Configurative Correlation and Conformational Analysis of Strictosidine and Vincoside Derivatives†

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On the basis of the configuration of C-15 of the secologanin unit, using detailed NMR analysis, the configuration of C-3, the solution conformation around C-14, and the glucosidic bridge, as well as those of the dihydropyran and tetrahydropyridine rings, were determined in the vincosamide and strictosamide derivatives **4b** and **5b**. The stereochemical analysis was extended by chemical correlation to the 4-benzylated strictosidine and vincoside derivatives **3c** and **3d**. Experimental proof was presented for the interpretation of the "anomalous" chemical shift of acetylated strictosamide derivatives.

In the presence of the enzyme strictosidine synthase, the coupling reaction of tryptamine (**1a**) and secologanin (**2a**) gives strictosidine (**3a**) with complete stereoselectivity.[2] However, in the absence of the enzyme, both strictosidine (**3a**) and vincoside (**3b**) are formed with low stereoselectivity.[3] The configuration of the new center of chirality C-3 has been a subject of controversy;[4] however, in the vincoside series this was determined unequivocally by X-ray diffraction analysis of *O*′,*O*′,*O*′,*O*′-tetraacetyl-4-(4″-bromobenzyl)vincoside (**3d**), prepared by direct coupling of N_b-4′-bromobenzyl-tryptamine (**1b**) and *O*′,*O*′,*O*′,*O*′-tetraacetylsecologanin (**2b**).[5] The coupling reaction gave exclusively the vincoside derivative, and isomeric strictosidine derivatives could not be obtained in other ways in appropriate crystalline form. Previously, the stereochemistry of C-3 in the strictosidine derivatives was derived by complicated multistep chemical correlations that involved the danger of unexpected configurational changes. Similar uncertainties were experienced in the case of the dolicanthoside and isodolicanthoside (4-methyl derivatives of strictosidine and vincoside) during the study of their CD spectra.[6,7] Therefore, in the strictosidine series, a rigorous proof of the configuration of C-3 was not possible for a long time. Recently, in our laboratory, this configuration has been proved by detailed NMR studies.[8] The confusion in the 4-methyl derivatives was eliminated by reinterpretation of the CD spectra.[9] It was still necessary, however, to place the stereochemistry of these terpenoid glycosides on a firm experimental base. The aim of the present work was to extend our previous results to other strictosidine and vincoside derivatives by preparative configurative correlations, as well as to demonstrate their conformations in solution.

Results and Discussion

The reaction sequences are shown in Scheme 1. Several conclusions were made and are enumerated as follows:

1. The starting point of the correlations was the result of the X-ray diffraction analysis of *O*′,*O*′,*O*′,*O*′-tetraacetyl-4-(4″-bromobenzyl)vincoside **(3d)**, which was prepared by the slightly modified method of Hutchinson et al.[5] As in the lactam series, the stereochemistry could be proved unequivocally by NMR spectroscopy; **3d** was transformed into *O*′,*O*′,*O*′,*O*′-tetraacetyl-18,19-dihydrovincosamide (**4b**, 84% yield) by catalytic hydrogenation involving saturation of the vinyl group, removal of the 4-bromobenzyl group, and spontaneous lactamization.

2. As *O*′,*O*′,*O*′,*O*′-tetraacetyl-4-(4″-bromobenzyl)strictosidine (**3c**) could not be prepared by direct coupling, it was prepared from strictosidine (**3a**)[8] by alkylation with 4-bromobenzyl bromide and subsequent acetylation (48% yield). After removal of the 4-bromobenzyl and saturation of the vinyl group, lactamization in aqueous sodium carbonate solution at 70 °C gave *O*′,*O*′,*O*′,*O*′-tetraacetyl-18,19-dihydrostrictosamide (**5b**, 84% yield).

3. For rigorous correlation it was obviously necessary to prepare **4b** and **5b** from starting materials that had been formed simultaneously in the same reaction mixture. Therefore, by a slight modification of the method of Battersby et al.,[3] tryptamine (**1a**) and secologanin (**2a**) were reacted to obtain strictosidine (**3a**) and vincoside (**3b**) in an approximately 1:1 ratio. However, in the reaction mixture, vincoside had already spontaneously lactamized to vincosamide (**4a**) and precipitated.[3] After filtration and recrystallization, pure **4a** was obtained **(**27% yield calculated from **2a**).[8] It was acetylated and hydrogenated to the same **4b** (47% yield) that was previously prepared according to point 1.

4. The mother liquor of the coupling reaction of point 3 afforded, after evaporation of the solvent, strictosidine (**3a**, 36% yield from **2a**), which was lactamized in aqueous sodium carbonate at 70 °C to strictosamide (**5a**, 80% yield).[3] This compound was acetylated and hydrogenated to the same **5b** (75% yield) that was previously prepared according to point 2.

These easy transformations under mild reaction conditions excluded the epimerization at any center of chirality. In the stereochemical analysis,[10] the main problem was to determine the dominant conformation around C-14. In both series, the Newman projections of the nine possible conformers around bonds C-3−C-14 and C-14−C-15 (**11**−**13**, **21**−**23**, **31**−**33**) may be characterized by the vicinal ^{1}H−^{1}H coupling constants according to the synclinal (sc) and antiperiplanar (ap) positions of the hydrogens attached to C-3, C-14, and C-15 in both series (Table 1 and Figure 1). In the **R** series, the *R* configuration of C-3 (H-3β in the usual representation) was derived according to the result

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Scheme 1. Configurative Correlation of Strictosidine and Vincoside Derivatives

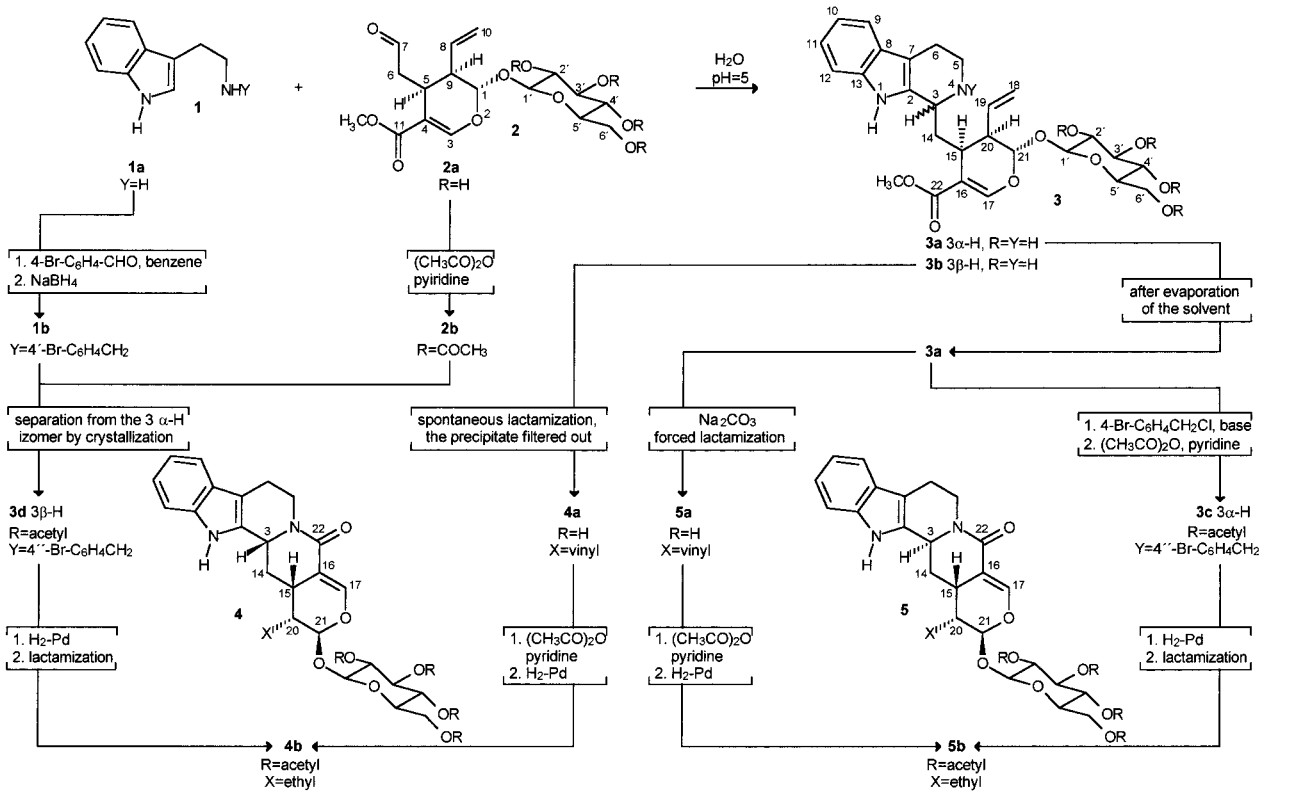

Table 1. Relative Orientation of H-3 and H-15 to H-14*proR* and H-14*proS*[a]

H-3	H-15	H-3	H-15	H-3	H-15	H-14	H-3	H-15	H-3	H-15	H-3	H-15
S11		**S12**		**S13**			**R11**		**R12**		**R13**	
ap	sc	ap	ap	ap	sc	*proR*	sc	ap	sc	sc	sc	sc
sc	ap	sc	sc	sc	sc	*proS*	ap	sc	ap	ap	ap	sc
S21		**S22**		**S23**			**R21**		**R22**		**R23**	
sc	sc	sc	ap	sc	sc	*proR*	ap	ap	ap	sc	ap	sc
ap	ap	ap	sc	ap	sc	*proS*	sc	sc	sc	ap	sc	sc
S31		**S32**		**S33**			**R31**		**R32**		**R33**	
sc	sc	sc	ap	sc	sc	*proR*	sc	ap	sc	sc	sc	sc
sc	ap	sc	sc	sc	sc	*proS*	sc	sc	sc	ap	sc	sc

[a] The letters ap and sc indicate antiperiplanar and synclinal orientation of the appropriate H's, respectively.

of the X-ray diffraction analysis,[5] while in the **S** series, the conformers were derived by preliminary supposition (based on our previous analysis of strictosidine[8]) of the opposite *S* configuration at C-3 (H-3α). Each C-14 conformer may exist in four ring conformers, according to the negative or positive half-chair conformation of the dihydropyran and tetrahydropyridine rings, respectively (**NN**, **NP**, **PN**, **PP**). Further issues were to determine the axial (**A**) or equatorial (**E**) position of the eventual benzyl group and the conformation around the glucosidic oxygen bridge. To facilitate the analysis, stereostructures were constructed by the ALCHEMY II program[12] for the possible conformers. Detailed analysis of the NMR data gave the following results for the stereostructures of the intermediates and final products in solution.

