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Chemistry of secologanin. Part 5.† Graphical analysis of the acidic deglycosylation of vincoside derivatives

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ABSTRACT: Acidic hydrolysis and cyclization were studied in vincoside glycosides ('natural' series) and their dihydro derivatives ('dihydro' series) in which either one or both N atoms were free or blocked by an alkyl group. For interpretation of the results, a graph was constructed in which 25 points (actually circles) represent a maximum of 81 aglycone types and 40 arrows indicate 131 possible cyclizations. The reaction matrix of the graph was under thermodynamic control and in most cases afforded the thermodynamically most stable product aglycones. In addition to the deglycosylation, two types of cyclization were observed. In azacyclizations, the preferred nucleophilic site is N-4 over N-1, and the preferred electrophilic site is C-22 in the glycosides, C-21 over C-19 and C-17 in aglycones. In oxacyclizations, the preferred nucleophilic site is O-17 over C-18 and C-21, and the preferred electrophilic site is C-19 over C-21 and C-17 in the 'natural' series, C-21 over C-17 in the 'dihydro' series. In one case, the kinetically favoured aglycone types which had been generated in the reaction mixture were trapped in a subsequent reaction (outside the graph) before thermodynamic equilibrium was attained. With the help of graphical analysis it was possible to justify the formation of the most favourable and actually isolated products and pathways out of a large number of possibilities. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: secologanin; vincoside derivatives; acidic deglycosylation; graphical analysis

INTRODUCTION

Vincoside (**03b**) is an alkaloid glycoside, which was isolated from *Catharanthus roseus* L.[2,3] and first prepared, together with the epimer strictosidine (**03c**), by Battersby and Parsons[2] in the coupling reaction of secologanin (**01a**) and tryptamine (**02a**). [The cyclic skeleton of the vincoside derivatives was numbered according to the biogenetic numbering system. The structures are shown or represented in this paper according to the following principles: aglycone types of the graph are indicated by serial number without any prefix (e.g. **21**), educts and products of deglycosylation and/or cyclization are labeled by the substitution pattern of the *educt* preceded by prefix **E** or **P** (e.g. **E-1U4P**), other compounds (in Scheme 1) are shown by numbers starting with **0** (e.g. **03b**).] Vincoside easily lactamizes into vincosamide (**04a**). Strictosidine (**03c**) is the precursor of a large number of indole alkaloids.[4,5] The key step in the biogenesis is deglycosylation, which opens the way to manifold structural and stereoisomerizations, and gives rise by further transformations to different types of indole alkaloids.[6] In a previous paper[7] we reported the acidic deglycosylation of simple lactam derivatives of secologanin, and analysed graphically the complicated situation after deglycosylation. If the tryptamine unit is built into the structure of the secologanin derivatives, the possibilities are multiplied. The aim of this work was to extend these investigations to the tryptamine derivatives of secologanin. Up to now, only enzymatic deglycosylation has been investigated.[8–10] As the 1- and 4-substituted derivatives of vincoside can be more easily prepared, studies were carried out in the vincoside series.

PREPARATION OF THE EDUCTS

Two series of the educts were studied depending on the presence ('natural') or absence ('dihydro', indicated by **H**) of the double bond between C-18 and C-19. In both series four types of derivatives were prepared, in which either one or both N atoms (N-1, N-4) were unprotected (**U**) (having an H atom) or protected (**P**) (by a methyl or benzyl group).

Vincoside [**E-1U4U**(= **03b**)], together with strictosidine (**03a**), was prepared by the coupling reaction of secologanin (**01a**) and tryptamine (**02a**) in slightly acidic aqueous solution. Under such conditions vincoside lactamized spontaneously to vincosamide (**04a**), which,

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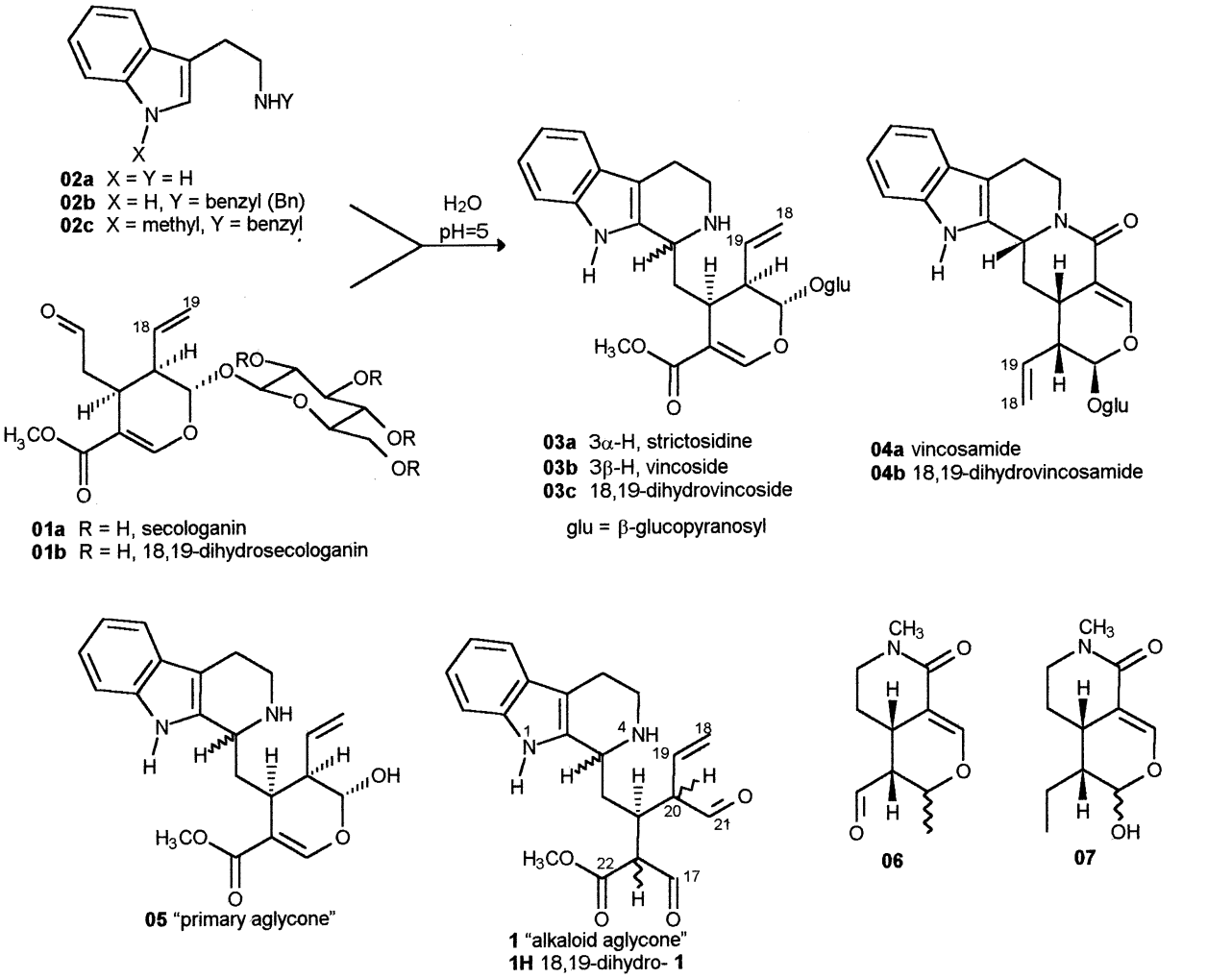

