Investigation of Pictet−Spengler Type Reactions of Secologanin with Histamine and Its Benzyl Derivative[†,⊥]

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The reaction of secologanin (**1**) (mainly in its tetraacetylated form **1a**) with histamine (**2**) and its benzyl derivative (**2b**) was investigated. With the benzylated amine (**2b**), the main product was the normal, tetraacetylated benzyl derivative of histeloside having the *R* configuration at the new center of chirality, C-1 (**5b**), with a small amount of an unidentified minor component (probably the 1*S* epimer **5a**). In a slightly acidic medium, the reaction with histamine (**2**) gave two products in an approximately 6:4 ratio. The main compound proved to be the normal, tetraacetylated derivative of the lactam histelosamide with *R* configuration at C-1 (**7b**), and the minor product was the tetraacetylisohisteloside with *S* configuration at the same C-1 center (**3a**). When the reaction was carried out under acid-free conditions, in addition to the epimeric pair of the normal tetraacetylated lactam (**7a**, **7b**) and the tetraacetylisohisteloside with 1*S* configuration (**3a**), tetraacetylneohistelosamide (**8b**) was also isolated, in which the cyclization took place at one of the cyclic nitrogens of the imidazole ring. Probably, this latter compound is an intermediate also in the formation of the normal isomers, but under slightly acidic conditions it rapidly isomerized into the normal alkaloid. The tendencies experienced previously in the tryptamine and dopamine series were observed also in the histamine series; that is, at C-1, the *R* configuration is favored over the *S* one, and lactamization is faster in the former than in the latter case. The structure of the products and their stereoschemistry were established by NMR spectroscopy.

It is well known, from the pioneering work of A. R. Battersby and his group, that secologanin (**1**) reacts with tryptamine and dopamine, giving strictosidine and vincoside, or deacetylisoipecoside and deacetylipecoside, respectively, which are parent compounds of the large class of terpenoid indole and ipecac alkaloids.[1,2] Recently, we investigated the regio- and stereoselectivity of these reactions in detail.[3−6] It now seems reasonable to presume that a similar reaction occurs between secologanin and the biogenic amine histamine.

A large number of alkaloids containing the imidazole ring have been isolated, which are, however, very different both in structure and in origin from the usual terpenoid indole and isoquinoline alkaloids.[7−9] These compounds were found both in plant families (Cactaceae, Euphorbiaceae, Orchidaceae, etc.) and in bacteria (e.g., *Aspergillus* species), fungi (e.g., *Streptomyces* and *Penicillium* species), and animal sources (mainly marine sponges). Many of these alkaloids could be derived formally or biogenetically from histidine or histamine. Some can even be supposed to form from histamine in a Pictet−Spengler reaction with an appropriate oxo compound (e.g., glochidine and glochidicine,[10,11] spinacine,[12,13] and spinaceamine[14]). However, products formed from secologanin and its derivatives have not been isolated. Of course, the question arises as to what is the reason for the absence of this type of alkaloid? Does histamine not react with secologanin, or is one of these reaction partners not available in plants containing the other partner, or is the enzyme catalyzing the reaction absent? Histamine has one active position for electrophilic substitution at a carbon atom, and, in addition, it also has a nitrogen atom of the imidazole ring as an alternative site for ring closure. Therefore, it would be expected to form both "normal" derivatives, such as those of tryptamine derivatives, and regioisomer "neo" compounds, in which N-3′ of the histamine unit is common in the two rings. Moreover, among dopamine derivatives, the reversibility of the reaction was observed, whereas in the tryptamine series this could not be demonstrated under similar reaction conditions. Such questions prompted us to investigate the reaction of secologanin with histamine (**2**) and its *N*-benzyl derivative (**2b**).

Results and Discussion

At first, the reactions were carried out in acetonitrile as a dipolar aprotic solvent, with the secologanin (**1**) used mainly in the form of its tetraacetyl derivative (**1a**), and histamine (**2**) and its benzyl derivative (**2b**) as the dihydrochloride salt. The histaminium salt was (partially) deprotonated by triethylamine.[15] With the benzyl derivative of histamine (**2b**), one main product, the tetraacetyl derivative of *N*-benzylhisteloside (**5b**), could be isolated from the reaction mixture together with about 10% of an impurity, which could be eliminated by chromatography, but was not obtained in sufficient quantity to establish its structure. This impurity was probably the benzylated 1*S* epimer (**5a**). To assign the configuration of the new center of chirality in the main product (**5b**), it was hydrogenated in the presence of palladium-charcoal with elimination of the benzyl and saturation of the vinyl group. Unfortunately, during this experiment, the acetyl groups were partially hydrolyzed, and to obtain a pure compound for analysis, the deacetylation was completed by treatment with methanolic sodium methanolate solution. Finally, the intermediate 14,15-dihydrohistelosamide (**7c**) obtained in this manner was reacetylated with the inclusion of an additional acetyl group at N-6 (**7d**). In this latter compound, the *R* configuration of C-1 was established un-

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Table 1. Chemical Shifts of Aromatic Protons in the Products of the Reactions[a]

compound	% in B	% in *C*	H-7	H-6	H-8
H3a	38	30	7.58		
H3b	<2	<2			
H4a	<2	<2			
H4b	<2	<2			
H7a	<2	8	7.53		
H7b	62	33	7.51		
H8a	<2	<2			
H8b	<2	29		6.72	7.42
H5a	10(?)				
H5b	90		7.49		
H6a	<2				
H6b	<2				

[a] In ppm, % = relative amount of isomers formed in the reaction, s = singlet, d = doublet. Reaction conditions in B: **2**·2HCl or **2b**·2HCl, **1a**, triethylamine, acetonitrile. Reaction conditions for C: **2**, **1a**, isopropanol.

equivocally by the coupling constants involving the H-10 atoms. As mild reaction conditions were applied during the lactamization and the subsequent transformations, no epimerization was expected at C-1 during these reactions; therefore it might be assumed that the configuration of C-1 was *R* also in the starting ester (**5b**).

The reaction of secologanin with histamine gave two main products, approximately in a 6:4 ratio. The lactam tetraacetylhistelosamide (**7b**) and the ester tetraacetylisohisteloside (**3a**) were separated by column chromatography. However, the formation of neo compounds could not be demonstrated. It was suspected that the proton associated with either triethylamine or one of the basic nitrogen atoms of the histamine was responsible for this phenomenon, as it is reported in the literature[16] that the initially formed neo compounds could easily be isomerized into the normal derivative in the presence of acid.

Therefore, the reaction was repeated with histamine base in 2-propanol, where the only proton source was the weak acidity of the solvent. From the reaction, which was stopped before completion, four coupled products could be isolated: in the normal series, the tetraacetylhistelosamide (**7b**) and its C-1 epimer (**7a**), tetraacetylsohisteloside (**3a**), and the neo compound tetraacetylneohistelosamide (**8b**). The reaction mixtures were separated by repeated column chromatography into pure individual components. Although the epimeric lactams **7a** and **7b** could not be separated, the former could be obtained by lactamization of **3a**, and the latter by the direct coupling reaction in the presence of the triethylammonium ion (see above).

We also tried to obtain the nonlactamized neo derivatives. Therefore, the coupling reaction was carried out with secologanin and histamine base in aqueous solution without any catalyst. Unfortunately, even under these conditions, only the lactam of the neo **R** series, i.e., neohistelosamide (**8c**) could be separated from the reaction mixture.

The relative amounts of the components of the crude product mixtures were estimated by the intensity of the low-field protons in the ^{1}H NMR spectrum of the histamine subunit (Table 1) and expressed as the percentage of the total amount of the products. The normal derivatives gave one singlet, while the neo compound gave two singlets in this region. Lactamization was followed by a decrease of the intensity of the singlet of the methoxycarbonyl group at about 3.5 ppm. Likewise, the presence of the vinyl and benzyl groups was established from the appropriate proton signals. Determination of the configuration of C-1 required stereochemical analysis (see later).