The stereostructure of *O′*,*O′*,*O*,*′O′*-tetraacetyl-18,19-dihydrovincosamide (**4b**) and -dihydrostrictosamide (**5b**). Unlike the tetracyclic derivatives, in the pentacyclic lactams the number of possible conformers around C-14 is limited, because in each series there are only two conformers in which N-4 and C-22 are sufficiently close for cyclization. These are **R12** and **R33** for **4b**, and **S13** and **S31** for **5b**. For these conformers, the vicinal coupling constants of protons H-3, H-14, and H-15 were estimated according to the dihedral angles of the appropriate pairs of C−H bonds. Because the four possible coupling patterns are different, comparison of the expected and measured coupling constants unequivocally established the conformation around C-14 (Table 2). In **4b**, H-14*proS* had large coupling constants (12.5 and 13.0 Hz), whereas H-14*proR* was observed to have small coupling constants (3.6 and 3.5 Hz) with the vicinal protons H-3 and H-15, respectively. This pattern of *J* values is appropriate only for conformer **R12** and establishes the axial orientation of H-3 and H-15 on the lactam ring. Conformer **R33** would require small coupling constants for both H-14 protons with each of the vicinal protons. In amide **5b**, H-3 had small coupling constants with H-14*proR* (2.8 Hz) and H-14*proS* (5.5 Hz). However, H-15 had a large coupling constant (13.5 Hz) with H-14*proS* and small one (4.9 Hz) with H-14*proR*. This coupling pattern corresponds to the conformer **S31** and established the equatorial position of H-3 to the lactam ring. **S13** would require large coupling constant between H-14*proR* and H-3, rather than between H-14*proS* and H-15. It should be noted that **R12** and **S31** are the only two C-14 conformers where the lactam ring can take up a half-chair conformation.

In consideration of the established *S* configuration of C-5 in loganin[13] (analogous to C-15 in the monoterpenoid indole alkaloids) as well as the independent determination of C-15

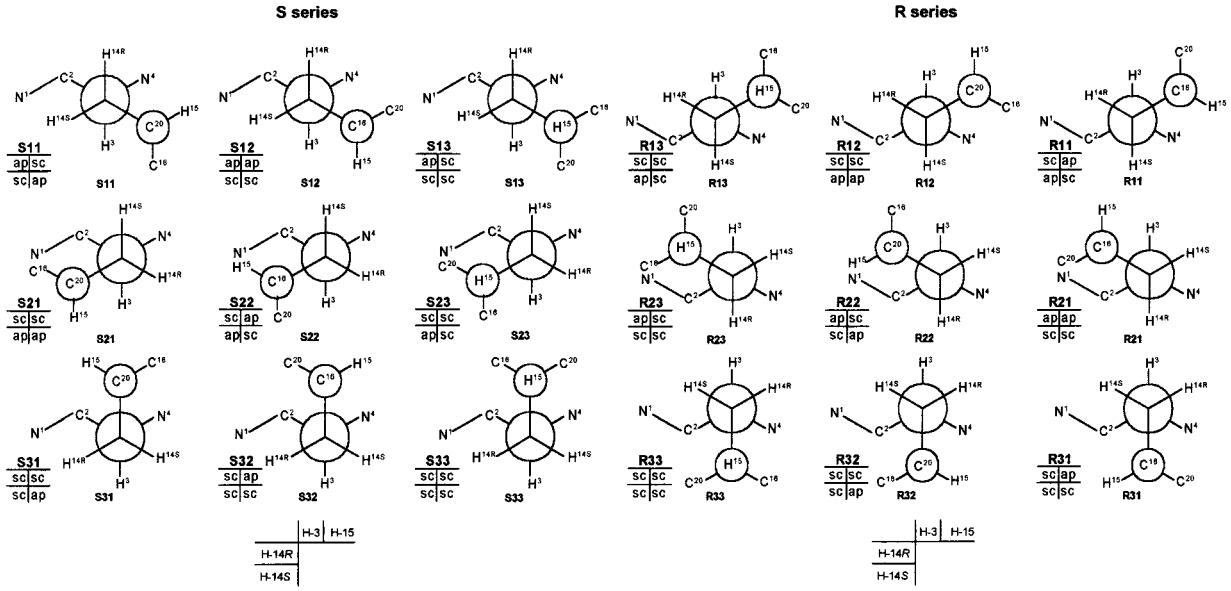

Figure 1. Newman formulas of the conformers around C-14. The letters ap and sc indicate antiperiplanar and synclinal orientation of the appropriate Hs, respectively.

Table 2. Comparison of Expected and Determined H−H Coupling Constants (*J*) around C-14

	expected *J* in				determined *J* (in Hz)	
interacting H-s	**S13**	**S31**	**R12**	**R33**	**4b**	**5b**
H-3−H-14*proR*	large	small	small	small	2.8	3.6
H-3−H-14*proS*	small	small	large	small	5.5	12.5
H-15−H-14*proR*	small	small	small	small	4.9	3.5
H-15−H-14*proS*	small	large	large	small	13.5	13.0

in **3d**,[5] these results also establish for **4b** the *R* (H-3β) and for **5b** the *S* (H-3α) configuration of C-3. They are in agreement with the X-ray diffraction analysis in the **R** series,[5] and further confirm our previous determination in the **S** series.[9]

The conformation of the dihydropyran ring was determined from the vicinal coupling constant $^3J_{20,21}$, which has a small value in both amide compounds **4b** (1.9 Hz) and **5b** (1.8 Hz). With respect to the configurations in secologanin, this value is characteristic for the trans diequatorial relationship of the two protons. This is possible only if the conformation of the ring is negative. Moreover, it involves the β-orientation of H-15 in both amides, as well as the β orientation in **4b** and the α orientation in **5b** of H-3 in the usual representation.

The conformation of the tetrahydropyridine ring was established from the interpretation of the NOESY spectrum. H-3 displayed a cross-peak with one of the H-5 protons in both amides. The interacting protons should be in a cis diaxial relationship that concerns H-5β in amide **4b** and H-5α in amide **5b**. In the first case this indicates a negative and in the second case a positive conformation of the tetrahydropyridine ring. These conformations were further confirmed by the observation that the other C-5 proton, that is, H-5α in **4b** and H-5β in **5b**, had a substantially higher δ value than its geminal partner (δ 5.14 vs 2.88, 5.02 vs 3.03, respectively). This strong paramagnetic shift is due to the anisotropic effect of the carbonyl group, which can be effective only in an equatorial orientation of the appropriate proton to the tetrahydropyridine ring.[14]

According to this analysis, the three-dimensional shape of **4b** and **5b** can easily be seen (Figure 2). In **4b**, which corresponds to the steric pattern **R12NN**, H-3 is in a β-axial orientation to the lactam ring, and C-2 takes the α equatorial orientation. The β equatorial orientation of C-5 to the lactam ring is in agreement with the data given in the discussion regarding the conformation of the tetrahydropyridine ring. The trans diequatorial attachment of this ring to the lactam ring endows the pentacyclic ring system with a flat shape. In **5b**, which corresponds to the steric pattern **S31NP**, and in which H-3 has the α-equatorial orientation to the lactam ring, C-2 should assume a β-axial position, and C-5 will necessarily be in the β-equatorial orientation. Cis attachment of the tetrahydropyridine ring to the lactam ring forces the indole ring system into a position approximatively perpendicular to the other part of the aglycon unit.

The latter statement was further supported by the strong diamagnetic shift of one of the acetyl methyl signals in **5b** (δ 1.20 ppm vs 2.07, 1.99, 1.88 ppm for the others), which gave the possibility to determine simultaneously the conformation around the glucosidic O bridge. This "anomalous" chemical shift is well-known in all acetylated strictosamide derivatives since the first publication[3] on strictosidine, but was not interpreted until recently. In **5b**, the long-range carbon−proton coupling of this H-methyl and H-2′ with the same carbonyl carbon was detected by selective INEPT experiments[15] that established that this acetyl group was attached to O-2′ of the β-D-glucopyranosyl unit. The same conclusion was made by Aimi et al.[16] in **5a** on the basis of HMBC measurements. In addition, in the NOESY spectrum of **5b**, cross-peaks of H-9 and H-11 with H-methyl were detected. This provides the first experimental proof for the steric proximity of the methyl group to the indole ring. Therefore the "anomalous" shift results as a consequence of the diamagnetic effect of the ring-current of the aromatic indole ring. This proximity is strongly dependent on the conformation around the glycosidic oxygen bridge. In our previous paper on the stereochemical analysis on strictosidine,[8] experimental and theoretical arguments were presented in favor of the most stable conformer around the glycosidic O bridge. In this conformer one of the nonbonding orbitals of the O bridge with the bond O-17−C-21, and the other with bond C-1′−O-5′ is in an ap position; that is, a double σ-conjugation is stabilizing this conformer. Model studies indicated that the

