Regio- and Stereoselectivity in the Coupling Reaction of Secologanin with Dopamine Derivatives†

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The coupling reaction of tetraacetylsecologanin with dopamine and its *N*-benzyl derivative was investigated. In both series, stereoisomers at C-1, as well as regioisomer normal and neo compounds, were formed. Moreover, the *N*-unsubstituted products were partially lactamized, and the *N*-benzyl derivatives epimerized at C-1. In the products, the *R* configuration of C-1 over the *S* and the formation of the normal structure over the neo one predominated. The epimerization of both epimers gave an equilibrium of *R* and *S* in a ratio of 7:3 and was interpreted by cleavage of the C-1−N-2 bond. The fact that lactamization was much faster in the *R* than in the *S* series was explained on the basis of the supposed transition states. The structure, the configuration of C-1, and in several cases the conformations were established by detailed NMR studies and supported by chemical correlations.

Introduction

A special class of isoquinoline alkaloids can be derived, formed, and prepared by coupling secologanin (**1**) with dopamine (**2**) and related compounds.[2] Typical representatives of these alkaloids are emetine and ipecoside from *Cephaelis ipecacuanha* A. Rich. (Rubiaceae). A. R. Battersby and co-workers were the first to demonstrate the terpenoid origin of the non-dopamine part of these alkaloids.[3] It was found that secologanin with dopamine at pH 5 gave 2-deacetylisoipecoside (deacetyl-**3c**) and 2-deacetylipecoside (deacetyl-**3d**) in approximately a 1:4 ratio. The structure and configurations of the products were predetermined by those of the coupling partners, except for the configuration of the newly formed center of chirality at C-1. However, regarding this point, there was some confusion because in the matrix of the reactions used in the chemical and stereochemical correlations, a hidden epimerization gave incorrect results. Finally, X-ray diffraction analysis of 7-*O*,8-*O*-dimethylipecoside (**3e**) proved unequivocally the *R* configuration at C-1.[4] In this way, the configurations of the compounds derived from ipecoside, i.e., representatives of the **R** series, were experimentally established. Later, from NMR measurements presented by Zenk and co-workers, the assignment of the configuration at C-1 was extended to the lactams of the **R** series [i.e., the alangiside (**7d**) derivatives, e.g., 8-*O*-methylalangiside] as well.[5] However, no direct determination was carried out in compounds having the 1*S* configuration, i.e., in the **S** series. Moreover, since in dopamine the C-2′ and C-6′ are chemically nonequivalent, it was expected that the coupling reaction might give normal (cyclization at C-6′) and neo (cyclization at C-2′) regioisomers. Although neo derivatives were isolated from *Cephaelis ipecacuanha* and *Alangium lamarckii* Thw. (Alangiaceae) by Nagakura and co-workers,[6−8] their formation in the coupling reaction of secologanin and dopamine was not described. Previously, there was some confusion about the biogenesis of these alkaloids as well. Now, it seems to be firmly established that labeled 2-deacetylipecoside (with 1*R*) was incorporated into alangiside (1*R*) and ipecoside (1*R*), whereas 2-deacetylisoipecoside (1*S*) is a precursor of the emetine alkaloids (1*S*).[9] De-Eknamkul and co-workers described the enzymatic condensation of secologanin and dopamine under cell-free conditions.[10] It was found that compounds of both the series **R** and **S** were formed. However, after purification of the crude enzyme preparation, only the activity of the enzyme catalyzing the formation of the compounds of the **R** series could be demonstrated. No mention was made concerning the formation of neo isomers or the possible isomerization of C-1 in the products obtained. Therefore, as an extension of our work on the chemistry of secologanin, the coupling reaction of secologanin and dopamine under chemical conditions was investigated.

Results and Discussion

Previous experiments on analogous reactions of the *β*-carboline series showed that the stereoselectivity of the coupling reaction could be strongly influenced by the substituent on the N atom (H, methyl, or benzyl group) and by the solvent (protic, dipolar-aprotic, or apolar).[11] However, in the dopamine series these conditions did not give dramatic changes in the stereoselectivity. Finally, to have mild conditions under which the reactions would be complete in a relatively short time, the reactions were carried out in acetonitrile or methanol with *O*,*O*,*O*,*O*-tetraacetylsecologanin (**1a**) and dopamine (**2**) or *N*-benzyldopamine (**2a**) prepared from homoveratrylamine (**2b**). Under such conditions, the coupling reaction was complete under reflux in less than 1 h. The thin-layer chromatogram showed several spots, which indicated that in both series (*N*-unsubstituted and *N*-alkylated) not only stereoisomers at C-1 but also normal and neo regioisomers were formed. Moreover, the *N*-unsubstituted products were partially cyclized to lactams, which were separated by preliminary column chromatography into sample A (amide fraction, **7a**, **7b**, **8b**) and sample B (ester fraction, **3a**, **4a**) according to the tetracyclic lactams and the tricyclic esters.[12] (See Chart 1 for structures.)

The relative amounts of the different components of the crude product mixtures (**3**−**4**, **5**−**6**, **7**−**8**) were estimated

† Part 8 in the series Chemistry of Secologanin. For Part 7, see: Károlyházy, L. et al.[1]

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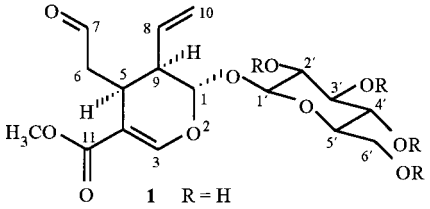
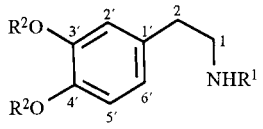
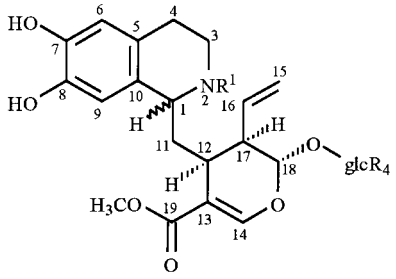
Chart 1



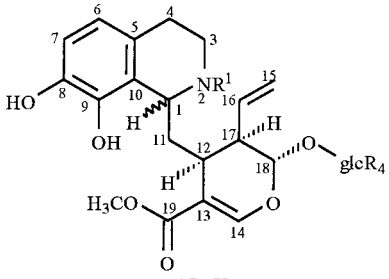
1 R = H
1a R = $COCH_3$



2 $R^1 = R^2 = H$
2a $R^1 = CH_2C_6H_5$, $R^2 = H$
2b $R^1 = H$, $R^2 = CH_3$



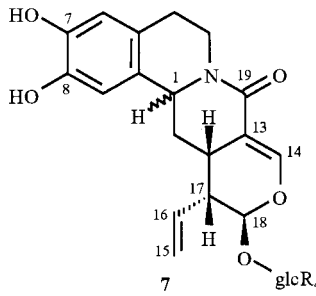
3 R = H
3a H-1α, R^1 = H, R = acetyl
3b H-1β, R^1 = H, R = acetyl
3c H-1α, R^1 = acetyl, R = H (isoipecoside)
3d H-1β, R^1 = acetyl, R = H (ipecoside)
3e H-1β, R^1 = acetyl, R = H, 7-*O*,8-*O*-dimethyl



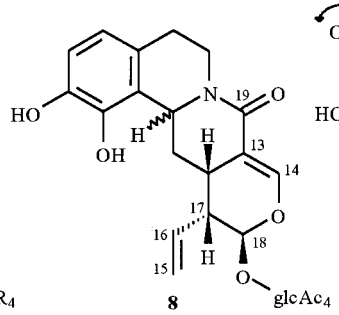
4 R=H
4a H-1α, R^1 = H, R = acetyl
4b H-1β, R^1 = H, R = acetyl
4c H-1α, R^1 = acetyl, R = H (neoisoipecoside)
4d H-1β, R^1 = acetyl, R = H (neoipecoside)

5 R^1 = benzyl
5a H-1α, R^1 = benzyl, R = acetyl
5b H-1β, R^1 = benzyl, R = acetyl

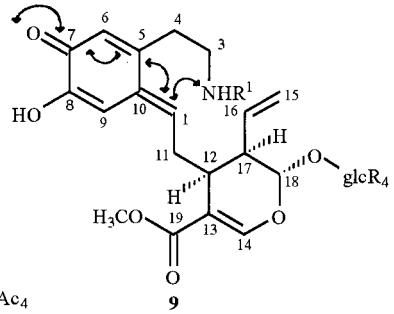
6 R^1 = benzyl
6a H-1α, R^1 = benzyl, R = acetyl
6b H-1β, R^1 = benzyl, R = acetyl



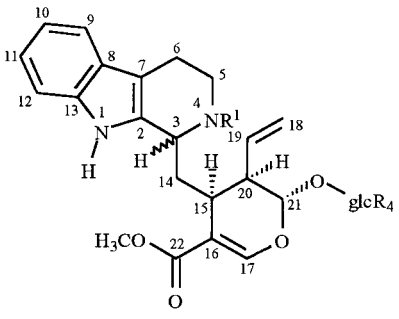
7
7a H-1α, R = acetyl
7b H-1β, R = acetyl
7c H-1β, R = H, (7-*O*-demethylalangiside)
7d H-1β,R = H, 7-*O*-methyl (alangiside)