Table 2. Product Distribution in the Reactions in Percent

			N-unsubstituted					*N*-substituted			
			open		lactam	open + lactam	nor/neo 1*S*/1*R*		open	nor/neo	1*S*/1*R*
normal	1*S*	**3a**	38 *30*	**7a**	<2 *8*	38 *38*	100 *71*	38 *38*	**5a** 10 (?)	100	10 (?)
	1*R*	**3b**	<2 *<2*	**7b**	62 *33*	62 *33*			**5b** 90		
neo	1*S*	**4a**	<2 *<2*	**8a**	<2 *<2*	<2 *<2*	<2 *29*	62 *62*	**6a** <2	0	90
	1*R*	**4b**	<2 *<2*	**8b**	2 *29*	<2 *29*			**6b** <2		
open/lactam			38 *30*		62 *70*						

[a] Figures in *italics* were obtained in an acid-free medium (see text).

Table 3. Relative Orientation of H-1 and H-11 to H-10*ProR* and H-10*ProS*[a]

H-1	H-11	H-1	H-11	H-1	H-11	H-10	H-1	H-11	H-1	H-11	H-1	H-11
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] ap and sc indicate antiperiplanar and synclinal positions of the appropriate protons, respectively.

The chromatograms of the crude reaction mixtures combined with NMR data provided the product distribution of the coupling reactions (Table 2). The data supported the conclusions drawn from data of the analogous reactions in the tryptamine and dopamine series. In the reaction, the 1*R* epimer was favored over the 1*S* epimer, and its amount increased in the benzylated compound. Likewise, compounds of the **R** series lactamized faster than those of the **S** series. It seems that in the formation of the regioisomers the presence or absence of the proton is important. In the presence of acid, in the form of ammonium ion, the formation of only the 1*S* epimer normal ester (**3a**) and the 1*R* epimer normal lactam (**7b**) could be detected.

Thus, the reacting components determined the construction of the products, and the appropriate ^{1}H and ^{13}C NMR parameters corresponded well to the expected values, so the main task was to establish the stereochemistry of the products. In this respect the situation was clear for the histelosamides. In both the **R** and the **S** series, rotation around carbon−carbon bonds attached to C-10 defined nine staggered conformations, which may be characterized by the synclinal or antiperiplanar position of H-1 and H-11 to H-10*proR* and H-10*proS* (Table 3). However, by analogy with the examples analyzed previously by our group,[4−6] in each series only two conformations have the side-chain nitrogen and methoxycarbonyl group in appropriate positions for lactamization (**R12** and **R33**, as well as **S13** and **S31**, respectively). In **7b**, the large coupling constants of H-1 and H-11 to the same H-10 proton define both the configuration of C-1 and the conformation around C-10 to be **R12**. The only remaining major stereochemical problem was the conformation of the tetrahydropyridine ring. The necessarily β-axial orientation of the H-1 proton in the usual representation involves the negative conformation of the tetrahydropyridine ring. This was further supported by the high chemical shift of one of the H-3 protons which was produced by the anisotropic effect of the lactam carbonyl group. This effect may operate only if the appropriate C−H bond is coplanar to it. Conformational analysis indicated that only H-3α may take up this

orientation and only in a negative conformation of the tetrahydropyridine ring. According to our previously applied stereochemical notation system,[4−6] the stereostructure of **7b** was characterized by **R12NN**.

The values of the analogous parameters in the ^{1}H NMR spectrum of the lactams **7c** and **7d** as well as of the neo lactams **8b** and **8c** were very close to those observed in that of **7b**. Consequently, their stereochemistry corresponds likewise to **R12NN**.

In the ^{1}H NMR spectrum of the lactam **7a**, only H-11 had a large coupling constant to one of the H-10 protons, which corresponds to the conformation **31** of the **S** series. Thus, in principle, this single value should be sufficient to establish the main features of the stereochemistry of **7a** (except for the conformation of the tetrahydropyridine ring; see below). Fortunately, in the same spectrum, the methyl singlet of one of the acetyl groups was also observed with a relatively low chemical shift (1.76 ppm). This "anomalous" chemical shift is well known from the literature and was observed herein, too, in all lactam derivatives of tetraacetylsecologanin and biogenic amines having the *S* configuration at the new center of chirality (in the tryptamine derivatives at ca. 1.20 ppm and in the dopamine derivatives at ca. 1.55 ppm). The phenomenon was analyzed in detail in our previous papers,[4,5] as well as work by Aimi et al.,[17] and is produced by the anisotropic effect of the aromatic ring when the C-2′ acetoxy group is in close proximity to it. This steric arrangement is possible only if the compound has **S31** stereochemistry, along with negative conformation in the dihydropyran and tetrahydropyridine rings, as well as a double σ-conjugated effect around the glucosidic *O*-bridge. In **7a**, the negative conformation of the tetrahydropyridine ring was confirmed by the high chemical shift of the H-3β atom.

Of the histeloside derivatives, the 2-benzyl compound **5b** of the **R** series and the parent compound **3a** of the **S** series could be isolated in sufficient amounts and with good purity. In these compounds, the rotation around C-10 is not blocked by lactamization, and all nine conformations in both series had to be considered during the structure determination.

In **5b** the configuration of C-1 was derived after lactamization as described above. The conformation of the dihydropyran ring is negative, according to the small value of the coupling constant $^3J_{16,17}$. The similar negative conformation of the tetrahydropyridine ring was derived from the existence of a ROESY (rotating frame Overhauser effect spectroscopy) cross-peak between the axial H-3 proton and one of the C-10 protons. This fact requires a *cis* diaxial relation of H-3 and C-10. Having C-1 with *R* configuration, H-1 has to have β and C-10 α orientation in the usual representation. The α-axial orientation of C-10 could be taken up only in the positive conformation of the tetrahydropyridine ring. Measurements of through-space interatomic distances on computer-generated molecular models supported this orientation. Finally, large coupling constants of H-1 and H-11 to the two different H-10 hydrogens indicated **(R)11** and **(R)22** as possible conformers around C-10. The distinction between the two possibilities was easy. In the ROESY spectrum, a strong cross-peak was observed between H-1 and H-16, indicating their proximity. Measurements on computer-generated models showed in the **R11NP** structure a 1.88 Å distance, and in the **R22NP** structure, a 4.72 Å distance. Thus, the complete stereochemistry of **5b** is characterized as **R11NP**. As the H-3β and H-4β protons gave cross-peaks with both hydrogens of the methylene group of the benzyl subunit, this observation indicates the β orientation of the benzyl group. This orientation is favorable because it involves the antiperiplanar orientation of the two sterically "bulky" ligands at C-1 and N-2.