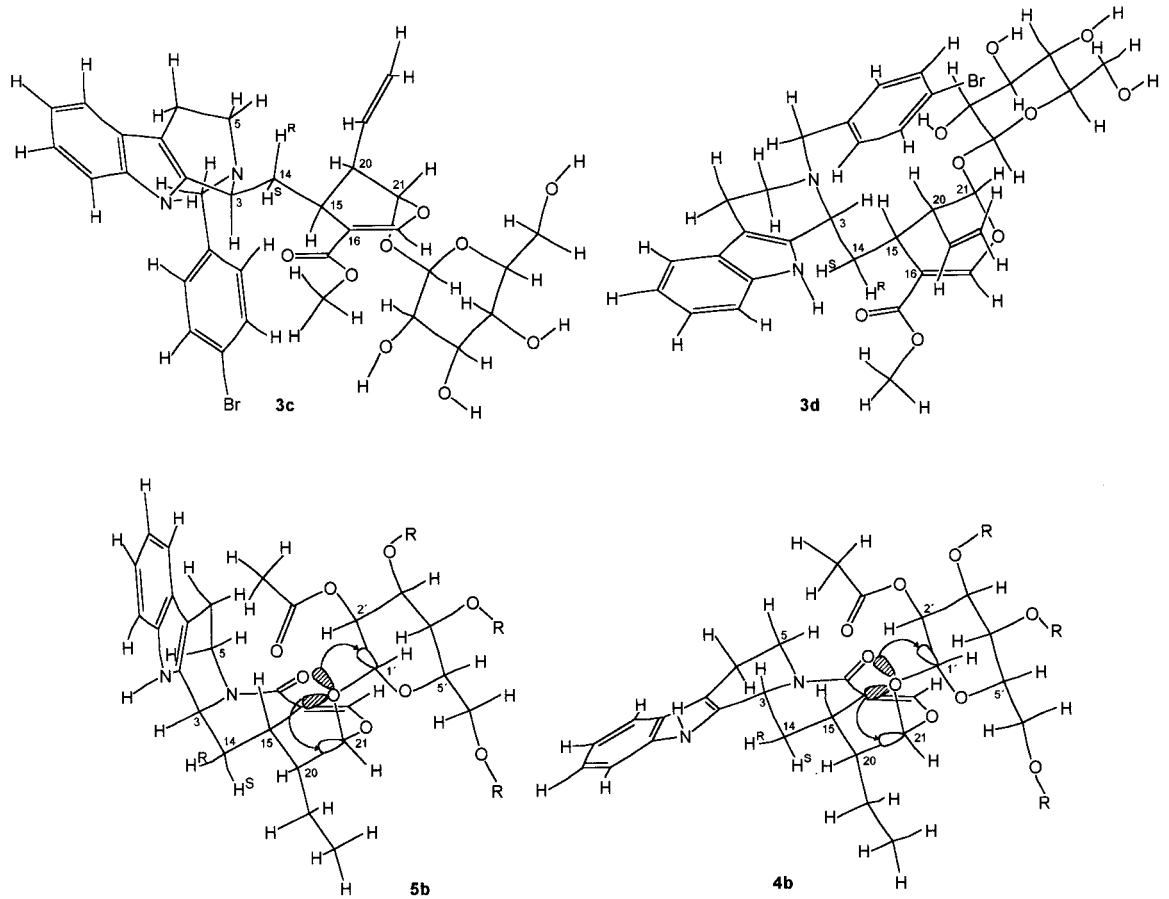

Figure 2. Three-dimensional structures of **3c**, **3d**, **4b**, and **5b** (R = acetyl).

2′-acetoxy group can approach the indole ring system perpendicularly only in this conformation. Although this acetyl group has some conformation mobility around the *O*-acetyl bond, its preferred, least crowded orientation closest to the indole ring is shown in Figure 2. In the spectrum of the acetylated vincosamide derivatives, no "anomalous" shift was expected or observed, because the indole ring system is far away from any of the acetyl groups of the β-D-glucopyranosyl unit in any conformation. However, as the double σ-conjugation is independent of the other parts of the molecule, it may be supposed that the same conformation around the O bridge is dominant in all glucosidic secologanin derivatives.

The stereostructures of *O*′,*O*′,*O*′,*O*′-tetraacetyl-4-(4″-bromobenzyl)strictosidine (**3c**) and -vincoside (**3d**) were considered next. The identical configuration of C-3 in the tetracyclic bases and the corresponding pentacyclic lactams was proved by transformation of **3c** into **5b,** and of **3d** into **4b** in two steps and under mild conditions. Accordingly, C-3 has the *S* configuration in **3c** (H-3α) and the *R* configuration in **3d** (H-3β). In both derivatives the small value of $^3J_{20,21}$ indicated the negative conformation of the dihydropyran ring.

The conformation of the tetrahydropyridine ring was derived from the NOESY spectrum. In both compounds, one of the H-14 protons gave a cross-peak with one of the H-5 protons. This is possible only if C-14 and the interacting H-5 are in a cis diaxial orientation. According to the established configuration of C-3, orientation of C-14 is β in **3c** and α in **3d**; therefore, the interacting H-5 proton (H-5β in the former and H-5α in the latter compound) should have axial orientation, which is possible only in **3c** in the negative, and in **3d** in the positive conformation of the tetrahydropyridine ring. In both compounds, the protons of the benzyl−CH_2 group gave cross-peaks with H-3 and with the equatorial H-5 proton. This means that the benzyl group in **3c** has an α-axial orientation and in **3d** has a β-axial orientation. In conclusion, the bulky ligands of C-3 and N-4 in both derivatives are in a trans diaxial position. Moreover, it should be noted that in both derivatives the benzyl protons gave NOE cross-peaks with the axial H-6 proton. This suggested an axial position of the benzyl group in which the C(H_2)−benzyl−C-1″ bond was ap to the N-4−C-5 bond.

In the tetracyclic bases, the conformation around C-14 is not fixed by cyclization; therefore, none of the nine staggered conformers around C-14 may be disregarded a priori. The situation is simpler in **3d**. One of the H-14 atoms has a large coupling constant with H-3, and the other with H-15, which established the ap orientation of the appropriate H atoms. **R11** and **R22** are the only two conformers corresponding to this coupling constant pattern. The distinction between these conformers was made by observing a medium-strong cross-peak between H-3 and H-20 in the NOESY spectrum of **3d**, which suggested a short, through-space distance between them. According to measurements on the computer-generated structures, these two protons are very close (1.9 Å) in conformer **R11,** which is the favored one. In **R22** the two protons would be too far (4.7 Å) apart for a NOE to be observed.

In **3c** the situation is more complicated; therefore, the carbon−proton coupling constants of this derivative were measured by an improved HETLOCK pulse sequence.[17] They were used together with ^{1}H−^{1}H coupling constants and NOE observations to determine the dominant conformation. The moderately large coupling constant (8.7 Hz)

Table 3. Comparison of Torsion Angles around C-14 with the Coupling Constants (*J*)

torsion angle of	in degrees, calcd for **S12d**	in degrees, calcd for **S22d**	measd *J* (in Hz)	
H-3−C-3−C-14−H-14*proR*	+166.0	+74.6	$^3J_{H3,H14R}$	8.7
H-3−C-3−C-14−H-14*proS*	−74.6	−166.0	$^3J_{H3,H14S}$	4.2
H-3−C-3−C-14−C-15	+46.6	−44.8	$^3J_{H3,C15}$	3.4
H-15−C-15−C-14−H-14*proR*	−130.1	−130.2	$^3J_{H14R,H15}$	5.8
H-15−C-15−C-14−H-14*proS*	+110.0	+110.0	$^3J_{H14S,H15}$	4.0
H-15−C-15−C-14−C-3	−11.0	−11.0	$^3J_{C3,H15}$	5.6
N-4−C-3−C-14−H-14*proR*	+46.1	−45.2	$^2J_{C3,H14R}$	**−6.0**
N-4−C-3−C-14−H-14*proS*	+165.5	+74.1	$^2J_{C3,H14S}$	**−2.6**

of H-3 with one of the H-14 atoms indicated one (approximately) ap orientation and excluded conformers of the **S3** series (**S31**, **S32**, **S33**), where both H-14 atoms should have sc orientation to H-3. H-15 has one small coupling constant to one of the H-14 protons (4.0 Hz). However, the coupling constant of H-15 to the other H-14 gave an ambiguous value (5.8 Hz) that corresponded to neither a clear sc, nor a clear ap orientation of the appropriate hydrogens and suggested a distorted conformation around the C-14−C-15 bond. To find the most advantageous conformation, in the computer-generated molecular models, H-14*proR* in the **S1** series and H-14*proS* in the **S2** series were kept in an ap orientation, and the secologanin subunit was turned around the C-14−C-15 bond by 360°, with continuous measurement of the through-space interatomic distances between the appropriate atoms of the secologanin and tryptamine subunits. In both series, only a relatively narrow torsion angle interval (between −20° and +5° around C-3−C14−C-15−H-15) was found in which no serious internal steric interferences would be expected. Finally, the torsion angle around C-3−C-14 was also slightly modified. As these conformers can be derived from **S12** and **S22** by a rotation of less than 60° around C-3−C-14 and C-14−C-15, respectively, the "distorted" structures remain in the original segment and are referred as the **S12d** and **S22d** conformers. The characteristic torsion angles of the two conformers and the value of the measured coupling constants that are influenced by these dihedral angles are shown in Table 3. The expected values of the coupling constants $^3J_{H14R-H15}$ and $^3J_{H14S,H15}$ in these structures were calculated using a modified Karplus-type equation.[18] The tabulated values of 6.1 and 2.6 Hz are in good agreement with the measured coupling constants 5.8 and 4.0 Hz, respectively. The expected $^3J_{C3,H15}$ coupling constant for these conformations was calculated to be 7.4 Hz by using the equation reported by Günther et al.[19] This is somewhat higher than the measured value (5.6 Hz); however, the applied equation does not consider the effect of the electronegative substituent (namely, the N-4 atom) on the coupling constant. Another study established[20] that such an effect reduced the coupling constant in steric arrangements corresponding to the conformers **S12d** and **S22d**, and thus the measured $^3J_{C3,H15}$ is also in agreement with the expected structures.