Scheme 1

after precipitation from the reaction mixture, was isolated by filtration.[11] 18,19-Dihydrovincoside [**E-1U4UH** (= **03c**)] was prepared from 4-benzyl-18,19-dihydrovincoside (**E-1U4PH**) by catalytic hydrogenolysis in dilute hydrochloric acid. The compound spontaneously lactamized in the slightly acidic medium to 18,19-dihydrovincosamide (**04b**). For studies on the cyclization of the aglycones, the lactams were used immediately.

4-Benzylvincoside (**E-1U4P**) and 4-benzyl-1-methylvincoside (**E-1P4P**) and their 18,19-dihydro derivatives (**E-1U4PH** and **E-1P4PH**) were prepared by the coupling reaction of secologanin (**01a**) or 8,10-dihydrosecologanin (**01b**) and *N*(b)-benzyltryptamine (**02b**) or *N*(b)-benzyl-*N*(a)-methyltryptamine (**02c**), respectively. As 1-methylvincoside and its 18,19-dihydro derivative lactamized rapidly, for studies of the cyclization their aglycones (**E-1P4U** and **E-1P4UH**) were prepared *in situ* by catalytic hydrogenolysis of the appropriate benzyl derivatives, **P-1P4P** and **P-1P4PH**, and used immediately. [All isolated aglycones were purified by chromatography and their structures (in most cases also including the stereochemistry) were proved by NMR spectroscopy. Experimental details will be described in a separate paper.]

RESULTS OF ACIDIC HYDROLYSIS AND CYCLIZATION

The acid-catalysed hydrolysis of educt glycosides was carried out in 2 M aqueous or aqueous methanolic hydrochloric acid at 100 °C for 2 h.

The educts and the isolated product aglycones and their aglycone types corresponding to the graph (see Scheme 8) are shown in Schemes 2 and 3. It can be seen that in the 'dihydro' series the secologanin subunit of the isolated aglycones retained its structure after cleavage and re-formation of the dihydropyran ring, and only the configuration of C-21 epimerized partially. However, in the isolated aglycones of the 'natural' series, the cleaved dihydropyran ring recessed to C-19 rather than to C-21 with the appropriate stereochemical consequences. This means that the structure of the secologanin subunit of our aglycones was completely analogous to aglycones **06** and **07** which were prepared previously under the same reaction conditions from bakankosines, i.e. simple lactam derivatives of secologanin.[7]

In educts of **1P4P** where both N atoms were protected (**E-1P4P** and **E-1P4PH**), the acid-catalysed hydrolytic

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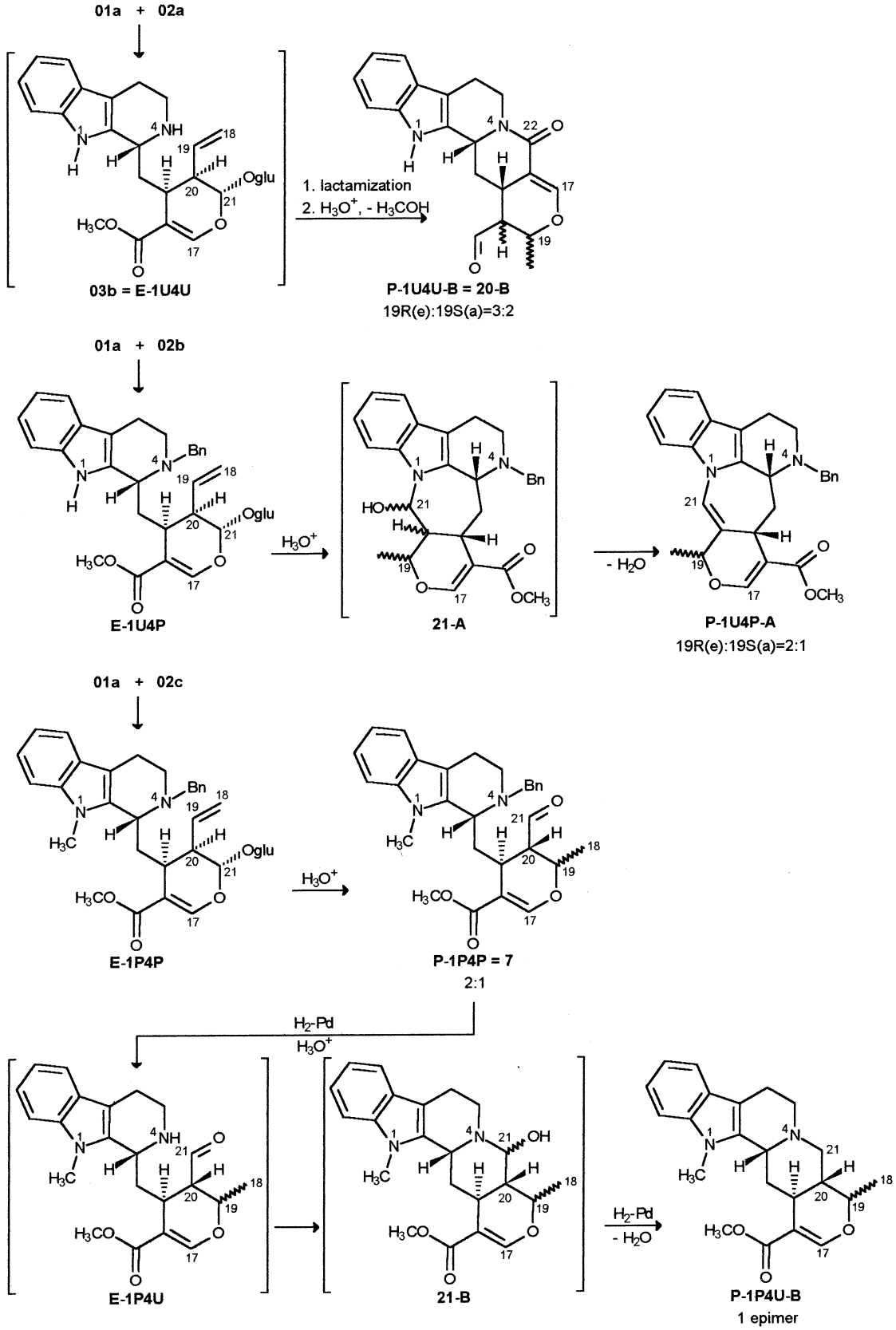

