Photosensitized oxidation, by single-electron transfer, of catharanthine and vindoline: a highly regio- and diastereoselective photocyanation reaction

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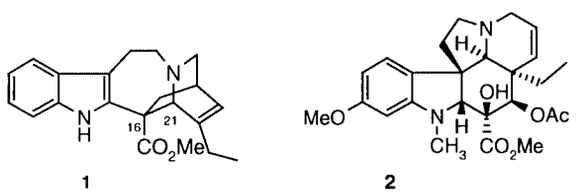
The irradiation, by visible light, of (+)-catharanthine **1** and of (−)-16-*O*-acetylvindoline **5** in the presence of cyanide ion and a catalytic amount of a photosensitizer known to produce singlet oxygen leads to (+)-3β-cyanocatharanthine **3** and the new (−)-16-*O*-acetyl-3α-cyanovindoline **6**. The complete stereostructural identification of these compounds has been ascertained by an accurate spectroscopic survey. High regio- and diastereoselectivities (de > 99%) are observed. Some experiments have been performed which confirm unambiguously that singlet oxygen is the oxidizing species in such photochemical conditions.

Introduction

Vinblastine (VLB) and vincristine (VCR), vinca alkaloids isolated from the Madagascan periwinkle, *Catharanthus Roseus*,[1] are well known and useful anticancer agents.[2] Since the early 1970s many synthetic approaches have been developed because these natural products are unfortunately in very low abundance in the plant material. In comparison with these dimeric alkaloids, catharanthine **1** and vindoline **2** (Chart 1) are more



1 **2**

Chart 1

plentiful in the Madagascan periwinkle, or are available by total synthesis.[3] As a consequence, their biomimetic coupling,[4] in order to obtain the intermediate anhydrovinblastine (precursor of VLB and VCR), has been the subject of many works. Since an oxidative fragmentation of the C16–C21 bond of catharanthine **1** occurs during this coupling, numerous research groups developed oxidative methods to realize this carbon–carbon bond cleavage. Such a fragmentation can be carried out either by a two-electron-transfer mechanism as the well known modified Polonovski reaction,[5] either by a one-electron-transfer mechanism in the presence of DDQ,[6] by Fe^{3+} catalysis,[7] or under oxidative electrochemical conditions.[8]

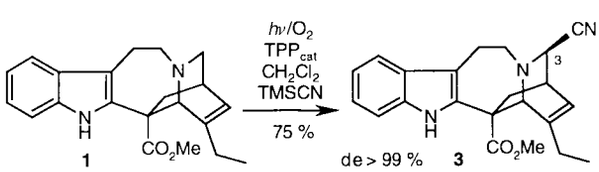
The discovery and development of new photochemical processes has led to a considerable increase in the use of photochemistry for the synthesis of elaborate molecules. Our increasing research activity in photooxidation by single-electron-transfer (SET) processes has focused not only on mechanism but also on discovering new, synthetically useful reactions. Thus, we have developed a photocatalytic general procedure for *in situ* generation of iminium cations. By hydrolysis of these iminium cations, we carried out a mild and useful method for *N*-demethylation[9] of some alkaloids. Trapping these iminium cations with cyanide ions[10,11] allows us to develop a highly mild and efficient way to generate α-aminonitriles, useful intermediates in the synthesis of various biologically active alkaloids. Applied to complex alkaloids,[10] this photocyanation reaction appears to be highly chemo-, regio- and diastereoselective.

In the present paper, the photocyanation of natural (+)-catharanthine **1** and (−)-vindoline **2** has been investigated. High selectivities are observed and new derivatives of those alkaloids have been obtained. The selectivity and mechanism of these oxidations are discussed.

Results and discussion

Photooxidation of catharanthine 1 by SET

The typical procedure used in our laboratory to realize the photocyanation of tertiary amines consists of the irradiation by visible light ($\lambda > 495$ nm), in the presence of catalytic amounts of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) and trimethylsilyl cyanide (TMSCN), under oxygen bubbling. Thus, photocyanation of catharanthine **1** led quantitatively to 3β-cyanocatharanthine **3**, which was recovered after crystallization in up to 75% yield (Scheme 1).



