 (C-14); 126.5 (C-9); 126.5 (C-8); 129.8 (C-15); 153.0 (C-13); 156.0 (C-11); 170.1 (O*C*OMe); 171.6 (*C*OOMe). MS (EI) *m/z* (%): 534(M^+, 13.7), 475(4.3), 387(4.7), 375(22.8), 282(38.4), 266(29.0), 252(10.1), 135(100), 121(43.0), 107(15.9), 93(11.4). Anal. Calcd for $C_{25}H_{31}N_2O_6Br$: C, 56.08; H, 5.83; Br, 14.92; N, 5.23. Found: C, 55.95; H, 5.58; Br, 14.72; N, 5.20.

10-Chlorovindoline (8b)

To a solution of vindoline (**1**) (1.0 g, 2.19 mmol) in 20 mL of dry benzene *N*-chlorosuccinimide (293 mg, 2.19 mmol) was added. After standing at rt for 2 days the reaction mixture was washed with 5% aqueous $NaHCO_3$ and then with water. The organic layer was dried with $MgSO_4$ and evaporated. The residue was washed with Et_2O and then with MeOH, yielding 956 mg (89.3%) of product (**8b**), mp 270-272 °C. TLC benzene-MeOH 140:3 R_f 0.6. IR (KBr) 3450, 1740, 1735, 1620 cm^{-1}. $[\alpha]_D^{22}$ -37.5 ° (c 1.00, CH_2Cl_2). ^1H NMR (500 MHz, DMSO-d_6): 0.45 (3H, t, H_3-18); 0.92 (1H, m, H_x-19); 1.51 (1H, m, H_y-19); 1.94 (3H, s, OCOMe); 2.17-2.27 (2H, m, H_2-6); 2.61 (4H, m, NMe, H_α-5); 2.70 (1H, s, H-21); 2.81 (1H, dm, H_α-3); 3.22-3.29 (1H, m, H_β-5); 3.41 (1H, dd, H_β-3); 3.60 (1H, s, H-2); 3.66 (3H, s, COOMe); 3.82 (3H, s, ArOMe); 5.10 (1H, dm, H-15); 5.18 (1H, s, H-17); 5.83 (1H, ddd, H-14); 6.44 (1H, s, H-12); 7.26 (1H, s, H-9); 8.83 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): 7.5 (C-18); 20.7 (OCO*Me*); 30.6 (C-19); 38.2

(NMe); 42.4 (C-20); 43.6 (C-6); 50.4 (C-3); 51.0 (C-5); 51.8 (COOMe); 52.2 (C-7); 56.1 (ArOMe); 66.0 (C-21); 75.8 (C-17); 78.6 (C-16); 82.8 (C-2); 94.9 (C-12); 110.4 (C-10); 123.7 (C-9); 124.6 (C-14); 125.8 (C-8); 129.8 (C-15); 152.3 (C-13); 155.2 (C-11); 170.1 (O*C*OMe); 171.6 (*C*OOMe). MS (EI) *m/z* (%): 490(M^+, 20.3), 431(6.5), 343(7.0), 330(29.6), 282(36.6), 250(7.8), 222(59.4), 208(15.5), 135(100), 121(44.5), 107(16.4), 93(11.8). Anal. Calcd for $C_{25}H_{31}ClN_2O_6$: C, 61.16; H, 6.36; Cl, 7.22; N, 5.70. Found: C, 61.22; H, 6.45; Cl, 7.41; N, 5.58.

12-Bromo-10-nitrovindoline (9)