Because the value of the measured vicinal coupling constants fitted both proposed conformers, the decision between them was made on the basis of $^2J_{C3,H14}$ coupling-constant values. It has been established for carbohydrates and for other compounds that, in H−C−C−O fragments, the value of $^2J_{C,H}$ depends on the dihedral angle of the hydrogen and the oxygen atoms.[21] The substituent has a negative contribution of about 2 Hz to the coupling in synperiplanar and sc orientation, and a positive contribution of about 2 Hz in ap arrangements. By comparison of the coupling constants in simple *O*-glucosides and 2′-deoxyribonucleosides, it was proved that the nitrogen atom has the same effect on the coupling constants.[22] In this case, the measured $^2J_{C3,H14}$ coupling constants are −6.0 and −2.6 Hz. In the **S22d** conformation, both hydrogens of the C-14 methylene group are sc to N-4, so that similar coupling constants should be expected. However, in **S12d**, the H-14*proR* is in the sc orientation, while H-14*proS* is in an ap orientation to N-4. Therefore, the measured data suggested that **S12d** is the dominant conformer of **3c**. Consequently, the signals showing −6.0 Hz and −2.6 Hz coupling constants with C-3 can be assigned to the H-14*proR* and H-14*proS* atoms, respectively. In agreement with this assignment and the dominance of the **S12d** conformation, the signal assigned to the H-14*proR* shows a 8.7 Hz coupling constant due to the spin−spin interaction with H-3.

The NOESY spectrum was also in agreement with this structure. For the evalution of the results, the cross-peak intensity corresponding to a hypothetical atomic pair distance of 3.3 Å was calculated by the two-spin approximation method and by using the NOE of the H-1′−H-5′ interaction (2.5 Å) as a reference value. The volume of all cross-peaks was integrated, and the higher or lower values compared to the reference integral were considered to be strong or weak. The distances of the atomic pairs having unambiguously defined orientation in the **S12d** conformer were compared with the cross-peak intensities. The through-space interatomic distances of the model corresponding to strong and weak cross-peaks lay in the 1.8−2.6 Å and 2.6−3.7 Å regions, respectively.

In summary, the conformation of the dihydropyran ring is negative in both compounds **3c** and **3d**; that of the tetrahydropyridine ring is negative in **3c** and positive in **3d**. The favored conformation around the methylene bridge is **S12d** in **3c**, and **R11** in **3d**. Consequently, the stereochemical notation of **3c** is **S12dNN**; that of **3d** is **R11NP**. The three-dimensional shapes of **3c** and **3d** are shown in Figure 2.

It is hoped that the results described here will assist in the interpretation of further details of the chemistry of secologanin, which will be the subject of subsequent papers, and that the stereochemical problems of this important class of alkaloids have been placed on a firm experimental base.

Experimental Section

General Experimental Procedures. NMR spectra were recorded on a Bruker AM-200 spectrometer at 200 MHz (^{1}H) and 50 MHz (^{13}C), on a Bruker AC-250 spectrometer at 250 MHz (^{1}H) and 62 MHz (^{13}C), on a Bruker AC-400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), or on a Bruker DRX-400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). TMS was used as the chemical-shift reference. COSY, NOESY, and selective TOCSY spectra were measured with the standard Bruker microprograms of the DISNMR or the XWINNMR software. In the phase-sensitive NOESY spectra a 600-ms mixing time was used. The cross-peak intensities were categorized as strong, medium, or weak by visual inspection of the spectra for all compounds except for **3c**, where the volumetric integration by the XWINNMR program was applied. The selective TOCSY spectra were measured with a 270° Gaussian-shaped selective excitation pulse, 20-, 40-, 70-, and 100-ms spin-lock times. Selective INEPT spectra were measured with 10-ms selective rectangular 90° ^{1}H pulses, the delays were optimized for 7-Hz couplings.

The organic solutions were dried with anhydrous sodium sulfate. TLC was carried out on Si gel plates eluting with $CHCl_3$−MeOH (4:1), unless indicated otherwise. Melting points are uncorrected. The optical rotation was measured at 583 nm (Na) on a Carl Zeiss polarimeter.

***N*b-4′-Bromobenzyltryptamine (1b).** To a solution of 4-bromobenzaldehyde (0.46 g, 2.5 mmol) in benzene (4.0 mL), tryptamine (**1a**, 0.40 g, 2.5 mmol) was added, the reaction mixture refluxed for 4 h, and the solvent evaporated. The residue was treated with absolute $(Et)_2O$ and, after filtration, gave *N*b-4′-bromobenzylidenetryptamine (**1**, HY = 4-bromobenzylidene) (0.76 g, 90.8%, R_f 0.82, mp 118−120 °C). The crude product (0.31 g, 1.0 mmol) was dissolved in CH_3OH (4.0 mL), and sodium tetrahydridoborate (0.06 g, 1,5 mmol) was added in portions with stirring at room temperature, then stirred for further 30 min, and finally refluxed for 2 h. After evaporation of the solvent, the residue was taken up in H_2O (3.0 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined $CHCl_3$ phase was dried and the solvent evaporated. The crude *N*b-4′-bromobenzyltryptamine (**1b**, 0.28 g, 90%, mp 78−80 °C) was used directly. For analysis it was dissolved in 5 M ethanolic HCl (0.05 mL), the hydrochloric acid salt precipitated by adding absolute $(Et)_2O$ (2.0 mL), and the precipitate was filtered and then washed with the same solvent: mp 227−230 °C (EtOH−hexane); *anal*. C 55.94%, H 4.91%, N 7.39%, Br 22.12%, calcd for $C_{17}H_{18}BrClN$, C 55.83%, H 4.96%, N 7.66%, Br 21.85%.

Secologanin (2a). Secologanin (**2a**) was isolated from *Lonicera xylosteum* L. according to a method elaborated in our Institute[23] [R_f 0.29; $CHCl_3$−MeOH (4:1)]. ^{1}H NMR (acetone-d_6, 200 MHz) δ 9.71 (1H, dd, $^3J_{6a,7}$ = 1.8, $^3J_{6b,7}$ = 1.2 Hz, H-7), 7.47 (1H, d, $^4J_{3,5}$ = 1.8 Hz, H-3), 5.61 (1H, H-8), 5.46 (1H, d, $^3J_{1,9}$ = 3.9 Hz, H-1), 5.32−5.16 (2H, m, H_2-10), 4.70 (1H, H-1′), 4.50, 4.34, 4.27 (each 1H, d, $^3J_{CH,OH}$ = 5−6 Hz, 2′,3′,4′-OH), 3.92−3.60 (3H, H_2-6′, 6′-OH), 3.64 (3H, s, OCH_3), 3.50−3.18 (5H, m, H-5,2′,3′,4′,5′), 2.83 (1H, ddd, $^2J_{6a,6b}$ = 17.5, $^3J_{5,6a}$ = 6.1, $^3J_{6a,7}$ = 1.8 Hz, H-6a), 2.75 (1H, m, H-9), 2.42 (1H, ddd, $^2J_{6a,6b}$ = 17.5, $^3J_{5,6b}$ = 7.4, $^3J_{6b,7}$ = 1.2 Hz, H-6b); ^{13}C NMR (acetone-d_6, 50 MHz) δ 202.0 (C-7), 168.2 (C-11), 153.6 (C-3), 135.4 (C-8), 120.9 (C-10), 110.3 (C-4), 100.4 (C-1′), 97.5 (C-1), 78.7, 78.5 (C-3′,5′), 75.1 (C-2′), 72.2 (C-4′), 63.5 (C-6′), 52.0 (OCH_3), 45.7 (C-9), 45.1 (C-6), 27.3 (C-5).

***O,O,O,O*-Tetraacetylsecologanin (2b).** Secologanin **2a** (7.5 g, 0.020 mol) was dissolved in a mixture of anhydrous pyridine (30 mL, 0.38 mol) and $(Ac)_2O$ (15 mL, 0.15 mol), stirred at room temperature for 2 h, poured on to ice (150 g), and extracted with $CHCl_3$ (3 × 90 mL). The combined $CHCl_3$ layer was washed with 2 M aqueous HCl (2 × 60 mL), 5% aqueous $NaHCO_3$ (60 mL), and H_2O (2 × 60 mL) and dried. Evaporation of the solvent gave *O,O,O,O*-tetraacetylsecologanin **2b** (9.2 g, 84.5%, R_f 0.69); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.71 (1H, dd, $^3J_{6a,7}$ = 1.6, $^3J_{6b,7}$ = 0.7 Hz, H-7), 9.42 (1H, d, $^4J_{3,5}$ = 1.9 Hz, H-3), 5.50 (1H, dt, $^3J_{8,10E}$ = 17.9, $^3J_{8,9}$ = $^3J_{8,10Z}$ = 8.9 Hz, H-8), 5.28 (1H, d, $^3J_{1,9}$ = 2.9 Hz, H-1), 5.23−4.97 (5H, m, H-10*E*, H-10*Z*, H-2′, H-3′, H-4′), 4.88 (1H, d, $^3J_{1',2'}$ = 7.9 Hz, H-1′), 4.29 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'a}$ = 4.4 Hz, H-6′a), 4.15 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5'6'b}$ = 2.3 Hz, H-6′b), 3.77−3.71 (1H, m, H-5′), 3.68 (3H, s, OCH_3), 3.28 (1H, dtd, $^3J_{5,6b}$ = 7.7, $^3J_{5,6a}$ = $^3J_{5,9}$ = 5.7, $^4J_{3,5}$ = 1.9 Hz, H-5), 2.92 (1H, ddd, $^2J_{6a,6b}$ = 17.8, $^3J_{5,6a}$ = 5.7, $^3J_{6a,7}$ = 1.6 Hz, H-6a), 2.85−2.76 (1H, m, H-9), 2.39 (1H, ddd, $^2J_{6a,6b}$ = 17.8, $^3J_{5,6b}$ = 7.7, $^3J_{6b,7}$ = 0.7 Hz, H-6b), 2.11, 2.03, 2.01, 1.91 (each 3H, s, CH_3-CO). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 205.9 (C-7), 170.6, 170.2, 169.4, 168.9 (4 CH_3CO of acetyl), 166.8 (C-11), 151.3 (C-3), 132.3 (C-8), 121.1 (C-10), 109.6 (C-4), 95.8 (C-1, C-1′); 72.3 (C-3′), 72.4 (C-2′), 70.6 (C-4′), 68.1 (C-5′), 61.6 (C-6′), 51.3 (CH_3O), 43.7 (C-9), 43.3 (C-6), 25.1(C-5), 20.7, 20.6, 20.1 (each CH_3-CO).