Scheme 2. Products of acidic hydrolysis of 'natural' glycosides.

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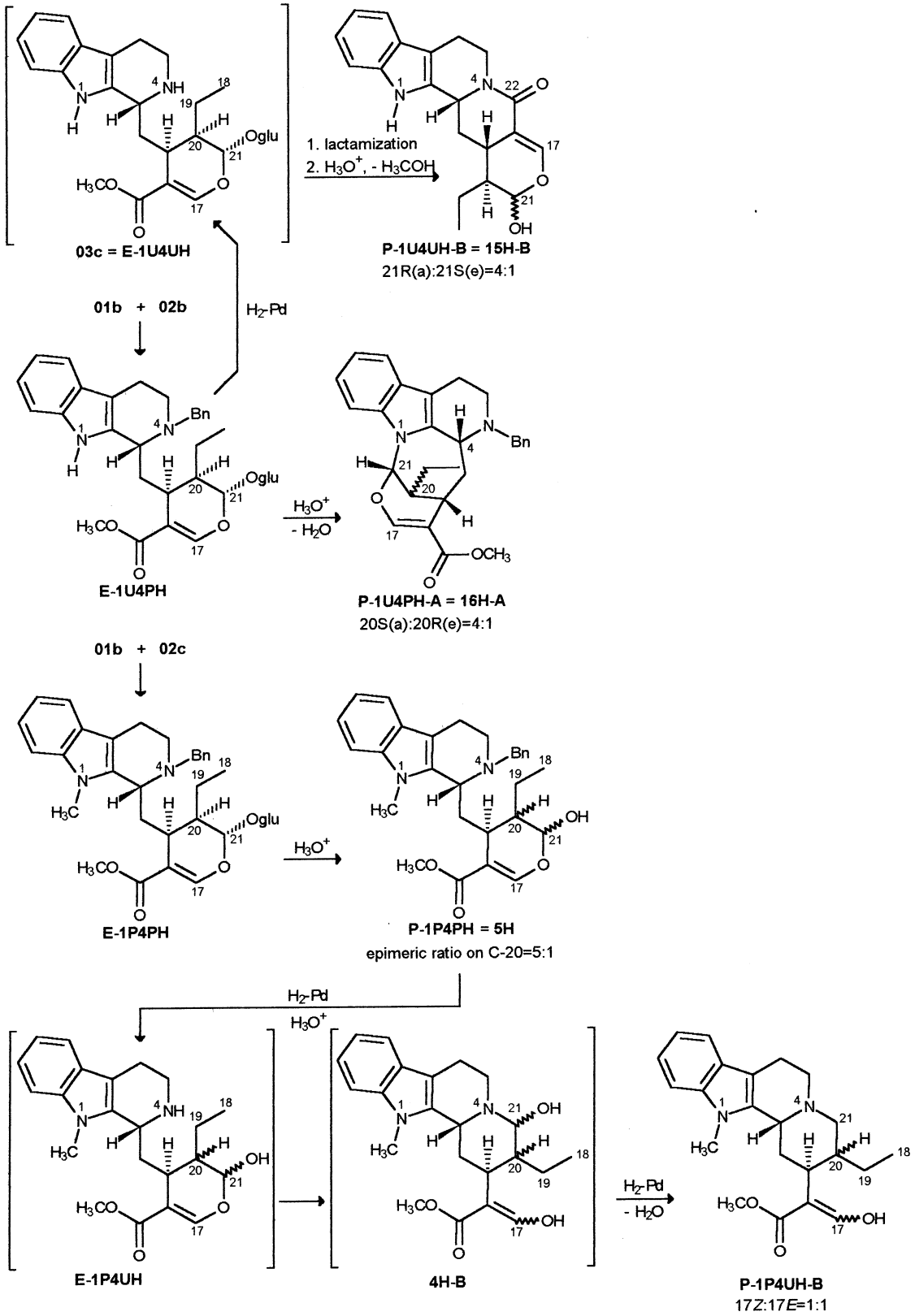

Scheme 3. Products of acidic hydrolysis of 'dihydro' glycosides.

