SYNTHESIS OF LYALOSIDE, A PROTOTYPAL β-CARBOLINE GLUCO INDOLE ALKALOID IN RUBIACEOUS PLANTS

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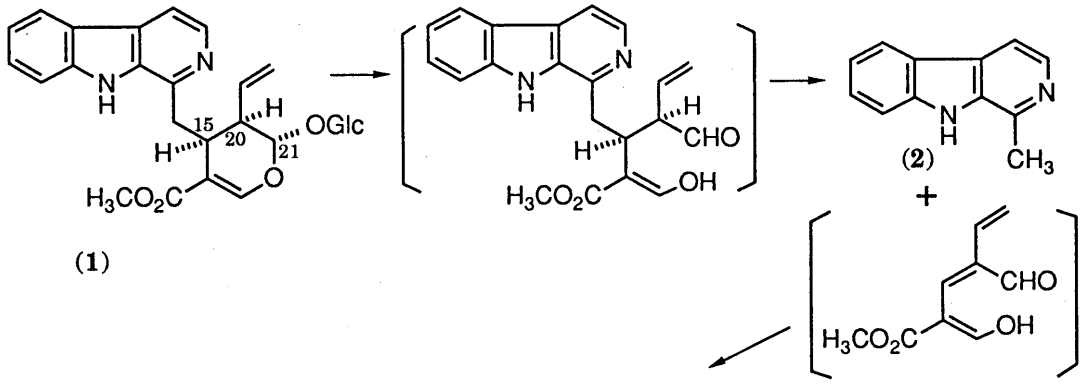
Lyaloside was synthesized, for the first time, from L-tryptophan and secologanin. This proved the stereochemistry of lyaloside unambiguously. Full assignments of ^{1}H- and ^{13}C-NMR spectra were performed on another natural glucoindole alkaloid of key importance, 5(*S*)-5-carboxystrictosidine, which was obtained during this synthesis.

KEYWORDS lyaloside; 5(*S*)-5-carboxystrictosidine; 5(*S*)-5-carboxyvincoside; β-carboline; glucoindole alkaloid; synthesis; stereochemistry; Ophiorrhiza;

Lyaloside (**1**) was first isolated from *Pauridiantha lyalli* by Cave et al.[1] In 1986 the same gluco alkaloid (**1**), together with its corresponding carboxylic acid, lyalosidic acid and other novel glucosidic alkaloids, was found from two species of Rubiaceous plants of genus *Ophiorrhiza* in this laboratory.[2] On that occasion we observed that a novel type fragmentation took place concomitantly when this class of β-carboline glucoalkaloids was subjected to enzymatic glucoside bond hydrolysis. This observation strongly indicated the possibility that the co-occurring harman (**2**) in the same plants could be an artifact arising from lyaloside and other closely related β-carboline-type gluco indole alkaloids.[2]