1 **3**

Scheme 1

This compound had been previously obtained by Sundberg *et al.* among a mixture of products, involving a one-electron-transfer mechanism either with DDQ[6] or under photooxidation[12] conditions. In both cases, yields were very modest, spectroscopic analysis was succinct and stereochemistry was not assigned. A particularly noteworthy observation is that the modified Polonovski oxidation, proceeding by a two-electron-transfer mechanism, reported by Langlois and co-workers,[13] led to a mixture of three other α-aminonitriles, among which compound **3** was not observed.

The structure of compound **3** has been unambiguously ascertained by complete spectroscopic determination. IR spectroscopic data revealed the presence of the characteristic cyano

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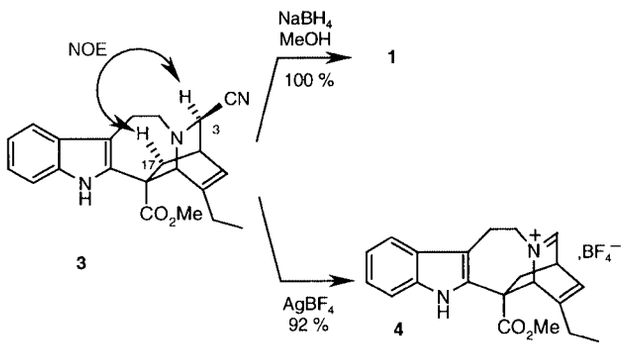
absorption peak at 2220 cm^{-1}. A 25 mass units increase in the molecular mass detected by mass spectroscopy confirmed the presence of a cyano group on the *iboga* skeleton. A complete ^1H NMR investigation with nuclear Overhauser effect (NOE) connectivities permitted us to assign all the chemical shifts and the absolute configuration of the new created stereogenic center. The absence of an ABX system attributed to C-5 and C-6 methylene protons and the presence of a doublet attributable to the H-21 proton confirmed that the introduction of the cyano group took place on the C-3 carbon atom. Furthermore, a significative NOE connection between H-3α and H-17β protons (Scheme 2) is consistent with the β stereochemistry of the cyano group on the C-3 carbon atom.



Scheme 2

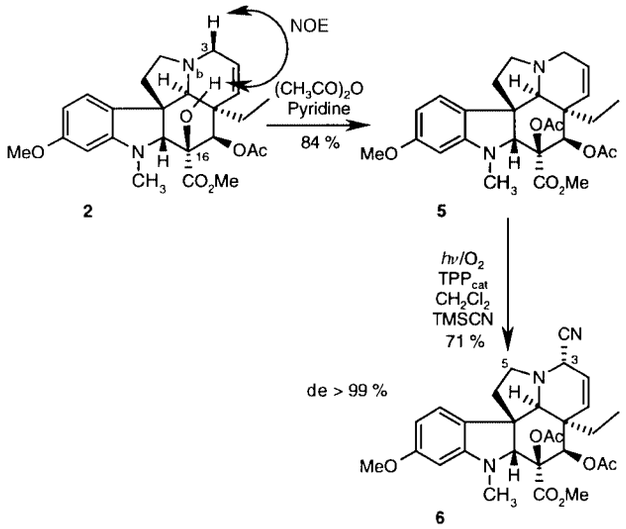
Confirmation of this structure has also been supported by several chemical proofs. Thus, sodium borohydride reduction of compound **3** gave quantitatively the starting material **1** (Scheme 2). Such a reactivity is typical of the reduction of an α-aminonitrile.[14] Furthermore, we isolated and characterized the iminium cation (see **4**) resulting from reaction of silver tetrafluoroborate with α-aminonitrile **3**.

Photooxidation of vindoline 2 by SET

Vindoline **2** was irradiated under our previously described conditions ($h\nu/O_2$/TPP/CH_2Cl_2/TMSCN). No oxidation occurred even after very long irradiation (one day). In the literature, Potier and co-workers noticed such a lack of unreactivity when they tried to oxidize vindoline **2** with hydrogen peroxide[15] or peroxy acids to prepare the corresponding *N*-oxide. However, vindoline **2** oxidation has been achieved by peroxidases[16] or in electrochemical[17] ways. In these cases, dimeric compounds were generally obtained in a mixture of products.