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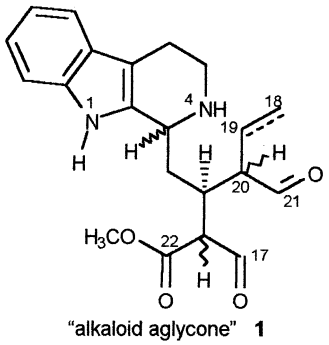
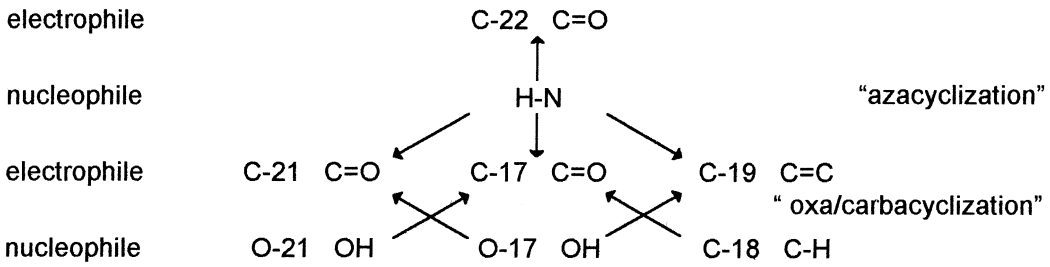
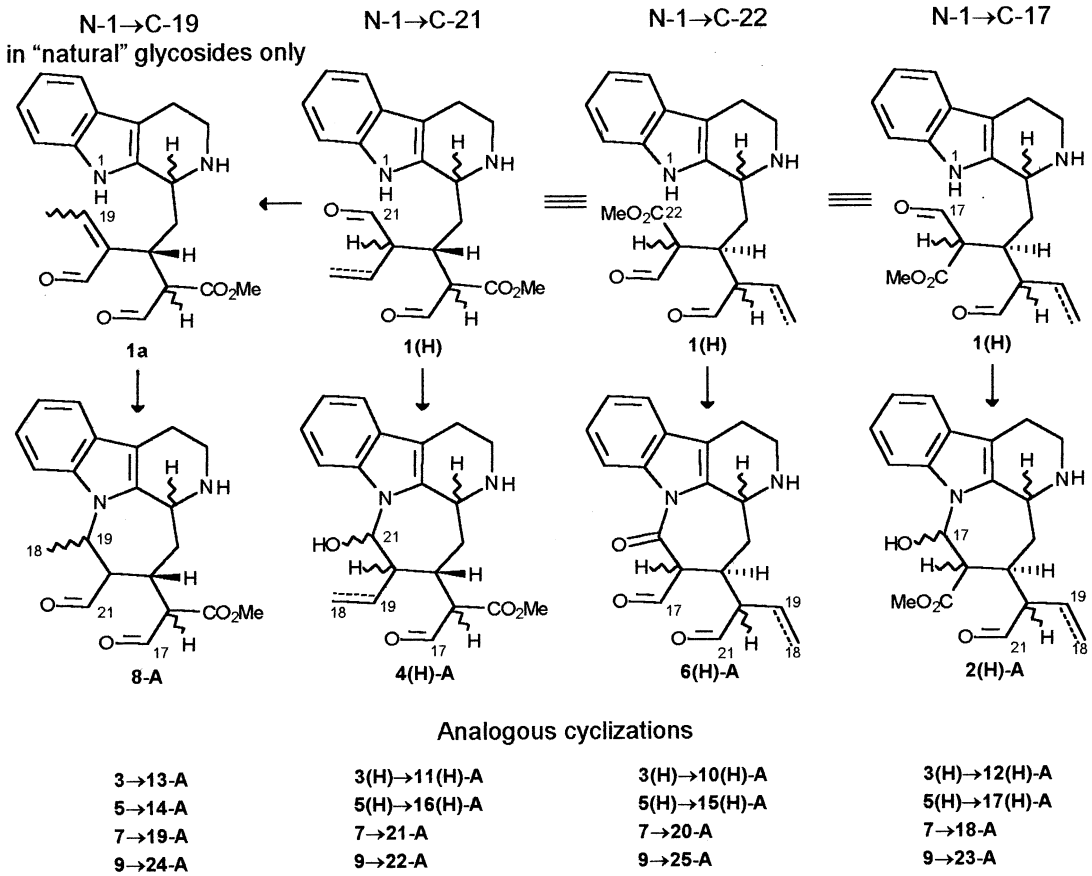




Scheme 4. Types of cyclization.

cyclization was blocked at the tetracyclic level and gave **P-1P4P** (= **7**) and **P-1P4PH** (= **5H**), respectively. In educts of type **1U4U**, where lactamization preceded deglycosylation (**E-1U4U** and **E-1U4UH**), the processes were stopped at the lactam level, and the appropriate aglycones **P-1U4U-B** (= **20-B**) and **P-1U4UH-B** (= **15H-B**) were isolated.

In educts of **1U4P** and **1P4U** where only one of the N



Scheme 5. Types of cyclization between N-1 and the secologanin unit.