Strictosidine (3a) and Vincosamide (4a). Tryptamine base (**1a**, 0.16 g, 0.10 mmol) and tryptaminium chloride (**1a**·HCl, 0.20 mmol) were dissolved in a mixture of H_2O (10 mL) and glacial HOAc (0.50 mL), secologanin (**2a**, 0.76 g, 0.20 mmol) was added, and the solution stirred in a N_2 atmosphere at 100 °C for 6 h. From the cooled reaction mixture the precipitated vincosamide (**4a**) was filtered, and the mother liquor extracted with EtOAc (3 × 30 mL). The combined organic layer was dried, and the solvent evaporated. The residue (**5a**) was crystallized from acetone (0.27 g, 27%). Isolation of strictosidine (**3a**, 0.39 g, 36%) from the mother liquor as well as its spectroscopic data were described previously.[8] The combined yield of the two products, **3a** and **5a**, is 0.66 g (63%). Spectroscopic data of vincosamide (**4a**): ^{1}H NMR (CD_3OD, 250 MHz) δ 7.61 (1H, d, H-17), 7.58 (1H, dd, $^3J_{9,10}$ = 7.6, $^4J_{9,11}$ = 1.2 Hz, H-9), 7.46 (1H, dd, $^3J_{11,12}$ = 7.9, $^4J_{10,12}$ = 1.2 Hz, 12-H), 7.24 (1H, ddd, $^3J_{11,12}$ = 7.9, $^3J_{10,11}$ = 7.1, $^4J_{9,11}$ = 1.2 Hz, H-11), 7.15 (1H, ddd, $^3J_{9,10}$ = 7.6, $^3J_{10,11}$ = 7.1, $^4J_{10,12}$ = 1.2 Hz, H-10), 5.71 (1H, dt, $^3J_{18Z,19}$ = 17.1, $^3J_{18E,19}$ = $^3J_{19,20}$ = 10.0 Hz, H-19), 5.67 (1H, d, $^3J_{20,21}$ = 1.6 Hz, H-21), 5.45 (1H, dd, $^3J_{18Z,19}$ = 17.1, $^2J_{18E,18Z}$ = 2.1 Hz, H-18*Z*), 5.35 (1H, dd, $^3J_{18E,19}$ = 10.0, $^2J_{18E,18Z}$ = 2.1 Hz, H-18*E*), 5.23 (1H, dd, $^3J_{3,14S}$ = 11.9, $^3J_{3,14R}$ = 3.8 Hz, H-3), 5.09 (1H, m, H-5α), 3.20−2.85 (5H, m, H-5*β*, H-6α, H-6*β*, H-15, H-20), 2.63 (1H, dt, $^2J_{14R,14S}$ = 13.2, $^3J_{3,14R}$ = 3.8, $^3J_{14R,15}$ = 3.8, H-14*proR*), 1.62 (1H, td, $^3J_{14S,15}$ = $^2J_{14R,14S}$ = 13.2, $^3J_{3,14S}$ = 11.9, H-14*proS*); ^{13}C NMR spectral data, the same as those reported by Heckendorf et al.[24]

***O′,O′,O′,O′*-Tetraacetyl-4-(4′′-bromobenzyl)strictosidine (3c) from 3a.** To a solution of strictosidine hydrochloride (**3a**·HCl, 0.27 g, 0.5 mmol) in MeCN (3.0 mL) 4-bromobenzyl chloride (0.1 g, 0.5 mmol) and Dowex-1 ion-exchange resin in the hydroxy ion form (0.5 g) was added and stirred at room temperature for 2 h. Then the resin was filtered and washed with acetonitrile (5 mL), the combined filtrate was dried, and the solvent was evaporated. The 4-(4′-bromobenzyl)strictosidine (**3**, R = H, Y = 4′-bromobenzyl, 0.17 g, 0.25 mmol) was stirred at room temperature for 2 h. The reaction mixture was poured onto ice (10 g), extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layer was washed with molar aqueous HCl (10 mL), 5% aqueous Na_2CO_3 solution (10 mL), H_2O (2 × 10 mL), dried, and the solvent evaporated. The *O′,O′,O′,O′*-tetraacetyl(4′′-bromobenzyl)strictosidine (**3c**) was obtained as a pale yellow solid (0.19 g, 51% calculated from **3a**, R_f 0.84); *anal*. C 57.69%, H 5.31%, N 3.12%, Br 9,13%, calcd for $C_{42}H_{47}N_2O_{13}Br$, C 58.11%, H 5.46%, N 3.23%, Br 9.21%; ^{1}H NMR (C_6D_6, 400 MHz) δ 7.98 (1H, br s, H-1), 7.65 (1H, m, H-9), 7.51 (2H, d, $^3J_{2''3''}$ = $^3J_{5''6''}$ = 8.5 Hz, H-3′′,5′′), 7.44 (1H, d, $^4J_{15,17}$ = 1.9, Hz, H-17), 7.3−7.2 (3H, m, H-10, H-11, H-12), 7.20 (2H, d, $^3J_{2''3''}$ = $^3J_{5''6''}$ = 8.5 Hz, H-2′′,6′′), 5.55 (1H, ddd, $^3J_{18Z,19}$ = 17.2, $^3J_{18E,19}$ = 10.4, $^3J_{19,20}$ = 9.4 Hz, H-19), 5.5−5.3 (3H, m, H-2′,3′,4′), 5.36 (1H, d, $^3J_{20,21}$ = 3.1 Hz, H-21), 5.01 (1H, dd, $^3J_{18E,19}$ = 10.4, $^2J_{18E,18Z}$ = 1.6 Hz, H-18*E*), 4.89 (1H, dd, $^3J_{18Z,19}$ = 17.2, $^2J_{18E,18Z}$ = 1.6 Hz, H-18*Z*), 4.78 (1H, d, $^3J_{1',2'}$ = 8.0 Hz, H-1′), 4.36 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'a}$ = 3.5 Hz, H-6′a), 3.99 (1H, dd, $^3J_{3,14R}$ = 8.7, $^3J_{3,14S}$ = 4.2 Hz, H-3), 3.94 (1H, dd, $^2J_{6'a,6'b}$ = 12.5 Hz, H-6′b), 3.67 (1H, d, $^2J_{NCHa,NCHb}$ = 13.2 Hz, Ha-benzyl-CH_2), 3.55 (1H, d, $^2J_{NCHa,NCHb}$ = 13.2 Hz, Hb-benzyl-CH_2), 3.30 (3H, s, OCH_3), 3.23 (1H, tdd, $^3J_{15,20}$ = $^3J_{14R,15}$ = 5.8; $^3J_{14S,15}$ = 4.2; $^4J_{15,17}$ = 1.9 Hz, H-15), 3.12 (1H, m, Hz, H-5′), 2.97 (1H, ddd, $^2J_{5\alpha,5\beta}$ = 13.3, $^3J_{5\beta,6\alpha}$ = 10.6, $^3J_{5\beta,6\beta}$ = 4.5 Hz, H-5*β*), 2.81 (1H, ddd, $^3J_{19,20}$ = 9.4; $^3J_{15,20}$ = 5.8, $^3J_{20,21}$ = 3.1 Hz, H-20), 2.80 (1H, ddd, $^2J_{6\alpha,6\beta}$ = 15.5, $^3J_{5\beta,6\alpha}$ = 10.6, $^3J_{5\alpha,6\alpha}$ = 5.3 Hz, H-6α), 2.71 (1H, ddd, $^2J_{5\alpha,5\beta}$ = 13.3, $^3J_{5\alpha,6\alpha}$ = 5.3, $^3J_{5\alpha,6\beta}$ = 1.4 Hz, H-5α), 2.29 (1H, ddd, $^2J_{6\alpha,6\beta}$ = 15.5, $^3J_{5\beta,6\beta}$ = 4.5, $^3J_{5\alpha,6\beta}$ = 1.4 Hz, H-6*β*), 2.27 (1H, dt, $^2J_{14R,14S}$ = 14.3, $^3J_{3,14S}$ = $^3J_{14S,15}$ = 4.2 Hz, H-14*S*), 1.83 (1H, ddd, $^2J_{14R,14S}$ = 14.3, $^3J_{3,14R}$ = 8.7, $^3J_{14R,15}$ = 5.8 Hz, H-14*R*), 1.80, 1.76, 1.69, 1.66 (each 3H, s, CH_3CO). The assignments were supported by a COSY spectrum. Some coupling constants were obtained from selective TOCSY measurements. ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 170.3, 169.4, 169.1 (each CH_3CO), 167.3 (C-22), 150.7 (C-17), 139.1 (C-1′′), 135.9a (C-2), 135.4a (C-13), 133.2 (C-19), 131.3c (C-3′′,5′′), 130.9c (C-2′′,6′′), 127.2 (C-8), 121.3 (C-11), 120.5 (C-18), 120.7 (C-4′′), 119.1 (C-10), 118.0 (C-9), 111.7 (C-16), 110.9 (C-12), 107.7 (C-7), 96.4 (C-21), 95.9 (C-1′), 72.3b (C-3′), 72.2b (C-5′), 70.7 (C-2′), 68.2 (C-4′), 61.6 (C-6′), 58.6 (C-3), 57.0 (CH_2-benzyl), 51.3 (CH_3O), 44.7 (C-20), 42.2 (C-5), 34.4 (C-14), 28.8 (C-15), 20.8, 20.7, 20.6, 20.2 (each CH_3CO), 16.6 (C-6); a, b, c, revised assignment is also possible. ^{13}C−^{1}H coupling constants in Hertz (the magnitude and the sign of the coupling constants were determined from the displacement of the signals in the