Previous remarks reported in the literature mentioned the possibility of a hydrogen bond between the proton of the hydroxy group on the C-16 carbon atom and the nitrogen Nb lone pair, due to the conformation of the six-membered boat-like ring C. In order to confirm this explanation, we studied by accurate NMR investigation the structure of this compound. Effectively, we found a significative NOE connection between the 3-β proton and the proton of the hydroxy group (Scheme 3). The nitrogen bearing its lone pair involved in the hydrogen bond is subsequently less readily oxidizable. This explains the unreactivity of vindoline **2** observed during our mild photooxidation conditions.

To circumvent this lack of reactivity, we acetylated the alcohol function of vindoline **2** with acetic anhydride in pyridine (Scheme 3). The resulting 16-*O*-acetylvindoline **5**, obtained in 84% yield, was then submitted to our usually photooxidation conditions. By this route we obtained quantitatively the new vinca-alkaloid 16-*O*-acetyl-3α-cyanovindoline **6**. This photocyanation occurred with total chemo-, regio- and diastereoselectivity control (de > 99%). 16-*O*-Acetyl-3α-cyanovindoline **6** was isolated by crystallization from hexane in 71% yield.



Scheme 3

The stereostructural identification of this new vindoline derivative **6** has been ascertained by an accurate spectroscopic survey. As previously observed in the case of 3β-cyanocatharanthine **3**, the IR spectrum was consistent with the proposed cyano derivative. The band at 2220 cm^{-1} can be assigned to the cyano group. In the same way, this presence is confirmed by a 25 mass units increase of the molecular mass in mass spectroscopy. The cyanation occurred on the C-3 carbon atom in the α stereochemistry upon consideration of the following arguments.

(i) A 4.35 ppm upfield chemical shift of the C-5 carbon atom with regard to that of the 16-acetylvindoline **5** is typical of a steric effect.

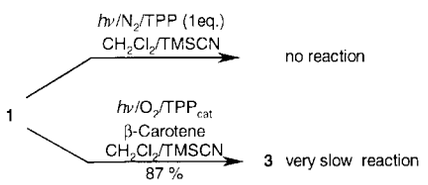
(ii) The disappearance of a small coupling constant ($^3J_{14,3\alpha}$ 2 Hz) between the H-14 and H-3α proton atoms observed in 16-*O*-acetylvindoline **5** contributes to confirm the regio- and stereochemistry of the cyanation.

(iii) Furthermore, a significative NOE connection between H-3β and H-5β protons (Scheme 3) indicates the α stereochemistry of the cyano group.

Photooxidation mechanism in the presence of TPP

Generally in photosensitized oxidation, two oxidizing species could be present in the reaction mixture. In fact, almost all the photosensitizers generate singlet oxygen. Notably, TPP has been reported to be an efficient singlet oxygen producer.[18,19] Thus, in order to determine whether the excited TPP (TPP*) or singlet oxygen was responsible for the single electron transfer, we have conducted further investigations to elucidate this competition:

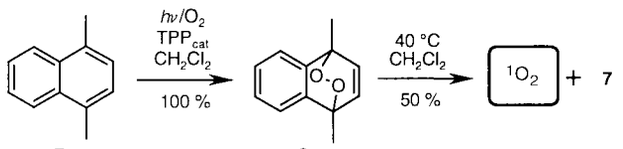
Irradiation of catharanthine **1** under nitrogen atmosphere in the presence of a stoichiometric amount of TPP leaves the starting material unchanged (Scheme 4).



Scheme 4

Photooxidation of catharanthine **1** in the presence of a catalytic amount of TPP, under oxygen atmosphere is significantly slower with addition of a well known singlet oxygen quencher such as β-carotene[18] (170 mg in 5 h *vs.* 1.2 g in 35 min).