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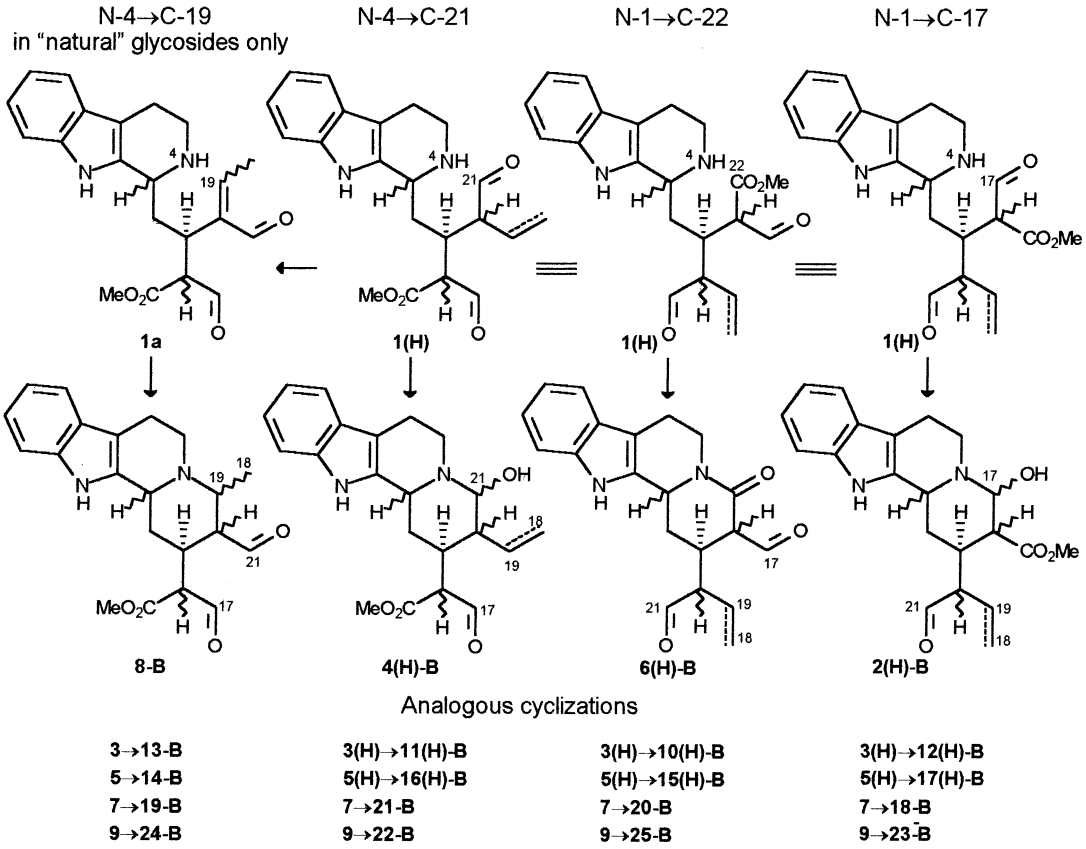

Scheme 6. Types of cyclization between N-4 and the secologanin unit.

atoms was unprotected, two subsequent cyclizations, one of them involving an N atom, afforded pentacyclic aglycones. From **E-1U4P** and **E-1U4PH** the final products **P-1U4P-A** and **P-1U4PH-A** were formed by acid-catalytic removal of one molecule of water, in the first case in a subsequent elimination reaction and in the second by direct substitution. As the educts of type **1P4U** could not be prepared in glycoside form, only the subsequent cyclizations could be studied on the aglycones prepared *in situ*. The structure of the final aglycones showed that aglycones **E-1P4U** and **E-1P4UH** cyclized to N-4, but the primary products were immediately further reduced to the final aglycones **P-1P4U-B** and **P-1P4UH-B** with simultaneous elimination of one molecule of water.

DESCRIPTION AND PROPERTIES OF THE GRAPH

The alkaloid aglycone **1** (Scheme 4) has four nucleophilic and four electrophilic centres which define two types of cyclizations, each of them in four variations. The first type runs between the secologanin subunit and one of the N atoms of the tryptamine subunit, and results in the formation of an azacycle ('*N*-cyclization'). In these cyclizations, N-1 or N-4 is the nucleophilic centre, and the aglycone types of the two series are distinguished by the letters **A** and **B**, respectively, when necessary. The electrophilic centres are C-22, C-21, C-17 and C-19 (in the vinyl–ethylidene isomerized educt **1a**). Individual cyclizations are shown in Schemes 5 and 6. The second type of cyclization takes place inside the secologanin subunit and results in the formation of an oxacycle or carbacycle ('*O*/*C*-cyclization'). In this case, the nucleophilic centres are O-17 and O-21 (oxacycle) and C-18 (vinylogous active methyl group in **1a**) (carbacycle); the electrophilic centres are C-17, C-21 and C-19 (again in the vinyl–ethylidene isomerized educt **1a**). The corresponding individual reactions are shown in Scheme 7. The pentacyclic aglycone types could be derived from the combination of these two types of cyclization. Double cyclizations in which the electrophilic site of the aza- and oxacyclizations is the same involve substitution with the formation of a bridged ring system (indicated by ○ in Scheme 8). A bridged system is also formed by subsequent intramolecular addition if the electrophilic site of the aza- and the nucleophilic site of the oxacyclization are part of the same C=C or C=O double bond (indicated by ● in Scheme 8). The other eight aglycone types have a fused ring system which is formed by addition when the electrophilic site of the aza- and the nucleophilic site of the oxacyclization belong to different double bonds.

For analysis of the experimental results in the frame of the possible aglycone types and cyclizations, a graph was