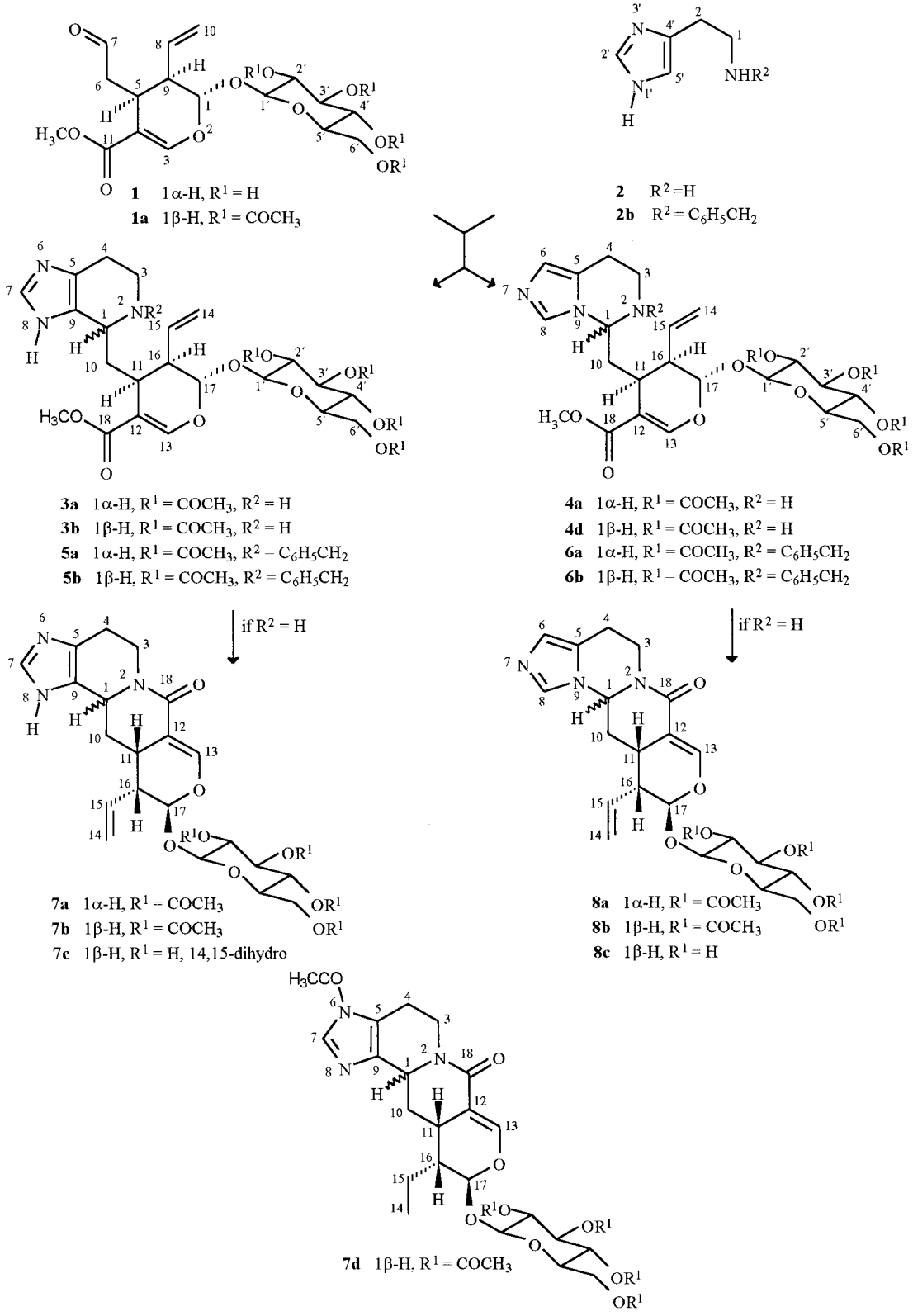
The configuration of C-1 in the ester compound **3a** was established likewise after lactamization. Since this reaction required an acid catalyst and a long reaction time, this suggested a 1*S* configuration at the new center of chirality. This was proved by the appearance of the "anomalous" chemical shift of one of the methyl singlets of the acetyl group at 1.76 ppm in the ^{1}H NMR spectrum recorded in $CDCl_3$. The relatively high value of the coupling constant $^3J_{15,16}$ (8.0 Hz) indicated the positive conformation of the dihydropyran ring in accordance with other unsubstituted, nonlactam derivatives of the **S** series (strictosidine,[3] tetraacetyl-*N*-deacetylisoipecoside[5]). It was further supported by a NOESY cross-peak between H-17 and one of the protons of C-10. The similar positive conformation of the tetrahydropyridine ring was derived by the same reasoning that applied to **5b**: in its NOESY spectrum, a cross-peak was observed between H-1 and the axial proton of C-3. This fact indicated that there is a short distance between these functionalities which requires their *cis* diaxial relationship. As the configuration of C-1 was proved to be *S*, this means that H-1 is in α orientation, according to the usual representation. However, an axial orientation of this proton is possible only in the positive conformation of the tetrahydropyridine ring. The large coupling constants of H-1 and H-11 to the two different protons of C-10 is characteristic only for **S11PP** and **S22PP** conformations around C-11. However, the distinction between them is not easy in this case, as they are the two most "strain-free" ones in which the least steric interactions are expected. Nevertheless, according to the measurements on a computer-generated model, one would expect between H-1 and H-17 a through-space distance shorter than 2.8 Å in **S22PP**, or longer than 4.8 Å in **S11PP**. As no cross-peak was observed in the NOESY spectrum of **3a** between the two protons in question, one may conclude that **S11PP** is the favored conformer around C-10. This conclusion was further supported by the fact that most of the relevant ^{1}H and ^{13}C NMR parameters of **3a** are very close to those of strictosidine, which has the same stereochemical notation. In strictosidine, the **S11** conformation was proved by measurement of heteronuclear coupling constants.[3]

The results presented in this paper prove that, like tryptamine and dopamine and their derivatives, histamine and its derivatives can and do react with secologanin and afford analogous products under controlled chemical conditions. However, as mentioned in the Introduction, such products have not been isolated from natural sources to date. Although other types of alkaloids derived from histamine have been isolated from plants, they are found only in species that belong to other plant families than the species containing either secologanin or its reaction products with tryptamine or dopamine. The cause of this observation is still unknown, but is certainly not due to the inability of secologanin to react with histamine.

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) or on a Bruker DRX-400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). The COSY, NOESY, and ROESY spectra were measured with the standard Bruker pulse programs of the XWINNMR software. For phase-sensitive NOESY spectra a 600 ms mixing time was used. The ROESY spectra were measured using a 300 ms CW pulse

Chart 1



attenuated to a power level corresponding to a 100 μs 90° pulse. The selective TOCSY spectra were measured with an improved DPFG sequence.[18]

The organic solutions were dried with anhydrous sodium sulfate. Thin-layer chromatography (TLC) was carried out on Si gel plates.

Secologanin (**1**) was isolated from *Lonicera xylosteum* L. (Caprifoliaceae) according to a method elaborated in our Institute.[19]

***N*$^{\alpha}$-Benzylhistamine Dihydrochloride (2b·2HCl).** Histamine (**2**, 0.450 g, 4 mmol) and benzaldehyde (0.4 mL, 4 mmol) were heated in benzene (0.30 mL) at 80 °C for 15 min. After evaporation of the solvent in vacuo, the residue was dissolved in MeOH (4 mL), $NaBH_4$ (0.16 g, 4.23 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. After evaporation of the solvent, the residue was dissolved in water (5 mL), stirred for 30 min at room temperature, and extracted with $CHCl_3$ (3 × 10 mL). The combined

organic phases were washed with water and dried, and the solvent was evaporated. The residue was taken up in cold MeOH and saturated with HCl. After crystallization (EtOH, Et_2O), N^{α}-benzylhistamine dihydrochloride (**2b·2HCl**) was obtained as a white crystalline product (0.45 g, 41%, mp 222−224 °C (lit.[20] 225−227 °C); *anal.* C 52.28%, H 6.12%, N 15.19%, calcd for $C_{12}H_{17}N_3Cl_2$, C 52.57%, H 6.25%, N 15.33%).

Reaction of *O,O,O,O*-Tetraacetylsecologanin (1a) with N^{α}-Benzylhistamine Dihydrochloride (2b·2HCl). N^{α}-Benzylhistamine dihydrochloride (**2b**·2HCl, 0.054 g, 0.2 mmol) was refluxed for 5 min in a mixture of acetonitrile (1.0 mL) and triethylamine (0.056 mL, 0.4 mmol) until partial dissolution occurred, then *O,O,O,O*-tetraacetylsecologanin (**1a**, 0.11 g, 0.2 mmol) was added, and the mixture was refluxed for 90 min. After evaporation of the solvent, the residue gave one spot by TLC in EtOAc−EtOH−H_2O (120:10:8) (R_f 0.55). The crude total product, after chromatography on silica gel (15 g) with EtOAc−EtOH−H_2O (120:10:8), afforded a beige amorphous solid, which proved to be *O′,O′,O′,O′*-tetraacetyl-2-benzylhisteloside [**5b**, 0.102 g, 69%, R_f 0.48 in EtOAc−EtOH−H_2O (120:10:8)]; *anal.* C 59.89%, H 6.21%, N 5.58%, calcd for $C_{37}H_{45}N_3O_{13}$, C 60.07%, H 6.13%, N 5.68%. IR (KBr) ν_{max} 1758, 1709, 1223, 1037 cm^{-1}.