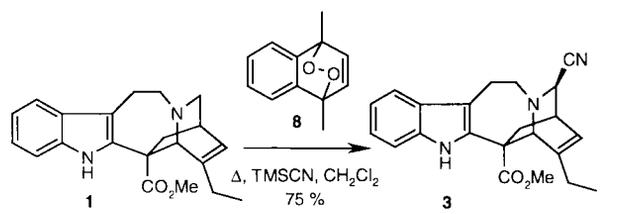
At first sight from these results, excited TPP (TPP*) seems not to be able to oxidize the catharanthine **1** by SET. So, this oxidation should be realized by singlet oxygen. In order to confirm that, we carried out an experiment where the only oxidizing species was doubtless singlet oxygen. This was accomplished by heating the 1,4-dimethylnaphthalene endoperoxide **8**, a well known chemical source of singlet oxygen under very mild conditions[18,20] (Scheme 5). This 1,4-dimethylnaphthalene



Scheme 5

endoperoxide **8** is readily produced in quantitative yield by TPP-sensitized photooxygenation of 1,4-dimethylnaphthalene **7** in dichloromethane at room temperature.

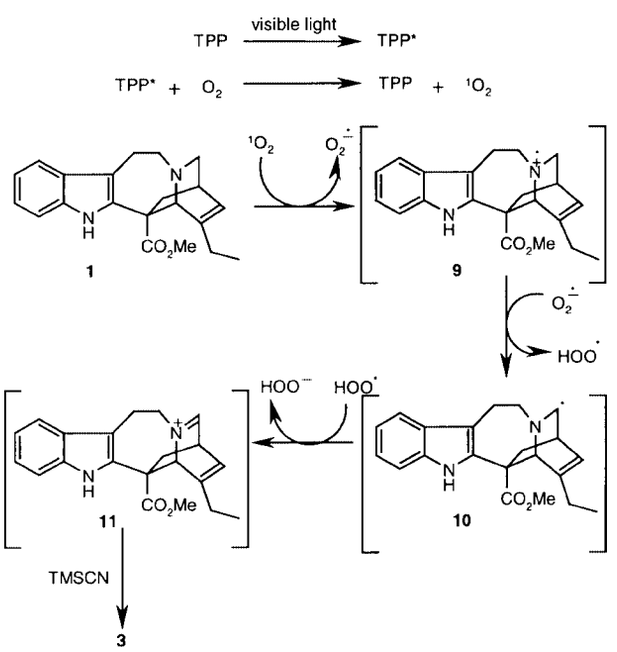
Catharanthine **1** was refluxed in dichloromethane in the dark under nitrogen atmosphere with the endoperoxide **8** and TMSCN (Scheme 6). The 3β-cyanocatharanthine **3** was then



Scheme 6

obtained in 75% yield. This result confirmed that singlet oxygen is able to oxidize catharanthine **1**.

According to those results, we propose for the TPP-sensitized photooxidation of catharanthine **1** the following mechanism (Scheme 7). Singlet oxygen could be produced by an energy



Scheme 7

transfer from TPP excited by visible light to ground-state oxygen. Then the singlet oxygen could oxidize catharanthine **1** by a single-electron transfer, giving rise to the corresponding radical cation **9** and superoxide anion. This last species, which is believed to be quite basic, could deprotonate the relatively acidic proton of the methylide iminium radical cation **9**. As the generated α-aminated carbon radical **10** is a strongly reducing species, it could be readily oxidized by a second electron transfer, leading to the iminium cation **11**. This last compound could be trapped with cyanide ion to give the cyano product 3β-cyanocatharanthine **3**.

Such a mechanism could also be invoked to explain our results concerning the TPP-sensitized photooxidation of 16-*O*-acetylvindoline **5**.

The key point for the high regioselectivity observed in these photooxidations is the control of the deprotonation of the radical cation **9**. In the 1980s Lewis[21] proposed that deprotonation of radical cations was ruled out by stereoelectronic control. The hydrogen atom abstracted is the one which allows an overlap between the half empty nitrogen lone-pair's and the emergent carbon radical's orbitals.