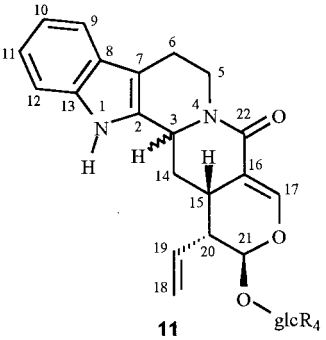
8
8a H-1α
8b H-1β



9
R^1 = benzyl, R = acetyl



10
10a H-3α, R^1 = H, R = H (strictosidine)
10b H-3β, R^1 = H, R = H (vincoside)
10c H-3α, R^1 = 4′′-bromobenzyl, R = acetyl
10d H-3β, R^1 = 4′′-bromobenzyl, R = acetyl



11
11a, H-3α, 18,19-dihydro, R = acetyl
11b, H-3β, 18,19-dihydro, R = acetyl
$glcR_4$ = β-D-glucopyranosyl, if R = H
$glcR_4$ = *O*′,*O*′,*O*′,*O*′-tetraacetyl-β-D-glucopyranosyl, if R = acetyl

by the intensity and multiplicity of the aromatic protons of the dopamine subunit in the ^{1}H NMR spectrum and expressed in percentage of the total amount of the products. The normal derivatives were easily distinguished from the neo ones, as the former had two singlet peaks and the latter two doublet peaks in the aromatic region of the ^{1}H NMR spectrum (Table 1). Lactamization was followed by a decrease of the intensity of the singlet of the methoxycarbonyl group at ~3.5 ppm. Likewise, the presence of the vinyl and benzyl groups was established by the appropriate

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

compound	%	H-6		H-7		H-9	
3a	12	6.49	s			6.34	s
3b	<2						
4a	12	6.73	d 8.1	6.39	d 8.1		
4b	<2						
7a	8	6.72	s			6.66	s
7b	40	6.66	s			6.62	s
8a	<2						
8b	28	6.72	d 8.0	6.49	d 8.0		
5a	16	6.69	s			6.45	s
5b	70	6.58	s			6.35	s
6a	<2						
6b	14	6.72	d 8.2	6.58	d 8.2		

[a] In ppm, % = relative amount of isomers formed in the coupling reaction, s = singlet, d = doublet.

proton signals. Determination of the configuration of C-1 required stereochemical analysis (see later).

The chromatograms combined with NMR data provided the product distribution of the reaction cascade (Table 2). These data reflected a "cross section" of the reactions at 1 h, rather than in the final state. At a longer reaction time (about 6 h) the lactamization was nearly complete, and epimerization was observed at C-1. Finally, the major components or isomeric pairs were isolated by repeated column chromatography, and their structures determined by NMR spectroscopy.

The epimerization of C-1 was investigated in detail for compounds **5a** and **5b**. The reaction was followed by the change of the intensity of the aromatic protons of the dopamine subunit in the ^{1}H NMR spectrum. The half-time of the reaction is about 36 h at room temperature in chloroform, i.e., definitely slower than that of the coupling reaction, but comparable to the half-time for the lactamization in the **S** series. In methanol or acetonitrile the epimerization was not observed. The equilibrium state could be approached from both sides, and the ratio of the 1*S* and 1*R* epimers was found to be 3:7 in the equilibrium mixture. No epimerization was observed after methylation of the phenolic hydroxyl groups or in the phenolic lactams, indicating the assistance of both the phenolic group(s) and the basic nitrogen in the process. During epimerization, the formation of the neo isomer from the normal one was not observed. Therefore, it was concluded that in the epimerization the C-1−N-2 bond was cleaved, rather than the C-1−C-10 bond. On the basis of these experimental facts, the isomerization was interpreted as proceeding through **9** according to the curved arrows. A similar isomerization was not observed in the analogous tryptamine derivatives.

The following conclusions were drawn about the selectivity of the coupling reaction based on the data of Table 2. (1) The stereoselectivity at C-1 is favored for the **R** series over the **S** series and further increased in the *N*-benzyl derivatives. (2) The lactamization is definitely faster in the **R** series than in the **S** series. Therefore with a short reaction time, derivatives of the **S** series could be obtained as esters, and those of the **R** series as lactams. (3) Formation of the normal isomers is slightly favored over the neo isomers and was slightly increased by *N*-benzylation.

The structural investigation of the compounds was assisted by previous results obtained in the β-carboline series.[11] In all derivatives (except **3a** and **4a**, see later) the $^3J_{H17,H18}$ coupling constant had a small value (1.7−2.8 Hz), which indicated the negative conformation of the dihydropyran ring.

With respect to stereochemical analysis, the lactam derivatives will be discussed first. Since the most detailed spectroscopic information was obtained for **7c**, this compound also served as a reference for the analysis of the other lactam derivatives. Compound **7c** was prepared by the direct coupling of secologanin (**1**) and dopamine (**2**). The rotation around the bonds C-1−C-11 and C-11−C-12 defines nine possible staggered conformers, which were characterized by the relative orientations (antiperiplanar or synclinal) of the hydrogens of C-11 to H-1 and H-12 (Table 3). As in the lactams in the tryptamine derivatives, in both the **R** and **S** series only two of the C-11 conformers have the nitrogen and the methoxycarbonyl group in an appropriate orientation for cyclization. According to our previous notation,[11] these are **R12** and **R33**, as well as **S13** and **S31**. In **7c**, one of the H-11 protons displayed large coupling constants to H-1 (11.5 Hz) and H-12 (13.3 Hz), which involve antiperiplanar orientation. This pattern corresponds to only one (**R12**) of the four preselected conformers. As the configuration at C-12 of the secologanin subunit was established to be *S* by X-ray diffraction analysis of 7-*O*,8-*O*-dimethylipecoside (7-*O*,8-*O*-dimethyl-**3d**),[4] and this involves the β axial orientation of H-12 to the lactam ring in the usual representation, the coupling constants mentioned previously established the β axial orientation of H-1 and the negative dihedral angle of the lactam ring along the C-11−C-12 bond, as well as the *R* configuration of C-1 in **7c**. The conformation of the tetrahydropyridine ring in **7c** is partially predetermined by the lactam ring. As the dihedral angle C-11−C-1−N-2−C-19 is necessarily negative, the orientation of C-10 and C-3 may be either α-equatorial−α-axial (cis) or α-equatorial−β-equatorial (trans). One of the H-3 protons displayed a high paramagnetic shift (4.65 ppm), which was caused by the magnetic anisotropy of the carbonyl group; consequently, it should be in the N−C−O plane. This is possible only for the H-3α in a negative conformation of the tetrahydropyridine ring. In a positive conformation, both H-3 atoms (α and β orientations) would be outside of this plane. This conformation is also in agreement with the coupling constant pattern of H-3 and H-4 atoms. In summary, the stereostructure of **7c** is described as **R12NN**.[14] These stereochemical results were also considered to be correct for the other derivatives, where not all these NMR parameters could be determined. The identities of the stereostructures were based on the similarity of the key parameters.

The amide fraction from the coupling reaction of *O*,*O*,*O*,*O*-tetraacetylsecologanin (**1a**) with dopamine (**2**) afforded **7b** and **8b** as pure products, but **7a** could be demonstrated only as an accompanying component. The presence of **8a** could not be established reliably because of its low concentration. As in **7c**, in **7b** and **8b** one of the hydrogens of the C-11 displayed large coupling constants with both vicinal hydrogens H-1 and H-12, and one of the H-3 atoms gave a signal at high chemical shift. According to these data, in both compounds, the configuration of C-1 is *R*, H-1 has a β axial orientation, the conformation around C-11 is **R12**, and the dihedral angle of the tetrahydropyridine ring has a negative value. Thus, they could be described likewise as **R12NN**.

In the **S** series, the normal lactam **7a** was found only as a minor product in a sample containing **7a** and **7b** in a 1:5 ratio. Although only a few spectroscopic characteristics of **7a** could be measured, its presence was clearly demonstrated in the ^{1}H NMR spectrum of the epimer mixture by an "anomalous" chemical shift (δ 1.51 instead of $\sim\delta$ 2.0)

Table 2. Product Distribution in the Coupling Reaction in Percent

		N-unsubstituted						*N*-substituted				
		open		lactam	open + lactam	nor/neo	1*S*/1*R*	open		nor/neo	1*S*/1*R*	
normal	1α	**3a**	12	**7a**	8	20	60	**5a**	16	86	16	
	1β	**3b**	<2	**7b**	40	40	32	**5b**	70			
neo	1α	**4a**	12	**8a**	<2	12	68	**6a**	<2	14	84	
	1β	**4b**	<2	**8b**	28	28	40	**6b**	14			
open/lactam			24		76							

Table 3. Relative Orientation of H-1 and H-12 to H-11*proR* and H-11*proS*[a]

H-1	H-12	H-1	H-12	H-1	H-12	H-11	H-1	H-12	H-1	H-12	H-1	H-12
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 position of the appropriate H's, respectively.

for the proton singlet of one of the acetyl groups. This signal is well known in all tetraacetyl lactam derivatives of the strictosidine (**10a**) (3*S*) and isoipecoside (**3c**) (1*S*), but not of the vincoside (**10b**) (3*R*) and ipecoside (**3d**) (1*R*) series.[5,11,15,16] The signal may be used for identification on the basis of the following arguments.