***O′,O′,O′,O′*-Tetraacetyl-2-benzylhisteloside (5b).** ^{1}H NMR ($CDCl_3$, 400 MHz) chemical shifts and coupling constants of overlapping signals were determined from a series of 1D TOCSY spectra measured by the selective excitation of the H-1, H-4α, H-10*proS*, and H-15 atoms. Double primes denote the atoms of the phenyl ring of the benzyl group: δ 7.56 (1H, s, H-7), 7.4−7.2 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.30 (1H, d, $^4J_{11,13}$ = 1.1 Hz, H-13), 5.48 (1H, ddd, $^3J_{14Z,15}$ = 17.1, $^3J_{14E,15}$ = 10.2, $^3J_{15,16}$ = 9.3 Hz, H-15), 5.25 (1H, t, $^3J_{2',3'} = {}^3J_{3',4'}$ = 9.4 Hz, H-3′), 5.19 (1H, t, $^3J_{3',4'} = {}^3J_{4',5'}$ = 9.4 Hz, H-4′), 5.13 (1H, d, $^3J_{16,17}$ = 4.4 Hz, H-17), 5.10 (1H, dd, $^3J_{2',3'}$ = 9.4, $^3J_{1',2'}$ = 8.0 Hz, H-2′), 5.09 (1H, dd, $^3J_{14E,15}$ = 10.2, $^2J_{14E,14Z}$ = 1.7 Hz, H-14*E*), 4.86 (1H, d, $^3J_{1',2'}$ = 8.1 Hz, H-1′), 4.84 (1H, dd, $^3J_{14Z,15}$ = 17.2, $^2J_{14E,14Z}$ = 1.7 Hz, H-14*Z*), 4.31 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'a}$ = 4.1 Hz, H-6′a), 4.23 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.4 Hz, H-6′b), 3.76 (1H, d, $^2J_{NCHa,NCHb}$ = 12.9 Hz, Ha-benzyl-CH_2), 3.76 (1H, ddd, $^3J_{4',5'}$ = 9.4, $^3J_{5',6'a}$ = 4.1, $^3J_{5',6'b}$ = 2.4 Hz H-5′), 3.62 (3H, s, OCH_3), 3.55 (1H, d, $^2J_{NCHa,NCHb}$ = 12.9 Hz, Hb-benzyl-CH_2), 3.51 (1H, dd, $^3J_{1,10S}$ = 9.1, $^3J_{1,10R}$ = 6.1 Hz, H-1), 3.31 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 14.2, $^3J_{3\alpha,4\beta}$ = 11.7, $^3J_{3\alpha,4\alpha}$ = 4.5 Hz, H-3α), 3.10 (1H, dd, $^2J_{3\alpha,3\beta}$ = 14.2, $^3J_{3\beta,4\beta}$ = 5.5 Hz, H-3*β*), 2.97 (1H, dt, $^3J_{10R,11}$ = 9.6, $^3J_{10S,11} = {}^3J_{11,16}$ = 5.4, H-11), 2.89 (1H, ddd, $^2J_{4\alpha,4\beta}$ = 16.2, $^3J_{3\alpha,4\beta}$ = 11.7, $^3J_{3\beta,4\beta}$ = 5.5 Hz, H-4*β*), 2.43 (1H, dd, $^2J_{4\alpha,4\beta}$ = 16.2, $^3J_{3\alpha,4\alpha,}$ = 4.5, H-4α), 2.15 (1H, ddd, $^2J_{10R10S}$ = 14.5, $^3J_{10R,11}$ = 9.6 Hz, $^3J_{1,10R}$ = 6.1, H-10*proR*), 2.12, 2.05, 2.04, 1.96 (each 3H, each s, CH_3CO), 2.06 (1H, ddd, $^3J_{15,16}$ = 9.3, $^3J_{11,16}$ = 5.4, $^3J_{16,17}$ = 4.4 Hz, H-16), 1.55 (1H, ddd, $^2J_{10R10S}$ = 14.5, $^3J_{1,10S}$ = 9.1, $^3J_{10S,11}$ = 5.4 Hz, H-10*proS*); ROESY cross-peaks (s, strong; m, medium; w, weak) H-1: H-10*proR* w, H-10*proS* m, H-11 w, H-14*Z* w, H-15 w, H-16 s; H-3α: H-3*β* s, H-4α s, H-4*β* m, H-10*proR* w, H-11 w; H-3*β*: H-3α s, H-4α m, H-4*β* s, Ha-benzyl-CH_2 m, Hb-benzyl-CH_2 w; H-4α: H-3α s, H-3*β* m, H-4*β* s; H-4*β*: H-3α m, H-3*β* s, H-4α s, Ha-benzyl-CH_2 w, Hb-benzyl-CH_2 w; H-10*proR*: H-1 w, H-3α w, H-10*proS* s, H-11 w, H-17 w; H-10*proS*: H-1 w, H-10*proR* s, H-11 w, H-15 w; H-11: H-1 w, H-3α w, H-10*proR* w, H-10*proS* w, H-16 s, H-19 w; H-14*Z*: H-1 w, H-14*E* s, H-15 s, H-16 s; H-15: H-1 w, H-10*proS* w, H-14*E* s, H-14*Z* s, H-16 w; H-16: H-1 s, H-11 s, H-14*Z* m, H-15 w; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.7, 170.2, 169.5, 169.1 (each CH_3CO), 167.5 (C-18), 150.6 (C-13), 133.4 (C-7), 139.7 (C-1″), 133.1 (C-15), 129.9 (C-3″), 129.9 (C-5″), 128.4 (C-2″), 128.4 (C-6″), 127.0 (C-4″), 119.8 (C-14), 111.9 (C-12), 96.5[a] (C-17), 95.6[a] (C-1′), 72.6[b] (C-3′), 72.1[b] (C-5′), 70.8 (C-2′), 68.3 (C-4′), 61.6 (C-6′), 56.9 (*C*H_2-benzyl), 51.8 (C-1), 51.2 (OCH_3), 43.9 (C-3), 42.0 (C-16), 33.1 (C-10), 26.2 (C-11), 20.7, 20.6, 20.6, 20.2 (each *C*H_3CO), 18.9 (C-4); C-5 and C-9 did not appear ([a, b]revised assignment is also possible).

Preparation of 14,15-Dihydrohistelosamide (7c). *O′,O′,O′,O′*-Tetraacetyl-2-benzylhisteloside (**5b**, 0.091 g, 0.123 mmol) was dissolved in a mixture of MeOH (8 mL) and glacial acetic acid (0.1 mL) and hydrogenated in the presence of 10% Pd on charcoal (0.04 g) at room temperature for 30 min. After filtration of the catalyst, the solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ (1.2 mL) and MeOH (0.8 mL), and 1 M methanolic $NaOCH_3$ (0.01 mL, 0.01 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. After evaporation of the solvent, 14,15-dihydrohistelosamide (**7c**) was obtained as a beige amorphous material [0.046 g, 83%, R_f 0.20 in MeCOOEt−*i*-PrOH−H2O (8:2:1)]; *anal.* C 56.00%, H 6.61%, N 9.19%, calcd for $C_{21}H_{29}N_3O_8$, C 55.87%, H 6.47%, N 9.31%; IR (KBr) ν_{max} 3600−3100, 1657, 1586, 1073 cm^{-1}; ^{1}H NMR (CD_3OD, 200 MHz) δ 7.60 (1H, s, H-7), 7.37 (1H, d, $^4J_{11,13}$ = 2.4 Hz, H-13), 5.62 (1H, d, $^3J_{16,17}$ = 1.7 Hz, H-17), 5.03 (1H, dt, $^2J_{3\alpha,3\beta}$ = 11.6, $^3J_{3\alpha,4\alpha}$ = 2.8, $^3J_{3\alpha,4\beta}$ = 2.8 Hz, H-3α), 4.68 (1H, d, $^3J_{1',2'}$ = 7.9 Hz, H-1′), 4.67 (1H, dd, $^3J_{1,10S}$ = 12.3, $^3J_{1,10R}$ = 3.6 Hz, H-1), 3.92 (1H, dd, $^2J_{6'a,6'b}$ = 11.7, $^3J_{5',6'b}$ = 1.1, H-6′b), 3.69 (1H, dd, $^2J_{6'a,6'b}$ = 11.7, $J_{5',6'a}$ = 4.3, H-6′a), 3.45−3.1 (5H, m, H-2′, H-3′, H-4′, H-5′, H-11), 3.0−2.6 (3H, m, H-3*β*, H-4α, H-4*β*), 2.48 (1H, dt, $^2J_{10S,10R}$ = 12.7, $^3J_{1,10R}$ = 3.6, $^3J_{10R,11}$ = 3.6 Hz, H-10*proR*), 1.87 (1H, m, H-16), 1.41 (1H, td, $J_{10S,10R}$ = 12.7, $^3J_{1,10S}$ = 12.3, $^3J_{10S,11}$ = 12.7 Hz, H-10*proS*), 1.37 (1H, m, H-15a), 1.10 (1H, m, H-15b), 0.97 (1H, t, $^3J_{14,15}$ = 7.1 Hz, H-14); ^{13}NMR (CD_3OD, 50 MHz) δ 166.5 (C-18), 148.9 (C-13), 136.2 (C-7), 134.3[a] (C-9), 126.4[a] (C-5), 109.6 (C-12), 99.6[b] (C-1′), 96.4[b] (C-17), 78.3[c] (C-3′), 77.9[c] (C-5′), 74.8 (C-2′), 71.6 (C-4′), 62.7 (C-6′), 55.4 (C-1), 40.6 (C-3), 39.9 (C-16), 32.1 (C-10), 28.2 (C-11), 22.9 (C-4), 18.9 (C-15), 12.5 (C-14) ([a−c]revised assignments are possible).

