SYNTHESIS OF VINCA ALKALOIDS AND RELATED COMPOUNDS. PART XCIII.[1] SKELETAL REARRANGEMENT OF CYCLOVINBLASTINE DERIVATIVES: FORMATION OF A NOVEL BISINDOLE SYSTEM

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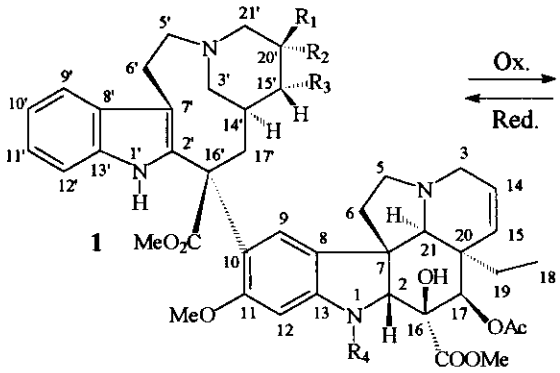
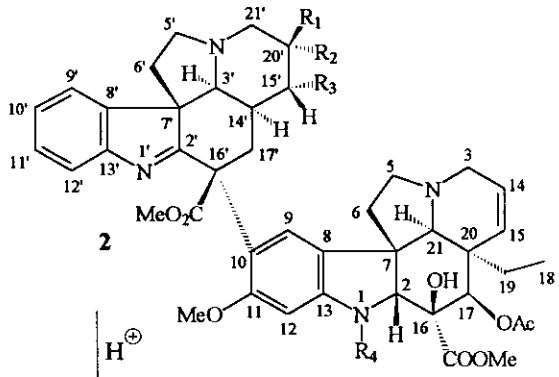
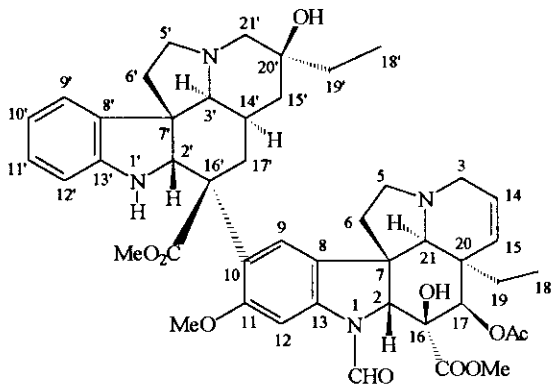
Abstract - Bisindole alkaloids of the vinblastine (VLB) type can be oxidized to give a Ψ-aspidosperma-aspidosperma type skeleton *via* 3'-7'-transannular cyclization. Acid catalysis triggers an aspidospermane→eburnane skeletal rearrangement of these cyclic derivatives, thus giving a novel bisindole system with a Ψ-eburnea-aspidosperma type skeleton. A previously unexplored aspect of this transformation is the observed retention or inversion at C(16') depending on the starting C(16') configuration. The present paper gives a detailed account of the synthetic aspect of this work together with preliminary NMR and CD results concerning the epimerization at C(16').

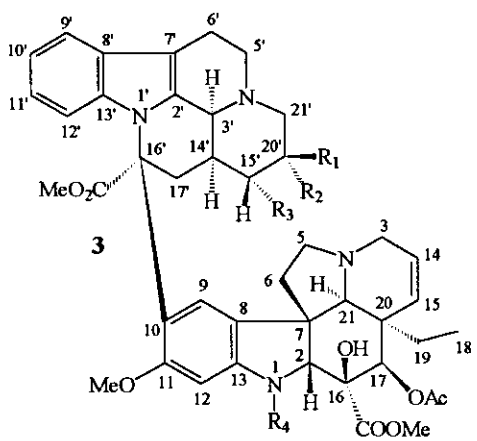
1 INTRODUCTION

Owing to their potential therapeutic benefit in cancer chemotherapy, bisindole (indole-indoline) alkaloids have been a focus of much research for the past few decades. Many such compounds exhibit exceptional antitumor activity, and among these vinblastine (VLB, **1a**) and vincristine (VCR, **1b**) (Scheme 1) are widely used in the clinical practice.[2a-f] One of our recent findings has shown that oxidation of **1** gives a Ψ-aspidosperma-aspidosperma type skeleton (**2**) *via* 3'-7'-transannular cyclization.[3,4] Acid catalysis in turn triggers an aspidospermane→eburnane skeletal rearrangement of **2** into **3**. A previously unexplored









4 1',2'-dihydrocyclovincristine **DH-CVCR**

	R_1	R_2	R_3	R_4	**1**	**2**	**3**
a	OH	Et	H	Me	vinblastine **VLB**	cyclovinblastine **CVLB**	isocyclovinblastine **iCVLB**
b	OH	Et	H	CHO	vincristine **VCR**	cyclovincristine **CVCR**	isocyclovincristine **iCVCR**
c	OH	Et	H	H	deformyl-vincristine **DF-VCR**	deformyl-cyclovincristine **DF-VCR**	deformyl-isocyclovincristine **DF-VCR**
d	Et			Me	leurosine **LE**	cycloleurosine **CLE**	isocycloleurosine **iCLE**

Scheme 1

aspect of the **2**→**3** transformation is the observed retention or inversion at C(16') depending on the C(16') configuration of **2**. This question has been investigated on a number representative derivatives of type (**2**). Here we report the synthetic results regarding the **1**→**2** and **2**→**3** transformations together with our preliminary NMR and CD results concerning the epimerization at C(16').

2 RESULTS AND DISCUSSION

2.1 3'-7'-transannular cyclization (1→2, processes)

Since VLB (**1a**) can be isolated from *Catharanthus roseus* in a much larger quantity than VCR (**1b**) which exhibits a higher therapeutic value, the efficient transformation of **1a** into **1b** is of utmost importance. Up to date the best approach appears to be the oxidation of VLB (**1a**) sulfate with chromyl acetate.[5] However, if the oxidation is carried out on the free base, the main product is not VCR (**1b**), but the cyclic derivative (**2a**) in which the original velbanamine part has undergone a 3'-7'-transannular cyclization into a Ψ-aspidosperma-type skeleton. The obtained 3'-7'-cyclovinblastine (CVLB, **2a**) could, in its sulfate form, be oxidized into 3'-7'-cyclovincristine (CVCR, **2b**) by chromyl acetate. The same product (CVCR, **2b**) was obtained *via* the oxidative **1**→**2** transformation of VCR base (**1b**). A similar oxidation of leurosine (LE, **1d**) into the respective cyclic product (CLE, **2d**) was achieved by using dichlorobis(benzonitrile)palladium(II) as catalyst in an aprotic solvent. This catalyst did not work in the case of **1a** and **1b**, probably because of the lack of an appropriate complex formation.

The reduction of CVCR (**2b**) with sodium borohydryde in acetic acid afforded vincristine (VCR, **1b**) *via* 3'-7'-ring fragmentation. Through deformylation of **1b** the known alkaloid *N*-deformylvincristine (DF-VCR, **1c**) was obtained. A selective 1'-2' reduction was achieved by using sodium cyanoborohydride yielding 1',2'-dihydrocyclovincristine (1',2'-DH-CVCR, **4**).

The cyclic derivatives (**2a-d**) as obtained by 3'-7'-transannular ring closure possess a 1',2'-dehydro-Ψ-aspidosperma-aspidosperma type skeleton. The only known natural representative of this skeleton is vincovalicine which was isolated from *Catharanthus ovalis*. The proposed, but not fully elucidated structure of vinkovalicine is similar to that of CVCR (**2b**), but in vinkovalicine the position of the OH group within the piperidine ring remained unidentified.[6] The published spectral data of vinkovalicine and those obtained for CVCR (**2b**) (see below) closely resemble, but chemical arguments indicate that the two compounds are nonidentical.[3]

2.2 Aspidosperma→eburnane type skeletal rearrangement (2→3 processes)

The aspidosperma→eburnane skeletal rearrangement, originally proposed by Wenkert and Wickberg,[7] was of fundamental importance in the development of subsequent biogenetic theories. The first *in vitro* realization of this theory by the rearrangement of vincadifformine into vincamine came from Le Men and co-workers,[8] thus supporting the presumed biogenetic connection between the *Aspidosperma* and *Vinca* alkaloids. Such a rearrangement is well known when starting from the "monomeric" vincadifformine, tabersonine (and their variously substituted derivatives)[9,10] or vindoline,[10c] but not in the case of the more

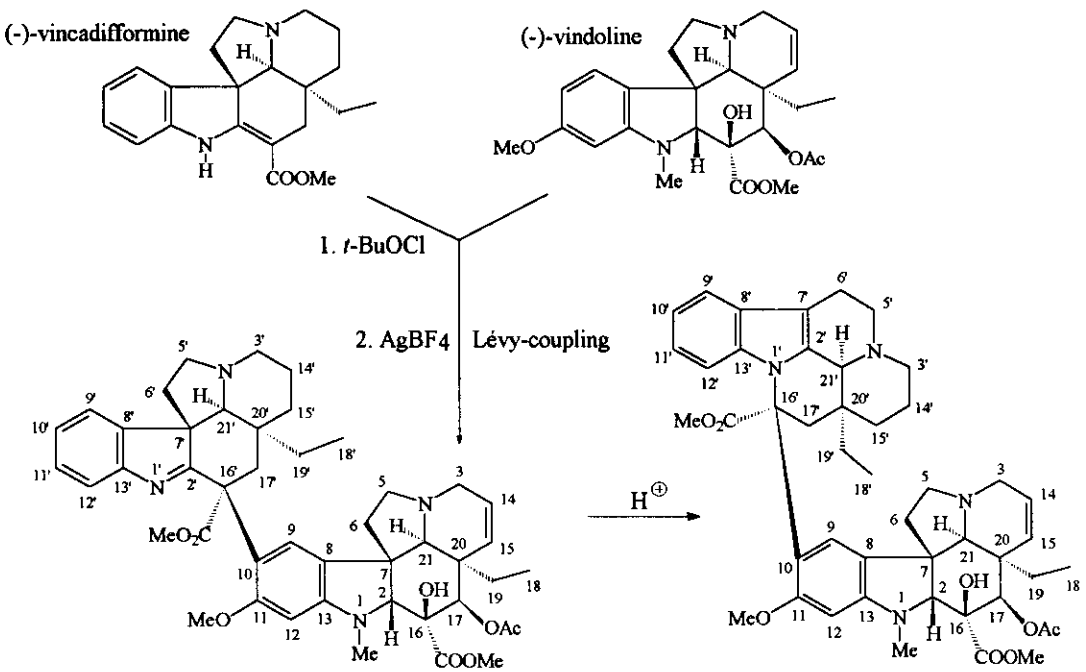
complex bisindoles of type (**2**). For the "monomeric" structures the rearrangement in all cases proceeds with retention of configuration at each point of ring anellation, however, the C(16) stereogenic center is particularly vulnerable to epimerization, giving C(16) epimeric mixtures.[9] Since the stereochemistry of the aspidospermane→eburnane skeletal rearrangement has not been investigated with a bulky substituent at C(16'), we attempted to trigger the rearrangement of the obtained cyclodimers (**2**) and to explore its stereochemical consequences. To this end, CVCR (**2b**) was deformylated at 0 °C in dilute sulfuric acid/methanol yielding DF-CVCR (**2c**), which even at room temperature rearranges to DF-iCVCR (**3c**) (Scheme 1). Reformylation of **3c** gave iCVCR (**3b**), while its reductive alkylation afforded iCVLB (**3a**). The latter product (iCVLB, **3a**) was also obtained in a protic solvent with strong acid or $BF_3 \bullet Et_2O$ starting from CVLB (**2a**). The same rearrangement can be achieved from CLE (**2d**) thus giving iCLE (**3d**).

The absolute configuration of the C(16') stereogenic center is not readily accessible in these compounds. First, we assumed that the bulky vindolinyl group retains its α orientation during the **2**→**3** process,[11] however, as discussed below, the results of our detailed NMR and CD studies indicated that all of these transformations proceed with inversion at C(16') (vindolinyl α→β). Also, in order to gain a fuller picture of the C(16') stereochemistry during the **2**→**3** process, the synthesis of unknown C(16')-C(10) connected aspidosperma-aspidosperma dimer (VV, **5**) was initiated (Scheme2).

To that end, (-)-vincadifformine was coupled with (-)-vindoline by utilizing the method of Lévy and co-workers[12] and the obtained VV dimer (**5**) (in which the vindolinyl group assumes a β orientation) was allowed to rearrange into the respective iVV dimer (**6**). The rate of this rearrangement was much slower than in the case of **2** and proceeded with retention at C(16').

The mechanism of the rearrangement of type-**2** dimers is not entirely clear. A thermodynamically controlled reversible coupling sequence[13] cannot be excluded. Accordingly, under the given experimental conditions a C(16')-C(10) bond fission may occur and the recoupling yields the more stable isomer in which the vindolinyl group assumes a β orientation.