10-Bromovindoline (**8a**) (1.07 g, 2 mmol) was dissolved in a mixture of 4 mL of $CHCl_3$ and 4 mL of AcOH at -15 °C. After addition of fuming nitric acid (0.18 mL) the dark reaction mixture was stirred at -15°C for 4 h. Then poured into ice, made alkaline with conc. NH_4OH and extracted with CH_2Cl_2. After drying with $MgSO_4$ the organic layer was evaporated and the residue was separated by preparative layer chromatography on silica gel. Elution with a mixture of benzene-MeOH 14:3 gave 798 mg (69%) of product (**9**), mp 234 °C. TLC benzene-MeOH 14:3 R_f 0.52. IR(KBr) 1740, 1600, 1510, 1490, 1315, 1250, 1225, 1040 cm^{-1}. $[\alpha]_D^{23}$ +156.6 ° (c 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): 0.59 (3H, t, H_3-18); 0.96 (1H, dq, H_x-19); 1.64 (1H, dq, H_y-19); 2.07 (3H, s, OCOMe); 2.21-2.43 (2H, m, H_2-6); 2.66 (1H, m, H_α-5); 2.83 (1H, s, H-21); 2.89 (1H, dm, H_α-3); 3.12 (3H, s, NMe); 3.44-3.53 (2H, m, H_β-5 + H_β-3); 3.81 (3H, s, OMe); 3.93 (1H, s, H-2); 3.99 (3H, s, OMe); 5.29 (1H, s, H-17); 5.32 (1H, dm, H-15); 5.92 (1H, ddd, H-14); 7.66 (1H, s, H-9); 9.16 (1H, s, OH). ^{1}H NMR (500 MHz, DMSO-d_6): 0.54 (3H, t, H_3-18); 0.72 (1H, m, H_x-19); 1.46 (1H, m, H_y-19); 1.95 (3H, s, OCOMe); 2.20-2.29 (1H, m, H_α-6); 2.33-2.41 (1H, m, H_β-6); 2.68-2.76 (1H, m, H_α-5); 2.88 (1H, dm, H_α-3); 3.00 (3H, s, NMe); 3.05 (1H, s, H-21); 3.27-3.33 (1H, m, H_β-5); 3.38 (1H, dd, H_β-3); 3.67 (3H, s, COOMe); 3.88 (3H, s, ArOMe); 3.91 (1H, s, H-2); 5.01 (1H, s, H-17); 5.19 (1H, dm, H-15); 5.88 (1H, ddd, H-14); 8.01 (1H, s, H-9); 8.72 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): 7.1 (C-18); 20.7 (OCO*Me*); 30.7 (C-19); 40.7 (NMe); 42.1 (C-6); 42.6 (C-20); 49.9 (C-5); 49.9 (C-3); 51.7 and 51.9 (C-7, COOMe); 62.1 (ArOMe); 64.8 (C-21); 75.5 (C-17); 78.8 (C-16); 84.0 (C-2); 99.1 (C-12); 119.9 (C-9); 124.8 (C-14); 129.7 (C-15); 131.6 (C-8); 135.6 (C-10); 153.4 (C-11); 155.0 (C-11); 169.9 (O*C*OMe); 170.8 (*C*OOMe). MS (EI) *m/z* (%): 579(M^+, 17.0), 549(6.0), 520(11.4), 432(16.6), 420(100), 402(36.3), 311(29.1), 282(21.2), 264(9.2), 135(42.4), 122(39.0), 107(9.9), 93(11.0). HRMS: calcd 579.12108 for $C_{25}H_{30}N_3O_8Br$, found 579.12159 (delta: 0.9 ppm).

In the course of the chromatographic separation 71 mg (7%) of 10-nitrovindoline (**6b**) was also isolated which was identified by comparison of its physical data with an authentic sample.

10-Chloro-12-nitrovindoline (10)

10-Chlorovindoline (**8b**) (1.18 g, 2.4 mmol) was dissolved in a mixture of 5 mL of $CHCl_3$ and 5 mL of AcOH at -15 °C. After addition of fuming nitric acid (0.22 mL) the dark reaction mixture was stirred at 0-5 °C for 4 h. Then poured into ice, made alkaline with conc. NH_4OH and extracted with CH_2Cl_2. After