Preparation of N_6,*O′,O′,O′,O′*-Pentaacetyl-14,15-dihydrohistelosamide (7d). 14,15-Dihydrohistelosamide (**7c**, 0.273 g, 0.605 mmol) was stirred in a mixture of Ac_2O (2.0 mL) and pyridine (2 drops) at room temperature for 8 h. Then, ice-cold H_2O (20 mL) was added, and the mixture was further stirred for 30 min. The reaction mixture was extracted with $CHCl_3$ (3 × 20 mL), and the combined organic phase was washed with aqueous 5% $NaHCO_3$ solution (20 mL) and H_2O (20 mL) and dried, and the solvent was evaporated. The beige amorphous solid residue proved to be N_6,*O′,O′,O′,O′*-pentaacetyl-14,15-dihydrohiselosamide (**7d**) [0.280 g, 70%, R_f 0.80 in MeCOOEt−*i*-PrOH−H_2O (8:2:1)]; *anal.* C 55.98%, H 5.95%, N 6.24%, calcd for $C_{31}H_{39}N_3O_{13}$, C 56.27%, H 5.94%, N 6.35%; IR (KBr) ν_{max} 1755, 1659, 1225, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, s, H-7), 7.37 (1H, d, $^4J_{11,13}$ = 2.4 Hz, H-13), 5.38 (1H, d, $^3J_{16,17}$ = 1.9 Hz, H-17), 5.24 (1H, t, $^3J_{2',3'}$ = 9.6, $^3J_{3',4'}$ = 9.6 Hz, H-3′), 5.12 (1H, m, H-3α), 5.10 (1H, t, $^3J_{3',4'}$ = 9.6, $^3J_{4',5'}$ = 9.6 Hz, H-4′), 5.01 (1H, dd, $^3J_{1',2'}$ = 8.1, $^3J_{2',3'}$ = 9.6 Hz, H-2′), 4.91 (1H, d, $^3J_{1',2'}$ = 8.1 Hz, H-1′), 4.61 (1H, dd, $^3J_{1,10S}$ = 11.3, $^3J_{1,10R}$ = 3.5 Hz, H-1), 4.32 (1H, dd, $^3J_{5',6'a}$ = 4.5, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′a), 4.15 (1H, dd, $^3J_{5',6'b}$ = 2.3, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′b), 3.77 (1H, ddd, $^3J_{4',5'}$ = 9.6 Hz, $^3J_{5',6'a}$ = 4.5 Hz, $^3J_{5',6'b}$ = 2.3 Hz, H-5′), 3.06 (1H, ddt, $^2J_{4\alpha,4\beta}$ = 16.7, $^3J_{3\beta,4\beta}$ = 4.4, $^3J_{3\alpha,4\beta}$ = 2.0 Hz, H-4*β*), 2.96 (1H, m, H-4α), 2.92 (1H, m, H-11), 2.83 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 13, $^3J_{3\beta,4\alpha}$ = 11.5, $^3J_{3\beta,4\beta}$ = 4.4 Hz, H-3*β*), 2.61 (3H, s, CH_3CN-6), 2.49 (1H, dt, $^2J_{10S,10R}$ = 13.2, $^3J_{1,10R} = {}^3J_{10R,11}$ = 3.5 Hz, H-10*proR*), 2.10, 2.03, 2.0, 1.95 (each 3H, s, CH_3-CO), 1.91 (1H, m, H-16), 1.42 (1H, td, $^2J_{10S,10R}$ = 13.2, $^3J_{10S,11}$ = 13.2, $^3J_{1,10S}$ = 11.3 Hz, H-10*proS*), 1.38 (1H, m, H-15a), 1.08 (1H, m, H-15b), 0.95 (1H, t, $^3J_{14,15}$ = 7.3, H-14); selected NOESY cross-peaks supporting the N-6 position of one of the acetyl groups (s, strong; m, medium; w, weak): CH_3CON-6, H-4 w, H-7s; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.8, 169.7, 169.6, 169.6 (each CH_3CO), 167.5 (CH_3CON), 163.7 (C-18), 146.9 (C-13), 139.8[a] (C-9), 136.8 (C-7), 125.2[a] (C-5), 109.0 (C-12), 96.2[b] (C-1'), 95.5[b] (C-17), 72.6[c] (C-5'), 72.3[c] (C-3'), 70.7 (C-2'), 68.5 (C-4'), 62.0 (C-6'), 54.1 (C-1), 38.6 (C-3), 38.1 (C-16), 30.1 (C-10), 27.4 (C-11), 23.9 (C-4), 23.7 (*C*H_3CON), 20.9, 20.8, 20.8, 20.8 (each *C*H_3CO), 17.8 (C-15), 12.1 (C-14) ([a−c]revised assignments are possible).

Reaction of *O,O,O,O*-Tetraacetylsecologanin (1a) with Histamine Dihydrochloride (2·2HCl). Histamine dihydrochloride (**2**·2HCl) (0.184 g, 0.1 mmol) was stirred in a mixture of acetonitrile (5 mL) and triethylamine (0.28 mL, 2 mmol) at 70 °C until partial dissolution occurred, then *O,O,O,O*-tetraacetylsecologanin (**1a**, 0.557 g, 1 mmol) was added, and the reaction mixture was further stirred for 5 h at 70 °C. After evaporation of the solvent, the residue gave on TLC in EtOAc−

i-PrOH−H_2O (8:2:1) the following spots: 0.91 (unreacted **1a**), 0.45 (**7b**), 0.10 (**3a**). The crude total product was chromatographed on silica gel (0.04−0.063; 40 g), with EtOAc−*i*-PrOH−H_2O (8:2:1) (each fraction 7 mL). After removal of the solvent, fractions 4−5 gave the starting material **1a** (0.110 g), fractions 8−17 **7b** (0.246 g, 49.6% based on **1a** consumed), and fractions 20−27 **3a** (0.160 g, 30.8%, based on **1a** consumed).