In the detailed analysis of the analogous β-carboline (tryptamine) derivative (*O*′,*O*′,*O*′,*O*′-tetraacetyl-18,19-dihydrostrictosamide **11a**, numbering according to the β-carboline derivatives), it was demonstrated by a selective INEPT experiment that the "anomalous" diamagnetic shift came from the hydrogens of the 2′-acetoxy group of the β-D-glucopyranosyl unit.[11] The same result was established by Aimi and co-workers in 7-*O*-methylisoalangiside tetraacetate (7-*O*,8-*O*-dimethyl-**7a**) on the basis of HMBC measurements.[17] The steric proximity of these hydrogens to H-9 and H-11 of the indole ring in **11a** was likewise established by cross-peaks in the NOESY spectrum. As the pentacyclic aglucon subunit is rigid, the distance between the interacting groups depends principally on the conformation around the glucosidic oxygen. Conformational analysis showed that the 2′-acetoxy group, independently of its rotation, can be proximate to the aromatic ring only in the **G11** conformation of the nine possible conformations around the glucosidic O bridge. Previously,[18] it was demonstrated that in this conformation one of the nonbonding orbitals of the O-21 atom is antiperiplanar to the O-17−C-21 bond, the other to the C-1′−O-5′ bond (stabilization by double σ-conjugation; this interaction is shown by curved arrows in Figure 2 at the appropriate sites of the three-dimensional picture of the tetrahedral intermediate toward the analogous **7a**). Therefore, it was clear that the anisotropic effect of the aromatic indole ring was responsible for the "anomalous" shift (∼1.2 ppm instead of ∼2.0 ppm) in **11a**. The presence of the same (although less diamagnetic) "anomalous" chemical shift in the spectrum of **7a** suggested the same steric arrangement in the dopamine derivative (the *S* configuration of C-1, conformation **S31** around C-11, a negative conformation of the dihydropyran and tetrahydropyridine rings, i.e., **S31NN**, and a **G11** conformation around the glucosidic O). The "anomalous" shift could not be observed either in **11b** or in **7b**.

The investigation of the stereochemistry of the tricyclic esters was more complicated because the conformations around C-11 were not fixed by ring formation.

In the *N*-unsubstituted series, the lactamization already started in the coupling reaction mixture. This subsequent reaction was so fast in the **R** series that the presence of **3b** and **4b** could not be demonstrated in the crude sample B. As in the **S** series, the lactamization was slower, and the appropriate normal **3a** and neo **4a** esters were obtained, but in a moderate yield. Because of their very similar chromatographic properties, the two regioisomers could not be separated. According to the proton signals in the aromatic region (Table 1), **3a** and **4a** were formed in a 1:1 ratio in the coupling reaction. Although most of their other signals (at least partially) overlapped, in the ^{13}C NMR spectrum two complete series of signals were noted, and the differences of the chemical shifts of the two compounds were in most cases less than 1 ppm. The highest difference (3.5 ppm) was observed in the chemical shift of C-1, which is sterically close to C-9, where the ligand is different in the two isomers (H in **3a** vs OH in **4a**). This shift difference might be ascribed to the γ-steric effect of the OH group in the neo isomer. To establish the configuration at C-1, the sample containing **3a** and **4a** was refluxed in acetonitrile in the presence of triethylamine and triethylammonium chloride. In the ^1H NMR spectrum of the isolated nonbasic product, the signal of the methoxycarbonyl protons disappeared, and an "anomalous" chemical shift was measured at 1.54 ppm, in the expected position. The appearance of this shift was a clear indication of the presence of the lactams having a 1*S* configuration (**7a** and **8a**). Control experiments established that the lactams could not be epimerized. Consequently, lactams **7a** and **8a** should be formed from **3a** and **4a**, respectively, also having a 1*S* configuration. A further analogy should be mentioned at this point. The value of $^3J_{H17,H18}$ in the epimeric pair **3a** and **4a** is relatively large (7 Hz) and close to the analogous value (8.8 Hz) in strictosidine (**10a**), which also suggested the positive conformation of the dihydropyran ring in these compounds. Conformational analysis of **10a** showed that the negative conformation is strongly disfavored. These observations were sufficient to establish the formation of the normal−neo isomer pair **3a** and **4a** in the coupling reaction and the *S* configuration at C-1, but further information about the conformation around C-11 and in the tetrahydropyridine ring could not be obtained. Therefore, the stereostructure should be given as **SXXPY**, where **X** and **Y** indicate unknown conformations.

From the coupling reaction with *N*-benzyldopamine (**2a**), compounds **5b** and **6b** of the **R** series were isolated in the pure state. The stereochemistry of **5b** was established by detailed NMR studies. The proton H-1 displayed a large coupling constant with one of the H-11 protons, and H-12

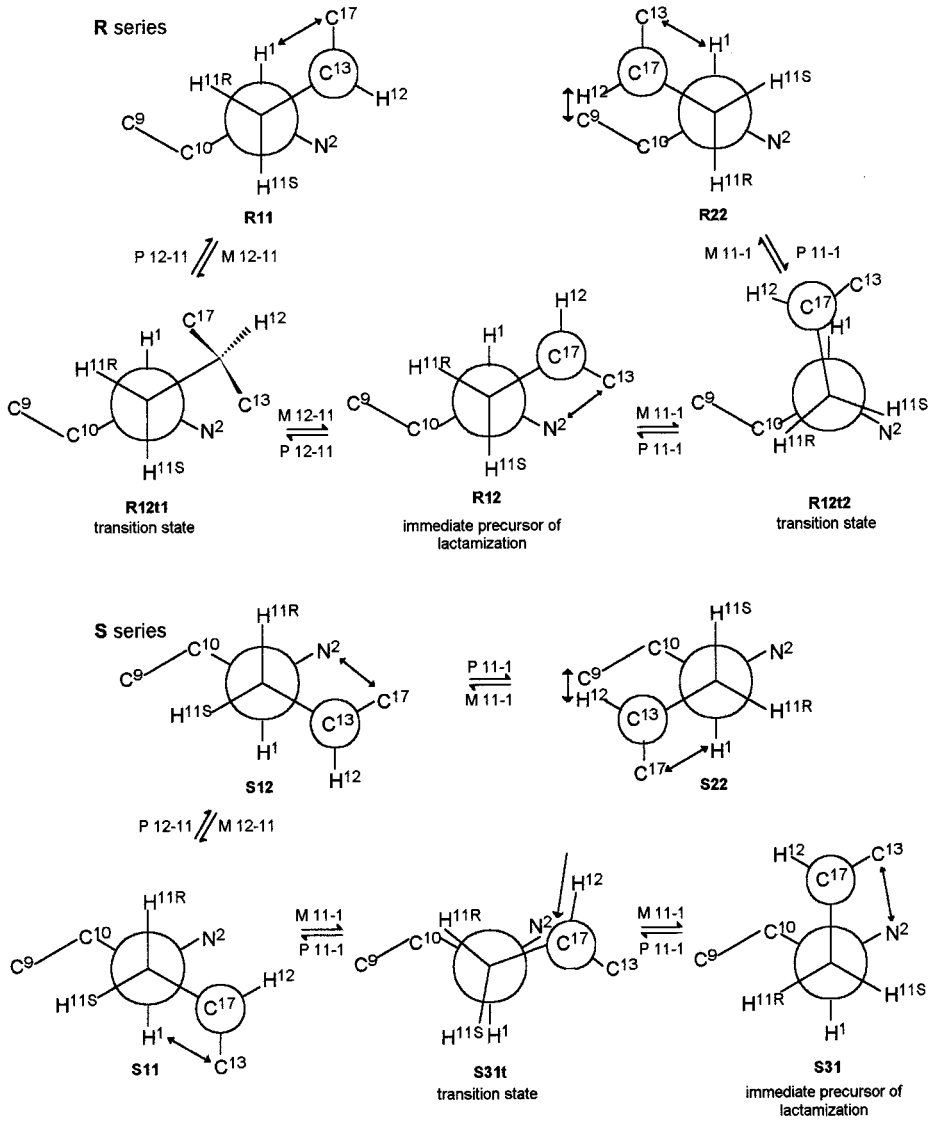


Figure 1. Transition states in the formation of the precursor conformers for the lactamization.