To our best knowledge the **2**→**3** transformation is the first reported case of Ψ-aspidospermane→Ψ-eburnane skeletal rearrangements observed in the VLB-type dimeric indole alkaloids. The dimeric bisindoles (**3a-d**), containing the Ψ-eburnea-aspidosperma skeleton, are the first known representatives of this novel bisindole system. Since the oxidative cyclization of VLB-type alkaloids may be effected even by air, some bisindole alkaloids with unelucidated structures[2a,c] may possess the above-discussed Ψ-aspidosperma-aspidosperma or Ψ-eburnane-aspidosperma skeleton.



Scheme 2

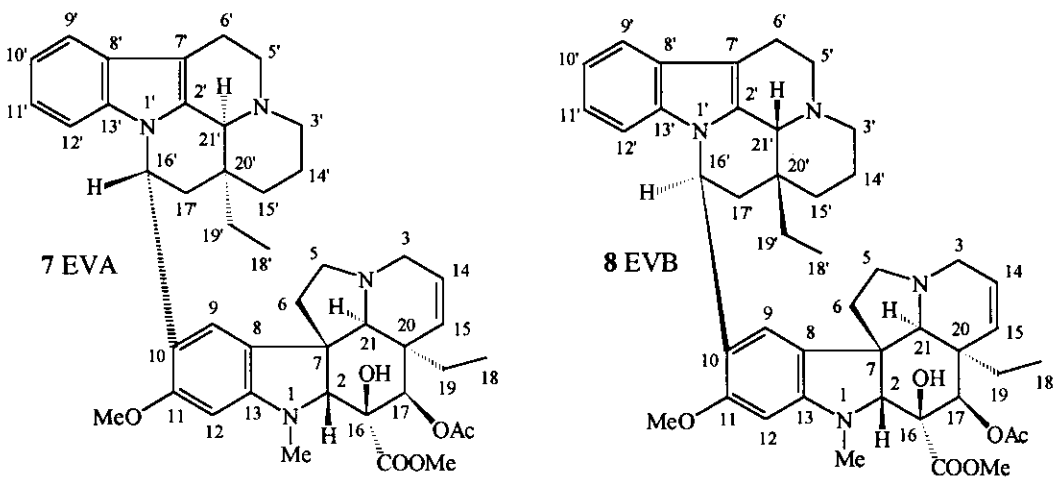
2.3 Structure elucidation

The structural identification of **2** and **3** was first accomplished by a mass spectrometric study,[14] however, the assignment of the C(16') configuration in compounds of type (**3**) remained ambiguous. In the CD spectra of **2** and **3** we found exciton couplets of opposite sign in the 200-230 nm spectral region. This suggested the possibility of a C(16') inversion during the **2** → **3** transformation as based on Kutney's rule which establishes an empirical correlation between the absolute stereochemistry at C(16') and the circular dichroism (CD) spectra of the VLB-type (**1**) bisindole alkaloids.[15] In particular, bisindoles of type (**1**) featuring an α-oriented vindoline moiety were found to give a *positive* couplet while those with an unnatural β-oriented vindoline unit a *negative* one in the 200-230 nm spectral region.[15] Since CD spectroscopy provides a simple and convenient tool for deriving the C(16') configuration, it is an intriguing question whether this empirical correlation can be extended toward bisindoles possessing a Ψ-aspidosperma-aspidosperma (**2**) or a Ψ-eburnane-aspidosperma (**3**) type skeleton. In analogy to the VLB-type bisindoles (**1**), a dipolar coupling between the electronic transitions can be anticipated for **2** and **3** due to the close proximity of the aromatic chromophores. However, in order to predict the sign of the split Cotton effect it is necessary to know the direction of the electric transition moments involved. Due to the low symmetry of chromophores, the evaluation of the polarization properties meets difficulties. Moreover,

subtle changes of substituents, skeletal conformation or conformational distribution around the bond connecting the two indole units may lead to distortions of the couplets. Therefore, without verification by other spectroscopic methods, the CD spectra alone do not provide unambiguous pieces of spectroscopic evidence for the absolute configuration at C(16'). This prompted us to assign the C(16') configuration by a detailed NMR study which proved to be a challenging task due to the complexity of structural and spectral features.

2.3.1 NMR spectroscopy

From an NMR spectroscopic point of view the determination of the C(16') configuration in **2** and **3** as well as in **5** and **6** is far from straightforward: Due to the lack of any hydrogen attached to C(16'), the only relevant NMR parameters indicative of the C(16') configuration are the inter-unit NOEs between the two indole moieties. The interpretation of these NOEs requires, in the first place, a secure knowledge of the dominant ring conformations as well as the preferential rotamers around the C(16')-C(10) bond connecting the two indole units. Therefore, the assignment of the C(16') configuration *via* an analysis of the few available inter-unit NOEs becomes a complex task. In order to facilitate this analysis and to provide a firm basis for the relevant structure elucidation problem we looked for suitable model compounds. We synthesized two such analogues (**7**) and (**8**) (Scheme 3), where a hydrogen atom is attached to C(16'), and gave a detailed analysis of their structure by NMR.[16, 17]



Scheme 3

The structural studies revealed that in **7** and **8** the rotation about the C(16')-C(10) bond is hindered and gives a strongly biased two-site chemical exchange system in which the signals due to the minor

component are broadened to the extent that they escape detection in a conventional ^{1}H NMR spectrum, but can be exposed in suitable NOE experiments.[17, 18] The minor and major rotamers are interchangeable by a *ca.* 180° rotation about the *C(16')-C(10)* bond. *Since the presence of this "hidden exchange partner"* can be the source of spectral and structural misinterpretation we explored this phenomenon further with regard to **2a-d**, **3a-d** and **5**, **6**. Our results have shown that such an unevenly populated slow two-site exchange process is a general feature of the investigated bisindoles. Although this structural property complicates the configurational assignment at C(16') even further, *via* a concerted analysis of molecular modeling calculations and NOE data we could derive the dominant conformations and give an unambiguous assignment of the C(16') configurations. A detailed discussion of the conformational analysis is out of the scope of the present paper and will be reported elsewhere. Here we focus mainly on the assignment of the stereogenic centers, particularly the C(16') configuration by interpreting the key NOEs in representative cases.

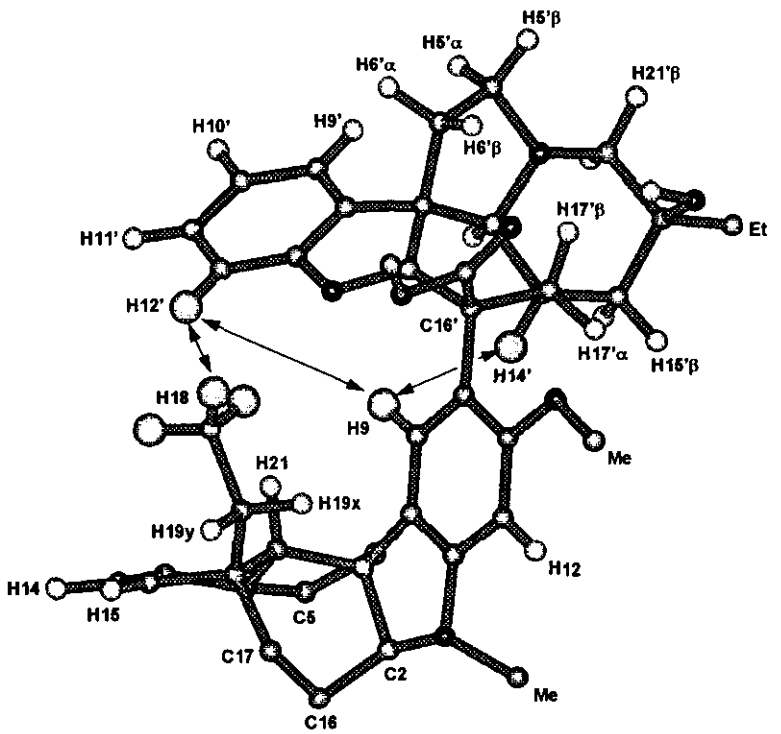


Figure 1. Perspective view of one low-energy conformation of CVLB (**2a**). The arrows depict characteristic inter-unit NOE connections consistent with this conformation.

Stereospecific assignments for 2a-d and 4, 5

The **1**→**2** oxidation leads to the formation of a new stereogenic center C(3') in **2a-d** and **4**. The measured strong H-3' ↔ H-14' NOE connections in these cyclic derivatives reveal that the H-3' proton assumes an α orientation, and therefore provide evidence for the C(3') configuration as depicted in Scheme 1. Although the C(16') configuration follows *a priori* from the synthetic route, the measured NOEs verify the α orientation of the vindolinyl group. The inter-unit NOEs reflect a rapid interconversion of some appreciably populated rotamers around the C(16')-C(10) bond in **2a-d** and **4**. As a representative example, Figure 1. shows one low-energy conformation of CVLB (**2a**) together with the respective inter-unit NOEs consistent with this geometry. The considerably strong H-9 ↔ H_2-17'α, H-14' and weak H_3-18 ↔ H-14' NOEs prove most directly that the vindolinyl group assumes an α orientation. Nevertheless, all of the inter-unit NOEs measured in **2a-d** and **4** can be rationalized in terms of the conformational characteristics obtained from molecular modeling calculations. In DH-CVCR (**4**) the β orientation of the H-2' proton follows readily from the measured H-2' ↔ H_2-6'β NOE. As opposed to **2a-d** and **4**, the stereoposition of the vindolinyl group in the VV dimer (**5**) needs to be determined experimentally. Figure 2. shows those

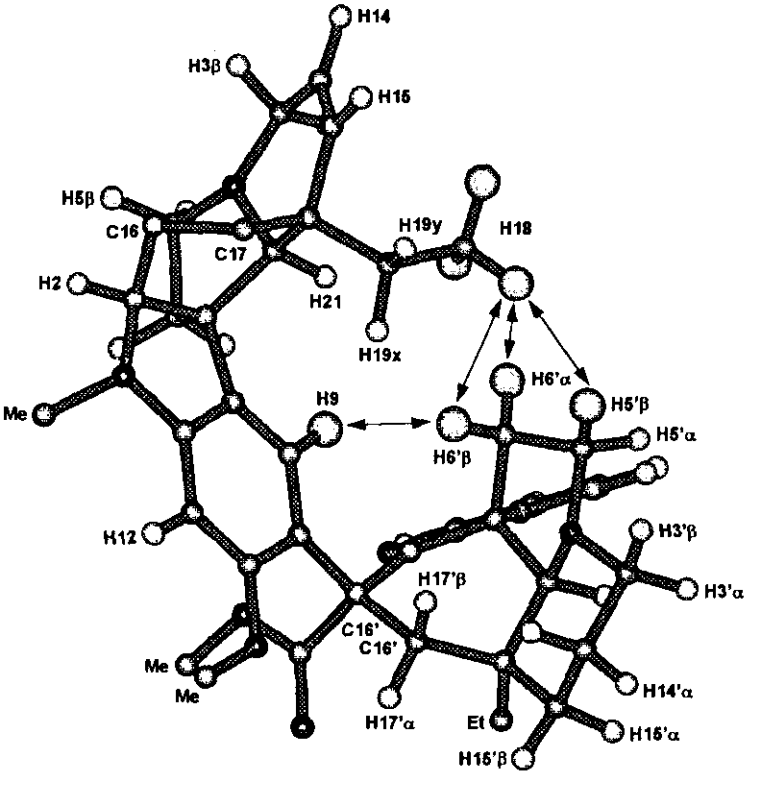


Figure 2. Perspective view of one low-energy conformation of VV (**5**). The arrows depict characteristic inter-unit NOE connections consistent with this conformation.

inter-unit NOE connections (H-9 ↔ H_2-6'β; H3-18 ↔ H_2-6'α, H_2-6'β, H_2-5'β) which provide the most clear evidence for the β orientation of the vindolinyl group.