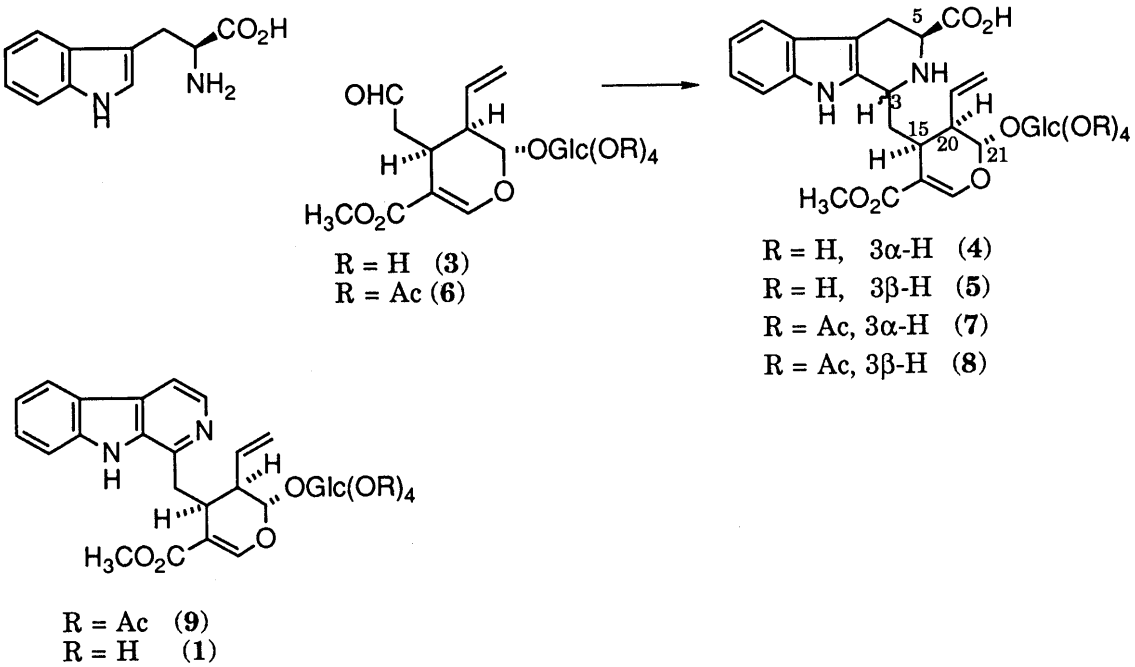


Lyaloside was first proposed to have the configurations of 15-αH, 20-βH, and 21-αH,[1] but later the configurations were revised to the correct ones, 15-αH, 20-αH, and 21-βH.[3] The ground of the structure revision, however, was not quite convincing, because the conclusion was deduced from re-examination of NMR spectrum in the light of that of an inseparable mixture of two lyaloside analogues, 6'-trans feruroyl- and 6'-trans sinapoyl lyalosides.[3] In this communication we report the first synthesis of natural lyaloside (**1**). This synthesis conclusively confirmed the lyaloside stereochemistry. We also synthesized 5(*S*)-5-carboxystrictosidine (**4**) as the intermediate. This compound, having the alternative name 3α,5α-tetrahydrodeoxycordifoline (TDC) (**4**), was originally found from *Anthocephalus cadamba* by Smith *et al.*, and was synthesized by the same authors.[4] Details of the spectroscopical data, however, have not been available. This paper describes full assignments of ^{1}H- and ^{13}C-NMR of this carboxy

gluco indole alkaloid (**4**) of key importance; **4** is 5-carboxy equivalent of strictosidine and is the most plausible biogenetic progenitor of a group of naturally occurring 5-carboxylated indole alkaloids.[5]

Synthesis of lyaloside was carried out as follows. Secologanin (**3**), isolated from *Lonicera morrowii*,[6] was condensed with L-tryptophan in Mellvain phosphate buffer of pH 4.5. Two compounds, **4** [7] and **5**,[8] were obtained in the respective yield of 20% and 8% after purification. Both were found to have the same molecular formula of $C_{28}H_{34}O_{11}N_2$. The ^{1}H-NMR signal for H-5 of the major epimer (**4**) was observed at δ 3.83 as a double double doublet with the coupling constants of $J_{5\alpha\text{-H},6\beta\text{-H}}$ = 11.8 Hz, $J_{5\alpha\text{-H},6\alpha\text{-H}}$= 4.2 Hz, $J_{5\alpha\text{-H},3\alpha\text{-H}}$= 1.5 Hz, while the corresponding signal of the minor epimer (**5**) was seen at δ 4.14 as a double doublet with coupling constants of $J_{5\alpha\text{-H},6\beta\text{-H}}$ = 8.4 Hz, $J_{5\alpha\text{-H},6\alpha\text{-H}}$ = 6.4 Hz. These and other data strongly indicated that **4** is 5(*S*)-5-carboxystrictosidine and **5** is its C-3 epimer. The spectral details are shown in the reference part of this communication.[7,8]

Next, acetylation of **4** was attempted, but a satisfactory result was not obtained. Therefore condensation of L-tryptophan with tetraacetyl secologanin (**6**) was carried out. An epimeric mixture of carboxylated gluco alkaloids (**7, 8**) was obtained in 40% yield. This mixture was then heated with potassium perchromate (4 mol eq) in the mixture of acetic acid - tetrahydrofurane- water for 5 min. The usual workup afforded lyaloside tetraacetate (**9**), $C_{35}H_{38}O_{13}N_2$, mp 154-155°C, which was identified with the sample derived from natural lyaloside.[2] Deacetylation of **9** using sodium methoxide in methanol gave lyaloside (**1**). The synthetic specimen showed complete identity with lyaloside of natural origin.[2]



R = H (**3**)
R = Ac (**6**)

R = H, 3α-H (**4**)
R = H, 3β-H (**5**)
R = Ac, 3α-H (**7**)
R = Ac, 3β-H (**8**)

R = Ac (**9**)
R = H (**1**)