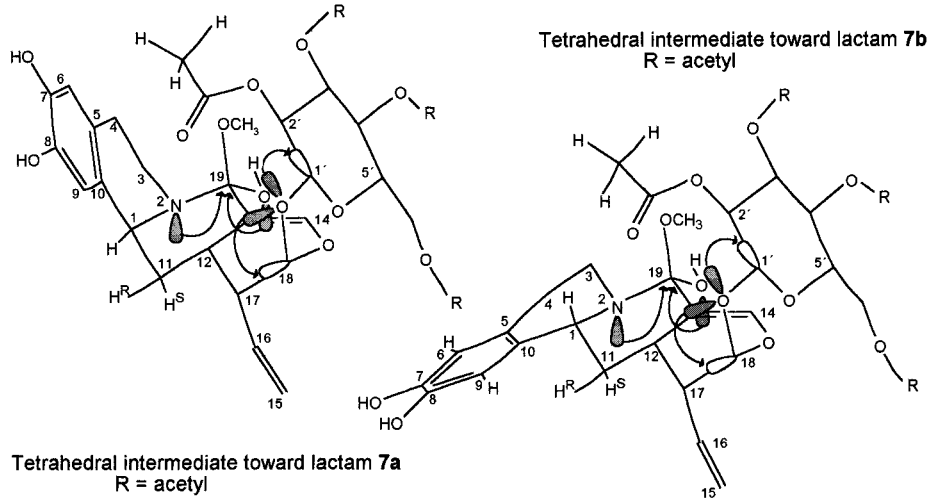


Figure 2. Three-dimensional structure of the tetrahedral intermediates giving the lactams **7a** and **7b**.

with the other H-11 proton. These data were in agreement only with the conformers (**R** or **S**)**11** and (**R** or **S**)**22** (Table 4). The actual stereostructure, out of the eight possibilities (conformer **11** or **22** in the **R** or **S** series with negative or positive dihedral angle in the tetrahydropyridine ring), was established by comparison of three pairs of through-space interatomic distances calculated from experimental NOE data ("calculated" values) and measured on computer-generated molecular models ("measured" values).[19] As shown in Table 4, there are large differences in the

Table 4. Comparison of Selected Through-Space Interatomic Distances in Å Derived from NOE Enhancements and Measured on Computer-Generated Models[a]

	calculated from NOE	measured on model							
		R11NN	**R11NP**	**R22NN**	**R22NP**	**S11NN**	**S11NP**	**S22NN**	**S22NP**
H-1−H-9	2.46	**2.89**	**2.51**	**2.88**	**2.60**	**2.51**	**2.88**	**2.52**	**2.88**
H-1−H-17	2.41	**1.88**	**1.87**	4.71	4.71	4.78	4.72	**1.87**	**1.88**
H-3ax−H-11a[b]	2.55	4.54	**2.12**	4.58	**1.96**	**2.05**	4.58	**2.11**	4.55
H-9−H-11b[c]	2.61	**2.02**	**2.44**	3.57	3.86	**2.50**	**2.08**	3.87	3.66

[a] Identical values for each of the structures indicated in the table (the first values were derived from NOEs, the second from molecular models): H-1−H-11a: 3.1, 3.0; H-3ax−H-3eq: 2.1, 1.8; H-4ax−H-4eq: 2.1, 1.7; H-11a−H-11b: 2.1, 1.7; H-12−H-17: 2.2, 2.4; H-12−H-18: 3.4, 3.7; H-17−H-18: 2.3, 2.5; H-16−H-15*Z*: 3.1, 3.1; H-16−H-15*E*: 2.4, 2.4; H-15*Z*−H-15*E*: 1.9, 1.9; H-4ax−H-6: 3.1, 2.9; H-4eq−H-6: 2.6, 2.5. [b] H-11a is ap to H-1. [c] H-11b is ap to H-12.

measured alternative values ("measured" values in bold fit well the calculated values; those in plain do not). Therefore, the short distance of H-1−H-17 justified the conformation (**R**)**11** around C-11, that of H-3ax−H-11a confirmed the *R* configuration of C-1, and that of H-9−H-11b supported the positive conformation of the tetrahydropyridine ring; that is, the stereochemical description of **5b** is **R11NP**. Further ^{1}H NMR data and analysis, not detailed here, indicated the trans diaxial orientation of the two large ligands C-11 and the benzyl group, at C-1 and N-2, respectively.

In **6b**, the ^{1}H NMR chemical shifts and the H,H coupling constants which were relevant for the conformation around C-11 and in the tetrahydropyridine ring showed values close to those found in **5b**. In the ^{13}C NMR spectrum of **5b** and **6b** the difference of the chemical shifts in the signal pairs of the secologanin subunit of the molecules was smaller than 1 ppm, except for the signal of C-1. The chemical shift difference at C-1 (3.5 ppm) was interpreted again as due to the γ-steric effect of the O-9 atom. These observations suggested the same stereochemistry for **6b** as in **5b**, i.e., **R11NP**.

Of the 2-benzyl derivatives in the **S** series, only the normal **5a** could be isolated from the coupling reaction in sufficient amount; the formation of the neo isomer **6a** could not be detected. The configuration of C-1 in **5a** was derived from the epimerization experiment. Unfortunately, **5a** could be purified only to 80% purity. According to the ^{1}H NMR spectrum, the minor component was the epimer **5b**. During epimerization, the intensity of the main signals decreased, and that of the minor ones increased. In the epimerization of **5b**, parallel to the decrease of the original signals, new resonances appeared which were identical to those of **5a**. So the changes in the intensities of the signals were mutually opposite and complementary in the spectra of the two samples. Finally, in the equilibrium state, the spectra of the two samples became identical. Comparison of the ^{1}H and ^{13}C NMR parameters of **5a** and **5b** with those of the analogous derivatives in the β-carboline series (**10c** and **10d**) also afforded reasonable correlations. As in **5b**, also in **5a** the two bulky ligands at C-1 and N-2 should be in a trans diaxial orientation, which involves a necessarily negative conformation of the tetrahydropyridine ring. Therefore, the epimerization of **5b** to **5a** (and vice versa) was accompanied by the inversion of the tetrahydropyridine ring. These conformational changes were supported by the values of the appropriate coupling constants of H-3 and H-4. Unfortunately, the experimental data were not sufficient to establish the conformation around C-11. Therefore, the stereochemistry of **5a** may be summarized as **SXXNN**. The fact that the equilibrium mixture contains the two epimers in a 3:7 ratio indicates a difference of ∼2 kJ/mol in the free enthalpy of formation between them. It would be inappropriate to interpret this small difference in structural terms.

At this point, it should be noted that the epimerization observed was not restricted to the *N*-benzyl derivatives. In the lactamization experiment of **3a** and **4a** described above, the ^{1}H NMR spectrum of the product mixture showed signals that should be assigned to the lactams having the 1*R* configuration (**7b** and **8b**). Therefore, the epimerization of C-1 should be considered as a general phenomenon in the dopamine derivatives of secologanin, and it may have some significance in the biogenesis. It is known that in the tryptamine series the coupling reaction is catalyzed by strictosidine synthase with complete stereoselectivity and that most of the alkaloids that contain the unrearranged carbon skeleton of the secologanin subunit have the 3*S* configuration (if it is present at all). The coupling reaction in the dopamine series in the presence of an enzyme is not completely clear yet.[10] However, compounds of both the 1*S* and 1*R* series were isolated from plants.[8] In the interpretation of the biosynthetic results (described mainly in refs 9, 10) this fact should be taken into consideration.

According to previous observations,[11,20] the lactamization took place under milder reaction conditions in the vincoside (**R**) series (e.g., **10b**) than in the strictosidine (**S**) series (e.g., **10a**). The same was found in the ipecoside and isoipecoside series (e.g., **3b** and **3a**, respectively). The phenomenon should be attributed to two factors. The first concerns the formation of the tetrahedral intermediate (cyclization), and the second that of the final product (lactam).

The rate of cyclization depends on the structure of the transition state between tricyclic educts and the tetrahedral intermediate and involves rotation along the appropriate bond(s). While the conformations around C-11 of the tetrahedral intermediates could be predicted to be close to that of the lactams, i.e., **R12** and **S31**, respectively, the analogous conformations of the tricyclic educts were unknown. However, in each series (**R** and **S**), five of the possible nine staggered conformers (Table 3) have H-1 (in **R/S31**, **R/S32**, **R/S33**) and/or H-12 (in **R/S13**, **R/S23**, **R/S33**) in a synclinal position to both H atoms of C-11. Consequently, large (non-H) ligands of C-1 and C-12 are definitely closer than the sum of the van der Waals radii of the appropriate atoms (measured on computer generated models) and therefore are less probable. The same is true for **R/S21**. Therefore all these conformers are less probable (although not improbable or even not impossible) in the equilibrium mixture. The remaining conformers (**R/S11**, **R/S12**, and **R/S22**, shown in Figure 1) can be mutually transformed by rotation along C-1−C-11 and/or C-11−C-12 without passing an eclipsed conformer in which two, non-hydrogen ligands are in a syn periplanar (eclipsed) orientation. Because in the **R** series the precursor for lactamization has the conformation **R12**, which is one of the favored conformers, it could be easily formed through **R12t1** or **R12t2** from any of the others. However, in the **S**

series, the precursor for lactamization having the less-favored conformation **S31** can be formed only through such an eclipsed **S31t** conformer in which two non-hydrogen ligands (N-2 and C-12, indicated by arrow) are in a syn periplanar orientation. Consequently, the lactamization requires higher activation energy and proceeds slowly.

In the second step, the elimination of methanol from the tetrahedral intermediate can take place easily if the leaving methoxy group has an axial orientation in which the elimination is facilitated by the double stereoelectronic effect owing to the nonbonding electron pairs of both the N-2 atom and the O of the geminal hydroxy group (see curved arrows at the reaction sites in Figure 2). However, this intermediate is rather crowded in the **S31** conformer because, as in the final lactam, the aromatic ring is in an axial orientation. The tetrahedral intermediate of **R12** has an uncrowded flat shape and is therefore lactamized more easily.