drying with $MgSO_4$ the organic layer was evaporated and the residue was separated by preparative layer chromatography on silica gel. Elution with a mixture of benzene-MeOH 14:3 gave 450 mg (35%) of product (**10**), mp 241-243 °C. TLC benzene-MeOH 14:3 R_f 0.5. IR(KBr) 1750, 1630, 1540, 1390, 1270, 1245, 1060 cm^{-1}. $[\alpha]_D^{28}$ -41.4 ° (c 1, CH_2Cl_2). ^1H NMR (500 MHz, DMSO-d_6): 0.52 (3H, t, H_3-18); 0.85 (1H, m, H_x-19); 1.55 (1H, m, H_y-19); 1.95 (3H, s, OCOMe); 2.18-2.26 (1H, m, H_α-6); 2.32-2.40 (1H, m, H_β-6); 2.48 (3H, s, NMe); 2.64-2.72 (1H, m, H_α-5); 2.84 (1H, dm, H_α-3); 2.93 (1H, s, H-21); 3.29 (1H, m, H_β-5); 3.41 (1H, dd, H_β-3); 3.64 (3H, s, COOMe); 3.87 (3H, s, ArOMe); 3.92 (1H, s, H-2); 5.10 (1H, s, H-17); 5.16 (1H, dm, H-15); 5.87 (1H, ddd, H-14); 7.69 (1H, s, H-9); 8.71 (1H, s, OH). ^{13}C NMR (500 MHz, DMSO-d_6): 7.2 (C-18); 20.7 (OCO*Me*); 30.7 (C-19); 37.5 (NMe); 42.3 (C-20); 42.8 (C-6); 50.1 (C-3); 50.3 (C-5); 52.0 (C-7, COOMe); 62.6 (ArOMe); 65.2 (C-21); 75.5 (C-17); 78.5 (C-16); 83.6 (C-2); 115.5 (C-10); 124.8 (C-14); 126.6 (C-9); 129.6 (C-15); 129.9 (C-13); 134.2 (C-8); 143.2 (C-13); 148.0 (C-11); 169.9 (O*C*OMe); 170.9 (*C*OOMe). MS (EI) *m/z* (%): 535(M^+, 24.9), 506(4.5), 476(14.3), 388(17.2), 376(100), 282(19.6), 267(36.3), 135(36.3), 122(31.1), 107(6.9), 93(7.7). HRMS: calcd 535.17159 for $C_{25}H_{30}N_3O_8Cl$, found 535.17139 (delta: -0.4 ppm).

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REFERENCES AND NOTES

1. L. Szabó, Cs. Szántay, E. Gács-Baitz, and M. Mák, *Tetrahedron Lett*., 1995, **36**, 5265.
2. Gedeon Richter Ltd., *Belg. Pat.*, 889,990 (*Chem. Abstr*., 1982, **97**, 216542).
3. (a) M. Fekete, P. Kolonits, and L. Novák, *Heterocycles*, 2005, **65**, 165. (b) P. D. Johnson, J.-H. Sohn, and V. H. Rawal, *J. Org. Chem.*, 2006, **71**, 7899.
4. J. P. Kutney, U. Bunzli-Trepp, T. Honda, J. Katsube, and B. R. Worth, *Helv. Chim. Acta,* 1978, **61**, 1554.
5. J. P. Kutney, T. Hibino, E. Jahngen, T. Okutani, A. Ratcliffe, A. M. Treasurywala, and S. Wunderly, *Helv. Chim. Acta*, 1976, **59**, 2858.
6. N. Langlois, F. Gueritte, Y. Langlois, and P. Potier, *J. Am. Chem. Soc*., 1976, **98**, 7017.
7. Preparation of 10-nitrovindoline (**6b**) with conc.nitric acid in a mixture of acetic acid and chloroform

at -20°C in 71% yield, see also H. Bölcskei, Cs. Szántay, Jr., M. Mák, M. Balázs, and Cs. Szántay, *Acta Pharm. Hung*., 1998, **68**, 87.

8. C. L. Perrin and G. A. Skinner, *J. Am. Chem. Soc*., 1971, **93**, 3389.
9. F. Reverdin, *Chem. Ber*., 1896, **29**, 997, 2595.
10. D. V. Nightingale, *Chem. Rev*., 1947, **40**, 117.
11. H. Gershon and M. W. McNeil, *J. Heterocycl. Chem.*, 1971, **8**, 821.
12. D. A. Conlon, J. E. Lynch, F. W. Hartner, J., R. A. Reamer, and R. P. Volante, *J. Org. Chem.*, 1996, **61**, 6425.
13. B. K. Hunter, L. D. Hall, and J. K. M. Sanders, *J. Chem. Soc., Perkin Trans. 1*., 1983, 657.
14. Cs. Szántay Jr., M. Balázs, H. Bölcskei, and Cs. Szántay, *Tetrahedron*, 1991, **47**, 1265.