In the case of the photooxidation of catharanthine **1**, the only hydrogen atom that can comply with Lewis's stereoelectronic control is the H-3β hydrogen atom. This could explain the regioselectivity observed in the formation of 3β-cyanocatharanthine **3**. For the photooxidation of 16-*O*-acetylvindoline **5**, the hydrogen atom satisfying the stereoelectronic control criterion for the deprotonation is the H-3α hydrogen atom. Moreover, in this case, the allylic position of this hydrogen confers an increase in its acidity, and the carbon radical generated is stabilized by delocalization.

For the photocyanation of catharanthine **1** as well as for 16-*O*-acetylvindoline **5**, the high stereoselectivity could be explained by the easier nucleophilic attack of cyanide ion on the less hindered side.

Conclusions

In this paper we studied the photocyanation of two complex alkaloids, catharanthine **1** and 16-*O*-acetylvindoline **5**. Our photooxidation reaction proceeding by single-electron transfer leads quantitatively with high regio- and diastereoselectivities (de > 99%) to the corresponding α-aminonitriles **3** and **6**, respectively. During this work we have elucidated which oxidizing species is responsible for these oxidations: singlet oxygen. Applied to 16-*O*-acetylvindoline **5**, this photocyanation allows us to envisage the synthesis of various derivatives which could be involved in a Potier coupling with catharanthine **1** in order to obtain new dimeric alkaloids.

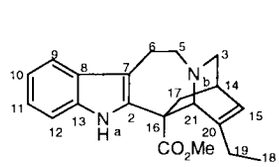
Our ongoing interest in photooxidation by visible light prompts us to try to improve our understanding of the different parameters which are important in controlling the evolution of an aminium radical cation. Further results concerning another evolution of the radical cation **9** of the catharanthine to a C16–C21 bond cleavage will be soon submitted for publication.

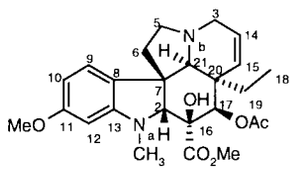
Experimental

All materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled from benzophenone–sodium prior to use. IR spectra (cm^{-1} with polystyrene calibration, in $CHCl_3$ unless otherwise noted) were recorded on a Perkin-Elmer 457 spectrophotometer or on a Philips PU9716 spectrophotometer. ^1H NMR (200 MHz in $CDCl_3$, reference: TMS, $\delta_H = 0.0$) and ^{13}C NMR (50.3 MHz in $CDCl_3$, reference: $CDCl_3$, $\delta_C = 77.0$) spectra were recorded on a Bruker AM200 spectrometer. Chemical shift data are reported in parts per million downfield from TMS, and coupling constants (*J*) are reported in Hz. GLC-MS spectra (EI and CI) were performed on an HP G1019A (70 eV, *m/z*) spectrometer. Elemental analyses were performed by the S.I.A.R. (Service Régional de Microanalyse de l'Université Paris VI). Flash column and thin-layer chromatography were

done by using aluminium oxide 90 (Merck, act. II–III) or silica gel 60 (230–400 Mesh). Optical rotations were measured on a Perkin Elmer 141 polarimeter; $[\alpha]_D$-values are given in 10^{-1} deg cm^2 g^{-1}.

To systematize comparison of the attribution of the NMR signals, structures **1** and **2** have the following numbering systems:





Photocyanation of catharanthine 1 with TPP

A solution of 1.20 g (3.57 mmol) of catharanthine **1** in CH_2Cl_2 (120 mL) to which were added TMSCN (1.19 mL, 8.92 mmol) and a catalytic amount of TPP (0.03 mmol) was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter ($\lambda > 495$ nm) at 20 °C, during 35 min. After reaction, monitored by TLC, 30 mL of 10% aq. Na_2CO_3 were added to the resulting reaction mixture. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with 10% aq. Na_2CO_3 (30 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The resulting cyano product was filtered on aluminium oxide (hexane–AcOEt 8 : 2) and was recrystallized from MeOH to give 966 mg (75%) of 3β-cyanocatharanthine **3** as a crystalline white solid, mp 186 °C; $[\alpha]_D^{25}$ +110 (*c* 1, $CHCl_3$); IR (KBr)/cm^{-1} 3360, 2950, 2230, 1730; ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.13 (3H, t, *J* 7.3, H_3-18), 1.77 (1H, dd, *J* 13.5, 2.2, H-17β), 2.26 (2H, m, H_2-19), 2.82 (1H, dd, *J* 13.5, 3.7, H-17α), 3.10 (3H, m, H-14, H_2-5), 3.39 (1H, m, H-6), 3.62 (1H, m, H-6), 3.75 (3H, s, OCH_3), 3.81 (1H, d, *J* 2.2, H-3α), 4.29 (1H, d, *J* 1.3, H-21), 5.98 (1H, m, H-15), 7.13 (1H, m, H-10), 7.18 (1H, m, H-11), 7.24 (1H, m, H-12), 7.50 (1H, m, H-9), 7.77 (1H, s, N^{a}H); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ_C 10.99 (C-18), 21.07 (C-6), 26.52 (C-19), 34.45 (C-14), 37.04 (C-17), 51.76 (C-5), 52.02 (C-3), 52.55 (CO_2CH_3), 54.55 (C-16), 59.97 (C-21), 110.27 (C-7), 110.54 (C-12), 118.16 (C-9), 119.66 (C-10), 120.22 (CN), 120.77 (C-11), 122.18 (C-15), 128.51 (C-8), 134.90 (C-13), 135.25 (C-2), 151.63 (C-20), 173.15 (C=O); MS (EI) *m*/*z* (rel. intensity) 361 ($M^{+\bullet}$, 25%), 334 (5), 229 (30), 228 (14), 214 (43), 201 (43), 168 (34), 160 (100), 154 (34), 107 (14) (Calc. for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.41; N, 11.62. Found: C, 73.00; H, 6.65; N, 11.88%).

Reduction of compound 3 with $NaBH_4$

$NaBH_4$ (169 mg, 4.45 mmol) was added to a solution of the cyano compound **3** (320 mg, 0.89 mmol) in 40 mL of MeOH at 0 °C. The reaction was monitored by TLC and stirred for 15 min. The reaction mixture was treated with 20 mL of 10% aq. Na_2CO_3, and MeOH was removed under reduced pressure. 50 mL of CH_2Cl_2 were added and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with aq. Na_2CO_3 (30 mL; 10%), dried over $MgSO_4$, and concentrated under reduced pressure. Catharanthine **1** (300 mg, 100%) was obtained as a white solid.

Catharanth-3-enium tetrafluoroborate 4

To a solution of 272 mg (0.75 mmol) of the cyano compound **3** in 20 mL of anhydrous THF under argon was added slowly a solution of 176 mg (0.90 mmol) of $AgBF_4$ in 8 mL of THF. The reaction was monitored by TLC. In the resulting mixture a white suspension of AgCN was observed just after the addition. After filtration the mixture was concentrated under reduced pressure and 293 mg (92%) of catharanth-3-enium salt **4** were obtained as a green solid, mp 130 °C; IR (KBr)/cm^{-1} 3350, 2960, 1730; ^{1}H NMR (200 MHz; acetone-d_6) δ 1.1 (3H, t, *J* 7.0, H_3-18), 1.7 (2H, m, H-6, -17), 2.4 (3H, m), 2.8 (1H, m), 3.6 (1H, m), 3.7 (3H, s, OCH_3), 4.7 (2H, m), 6.6 (2H, m), 7.0–7.6 (4H, m, H-9, -10, -11, -12), 9.4 (1H, d, *J* 4.5, H-3), 10.0 (1H, s, N^{a}H).