Stereospecific assignments for 3a-d and 6

In a previous communication we thoroughly explored the structure and dynamics of the model compounds EVA (**7**) as well as EVB (**8**),[17] which turned out to provide a reliable basis for the assignment of the C(16') configuration in **3a-d** and **6**. For the sake of comparison, Figure 3 shows the predominant conformation of the EVA dimer (**7**) together with the corresponding NOEs consistent with this minimum-energy conformation. In the EVA dimer (**7**) considerable NOEs, diagnostic of an α–oriented vindolinyl group, were measured between H-9 and H-17'α as well as H-9 and H-21'. Moreover, as a conspicuous conformational feature of EVA (**7**), the C(18)-C(19) ethyl group lies, in the dominant conformer, underneath the aromatic ring of the eburnamine unit, thus giving rise to the measured H_3-18 ↔ H-9', H-10', H-11', H-12' and H_2-19x ↔ H-12' NOE connections. This also explains the highly shielded nature of the H_3-18 protons ($\delta_{H3\text{-}18}$= -0.36 ppm in $CDCl_3$). In contrast to this, in the iVV dimer (**6**) the H-9 proton shows NOE connections with H_2-15'β and H-12', while H_3-18 gives NOE to H_2-15'α, H_2-15'β and H_2-

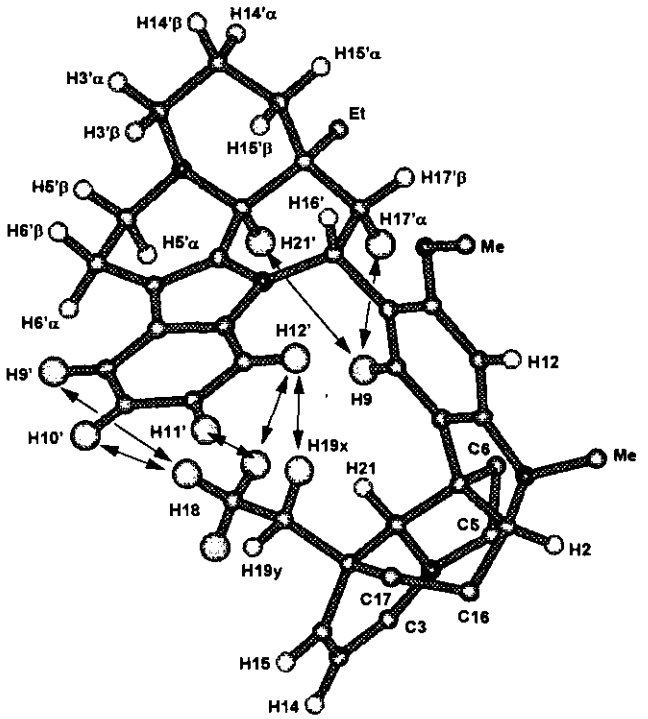


Figure 3. Perspective view of one low-energy conformation of EVA (**7**). The arrows depict characteristic inter-unit NOE connections consistent with this conformation.

14'β. Moreover, significant NOEs were measured between H_2-6α and the aromatic H-12' and H-11' protons. This picture is consistent with the β orientation of the vindolinyl group and with the calculated minimum-energy conformation as depicted in Figure 4. The inter-unit NOEs measured in **3a-d** are also in line with this conclusion (see experimental).Due to rotational isomerization about the C(16')-C(10) bond, the ^{1}H NMR spectra, especially those of **3a-c**, teem with "hidden exchange partners". In **3d** the strain in the Ψ-eburnamine unit induced by the oxirane ring leads to a departure of the skeletal conformation with respect to that found for **3a-c**, thus the population of the minor conformer increases to 30 %. A detailed analysis will be given elsewhere.

2.3.2 CD spectroscopy

The CD data of the discussed compounds (**2a-d**, **3a-d**, **5**, **6**) together with the model compounds (**7**, **8**) are listed in Table 1. In agreement with the sign pattern of **1**, the majority of the cyclo (**2**) and isocyclo (**3**) derivatives gave a definite *positive* exciton couplet for isomers featuring an α oriented vindoline and a *negative* couplet for the β isomers, respectively. Negative couplets with higher (2:1 to 3:1) first long-

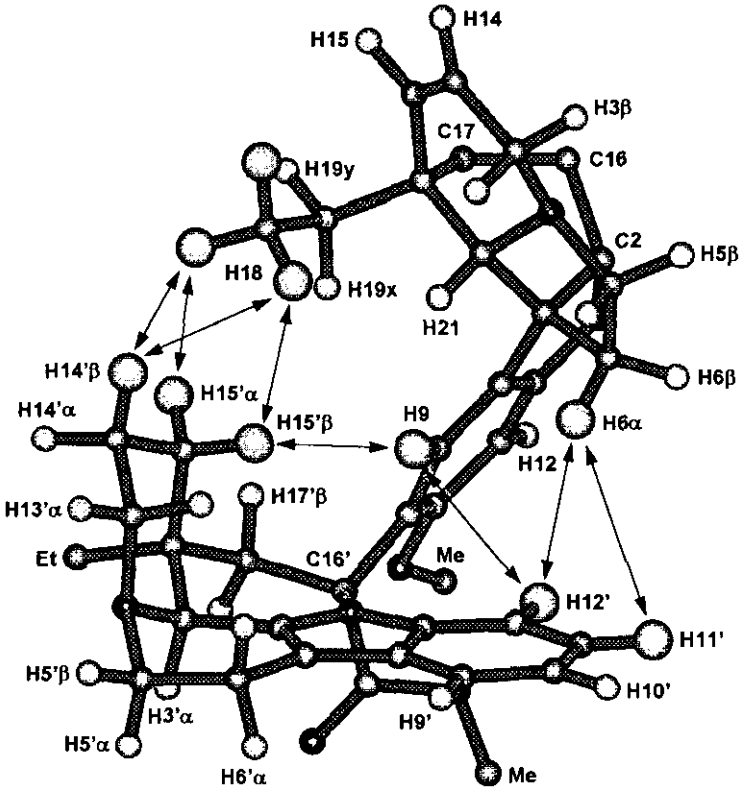


Figure 4. Perspective view of one low-energy conformation of iVV (**6**). The arrows depict characteristic inter-unit NOE connections consistent with this conformation.

wavelength band intensities were measured for **8** (EVB), **6** (iVV) and **3a** (iCVLB) with β-vindolinyl *orientation, while the α–isomers* 7 (EVA), **2a** (CVLB) and **2d** (CLE) exhibited positive couplets with a less intense first long-wavelength band. Positive couplets with lower band intensities ($\sum\overline{\Delta\varepsilon} < 32$) were measured in the spectra of the α-isomers **2b** (CVCR) and **2c** (DF-CVCR). The β-isomers **3b** (iCVCR) and **3d** (iCLE) showed negative couplets with a strongly decreased intensity of the positive band. Surprisingly, no positive band was observed in the CD spectrum of **5** (VV, β isomer on the basis of NMR), see Table 1. The positive band (or shoulder) between 245 and 260 nm in the CD spectra of all derivatives studied is likely to be contributed by the positive band of vindoline at 252 nm. Clearly, a distorted couplet with decreased band intensities is expected for models which are present as a slowly interconverting mixture of the major and minor rotamers (cf. the NMR and CD properties of **3d**).

Table 1 CD spectra of cyclo and isocyclo vinca alkaloids[a]

Compound	Orientation of vindoline	λ (Δε)						
2a	α		296		253		224.5	211
CVLB			(-10.9)		(17.4)		(9.3)	(-31.7)
2b	α	303	281		253	235	223	204
CVCR		(-17.4)	(sh)		(19.9)	(-4.4)	(13.9)	(-17.9)
2c	α	~310	291		249.5		221	208
DF-CVCR		(sh)	(-8.2)		(10.2)		(6.3)	(-21.4)
2d	α	~310	288.5		255		225	211.5
CLE		(sh)	(-13.8)		(26.9)		(18.7)	(-37.3)
3a	β	307.5	~295		250.5		220	204
iCVLB		(-5.2)	(sh)		(9.0)		(-42.0)	(14.5)
3b	β	309.5	292.5		256.5		230	201.5
iCVCR		(-3.3)	(-3.2)		(12.3)		(-32.8)	(4.7)
3c	β	~302	~295	~283 (sh)	~255	~246	219	204
DF-iCVCR		(-8.0)	(sh)	~272 (-2.0)	(sh)	(5.0)	(-40.0)	(16.0)
3d	β	311	~295	~280	~255	243	219	204
iCLE		(-5.2)	(sh)	(sh)	(sh)	(19.2)	(-44.5)	(0.5)
5	β	~300	287.5	264	~247		221	~200
VV		(sh)	(-4.8)	(10.9)	(sh)		(-25.8)	(-22.5)[b]
6	β	309			256	~247	223	204.5
iVV		(-9.6)			(10.8)	(sh)	(-70.8)	(27.3)
7	α	306	290.5		258		224	205
EVA		(3.3)	(4.5)		(24.6)		(18.7)	(-76.2)
8	β	307	290.5	278	257.5	~233	~219	~204
EVB		(-7.6)	(-6.1)	(-6.2)	(8.1)	(sh)	(-53.7)	(27.9)

[a]For experimental conditions; see experimental section. [b]Week negative extremum at 211.5 nm (Δε=-3.1) indicating the CD contribution of a positive band in this region.

In summary, the present CD study extends the applicability of the exciton chirality rule of Kutney for bisindoles possessing a Ψ-aspidosperma-aspidosperma (**2a-d**), aspidosperma-aspidosperma (**5**) or Ψ-eburnane-aspidosperma (**3a-d**) and eburnane-aspidosperma (**6**, **7**, **8**) ring systems. Except for the region between 245-260 nm which contains at least one positive band in the case of both α and β derivatives, the short-wavelength region (200-225 nm) in the spectra of α derivatives features a positive exciton couplet, while that of the β isomers a negative couplet. The almost enantiomeric relationship of the spectra and the sign of the exciton couplet are indicative of the configuration at C-16'. Besides, distortions at the CD couplet may reflect the presence of a rotameric equilibrium about the inter-unit bond.

3 EXPERIMENTAL

3.1 Spectroscopy

Optical rotation measurements were carried out on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1000 spectrophotometer. CD spectra were recorded on a Jobin-Yvon VI dichrograph at room temperature in ethanol, c=0.1-0.7 mM, pathlength 0.2-0.02 cm. The liquid secondary ion mass spectrometric (LSIMS) analysis was performed on a Finnigan MAT 9559 hybrid tandem mass spectrometer, operated at an accelerating voltage of 5 kV. The ions were produced by using a cerium ion gun of 20 kV, the liquid matrix used was m-nitrobenzyl alcohol. For structure identification the product ion spectra were used as obtained by B/E studies in the first field free region. All ^{1}H and ^{13}C NMR spectra were recorded on a Varian ^{UNITY}*INOVA* 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) with internal deuterium lock in $CDCl_3$ at 30 °C (compounds **2a**, **2c**, **2d**, **3c**, **3d**; **4**, **5**, **6**) or 25 °C (compounds **2b**, **3a**, **3b**). Chemical shifts are given relative to δ_{TMS}=0.00 ppm. ^{1}H and ^{13}C chemical shift assignments were arrived at by a concerted use of standard high-field one- and two-dimensional (2D) NMR methods: 2D ^{1}H-^{1}H and ^{13}C-^{1}H shift correlation (DQFCOSY, NOESY, HSQC, HMBC) and selective 1D experiments (1D-TOCSY, DPFGNOE). The obtained scalar and NOE connectivities provided abundant information to ensure unambiguous spectral assignments. All pulse programs were run by using the standard spectrometer software package and utilizing its pulsed field gradient facility. NOEs were measured in non-degassed samples by using 0.5 s mixing time and 2 s relaxation delay.

3.2 Synthesis

General remarks

All reactions were run under inert atmosphere with the exclusion of light and moisture and by using absolute solvents. As used below, the term "extractive workup" refers to the following procedure: a)

Pouring the reaction mixture into dilute ice-cold ammonium hydroxide solution. b) Extracting the aqueous phase with CH_2Cl_2 at pH 9. c) Washing the combined organic solution with dilute ammonia [NH_4OH/H_2O (1:1)], then with brine and water, drying over $MgSO_4$ and evaporating the solvent at reduced pressure. The progress of all reactions were monitored by TLC using precoated Merck $60F_{254}$ silica gel sheets. Indole compounds were characterized with cerium(IV) ammonium sulfate (CAS, 1% in 85 % phosphoric acid) and other compounds were visualized by UV or iodine vapor. Flash chromatography was performed with the indicated solvents on Merck silica gel 60 (230-400 mesh); for column chromatography Merck silica gel 60 (70-230 mesh) was employed. Preparative layer chromatography (PLC) was carried out on 1 mm thick layers of Merck silica gel $PF_{254+366}$ coated on glass plates. Melting points are uncorrected.