***O′,O′,O′,O′*-Tetraacetylisohisteloside (3a):** beige amorphous solid (R_f 0.66 in $CHCl_3$−*i*-PrOH−MeOH−H_2O (9:3:4:1)); *anal*. C 55.34%, H 6.05%, N 6.47%, calcd for $C_{30}H_{39}N_3O_{13}$: C 55.47%, H 6.05%, N 6.47%; IR (KBr) ν_{max} 1755, 1226, 1038 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.64 (1H, s, H-13), 7.58 (1H, s, H-7), 5.75 (1H, ddd $^3J_{14Z,15} = 17.3$, $^3J_{14E,15} = 10.6$, $^3J_{15,16} = 8.0$ Hz, H-15), 5.54 (1H, d, $^3J_{16,17} = 8.0$ Hz, H-17), 5.33 (1H, dd, $^3J_{14Z,15} = 17.3$, $^2J_{14E,14Z} = 1.4$ Hz, H-14*Z*), 5.31 (1H, t, $^3J_{2',3'} = {}^3J_{3',4'} = 9.5$ Hz, H-3′), 5.28 (1H, dd, $^3J_{14E,15} = 10.6$, $^2J_{14E,14Z} = 1.4$ Hz, H-14*E*), 5.13 (1H, d, $^3J_{1',2'} = 8.1$ Hz, H-1′), 5.05 (1H, t, $^3J_{3',4'} = {}^3J_{4',5'} = 9.5$ Hz, H-4′), 4.91 (1H, dd, $^3J_{2',3'} = 9.5$, $^3J_{1',2'} = 8.1$ Hz, H-2′), 4.32 (1H, $^2J_{6'a,6'b} = 12.4$, $^3J_{5',6'a} = 4.5$ Hz, H-6′a), 4.17 (1H, $^2J_{6'a,6'b} = 12.4$, $^3J_{5',6'b} = 2.5$ Hz, H-6′b), 4.13 (1H, dd, $^3J_{1,10R} = 10$, $^3J_{1,10S} = 3.2$ Hz, H-1), 3.96 (1H, ddd, $^3J_{4',5'} = 9.5$, $^3J_{5',6'a} = 4.5$, $^3J_{5',6'b} = 2.5$ Hz H-5′), 3.75 (3H, s, OCH_3), 3.45 (1H, dt, $^2J_{3\alpha,3\beta} = 12.7$, $^3J_{3\beta,4\beta} = {}^3J_{3\beta,4\alpha} = 5.4$ Hz, H-3β), 3.17 (1H, ddd, $^2J_{3\alpha,3\beta} = 12.7$, $^3J_{3\alpha,4\beta} = 8.2$, $^3J_{3\alpha,4\alpha} = 5.4$ Hz H-3α), 2.97 (1H, dt, $^3J_{10S,11} = 10.8$, $^3J_{10R,11} = {}^3J_{11,16} = 4.8$, H-11), 2.87 (1H, m, H-4β), 2.77 (1H, dt, $^2J_{4\alpha,4\beta} = 15.6$, $^3J_{3\alpha,4\alpha} = {}^3J_{3\beta,4\alpha} = 5.4$ Hz, H-4α), 2.65 (1H, td, $^3J_{15,16} = {}^3J_{16,17} = 8.0$, $^3J_{11,16} = 4.8$ Hz, H-16), 2.14 (1H, ddd, $^2J_{10R,10S} = 14.3$, $^3J_{10S,11} = 10.8$, $^3J_{1,10S} = 3.2$ Hz, H-10*proS*) 2.03, 2.02, 2.00, 1.97 (each 3H, each s, CH_3COO), 1.96 (1H, overlap, H-10*proR*); NOESY cross-peaks (in CD_3OD; s, strong; m, medium; w, weak) H-1: H-3α w, H-10*proS* m, H-11 w; H-3α: H-1 w, H-3β s, H-4α m; H-3β: H-3α s, H-4β m, H-4α w; H-4α: H-3α m, H-3β w, H-4β s; H-4β: H-3β m, H-4α s; H-10*proR*: H-10*proS* s, H-11 w, H-15 w; H-10*proS*: H-1 m, H-10*proR* s, H-17 s; H-11: H-1 w, H-10*proR* w, H-16 s; H-13: OCH_3 w; H-14*Z*: H-14*E* s, H-15 w, H-16 m; H-14*E*: H-14*Z* s, H-15 s; H-15: H-15*proR* w, H-14*E* s, H-14*Z* w, H-16 w, H-17 w; H-16: H-11 s, H-14*Z*: m, H-15 w, H-17 m; H-17: H-10*proS* m, H-15 w, H-16m, H-1′ m; ^{13}C NMR (CD_3OD, 50 MHz) δ 170.7, 170.2, 169.4, 169.4 (each CH_3CO), 168.4 (C-18), 152.9 (C-13), 133.7[a] (C-7), 133.2[a] (C-15), 119.7 (C-14), 110.1 (C-12), 97.0b (C-17), 96.9[b] (C-1′), 72.5[c] (C-5′), 72.1[c] (C-3′), 70.9 (C-2′), 68.1 (C-4′), 61.6 (C-6′), 51.7 (OCH_3), 51.4 (C-1), 43.9 (C-16), 42.0 (C-3), 35.0 (C-10), 30.4 (C-11), 22.9 (C-4), 20.7, 20.6, 20.6, 20.6 (each CH_3CO); C-5 and C-9 did not appear ([a−c]revised assignments are possible).

***O′,O′,O′,O′*-Tetraacetylhistelosamide (7b):** beige amorphous solid [R_f 0.51 in MeCOOEt−*i*-PrOH−H_2O (8:2:1)]; *anal*. C 56.12%, H 5.81%, N 6.65%, calcd for $C_{29}H_{35}N_3O_{12}$, C 56.39%, H 5.71%, N 6.80%; IR (KBr) ν_{max} 1755, 1662, 1226, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.51 (1H, s, H-7), 7.43 (1H, d, $^4J_{11,13} = 2.4$ Hz, H-13), 5.42 (1H, dt, $^3J_{14Z,15} = 17.2$, $^3J_{14E,15} = 9.6$, $^3J_{15,16} = 9.6$ Hz, H-15), 5.27 (1H, d, $^3J_{16,17} = 1.9$ Hz, H-17), 5.3−4.9 (7H, m, H-1′, H-2′, H-3′, H-4′, H-3α, H-14*Z*, H-14*E*), 4.65 (1H, dd, $^3J_{1,10S} = 11.7$, $^3J_{1,10R} = 3.8$ Hz, H-1), 4.31 (1H, dd, $^2J_{6'a,6'b} = 12.3$, $^3J_{5',6'a} = 4.4$ Hz, H-6′a), 4.14 (1H, dd, $^2J_{6'a,6'b} = 12.3$, $^3J_{5',6'b} = 2.2$ Hz, H-6·b), 3.76 (ddd, $^3J_{4',5'} = 9.8$, $^3J_{5',6'a} = 4.4$, $^3J_{5',6'b} = 2.2$ Hz, H-5′), 3.0−2.6 (3H, m, H-3β, H-4α, H-11), 2.69 (1H, ddd, $^3J_{15,16} = 9.6$, $^3J_{11,16} = 5.9$, $^3J_{16,17} = 1.9$ Hz, H-16), 2.60 (1H, m, H-4β), 2.45 (1H, dt, $^2J_{10S,10R} = 13.4$, $^3J_{1,10R} = {}^3J_{10R,11} = 3.8$ Hz, H-10*proR*), 2.10, 2.04, 2.01, 1.97 (each 3H, s, CH_3CO), 1.36 (1H, td, $^2J_{10S,10R} = 13.4$, $^3J_{10S,11} = 13.4$, $^3J_{1,10S} = 11.7$ Hz, H-10*proS*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 170.3, 169.8, 169.7 (each CH_3CO), 163.7 (C-18), 146.9 (C-13), 134.6 (C-7), 131.9 (C-15), 120.8 (C-14), 109.0 (C-12), 96.5[a] (C-17), 96.2[a] (C-1′), 72.6[b] (C-5′), 72.4[b] (C-3′), 70.7 (C-2′), 68.4 (C-4′), 61.9 (C-6′), 54.3 (C-1), 42.8 (C-16), 39.2 (C-3), 31.2 (C-10), 26.3 (C-11), 22.0 (C-4), 20.9, 20.9, 20.8, 20.8 (each CH_3CO); C-5 and C-9 did not appear ([a,b]revised assignments are possible).

Alternative Reaction of *O,O,O,O*-Tetraacetylsecologanin (1a) with Histamine (2). Histamine (**2**, 0.230 g, 2.07 mmol) and *O,O,O,O*-tetraacetylsecologanin (**1a**, 1.15 g, 2.07 mmol) were dissolved in 2-propanol (5 mL) and stirred at 70 °C for 4.5 h. After evaporation of the solvent, the residue gave on TLC in EtOAc−*i*-PrOH−H_2O (8:2:1) the following spots: 0.90 (unreacted **1a**), 0.46 (**7a** and **7b**), 0.38 (**8b**), 0.04 (**3a**). The crude total product was chromatographed on silica gel (0.04−0.063; 85 g) with $CHCl_3$−EtOH (10:1) and (after fraction 50) $CHCl_3$− *i*-PrOH−MeOH−H_2O (9:3:4:1) (each fraction 8 mL). After removal of the solvent, the combined fractions 6−16 gave the starting material **1a** (0.550 g), fractions 20−29 **8b** (0.185 g, 27.8% based on **1a** consumed), and fractions 31−50 a mixture of **7b** and **7a** in an approximately 4:1 ratio (0.264 g, 39.9% based on **1a** consumed), which could not be separated. Fractions 58−66 treated likewise gave **3a** (0.205 g, 29.2% based on **1a** consumed).