HETLOCK spectrum[15]): $^3J_{C15,H3} = +3.2$, $^3J_{C3,H15} = +5.5$, $^3J_{C20,H18Z} = +6.3$, $^3J_{C20,H18E} = +11.6$, $^2J_{C20,H21} = +0.3$, $^3J_{C15,H19} = +5.1$, $^2J_{C20,H15} = -7.1$, $^2J_{C15,H20} = -3.5$, $^2J_{C15,H14S} = -5.0$, $^2J_{C3,H14S} = -2.6$, $^2J_{C3,H14R} = -6.0$, $^2J_{C14,H3} = -4.0$, $^2J_{C14,H15} = -5.3$. The cross-peak intensities of the NOESY spectrum were obtained from volume integration by the XWINNMR program. The intensity of the NOE interaction corresponding to 3.3 Å distance of two hydrogens were calculated by the two independent spin approximation from the known 2.5 Å distance of H-1′ and H-5′ hydrogens and from the measured cross-peak intensity of this interaction. NOEs larger and smaller than the calculated value are denoted as strong (s) and weak (w), respectively. List of NOESY cross-peaks: H-1, H-3 s, H-12 w, H-14*proS* w, H-15 s; H-3, H-14*proS* s, H-14*proR* w, H-15 s, H-20 w, Ha-benzyl-CH_2 s, Hb-benzyl-CH_2 w; H-5α, H-5*β* s, H-6*β* w, Hb-benzyl-CH_2 s; H-5*β*, H-5α s, H-6*β* s, H-14*proR* s; H-6α, H-6*β* s, H-9 w, Ha-benzyl-CH_2 w, Hb-benzyl-CH_2 s; H-6*β*, H-5*β* s, H-6α s, H-9 w; H-9, H-6α w, H-6*β* w, H-10 s; H-14*proR*, H-3 w, H-5*β* s, H-14*proS* s, H-15 w, H-20 w; H-14*proS*, H-3 s, H-14*proR* s, H-15 w; H-15, H-1 s, H-3 s, H-14*proR* w, H-14*proS* w, H-20 s, H-2″ w, Ha-benzyl-CH_2 w; H-18*E*, H-18*Z* s, H-19 s; H-18*Z*, H-18*E* s, H-20 s; H-19, H-18*E* s, H-20 w; H-20, H-3 w, H-14*proR* w, H-15 s, H-18*Z* s, H-19 w, H-21 s; H-21, H-20 s, H-18*Z* w; Ha-benzyl-CH_2, H-3 s, H-6α w, H-15 w, Hb-benzyl-CH_2 s, H-2″ 2.6 s; Hb-benzyl-CH_2, H-5α 2.3 s, H-6α 2.3 s, Ha-benzyl-CH_2 s, H-2″ s.

***O′,O′,O′,O′*-Tetraacetyl-4-(4″-bromobenzyl)vincoside (3d).** N_b-4′-bromobenzyltryptaminium chloride (**1b**·HCl, 0.25 g, 0.06 mmol) was dissolved in H_2O (3.0 mL) and, after the addition of 5% aqueous Na_2CO_3 solution (1 mL), was extracted with $CHCl_3$ (3 × 3.0 mL). The combined $CHCl_3$ solution was washed with H_2O (2 × 3 mL), dried, and the solvent evaporated. The residue was taken up in C_6H_6 (5.0 mL), *O*,*O*,*O*,*O*-tetraacetylsecologanin (**2b**, 0.34 g, 0.6 mmol) was added, and the reaction mixture refluxed for 3 h. The solvent was evaporated, and the residue crystallized from MeOH−H_2O (1:1, 1.5 mL). *O′*,*O′*,*O′*,*O′*-Tetraacetyl-4-(4″-bromobenzyl)vincoside (**3d**) was obtained as colorless crystals (0.48 g, 91%, R_f 0.86, mp 159−160 °C, $[\alpha]_D^{25}$ −63° (*c* 0.1, MeOH); IR (KBr), cm^{-1}: 1715, 1680 (*ν*C=O); *anal*. C 57.53%, H 5.35%, N 3.17%, Br 9.15%, calcd for $C_{42}H_{47}N_2O_{13}Br$, C 58.11%, H 5.46% N 3.23%, Br 9.21%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.10 (1H, br s, H-1), 7.51 (1H, dd, $^3J_{9,10} = 8.3$, $^4J_{9,11} = 1.4$ Hz, H-9), 7.49 (2H, d, $^3J_{2″,3″}$ Hz = $^3J_{5″,6″} = 8.4$ Hz, H-3″,5″), 7.32 (1H, dd, $^3J_{11,12} = 7.9$, $^4J_{10,12} = 1.2$ Hz, H-12), 7.31 (1H, d, $^4J_{15,17} = 1.4$ Hz, H-17), 7.24 (2H, d, $^3J_{2″,3″}$ Hz = $^3J_{5″,6″} = 8.4$ Hz, H-2″,6″), 7.14 (1H, ddd, $^3J_{11,12} = 7.9$, $^3J_{10,11} = 7.1$, $^4J_{9,11} = 1.4$ Hz, H-11), 7.10 (1H, ddd, $^3J_{9,10} = 8.3$, $^3J_{10,11} = 7.1$, $^4J_{9,11} = 1.4$ Hz, H-10), 5.53 (1H, ddd, $^3J_{18Z,19} = 17.2$, $^3J_{18E,19} = 10.2$, $^3J_{19,20} = 9.5$ Hz, H-19), 5.30−5.08 (3H, m, H-2′,3′,4′), 5.18 (1H, dd, $^3J_{18E,19} = 10.2$, $^2J_{18E,18Z} = 1.8$ Hz, H-18*E*), 5.16 (1H, d, $^3J_{20,21} = 4.0$ Hz, H-21), 4.88 (1H, d, $^3J_{1′,2′} = 8.1$ Hz, H-1′), 4.86 (1H, dd, $^3J_{18Z,19} = 17.2$, $^2J_{18E,18Z} = 1.8$ Hz, H-18*Z*), 4.35 (1H, dd, $^2J_{6′a,6′b} = 12.4$, $^3J_{5′,6′a} = 4.1$ Hz, H-6′a), 4.24 (1H, dd, $^2J_{6′a,6′b} = 12.4$, $^3J_{5′,6′b} = 2.3$ Hz, H-6′b), 3.76 (1H, m, H-5′), 3.76 (1H, d, $^2J_{NCHa,NCHb} = 13.1$ Hz, Ha-benzyl-CH_2), 3.61 (3H, s, OCH_3), 3.59 (1H, $^2J_{NCHa,NCHb} = 13.1$ Hz, Hb-benzyl-CH_2), 3.48 (1H, dd, $^3J_{3,14S} = 9.4$, $^3J_{3,14R} = 5.5$ Hz, H-3), 3.41 (1H, ddd, $^2J_{5α,5β} = 13.7$, $^3J_{5α,6β} = 11.8$, $^3J_{5α,6α} = 4.8$ Hz, H-5α), 3.16 (1H, ddd, $^2J_{5α,5β} = 13.7$, $^3J_{5β,6β} = 5.7$, $^3J_{5β,6α} = 1.0$ Hz, H-5*β*), 3.06 (1H, dtd, $^3J_{14R,15} = 9.5$, $^3J_{14S,15} = {}^3J_{15,20} = 5.3$, $^4J_{15,17} = 1.4$ Hz, H-15), 2.96 (1H, ddd, $^2J_{6α,6β} = 16.2$, $^3J_{5α,6β} = 11.8$, $^3J_{5β,6β} = 5.7$ Hz, H-6*β*), 2.57 (1H, ddd, $^2J_{6α,6β} = 16.2$, $^3J_{5α,6α,} = 4.8$, $^3J_{5β,6α} = 1.0$ Hz, H-6α), 2.30 (1H, ddd, $^2J_{14R14S} = 14.3$, $^3J_{14R,15} = 9.5$ Hz, $^3J_{3,14R} = 5.5$, H-14*proR*), 2.12, 2.05, 2.04, 1.96 (each 3H, s, CH_3CO), 2.00 (1H, ddd, $^3J_{19,20} = 9.5$, $^3J_{15,20} = 5.3$, $^3J_{20,21} = 4.0$ Hz, H-20), 1.52 (1H, ddd, $^2J_{14R14S} = 14.3$, $^3J_{3,14S} = 9.4$, $^3J_{14S,15} = 5.3$ Hz, H-14*proS*); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 170.8, 170.2, 169.4, 169.1 (each CH_3CO), 167.4 (C-22), 150.7 (C-17), 138.9 (C-1″), 135.7 (C-13), 134.8 (C-2), 133.7 (C-19), 131.4c (C-3″,5″), 131.3c (C-2″,6″), 127.4 (C-8), 121.3 (C-11), 120.8 (C-4″), 119.6 (C-18), 119.2 (C-10), 118.0 (C-9), 111.7 (C-16), 110.8 (C-12), 106.8 (C-7), 96.2 (C-21), 95.8 (C-1′), 72.5b (C-3′), 72.1b (C-5′), 70.7 (C-2′), 68.2 (C-4′), 61.7 (C-6′), 56.4 (CH_2), 51.3a (OCH_3), 51.2a (C-3), 44.3 (C-5), 42.4 (C-20), 33.8 (C-14), 26.4 (C-15), 20.8, 20.6, 20.5, 20.2 (each CH_3-CO); 17.1 (C-6); a, b, c, revised assignment is also possible. NOESY cross-peaks (s, strong; m, medium; w, weak; v, very weak): H-1, H-3 w, H-12 w, H-15 w; H-3, H-14*proR* w, H-14*proS* v, H-15 w, H-18*Z* w, H-20 m, H-2′ m, Hb-benzyl-CH_2 m; H-5α, H-5*β* s, H-6α v, H-14*proS* v, H-15 v; H-5*β*, H-5α s, H-6*β* v, Ha-benzyl-CH_2 w; H-6α, H-5α v, H-6*β* s, H-9 w; H-6*β*, H-5*β* v, H-6α s, H-9 v, Ha-benzyl-CH_2 v, Hb-benzyl-CH_2 v; H-9, H-6α w, H-6*β* v, H-10 s; H-10, H-9 s; H-11, H-12 s; H-12, H-1 w, H-11 s; H-14*proR*, H-3 v, H-14*proS* s, H-15 v, H-19 w; H-14*proS*, H-3 v, H-5α v, H-14*proR* s, H-15 w; H-15, H-3 w, H-5α v, H-14*proR* v, H-14*proS* w, H-20 s, H-2″ m; H-18*E*, H-18*Z* s, H-19 s; H-18*Z*, H-18*E* s, H-19 w, H-20 s; H-19, H-14*proR* w, H-18*E* s, H-18*Z* w, H-20 v; H-20, H-3 m, H-15 s, H-18*Z* s, H-19 v, H-21 s, H-2″ w; H-21, H-20 s, H-1′ m; Ha-benzyl-CH_2, H-5*β* w, H-6*β* w, Hb-benzyl-CH_2 s, 2″-H m; Hb-benzyl-CH_2, H-3 m, H-6*β* v, Ha-benzyl-CH_2 s, H-2″ m.

