Investigation of the Coupling Reaction of Tetraacetylsecologanin with Oxotryptamine and Its Derivative†

Ágnes Patthy-Lukáts,‡ Gyula Beke,‡ László F. Szabó,*,‡ and Benjamin Podányi§

Department of Organic Chemistry, Semmelweis University, Hőgyes u. 7, H-1092 Budapest, and Chinoin Pharmaceutical and Chemical Works, Ltd., Tó u. 1-5, H-1045, Budapest, Hungary

Received March 23, 2001

The coupling reaction of tetraacetylsecologanin with 2,3-dihydro-2-oxotryptamine and its N_b-benzyl derivative was investigated. With the benzylated amine, the reaction was stopped at the tetracyclic ester level, and with the unsubstituted amine it was immediately followed by lactamization. In both cases, the products were formed with high stereoselectivity at C-3, but as an epimeric pair of 7*R* and 7*S* in a ratio of 1:3. The bulky benzyl substituent at N-4 directed the stereoselectivity at C-3 in favor of the *S* configuration. In the nonbenzylated compounds, the reversible coupling reaction is probably nonstereoselective, but in lactamization the 3*R* epimer is sterically favored and faster and gives the final lactam in this configuration. The formation of the spiro compounds may serve as a model reaction in the interpretation of the stereoselectivity of the coupling reaction of secologanin with tryptamine in the presence of strictosidine synthase.

As is well known from the literature, there is a special group of terpenoid indole alkaloids, which can be formally derived from secologanin (**1a**) and 2,3-dihydro-2-oxotryptamine (**2a**) (expressed henceforth in the paper as oxotryptamine).[2−6] Their total number exceeds 120.[7] Two typical representatives are rhynchophylline and isorhynchophylline. Moreover, the hemiterpenoid derivatives elacomine and isoelacomine, having an isobutyl group at C-3 instead of the secologanin subunit, were also isolated from *Elaeagnus commutata* Bernh. (Elaeagnaceae).[8,9] Many terpenoid indole alkaloids have been obtained from plant species which also contain the analogous indole derivatives, and their subclasses are related to those of the indole analogues. The biogenesis of this class of alkaloids has not been investigated thoroughly. However, as oxotryptamine was not isolated from any plant species to date, it is supposed that the oxindole alkaloids are not formed by direct coupling of secologanin and oxotryptamine, but by rearrangement of the appropriate β-carboline derivatives.[10,11] The biotransformation of β-carboline type indole alkaloids into spirooxindole-type alkaloids has been demonstrated,[12] and several analogous rearrangements in vivo and in vitro are described in both older and newer literature.[13−16] In the 1970s, R. T. Brown and associates published several papers[17−19] about the coupling reaction of oxotryptamine and secologanin aglucon that indicated the formation of this type of compound under abiotic conditions. In our systematic work of the coupling reaction of secologanin with biogenic amines[1,20] we have investigated the direct coupling of secologanin and oxotryptamine.

Results and Discussion

In accordance with our previous work, the reactions were carried out with tetraacetylsecologanin (**1b**) and oxotryptamine (**2a**) or its N_b-benzyl derivative (**2b**) in a polar solvent (Chart 1). It should be mentioned that strictosidine synthase enzyme did not catalyze the reaction. With oxotryptamine, the product **4a** of the coupling reaction was spontaneously lactamized in the same reaction mixture and gave the 3*R* lactams of an epimeric pair at C-7 (3*R*,7*R*-**6** and 3*R*,7*S*-**6**).[21] To see the results without the possibility of lactamization, the reactions were carried out also with N_b-benzyl oxotryptamine, and in that case the 3*S* benzyl derivatives were formed again as an epimeric pair at C-7 (3*S*,7*R*-**4b** and 3*S*,7*S*-**4b**). In both epimeric pairs the epimer in which the through-space distance is shorter between H-3 and H-9 was formed in a smaller amount.

In the characterization and interpretation of the stereochemical results, with one exception the same stereoelements were considered and indicated as in our previous analysis of the tryptamine[20] and dopamine[1] derivatives, i.e., configuration at C-3 (**R** or **S**), nine staggered conformations around C-14 (**11**, **12**, ... **33**), and conformation of the dihydropyran ring (**N** or **S**). However, in the case of the flexible pyrrolidine ring, a single envelope having the C-14 atom at the flap of the ring was selected, and instead of its helicity, the chirality at C-7 (**R** or **S**) was considered. In this conformation, the C-14 and the eventual substituent of N-4 can take up a *trans*-diaxial orientation. The axial or equatorial position of the benzyl group was indicated by **A** or **E**, if it was necessary at all. Each of the conformers mentioned so far may exist in nine staggered conformers by rotation around the glucosidic oxygen. However, at this last stereogenic element only a single conformer was considered according to our argument that is presented in detail later.

In the structure determination of the oxindole alkaloids isolated from plants, recently Aimi and associates successfully applied the CD technique.[23] However, according to our previous work, we preferred to use detailed NMR spectroscopic parameters, because this method gave information about both the configuration and the conformation. The structure investigation of the compounds was helped by the results obtained for the tryptamine[20] and dopamine[1] derivatives of secologanin. Many parameters of the ^{1}H and ^{13}C NMR spectra were close in the three series.

The spiro structure was proved unequivocally by the signal of the quaternary carbon atom C-7 at ∼57 ppm. Lactamization was easily established by the absence of the

† Part 9 in the series Chemistry of Secologanin. For Part 8, see: Beke, Gy., et al.[1]