Preparation of 2a (3',7'-cyclovinblastine, *CVLB*)

Starting from **1a** (VLB): A solution of chromium(VI) oxide (CrO_3, 250 mg; 2.5 mmol) in Ac_2O (47 mL) was added dropwise over 5 min at -50-55 °C to a solution of VLB (**1a**) base (500 mg; 0.61 mmol) dissolved in the mixture of CH_2Cl_2 (100 mL) and AcOH (12 mL). The reaction mixture was stirred for 2-6 h at -40 °C until consumption of VLB [TLC: CH_2Cl_2/MeOH (20/2), R_F CVLB>VLB]. Extractive workup and purification by column chromatography with CH_2Cl_2-(0.5-1%) MeOH) yielded 0.12 g (24 %) of CVLB (**2a**).

mp 169-172 °C (amorphous); $[\alpha]_{546}^{25}$ -149° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3458, 2931, 1739, 1618, 1503, 1456, 1432, 1372, 1234, 1041, 917, 733. *MS* m/z(rel. int %): 809/MH+ (100); 807(60); 749(18); 577(27); 410(45); 353(36); 281(41). ^{1}H NMR ($CDCl_3$) δ: 0.41 (3H, t, J=7.3 Hz, H_3-18); 0.92 (3H, t, J=7.1 Hz, H_3-18'); 1.11-1.21 (1H, m, H_2-19x); 1.35-1.50 (3H, m, H_2-19', H_2-15'α); 1.58-1.80 (4H, m, H_2-19y, H-14', H_2-15'β, H_2-6'α); 2.07 (3H, s, H_3-COMe); 2.14 (1H, d, J=14.2 Hz, H_2-17'α); 2.17-2.24 (1H, m, H_2-6α); 2.26-2.40 (2H, m, H_2-6β, H_2-5α); 2.52 (1H, d, J=11.4 Hz, H_2-21'α); 2.55 (1H, s, H-21); 2.70 (3H, s, H_3-NMe); 2.73 (1H, d, J=16.4 Hz, H_2-3α); 2.82 (1H, s, H-3'); 2.88 (1H, s, 20'-OH); 2.93 (1H, td, J=11.9 Hz and 6.3 Hz, H_2-6'β); 3.00-3.09 (2H, m, H_2-21'β, H_2-5'α); 3.21-3.28 (1H, m, H_2-5'β); 3.37 (1H, td, J=9.2 Hz and 4.1 Hz, H_2-5β); 3.46 (1H, ddd, J=15.9 Hz, 4.8 Hz and 1.3 Hz, H_2-3β); 3.67 (3H, s, H_3-16'-CO_2Me); 3.68 (1H, t, J=14.0 Hz, H_2-17'β); 3.74 (1H, s, H-2); 3.78 (3H, s, H_3-11-OMe); 3.79 (3H, s, H_3-16-CO_2Me); 5.20 (1H, dt, J=10.2 Hz and 1.5 Hz, H-15); 5.50 (1H, s, H-17); 5.81 (1H, ddd, J=10.1 Hz, 4.9 Hz and 1.6 Hz, H-14); 6.14 (1H, s, H-12); 6.88 (1H, s, H-9); 7.17 (1H, td, J=7.4 Hz and 1 Hz, H-11'); 7.25 (1H, td, J=7.6 Hz and 1.2 Hz, H-10'); 7.34 (1H, d, J=7.3 Hz, H-9'); 7.44 (1H, d, J=7.7 Hz, H-12'); 9.54 (1H, br s, 16-OH). ^{13}C NMR ($CDCl_3$) δ: 7.2 (C-18'); 7.6 (C-18); 21.0 (AcMe); 30.9 (C-19); 32.2 (C-14'); 32.7 (C-19'); 36.7 (C-6'); 37.3 (C-17'); 38.5 (NMe); 39.6 (C-15'); 42.9 (C-20); 43.7 (C-6); 51.2 (C-

3); 52.2 (16-CO_2Me); 52.2 (C-5); 52.5 (16'-CO_2Me); 53.1 (C-5'); 53.1 (C-7); 55.9 (11-OMe); 56.1 (C-16'); 61.0 (C-21'); 63.5 (C-7'); 67.3 (C-21); 71.1 (C-20'); 71.5 (C-3'); 76.6 (C-17); 79.6 (C-16); 83.5 (C-2); 94.5 (C-12); 120.7 (C-9'); 120.9 (C-12'); 121.4 (C-9); 123.1 (C-8); 123.8 (C-10); 123.8 (C-14); 125.8 (C-11'); 127.5 (C-10'); 130.7 (C-15); 147.8 (C-8'); 152.2 (C-13); 153.6 (C-13'); 158.7 (C-11); 170.8 (AcC=O); 172.0 (16-C=O); 174.2 (16'-C=O); 183.6 (C-2'). Measured H ↔ H NOE connections: H-9 ↔ H_2-17'α, H-14', H_3-16'-CO_2Me, H-12'; H_3-18 ↔ H-12', H_3-16'-CO_2Me, H-14'; H_3-16'-CO_2Me ↔ H_3-11-OMe, H-9, H_3-18; H_3-11-OMe ↔ H_3-16'-CO_2Me, 12'; H-12' ↔ H_3-18, H-21, H_3-11-OMe, H-9.

Preparation of 2b (3',7'-cyclovincristine, CVCR)

Starting from **1b** (VCR): A cooled solution of CrO_3 (500 mg; 5 mmol) in Ac_2O (50 mL) was added dropwise at -50-55 °C over 5 min to a solution of VCR (**1b**) base (1.20 g; 1.45 mmol) dissolved in a mixture of CH_2Cl_2 (170 mL), AcOH (30 mL) and MeOH (2 mL). The reaction was allowed to warm up to -20 °C and was stirred at this temperature for 15-18 h, during which time the second portion of MeOH (1 mL) and then CrO_3 (150 mg; 1.5 mmol) was added to complete the conversion of VCR (**1b**) to CVCR (**2b**) [TLC: CH_2Cl_2/MeOH (10/1), R_F CVCR>VCR]. The reaction was quenched at -50 °C, and after extractive workup 1.15 g of crude product was obtained. Purification of 500 mg by column chromatography eluting with CH_2Cl_2-(0.5-3 %) MeOH afforded 238 mg (46 %) of CVCR (**2b**).

Staring from **2a** (CVLB): The pH of the solution of CVLB (**2a**) (80 mg) in MeOH (1 mL) was adjusted to 4 with a solution of 1% H_2SO_4 in EtOH. After the addition of Et_2O to the solution, 80 mg of CVLB (**2a**) sulfate (mp 255-260 °C, amorphous) was precipitated. CrO_3 (40 mg; 0.4 mmol) in Ac_2O (3.2 mL) was added at -55 °C to a solution of CVLB (**2a**) sulfate (80 mg; 0.09 mmol) in a mixture of CH_2Cl_2 (20 mL) and AcOH (2 mL) and the solution was stirred at -55 °C for 20 min. The extractive workup with CH_2Cl_2 (3x15 mL) yielded 67 mg of crude product, which upon purification by PLC with Et_2O/benzene/EtOH/Et_2NH (100/5/5/5) resulted in 21 mg (29 %) of CVCR (**2b**).

mp 214-219 °C (amorphous); $[\alpha]_D^{25}$ -133° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3440, 2931, 1737, 1681, 1601, 1501, 1454, 1369, 1228, 1032, 917, 733. *MS* m/z(rel. int %): 823/MH+ (100); 821(61); 791(14); 763(11); 555(5.6); 524(8.3); 379(22); 355(28); 353(27); 327(33); 281(46). CVCR (**2b**) gives diffuse, exchange broadened NMR spectra at 25 °C due to the rotation of the CHO group. M and m superscripts denote resonances due to the major and minor rotamers, respectively. ^1H NMR ($CDCl_3$) δ: 0.53 (3H, br, H_3-18^M); 0.64 (3H, br, H_3-18^m); 0.93 (3H, br t, J=7.5 Hz, H_3-18'); 0.94-1.06 (1H, br m, H_2-$19x^M$); 1.06-1.20 (1H, br m, H_2-$19x^m$); 1.34-1.54 (4H, br, H_2-19', H_2-15'α, H_2-19y); 1.55-1.87 (3H, br, H-14', H_2-15'β, H_2-6'α); 2.04 (3H, s, H_3-$COMe^M$); 2.07 (3H, s, H_3-$COMe^m$); 1.96-2.30 (3H, br, H_2-17'α, H_2-6α, H_2-6β); 2.53

(1H, br d, J=10.5 Hz, H_2-21'α); 2.61 (1H, br, m, H_2-5α); 2.78-3.14 (7H, br m, H-3', 20'-OH, H-21, H_2-3α, H_2-21'β, H_2-6'β, H_2-5'α); 3.27 (1H, br, H_2-5'β); 3.40-3.50 (2H, br, H_2-5β, H_2-3β); 3.69 (3H, s, H_3-16'-CO_2Me); 3.70-3.80 (1H, br, H_2-17'β); 3.72 (3H, s, H_3-16-CO_2Me); 3.78 (3H, s, H_3-11-OMe^m); 3.87 (3H, s H_3-11-OMe^M); 4.53 (1H, s, H-2^m); 4.77 (1H, s, H-2^M); 5.16 (1H, s, H-17^M); 5.21 (1H, s, H-17^m); 5.30-5.48 (1H, br m, H-15); 5.86-6.02 (1H, br m, H-14); 6.81 (1H, s, H-12^M); 7.16 (1H, s, H-9); 7.21 (1H, br, H-11'); 7.28 (1H, br, H-10'); 7.40 (1H, br, H-9'); 7.50 (1H, br, H-12'); 7.69 (1H, s, H-12^m); 8.17 (1H, s, CHO^m); 8.75 (1H, s, CHO^M); 9.36 (1H, br, 16-OH). ^{13}C NMR ($CDCl_3$) δ: 7.2 (C-18'); 7.5 (C-18^M); 7.6 (C-18^m); 21.0 (AcMe); 30.0 (C-19^M); 30.2 (C-19^m); 32.2 (C-14'); 32.7 (C-19'); 36.6 (C-6'); 37.3 (C-17'); 39.6 (C-15'); 40.9 (C-6); 42.3 (C-20^M); 42.5 (C-20^m); 49.9 (C-5); 50.3 (C-3); 52.8 (16'-CO_2Me^M, 16-CO_2Me^M); 52.6, 53.0 (16'-CO_2Me^m, 16-CO_2Me^m); 53.1 (C-5'); 56.1 (11-OMe); 56.3 (C-16'); 61.0 (C-21'); 63.6 (C-$7'^M$); 63.8 (C-$7'^m$); 65.2 (C-21^m); 65.5 (C-21^M); 71.0 (C-20'); 71.5 (C-3'); 72.3 (C-2^M); 74.2 (C-2^m); 75.6 (C-17^m); 76.7 (C-17^M); 79.7 (C-16^M); 81.4 (C-16^m); 95.4 (C-12^M); 101.9 (C-12^m); 120.7 (C-9'); 121.1 (C-12'); 122.3 (C-9^m); 122.5 (C-9^M); 123.6 (C-8); 124.2 (C-14^M); 124.4 (C-14^m); 126.1 (C-11'); 127.7 (C-10'); 130.1 (C-10); 130.3 (C-15); 140.5 (C-13); 147.8 (C-8'); 153.3 (C-13'); 158.5 (C-11); 160.4 (CHO^M); 160.6 (CHO^m); 170.0 ($AcC=O^m$); 170.2 ($AcC=O^M$); 170.4 (16-$C=O^m$); 170.6 (16-$C=O^M$); 173.3 (16'-$C=O^m$); 173.4 (16'-$C=O^M$); 182.7 (C-2'). Measured H ↔ H inter-unit NOE connections: H_3-18 ↔ H-12'; H-9 ↔ H_2-17'α, H-14'.