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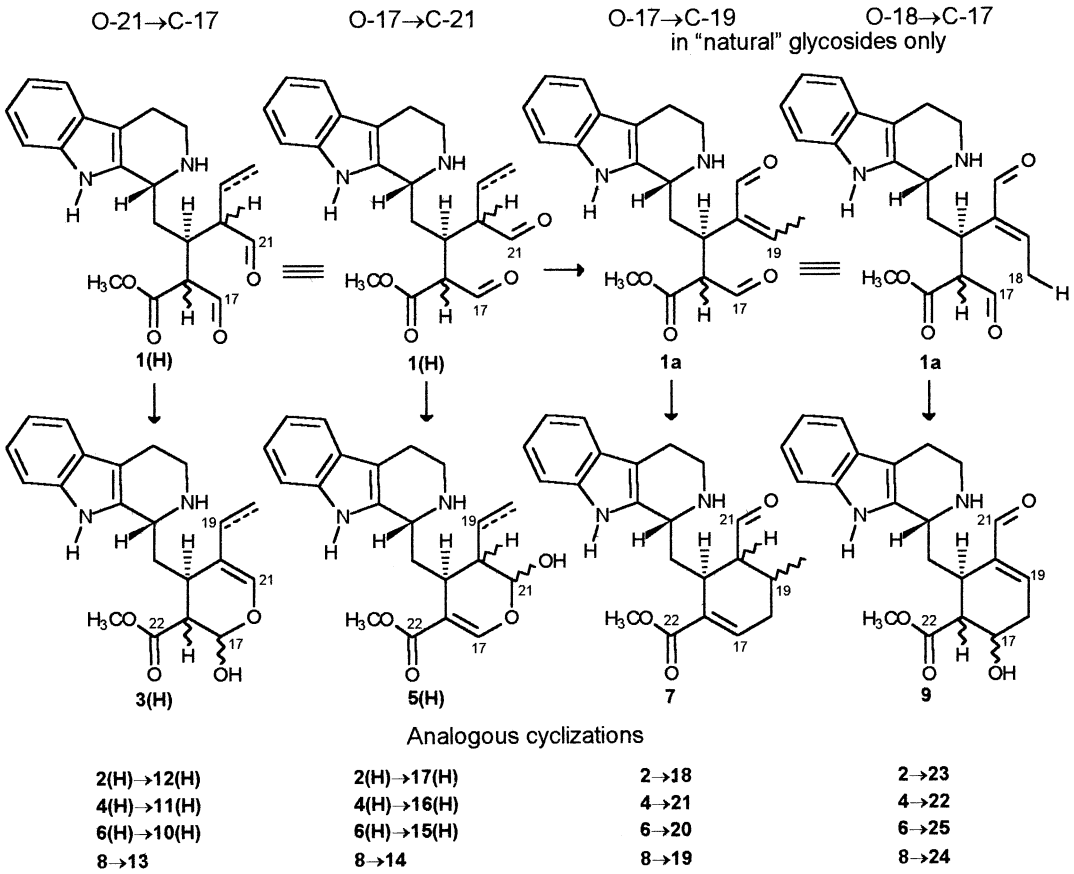

Scheme 7. Types of cyclization inside the secologanin unit.

constructed (Scheme 8). The 'points' (actually large circles) on the graph represent in symbolic form the possible aglycone types which can be derived from the tricyclic type alkaloid aglycone **1(H)** by single or double cyclization. The connections between the 'points' are shown by arrows corresponding to possible cyclizations which should be considered, at least in principle, as equilibria. The total number and distribution of the aglycone types are shown in Table 1. The structures of the educt glycosides and the actually isolated product aglycones are *not* shown on the graph, but in Schemes 2 and 3. On the graph, the aglycone types are symbolized by circles containing a serial number without any prefix, the locants of and the electron flow between atoms which take immediately part in cyclization, as well as the structure of the leaving molecule (water, methanol, methane) in the substitution reactions. However, the aglycones which are identical with or correspond to the isolated aglycones are represented by the substitution pattern of the appropriate educt (e.g. **1U4P**) on the graph, and their detailed structures are included in Schemes 2 and 3.

The '*N*-cyclized' tetracyclic aglycone types are represented on the inner part of the graph in the horizontal and vertical diagonals, the '*O*/*C*-cyclized' tetracyclic aglycone types on the oblique diagonals and the pentacyclic aglycone types on the periphery of the graph. One can see that each pentacyclic aglycone can be derived (and in some cases is really formed) in two ways, depending on the order of the cyclizations. Bold arrows show the most probable pathways. These cyclizations may be followed by further transformations (elimination, reduction) affording the isolated aglycones.

Our graphical analysis is based on the assumption that the 'primary aglycone' **05** immediately formed during acidic deglycosylation may exist in equilibrium with a further 11 structural isomers.[8] All of them are represented by the single tricyclic oxo formula **1** ('alkaloid aglycone' on the graph). Its structure is shown [together with some further isomers, **1a**, **3(H)**, **5(H)**, **7** and **9**] in Scheme 7. Likewise, the tetracyclic aglycone types **2(H)**, **4(H)**, **6(H)** and **8** are shown by the appropriate oxo form in Schemes 5 and 6. In some aglycone types, which are indicated by VE on the graph, the eventually present vinyl group can and really does isomerize into the more stable ethylidene group (see isomerization **1**⟶**1a** in Schemes 5–7). Many cyclizations can be derived from these izomerized aglycone types (see below). Aglycone types derived from both the 'natural' and the 'dihydro' glycosides (and also **13** and **14**) are represented on the upper part of the graph and those derived from the 'natural' glycosides, only, (except **13** and **14**) on the lower part. Stereochemistry in the construction of the graph could not be considered.