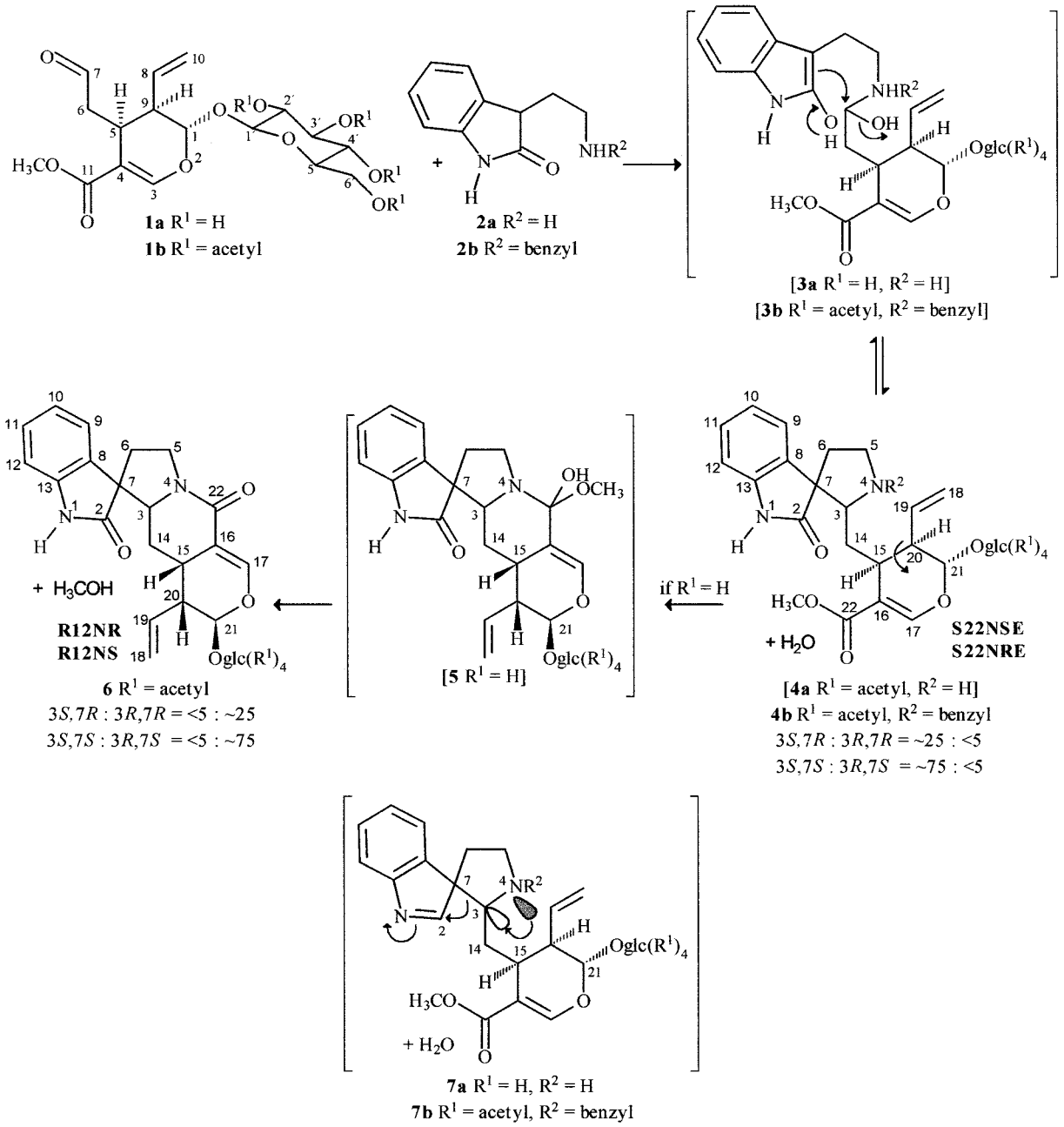
* To whom correspondence should be addressed. Tel: 36 12 17 12 95. Fax: 36 12 17 08 51. E-mail: szalasz@szerves.sote.hu.

‡ Semmelweis University.

§ Chinoin Pharmaceutical and Chemical Works, Ltd.

10.1021/np010153f CCC: $20.00
Published on Web 07/19/2001

Chart 1



singlet signal of protons of the methoxycarbonyl group at ~3.5 ppm, and the presence of the benzyl group was shown by the appropriate proton signals in the aromatic region. The small value of the H,H coupling constant $^3J_{20,21}$ proved the negative conformation of the dihydropyran ring. As the construction of the compounds was mainly determined by the structure of the educts and supported by the appropriate ^{1}H and ^{13}C NMR signals at the expected chemical shifts and multiplicities, the efforts were concentrated again on the stereochemistry of the compounds.

In this respect, the problem is simple in the lactams **6**, where the cyclization allowed only two of the nine possible conformers around C-14 in each series, **R12** and **R33**, as well as **S13** and **S31**, respectively. The structures can be characterized unequivocally by the coupling constants of H-14*R* and H-14*S* with H-3 and H-15 (Figure 1). In 3*R*,7*R*-**6**, one of the H-14 protons had large coupling constants to H-3 as well as to H-15 that involved their antiperiplanar orientation. This pattern is in accord only with conformer **R12**. As the *S* configuration of C-15 was determined by X-ray diffraction analysis in *O*′,*O*′,*O*′,*O*′-tetraacetyl-4-(4″-bromobenzyl)vincoside,[24] the same configuration should be assumed in the spirooxo series as well. This involves *β*-pseudoaxial orientation of H-3 and H-15 in the usual representation and, in addition, the necessarily negative dihedral angle in the lactam ring along C-3−C-14. These assignments were confirmed by NOE interaction of the other H-14 proton with H-3 and H-15. Moreover, the values of most of the relevant coupling constants were close to those found in vincosamide and its derivatives.[20]

In 3*R*,7*S*-**6**, H-3 had a large coupling constant with one of the H-14 atoms and a small one with the other. This fact excluded **R33** and **S31** as possible conformers for lactamization. Formally, **S13** would be compatible with it, but in this conformer the N-4−C-22 through-space distance is over 2.5 Å, which would be too long for a C−N bond. Unfortunately, the coupling constant of H-15 with the two H-14 atoms could not be measured because of some overlap