Reduction to **1b** (VCR): $NaBH_4$ (58 mg; 1.5 mmol) was added portionwise to a solution of CVCR (**2b**) (500 mg; 0.608 mmol) in AcOH (20 mL) and CH_2Cl_2 (10 mL) and the resulting mixture was stirred for 2 h at rt [TLC: CH_2Cl_2/MeOH (20/2), R_F CVCR>VCR]. Extractive workup and purification by column chromatoghraphy with CH_2Cl_2-(1-5 %) MeOH) yielded 400 mg (79 %) of VCR (**1b**). (Physical data were identical with those obtained for the natural VCR).[2a,b,e]

Preparation of 2c (*N*-deformylcyclovincristine, DF-CVCR)

Starting from **2b** (CVCR): A solution of CVCR (**2b**) (300 mg; 0.36 mmol) in 0.05 M H_2SO_4/MeOH (35 mL) was left to stand at 0 °C until total consumption (5-7 days) of CVCR (**2b**) [TLC: CH_2Cl_2/MeOH (20/2), R_F DF-CVCR>CVCR>DF-iCVCR]. After evaporation of the solvent at 40 °C the residue was worked up in the usual extractive way yielding 260 mg of crude product. Purification by column chromatoghraphy with CH_2Cl_2-(0.5-3 %) MeOH afforded 96 mg (33 %) of DF-CVCR (**2c**) and 108 mg (36 %) of DF-iCVCR. Further purification was achieved by PLC with toluene/diethylamine (100/3) resulting in 70 mg (24 %) of DF-CVCR (**2c**).

mp 167-173 °C (amorphous); $[\alpha]_D^{25}$ -146° (c 1.2, $CHCl_3$). *IR* (KBr, cm^{-1}): 3419, 2961, 2243, 1738, 1621,

1555, 1501, 1455, 1372, 1253, 1040, 917, 732. *MS* m/z(rel. int %): 795/MH+ (100); 793(82); 763(15); 735(18); 635(10); 577(8); 526(27); 365(32); 353(31); 281(30). ^{1}H NMR ($CDCl_3$) δ: 0.44 (3H, t, J=7.2 Hz, H_3-18); 0.92 (3H, t, J=7.5 Hz, H_3-18'); 1.18-1.28 (1H, m, H_2-19x); 1.36-1.50 (3H, m, H_2-19', H_2-15'α); 1.50-1.59 (1H, m, H_2-19y); 1.65-1.82 (3H, m, H_2-15'β, H-14', H_2-6'α); 2.09 (3H, s, H_3-COMe); 2.13 (1H, d, J=7.9 Hz, H_2-17'α); 2.24-2.36 (3H, m, H_2-5α, H_2-6); 2.42 (1H, s, H-21); 2.53 (1H, d, J=10.8 Hz, H_2-21'α); 2.72 (1H, d, J=16.2 Hz, H_2-3α); 2.84 (1H, s, H-3'); 2.86-2.95 (2H, m, H_2-6'β, 20'-OH); 3.00-3.10 (2H, m, H_2-21'β, H_2-5'α); 3.21-3.29 (1H, br, H_2-5'β); 3.28-3.36 (1H, m, H_2-5β); 3.47 (1H, dd, J=15.9 Hz and 4.5 Hz, H_2-3β); 3.67 (3H, s, H_3-16'-CO_2Me); 3.70 (1H, t, J=13.6 Hz, H_2-17'β); 3.73 (3H, s, H_3-11-OMe); 3.77 (3H, s, H_3-16-CO_2Me); 4.13 (1H, d, J=3.1 Hz, H-2); 4.57 (1H, d, J=3.1 Hz, NH); 5.24 (1H, d, J=10.0 Hz , H-15); 5.55 (1H, s, H-17); 5.80 (1H, dd, J=10.0 Hz and 3.0 Hz, H-14); 6.22 (1H, s, H-12); 6.90 (1H, s, H-9); 7.18 (1H, t, J=7.5 Hz, H-10'); 7.26 (1H, td, J=7.6 Hz and 1.1 Hz, H-11'); 7.34 (1H, br, H-12'); 7.44 (1H, d, J=7.6 Hz, H-9'), 9.44 (1H, br s, 16-OH). ^{13}C NMR ($CDCl_3$) δ: 7.2 (C-18'); 7.7 (C-18); 20.9 (AcMe); 31.4 (C-19); 32.1 (C-14'); 32.7 (C-19'); 36.7 (C-6'); 37.4 (C-17'); 39.6 (C-15'); 42.0 (C-6); 43.5 (C-20); 51.2 (C-3); 52.5 (16'-CO_2Me); 52.6 (16-CO_2Me); 52.7 (C-5); 52.9 (C-7); 53.1 (C-5'); 55.9 (11-OMe); 56.2 (C-16'); 61.0 (C-21'); 63.5 (C-7'); 68.3 (C-21); 71.0 (C-20'); 71.4 (C-3'); 74.0 (C-2); 76.6 (C-17); 79.7 (C-16); 93.9 (C-12); 120.8 (C-9'); 120.9 (C-12'); 121.9 (C-9); 123.1 (C-8); 123.3 (C-10); 123.8 (C-14); 125.8 (C-10'); 127.5 (C-11'); 130.4 (C-15); 147.7 (C-8'); 148.7 (C-13); 153.6 (C-13'); 158.5 (C-11); 170.6 (AcC=O); 172.9 (16-C=O); 174.2 (16'-C=O); 183.7 (C-2'). Measured H ↔ H inter-unit NOE connections: H-9 ↔ H_2-17'α, H-14', H_3-16'-CO_2Me, H-12'; H-12' ↔ H_3-18, H-21, H_3-11-OMe, H-9; H_3-18 ↔ H-12', H_3-16'-CO_2Me, H-14'; H_3-16'-CO_2Me ↔ H_3-11-OMe, H-9, H_3-18.

Preparation of 2d (cycloleurozine, CLE)

Starting from **1d** (LE): To a solution of LE (**1d**) (1.8 g; 2.22 mmol) in a mixture of EtOAc (240 mL) and CH_2Cl_2 (20 mL), 916 mg (2.39 mmol) of $Pd(PhCN)_2Cl_2$ catalyst was added in portions over 20 min with rapid stirring. (During the addition a dark brown solid had precipitated indicating the progress of oxidation.) After being stirred for an additional 20 min, the suspension was treated with 5N Et_3N/EtOAc (460 μL) and the stirring was continued for 10-20 h at rt [TLC: CH_2Cl_2/MeOH (20/2), R_F CLE>LE]. The resulting mixture was then diluted with MeOH (20 mL) and the complex was reduced by adding small amounts of $NaBH_4$. The black precipitate was filtered through Celite, the solvent was evaporated at reduced pressure and the residue was taken up in CH_2Cl_2 (300 mL). After washing, drying and evaporation, from the organic solution 1.73 g crude CLE (**2d**) was obtained. The rest of PhCN was removed by repeated trituration with petroleum ether. The boron complex of the remaining starting

compound can be decomposed by refluxing the crude product for 1-2 h in a solution of 5 % Et_3N/MeOH [TLC: CH_2Cl_2/MeOH (20/2), R_F LE*BH_3>CLE>LE]. After evaporation of the solvent the product was purified by flash chromatography with CH_2Cl_2-(0.5-1.5 %) MeOH) to yield 1.05 g (58.6 %) of CLE (**2d**). Following the same procedure with leurosine *N*(4')-oxide (pleurosine), **2d** can also be obtained in a slightly extended reaction time.

mp 185-188 °C (amorphous); $[\alpha]_D^{25}$ -113° (c 1.4, $CHCl_3$). *IR* (KBr, cm^{-1}): 3465, 2964, 1740, 1618, 1503, 1457, 1372, 1243, 1042, 751. *MS* m/z(rel. int %): 807/MH+ (100); 805(60); 775(8); 747(16); 647(17); 539(10); 538(10); 379(18); 272(13). ^{1}H NMR ($CDCl_3$) δ: 0.53 (3H, t, J=7.3 Hz, H_3-18); 0.98 (3H, t, J=7.5 Hz, H_3-18'); 1.14-1.24 (1H, m, H_2-19x); 1.54-1.70 (4H, m, H_2-19', H_2-19y, H_2-6'α); 1.96 (1H, d, J=14.0 Hz, H_2-17'α); 2.03 (1H, d, J=13.2 Hz, H_2-14'α); 2.08 (3H, s, H_3-COMe); 2.14-2.23 (1H, m, H_2-6α); 2.23-2.32 (1H, m, H_2-6β); 2.36-2.45 (1H, m, H_2-5α); 2.62 (1H, s, H-21); 2.66-2.75 (1H, m, H_2-6'β); 2.71 (3H, s, H_3-NMe); 2.76-2.86 (3H, m, H_2-3α, H_2-15'β, H_2-5'α); 2.93 (1H, d, J=2.8 Hz, H-3'); 2.97 (1H, d, J=12.6 Hz, H_2-21'α); 3.15 (1H, t, J=7.3 Hz, H_2-5'β); 3.36 (1H, td, J=9.3 Hz and 3.8 Hz, H_2-5β); 3.37 (1H, d, J=12.6 Hz, H_2-21'β); 3.46 (1H, d, J=16.2 Hz, H_2-3β); 3.46 (1H, t, J=8.5 Hz, H_2-17'β); 3.70 (3H, s, H_3-16'-CO_2Me); 3.74 (1H, s, H-2); 3.79 (3H, s, H_3-11-OMe); 3.80 (3H, s, H_3-16-CO_2Me); 5.23 (1H, d, J=10.2 Hz, H-15); 5.49 (1H, s, H-17); 5.83 (1H, dd, J=10.2 Hz and 4.7 Hz, H-14); 6.15 (1H, s, H-12); 6.88 (1H, s, H-9); 7.16 (1H, t, J=7.5 Hz, H-10'); 7.25 (1H, t, J=7.6 Hz, H-11'); 7.31 (1H, d, J=7.0 Hz, H-9'); 7.45 (1H, d, J=7.5 Hz, H-12'); 9.63 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ: 7.7 (C-18); 8.5 (C-18'); 21.0 (AcMe); 29.4 (C-19'); 30.9 (C-19); 33.4 (C-17'); 33.6 (C-14'); 35.5 (C-6'); 38.4 (NMe); 42.9 (C-20); 43.8 (C-6); 50.9 (C-3); 51.7 (C-5); 52.1 (C-21', C-5', 16-CO_2Me); 52.6 (16'-CO_2Me); 53.1 (C-7); 55.2 (C-16'); 55.8 (11-OMe); 61.2 (C-15'); 61.3 (C-20'); 62.5 (C-3'); 62.8 (C-7'); 66.9 (C-21); 76.5 (C-17); 79.6 (C-16); 83.4 (C-2); 94.4 (C-12); 120.8 (C-12'); 120.9 (C-9'); 121.8 (C-9); 123.1 (C-8); 123.7 (C-10); 123.9 (C-14); 125.8 (C-10'); 127.4 (C-11'); 130.6 (C-15'); 147.6 (C-8'); 152.3 (C-13); 153.4 (C-13'); 158.3 (C-11); 170.7 (AcC=O); 171.9 (16-C=O); 174.0 (16'-C=O); 183.3 (C-2'). Measured H ↔ H inter-unit NOE connections: H-9 ↔ H-14', H_2-17'α, H_3-16'-CO_2Me, H-12'; H-12' ↔ H_3-18, H-21, H_3-11-OMe, H-9; H_3-18 ↔ H-12', H_3-16'-CO_2Me, H-14'; H_3-16'-CO_2Me ↔ H-9, H_3-18, H_3-11-OMe; H_3-11-OMe ↔ H_3-16'-CO_2Me, H_2-17'α, H-14', H-12'.

Preparation of 3a (isocyclovinblastine, iCVLB)

Starting from 2a (CVLB): A solution of CVLB (**2a**) (10 mg; 0.012 mmol) dissolved in 0.02 M H_2SO_4/MeOH (3 mL) was allowed to stand at rt until consumption of CVLB (**2a**) [7 days; TLC: CH_2Cl_2/MeOH (20/2), R_F CVLB>iCVLB]. The extractive workup and purification by column

chromatography with CH_2Cl_2-(0.5-2 %) MeOH yielded 5 mg (50 %) of iCVLB (**3a**).

Starting from **3c** (DF-iCVCR): 80 mg (1.2 mmol) of $NaBH_3CN$ was added portionwise to a solution of DF-iCVCR (**3c**) (250 mg; 0.31 mmol) in AcOH (5 mL) and 30 % aqueous formaldehyde (3.2 mL). The reaction mixture was stirred for 4-7 h at rt [TLC: toluene/Et_2NH (8/1), R_F iCVLB>DF-iCVCR]. The extractive workup resulted in 230 mg of crude product, which was purified by column chromatography with CH_2Cl_2-(0.5-2%) MeOH and then by repeated preparative TLC [CH_2Cl_2/MeOH (100/5)]. In this way 120 mg (48 %) of iCVLB (**3a**) was obtained.