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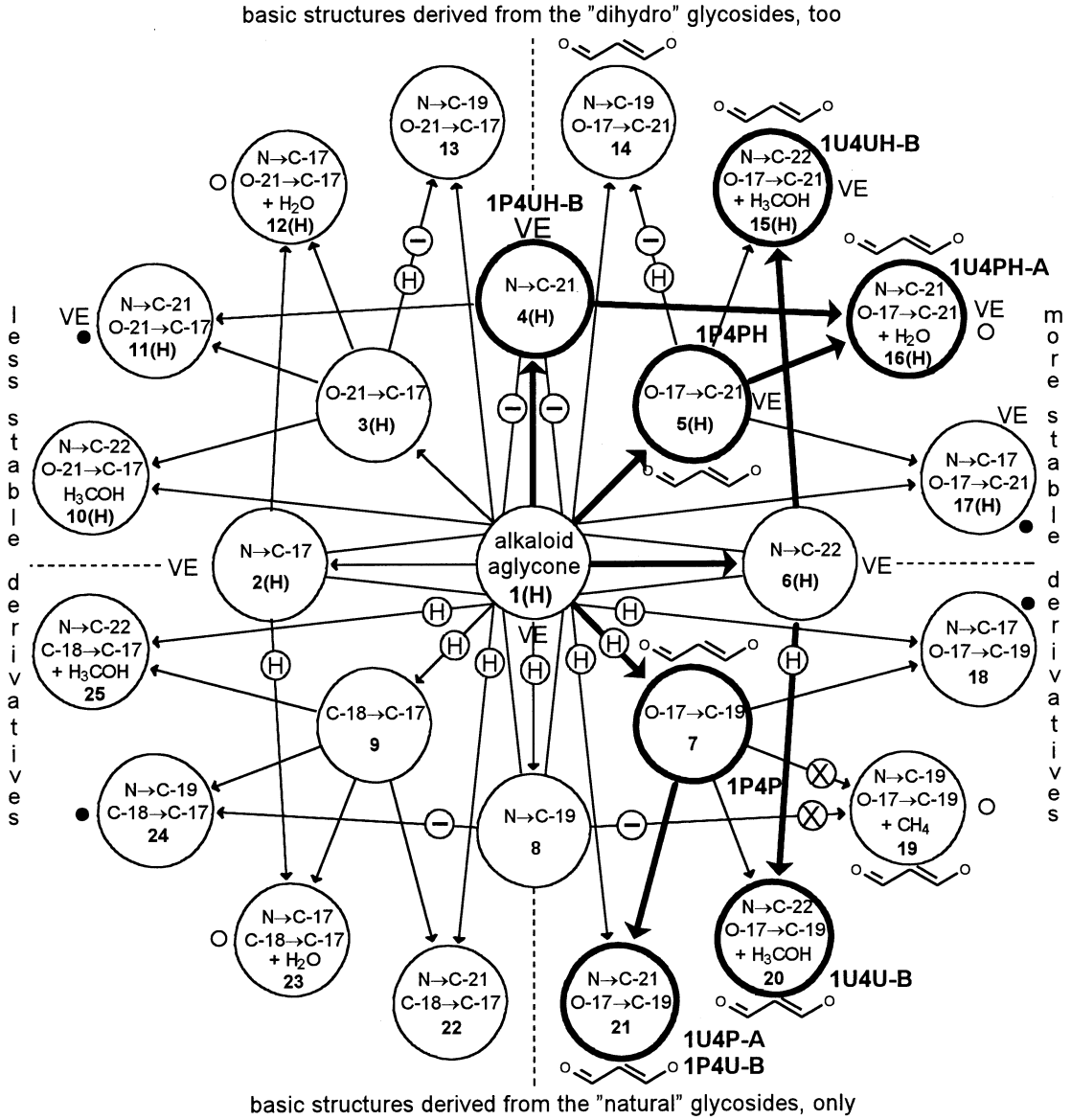

Scheme 8. Graph of the alkaloid aglycone types. For explanation of the labels, see text.

As Table 1 shows, 81 tri-, tetra- and pentacyclic aglycone types are represented by 25 circles on the graph. However, in their formation there are limitations. Some of them are rigorous and depend on the absence of structural conditions, others make cyclizations energetically more difficult and less probable.

1. The participation of C-18 as a nucleophile (in the form of a vinylogous active methyl group in the cyclization C-18 → C-17) and C-19 as an electrophile (activated by a conjugated carbonyl group in the cyclization O-17 → C-19) require the presence of a double bond in the C-19–C-20 position formed by isomerization of the vinyl to the ethylidene group. As in the 'dihydro' glycosides this double bond is absent, all cyclizations depending on it and indicated by H in small circles on

Table 1. Number of aglycone types represented on the graph

Type of aglycone	'Natural' series	'Dihydro' series	Together	Cyclizations
Tricyclic	1	1	2	
O/C-Tetracyclic (+ VE)	4 (+ 1)	2	7	7
N-Tetracyclic **A** + **B**(+ VE)	4 + 4 (+ 3 + 3)	3 + 3	20	20
Pentacyclic **A** + **B** (+ VE)	16 + 16 (+ 4 + 4)	6 + 6	52	2 × 52
Total	60	21	81	131

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the arrows are blocked, and neither of the aglycone types represented on the lower part of the graph, or **13** and **14**, can be formed.

2. If in the 'natural' series the activation of C-18 or C-19 was suspended in the first cyclization by addition to C-21 or C-19, the second cyclization indicated by a minus sign in a small circle on the arrow is blocked.
3. A special case is the aglycone type **19**. Its formation would involve in either way elimination of methane (indicated by X in a small circle). As the *C*-methyl group cannot be a leaving group, the formation of **19** is unreal and necessarily disregarded.
4. Aglycone types in which the energetically favorable and therefore stabilizing, 'mutually heteroconjugated' *β*-oxyacryloyl (O=C—C=C—O) system is retained, are indicated by a small partial substructure at the symbols of the aglycone types, and found [together with **17(H)** and **18**] on the right side of the graph. Cyclizations in which C-17 takes part as an electrophile saturate the C=C double bond of this substructure, and the appropriate aglycone types are less favourable. It should be emphasized that this limitation does not exclude these latter aglycone types from the equilibrium (in bakankosine derivatives their presence was demonstrated), but they are less probable as final aglycones.

GRAPHICAL ANALYSIS OF THE DEGLYCOSYLATION AND ACIDIC REARRANGEMENT

At the beginning of our analysis, it should be remembered that the primary aglycone **05** is one of the 12 structural isomers which are present in the reaction mixture of the deglycosylation equilibrium, and neither of them should be neglected, at least in principle, in the subsequent cyclizations.

All aglycone types which are identical with or correspond to the *actually isolated* aglycones are found on the right side of the graph, the 'dihydro' aglycone types on the upper part and the 'natural' aglycone types in the lower quadrant. The direction of the cyclization inside the secologanin subunit is O-17 → C-19 in the 'natural' series and O-17 → C-21 in the 'dihydro' series. The same pattern of oxacyclization can be found in the bakankosine aglycones **06** and **07**. In the acidic deglycosylation of the bakankosine derivatives it has been demonstrated by H–D exchange and supported by theoretical considerations and also by estimation of free enthalpies of formation that the deglycosylation was under thermodynamic control, and the isolated **06** and **07** proved to be most stable.[7] The analogy suggests that O17 → C-19 (in the 'natural' series) and O-17 → C-21 (in the 'dihydro' series) are the energetically most preferred oxacyclizations in vincoside derivatives also.

In educts **E-1P4P** and **E-1P4PH**, in which both N atoms are protected, the hydrolytic process is necessarily blocked at the tetracyclic level and gave the most stable isomers **P-1P4P** (= **7**) and **P-1P4PH** (= **5H**), respectively.