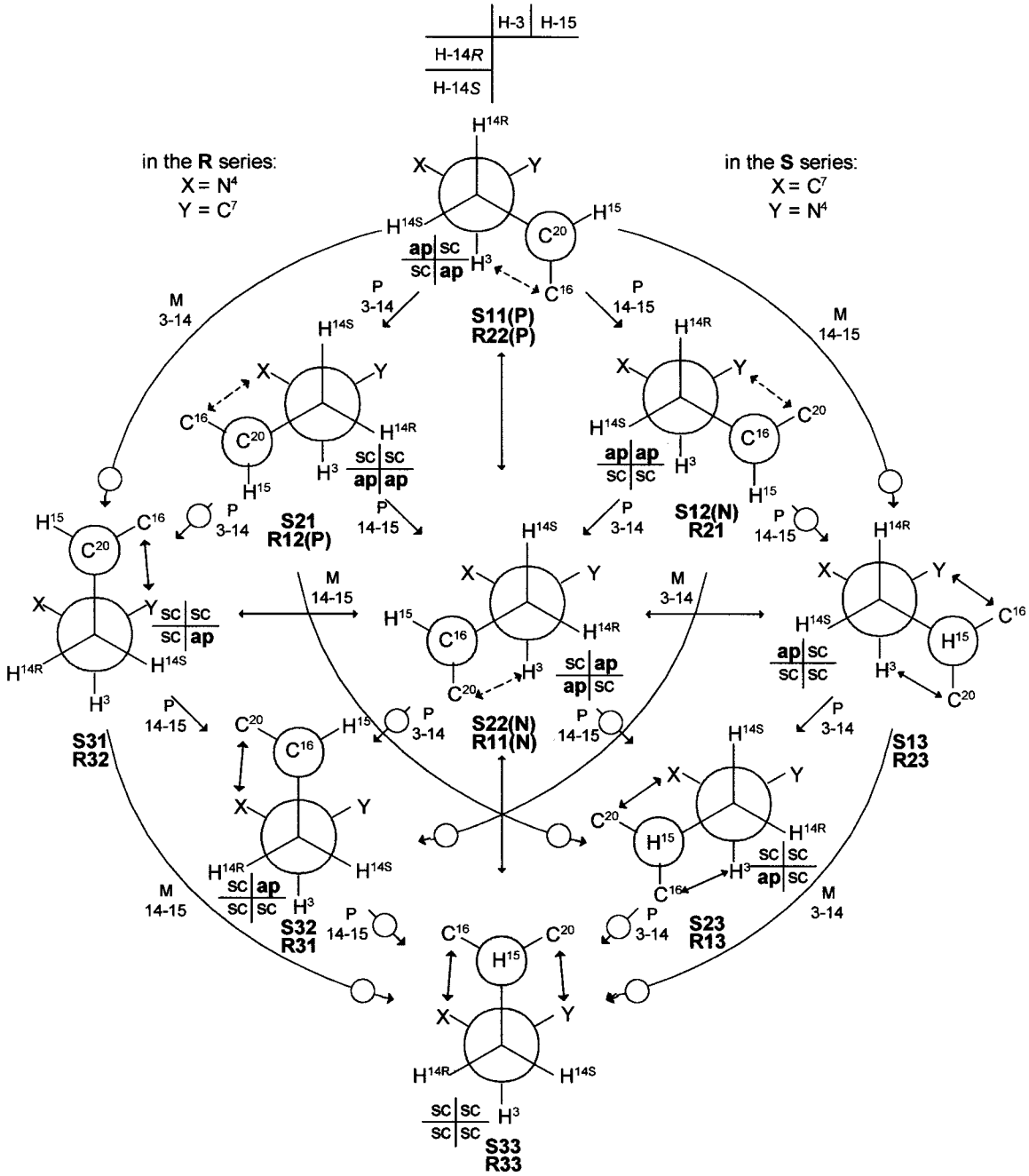


Figure 1. Graph of the possible staggered conformer around C-14. Conformers containing plain arrows indicate conformers with steric interference in any conformation of the dihydropyran ring. Dashed arrows indicate steric interferences which are absent in **N** and/or **P** conformations of the dihydropyran ring. Bulky ligands of C-3 and C-15 are represented by the atoms directly attached to them. Letters sc and ap show synclinal and antiperiplanar orientations, respectively, of the appropriate pairs of hydrogens. ○ indicates rotations which pass a conformation having non-hydrogen ligands in eclipsed orientation.

with other signals. However, the differences between the ^{13}C NMR chemical shifts of the 3*R*,7*R*-**6** and 3*R*,7*S*-**6** lactams are less than 2 ppm, and that between the proton−proton coupling constants is less than 1 Hz. These facts supported the **R** configuration of C-3 and the **12** conformation around C-14 also in the 7*S* epimer lactam.

The configuration of C-7 was assigned in the two epimers according to the following NMR parameters: H-9 had a NOE interaction in the 7*R* epimer lactam with the H-14 atom antiperiplanar to H-15 (H-14*S*), and in the 7*S* epimer with H-3. Moreover, in the 7*R* epimer, H-14*S* exhibited a chemical shift 0.5 ppm lower than the 7*S* epimer, which could be interpreted by the diamagnetic anisotropic effect of the aromatic ring. According to these data, the stereochemical description of the two lactams 3*R*,7*R*-**6** and 3*R*,7*S*-**6** is **R12NR** and **R12NS**, respectively.

In the tetracyclic benzylated esters, i.e., in the 7*R* and 7*S* epimers of 3*S*-**4b**, the number of conformers around C-14 are not restricted by cyclization. The values of most of the ^{1}H and ^{13}C chemical shifts were very close in the two compounds, and this fact suggested a stereoisomeric relation. In the 7*S* epimer of 3*S*-**4b**, the H-3 and H-15 protons had large coupling constant with two different H-14 protons, and these data selected structures (**R/S**)**11** and (**R/S**)**22** as only possible conformers (Figure 1). In the 7*R* epimer, the coupling constant pattern was the same; however, the difference between the high and low values is much smaller. Therefore, besides proton−proton, carbon−

Table 1. Comparison of Selected H−H Through-Space Interatomic Distances (in Å) Measured on Computer-Generated Models and ^{1}H NMR Data[a]

selected atoms	R11NRE	R11NSE	S11NRE	S11NSE	R22NRE	R22NSE	**S22NRE**	7*R*-**7b**	**S22NSE**	7*S*-**7b**
H-14(apH-15)−HB*R*[b]	4.429	4.469	3.669	3.660	3.351	3.412	**2.153**	Ia[d]	**2.140**	Ia[e]
−HB*S*[b]	3.608	3.530	4.239	4.225	**2.081**	**2.026**	3.197		3.182	
H-20−H-3	1.881	1.887	4.722	4.725	4.722	4.725	**1.887**	Ia[d]	**1.888**	Ia[e]
H-20−H-14apH3	3.629	3.620	**2.480**	**2.481**	**2.480**	**2.481**	3.650		3.650	
H-20−Car[c]	5.031	4.435	3.312	3.308	5.824	4.888	**2.054**	1.38[f]	4.026	
H-20−O-2	4.561	5.637	4.940	6.562	5.344	4.485	5.039		**2.116**	2.93[f]

[a] Short distances expected to involve steric interaction are in bold. [b] HB*R* and HB*S* indicate the *HproR* and *HproS* of the benzylmethylene group. [c] Shortest distance between H-20 and one of the carbon atoms of the benzene ring of the indole subunit. [d] Steric interaction detected by a strong NOESY cross-peak. [e] Steric interaction detected as intensive signal in the NOE difference spectrum. [f] Chemical shift of H-20 in ppm.

proton coupling constants (determined from 2D HETLOCK NMR spectra) were also analyzed. This approach confirmed the ^{1}H NMR data, namely, that the obtained coupling constants around C-14 are not in full agreement with either of the two true staggered conformations. This phenomenon can be explained by the presence of one distorted, (**R/S**)**11** *or* (**R/S**)**22**, conformer or by a rapid equilibrium having the (**R/S**)**11** *and* the (**R/S**)**22** conformers as the dominant components. As each stereostructure may exist as an epimeric pair of 7*R* and 7*S*, and the negative conformation of the dihydropyran ring was proved by the $^3J_{20,21}$ coupling constant, eight possible structures had to be considered. The actual structure was established by analyzing three pairs of through-space interatomic H−H distances measured on computer-generated molecular models ("measured" values) and detected by NOE interactions or ^{1}H chemical shifts. The results are shown in Table 1, where the short distances up to 3 Å are highlighted in bold. As in both compounds a short distance was detected between one of the benzyl CH_2 protons and the H-14 proton antiperiplanar to H-15, data of Table 1 indicated (**R/S**)**22** as the preferred conformer over (**R/S**)**11**. The *S* configuration at C-3 was established by the fact that in both compounds a short distance could be demonstrated between H-20 and H-3, and not between H-20 and H-14 antiperiplanar to H-3. The distinction between the 7*R* and 7*S* epimers was easily made by the observed difference in the chemical shift of H-20, which appeared at 1.38 ppm in the 7*R* epimer and at 2.93 ppm in the 7*S* epimer. As shown in the computer-generated stereostructures in Figure 2, H-20 can approach the carbonyl group only in **S22NSE** (= 3*S*,7*S*-**4b**), and the plane of the aromatic ring only in **S22NRE** (= 3*S*,7*R*-**4b**). It is well known that the carbonyl group induces a paramagnetic shift and the aromatic ring a diamagnetic shift on hydrogens having a position like H-20. Therefore, the striking difference in the chemical shift of H-20 of the two epimers was interpreted by the opposite magnetic anisotropic effects in the two compounds. In all other selected structures of Table 1, the through-space distances in question are much longer. Moreover, a relatively short distance is observed between H-3 and O-2 in the structure of 3*S*,7*R*-**4b** (Figure 2), and it is reflected by the increased chemical shift of H-3 (0.3 ppm) in this isomer compared to that value in its epimer, due to the paramagnetic shift of the C(2)═O carbonyl group.