mp 170-172 °C (amorphous); $[\alpha]_D^{25}$ -142° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3454, 2932, 2244, 1739, 1619, 1500, 1452, 1371, 1248, 1040, 912, 736. *MS* m/z(rel. int %): 809/MH+ (100); 807(63); 749(18); 648(12); 540(14); 352(31); 281(42). ^1H NMR ($CDCl_3$) δ: 0.41 (3H, t, J=7.4 Hz, H_3-18); 0.85 (3H, t, J=7.6 Hz, H_3-18'); 1.06-1.24 (2H, m, H_2-19x, H_2-15'β); 1.36 (1H, dd, J=13.1 Hz and 5.5 Hz, H_2-15'α); 1.50-1.62 (1H, m, H_2-19y); 1.62-1.80 (2H, m, H_2-19'); 1.84-1.94 (1H, m, H_2-6α);. 2.05 (3H, s, H_3-COMe); 2.03-2.18 (2H, m, H_2-5α, H_2-6β); 2.24 (1H, s, H-21); 2.34 (1H, d, J=14.6 Hz, H_2-17'β); 2.34-2.45 (1H, br m, H-14'); 2.46 (2H, s, H_2-21'); 2.58-2.70 (2H, m, H_2-3α, H_2-6'α); 2.74 (3H, s, H_3-NMe); 3.00-3.10 (1H, m, H_2-6'β); 3.10-3.20 (1H, m, H_2-5β); 3.22-3.40 (3H, m, H_2-3β, H_2-5'); 3.46-3.54 (1H, m, H_2-17'α); 3.54 (3H, s, H_3-16'-CO_2Me); 3.73 (1H, s, H-2); 3.79 (3H, s H_3-16-CO_2Me); 3.83 (3H, s, H_3-11-OMe); 4.28 (1H, d, J=4.7 Hz); 5.2 (1H, d, J=10.3 Hz, H-15); 5.45 (1H, s, H-17); 5.73 (1H, dd, J=10.0 Hz and 3.9 Hz, H-14); 6.14 (1H, s, H-12); 6.33 (1H, s, H-9); 6.86-7.00 (2H, m, H-11', H-12'); 7.05 (1H, t, J=6.8 Hz, H-10'); 7.46 (1H, d, J=7.7 Hz, H-9'); 9.50 (1H, br, OH). ^{13}C NMR ($CDCl_3$) δ: 6.9 (C-18'), 8.4 (C-18), 17.6 (C-6'), 21.1 (AcMe), 29.0 (C-19'), 29.4 (C-14'), 31.1 (C-19), 37.5 (C-15'), 38.1 (NMe), 39.0 (C-17'), 42.7 (C-20), 43.1 (C-6), 50.5 (C-5', C-3), 51.3 (C-5), 52.2 (16-CO_2Me), 52.3 (16'-CO_2Me), 53.0 (C-7), 54.0 (C-3'), 55.3 (C-21'), 55.6 (11-OMe), 64.8 (C-16'), 66.8 (C-21), 71.5 (C-20'), 76.0 (C-17), 79.5 (C-16), 83.3 (C-2), 93.6 (C-12), 106.7 (C-7'), 115.4 (C-12'), 117.7 (C-9'), 119.5 (C-10'), 120.2 (C-10), 120.3 (C-11'), 122.3 (C-9), 123.1 (C-8), 124.0 (C-14), 128.8 (C-8'), 129.9 (C-15), 131.6 (C-2'), 135.8 (C-13'), 153.1 (C-13), 157.2 (C-11), 170.8 (AcC=O), 171.9 (16'-C=O, 16-C=O). Measured H↔H NOE connections: H-9 ↔ H_2-15'β, H-12', H_2-17'β; H_2-6α ↔ H-12'+H-11'; H_3-18 ↔ H_2-17'α.

Preparation of 3b (isocyclovincristine, iCVCR)

Starting from **3c** (DF-iCVCR): A solution of DF-iCVCR (**3c**) (1.70 g; 2.14 mmol) in the mixture of HCOOH (24 mL) and Ac_2O (4 mL) was allowed to stand at rt for 30-40 min [TLC: CH_2Cl_2/MeOH (20/1.5), R_F iCVCR > DF-iCVCR]. The extractive workup afforded 1.56 g of crude product, which after purification by column chromatography with CH_2Cl_2-(0.5-3 %) MeOH yielded 1.14 g (65 %) of iCVCR

(**3b**) with a pale yellow color. The contamination could be removed by repeated preparative TLC [CH_2Cl_2/MeOH (100/3)], which resulted in 0.70 g (40 %) of iCVCR (**3b**).

mp 179-182 °C (amorphous); $[\alpha]_D^{25}$ -135° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3453, 2924, 2246, 1739, 1682, 1598, 1496, 1453, 1229, 1033, 911, 842, 731, 646, 468. *MS* m/z(rel. int %): 823/MH+ (100); 821(96), 716(22); 583(35); 554(30); 355(80); 352(81). iCVCR (**3b**) gives exchange broadened NMR spectra at 25 °C due to the rotation of the CHO group. M and m superscripts denote resonances due to the major and minor rotamers (~1.8:1), respectively. ^{1}H NMR ($CDCl_3$) δ: 0.45 (3H, br t, J=6 Hz, H_3-18); 0.88 (3H, t, J=7.3 Hz, H_3-18'); 0.86-0.98 (1H, m, H_2-19x); 1.10 (1H, t, J=12.6 Hz, H_2-15'β); 1.22-1.34 (1H, m, H_2-19y); 1.38 (1H, d, J=13.1 Hz, H_2-15'α); 1.44 (1H, br, 20'-OH); 1.60-1.82 (3H, m, H_2-19', H_2-6α); 1.97 (3H, s, H_3-$COMe^M$); 2.00 (3H, s, H_3-$COMe^m$); 2.01-2.16 (1H, br m, H_2-6β); 2.30-2.52 (5H, br m, H_2-5α, H-14', H_2-21', H-21); 2.54-2.67 (2H, m, H_2-17'β, H_2-6'α); 2.72 (1H, d, J=14.7 Hz, H_2-3α); 2.95-3.08 (1H, br m, H_2-6'β); 3.22-3.32 (3H, m, H_2-5'β, H_2-5β, H_2-3β); 3.32-3.42 (1H, m, H_2-5'α); 3.44 (1H, dd, J=14.8 Hz and 4.6 Hz, H_2-17'α); 3.57 (3H, s, H_3-16'-CO_2Me); 3.69 (3H, s, H_3-16-CO_2Me^M); 3.75 (3H, s, H_3-16-CO_2Me^m); 3.91 (3H, s, H_3-11-OMe); 4.33 (1H, br d, J=5.3 Hz, H-3'); 4.46 (1H, s, H-2^m); 4.69 (1H, s, H-2^M); 5.07 (1H, s, H-17^M); 5.10 (1H, s, H-17^m); 5.38 (1H, br d, J=9.7 Hz, H-15); 5.78-5.88 (1H, br m, H-14); 6.36 (1H, s, H-9^m); 6.43 (1H, s, H-9^M); 6.85 (2H, br s, H-12^M, H-12'); 6.92 (1H, t, J=8.0 Hz, H-11'); 7.07 (1H, t, J=7.2 Hz, H-10'); 7.49 (1H, d, J=7.8 Hz, H-9'); 7.79 (1H, s, H-12^m); 8.23 (1H, s, CHO^m); 8.60 (1H, br, 16-OH); 8.83 (1H, s, CHO^M). ^{13}C NMR ($CDCl_3$) δ: 6.9 (C-18'); 7.1 (C-18^m); 7.3 (C-18^M); 17.4 (C-6'); 20.9 (AcMe); 29.0 (C-19'); 29.3 (C-14'); 31.1 (C-19); 37.2 (C-$15'^M$); 37.3 (C-$15'^m$); 37.9 (C-17'); 39.8 (C-6^m); 40.2 (C-6^M); 41.8 (C-20^M); 41.9 (C-20^m); 49.0 (C-5); 49.8 (C-3^M); 49.9 (C-3^m); 50.5 (C-5'); 52.5 (16'-CO_2Me, 16-CO_2Me); 52.7 (C-7^M); 52.8 (C-7^m); 53.8 (C-3'); 55.2 (C-21'); 55.9 (11-OMe); 64.0 (C-21^m); 64.4 (C-21^M); 65.0 (C-$16'^M$); 65.1 (C-$16'^m$); 71.2 (C-20'); 72.0 (C-2^M); 73.8 (C-2^m); 75.5 (C-17^m); 76.5 (C-17^M); 79.9 (C-16^M); 81.6 (C-16^m); 94.8 (C-12^M); 101.7 (C-12^m); 107.1 (C-$7'^m$); 107.2 (C-$7'^M$); 114.5 (C-$12'^M$); 114.6 (C-$12'^m$); 117.9 (C-9^m); 118.0 (C-9^M); 119.6 (C-$10'^m$); 119.7 (C-$10'^M$); 120.4 (C-$11'^m$); 120.5 (C-$11'^M$); 122.3 (C-$9'^m$); 123.4 (C-8^m); 123.6 (C-8^M, C-9^M); 124.3 (C-14^M); 124.5 (C-14^m); 126.4 (C-10); 128.7 (C-$8'^m$); 128.8 (C-$8'^M$); 129.6 (C-15); 131.7 (C-2'); 136.0 (C-$13'^M$); 136.1 (C-$13'^m$); 141.2 (C-13^m); 141.4 (C-13^M); 156.9 (C-11^m); 157.3 (C-11^M); 159.9 (CHO^M); 160.4 (CHO^m); 170.0 (16-C=O^m); 170.2 (AcC=O^m); 170.3 (AcC=O^M); 170.4 (16-C=O^M); 171.2 (16'-C=O^M); 171.3 (16'-C=O^m). Measured H ↔ H NOE connections: H-9 ↔ H_2-15'β, H-12'; H_2-6α ↔ H-12', H-11'; H_3-18 ↔ H_2-17'α, H_2-17'β.

Preparation of 3c (*N*-deformylisocyclovincristine, DF-iCVCR)

Starting from **2b** (CVCR): A solution of CVCR (**2b**) (130 mg; 0.16 mmol) in 0.02 M H_2SO_4/MeOH (25 mL) was stirred at 70 °C for 6-7 h until TLC indicated the complete consumption of the starting compound [TLC: CH_2Cl_2/MeOH (20/2), R_F DF-CVCR>CVCR>DF-iCVCR]. After evaporation of the solvent, the usual extractive workup yielded 124 mg of crude product. Purification by column chromatography with CH_2Cl_2-(0.25-0.5 %) MeOH afforded 87 mg (68 %) of DF-iCVCR (**3c**). The light yellow color could be removed by Merck aluminum oxide II-III adsorbent with CH_2Cl_2-(0.25-0.5 %) MeOH resulting in 69 mg (54 %) of DF-iCVCR (**3c**).

mp 173-180 °C (amorphous); $[\alpha]_D^{25}$ -197° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3421, 2947, 1739, 1622, 1500, 1453, 1372, 1253, 1146, 1039, 737. *MS* m/z(rel. int %): 795/MH+ (63); 793(40); 735(11); 577(12); 551(20); 549(21); 523(14); 355(29); 352(30); 341(31); 327(49); 281(100); 267(58). ^{1}H NMR ($CDCl_3$) δ: 0.47 (3H, t, J=7.3 Hz, H_3-18); 0.83 (3H, t, J=7.5 Hz, H_3-18'); 1.14-1.34 (3H, m, H2-15', H_2-19x); 1.38-1.50 (1H, m, H_2-19y); 1.60-1.80 (2H, m, H_2-19'); 1.82-2.00 (2H, m, H_2-6α, H_2-5α); 2.01 (1H, s, H-21); 2.06-2.16 (1H, m, H_2-6β); 2.08 (3H, s, H_3-COMe); 2.30-2.48 (4H, m, H_2-17'β, H-14', H_2-21'); 2.56-2.68 (2H, m, H_2-6'α, H_2-3α); 3.00-3.10 (2H, m, H_2-6'β, H_2-5β); 3.25 (1H, dd, J=13.5 Hz and 6.2 Hz, H_2-5'β); 3.32 (1H, dd, J=16.1 Hz and 4.8 Hz, H_2-3β); 3.39 (1H, td J=13.5 Hz and 6.0 Hz, H_2-5'α); 3.50 (1H, dd, J=15.1 Hz and 5.2 Hz, H_2-17'α); 3.56 (3H, s, H_3-16'-CO_2Me); 3.75 (3H, s, H_3-16-CO_2Me); 3.80 (3H, s, H_3-11-OMe); 4.11 (1H, d, J=3.1 Hz, H-2); 4.31 (1H, d, J=4.7 Hz, H-3'); 4.77 (1H, d, J=2.4 Hz, NH); 5.27 (1H, d, J=10.6 Hz, H-15); 5.58 (1H, s, H-17); 5.68 (1H, dd, J=10.2 Hz and 3.7 Hz, H-14); 6.25 (1H, s, H-9); 6.27 (1H, s, H-12); 6.95 (1H, t, J=7.5 Hz, H-11'); 7.05 (1H, t, J=7.2 Hz, H-10'); 7.09 (1H, d, J=8.4 Hz, H-12'); 7.46 (1H, d, J=8.0 Hz, H-9'); 9.37 (1H, br, OH). ^{13}C NMR ($CDCl_3$) δ: 6.8 (C-18'); 8.4 (C-18); 17.6 (C-6'); 21.0 (AcMe); 28.9 (C-19'); 29.6 (C-14'); 32.0 (C-19); 36.8 (C-15'); 38.4 (C-17'); 41.4 (C-6); 43.5 (C-20); 50.4 (C-5'); 50.8 (C-3); 52.3 (16'-CO_2Me, C-5); 52.4 (C-7); 52.6 (16-CO_2Me); 54.2 (C-3'); 55.1 (C-21'); 55.6 (11-OMe); 64.9 (C-16'); 69.2 (C-21); 71.6 (C-20'); 74.2 (C-2); 75.7 (C-17); 79.5 (C-16); 93.4 (C-12); 106.5 (C-7'); 115.4 (C-12'); 117.7 (C-9'); 119.4 (C-10'); 119.6 (C-10); 120.4 (C-11'); 123.1 (C-9); 123.6 (C-8, C-14); 128.6 (C-8'); 129.5 (C-15); 131.3 (C-2'); 135.7 (C-13'); 149.6 (C-13); 157.0 (C-11); 170.6 (AcC=O); 171.8 (16'-C=O); 173.1 (16-C=O). Measured H ↔ H inter-unit NOE connections: H-9 ↔ H_2-15'β, H-12'; H_2-6α ↔ H-12', H-11'; H_3-18 ↔ H_2-17'.