In summary, it can be established that the coupling reaction between the derivatives of secologanin and dopamine gave both the tricyclic esters and the tetracyclic lactam glucosides in the **R** and **S**, as well as the normal and neo series, and was accompanied by epimerization at C-1 at the ester level. The stereochemistry of the reactions may help to interpret the analogous biogenetic reactions as well.

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). Internal TMS was used for chemical shift reference. NOESY spectra of **5b** were measured with 0.3, 0.6, and 0.9 s mixing times using the standard Bruker microprogram of the XWINNMR software. The cross-peak intensities were determined by volumetric integration in the XWINNMR program. The hydrogen−hydrogen distances were calculated on the basis of the known 1.9 Å distance of the geminal H_2-15 hydrogens using the isolated two-spin approximation. Similar distances were calculated for the same atomic pairs in all three experiments; the values obtained with 0.9 s mixing time are reported. 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. Thin-layer chromatography (TLC) was carried out on Si gel plates.

Secologanin (**1**) was isolated from *Lonicera xylosteum* L. according to a method elaborated in our Institute.[21]

Reaction of *O,O,O,O*-Tetraacetylsecologanin with Dopamine. Dopamine hydrobromide (**2**·HBr, 0.18 g, 0.5 mmol) was refluxed in a mixture of acetonitrile (2.0 mL) and triethylamine (0.07 mL, 0.5 mmol) until partial dissolution, then *O,O,O,O*-tetraacetylsecologanin (**1a**, 0.28 g, 0.5 mmol) was added, and the mixture was refluxed for 10 min. After evaporation of the solvent, the residue showed the following spots on TLC with $CHCl_3$−MeOH (4:1): **8b** (R_f 0.77), **7a** and **7b** (R_f 0.72), **3a** and **4a** (R_f 0.41). The crude total product was chromatographed on Si gel (35 g) with $CHCl_3$−MeOH (4:1) (each fraction 3 mL). The combined fractions 13−25 gave, after removal of the solvent in vacuo, fraction A ("amide" fraction, 0.196 g, 59%). Fractions 27−36, treated likewise, gave fraction B ("ester" fraction, 0.109 g, 32%). Fraction A was rechromatographed on Si gel (20 g) with $CHCl_3$−Me_2CO (5:1) (each fraction 4 mL). Fractions 22−38 were combined and after evaporation of the solvent gave *O′,O′,O′,O′*-tetraacetyl-neoalangiside (**8b**) (0.056 g, 21%), and fractions 47−76, treated likewise, gave a beige amorphous solid [0.10 g, 37%, R_f 0.17 in $CHCl_3$−Me_2CO (5:1)], which proved to be a mixture of 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetylisoalangiside (**7a**) and 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetylalangiside (**7b**) in a ratio of 1:5. Rechromatography once more gave pure **7b**. Fraction B, a beige amorphous powder, contained two components in approximatively a 1:1 ratio which could not be separated and, according to the subsequent analysis, were established to be *O′,O′,O′,O′*-tetraacetyl-2-deacetylisoipecoside (**3a**) and *O′,O′,O′,O′*-tetraacetyl-2-deacetylneoisoipecoside (**4a**).

***O′,O′,O′,O′*-Tetraacetyl-2-deacetylisoipecoside (3a) and *O′,O′,O′,O′*-Tetraacetyl-2-deacetylneoisoipecoside (4a).** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55, 7.51 (each 1H, s, H-14), 6.73 (1 H, d, $^3J_{6,7}$ = 8.1 Hz, H-6 in **4a**) 6.49 (1H s, H-6 in **3a**), 6.39 (1H, d, $^3J_{6,7}$ = 8.1 Hz, H-7 in **4a**), 6.34 (1H, s, H-9 in **3a**), 5.6 (2H, m, H-16), 5.4, 5.5 (each 1H, d, $^3J_{17,18}$ = 7 Hz, H-18), 4.4, 3.95 (each 1H, m, H-1), 3.79, 3.75 (each 3H, s, OCH_3), 1.83 (each 1H, m, H-11*proR*). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6−169.1 (C-19, four *O′*-CH_3*C*O), 154.3, 154.0 (C-14), 144.4, 143.5, 142.7, 140.8 (C-7 in **3a**, C-8 in **3a** and **4a**, C-9 in **4a**), 132.6, 132.1 (C-16), 122.9, 122.8, 122.3, 120.0 (C-5, C-10), 120.4, 119.5 (C-15), 120.0, 116.1, 115.2, 112.9 (C-6 in **3a** and **4a**, C-7 in **4a**, C-9 in **3a**), 108.3, 108.2 (C-13), 97.0, 96.9, 96.8, 96.6 (C-18, C-1′), 72.4 (C-3′), 71.7 (C-5′), 70.6 (C-2′), 67.9 (C-4′), 61.4 (C-6′), 52.8 (C-1 in **3a**), 52.3 (OCH_3), 49.3 (C-1 in **4a**), 43.1, 43.0 (C-17), 39.9, 38.0 (C-3), 34.7, 31.9 (C-11), 29.5, 29.1 (C-12), 24.4 (C-4), 20.5−20.4 (*C*H_3CO).

Lactamization Experiment of 3a and 4a. The mixture of *O′,O′,O′,O′*-tetraacetyl-2-deacetylisoipecoside (**3a**) and *O′,O′,O′,O′*-tetraacetyl-2-deacetylneoisoipecoside (**4a**) (0.092 g, 0.133 mmol) was dissolved in MeCN (1 mL), Et_3N (0.019 mL, 0.133 mmol) and Et_3NHCl (0.018 g, 0.133 mmol) were added, and the reaction mixture was refluxed for 6 h. After evaporation of the solvent, the residue gave on TLC (MeCOOEt:C_6H_6, 2:1) the following spots: **8a** and **8b** (R_f 0.25), **7a** and **7b** (R_f 0.38). The crude total product was taken up in $CHCl_3$ (10 mL) and consecutively washed with 2 M aqueous HCl (2 × 5 mL) and water (4 × 5 mL), dried, and evaporated, affording a beige amorphous solid (0.037 g), which proved to be a mixture of the following products: 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetyl-neoisoalangiside (**8a**, 20%), 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetylneoalangiside (**8b**, 13%), 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetylisoalangiside (**7a**, 48%), and 7-*O*-demethyl-*O′,O′,O′,O′*-tetraacetylalangiside (**7b**, 19%). ^{1}H NMR signals used in identification of the products ($CDCl_3$): in **7a** δ 7.35 (1H, d, $^4J_{12,14}$ = 2.3 Hz, H-14), 1.55, 1.94 (3H×2, both s, CH_3CO); in **7b** δ 7.44 (1H, d, $^4J_{12,14}$ = 2.3 Hz, H-14); in **8a** δ 7.17 (1H, d, $^4J_{12,14}$ = 2.6 Hz, H-14), 1.55, 1.94 (3H×2, both s, CH_3CO); in **8b** δ 7.48 (1H, d, $^4J_{12,14}$ = 2.4 Hz, H-14).

7-*O*-Demethyl-*O′,O′,O′,O′*-tetraacetylalangiside (7b). ^{1}H NMR (C_6D_6, 400 MHz): δ 7.82 (1H, d, $^4J_{12,14}$ = 2.1 Hz, H-14), 6.62 (2H, s, H-6, H-9), 5.48−5.32 (3H, m, H-2′, H-3′, H-4), 5.28 (1H, d, $^3J_{17,18}$ = 1.6 Hz, H-18), 5.24 (1H, m, H-16), 4.9−4.83 (3H, m, H_2-15, H-3α), 4.78 (1H, d, $^3J_{1',2'}$ = 7.8 Hz, H-1′), 4.33 (1H, dd, $^3J_{1,11S}$ = 12.5, $^3J_{1,11R}$ = 3.5, H-1), 4.30 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'a}$ = 3.8 Hz, H-6′a), 3.98 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'b}$ = 2.0 Hz, H-6′b), 3.17 (1H, m, H-5′), 2.89 (1H, m, H-12), 2.70−2.56 (2H, m, H-3β, 4-Hα), 2.34 (1H, ddd, $J_{16,17}$ = 9.9, $J_{12,17}$ = 5.9, $J_{17,18}$ = 1.6 Hz, H-17), 2.22 (1H, m, H-4β), 1.80 (1H, dt, $^2J_{11R,11S}$ = 12.5, $^3J_{1,11R}$ = $^3J_{11R,12}$ = 3.5 Hz, H-11pro*R*), 2.01 (3H, s, CH_3−CO), 1.70 (9H, s, CH_3−CO), 1.29 (1H, q, $^2J_{11R,11S}$ = $^3J_{11S,12}$ = $^3J_{1,11S}$ = 12.5 Hz, H-11pro*S*). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.8, 170.1, 169.9, 169.6 (each CH_3*C*O), 163.9 (C-19), 147.2 (C-14), 143.4[a] (C-7), 143.2[a] (C-8), 131.6 (C-16), 128.0[b] (C-5), 126.7[b] (C-10), 120.7 (C-15), 115.2[c] (C-6), 112.3[c] (C-9), 108.3 (C-13), 96.3[d] (C-18), 96.1[d] (C-1′), 72.3[e] (C-5′), 72.3[e] (C-3′), 70.6 (C-2′), 68.2 (C-4′), 61.8 (C-6′), 55.7 (C-1), 42.6 (C-17), 40.1 (C-3), 33.4 (C-11), 28.3 (C-4), 26.5 (C-12), 20.8, 20.6, 20.6, 20.6 (each *C*H_3CO); [a−e]revised assignment is also possible.