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7) 5(*S*)-5-Carboxystrictosidine (**4**); Amorph. powder, $C_{28}H_{34}O_{11}N_2$ (FAB-MS M+1; m/z 575.2242; Calcd for $C_{28}H_{35}O_{11}N_2$, 575.2240). UV λmax (EtOH); 222, 240(sh), 272(sh), 278(sh), and 289 nm. ^{1}H-NMR (CD_3OD) (500MHz), δ; 2.14 (ddd, *J*= 15.1, 12.4, 3.6 Hz, H-14α), 2.35 (ddd, *J*= 14.9, 11.9, 3.0 Hz, H 14β), 2.68 (ddd, *J*= 8.6, 8.6, 4.9 Hz, H-20), 2.95 (ddd, *J*= 16.2, 12.2, 2.5 Hz, H-6β), 2.99 (ddd, *J*= 12.5, 4.2, 4.2 Hz, H-15), 3.16 (t-like, H-2'), 3.16 (t-like, H-4'), 3.31-3.32 (m, H-5'), 3.33 (dd, *J*= 9.0, 9.0 Hz, H-3'), 3.37 (dd, *J*= 16.6, 4.4 Hz, H-6α), 3.58 (dd, *J*=11.7, 7.1 Hz, H-6'a), 3.70 (3H, s, $COOC\underline{H}_3$), 3.83 (ddd, *J*= 11.8, 4.2, 1.5 Hz, H-5), 3.93 (dd, *J*= 11.7, 2.0 Hz, H-6'b), 4.51 (d, *J*=11.3 Hz, H-3), 4.72 (d, *J*= 7.0, Hz, H-1'), 5.17 (d, *J*= 11.0 Hz, H-18 cis), 5.28 (d, *J*= 17.6 Hz, H-18 trans), 5.75 (ddd, *J*= 17.8, 10.5, 7.5 Hz, H-19), 5.83 (d, *J*= 9.3 Hz, H-21), 6.95 (dd, *J*= 7.6, 7.6 Hz, H-10), 7.03 (dd, *J*=7.5, 7.5 Hz, H-11), 7.21 (d, *J*= 8.3 Hz, H-12), 7.38 (d, *J*= 8.1 Hz, H-9), and 7.72 (s, H-17). ^{13}C-NMR (CD_3OD) (125MHz), δ; 22.4 (C-6), 31.1 (C-15), 33.0 (C-14), 43.7 (C-20), 51.4 (C-16-$COOCH_3$). 51.6 (C-3), 57.9 (C-5), 61.6 (C-6'), 70.2 (C-4'), 73.0 (C-2'), 76.4 (C-3'), 77.3 (C-5'), 95.8(C-21), 98.8 (C-1'), 106.8 (C-16), 107.0 (C-7), 110.7 (C-12), 117.6 (C-9), 118.3 (C-18), 119.1 (C-10), 121.2 (C-11), 125.9 (C-8), 128.7 (C-2), 133.5 (C-19), 136.9 (C-13), 155.7 (C-17), 170.2 (C-16-$\underline{C}OOCH_3$), and 171.8 (C-5 COOH).

8) 5(*S*)-5-Carboxyvincoside (**5**); Amorphous powder,$C_{28}H_{34}O_{11}N_2$ (FAB-MS ; M+1, m/z 575.2248; Calcd for $C_{28}H_{35}O_{11}N_2$; 575.2241). UV λmax (EtOH); 222, 240 (sh), 272 (sh), 278 (sh), and 289 nm. ^{1}H-NMR (CD_3OD) (270MHz), δ; 2.22 (m, H-14β), 2.34 (m, H-14α), 2.81 (ddd, *J*= 6.9, 8.2, 4.3 Hz, H-20), 3.2 (m, H-15), 3.65 (dd, *J*= 12.2, 6.6 Hz, H-6'b), 3.94 (dd, *J*= 12.2, 1.7 Hz, H-6'a), 4.14 (dd, *J*= 8.4, 6.4 Hz, H-5), 4.65 (m, H-3), 5.30 (d, *J*= 11.2 Hz, H-18 cis), 5.35 (d, *J*= 16.0 Hz, H-18 trans), 5.61 (d, *J*= 6.9 Hz, H-21), 5.92 (ddd, *J*= 16.0, 11.2, 8.2 Hz, H-19), 7.04 (t-like, H-10), 7.14 (t-like, H-11), 7.36 (d, *J*= 8.2 Hz, H-12), 7.48 (d, *J*= 7.9 Hz, H-9), and 7.60 (s, H-17).

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