Preparation of 3d (isocycloleurosine, iCLE)

Starting from **2d** (CLE): 200 μL of BF_3*Et_2O was added to the solution of CLE (**2d**) (590 mg; 0.73 mmol) in MeOH (100 mL), and the reaction mixture was heated under reflux for 2 h [TLC: CH_2Cl_2/MeOH

(10/0.5), R_F CLE>iCLE]. After evaporation of the solvent the extractive workup yielded 580 mg of crude product. Purification by flash chromatography with CH_2Cl_2-(0.5-1.5 %) MeOH) afforded 477 mg (80 %) of iCLE (**3d**) with a pale yellow color. Further purification by repeated preparative TLC [CH_2Cl_2/MeOH (100/3)] resulted in 325 mg (55 %) of iCLE (**3d**).

mp 185-187 °C (amorphous); $[\alpha]_D^{25}$ -100° (c 1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3465, 2965, 1743, 1619, 1504, 1452, 1371, 1229, 1040, 835.9, 741. *MS* m/z(rel. int %): 807/MH+ (100); 805(58); 747(16); 647(9); 351(13); 272(20). The NMR spectra of iCLE (**3d**) shows two sets of resonances at 30 °C due to interconverting rotatmers around the C(16')-C(10) bond. M and m superscripts denote resonances due to the major and minor rotamers (2:1), respectively. ^{1}H NMR ($CDCl_3$) δ: 0.37 (3H, t, J=7.3 Hz, H_3-18^M); 0.69 (3H, t, J=7.3 Hz, H_3-18^m); 0.88 (3H, t, J=7.5 Hz, H_3-18'^{M}); 0.94 (3H, t, J=7.5 Hz, H_3-18'^{m}); 0.98-1.08 (1H, m, H_2-19x^M); 1.38-1.48 (1H, m, H_2-19x^m); 1.48-1.55 (1H, m, H_2-19'x^M); 1.55-1.75 (3H, m, H_2-19y^M, H_2-19'y^M, H_2-17'β^M, H_2-19'^{m}); 1.77-1.86 (1H, m, H_2-6α^M); 1.86-1.94 (1H, m, H_2-19y^m); 2.05 (3H, s, H_3-COMe^M); 2.06-2.16 (1H, m, H_2-6β^M); 2.12 (3H, s, H_3-COMe^m); 2.20-2.27 (1H, m, H_2-5α^M); 2.27-2.38 (2H, m, H_2-6^m); 2.43 (1H, s, H-21^M); 2.52-2.60 (3H, m, H_2-17'^{m}, H_2-5α^m); 2.62 (1H, dd, J=15.4 Hz and 4.1 Hz, H_2-6'α^M); 2.67 (3H, s, H_3-NMe^m); 2.64-2.70 (1H, m, H_2-6'α^m); 2.72 (1H, d, J=16.5 Hz, H_2-3α^M); 2.74 (1H, s, H-15'^{M}, H-21^m); 2.78 (3H, s, H_3-11-OMe^m); 2.79 (3H, s, H_3-NMe^M); 2.77-2.90 (1H, m, H_2-17'α^M, H-15'^{m}, H_2-21'α^m, H_2-3α^m); 2.97 (1H, d, J=12.7 Hz, H_2-21'α^M); 3.00-3.12 (1H, m, H_2-6'β^{M,m}, H_2-5'α^m, H-14'^{m}); 3.20 (1H, d, J=12.7 Hz, H_2-21'β^M); 3.20-3.40 (5H, m, H_2-5β^M, H_2-5'^{M}, H_2-3β^M, H-14'^{M}, H_2-5'β^m, H_2-19'β^m); 3.46 (1H, td, J=9.6 Hz and 5.2 Hz, H_2-5β^m); 3.53 (1H, dd, J=16 Hz and 4.7 Hz, H_2-3β^m); 3.64 (3H, s, H_3-16'-CO_2Me^M); 3.79 (1H, s, H-2^M, H_3-16'-CO_2Me^m); 3.80 (3H, s, H_3-16-CO_2Me); 3.85 (3H, s, H_3-11-OMe^M); 3.95 (1H, d, J=10.1 Hz, H-3'^{m}); 4.31 (1H, d, J=10.6 Hz, H-3'^{M}); 5.19 (1H, d, J=10.1 Hz, H-15^M); 5.32 (1H, d, J=10.3 Hz, H-15^m); 5.35 (1H, s, H-17^M); 5.54 (1H, s, H-17^m); 5.80 (1H, dd, J=10.1 Hz and 3.7 Hz, H-14^M); 5.88 (1H, s, H-12^m); 5.91 (1H, dd, J=10.2 Hz and 3.8 Hz, H-14^m); 6.15 (1H, s, H-12^M); 6.35 (1H, d, J=8.3 Hz, H-12'^{m}); 6.41 (1H, s, H-9^M); 6.66 (1H, d, J=9 Hz, H-12'^{M}); 6.67 (1H, s, H-9^m); 6.77 (1H, t, J=8.1 Hz, H-11'^{m}); 6.87 (1H, t, J=8.2 Hz, H-11'^{M}); 6.96 (1H, t, J=7.7 Hz, H-10'^{m}); 7.02 (1H, t, J=7.7 Hz, H-10'^{M}); 7.40 (1H, d, J=7.7 Hz, H-9'^{m}); 7.46 (1H, d, J=7.8 Hz, H-9'^{M}); 9.61 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ: 7.4 (C-18^M); 7.5 (C-18^m); 8.2 (C-18'^{M}); 8.6 (C-18'^{m}); 17.0 (C-6'^{M}); 18.1 (C-6'^{m}); 20.9 (AcMe^{M,m}); 26.9 (C-19'^{M}); 27.8 (C-19'^{m}); 28.0 (C-14'^{M}); 28.5 (C-14'^{m}); 30.5 (C-19^M); 30.6 (C-19^m); 36.2 (C-17'^{m}); 37.9 (NMe^M); 38.1 (NMe^m); 42.0 (C-17'^{M}); 42.5 (C-20^M); 42.8 (C-20^m); 43.1 (C-6^M); 44.4 (C-6^m); 46.9 (C-21'^{M}); 49.6 (C-21'^{m}); 49.9 (C-3'^{M}); 50.3 (C-3^M); 50.6 (C-5^M); 50.8 (C-3'^{m}, C-3^m); 51.5 (C-5^m); 51.7 (C-5'^{M}); 52.1 (16'-CO_2Me^M, 16-CO_2Me^{M,m}); 52.5 (C-5'^{m}); 52.6 (16'-CO_2Me^m); 52.7 (C-7^M); 53.0 (C-7^m); 55.4 (11-OMe^m); 56.0 (11-OMe^M); 58.7 (C-15'^{M,m}); 59.6 (C-20'^{M});

60.2 (C-20^{m}); 64.2 (C-16'^{M}); 65.5 (C-21^{M}); 66.6 (C-21^{m}); 68.4 (C-16'^{m}); 76.1 (C-17^{M}); 76.2 (C-17^{m}); 79.4 (C-16^{M,m}); 83.1 (C-2^{M}); 83.6 (C-2^{m}); 93.5 (C-12^{M}); 94.8 (C-12^{m}); 106.1 (C-7'^{m}); 106.5 (C-7'^{M}); 111.8 (C-12'^{m}); 114.5 (C-12'^{M}); 116.3 (C-10^{m}); 117.3 (C-9'^{m}); 117.4 (C-10^{M}); 117.5 (C-9'^{M}); 119.0 (C-10'^{m}); 119.2 (C-10'^{M}); 120.0 (C-11'^{m}); 120.3 (C-11'^{M}); 121.0 (C-9^{m}); 122.8 (C-9^{M}); 123.7 (C-8^{M}); 124.0 (C-8^{m}, C-14^{m}); 124.3 (C-14^{M}); 127.9 (C-8'^{m}); 128.1 (C-8'^{M}); 129.9 (C-15^{M}); 130.2 (C-15^{m}); 132.1 (C-2'^{m}); 132.7 (C-2'^{M}); 135.7 (C-13'^{M}); 137.7 (C-13'^{m}); 153.2 (C-13^{M}); 153.8 (C-13^{m}); 157.5 (C-11^{M}); 159.2 (C-11^{m}); 170.6 (AcC=O^{M,m}); 171.5 (16-C=O^{M}); 171.6 (16'-C=O^{M}, 16-C=O^{m}); 172.0 (16'-C=O^{m}). Measured H ↔ H inter-unit NOE connections: H_3-18^{M} ↔ H_3-18'^{M}; H-9^{M} ↔ H_2-15'β^{M}, H-12'^{M}; H_2-6α^{M} ↔ H-12'^{M}, H-11'^{M}; H_3-11-OMe^{M} ↔ H_3-16'-CO_2Me^{M}; H_3-18^{m} ↔ H-12'^{m}, H-11'^{m}, H_3-16'-CO_2Me^{m}; H_2-19'x^{m} ↔ H-12'^{m}.

Preparation of 4 (1',2'-dihydrocyclovincristine, DH-CVCR)

Starting from **2b** (CVCR): Sodium cyanoborohydride (20 mg; 0.32 mmol) was added portionwise to a solution of CVCR (**2b**) (80 mg; 0.097 mmol) in AcOH (2 mL) at 10 °C and the resulting mixture was stirred until consumption of the starting compound [TLC: CH_2Cl_2/MeOH (20/1.5), R_F DH-CVCR>CVCR]. After the usual workup, the crude product was purified by column chromatography with CH_2Cl_2-(1-3 %) MeOH affording 45 mg (56 %) of 1',2'-dihydro-CVCR (**4**).

mp 183-187 °C (amorphous); $[\alpha]_D^{25}$ -96° (c 0.6, $CHCl_3$). *IR* (KBr, cm^{-1}): 3462, 2951, 2245, 1739, 1682, 1600, 1500, 1465, 1370, 1226, 1033, 913, 733, 469. *MS* m/z(rel. int %): 825/MH+ (100); 823(50); 765(7); 694(13); 555(10); 270(63). DH-CVCR (**4**) gives exchange broadened NMR spectra at 25 °C due to the rotation of the CHO group. M and m superscripts denote resonances due to the major and minor rotamers (~1.9:1), respectively. ^{1}H NMR ($CDCl_3$) δ: 0.55 (3H, t, J=7.2 Hz, H_3-18^{M}); 0.58 (3H, t, J=7.1 Hz, H_3-18^{m}); 0.93 (3H, t, J=7.8 Hz, H_3-18'^{M}); 0.94 (3H, t, J=7.3 Hz, H_3-18'^{m}); 1.00-1.18 (1H, br m, H_2-19x); 1.33-1.50 (4H, m, H_2-19'^{M}, H_2-19'x^{m}, H_2-19y, H_2-15'α); 1.50-1.60 (1H, m, H_2-19'y^{m}); 1.77 (1H, d, J=15.8 Hz, H_2-15'β); 1.90-2.16 (4H, br, H-3', H-14', H_2-21'α, H_2-6α); 2.03 (3H, s, H_3-COMe^{M}); 2.06 (3H, s, H_3-COMe^{m}); 2.16-2.34 (3H, br m, H_2-6β, H_2-6'α, H_2-17'α); 2.42-2.58 (1H, br, H_2-5'α); 2.62-2.82 (2H, br, m, H_2-6'β, H_2-5α); 2.88-3.16 (5H, br m, H_2-17'β, H_2-21'β, H_2-3α, H-21, H_2-5'β); 3.44-3.52 (2H, m, H_2-5β, H_2-3β); 3.63 (3H, s, H_3-16'-CO_2Me^{m}); 3.64 (3H, s, H_3-16'-CO_2Me^{M}); 3.71 (3H, s, H_3-16-CO_2Me^{M}); 3.77 (3H, s, H_3-16-CO_2Me^{m}); 3.84 (3H, s, H_3-11-OMe^{M}); 3.86 (3H, s, H_3-11-OMe^{m}); 4.53 (s, H-2^{m}); 4.77 (1H, s, H-2^{M}); 5.00-5.20 (1H, br, H-2'); 5.07 (1H, s, H-17^{M}); 5.10 (1H, s, H-17^{m}); 5.38 (1H, d, J=10.1 Hz, H-15); 5.90-6.00 (1H, m, H-14); 6.51 (1H, d, J=7.8 Hz, H-12'); 6.72 (1H, t, J=7.4 Hz, H-10'); 6.74 (1H, s, H-12^{M}); 6.99 (1H, t, J=7.5 Hz, H-11'); 7.07 (1H, d, J=7.5 Hz, H-9'); 7.15 (1H, br s, H-9); 7.64 (1H, s, H-12^{m}); 8.18 (1H, s, CHO^{m}); 8.75 (1H, s, CHO^{M}). ^{13}C NMR ($CDCl_3$) δ: 7.3 (C-18', C-18);