16-*O*-Acetylvindoline 5

A solution of 1.05 g (2.30 mmol) of vindoline **2** in 5 mL (61.93 mmol) of pyridine, to which were added 5 mL (52.95 mmol) of acetic anhydride, was heated to 100 °C during 2 h. The initially yellow solution turned red. The reaction was found to be complete on TLC (Al_2O_3; CH_2Cl_2). Excess of acetic anhydride was hydrolyzed with 10 mL of water. The solution was then neutralized by the addition of NH_4OH (2 M; 3 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with aq. Na_2CO_3 (20 mL; 10%), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting product was purified by flash chromatography on aluminium oxide (CH_2Cl_2–hexane 4 : 6, followed by CH_2Cl_2, then CH_2Cl_2–MeOH 98 : 2 and finally MeOH) and was recrystallized from Et_2O to give 962 mg (84%) of 16-*O*-acetylvindoline **5** as a crystalline white solid, mp 138 °C; $[\alpha]_D^{25}$ −70 (*c* 2, $CHCl_3$); IR (KBr)/cm^{-1} 2950, 1750, 1610; ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.50 (3H, t, *J* 7.4, H_3-18), 1.34 (2H, m, H_2-19), 1.98 (6H, s, CH_3CO), 2.20 (3H, m, H-5α, -6), 2.52 (1H, s, H-21α), 2.65 (1H, ddd, *J* 16.0, 1.8, 1.8, H-3α), 2.71 (3H, s, N^aCH_3), 3.24 (1H, m, H-5β), 3.31 (1H, ddd, *J* 16.0, 5.0, 2.3, H-3β), 3.73 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.92 (1H, s, H-2), 5.20 (1H, ddd, *J* 10.1, 2.3, 1.8, H-15), 5.47 (1H, s, H-17α), 5.84 (1H, ddd, *J* 10.1, 5.0, 1.8, H-14), 6.07 (1H, d, *J* 2.2, H-12), 6.30 (1H, dd, *J* 8.2, 2.2, H-10), 6.92 (1H, d, *J* 8.2, H-9); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ 7.62 (C-18), 20.80 (CH_3CO_2), 21.11 (CH_3CO_2), 31.36 (C-19), 38.45 (N^aCH_3), 42.55 (C-20), 44.07 (C-6), 51.03 (C-3), 52.02 (CO_2CH_3), 52.54 (C-5), 52.74 (C-7), 55.20 (OCH_3), 68.08 (C-21), 74.67 (C-17), 79.60 (C-2), 82.69 (C-16), 96.07 (C-12), 104.58 (C-10), 122.74 (C-9), 125.42 (C-14), 127.72 (C-8), 129.18 (C-15), 153.06 (C-13), 160.61 (C-11), 168.91 (CH_3CO_2), 169.47 (CO_2CH_3), 170.13 (CO_2CH_3); MS (EI) *m*/*z* (rel. intensity) 498 ($M^{+\bullet}$, 2%), 296 (7), 189 (43), 188 (40), 174 (20), 161 (21), 135 (100), 122 (16), 121 (39), 107 (16), 93 (7) (Calc. for $C_{27}H_{34}N_2O_7$: C, 65.04; H, 6.87; N, 5.62. Found: C, 64.92; H, 6.89; N, 5.53%).

Photocyanation of 16-*O*-acetylvindoline 5 with TPP

A solution of 981 mg (1.97 mmol) of 16-*O*-acetylvindoline **5** in CH_2Cl_2 (50 mL), to which were added TMSCN (527 μL, 3.94 mmol) and a catalytic amount of TPP (0.02 mmol), was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter ($\lambda > 495$ nm) at 20 °C, during 40 min. The reaction was monitored by TLC (Al_2O_3; hexane–AcOEt 8 : 2). The resulting reaction mixture was quenched by 20 mL of 10% aq. Na_2CO_3. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with aq. Na_2CO_3 (20 mL; 10%), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting cyano product was filtered on aluminium oxide (CH_2Cl_2–hexane 9 : 1) and was recrystallized from hexane to give 731 mg (71%) of 16-*O*-acetyl-3α-cyanovindoline **6**, as a crystalline white solid, mp 128 °C; $[\alpha]_D^{25}$ −84 (*c* 1, $CHCl_3$); IR (KBr)/cm^{-1} 2950, 2220, 1750, 1610; ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.64 (3H, t, *J* 7.4, H_3-18), 1.37 (2H, m, H_2-19), 1.94 (3H, s, CH_3CO), 1.99 (3H, s, CH_3CO), 2.20 (2H, m, H_2-6), 2.75 (3H, s, $NaCH_3$), 2.91 (1H, m, H-5α), 3.05 (1H, s, H-21), 3.21 (1H, m, H-5β), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.87 (1H, s, H-2), 4.27 (1H, dd, *J* 5.5, 1.5, H-3), 5.42 (1H, s, H-17), 5.58 (1H, dd, *J* 9.8, 1.5, H-15), 5.90 (1H, dd, *J* 9.8, 5.5, H-14), 6.10 (1H, d, *J* 2.2, H-12), 6.33 (1H, dd, *J* 8.2, 2.2, H-10), 6.97 (1H, d, *J* 8.2, H-9); ^{13}C NMR (50.3 MHz; $CDCl_3$) δ 7.68 (C-18), 20.77 (CH_3CO_2), 21.04 (CH_3CO_2), 31.16