7-*O*-Demethyl-*O′,O′,O′,O′*-tetraacetylisoalangiside (7a) and 7-*O*-Demethyl-*O′,O′,O′,O′*-tetraacetylalangiside (7b) (a mixture in 1:5 ratio). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.43 (1H, d, $^4J_{12,14}$ = 2.4 Hz, H-14), 7.34 (0.2H, d, $^4J_{12,14}$ = 2.5 Hz, H-14, in **7a**), 6.72 (0.2H, s, H-6, in **7a**), 6.66 (1H, s, H-6), 6.66 (0.2H, s, H-9, in **7a**), 6.62 (1H, s, H-9), 5.42 (1H, dt, $^3J_{15Z,16}$ = 17.1, $^3J_{15E,16}$ = 9.4, $^3J_{16,17}$ = 9.4 Hz, H-16), 5.28 (1H, d, $^3J_{17,18}$ = 1.9 Hz, H-18), 4.8−5.3 (6H, m, H-1′, H-2′, H-3′, H-4′, H-15*Z*, H-15*E*), 4.65 (1H, dd, $^3J_{1,11R}$ = 2.5, $^3J_{1,11S}$ = 11.9 Hz, H-1), 4.74 (1H, m, H-3α), 4.33 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, H-6′a), 4.14 (1H,

dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.1 Hz, H-6′b), 3.77 (1H, ddd, $^3J_{4',5'}$ = 9.7, $^3J_{5',6'a}$ = 4.5, $^3J_{5',6'b}$ = 2.1 Hz, H-5′), 2.5−3.0 (5H, m, H-3*β*, H-4α, H-4*β*, H-12, H-17), 2.17 (1H, ddd, $^2J_{11S,11R}$ = 13, $^3J_{1,11R}$ = 2.5, $^3J_{11R,12}$ = 3.3 Hz, H-11*proR*), 2.11, 2.04, 2.02, 1.97 (each 3H, s, CH_3CO), 2.09, 2.03, 1.94, 1.51 (each 0.6H, s, CH_3CO, in **7a**), 1.41 (1H, td, $^2J_{11S,11R}$ = 13, $^3J_{1,11S}$ = 11.9, $^3J_{11S,12}$ = 13.0 Hz, H-11*proS*).

7-*O*-Demethyl-*O′*,*O′*,*O′*,*O′*-tetraacetylneoalangiside (8b). A beige amorphous solid [R_f 0.28 in $CHCl_3$−Me_2CO (5:1)]): *anal*. C 58.02%, H 5.45%, N 2.03%, calcd for $C_{32}H_{37}NO_{14}$, C 58.27%, H 5.65%, N 2.12%; UV (EtOH) λ_{max} (log ϵ) 208 (4.35), 232 (4.19), 280 (3.55) nm; IR (KBr) ν_{max} 3600−3300, 1745, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (1H, d, $^4J_{12,14}$ = 2.5 Hz, H-14), 6.72 (1H, d, $^3J_{6,7}$ = 8.0 Hz, H-6), 6.49 (1H, d, $^3J_{6,7}$ = 8.0 Hz, H-7), 5.44 (1H, dt, $^3J_{15Z,16}$ = 17.1, $^3J_{15E,16}$ = $^3J_{16,17}$ = 10 Hz, H-16), 5.29 (1H, d, $^3J_{17,18}$ = 1.9 Hz, H-18), 5.27 (1H, t, $^3J_{2',3'}$ = 9.7, $^3J_{3',4'}$ = 9.7 Hz, H-3′), 5.21 (1H, dd, $^2J_{15Z,15E}$ = 1.8, $^3J_{15Z,16}$ = 17.1 Hz, H-15*Z*), 5.14 (1H, dd, $^2J_{15Z,15E}$ = 1.8, $^3J_{15E,16}$ = 10 Hz, H-15*E*), 5.13 (1H, t, $^3J_{3',4'}$ = 9.7, $^3J_{4',5'}$ = 9.7 Hz, H-4′), 5.06 (1H, dd, $^3J_{1',2'}$ = 8, $^3J_{2',3'}$ = 9.7 Hz, H-2′), 4.95 (1H, d, $^3J_{1',2'}$ = 8 Hz, H-1′), 4.91 (1H, dd, $^3J_{1,11\alpha}$ = 11.0, $^3J_{1,11\beta}$ = 2.2 Hz, H-1), 4.86 (1H, m, H-3α), 4.30 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'a}$ = 4.5 Hz, H-6′a), 4.16 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.2 Hz, H-6′b), 3.77 (1H, ddd, $^3J_{4',5'}$ = 9.7, $^3J_{5',6'a}$ = 4.5, $^3J_{5',6'b}$ = 2.2 Hz, H-5′), 2.99 (1H, m, H-12), 2.65−2.75 (3H, m, H-4α, H-11*β*, H-17), 2.55 (1H, dt, $^2J_{4\alpha,4\beta}$ = 15.7, $^3J_{3\alpha,4\beta}$ = 2.4, $^3J_{3\beta,4\beta}$ = 2.4 Hz, H-4*β*), 2.38 (1H, td, $^2J_{3\alpha,3\beta}$ = 12.6, $^3J_{3\beta,4\alpha}$ = 12.6, $^3J_{3\beta,4\beta}$ = 2.4 Hz, H-3*β*), 2.10, 2.04, 2.02, 2.01 (each 3H, s, CH_3CO), 1.19 (1H, td, $^2J_{11\alpha,11\beta}$ = 13, $^3J_{1,11\alpha}$ = 11.0, $^3J_{11\alpha,12}$ = 13 Hz, H-11α); ^{13}C NMR (CD_3OD, 50 MHz) 171.0, 170.0, 169.0, 169.5 (each CH_3CO), 163.9 (C-19), 147.0 (C-14), 141.9[a] (C-8), 141.8[a] (C-9), 131.9 (C-16), 128.5[b] (C-5), 123.1[b] (C-10), 120.3 (C-15), 119.7[c] (C-6), 114.0[c] (C-7), 108.8 (C-13), 96.8[d] (C-1′), 96.4[d] (C-18), 72.3[e] (C-5′), 72.2[e] (C-3′), 70.7 (C-2′), 68.2 (C-4′), 61.8 (C-6′), 54.1 (C-1), 42.6 (C-17), 39.2 (C-3), 31.0 (C-11), 29.4 (C-4), 27.4 (C-12), 20.8, 20.6, 20.6, 20.6 (each CH_3CO); [a−e]revised assignment is also possible.

Reaction of *O*,*O*,*O*,*O*-Tetraacetylsecologanin with *N*-Benzyldopamine. *N*-Benzyldopamine hydrobromide (**2a**·HBr, 0.114 g, 0.35 mmol) was dissolved in a mixture of H_2O (1.00 mL) and $CHCl_3$ (4.0 mL), and 1 M aqueous solution of NaOH (0.35 mL, 0.35 mmol) was added dropwise and with stirring. After separation of the phases, the aqueous phase was extracted with $CHCl_3$ (3 times, 4.0 mL), the combined organic phase was washed with H_2O and dried, and the solvent was evaporated. The residue (*N*-benzyldopamine, 0.071 g, 0.3 mmol, **2b**) was dissolved in CH_3OH (1.00 mL), *O*,*O*,*O*,*O*-tetraacetylsecologanin (**1a**, 0.163 g, 0.30 mmol) was added, and the reaction mixture was stirred at 50 °C for 30 min. After evaporation of the solvent, the residue gave the following spots on TLC [$CHCl_3$−Me_2CO (5:1)]: **6b** (R_f 0.46), **5b** (R_f 0.35), and **5a** (R_f 0.21). The crude product was purified and separated by column chromatography on Si gel (30 g) with $CHCl_3$−Me_2CO (5:1) (each fraction 3 mL). Fractions containing single compounds were combined, and the eluent was evaporated. Fractions 25−28 gave *O′*,*O′*,*O′*,*O′*-tetraacetyl-2-deacetyl-2-benzylneoipecoside (**6b**) (0.026 g, 11.6%), fractions 29−40 gave *O′*,*O′*,*O′*,*O′*-tetraacetyl-2-deacetyl-2-benzylipecoside (**5b**) (0.115 g, 50.2%), and fractions 46−61 gave *O′*,*O′*,*O′*,*O′*-tetraacetyl-2-deacetyl-2-benzylisoipecoside (**5a**) and *O′*,*O′*,*O′*,*O′*-tetraacetyl-2-deacetyl-2-benzylipecoside (**5b**) in a 4:1 ratio as a colorless, amorphous solid [0.015 g, 6.5%; R_f 0.19 in $CHCl_3$−Me_2CO (5:1)].