***O′,O′,O′,O′*-Tetraacetyl-18,19-dihydrovincosamide (4b) Prepared from 3d.** *O′*,*O′*,*O′*,*O′*-Tetraacetyl-4-(4″-bromobenzyl)vincoside (**3d**, 0.43 g, 0.5 mmol) was dissolved in absolute MeOH (10.0 mL) and hydrogenated in the presence of 10% Pd on charcoal at room temperature for 30 min, then the catalyst was filtered, and the solution stirred for 2 h. After evaporation of the solvent *O′*,*O′*,*O′*,*O′*-tetraacetyl-18,19-dihydrovincosamide (**4b**) was obtained as a pale yellow amorphous solid (0.28 g, 84%, R_f 0.84); *anal*. C 60.61%, H 5.85%, N 4.02%, calcd for $C_{34}H_{40}N_2O_{12}$, C 61.05%, H 6.03%, N 4.19%; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.00 (1H, br s, H-1), 7.51 (1H, dd, $^3J_{9,10} = 7.5$, $^4J_{9,11} = 1.2$ Hz, H-9), 7.42 (1H, d, $^4J_{15,17} = 2.5$ Hz, H-17), 7.34 (1H, dd, $^3J_{11,12} = 8.0$, $^4J_{10,12} = 1.2$ Hz, H-12), 7.19 (1H, ddd, $^3J_{11,12} = 8.0$, $^3J_{10,11} = 7.5$, $^4J_{9,11} = 1.2$, Hz, H-11), 7.12 (1H, $^3J_{10,11} =$ td, 7.5, $^3J_{9,10} = 7.5$, $^4J_{10,12} = 1.2$ Hz, H-10), 5.40 (1H, d, $^3J_{20,21} = 1.9$ Hz, H-21), 5.26 (1H, t, $^3J_{2′,3′} = {}^3J_{3′,4′} = 9.8$ Hz, H-3′), 5.14 (1H, m, H-5α), 5.10 (1H, t, $^3J_{3′,4′} = {}^3J_{4′,5′} = 9.8$ Hz, H-4′), 5.02 (1H, dd, $^3J_{1′,2′} = 8.0$, $^3J_{2′,3′} = 9.8$ Hz, H-2′), 4.93 (1H, d, $^3J_{1′,2′} = 8.0$ Hz, H-1′), 4.83 (1H, m H-3), 4.34 (1H, dd, $^3J_{6′a,6′b} = 12.6$, $^3J_{5′,6′a} = 3.9$ Hz; H-6′a), 4.15 (1H, dd, $^3J_{6′a,6′b} = 12.6$, $^3J_{5′,6′b} = 2.0$ Hz, H-6′b), 3.78 (1H, ddd, $^3J_{4′,5′} = 9,8$, $^3J_{5′,6′a} = 3.9$, $^3J_{5′,6′b} = 2.0$ Hz, H-5′), 2.96 (1H, dddd, $^3J_{14S,15} = 13.0$, $^3J_{15,20} = 6.2$, $^3J_{14R,15} = 3.5$, $^4J_{15,17} = 2.5$ Hz, H-15), 2.88 (1H, m, H-5*β*), 2.80 (2H, H_2-6), 2.23 (1H, dt, $^2J_{14R,14S} = 12.7$, $^3J_{3,14R} = {}^3J_{14R,15} = 3.6$ Hz, H-14*proR*), 2.11, 2.04, 2.02, 1,98 (each 3H, s, CH_3-CO),1.90 (1H, dddd, $^3J_{19b,20} = 9.8$, $^3J_{15,20} = 6.2$, $^3J_{19a,20} = 5.0$, $^3J_{20,21} = 1.9$ Hz, H-20), 1.66 (1H, q, $^2J_{14R,14S} = {}^3J_{3,14S} = {}^3J_{14S,15} = 12.7$ Hz, H-14*proS*), 1.36 (1H, dqd, $^2J_{19a,19b} = 14.3$, $^3J_{18,19} = 7.5$, $^3J_{19a,20} = 5.0$ Hz, H-19a), 1.13 (1H, ddq, $^2J_{19a,19b} = 14.3$; $^3J_{19b,20} = 9.8$; $^3J_{18,19} = 7.5$ Hz, H-19b), 0.95 (3H, t, $^3J_{18,19} = 7.5$ Hz, H-18). Further ^{1}H coupling constants determined in C_6D_6: $^5J_{3,6α} = 2.3$, $^2J_{5α,5β} = 12.3$, $^3J_{5α,6α} = 4.8$, $^3J_{5α,6β} = 1.3$, $^3J_{5β,6α} = 12,3$, $^3J_{5β,6β} = 3.3$, $^2J_{6α,6β} = 14.5$ Hz; ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 170,6, 169.9, 169.8, 169.5 (each CH_3CO), 163.3 (s, C-22), 146.7 (d, C-17), 136.4 (s, C-13), 132.9 (s, C-2), 126.7 (s, C-8), 122.1 (d, C-11), 119.7 (d, C-10), 118.3 (d, C-9), 111.0 (d, C-12), 109.4 (s, C-16), 108.6 (s, C-7), 95.9 (d, C-21), 95.0 (d, C-1′), 72.3 (d, C-3′), 72.1 (d, C-5′), 70.6 (d, C-2′), 68.3 (d, C-4′), 61.8 (t, C-6′), 53.2 (d, C-3), 39.5 (t, (C-5), 38.0 (d, C-20), 31.1 (t, C-14), 27.4 (d, C-15), 21.0 (t, C-6), 20.7−20.5 (*C*H_3CO), 17.6 (t, C-19), 11.9 (q, C-18); NOESY cross-peaks H-3, H-14*proR* w, H-15 w; H-5α, H-5*β* s, H-6α w; H-5*β*, H-5α s, H-6*β* w; H-6α, H-5α w, H-6*β* s; H-6*β*, H-5*β* w, H-6αs; H-14*proR*, H-3 w, H-14*proS* s; H-14*proS*, H-14*proR* s; H-15, H-3 w, H-20 m; H_3-18, H-21 s, H_2-19 m; H_2-19, H_3-18 m, H-20 m; H-20, H-15 m, H_2-19 m, H-21 m; H-21, H_3-18 s, H-20 m, H-1′ m.

***O′,O′,O′,O′*-Tetraacetyl-18,19-dihydrovincosamide (4b) Prepared from Vincosamide (4a).** In a mixture of absolute pyridine (2.0 mL) and $(Ac)_2O$ (0.8 mL, 8.0 mmol) vincosamide (**4a**, 0.25 g, 0.4 mmol) was stirred at room temperature for 2 h, the reaction mixture was poured on to ice (5.0 g), and extracted with EtOAc (3 × 10 mL). The organic layer was washed with 5% aqueous Na_2CO_3 solution (2 × 10 mL) and H_2O (10 mL), dried with anhydrous Na_2SO_4, and the solvent evaporated. The *O′*,*O′*,*O′*,*O′*-tetraacetylvincosamide (**4c** = **4**, R = acetyl, X = vinyl) was obtained as a pale yellow powder (0.26 g, single spot, R_f 0.86) and was used immediately.

O′,*O′*,*O′*,*O′*-Tetraacetylvincosamide (**4c**) was dissolved in absolute methanol (3.0 mL) and hydrogenated in the presence

of 10% Pd on charcoal at room temperature for 20 min. After filtration of the catalyst and evaporation of the solvent, *O′*,*O′*,*O′*,*O′*-tetraacetyl-18,19-dihydrovincosamide (**4b**) was obtained as a pale yellow amorphous powder (0.16 g, 47% calculated from **4a**, single spot, R_f 0.84). The spectroscopic data established the identity to *O′*,*O′*,*O′*,*O′*-tetraacetyl-18,19-dihydrovincosamide (**4b**) prepared from *O′*,*O′*,*O′*,*O′*-tetraacetyl-4-(4″-bromobenzyl)vincoside (**3d**) (see above).

