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Final Solution on the Long-Standing Structural Arguments on the C-3 Stereochemistries of Three Glucoindole Alkaloids: Palicoside, Dolichantoside, and Isodolichantoside – Through Chemical Conversions and Spectroscopic Studies

Osamu OHMORI, Kyoko KUMAZAWA, Hiroyuki HOSHINO, Takako SUZUKI, Yuka MORISHIMA, Hiroko KOHNO, Mariko KITAJIMA, Shin-ichiro SAKAI, Hiromitsu TAKAYAMA, and Norio AIMI*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

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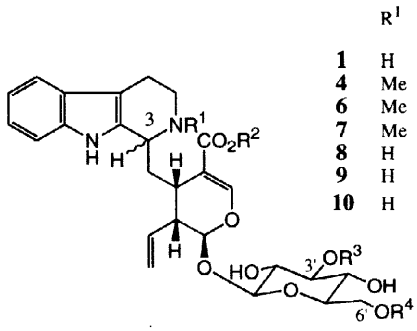
Abstract: Three natural strictosidine/vincoside-class glucoindole alkaloids have been chemically correlated with strictosidinic acid possessing a rigorously established stereostructure. The C-3 stereochemistry of palicoside, dolichantoside, and isodolichantoside has been firmly proved to be (*S*), (*S*), and (*R*), respectively.

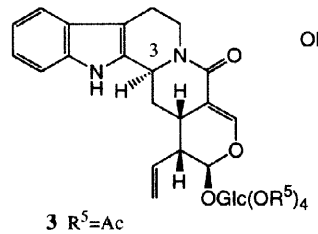
Keywords: Alkaloids; Circular dichroism; Indoles; Stereochemistry

Strictosidine (**1**)[1, 2] was found in nature in the late 1960s and is now believed to be the universal biosynthetic intermediate of over 1,400 natural monoterpenoid indole alkaloids. The enzyme that catalyzes its formation from tryptamine and secologanin (**2**) has been purified and the c-DNA was cloned by Zenk and Kutchan.[1] In contrast to the extensive studies on the biological side, chemical and spectroscopic studies on this important molecule have been left far behind. It is only in these recent years that full details of the chemical and spectroscopic data of **1** and its related molecules have been presented and rigorous structural discussions have been developed in scientific journals. In 1997 Szabó *et al.* performed the "first direct and detailed stereochemical analysis" of **1**.[2] In the same year we studied the molecular structure of strictosamide tetraacetate (**3**) by extensive use of NMR pulse techniques.[3] Up to the present day more than 30 strictosidine-class glucoindole alkaloids have been found in nature,[4] but their structures, in particular the stereochemistries at the C-3 position, are often not sufficiently substantiated. Obviously, more direct and rigorous chemical proofs are awaited.

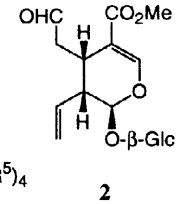
Palicoside (**4**) was found in a Brazilian plant, *Palicourea marcgravii*, by Itokawa *et al.*[5] They proposed C3-*S* (H3-α) stereochemistry to this compound based on spectroscopic and chemical reasons. One of the chemical proofs that they described was the observed structural change of **4** to strictosamide (**5**) in hot DMSO, which is a



	R^1	R^2	R^3	R^4	H3
1	H	Me	H	H	α (*S*)
4	Me	H	H	H	α
6	Me	Me	H	H	α
7	Me	Me	H	H	β (*R*)
8	H	H	H	H	α
9	H	H	H	α-Glc	α
10	H	H	α-Glc	H	α



3 R^5=Ac
5 R^5=H



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rather unusual reaction. Garson *et al.*, [6] who obtained the same compound from another source, supported the C3-*S* configuration by referring to a report of Zenk *et al.* on the CD spectrum.[7] Unfortunately, however, applicability of this report for this compound has not been well substantiated.

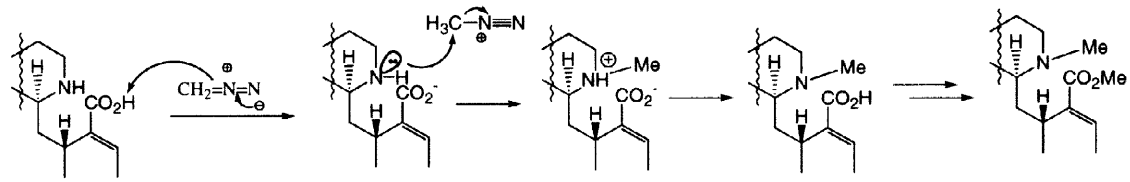
In 1978 Coune and Angenot found dolichantoside (**6**) in *Strychnos gossweileri*, an African species of *Strychnos*.[8] Two years later, they isolated isodolichantoside (**7**) from the same plant.[9] These two compounds differ only in the configuration of the C-3 position and the most evident difference is their CD Cotton effects at the region of 270-300 nm; dolichantoside shows positive Cotton effects, whereas isodolichantoside has negative ones. By applying Brown's report[10] to these Cotton effects the authors concluded that dolichantoside had C3-*S* configuration, and thus it was N_b-methylstrictosidine (**6**), whereas isodolichantoside was N_b-methylvincoside (**7**).