At first sight, the stereochemical outcome of the coupling reaction and the lactamization might be surprising in comparison with those of the tryptamine and dopamine derivatives. While lactamization gave the 3*R* epimers in all three series, the coupling reaction with the benzylated amines gave the ester coupling products preferentially as the 3*R* epimers in the β-carboline and isoquinoline series and 3*S* epimers in the spirooxindole series.

Detailed conformational analysis gave an answer for the problem. This was carried out by measuring the through-space distances of selected elements in computer-generated models of the possible stereoisomers. The most stable structure was selected in the following manner (Figure 1): (1) Those C-14 conformers in which H-3 and/or H-15 had synclinal orientation to both H-14 atom(s) contain steric interferences, because the bulky ligands of C-3 (C-7 and N-4) and of C-15 (C-20 and C-16) are mutually close [(**R/S**)**13**, (**R/S**)**23**, (**R/S**)**31**, (**R/S**)**32**, (**R/S**)**33**, Newman formulas containing plain arrows]. Moreover, in conformers (**R/S**)**21** there is a serious steric interference between the oxindole subunit and the ligand of C-16 (methoxycarbonyl in **S21**) or of C-20 (vinyl or H-20 in **R21**). Therefore, all these stereostructures should be considered "disfavored" and less probable. (2) The remaining C-14 conformers have such steric interferences (indicated by dashed arrows), which are absent in certain conformers (indicated by **N** or **P** in parentheses) of the dihydropyran ring; that is, H-3 has no steric interference with the ligand of C-16 (methoxycarbonyl group) if the dihedral angle is positive (**S11P**, **R12P**, **R22P**) or with the ligand of C-20 (H-20) if the dihedral angle is negative (**R11N**, **S12N**, **S22N**). All these stereostructures may be considered "favored", except **R22P**, with an additional serious steric interference between O-22 and O-2 (in **R22PR**) or H-9 (in **R22PS**) shown by bold arrows in Figure 2.

Unfortunately, in the nonbenzylated series the coupling reaction was followed by rapid lactamization. It is well known that in the spirooxindole series, the coupling reaction is reversible through **3**, and the different stereoisomers can be mutually interconverted by epimerization of the centers of chirality C-3 and/or C-7.[12,13] Therefore, stereochemistry of the intermediate esters could be neither established directly nor derived from that of the lactams. Like in the tryptamine and dopamine series, the lactamization proved to be stereoselective in favor of the 3*R* configuration. As pointed out above, the only appropriate conformations for lactamization are **R12** and **S31**. According to our previous detailed analysis on the dopamine derivatives,[1] the lactamization is under kinetic control, and the configuration at C-3 in the lactams depends on the transition conformation before the cyclization. **R12** is a "favored" conformer that can easily be formed from any other "favored" ones (except **R22P**) through **3a** and by rotation around C-3−C-14 and/or C-14−C-15 involving intermediate conformations, in which bulky ligands were not in an eclipsed orientation (Figure 1). However, **S31** is an "unfavored" conformer that could be formed from any of the favored ones only by rotation around C-3−C-14 and/or C-14−C-15 involving an intermediate conformation in which the bulky substituents should take up an eclipsed orientation (rotations indicated by ○ in Figure 1). Therefore its formation is less probable and slow.

Because the coupling reaction with N_b-benzyloxotryptamine was necessarily stopped at the ester level, the stereochemistry of the isolated products 3*S*,7*R*-**4b** and

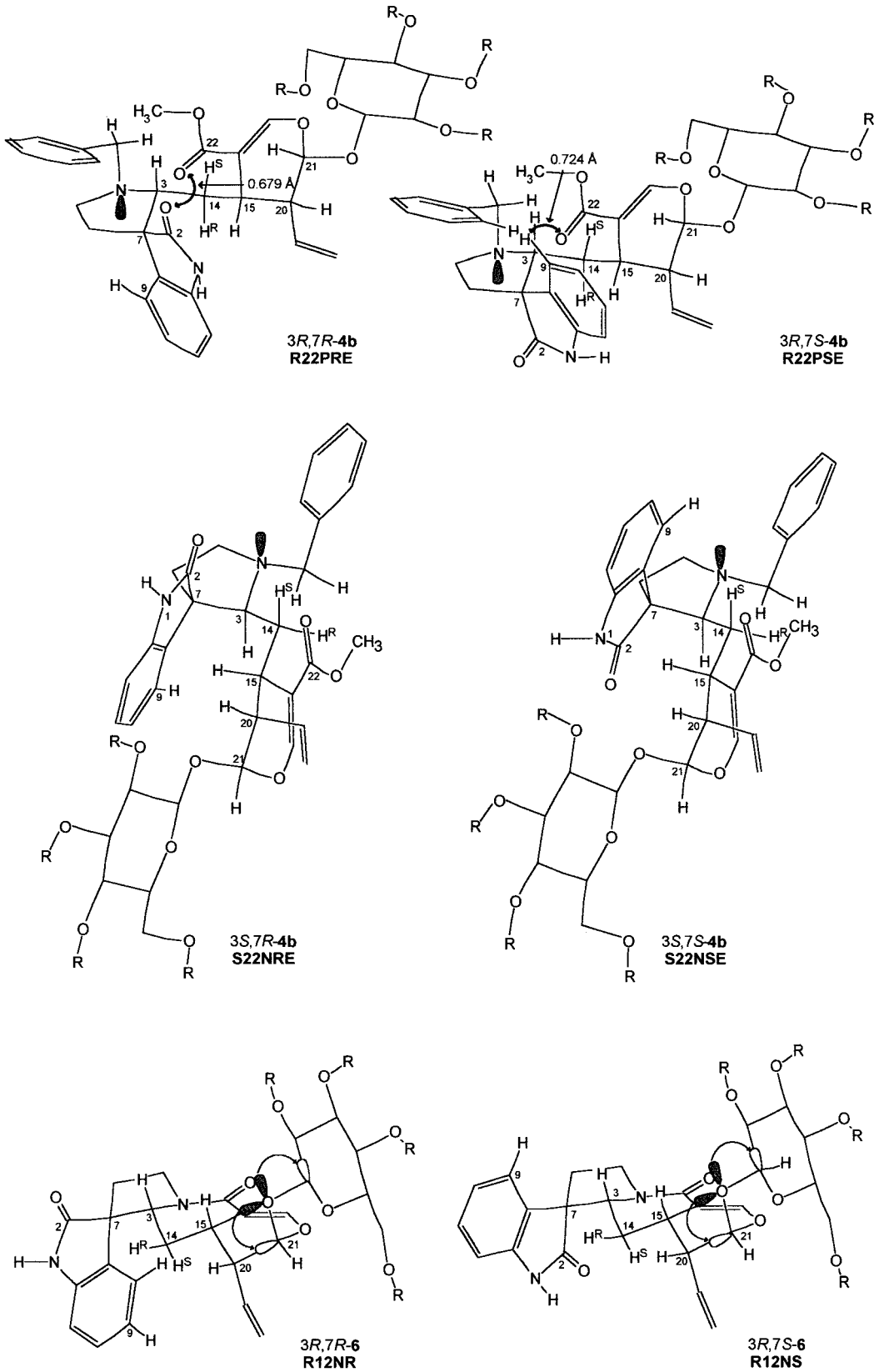


Figure 2. Three-dimensional representations of the spirooxindole compounds and their stereochemical descriptors. R = acetyl. Bold arrows show strong steric interferences.