20.9 (AcMe); 27.8 (C-14$'^{m}$); 28.0 (C-14$'^{M}$); 30.1 (C-19^{M}); 30.2 (C-19^{m}); 32.2 (C-17'); 33.6 (C-20'); 39.2 (C-6'); 40.2 (C-15'); 40.4 (C-6^{m}); 40.6 (C-6^{M}M); 42.3 (C-20^{M}); 42.4 (C-20^{m}); 49.6 (C-5); 50.2 (C-3); 52.4 (16'-CO_2Me); 52.6 (16-CO_2Me^{m}); 52.8 (16-CO_2Me^{M}); 54.3 (C-5'); 56.1 (11-OMe); 63.7 (C-21'); 64.8 (C-21^{m}); 65.1 (C-21^{M}); 66.5 (C-7'); 70.9 (C-20'); 72.3 (C-2^{M}); 73.3 (C-3'); 74.2 (C-2^{m}); 75.6 (C-17^{m}); 76.6 (C-17^{M}); 79.8 (C-16^{M}); 81.5 (C-16^{m}); 95.1 (C-12^{M}); 101.8 (C-12^{m}); 109.0 (C-12'); 118.7 (C-10'); 122.7 (C-9'); 123.4 (C-9^{m}); 124.6 (C-9^{M}, C-14); 124.9 (C-8^{m}); 125.1 (C-8^{M}); 127.8 (C-11'); 129.1 (C-10); 130.0 (C-15); 137.4 (C-8'); 140.7 (C-13^{m}); 140.9 (C-13^{M}); 149.2 (C-13$'^{M}$); 149.4 (C-13$'^{m}$); 157.7 (C-11^{m}); 158.1 (C-11^{M}); 160.0 (CHO^{M}); 160.5 (CHO^{m}); 170.1 (16-C=O^{m}); 170.2 (AcC=O); 170.6 (16-C=O^{M}); 176.4 (16'-C=O). Measured H ↔ H inte-unit NOE connections: H-9 ↔ H-14', H_2-17'α, H-2'; H-12' ↔ H_3-18, H_2-19; H_3-18 ↔ H-12', H-14', H_2-17'α, H_2-15'α; H_3-11-OMe ↔ H-2'.

Preparation of 5 (vincadifformine-vindoline dimer, VV)

Coupling of (-)-vincadifformine with (-)-vindoline: To a stirred solution of (-)-vincadifformine (1.0 g; 2.9 *mmol) in* CH_2Cl_2 *(120 mL) and* Et_3N (0.44 mL, 3.18 *mmol)* at 0 °C, freshly prepared *t*-butyl hypochlorite was added dropwise until the total consumption of the starting compound [TLC: CH_2Cl_2/MeOH (10/0.25), R_F 16-chlorovincadifformine > vincadifformine]. The reaction mixture was then washed with ice-water (3x20 mL), the dried solvent evaporated at 40 °C under reduced pressure to give a residue, which was further dried in *vacuo*. The resulting chloroderivative and (-)-vindoline (1.28 g, 2.8 mmol) was dissolved in acetone (20 mL) and the solution was treated with silver tetrafluoroborate (1.70 g, 8.73 mmol) at 0 °C with rapid stirring. After being stirred for 25 min at rt, the heterogenous reaction mixture was worked up by the standard extractive method providing a reddish-brown amorphous residue, which was purified by flash chromatography [heptane/EtOAc/MeOH (100/100/10)] to yield 1.02 g (46 %) of VV (**5**) dimer. Further purification by repeated preparative TLC [CH_2Cl_2/MeOH (100/5)] afforded 630 mg (28 %) of VV (**5**) dimer.

mp 249-250 °C (amorphous); $[\alpha]_D^{25}$ -171° (c 0.1, $CHCl_3$). *IR* (KBr, cm^{-1}): 3446, 2944, 2778, 1734, 1616, 1500, 1464, 1372, 1297, 1225, 1039, 746. *MS* m/z(rel. int %): 793/MH+ (100); 792(46); 791(45); 733(20); 633(10); 379(14); 336(60); 124(31). ^{1}H NMR ($CDCl_3$) δ: 0.44 (3H, t, J=7.5 Hz, H_3-18); 0.60 (3H, t, J=7.0 Hz, H_3-18'); 0.62-0.74 (1H, m, H_2-19'x); 0.98-1.08 (1H, m, H_2-19'y), 1.14 (1H, td, J=13.8 Hz and 5.0 Hz, H_2-15'α); 1.22-1.34 (1H, m, H_2-19x); 1.44-1.52 (1H, m, H_2-14'α); 1.52-1.62 (2H, m, H_2-15'β, H_2-6'α); 1.62-1.72 (1H, m, H_2-19y); 1.74-1.86 (1H, m, H_2-14'β); 2.07 (3H, s, H_3-COMe); 2.14 (1H, t, J=10.0 Hz, H_2-3'α); 2.26-2.48 (6H, br m, H_2-6, H_2-5α, H-21', H-21, H_2-6'β); 2.48-2.56 (1H, m, H_2-5'α); 2.66-2.76 (2H, m, H_2-3α, H_2-17'α); 2.68 (3H, s, H_3-NMe); 2.86 (1H, t, J=7.2 Hz, H_2-5'β); 3.02 (1H, dd,

J=10.0 Hz and 2.8 Hz, H_2-3'β); 3.10 (1H, d, J=13.7 Hz, H_2-17'β); 3.32 (1H, br m, H_2-5β); 3.43 (1H, dd, J=15.8 Hz and 3.2 Hz, H_2-3β); 3.67 (3H, s, H_3-16'-CO_2Me); 3.73 (4H, br s, H_3-11-OMe, H-2); 3.79 (3H, s, H_3-16-CO_2Me); 5.26 (1H, d, J=10.0 Hz, H-15); 5.51 (1H, s, H-17); 5.80 (1H, dd, J=10.0 Hz and 4.0 Hz, H-14); 6.05 (1H, s, H-12); 6.74 (1H, br s, H-9); 7.20 (1H, t, J=7.3 Hz, H-10'); 7.29-7.35 (2H, m, H-11', H-9'); 7.62 (1H, d, J=7.7 Hz, H-12'); 9.27 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ: 7.4 (C-18'); 7.9 (C-18); 21.0 (AcMe); 22.0 (C-14'); 28.7 (C-19'); 30.9 (C-19); 33.1 (C-15'); 36.8 (C-20'); 37.3 (C-6'); 38.0 (NMe); 39.2 (C-17'); 43.0 (C-20); 43.8 (C-6); 50.9 (C-3); 51.3 (C-3'); 52.0 (C-5); 52.1 (16-CO_2Me); 52.4 (16'-CO_2Me); 53.2 (C-7); 54.0 (C-5'); 55.7 (11-OMe); 62.5 (C-7'); 68.0 (C-21); 76.1 (C-17); 78.2 (C-21'); 79.5 (C-16); 83.3 (C-2); 94.3 (C-12); 120.7 (C-9'); 121.1 (C-12'); 123.3 (C-8, C-9, C-10); 123.8 (C-14); 125.7 (C-10'); 127.2 (C-11'); 130.3 (C-15); 148.1 (C-8'); 152.7 (C-13); 152.9 (C-13'); 159.0 (C-11); 170.7 (AcC=O); 171.9 (16-C=O); 175.4 (16'-C=O); 187.5 (C-2'). Measured H ↔ H inter-unit NOE connections: H_3-18 ↔ H_2-6'α, H_2-6'β, H-5'β, H_3-16'-CO_2Me; H-9 ↔ H_2-6'β, H_2-17'β; H_3-16'-CO_2Me ↔ H_3-18, H_2-19x.

Preparation of 6 [iso(vincadifformine-vindoline) dimer, iVV]

Starting from **5** (VV): The pH of the solution of VV dimer (**5**) (200 mg; 0.25 mmol) dissolved in MeOH (60 mL) was adjusted to 4 by BF_3•Et_2O, then the mixture was heated under reflux for 70-75 h [TLC: silica, CH_2Cl_2/MeOH (20/1), R_F VV>iVV]. The extractive workup yielded 190 mg of crude product, which after purification by preparative TLC [CH_2Cl_2/MeOH (100/5)] resulted in 130 mg (65 %) of iVV (**6**).

mp 179-180 °C (amorphous); $[\alpha]_{546}^{25}$ -268° (c 0.86, $CHCl_3$). *IR* (KBr, cm^{-1}): 2947, 2249, 1740, 1616, 1501, 1456, 1337, 1226, 1164, 1040, 912, 732, 542. *MS* m/z(rel. int %): 793/MH+ (100); 792(37); 791(46); 733(31); 603(28); 577(62); 379(17); 337(20); 281(31); 221(32); 207(47). ^{1}H NMR ($CDCl_3$) δ: 0.32 (3H, t, J=7.4 Hz, H_3-18); 0.89 (3H, t, J=7.5 Hz, H_3-18'), 0.99 (1H, d, J=13.4 Hz, H_2-15'α); 1.04-1.14 (1H, m, H_2-19x); 1.12-1.22 (2H, m, H_2-14'β, H_2-15'β); 1.47-1.60 (2H, m, H_2-19y, H_2-19'x); 1.60-1.72 (1H, m, H_2-14'α); 1.80-1.90 (1H, m, H_2-6α); 1.98-2.06 (1H, m, H_2-5α); 2.05 (3H, s, H_3-COMe); 2.06-2.20 (2H, m, H_2-6β, H_2-19'y); 2.21(1H, s, H-21); 2.48 (1H, t, J=11.0 Hz, H_2-3'β); 2.52 (1H, d, J=14.9 Hz, H_2-17'β); 2.57-2.64 (2H, m, H_2-3'α, H_2-6'α); 2.64 (1H, d, J=15.9 Hz, H_2-3α); 2.73 (3H, s, H_3-NMe); 2.98-3.08 (1H, m, H_2-6'β); 3.09 (1H, d, J=15.0 Hz, H_2-17'α); 3.15 (1H, td, J=9.4 Hz and 4.0 Hz, H_2-5β); 3.26-3.36 (3H, m, H_2-5', H_2-3β); 3.54 (3H, s, H_3-16'-CO_2Me); 3.71 (1H, s, H-2), 3.78 (3H, s, H_3-16-CO_2Me); 3.85 (3H, H_3-11-OMe); 4.03 (1H, s, H-21'); 5.23 (1H, d, J=10.2 Hz, H-15); 5.42 (1H, s, H-17); 5.76 (1H, dd, J=10.2 Hz and 5.0 Hz, H-14); 6.15 (1H, s, H-12); 6.19 (1H, s, H-9); 6.93 (1H, t, J=8.2 Hz,

H-11'); 7.03 (1H, d, J=8.4 Hz, H-12'); 7.04 (1H, t, J=7.9 Hz, H-10'); 7.47 (1H, d, J=7.7 Hz, H-9'); 9.40 (1H, br s, OH). ^{13}C NMR ($CDCl_3$) δ: 7.6 (C-18'); 7.9 (C-18); 17.1 (C-6'); 20.9 (C-14'); 21.1 (AcMe); 26.3 (C-15'); 29.5 (C-19'); 30.7 (C-19); 34.8 (C-20'); 38.2 (NMe); 42.7 (C-20, C-17'); 43.8 (C-6); 44.6 (C-3'); 50.4 (C-3); 50.9 (C-5', C-5); 52.2 (16-CO_2Me); 52.4 (16'-CO_2Me); 53.2 (C-7); 55.6 (11-OMe); 59.2 (C-21'); 65.5 (C-16')*; 66.4 (C-21); 76.2 (C-17); 79.7 (C-16); 83.5 (C-2); 93.9 (C-12); 106.0 (C-7'); 115.1 (C-12'); 117.6 (C-9'); 119.4 (C-10'); 120.2 (C-10); 120.3 (C-11'); 122.6 (C-8); 122.7 (C-9); 123.9 (C-14); 128.8 (C-8'); 130.2 (C-15); 132.7 br (C-2'); 135.6 (C-13'); 153.0 (C-13); 157.6 (C-11); 170.7 (AcC=O); 171.8 (16-C=O, 16'-C=O) * detected at 75 MHz (30 °C). Measured H ↔ H inter-unit NOE connections: H_3-18 ↔ H_2-15'α, H_2-15'β, H_2-14'β; H-9 ↔ H_2-15'β, H-12'; H_2-6α ↔ H-12', H-11'; H_3-11-OMe ↔ H_3-16'-CO_2Me.

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