In 1993 a question was raised by Arbain *et al.* and they argued that the formerly proposed structures for dolichantoside and isodolichantoside should be revised.[11] They tried to apply the report of Zenk[7] to the positive Cotton effect at around 220nm in the CD spectrum of dolichantoside, and claimed that its C3 configuration should be *R* (H3-β).

In 1996 Angenot *et al.* reexamined the C-3 stereochemistry and developed a counter argument. They compared the CD spectrum of dolichantoside (**6**) with that of an authentic sample of strictosidine prepared by enzymatic condensation of tryptamine and secologanin, and claimed that dolichantoside has C3-*S* configuration as they first reported.[12]

In order to finalize the confusing arguments concerning stereochemistry of these three natural glucoindole alkaloids, we started our study on chemical conversion. In this paper we describe a chemical correlation of palicoside (**4**) and dolichantoside (**6**) with strictosidinic acid (**8**).

We chose strictosidinic acid (**8**) as the starting material for the reason that it possesses C3-*S* (H3-α) configuration established rigorously by the chemical correlation with strictosamide.[11, 13] Methylation of **8** with ethereal diazomethane yielded the corresponding methyl ester **1** and N_b-methylated methyl ester **6**[14] in 17.1% and 35.2%, respectively. Szabó *et al.* obtained strictosidine **1** from tryptamine and secologanin (**2**). The ester **1** that we obtained was identical with strictosidine that Szabo has fully characterized.[2, 15] In this reaction we obtained *N*, *O*-dimethylated compound **6** as the major product. Formation of **6** from **8** involves *N*-methylation of a secondary amine moiety with diazomethane. The mechanism of this reaction is depicted as shown in the Scheme 1. It is noteworthy that the reaction proceeds only in the presence of the carboxyl moiety in the same molecule; no reaction occurred when strictosidine, which is the corresponding methyl ester of strictosidinic acid (**8**), was used as the starting material. Similar *N*-methylation reaction has been observed when geissoschizine or a closely related molecule was submitted to diazomethane methylation, where *N*-quaternization occurred.[16] In the latter cases presence of an acidic enol function helped *N*-methylation.



Scheme 1

Hydrolysis of methyl ester **6** (C3-*S*, H3-α) with 0.5N aqueous lithium hydroxide in THF yielded the

corresponding carboxylic acid,[17] whose physical and spectroscopic data were identical with those of palicoside (**4**) reported in the literature[5] (^{1}H and ^{13}C-NMR spectra, IR spectrum, melting point, CD spectrum[5, 6] and high resolution FAB-mass spectrum). Since it is out of the bounds of possibility to occur the epimerization at the C3 position under the mild reaction conditions used above (i. CH_2N_2, ii. LiOH, aq. THF, rt), the correlation here clearly demonstrated that palicoside has C3-*S* (H3-α) configuration.

We obtained N_b-methylstrictosidine (**6**)[14] as described above. Angenot *et al.* claimed that compound **6** is dolichantoside,[12] while Arbain *et al.* argued that **6** is isodolichantoside.[11] We compared the spectral data of **6**, including CD spectra, with those in the literature[8, 12] and we found that **6** was identical to dolichantoside, not to isodolichantoside. Now the C-3 configuration of dolichantoside was proved to be *S* as Coune and Angenot first reported.[9] To make this point more clear, we prepared dolichantoside and isodolichantoside[18] through condensation of **2** with N_b-methyltryptamine.[19] Direct comparison of the obtained molecules supported the above conclusion.

Having the structures firmly established, we then examined the CD spectra. The CD spectra of **6** and **7** that we measured are shown in Figure 1.

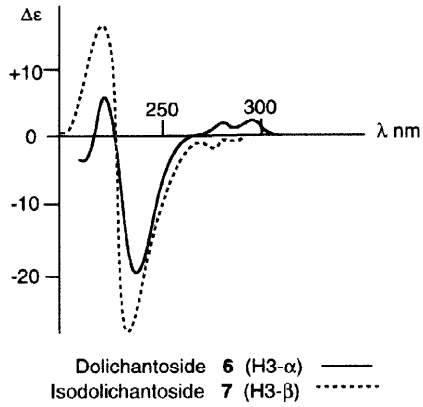


Fig. 1 CD Spectra (MeOH)

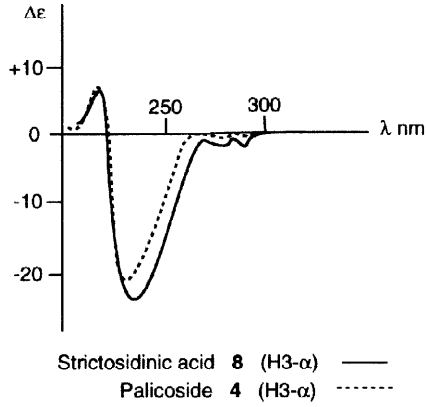


Fig. 2 CD Spectra (MeOH)