3*S*,7*S*-**4b** could be established. Their subsequent conformational analysis demonstrated that, on one hand, in all "favored" structures the benzyl group in pseudoaxial orientation was strongly disfavored, because of its interference with O-2 or H-9. On the other hand, for insertion of the benzyl group into equatorial orientation there is enough space only in the **22** conformers around C-14. As **R22P** is disfavored by another interference (see above), the only favored one is **S22N**. Thus, the isolated products 3*S*,7*R*-**4b** and 3*S*,7*S*-**4b** were the stereoisomers **S22NRE** and **S22NSE**, respectively.

The conformation around the glucosidic oxygen was analyzed in detail previously.[1,20] In the acetylated derivative of the 3*S* epimer strictosamide and of the 1*S* epimer

isoalangiside derivative, the protons of the 2′-acetoxy group appeared at an unusually low δ value (1.20 and 1.55, respectively) that indicated the steric proximity of this methyl group to the plane of the aromatic ring. It was demonstrated that this is possible only in such a conformation (named **G11**) that is stabilized by a double σ-conjugation (indicated in the three-dimensional formulas). In the present case, the 3*S* lactams were not formed, and therefore, the experimental support failed. However, the same interactions should likewise operate in the secologanin subunit of the compounds described in the present paper, and the conformation **G11** around the glucosidic oxygen is shown correctly in the three-dimensional formulas of Figure 2.

It was detailed elsewhere[25] that our stereochemical results might explain the high 3*S* stereoselectivity of the coupling reaction of secologanin and tryptamine in the presence of strictosidine synthase. As established in the present paper, bulky substituents of N-4 direct the chirality toward the formation of the 3*S* epimer in the spirooxindole system. It may be supposed that the formation of the β-carboline system runs through a spiroindolenine intermediate **7**,[26,27] which might be considered as a sterically close analogue of the spirooxindole structure **3**. Moreover, in the coupling reaction, the enzyme might work like the benzyl group, except that its attachment to N-4 would be temporary rather than constant. In the subsequent, stereoconservative 1,2-rearrangement into the β-carboline system, it could leave the N-4 atom, by retention of the *S* configuration at C-3. Perhaps, from this aspect, too, our work will be helpful to other authors.

Experimental Section

General Experimental Procedures. The NMR spectra were recorded on either a Bruker AM-200 spectrometer at 200 MHz (^{1}H) or 50 MHz (^{13}C), a Bruker AC-250 spectrometer at 250 MHz (^{1}H) and 62 MHz (^{13}C), or a Bruker DRX-400 spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C). Internal TMS was used for chemical shift reference. The difference NOE, COSY, NOESY, HMQC, and HMBC spectra were measured with the standard Bruker pulse programs of the DISNMR or the XWINNMR software. For phase-sensitive NOESY spectra, a 600 ms mixing time was used. Integration of the cross-peak volumes in NOESY maps was performed using the XWINNMR software. HETLOCK measurements[28] were carried out using a probehead equipped with an actively shielded z-gradient coil. For TOCSY transfer the radio frequency power was attenuated to provide a 90° ^{1}H pulse of 34 ms. Sine-shaped gradient pulses were used, of 1 ms duration.

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

Secologanin (**1a**) was isolated from *Lonicera xylosteum* L. (Caprifoliaceae) according to a method elaborated in our department.[29]

Reaction of *O,O,O,O*-Tetraacetylsecologanin (1b) with 2,3-Dihydro-2-oxotryptamine (2a). 2-Oxo-2,3-dihydrotryptaminium chloride[30] (0.10 g, 0.5 mmol) was dissolved in absolute MeOH, triethylamine (0.072 mL, 0.5 mmol) and *O,O,O,O*-tetraacetylsecologanin (0.27 g, 0.5 mmol) were added, and the reaction mixture was refluxed for 1 h. After removal of the solvent at reduced pressure, the residue was taken up in $CHCl_3$ (10 mL) and extracted with H_2O (2 × 3 mL). The organic layer was dried and the solvent evaporated. The crude product gave on TLC two spots in an approximate ratio of 3:1 [R_f 0.32 and 0.20 in $CHCl_3$−MeCOMe (7:3)]. Recrystallization of the residue from absolute EtOH gave colorless crystals assigned as 3*R*,7*S*-*O*′,*O*′,*O*′,*O*′-tetraacetyl-2-oxo-2,3-dihydrospirovincosamide (3*R*,7*S*-**6**) [0.23 g, 68%, single spot, mp 283 °C, R_f 0.73 in $CHCl_3$−MeOH (4:1), 0.29 in $CHCl_3$−MeCOMe (7:3)]; *anal.* C 59.62%, H 5.51%, N 4.01%, calcd for $C_{34}H_{38}O_{13}N_2$, C 59.82%, H 5.61%, N 4.10%. After evaporation of the solvent, the residue of the mother liquid of the crystallization was chromatographed on a Si gel column (20 g) with $CHCl_3$−MeOH (4:1) (each fraction 1 mL), and combined fractions 1−8 gave, after evaporation of the solvent, a colorless solid that proved to be 3*R*,7*R*-*O*′,*O*′,*O*′,*O*′-tetraacetyl-2-oxo-2,3-dihydrospirovincosamide (3*R*,7*R*-**6**) (compound **B**) [0.08 g, 23%, single spot, mp 162−164 °C, R_f 0.70 in $CHCl_3$−MeOH (4:1), 0.16 in $CHCl_3$−MeCOMe (7:3)]; *anal.* C 59.58%, H 5.50%, N 5.05%, calcd for $C_{34}H_{38}O_{13}N_2$, C 59.82%, H 5.61%, N 5.10%.