***O′,O′,O′,O′*-Tetraacetylisohisteloside (3a):** *anal*. C 55.20%, H 6.15%, N 6.37%, calcd for $C_{30}H_{39}N_3O_{13}$, C 55.47%, H 6.05%, N 6.47%; spectroscopic data, see above.

***O′,O′,O′,O′*-Tetraacetylhystelosamide (7b) and *O′,O′,-O′,O′*-tetraacetylisohystelosamide (7a)**: beige amorphous solid [R_f 0.25 in $CHCl_3$−EtOH (10:1)]; IR (KBr) ν_{max} 1757, 1662, 1606, 1226, 1064, 1035 cm^{-1}; ^1H NMR (C_6D_6, 200 MHz) δ major (**7b**) 7.73 (1H, s, H-7), 7.31 (1H, d, $^4J_{11,13} = 2.4$ Hz, H-13), 5.50−4.75 (9H, m, H-1′, H-2′, H-3′, H-4′, H-15, H-17, H-3α, H-14*Z*, H-14*E*), 4.57 (1H, dd, $^3J_{1,10S} = 11.7$, $^3J_{1,10R} = 4.4$ Hz, H-1), 4.28 (1H, dd, $^2J_{6'a,6'b} = 12.4$, $^3J_{5',6'a} = 4.4$ Hz, H-6′a), 4.06 (1H, dd, $^2J_{6'a,6'b} = 12.4$, $^3J_{5',6'b} = 2.4$ Hz, H-6′b), 3.42 (ddd, $^3J_{4',5'} = 9.8$, $^3J_{5',6'a} = 4.4$, $^3J_{5',6'b} = 2.4$ Hz, H-5′), 3.1−2.2 (6H, m, H-3β, H-4α, H-4β, H-11, H-16, H-10*proR*), 1.97, 1.74, 1.74, 1.73 (each 3H, s, CH_3CO), 1.43 (1H, td, $^2J_{10S,10R} = 13.4$, $^3J_{10S,11} = 13.4$, $^3J_{1,10S} = 11.7$ Hz, H-10*proS*); minor (7a) 7.61 (1H, d, $^4J_{11,13} = 2.4$ Hz, H-13), 7.36 (1H, s, H-7); selected signals from the ^1H NMR spectrum measured in $CDCl_3$ (200 MHz) δ major (**7b**) 7.51 (1H, s, H-7), 7.43 (1H, d, $^4J_{11,13} = 2.2$ Hz, H-13), 2.10, 2.04, 2.02, 1.97 (each 3H, s, CH_3CO); minor (7a) 7.53 (1H, s, H-7), 7.35 (1H, d, $^4J_{11,13} = 2.2$ Hz, H-13), 2.09, 2.01, 1.93, 1.69 (each 3H, s, CH_3CO); ^{13}C NMR ($CDCl_3$, 50 MHz) δ major (**7b**), see above.

***O′,O′,O′,O′*-Tetraacetylneohistelosamide (8b):** white amorphous solid [R_f 0.40 in $CHCl_3$−EtOH (10:1)]; *anal*. C 56.59%, H 5.91%, N 6.73%, calcd for $C_{29}H_{35}N_3O_{12}$, C 56.39%, H 5.71%, N 6.80%; IR (KBr) ν_{max} 1756, 1667, 1616, 1228, 1065, 1036 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.42 (1H, s, H-8), 7.38 (1H, d, $^4J_{11,13} = 2.3$, H-13), 6.72 (1H, s, H-6), 5.67 (1H, dd, $^3J_{1,10S} = 10.2$, $^3J_{1,10R} = 4.2$ Hz, H-1), 5.50 (1H, dt, $^3J_{14Z,15} = 17.0$, $^3J_{14E,15} = 9.1$, $^3J_{15,16} = 9.1$ Hz, H-15), 5.40−4.90 (6H, m, H-1′, H-2′, H-3′, H-4′, H-14*Z*, H-14*E*), 5.33 (1H, d, $^3J_{16,17} = 1.9$ Hz, H-17), 4.84 (1H, m, H-3α), 4.32 (1H, dd, $^2J_{6'a,6'b} = 12.5$, $^3J_{5',6'b} = 2.2$ Hz, H-6′b), 4.14 (1H, dd, $^2J_{6'a,6'b} = 12.5$, $^3J_{5',6a} = 4.5$ Hz, H-6′a), 3.81 (1H, ddd, $^3J_{4',5'} = 9.8$ Hz, $^3J_{5',6'a} = 4.5$ Hz, $^3J_{5',6'b} = 2.2$ Hz, H-5′), 3.07−2.69 (5H, m, H-3β, H-4α, H-4β, H-11, H-16), 2.55 (1H, dt, $^2J_{10S,10R} = 12.8$, $^3J_{1,10R} = 4.2$, $^3J_{10R,11} = 4.2$ Hz, H-10*proR*), 2.11, 2.04, 2.01, 1.95 (each 3H, s, CH_3-CO), 1.65 (1H, td, $^2J_{10S,10R} = {}^3J_{10S,11} = 12.8$, $^3J_{1,10S} = 10.2$ Hz, H-10*proS*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.3, 169.7, 169.3, 169.2 (each CH_3CO), 162.2 (C-18), 147.4 (C-13), 131.8 (C-15), 130.9 (C-8), 126.1 (C-5), 124.2 (C-6), 121.2 (C-14), 107.2 (C-12), 96.9[a] (C-17), 95.8[a] (C-1′), 72.0 (C-5′, C-3′), 70.3 (C-2′), 67.9 (C-4′), 66.8 (C-1), 61.5 (C-6′), 42.3 (C-16), 37.9 (C-3), 32.0 (C-10), 23.8 (C-11), 20.7 (C-4), 20.5, 20.3, 20.3, 20.3 (each CH_3-CO) ([a]revised assignment is also possible).

Preparation of *O′,O′,O′,O′*-Tetraacetylisohistelosamide (7a). *O′,O′,O′,O′*-Tetraacetylisohisteloside (**3a**, 0.074 g, 0.12 mmol) was dissolved in acetonitrile (4.0 mL). Triethylamine (0.017 mL, 0.12 mmol) and triethylamine HCl (0.017 g, 0.12 mmol) were added and refluxed for 18 h. After evaporation in vacuo, the residue was chromatographied on silica gel (0.04−0.063, 10 g) with EtOAc−EtOH−H_2O (120:10:8) (each fraction 7 mL). The combined fractions 7−12 (each 5 mL) after removal of the solvent gave *O′,O′,O′,O′*-tetraacetylisohistelosamide as a beige amorphous solid [**7a**, 0.050 g, 67%, R_f 0.26 in MeCOOEt−EtOH−H_2O (120:10:8)]; *anal*. C 56.64%, H 5.86%, N 6.92%, calcd for $C_{29}H_{35}N_3O_{12}$, C 56.39%, H 5.71%, N 6.80%; ^1H NMR (C_6D_6, 70 °C, 400 MHz) (chemical shift and coupling constants of H-10*proS* were determined from the 1D TOCSY spectrum measured by the selective excitation of H-1) δ 7.62 (1H, d, $^4J_{11,13} = 2.4$ Hz, H-13), 7.11 (1H, s, H-7), 5.49 (1H, dt, $^3J_{14Z,15} = 17.1$, $^3J_{14E,15} = {}^3J_{15,16} = 10.1$ Hz, H-15), 5.31 (1H, t, $^3J_{2',3'} = {}^3J_{3',4'} = 9.5$ Hz, H-3′), 5.18 (1H, d, $^3J_{16,17} = 2.0$ Hz, H-17), 5.15 (1H, t, $^3J_{3',4'} = {}^3J_{4',5'} = 9.5$ Hz, H-4′), 5.06 (1H,