In all other types of educts, the hydrolytic process could give pentacyclic aglycones. In the 'dihydro' series four (right upper quadrant), in the 'natural' series eight aglycone types (right half of the graph) can be derived. However, aglycone types **17** and **18** as final products are less probable in both series according to limitation 4. Aglycone type **19** should be considered as unrealistic according to limitation 3. In the 'dihydro' series aglycone type **14** cannot be formed, as both pathways are blocked (through **8** according to limitation 1, through **5** according to limitations 1 and 2). Even in the 'natural' series, aglycone type **14** is less probable as the final aglycone, because its formation would involve cyclization step O-17 → C-21, giving rise to a secologanin subunit which is less stable under the applied experimental conditions. Hence in the 'dihydro' series aglycone types **15** and **16** and in 'natural' series also the same aglycone types and **20** and **21** may be expected to be formed.

In the educts **E-1U4U** and **E-1U4UH**, in which both N atoms are unprotected, the azacyclization is faster than the deglycosylation, and the subsequent hydrolysis afforded the lactam aglycones **P-1U4U-B** (= **20-B**) and **P-1U4UH-B** (= **15H-B**), respectively, again in their most stable form in the secologanin subunit. The fact that lactamization prefers N-4 rather than N-1 was also expected because N-4 has a higher nucleophilicity than N-1 and a six-membered ring is formed faster than a seven-membered ring. Even from the thermodynamic point of view, lactamization to N-1 would be less preferred, as the amide group could not take up the stable planar arrangement. In the formation of aglycone types **1P4P(H)** and **1U4U(H)** the shortest pathways are unequivocal and indicated by bold arrows on the graph.

The acidic hydrolysis of the educts **E-1U4P** and **E-1U4PH** has alternatives both in the direction of the azacyclization and in the pathway. As N-4 is protected, only N-1 can take part in it as a nucleophile, and the formation of **A**-type aglycones is expected. However, participation of both electrophilic centres C-21 and C-22 are real possibilities. The structure of the isolated aglycones **P-1U4P-A** and **P-1U4PH-A** correspond to aglycone types **21-A** and **16H-A**, respectively. The cyclization was accompanied by the entropically favourable removal of one molecule of water, in the 'dihydro' aglycone simultaneously by substitution, in the 'natural' aglycone in a subsequent reaction by elimination. In both aglycone types, the secologanin subunit took up the more stable state, but the N-1 atom cyclized to C-21, rather than to C-22. The direction of the azacyclization can easily be interpreted by the well known fact that the reactivity of the formyl group is higher against nucleophiles than that of the ethoxycarbonyl group. This cyclization seems to be even thermodynamically more favourable. The alternative cyclization to C-22 would

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give the tetrahedric intermediate which, however, could not be stabilized into a lactam because the amide group could not obtain the energetically more stable planar arrangement in the seven-membered fused or bridged ring. The graph clearly shows that the shortest pathway to aglycone type **21-A** is unequivocal through **7**, as the second step of the alternative pathway through **4** is blocked according to limitation 2. However, for the formation of aglycone type **16H-A**, two real pathways are open, through either **5H** or **4H**. No experimental data could be found to make a decision.

As 1-methylvincoside and its dihydro derivative could not be prepared, the acidic rearrangements were studied on the aglycones **E-1P4U** and **E-1P4UH** generated from 1-methyl-4-benzylvincoside aglycone **P-1P4P** and its dihydro derivative **P-1P4PH** and used immediately without isolation. (If reduction of C-21 had preceded debenzylation, cyclization to C-21 could not have been expected.) Of course, the educt aglycones already had the secologanin subunit in its most stable form, but studies on bakankosine derivatives proved that the manifold isomerizations were still possible at this level. In fact, these isomerizations proceeded in the acidic medium of the catalytic debenzylation and gave the isolated aglycones **P-1P4U-B** and **P-1P4UH-B**, respectively. The steps can be easily reconstructed. In both cases, N-4 as the only free N nucleophile and C-21 as the more reactive electrophile took part in the azacyclization, giving the intermediate aglycone types **21-B** and **4H-B**, respectively, which afforded the isolated aglycones by further hydrogenation and elimination of water. Cyclization to C-22 would have given the thermodynamically more stable lactam aglycones **20** and **15H**; however, the more rapidly formed aglycone types **21-B** and **4H-B** were trapped by subsequent hydrogenation before having reached the complete thermodynamic equilibrium. The shortest pathway of the formation of **21-B** is straightforward through **7**, as the alternative pathway through **4** is blocked according to limitation 2. Formation of the aglycone type **4H-B** involves the cleavage of the hemiacetalic oxacycle and recyclization through the tricyclic alkaloid aglycone **1(H)** to the more stable hemiaminal **4H-B** which was trapped as mentioned previously. In this case, of course, the oxacycle could not be regenerated.

The results of the graphical analysis can be summarized as follows. The reaction matrix represented by the graph is under thermodynamic control and with one exception afforded the thermodynamically most stable product aglycones. When N-1 was blocked, but N-4 free, and the aglycone was generated in the reaction mixture, the kinetically favoured aglycone types were trapped in a subsequent reaction before thermodynamic equilibrium was attained. When N-4 was blocked, but N-1 free, the most stable aglycones were formed by the cyclization N-1 $\rightarrow$ C-21, because lactamization (N-1 $\rightarrow$ C-22) was hindered by lack of obtaining the planar form of the amide group. When both N atoms were free, azacyclization preceded deglycosylation, and the preferred site of lactamization was N-4 with the formation of a lactam which proved to be the most stable substructure during deglycosylation also. When both N atoms were blocked, the cyclization was stopped at the tetracyclic level. The secologanin subunit of all vincoside aglycones was stabilized in its thermodynamically most favoured state, i.e. according to the cyclization O-17 $\rightarrow$ C-19 in the 'natural' series and O-17 $\rightarrow$ C-21 in the 'dihydro' series (except for the aglycone type in which the cleaved oxacycle could not be regenerated because of the absence of an appropriate functional group). With the help of the graphical analysis, it was possible to justify the formation of all actually isolated products and the shortest pathways out of a large number of possibilities.

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