3*R*,7*S*-*O*′,*O*′,*O*′,*O*′-Tetraacetyl-2,3-dihydro-2-oxospirovincosamide (3*R*,7*S*-6): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.20 (1H, br s, H-1), 7.42 (1H, d, $^4J_{15,17}$ = 2.4 Hz, H-17), 7.27 (1H, td, $^3J_{10,11}$ = 7.6, $^3J_{11,12}$ = 7.6, $^4J_{9,11}$ = 1.3 Hz, H-11), 7.22 (1H, d, $^3J_{9,10}$ = 7.6 Hz, H-9), 7.09 (1H, td, $^3J_{9,10}$ = 7.6, $^3J_{10,11}$ = 7.6, $^4J_{10,12}$ = 1.0 Hz; H-10), 6.91 (1H, d, $^3J_{11,12}$ = 7.6 Hz, H-12), 5.42 (1H, dt, $^3J_{18E,19}$ = 10.0, $^3J_{18Z,19}$ = 17.0, $^3J_{19,20}$ = 9.8 Hz, H-19), 5.24 (1H, t, $^3J_{2',3'}$ = 9.7, $^3J_{3',4'}$ = 9.7 Hz, H-3′), 5.19 (1H, d, $^3J_{20,21}$ = 1.9 Hz, H-21), 5.12 (1H, dd, $^3J_{18Z,19}$ = 17.0, $^2J_{18E,18Z}$ = 1.7 Hz, H-18*Z*), 5.07 (1H, t, $^3J_{3',4'}$ = 9.7, $^3J_{4',5'}$ = 9.7 Hz, H-4′), 5.03 (1H, dd, $^3J_{18E,19}$ = 10.0, $^2J_{18E,18Z}$ = 1.7 Hz, H-18*E*), 4.96 (1H, dd, $^3J_{1',2'}$ = 8.0, $^3J_{2',3'}$ = 9.7 Hz, H-2′), 4.90 (1H, d, $^3J_{1',2'}$ = 8.0 Hz, H-1′), 4.27 (1H, dd, $^3J_{5',6'a}$ = 4.6, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′a), 4.12 (1H, dd, $^3J_{5',6'b}$ = 2.2, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′b), 4.12 (1H, m, H-5a), 3.96 (1H, dd, $^3J_{3,14R}$ = 4.0, $^3J_{3,14S}$ = 10.6 Hz, H-3), 3.81 (1H, m, H-5b), 3.73 (1H, ddd, $^3J_{4',5'}$ = 9.7, $^3J_{5',6'a}$ = 4.6, $^3J_{5',6'b}$ = 2.2 Hz, H-5′), 2.68 (1H, m, H-15), 2.50 (1H, ddd, $^3J_{19,20}$ = 9.8, $^3J_{15,20}$ = 5.6, $^3J_{20,21}$ = 1.9 Hz, H-20), 2.30 (2H, m, H-6a, H-6b), 1.35 (2H, m, H-14*proR*, H-14*proS*), 2.10, 2.06, 2.05, 2.04 (each 3H, s, H_3CCO); ^{13}C NMR ($CDCl_3$, 62 MHz) δ 179.1 (s, C-2), 170.6, 170.0, 169.7, 169.5 (each s, CH_3CO), 162.9 (s, C-22), 146.0 (d, C-17), 141.8 (s, C-13), 131.9 (d, C-19), 128.9 (d, C-11), 128.0 (s, C-8), 122.6 (d, C-9), 122.6 (d, C-10), 120.3 (t, C-18), 110.2 (d, C-12), 108.3 (s, C-16), 96.3 (d, C-21, 96.0 (d, C-1′), 72.3 (d, C-3′), 72.1 (d, C-5′), 70.5 (d, C-2′), 68.2 (d, C-4′), 64.4 (d, C-3), 61.7 (t, C-6′), 56.6 (s, C-7), 44.5 (t, C-5), 42.9 (d, C-20), 32.8 (t, C-6), 27.7 (d, C-15), 25.8 (t, C-14), 20.7, 20.6, 20.6, 20.5 (each s, CH_3CO). Results of NOE difference experiments (irradiated H, NOE enhancement in %): H-3, H_2-6 1.1, H-9 4.7, H-15 4.6; H_2-6, Hα-5 5.0, Hβ-5 5.0, H-9 4.9; H-9, H-3 2.6; H-12, H-11 6.4; H-15, H-3 5.1, H_2-14 1.4, H-17 0.9, H-20 2.2; H-20, H-15 3.3, H-21 5.8.

3*R*,7*R*-*O*′,*O*′,*O*′,*O*′-Tetraacetyl-2,3-dihydro-2-oxospirovincosamide (3*R*,7*R*-6): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 8.15 (1H, br s, H-1), 7.43 (1H, d, $^4J_{15,17}$ = 2.4 Hz, H-17), 7.27 (1H, td, $^3J_{10,11}$ = 7.6, $^3J_{11,12}$ = 7.6, $^4J_{9,11}$ = 1.3 Hz, H-11), 7.01 (1H, td, $^3J_{9,10}$ = 7.6, $^3J_{10,11}$ = 7.6, $^4J_{10,12}$ = 1.0 Hz, H-10), 6.94 (1H, d, $^3J_{11,12}$ = 7.6 Hz, H-12), 6.92 (1H, d, $^3J_{9,10}$ = 7.6 Hz, H-9), 5.29 (1H, t, $^3J_{2',3'}$ = 9.7, $^3J_{3',4'}$ = 9.7 Hz, H-3′), 5.26 (1H, dt, $^3J_{18Z,19}$ = 17.0, $^3J_{18E,19}$ = 9.6, $^3J_{19,20}$ = 9.6 Hz, H-19), 5.20 (1H, d, $^3J_{20,21}$ = 2.1 Hz, H-21), 5.08 (1H, t, $^3J_{3',4'}$ = 9.7, $^3J_{4',5'}$ = 9.7 Hz, H-4′), 5.05 (1H, dd, $^3J_{18Z,19}$ = 17.0, $^2J_{18E,18Z}$ = 2.0 Hz, H-18*Z*), 5.00 (1H, dd, $^3J_{18E,19}$ = 9.6, $^2J_{18E,18Z}$ = 2.0 Hz, H-18*E*), 4.98 (1H, dd, $^3J_{1',2'}$ = 8.0, $^3J_{2',3'}$ = 9.7 Hz, H-2′), 4.88 (1H, d, $^3J_{1',2'}$ = 8.0 Hz, H-1′), 4.28 (1H, dd, $^3J_{5',6'a}$ = 4.6, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′a), 4.12 (1H, dd, $^3J_{5',6'b}$ = 2.2, $^2J_{6'a,6'b}$ = 12.6 Hz, H-6′b), 4.11 (1H, dd, $^3J_{3,14R}$ = 3.8, $^3J_{3,14S}$ = 11.5 Hz, H-3), 4.06 (2H, m, H-5a, H-5b), 3.73 (1H, ddd, $^3J_{4',5'}$ = 9.7, $^3J_{5',6'a}$ = 4.6, $^3J_{5',6'b}$ = 2.2 Hz, H-5′), 2.76 (1H, m, H-15), 2.51 (1H, ddd, $^3J_{19,20}$ = 9.6, $^3J_{15,20}$ = 5.7, $^3J_{20,21}$ = 2.1 Hz, H-20), 2.51 (1H, m, H-6a), 2.09, 2.02, 2.01, 1.99 (each 3H, s H_3CCO), 2.05 (1H, m, H-6b), 1.38 (1H, dt, $^2J_{14R,14S}$ = 12.7, $^3J_{3,14R}$ = 3.8, $^3J_{14R,15}$ = 3.8 Hz, H-14*proR*), 0.85 (1H, td, $^2J_{14R,14S}$ = 12.7, $^3J_{14S,15}$ = 12.7, $^3J_{3,14S}$ = 11.5 Hz, H-14*proS*); ^{13}C NMR (62 MHz, $CDCl_3$) δ 178.1 (s, C-2), 170.7, 170.2, 169.6, 169.5 (each s, CH_3CO), 163.3 (s, C-22), 146.0 (d, C-17), 140.5 (s, C-13), 131.4 (d, C-19), 129.8 (s, C-8), 128.7 (d, C-11), 124.0 (d, C-9), 123.0 (d, C-10), 120.7 (t, C-18), 110.7 (s, C-12), 108.1 (s,C-16), 96.1 (d, C-21), 95.9 (d, C-1′), 72.4 (d, C-3′), 72.3 (d, C-5′), 70.5 (d, C-2′), 68.3 (d, C-4′), 63.4 (d, C-3), 61.8 (t, C-6′), 57.6 (s, C-7), 44.5 (t, C-5), 42.8 (d, C-20), 33.5 (t, C-6), 27.2 (d, C-15), 26.1 (t, C-14), 20.8, 20.8, 20.7, 20.7 (each s, CH_3-CO of acetyl). Results of NOE difference experiments (irradiated H, NOE enhancement in %): H-9, Hα-5 1.2, H-14*proS* 0.5; H-14*proS*, H-9 2.6, H-14*proR* 11.9, H-15 1.9, H-19 5.7,

H-18*Z* 1.6; H-14*proR*, H-3 5.5, H-14*proS* 16.2, H-15 4.8, H-20 1.6; H-15, H-3 6.5, H-14*proR* 3.1, H-17 0.9, H-20 3.9.