dd, $^3J_{2',3'}$ = 9.5, $^3J_{1',2'}$ = 8.0 Hz, H-2′), 5.05 (1H, dd, $^2J_{3\alpha,3\beta}$ = 12.7, $^3J_{3\beta,4\beta}$ = 5.8 Hz, H-3*β*), 4.99 (1H, dd, $^3J_{14E,15}$ = 10.1, $^2J_{14E,14Z}$ = 2.0 Hz, H-14*E*), 4.91 (1H, dd, $^3J_{14Z,15}$ = 17.1, $^2J_{14E,14Z}$ = 2.0 Hz, H-14*Z*), 4,70 (1H, d, $^3J_{1',2'}$ = 8.0 Hz, H-1′), 4.43 (1H, dd, $^3J_{1,10S}$ = 6.0, $^3J_{1,10R}$ = 2.4, Hz, H-1), 4.20 (1H, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'a}$ = 4.5 Hz, H-6′a), 3.98 (1H, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.4 Hz, H-6′b), 3.20 (1H, ddd, $^3J_{4',5'}$ = 9.5, $^3J_{5',6'a}$ = 4.5, $^3J_{5',6'b}$ = 2.4 Hz H-5′), 2.83−2.68 (2H, m, H-4*β*, H-11), 2.58 (1H, ddd, $^2J_{10R,10S}$ = 13.5, $^3J_{10R,11}$ = 4.7, $^3J_{1,10R}$ = 2.4 Hz, H-10*proR*), 2.50 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 12.7, $^3J_{3\alpha,4\beta}$ = 11.7, $^3J_{3\alpha,4\alpha}$ = 4.7 Hz, H-3α), 2.32 (1H, ddd, $^3J_{15,16}$ = 10.1, $^3J_{11,16}$ = 6.2, $J_{16,17}$ = 2.0 Hz, H-16), 1.93 (1H, dd, $^2J_{4\alpha,4\beta}$ = 15.4, $^3J_{3\alpha,4\alpha}$ = 4.7 Hz, H-4α), 1.82, 1.72, 1.71, 1.70 (each 3H, s, *C*H$_3$CO), 1.73 (1H, td, $^2J_{10R,10S}$ = $^3J_{10S,11}$ = 13.5, $^3J_{1,10S}$ = 6.0 Hz, H-10*proS*); selected signals from the ^{1}H NMR spectrum measured in CDCl$_3$ (200 MHz) *δ* 7.58 (1H, s, H-7), 7.34 (1H, d, $^4J_{11,13}$ = 1.7 Hz, H-13) 2.09, 2.01, 1.96, 1.76 (each 3H, s, *C*H$_3$CO); NOESY cross-peaks (in C$_6$D$_6$) H-1: H-3α m, H-3*β* w, H-11 w, H-10*proR* m, H-10*proS* s; H-3α: H-1 m, H-3*β* s, H-3*β*: H-1 w, H-3*β* s; H-4α: H-4*β* m; H-10*proR*: H-1 w, H-10*proS* m, H-11 w, H-16 w; ^{13}C NMR (C$_6$D$_6$, 100 MHz) *δ* 170.7, 170.5, 169.8, 169.7 each s (CH$_3$*C*O), 165.3 (C-18), 147.0 (C-13), 134.6 (C-9), 133.6 (C-15), 120.7 (C-14), 111.3 (C-16), 96.8, 96.6 (C-17, C-1′), 73.6, 73.0 (C-3′, C-5′), 71.6 (C-2′), 69.1 (C-4′), 62.1 (C-6′), 55.3 (C-1), 43.5 (C-3, C-16), 26.6 (C-10), 24.9 (C-11), 22.6 (C-4), 20.9, 20.8 (each *C*H$_3$CO).

Preparation of Neohistelosamide (8c). Histamine (0.167 g, 1.5 mmol) and secologanin (0.583 g, 1.5 mmol) were dissolved in water (3 mL), and the mixture was heated at 60 °C for 150 min. After evaporation of the solvent, the residue gave on TLC in CHCl$_3$−*i*-PrOH−MeOH−H$_2$O (9:3:4:1) the following spots: 0.80 (unreacted **1a**), 0.37 (**8c**). The crude total product was flash chromatographed on silica gel (30 g, each fraction 10 mL) with CHCl$_3$−*i*-PrOH−MeOH−H$_2$O (9:3:4:1). After removal of the solvent, fractions 11 and 12 gave the starting material **1a** (0.04 g), and fractions 14−21 gave neohistelosamide **8c** [beige amorphous solid, 0.426 g, 68% based on **1a** consumed; R_f 0.36 in CHCl$_3$−*i*-PrOH−MeOH−H$_2$O (9:3:4:1)]; *anal*. C 55.95%, H 6.17%, N 9.19%, calcd for C$_{21}$H$_{27}$N$_3$O$_8$, C 56.12%, H 6.06%, N 9.35%; IR (KBr) ν_{max} 3700−3100, 1659, 1074 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) *δ* 7.76 (1H, s, H-8), 7.47 (1H, d, $^4J_{11,13}$ = 2.3 Hz, H-13), 6.76 (1H, s, H-6), 5.78 (1H, dd, $^3J_{1,10S}$ = 10.6, $^3J_{1,10R}$ = 4.2 Hz, H-1), 5.54 (1H, d, $^3J_{16,17}$ = 1.8 Hz, H-17), 5.57 (1H, dt, $^3J_{14Z,15}$ = 17.2, $^3J_{14E,15}$ = 9.8, $^3J_{15,16}$ = 9.8 Hz, H-15), 5.54 (1H, d, $^3J_{16,17}$ = 2 Hz, H-17), 5.35 (1H, dd, $^2J_{14Z,14R}$ = 2.2, $^3J_{14Z,15}$ = 17.2 Hz, H-14*Z*), 5.27 (1H, dd, $^2J_{14Z,14E}$ = 2.2, $^3J_{14E,15}$ = 9.8 Hz, H-14*E*), 4.72 (1H, ddd, $^2J_{3\alpha,3\beta}$ = ∼12, $^3J_{3\alpha,4\alpha}$ = 4,7, $^3J_{3\alpha,4\beta}$ = 3.3 Hz, H-3α), 4,69 (1H, d, $^3J_{1',2'}$ = 7.8, H-1′), 3.90 (1H, dd, $^2J_{6'a,6'b}$ = 11.9, $^3J_{5',6'b}$ = 1.5 Hz, H-6′b), 3.67 (1H, dd, $^2J_{6'a,6'b}$ = 11.9, $^3J_{5',6a}$ = 5.4 Hz, H-6′a), 3.45−2.7 (10H, m, H-2′,-3′,-4′,-5′, H-3*β*, H-4α, H-4*β*, H-10*R*, H-11, H-16), 1.65 (1H, ddd, $^2J_{10S,10R}$ = 13.5, $^3J_{10S,11}$ = 12.6, $^3J_{1,10S}$ = 10.6 Hz, H-10*proS*); ^{13}C NMR (CD$_3$OD, 50 MHz) *δ* 165.5 (C-18), 149.9 (C-13), 133.9 (C-8), 133.4 (C-15), 128.2 (C-5), 124.3 (C-6), 121.1 (C-14), 108.4 (C-12), 99.9[a] (C-1′), 97.7[a] (C-17), 78.4[b] (C-5′), 78.1[b] (C-3′), 74.9 (C-2′), 71,7 (C-4′), 68.7 (C-1), 62.8 (C-6′), 44.2 (C-16), 39.6 (C-3), 33.4 (C-10), 25.3 (C-11), 21.7 (C-4) ([a,b]revised assignments are possible).

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References and Notes

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(15) Histamine derivatives of secologanin are unknown from plant sources and therefore may not be considered as natural products. However, for the sake of simplicity, alkaloid-like names are used for the compounds described in this paper, i.e., the parent name histeloside for the tricyclic esters and the name histelosamide for the lactams. In the formulas, a numbering system analogous to the ipecoside derivatives[5] was applied. In accordance with our previous papers,[4] in the descriptions of the stereogenic elements, the letters R and S are used for the configuration of the new chiral center C-1, the numbers 11, 12, etc. for the rotation pattern around the methylene bridge, the letters N and P for the negative and positive conformation of the dihydropyran and tetrahydroyridine rings, and the letters A and E for the axial and equatorial position of the eventual benzyl group, respectively.
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