***O′*,*O′*,*O′*,*O′*-Tetraacetyl-2-deacetyl-2-benzylisoipecoside (5a)**: *anal*. C 61.11%, H 5.92%, N 1.72%, calcd for $C_{40}H_{47}NO_{15}$, C 61.45%, H 6.06%, N 1.79%; ^1H NMR ($CDCl_3$, 400 MHz) 7.40−7.20 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.26 (1H, d, $^4J_{12,14}$ = 2 Hz, H-14), 6.69 (1H, s, H-6), 6.45 (1H, s, H-9), 5.52 (1H, td, $^3J_{16,17}$ = 10.0, $^3J_{15E,16}$ =10.0, $^3J_{15Z,16}$ = 17.0 Hz, H-16), 5.32 (1H, d, $^3J_{17,18}$ = 2.4 Hz, H-18), 5.30−5.12 (3H, m, H-2′, H-3′, H-4′), 5.16 (1H, dd, $^2J_{15E,15Z}$ = 1.2, $^3J_{15E,16}$ = 10.0 Hz, H-15*E*), 4.90 (1H, dd, $^2J_{15E,15Z}$ = 1.2, $^3J_{15Z,16}$ = 17.0 Hz, H-15*Z*), 4.81 (1H, d, $^3J_{1',2'}$ = 7.9 Hz, H-1′), 4.35 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'a}$ = 4.3 Hz, H-6′a), 4.16 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'b}$ = 2.2 Hz, H-6′b), 3.77 (1H, ddd, $^3J_{4',5'}$ = 10.1, $^3J_{5',6'a}$ = 4.3, $^3J_{5',6'b}$ = 2.2 Hz, H-5′), 3.71 (1H, d, $^2J_{NCHa,NCHb}$ = 12.9 Hz, H-benzyl-CHa), 3.63 (1H, d, $^2J_{NCHa,NCHb}$ = 12.9 Hz, H-benzyl-CHb), 3.57 (3H, s, OCH_3), 3.43 (1H, dd, $^3J_{1,11S}$ = 3.2, $^3J_{1,11R}$ = 9.8 Hz, H-1), 3.18 (1H, td, $^2J_{3\alpha,3\beta}$ = 12.0, $^3J_{3\beta,4\beta}$ = 5.2, $^3J_{3\beta,4\alpha}$ = 12.0 Hz, H-3*β*), 2.96−2.75 (4H, m, H-3α, H-4α, H-12, H-17), 2.44 (1H, dd, $^2J_{4\alpha,4\beta}$ = 16.7, $^3J_{3\beta,4\beta}$ = 5.2 Hz, H-4*β*), 2.20 (1H, m, H-11*S*), 2.13, 2.05, 2.04, 1.87 (each 3H, s, CH_3CO), 1.68 (1H, ddd, $^2J_{11R,11S}$ = 13.5, $^3J_{1,11R}$ = 9.8, $^3J_{11R,12}$ =3.3 Hz, H-11*R*); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.2, 170.7, 170.1, 169.5 (each CH_3CO), 166.9 (C-19), 149.3 (C-14), 143.7[a] (C-7), 140.8[a] (C-8), 139.6 (C-1″), 132.6 (C-16), 129.5[b] (C-5), 129.3 (C-3″, C-5″), 128.2 (C-2″, C-6″), 127.0 (C-4″), 126.3[b] (C-10), 120.7 (C-15), 115.4[c] (C-9), 115.0[c] (C-6), 112.3 (C-13), 95.3[d] (C-18), 94.5[d] (C-1′), 72.4[e] (C-5′), 71.9[e] (C-3′), 70.9 (C-2′), 68.3 (C-4′), 61.5 (C-6′), 57.4 (CH_2-benzyl), 56.9 (C-1), 51.2 (OCH_3), 42.8 (C-17), 42.6 (C-3), 34.6 (C-11), 26.8 (C-12), 23.0 (C-4), 20.8, 20.6, 20.2, 20.1 (each CH_3CO); [a−e] revised assignment is also possible. The sample contains the signals of **5b** with 20% intensity.

***O′*,*O′*,*O′*,*O′*-Tetraacetyl-2-deacetyl-2-benzylipecoside (5b):** white amorphous solid [R_f 0.34 in $CHCl_3$−Me_2CO (5:1)]); *anal*. C 61.12%, H 5.95%, N 1.74%, calcd for $C_{40}H_{47}NO_{15}$, C 61.45%, H 6.06%, N 1.79%; UV (EtOH) λ_{max} (log ϵ) 212 (4.48), 228 (4.20), 291 (3.69) nm; IR (KBr) ν_{max} 3600−3300, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.32 (4H, m, H-2″, H-3″, H-5″, H-6″), 7.25 (1H, d, $^4J_{12,14}$ = 2.1 Hz, H-14), 7.23 (1H, m, H-4″), 6.58 (1H, s, H-6), 6.35 (1H, s, H-9), 5.43 (1H, td, $^3J_{15E,16}$ = 10.1, $^3J_{15Z,16}$ = 17.1, $^3J_{16,17}$ = 10.1 Hz, H-16), 5.28−5.1 (3H, m, H-2′,-3′,-4′), 5.12 (1H, dd, $^2J_{15E,15Z}$ = 2.1, $^3J_{15E,16}$ = 10.1 Hz, H-15*E*), 5.03 (1H, d, $^3J_{17,18}$ = 3.1 Hz, H-18), 4.84 (1H, d, $^3J_{1'}$,$_{2'}$ = 8.2 Hz, H-1′), 4.73 (1H, dd, $^2J_{15E,15Z}$ = 2.1, $^3J_{15Z,16}$ = 17.1 Hz, H-15*Z*), 4.33 (1H, dd, $^2J_{6'a,6'b}$ =12.6 Hz, $^3J_{5',6'a}$ = 4 Hz, H-6′a), 4.27 (1H, dd, $^2J_{6'a,6'b}$ =12.6 Hz, $^3J_{5',6'b}$ = 2.7 Hz, H-6′b), 3.79 (1H, d, $^2J_{NCHa,NCHb}$ = 12.8 Hz, H-benzyl-CHa), 3.73 (1H, m, H-5′), 3.63 (3H, s, OCH_3), 3.54 (1H, d, $^2J_{NCHa,NCHb}$ = 12.8 Hz, H-benzyl-CHb), 3.42 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 14.1, $^3J_{3\alpha,4\alpha}$ = 5.2, $^3J_{3\alpha,4\beta}$ = 12.6 Hz, H-3α), 3.33 (1H, dd, $^3J_{1,11S}$ = 11.7, $^3J_{1,11R}$ =3.2 Hz, H-1), 3.05 (1H, m, H-12), 3.03 (1H, dd, $^2J_{3\alpha,3\beta}$ = 14.1, $^3J_{3\beta,4\beta}$ = 6.5 Hz, H-3*β*), 2.91 (1H, ddd, $^2J_{4\alpha,4\beta}$ = 16.9, $^3J_{3\alpha,4\beta}$ = 12.6, $^3J_{3\beta,4\beta}$ = 6.5 Hz, H-4*β*), 2.37 (1H, ddd, $^2J_{11R,11S}$ = 14.3, $^3J_{1,11S}$ = 11.7, $^3J_{11S,12}$ = 2.7 Hz, H-11*S*), 2.34 (1H, m, H-4α), 2.13, 2.06, 2.04, 1.95 (each 3H, s, CH_3CO), 1.92 (1H, ddd, $^3J_{12,17}$ = 6, $^3J_{16,17}$ = 10.1, $^3J_{17,18}$ = 3.1 Hz, H-17), 1.11 (1H, ddd, $^2J_{11R,11S}$ = 14.3, $^3J_{1,11R}$ = 3.2, $^3J_{11R,12,}$= 11.0 Hz, H-11*R*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 171.0, 170.4, 169.6, 169.3 (each CH_3CO), 167.6 (C-19), 149.7 (C-14), 142.3 (C-7), 142.3 (C-8), 139.8 (C-1″), 133.4 (C-16), 130.4[a] (C-5), 129.9 (C-3″), 129.9 (C-5″), 128.4 (C-2″), 128.4 (C-6″), 127.0 (C-4″), 125.8[a] (C-10), 119.8 (C-15), 115.3[b] (C-6), 114.0[b] (C-9), 112.4 (C-13), 96.3[c] (C-18), 95.3[c] (C-1′), 72.6[d] (C-3′), 72.0[d] (C-5′), 70.8 (C-2′), 68.3 (C-4′), 61.7 (C-6′), 56.9 (CH_2-benzyl), 53.9 (C-1), 51.2 (OCH_3), 43.0 (C-3), 41.6 (C-17), 34.4 (C-11), 24.9 (C-12), 21.6 (C-4), 20.7, 20.6, 20.6, 20.1 (each CH_3-CO); [a−d]revised assignment is also possible.