Reaction of *O,O,O,O*-Tetraacetylsecologanin (1b) with N_b-Benzyl-2,3-dihydro-2-oxotryptamine (2b). N_b-Benzyl-2,3-dihydro-2-oxotryptaminium chloride[22] (0.152 g, 0.5 mmol) was dissolved in absolute MeOH (2.0 mL), then triethylamine (0.072 mL, 0.5 mmol) and *O,O,O,O*-tetraacetylsecologanin (0.270 g, 0.5 mmol) were added, and the reaction mixture was refluxed for 2 h. After removal of the solvent in vacuo, the residue was taken up in $CHCl_3$ (10 mL) and extracted with water (2 × 3 mL), the organic phase was dried, and the solvent was evaporated. The crude pale beige product gave two main spots in a ratio of approximately 3:1 [TLC, in $CHCl_3$−MeCOMe (7:3), R_f 0.75 and 0.60, respectively]. Recrystallization from absolute EtOH gave colorless crystals of 3*S*,7*S*-*O*′,*O*′,*O*′,*O*′-tetraacetyl-4-benzyl-2-oxo-2,3-dihydrospirostrictosidine (3*S*,7*S*-**4b**) [mp 268−270 °C, R_f 0.78 in $CHCl_3$−MeCOMe (7:3); *anal.* C 62.51%, H 5.93%, N 3.42%, calcd for $C_{42}H_{48}N_2O_{14}$, C 62.68%, H 6.01%, N 3.48%]. The solvent of the mother liquid was evaporated, and the residue chromatographed on a Si gel column (10 g) with $CHCl_3$−MeCOMe (7:3). Combined fractions 1−6 (each 0.5 mL), after removal of the solvent, gave a further amount of 3*S*,7*S*-**4b** (the total amount was 0.26 g, 65%). Fractions 9−15 gave a colorless solid sample of 3*S*,7*S*-*O*′,*O*′,*O*′,*O*′-tetraacetyl-4-benzyl-2-oxo-2,3-dihydrospirostrictosidine (3*S*,7*R*-**4b**) [0.040 g, 10%, R_f 0.63 in $CHCl_3$−MeCOMe (7:3); *anal.* C 62.48%, H 5.89%, N 3.44%, calcd for $C_{42}H_{48}N_2O_{14}$, C 62.68%, H 6.01%, N 3.48%].

3*S*,7*S*-*O*′,*O*′,*O*′,*O*′-Tetraacetyl-4-benzyl-2,3-dihydro-2-oxospirostrictosidine (3*S*,7*S*-4b): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.94 (1H, br s, H-1), 7.52 (1H, d, $^3J_{9,10}$ = 7.4 Hz, H-9), 7.45−7.20 (6H, m, H-11, H-2″, H-3″, H-4″, H-5″, H-6″), 7.12 (1H, t, $^3J_{9,10}$ = 7.4, $^3J_{10,11}$ = 7.4 Hz, H-10), 7.11 (1H, d, $^4J_{15,17}$ = 2.2 Hz, H-17), 7.04 (1H, d, $^3J_{11,12}$ = 7.6 Hz, H-12), 5.55−5.10 (3H, m, H-2′, H-3′, H-4′), 5.55−5.45 (2H, m, H-19, H-18*Z*), 5.35−5.1 (1H, m, H-18*E*), 5.22 (1H, d, $^3J_{20,21}$ = 2.1 Hz, H-21), 4.77 (1H, m, H-1′), 4.31 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'a}$ = 4.3 Hz, H-6′a), 4.15 (1H, dd, $^2J_{6'a,6'b}$ = 12.5, $^3J_{5',6'b}$ = 2.3 Hz, H-6′b), 4.03 (1H, d, $^2J_{NCHa,NCHb}$ = 13.2 Hz, Hb-benzyl-CH_2), 3.72 (1H, m, H-5′), 3.29 (3H, s, CH_3O), 3.17 (1H, m, H-5β), 3.11 (1H, dd, $^3J_{3,14S}$ = ∼10.5, $^3J_{3,14R}$ = ∼2 Hz, H-3), 3.03 (1H, d, $^2J_{NCHa,NCHb}$ = 13.2 Hz, Ha-benzyl-CH_2), 2.93 (1H, m, H-20), 2.46 (1H, m, H-5α), 2.35 (1H, m H-6a), 2.22 (1H, m, H-15), 2.15, 2.04, 2.04, 1.78 (each 3H, s, H_3CCO), 1.89 (1H, td, $^2J_{14R,14S}$ = ∼13, $^3J_{3,14S}$ = ∼10.5, $^3J_{14S,15}$ = ∼1.5 Hz, H-*14proS*), 1.81 (1H, m, H-6b), 1.40 (1H, td, $^2J_{14R,14S}$ = ∼13, $^3J_{14R,15}$ = ∼13, $^3J_{3,14R}$ = ∼2 Hz, H-14*proR*) ^{13}C NMR (62 MHz, $CDCl_3$) δ 180.1 (s, C-2), 170.7, 170.1, 170.1, 169.3 (each s, CH_3CO), 167.3 (d, C-22),149.1 (d, C-17), 140.6 (s, C-13), 140.2 (s, C-1″), 135.5 (d, C-19), 132.5 (s, C-8), 128.2 (each d, C-2″, C-3″, C-5″, C-6″), 126.7 (d, C-4″), 125.4 (d, C-9), 122.3 (d, C-10), 120.8 (t, C-18), 111.5 (s, C-16) 110.2 (d, C-12), 95.1 (d, C-21), 94.4 (d, C-1′), 72.5 (d, C-3′), 72.0 (d, C-5′), 70.6 (d, C-2′), 68.1 (d, C-4′), 66.9 (d, C-3), 61.5 (t, C-6′), 57.9 (t, CH_2-benzyl), 56.8 (s, C-7), 52.6 (t, C-5), 51.1 (q, CH_3O), 41.7 (d, C-15), 35.5 (t, C-6), 27.3 (t, C-14), 27.3 (d, C-11), 25.4 (d, C-20), 20.8, 20.7, 20.7, 20.0 (each s, CH_3CO). Results of NOE difference experiments (irradiated H, NOE enhancement in %): H-9, H-5β 1.6, H-10 12.2, H-14*proR* 2.2; H-14*proS*, H-3 2.9, H-9 0.8, H-14*proR* 21.3, H-17 0.7, N−CHa 9.8, N−CHb −1.1; H-20, H-3 6.2, 15-H 11.7, H-21 13.2; N-CHa, H-14*proS* 9.1, H-14*proR* −2.3, NCHb 22.4.