Strictosamide (5a). Strictosidine hydrochloride[8] (**3a**·HCl, 0.27 g, 0.5 mmol) was stirred in 5% aqueous Na_2CO_3 solution at 70 °C for 2 h. The cooled reaction mixture was extracted with EtOAc (3 × 10 mL), the combined organic layer was washed with H_2O (2 × 5 mL) and dried, and the solvent was evaporated. Strictosamide (**5a**) was obtained as a pale yellow solid (0.19 g, 80%, single spot, R_f 0.30); ^{1}H NMR (CD_3OD, 250 MHz) δ 7.55 (1H, dd, $^3J_{11,12} = 7.3$, $^4J_{10,12} = 1.2$ Hz, H-12), 7.54 (1H, d, $^4J_{15,17} = 2.4$ Hz, H-17), 7.49 (1H, dd, $^3J_{9,10} = 8.0$, $^4J_{9,11} = 1.2$ Hz, H-9), 7.24 (1H, td, $^3J_{10,11} = {}^3J_{11,12} = 7.3$, $^4J_{9,11} = 1.2$ Hz, H-11), 7.15 (1H, ddd, $^3J_{9,10} = 8.0$, $^3J_{10,11} = 7.3$, $^4J_{10,12} = 1.2$ Hz, H-10), 5.82 (1H, dt $^3J_{18Z,19} = 17.1$, $^3J_{18E,19} = {}^3J_{19,20} = 10.0$ Hz, H-19), 5.57 (1H, d, $^3J_{20,21} = 1.8$ Hz, H-21), 5.53 (1H, dd, $^3J_{18Z,19} = 17.1$, $^2J_{18E,18Z} = 2.1$ Hz, H-18*Z*), 5.48 (1H, dd, $^3J_{18E,19} = 10.0$, $^2J_{18E,18Z} = 2.1$ Hz, H-18*E*), 5.23 (1H, dd, $^3J_{3,14R} = 2.0$, $^3J_{3,14S} = 6.1$ Hz, H-3), 5.11 (1H, m, H-5β), 4,74 (1H, d, $^3J_{1',2'} = 7.9$ Hz, H-1′), 3.97 (1H, $^2J_{6'a,6'b} = 11.7$, $^3J_{5',6'a} = 1.7$ Hz, H-6′a), 3.65 (1H, $^2J_{6'a,6'b} = 11.7$, $^3J_{5',6'b} = 5.2$ Hz, H-6′b), 3.20−3.50 (4H, m, H-2′,3′,4′,5′), 2.80−3.35 (5H, m, H-5α, H-6α, H-6β, H-15, H-20), 2.63 (1H, ddd, $^2J_{14R,14S} = 14.0$, $^3J_{14R,15} = 4.3$, $^3J_{3,14R} = 2.0$ Hz, H-14*proR*), 2.20 (1H, td, $^2J_{14R,14S} = {}^3J_{14S,15} = 14.0$, $^3J_{3,14S} = 6.1$ Hz, H-14*proS*; ^{13}C NMR spectral data are comparable to those reported by Heckendorf et al.[24]

***O′*,*O′*,*O′*,*O′*-Tetraacetyl-18,19-dihydrostrictosamide (5b) from 5a.** Strictosamide (**5a**, 0.14 g, 0.25 mmol) was stirred in a mixture of absolute pyridine (1.5 mL) and $(Ac)_2O$ (0.6 mL) at room temperature for 2 h, then poured onto ice (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layer was washed with molar aqueous HCl (10 mL), 5% aqueous Na_2CO_3 solution (10 mL), H_2O (2 × 10 mL) and dried. After evaporation of the solvent *O′*,*O′*,*O′*,*O′*-tetraacetylstrictosamide (**5c** = **5**, R = acetyl, X = vinyl) was obtained as a yellow solid (0.16 g, single spot, R_f 0.87). The sample was used immediately for preparation of **5b**.

O′,*O′*,*O′*,*O*-Tetraacetylstrictosamide **5c** (0.15 g, 0.23 mmol) was dissolved in MeOH (10 mL), and hydrogenated in the presence of 10% Pd on charcoal (0.10 g) at room temperature for 30 min. After filtration of the catalyst and evaporation of the solvent, *O′*,*O′*,*O′*,*O′*-tetraacetyl-18,19-dihydrostrictosamide (**5b**) was obtained as a pale yellow amorphous solid (0.14 g, 70%, single spot, R_f 0.84); *anal*. C 60.72%, H 5.76%, N 3.97%, calcd for $C_{34}H_{40}N_2O_{12}$, C 61.05%, H 6.03%, N 4.19%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.35 (1H, br s, H-1), 7.41 (1H, dd, $^3J_{9,10} = 7.9$, $^4J_{9,11} = 1.2$ Hz, H-9), 7.38 (1H, dd, $^3J_{11,12} = 8.2$, $^4J_{10,12} = 1.2$ Hz, H-12), 7.36 (1H, d, $^4J_{15,17} = 2.6$ Hz, H-17), 7.18 (1H, ddd, $^3J_{11,12} = 8.2$, $^3J_{10,11} = 7.1$, $^4J_{9,11} = 1.2$ Hz, H-11), 7.09 (1H, ddd, $^3J_{9,10} = 7.9$, $^3J_{10,11} = 7.1$, $^4J_{10,12} = 1.2$ Hz, H-10), 5.38 (1H, d, $^3J_{20,21} = 1.8$ Hz, H-21), 5.12 (1H, m, H-3′), 5.02 (1H, Hz, ddd, $^2J_{5\alpha,5\beta} = 13.0$, $^3J_{5\beta,6\beta} = 6.0$, $^3J_{5\beta,6\alpha} = 1.0$ Hz, H-5β), 5.01 (1H, dddd, $^3J_{3,14S} = 5.5$, $^3J_{3,14R} = 2.8$, $^5J_{3,6\beta} = 2.5$, $^5J_{3,6\alpha} = 1.0$ Hz, H-3), 4.98 (1H, m, H-4′), 4.75 (2H, m, H-1′, H-2′), 4.27 (1H, dd, $^3J_{6'a,6'b} = 12.6$, $^3J_{5',6'a} = 3.9$ Hz, H-6′a), 4.10 (1H, dd, $^3J_{6'a,6'b} = 12.6$, $^3J_{5',6'b} = 2.2$ Hz, H-6′b), 3.69 (1H, m, H-5′), 3.03 (1H, m, H-5α), 2.96 (1H, dtd, $^3J_{14S,15} = 13.6$, $^3J_{15,20} = {}^3J_{14R,15} = 5.0$, $^4J_{15,17} = 2.6$ Hz, H-15), 2.70 (2H, m, H_2-6), 2.27 (1H, ddd, $^2J_{14R,14S} = 13.6$, $^3J_{14R,15} = 4.9$, $^3J_{3,14R} = 2.8$ Hz, H-14*proR*), 2.18 (1H, td, $^2J_{14R,14S} = {}^3J_{14S,15} = 13.6$ Hz, $^3J_{3,14S} = 5.5$ Hz, H-14*proS*), 2.07, 1.99, 1.88, 1.20 (each 3H, s, CH_3CO). 1.82 (1H, dtd, $^3J_{19b,20} = 9.7$, $^3J_{19a,20} = {}^3J_{15,20} = 5.2$, $^3J_{20,21} = 1.8$ Hz, H-20), 1.54 (1H, dqd, $^2J_{19a,19b} = 14.2$, $^3J_{18,19} = 7.5$, $^3J_{19a,20} = 5.2$ Hz, H-19a), 1.22 (1H, ddq, $^2J_{19a,19b} = 14.2$, $^3J_{19b,20} = 9.7$, $^3J_{18,19} = 7.5$ Hz, H-19b), 1.02 (3H, t, $^3J_{18,19} = 7.5$ Hz, H_3-18); further ^{1}H coupling constants determined in C_6D_6, $^5J_{3,6\alpha} = 1.0$, $^5J_{3,6\beta} = 2.5$, $^2J_{5\alpha,5\beta} = 13.0$, $^3J_{5\alpha,6\alpha} = 5.2$, $^3J_{5\alpha,6\beta} = 12.5$, $^3J_{5\beta,6\alpha} = 1.0$, $^3J_{5\beta,6\beta} = 6.0$, $^2J_{6\alpha,6\beta} = 15.3$, $^3J_{1',2'} = 8.2$, $^3J_{2',3'} = 9.9$, $^3J_{3',4'} = 9.5$, $^3J_{4',5'} = 9.9$; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 170.0, 169.5, 169.0 (each CH_3CO), 164.9s (C-22), 146.9d (C-17), 136.1s (C-13), 132.8 (C-2), 127.5s (C-8), 122.2d (C-11), 119.8d (C-10), 118.0d (C-9), 111.3d (C-12), 110.7s (C-16), 108.5s (C-7), 95.1d (C-21), 93.8 (C-1′), 72.1, 72.0 (C-3′, C-5′), 68.3 (C-4′), 61.7 (C-6′), 70.0 (C-2′), 53.5d (C-3), 43.7t (C-5), 37.9d (C-20), 25.7t (C-14), 24.8d (C-15), 21.0t (C-6), 20.7, 20.6, 20.5, 19.2 (CH_3CO of acetyl), 17.6t (C-19), 12.2q (C-18); NOESY cross-peaks (in C_6D_6), H-3, H-5α s, H-5β w, H-14*proR* m, H-14*proS* m; H-5α, H-3 s, H-5β s, H-6α w; H-5β, H-3 w, H-5α s; H-6α, H-6β s, H-9 m; H-6β, H-6α s, H-9 w; H-9, H-6α m, H-6β w, H-10 m, 2′-OAc m; H-10, H-9 m, H-11 m; H-11, H-10 m, H-12 m, 2′-OAc v; H-12, H-11 m, H-14*proS* w; H-14*proS*, H-3 m, H-12 w, H-14*proR* m; H-14*proR*, H-3 m, H-14*proS* m, H-15 w; H-15, H-14*proR* w, H-20 s, 2′-OAc w; H-17, H-1′ w; H_3-18, H-19a m, H-19b w, H-20 m, H-21 s; H-19a, H_3-18 m, H-19b s; H-19b, H_3-18 m, H-19a m, H-20w, H-21w; H-20, H-15 s, H_3-18 m, H-19b w, H-21 s; H-21, H_3-18 m, H-19b w, H-20 s, H-1′ m.

***O′*,*O′*,*O′*,*O′*-Tetraacetyl-18,19-dihydrostrictosamide (5b) from 3c.** *O′*,*O′*,*O′*,*O′*-Tetraacetyl-4-(4″-bromobenzyl)strictosidine (**3c**, 0.17 g, 0.2 mmol) was dissolved in absolute MeOH and hydrogenated in the presence of 10% Pd on charcoal (0.05 g) at room temperature for 30 min. Triethylamine (0.07 mL, 0.5 mmol) was added and the reaction mixture refluxed for 1 h. After evaporation of the solvent, the residue was dissolved in EtOAc (10 mL) and extracted with H_2O (2 × 5 mL). The organic phase was dried and the solvent evaporated. *O′*,*O′*,*O′*,*O′*-Tetraacetyl-18,19-dihydrostrictosamide (**5b**) was obtained as a pale yellow amorphous solid (0.11 g, 84%, single spot, R_f 0.84). According to its spectroscopic data, the sample was identical to **5b** obtained from **5a**.

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References and Notes

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