(C-19), 38.84 ($NaCH_3$), 42.25 (C-20), 43.18 (C-6), 48.19 (C-5), 49.50 (C-3), 52.08 (CO_2CH_3), 52.55 (C-7), 55.23 (OCH_3), 62.58 (C-21), 74.25 (C-17), 79.17 (C-2), 82.69 (C-16), 96.53 (C-12), 104.95 (C-10), 115.21 (CN), 119.98 (C-9), 122.81 (C-14), 125.75 (C-8), 134.46 (C-15), 152.95 (C-13), 161.00 (C-11), 168.30 (CH_3CO_2), 168.66 (CH_3CO_2), 169.97 (CO_2CH_3); MS (CI) *m*/*z* (rel. intensity) 524 (MH^+, 100%), 497 (15).

1,4-Dimethylnaphthalene endoperoxide 8

A solution of 1.00 g (641 mmol) of 1,4-dimethylnaphthalene **7** in CH_2Cl_2 (50 mL), to which was added a catalytic amount of TPP (0.50 mmol), was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter ($\lambda > 495$ nm), keeping the temperature below 15 °C. The reaction was monitored by TLC (SiO_2; CH_2Cl_2) and found to be complete after 2 h. The only product formed was 1,4-dimethylnaphthalene endoperoxide **8**. The crude reaction mixture could be directly used in the following oxidation reaction after concentration of the solvent, keeping the temperature below 25 °C.

Photooxidation of catharanthine 1 with TPP and β-carotene

A solution of 170 mg (0.51 mmol) of catharanthine **1** in CH_2Cl_2 (60 mL), to which were added TMSCN (150 μL, 1.21 mmol), a catalytic amount of TPP (0.02 mmol) and β-carotene (300 mg), was irradiated under oxygen bubbling with a 1800 W xenon lamp through a UV cut-off glass filter ($\lambda > 495$ nm) at 20 °C. Reaction was monitored by TLC (Al_2O_3; CH_2Cl_2–cyclohexane 7:3), and was found to be complete after 5 h under irradiation. A solution of 10% aq. Na_2CO_3 (20 mL) was then added to the resulting reaction mixure. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with aq. Na_2CO_3 (20 mL; 10%), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting cyano product was filtered on aluminium oxide (hexane, then AcOEt) to give 160 mg (87%) of 3β-cyanocatharanthine **3**, as an amorphous solid.

Photocyanation of catharanthine 1 with 1,4-dimethylnaphthalene endoperoxide 8

A solution of 1.688 g (8.98 mmol) of 1,4-dimethylnaphthalene endoperoxide **8** in CH_2Cl_2 (50 mL), to which were added 274 mg (0.81 mmol) of catharanthine **1** and TMSCN (272 μL, 2.03 mmol), was refluxed in the dark. Formation of 3β-cyanocatharanthine **3** and disappearance of catharanthine **1** was monitored by TLC on aluminium oxide (CH_2Cl_2). Formation of 1,4-dimethylnaphthalene **7** and disappearance of 1,4-dimethylnaphthalene endoperoxide **8** was monitored by TLC on silica gel (CH_2Cl_2). Reaction was found to be complete after 4 h. The resulting reaction mixure was then quenched by 10 mL of 10% aq. Na_2CO_3. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with aq. Na_2CO_3 (20 mL; 10%), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting cyano product was filtered on aluminium oxide (hexane, then CH_2Cl_2) and was recrystallized from MeOH to give 219 mg (75%) of 3β-cyanocatharanthine **3**, as a crystalline white solid.

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