3*S*,7*R*-*O*′,*O*′,*O*′,*O*′-Tetraacetyl-4-benzyl-2,3-dihydro-2-oxospirostrictosidine (3*S*,7*R*-4b): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.83 (1H, br s, H-1), 7.47−7.32 (5H, m, H-2″, H-3″, H-4″, H-5″, H-6″), 7.43 (1H, d, $^3J_{9,10}$ = 7.5 Hz, H-9), 7.30 (1H, t, $^3J_{10,11}$ = $^3J_{11,12}$ = 7.5 Hz, H-11), 7.19 (1H, d, $^4J_{15,17}$ = 2.3 Hz, H-17), 7.07 (1H, t, $^3J_{9,10}$ = 7.5, $^3J_{10,11}$ = 7.5 Hz, H-10), 6.90 (1H, d, $^3J_{11,12}$ = 7.5 Hz, H-12), 5.27 (1H, dt, $^3J_{18Z,19}$ = 17.1, $^3J_{18E,19}$ = 10.2 H, $^3J_{19,20}$ = 10.2 Hz, H-19), 5.25−5.05 (3H, m, H-2′, H-3′, H-4′), 5.09 (1H, dd, $^2J_{18Z,18E}$ = 2.2, $^3J_{18E,19}$ = 10.2 Hz, H-18*E*), 5.02 (1H, d, $^3J_{20,21}$ = 2.4 Hz, H-21), 4.92 (1H, dd, $^2J_{18Z,18E}$ = 2.2 H, $^3J_{18Z,19}$ = 17.1 Hz, H-18*Z*), 4.78 (1H, d, H-1′), 4.30 (1H, dd, $^3J_{5'-6'a}$ = 4.6 Hz, H-6′a), 4.27 (1H, d, $^2J_{NCHa,NCHb}$ = 13.1 Hz, Hb-benzyl-CH_2), 4.15 (1H, dd, $^2J_{6'a,6'b}$ = 12.4, $^3J_{5',6'b}$ = 2.4 H, H-6′b), 3.72 (1H, m, H-5′), 3.67 (3H, s, OCH_3), 3.43 (H, dd, $^3J_{3,14R}$ = 3.9, $^3J_{3,14S}$ = 8.6 Hz, H-3), 3.25 (1H, d, $^2J_{NCHa,NCHb}$ = 13.1 Hz, Ha-benzyl-CH_2), 3.09 (1H, ddd, $^2J_{5\alpha,5\beta}$ = 8.7, $^3J_{5\beta,6\beta}$ = 9.0 Hz, H-5β), 2.52 (1H, q, $^2J_{5\alpha,5\beta}$ = 8.7, $^3J_{5\alpha,6\alpha}$ = 8.7; $^3J_{5\alpha,6\beta}$ = 8.7 Hz, H-5α), 2.32 (1H, ddd, $^3J_{5\beta,6\beta}$ = 9.0$^2J_{6\alpha,6\beta}$ = 12.6, $^3J_{5\alpha,6\alpha}$ = 8.7; $^3J_{5\beta,6\alpha}$ = 3.2 Hz, H-6α), 2.22 (1H, m, H-15), 2.12, 2.05, 2.04, 2.00 (each 3H, s, H_3CCO), 1.94 (1H, dt, $^2J_{6\alpha,6\beta}$ = 12.6, $^3J_{5\beta,6\beta}$ = 9.0, $^3J_{5\alpha,6\beta}$ = 8.7 Hz, H-6β), 1.78 (1H, ddd, $^2J_{14R,14S}$ = 14.9, $^3J_{3,14S}$ = 8.6, $^3J_{14S,15}$ = 4.4 Hz, H-14*proS*), 1.38 (1H, ddd, $^3J_{19,20}$ = 10.2, $^3J_{15,20}$ = 5.6; $^3J_{20,21}$ = 2.4 Hz, H-20), 1.31 (1H, ddd, $^2J_{14R,14S}$ = 14.9, $^3J_{14R,15}$ = 6.1, $^3J_{3,14R}$ = 3.9 Hz, H-14*proR*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.7 (s, C-2), 170.7, 170.6, 170.2, 169.5 (each s, CH_3CO), 167.0 (d, C-22), 149.7 (d, C-17), 140.6 (s, C-1″), 140.8 (s, C-13), 134.0 (s, C-8), 132.6 (d, C-19), 128.6 (each d, C-2″, C-6″), 128.2 (each d, C-3″, C-5″), 127.7 (d, C-4″), 126.7 (d, C-11), 125.6 (d, C-9), 122.1 (d, C-10), 120.9 (t, C-18), 111.7 (s, C-16), 109.7 (d, C-12), 95.2 (d, C-21), 94.7(d, C-1′), 72.6 (d, C-3′), 72.2 (d, C-5′), 71.3 (d, C-3), 70.6 (d, C-2′), 68.3 (d, C-4′), 61.8 (t, C-6′), 57.8 (t, CH_2-benzyl), 56.7 (s, C-7), 53.1 (t, C-5), 51.2 (q, OCH_3), 44.0 (d, C-20), 36.3 (t, C-6), 30.3 (t, C-14), 25.7 (d, C-15), 20.8, 20.6, 20.6, 20.3 (each q, CH_3CO). Coupling constants in Hz (determined in a HETLOCK experiment): $^1J_{C3,H3}$ = +137.0; $^2J_{C3,H14a}$ = −5.9; $^2J_{C3,H14b}$ = −5.1; $^3J_{C3,H15}$ = +4.3; $^3J_{C15,H3}$ = +3.4; $^3J_{C15,H19}$ = +5.1; $^3J_{C18,H20}$ = +5.7; $^1J_{C20,H20}$ = +136.2; $^2J_{C20,H15}$ = −2.8; $^3J_{C20,H18Z}$ = +6.6; $^3J_{C20,H18E}$ = +11.5. NOESY cross-peaks (H, cross-peak with, s, strong; m, medium; w, weak; vw, very weak): H-1, H-12 m, H-15 vw, H-18*E*; H-3, H-5α w, H-14a w, H-15 m, H-20 w, N−CHa vw, N−CHb w; H-5α, H-3 w, H-5β s, H-6α w, N-CHb w; H-5β, H-5α s, H-6β w, H-2″ w; H-6α, H-5α w, H-6β s; H-6β, H-5β w, H-6α s, H-9 w; H-9, H-6β w, H-10 m; H-10, H-9 m, H-11 m; H-12, H-1 m, H-11m; H-14a, H-3 w, H-14b m, N-CHa w; H-14b, H-14a m, H-2″ w; H-15, H-3 m, H-20 m N-CHa w; H-17, OCH_3 w; H-18*Z*, H-18*E* s, H-20 m; H-18*E*, H-18*Z* s, H-19 m; H-19, H-18*E* m, H-20 vw; H-20, H-3 w, H-15 m, H-18*Z* m, H-19 vw, H-21 m; H-21, H-20 m, H-1′.

Acknowledgment. Financial support of this work by the National Scientific Research Foundation, Budapest, Hungary, is gratefully acknowledged.

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NP010153F