***O′*,*O′*,*O′*,*O′*-Tetraacetyl-2-deacetyl-2-benzylneoipecoside (6b):** white amorphous solid [R_f 0.45 in $CHCl_3$–Me_2CO (5:1)]); *anal*. C 61.15%, H 5.91%, N 1.69%, calcd for $C_{40}H_{47}NO_{15}$, C 61.45%, H 6.06%, N 1.79%; UV (EtOH) λ_{max} (log ϵ) 210 (4.54), 228 (4.23), 282 (3.53) nm; IR (KBr) ν_{max} 3600−3300, 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.42−7.35 (4H, m, H-2″, H-3″, H-5″, H-6″), 7.27 (1H, d, $^4J_{12,14}$ = 2.1 Hz, H-14), 7.25 (1H, m, H-4″), 6.72 (1H, d, $^3J_{6,7}$ = 8.2 Hz, H-6), 6.58 (1H, d, $^3J_{6,7}$ = 8.2 Hz, H-7), 5.64 (1H, dt, $^3J_{15Z,16}$ = 17.1, $^3J_{15E,16}$ = $^3J_{16,17}$ = 10.1 Hz, H-16), 5.3−5.1 (4H, m, H-15*E*, H-2′, H-3′, H-4′), 5.05 (1H, d, $^3J_{17,18}$ = 2.8 Hz, H-18), 4.84 (1H, d, $^3J_{1',2'}$ = 7.6 Hz, H-1′), 4.80 (1H, dd, $^2J_{15E,15Z}$ = 1.9, $^3J_{15Z,16}$ = 17.1 Hz, H-15*Z*), 4.33 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'a}$ = 3.9 Hz, H-6′a), 4.23 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.5 Hz, H-6′b), 3.79 (1H d, $^2J_{NCHa,NCHb}$ = 12.7 Hz, H-benzyl-CHb), 3.73 (1H, m, H-5′), 3.63 (3H, s, OCH_3), 3.6−3.4 (2H m, H-1, H-3α), 3.52 (1H, d, $^2J_{NCHa,NCHb}$ = 12.7 Hz, H-benzyl-CHa), 3.17 (1H, m, H-12), 3.08 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 14.0, $^3J_{3\beta,4\beta}$ = 6.6, $^3J_{3\beta,4\alpha}$ < 1 Hz, H-3*β*), 2.96 (1H, ddd, $^2J_{4\alpha,4\beta}$ = 17.4, $^3J_{3\alpha,4\beta}$ = 12.1, $^3J_{3\beta,4\beta}$ = 6.6 Hz, H-4*β*), 2.43 (1H, dd, $^2J_{4\alpha,4\beta}$ = 17.4, $^3J_{3\alpha,4\alpha}$ = 3.4, $^3J_{3\beta,4\alpha}$ < 1 Hz, H-4α), 2.39 (1H, ddd, $^2J_{11R,11S}$ = 15.1, $^3J_{1,11R}$ = 3.2, $^3J_{11R,12}$ = 9.8 Hz, H-11*R*), 2.12, 2.06, 2.04, 1.95 (each 3H, s, CH_3-CO), 2.1−1.9 (1H, m, H-17), 1.29 (1H, ddd, $^2J_{11R,11S}$ = 15.1, $^3J_{1,11S}$

= 11.9, $^3J_{11S,12}$ = 3.9, Hz, H-11*S*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.9, 170.8, 169.5, 169.1 (each CH_3CO), 167.4 (C-19), 149.9 (C-14), 141.3 (C-8), 141.3 (C-9), 139.8 (C-1″), 134.7 (C-16), 129.9 (C-3″), 129.9 (C-5″), 128.4 (C-2″), 128.4 (C-6″), 127.0 (C-4″), 126.4, 124.5 (C-5, C-10), 120.8 (C-6), 113.2 (C-7), 119.9 (C-15), 112 (C-13), 96.2, 95.4 (C-18, C-1′), 72.6, 72.2 (C-3′, C-5′), 70.7 (C-2′), 68.2 (C-4′), 61.6 (C-6′), 57.0 (CH_2-benzyl), 51.2 (OCH_3), 50.4 (C-1), 42.4 (C-3), 41.6 (C-17), 34.8 (C-11), 25.7 (C-12), 21.4 (C-4), 20.8, 20.7, 20.6, 20.2 (each CH_3CO).

Epimerization Experiments. The epimerizations were carried out with **5b** or a mixture of 80% **5a** and 20% **5b** (0.16. g, 2 mmol), in dry and acid-free $CDCl_3$ (0.70 mL) at 20 or 60 °C. In each case the equilibrium was set in at 31:69 ratio of 1*S*:1*R*. The changes were checked by measuring the intensity of the signals of H-6 and H-9 in **5a** (6.67 and 6.42 ppm) and **5b** (6.55 and 6.33 ppm). No isomerization was observed in acetonitrile or methanol. Epimerizations using **6b**, **11**, or **7b** gave likewise negative results.

7-*O*-Demethylalangiside (7c). To the solution of dopamine hydrobromide (**2**·HBr, 0.140 g, 0.59 mmol) in H_2O (0.40 mL) was added dropwise 1 M aqueous NaOH solution (0.60 mL, 0.60 mmol), followed by secologanin (**1**, 0.23 g, 0.59 mmol). The reaction mixture was stirred at 50 °C for 15 min. After evaporation of the solvent, the crude product was chromatographed on Si gel (37 g) with MeCOOEt−*i*-PrOH−H_2O (8:2:1) (each fraction 2.3 mL). Fractions 45−63 were combined and, after evaporation of the solvent, gave *O*-demethylalangiside as an amorphous beige solid (**7c**) [0.189 g, 65%, R_f 0.54 in MeCOOEt−*i*-PrOH−H_2O (8:2:1)]: *anal.* C 58.12%, H 5.88%, N 2.85%, calcd for $C_{24}H_{29}NO_{10}$, C 58.65%, H 5.95%, N 2.85%; UV (EtOH) λ_{max} (log ϵ) nm 208 (4.41), 234 (4.29), 288 (3.74); IR (KBr) ν_{max} cm^{-1} 3600−3200, 1624; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.40 (1H, d, $^4J_{12,14}$ = 2.4, H-14), 6.65 (1H, s, H-6), 6.54 (1H, s, H-9), 5.53 (1H, dt, $^3J_{15Z,16}$ = 17, $^3J_{15E,16}$ = 10, $^3J_{16,17}$ = 10 Hz, H-16), 5.49 (1H, d, $^3J_{17,18}$ = 2 Hz, H-18), 5.28 (1H, dd, $^2J_{15Z,15R}$ = 2, $^3J_{15Z,16}$ = 17 Hz, H-15*Z*), 5.19 (1H, dd, $^2J_{15Z,15R}$ = 2, $^3J_{15E,16}$ = 10 Hz, H-15*E*), 4.70 (1H, dd, $^3J_{1,11S}$ = 11.5, $^3J_{1,11R}$ = 3.8 Hz, H-1), 4.69 (1H, d, $^3J_{1',2'}$ = 7.9, H-1′), 4.65 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 12.5, $^3J_{3\alpha,4\alpha}$ = 4.3, $^3J_{3\alpha,4\beta}$ = 3.5 Hz, H-3α), 3.90 (1H, dd, $^2J_{6'a,6'b}$ = 11.9, $^3J_{5',6'b}$ = 1.9 Hz, H-6′b), 3.67 (1H, dd, $^2J_{6'a,6'b}$ = 11.9, $^3J_{5',6a}$ = 5.5 Hz, H-6′a), 3.25−3.41 (3H, m, H-3′,-4′,-5′), 3.15−3.23 (1H, m, H-12), 3.20 (1H, dd, $^3J_{1',2'}$ = 7.9, $^3J_{2',3'}$ = 9.1, H-2′), 2.89 (1H, ddd, $^2J_{3\alpha,3\beta}$ = 12.5, $^3J_{3\beta,4\alpha}$ = 11.3, $^3J_{3\beta,4\beta}$ = 3.5 Hz, H-3*β*), 2.7 (1H, m, H-4α), 2.70 (1H, ddd, $^3J_{12,17}$ = 5.7, $^3J_{16,17}$ = 10, $^3J_{17,18}$ = 2 Hz, H-17), 2.58 (1H, dt, $^2J_{4\alpha,4\beta}$ = 15.5, $^3J_{3\alpha,4\beta}$ = 3.5, $^3J_{3\beta,4\beta}$ = 3.5 Hz, H-4*β*), 2.29 (1H, dt, $^2J_{11R,11S}$ = 13.3, $^3J_{1,11R}$ = 3.8, $^3J_{11R,12}$ = 3.8 Hz, H-11*R*), 1.36 (1H, td, $^2J_{11R,11S}$ = 13.3, $^3J_{1,11S}$ = 11.5, $^3J_{11S,12}$ = 13.3, H-11*S*); ^{13}C NMR (CD_3OD, 50 MHz) 165.9 (C-19), 148.7 (C-14), 145.1 (C-7), 145.1 (C-8), 133.8 (C-16), 129.1[a] (C-5), 127.4[a] (C-10), 120.4 (C-15), 116.1[b] (C-9), 113.4[b] (C-6), 109.2 (C-13), 99.6 (C-18), 97.5 (C-1′), 78.1[c] (C-5′), 77.9[c] (C-3′), 74.7 (C-2′), 71.5 (C-4′), 62.6 (C-6′), 56.7 (C-1), 44.3 (C-17), 41.1 (C-3), 34.7 (C-11), 29.2 (C-4), 27.5 (C-12); [a−c]revised assignment is also possible.

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References and Notes

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