Until now, the report of Brown[10] that correlates the Cotton effect sign in the 270-300 nm region to the C-3 configuration of tetrahydro-β-carboline-type glycoalkaloids has been accepted without any significant criticism. We found that this report was not applicable to **4** and other molecules whose carboxylic acid function is not esterified. Palicoside (**4**) evidently has H3-α (C3-*S*) configuration (*vide supra*) but as shown in Figure 2, **4** shows negative Cotton effects between 270 and 300 nm instead of the expected positive Cotton effects from Brown's report. The situations was the same in other carboxylic acid-type derivatives such as strictosidinic acid (**8**), hunterioside (**9**) and hunterioside B (**10**).[20] Further studies are under way in our laboratory.

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14) ^{1}H-NMR (CD_3OD, 500MHz) δ: 7.50 (s, H17), 7.38 (d J=7.7 H12), 7.29 (d J=7.7 H9), 7.04 (ddd J=7.7, 7.7, 1.2 H11), 6.96 (ddd J=7.7, 7.7, 1.2 H12), 5.81 (ddd J=17.2, 10.6, 10.6 H19), 5.60 (d J=6.1 H21), 5.25 (d J=17.2 H18), 5.23 (d J=10.6 H18), 4.69 (d J=7.8 H1'), 3.89 (dd J=11.8, 2.0 H6'), 3.85 (overlapped H3), 3.68 (s CO_2Me), 3.67 (dd J=6.1, 11.8 H6'), 3.37 (dd J=9.8, 8.5 H3'), 3.30 (m H5' and H5), 3.27 (m H4'), 3.21 (dd J=7.8, 9.3 H2'), 3.19 (m H5), 2.96 (m H15), 2.87 (m H6), 2.66 (m H6), 2.47 (s N_b-Me), 2.16 (m H14), 1.96 (m H14). High resolution FAB-MS: m/z 545.2495 (calcd. m/z 545.2499 for $C_{28}H_{37}O_9N_2$ $[M+H]^+$). CD spectrum ; λ nm(Δε) in MeOH: 213(-2.70), 216(0), 223(+6.30), 228(0), 237(-22.80), 266(0), 287(+0.90), 289(+0.30), 294(+1.20).

15) CD spectrum; λ_{ext} nm(Δε) in MeOH: 210.6 (0), 222.8 (+14.3), 228.9 (0), 237.4 (-25.5), 276.4 (-0.86), 286.8 (-0.17), 290.2 (-0.90), 293.2 (0), 297.6 (+0.65), 338.6 (0).

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17) m.p.: 201.5~203.0°C from MeOH (lit: 206~208°C). High resolution FAB-MS: *m/z* 531.2339, (calcd. *m/z* 531.2343 for $C_{27}H_{35}N_2O_9$ $[M+H]^+$). ^{1}H-NMR: (500MHz DMSO-d_6) δ : 10.69 (s *N*a-H), 7.45 (s H17), 7.33 (d J=7.8 H9), 7.23 (d J=7.8 H12), 6.98 (dd J=7.8, 7.8 H11), 6.90 (dd J=7.8, 7.8 H10), 5.75 (ddd J=17.3, 10.5, 6.9 H19), 5.47 (d J=8.6 H21), 5.24 (d J=17.3 H18), 5.17 (d J=10.5 H18), 4.56 (d J=7.8 H1'), 3.79 (br-d J=8.3 H3), 3.63 (d J=11.2 H6'), 3.38 (dd J=11.7, 6.3 H6'), 3.10 (m H15), 3.02 (overlapped H5), 2.93-3.18 (H2'-H5'), 2.86 (m H5), 2.76 (m H6), 2.49 (overlapped H6 and H20), 2.42 (N_b-Me), 1.89 (br-t like J=9.1 H14), 1.66 (br-t like J=9.1 H14); CD spectrum : λ_{ext} nm(Δε) in MeOH: 220(+6.02), 221(0), 232(-20.76), 260(0), 282(-0.33), 285(0), 288(-0.66), 291(0).

18) ^{1}H-NMR (CD_3OD, 500MHz) δ: 7.66 (s H17), 7.43 (d J=7.8 H9), 7.29 (d J=8.1 H12), 7.09 (ddd J=7.6, 7.6, 1.0 H11), 7.00 (ddd J=7.6, 7.6, 1.0 H10), 5.84 (ddd J=17.8, 10.3, 10.3 H19), 5.67 (d J=7.8 H21), 5.34 (d J=17.3 H18), 5.28 (d J=10.2 H18), 4.73 (d J=8.0 H1'), 4.26 (br-s H3), 3.88 (dd J=12.0, 2.0 H6'), 3.74 (s CO_2Me), 3.59 (dd J=12.0, 6.7), 3.45 (m H5), 3.36 (dd J=9.0, 9.0 H3'), 3.2-3.3 (H2'-H5'), 3.16 (m H15), 3.00 (m H6), 2.88 (m H6), 2.76 (s N_b-Me), 2.73 (m H20), 2.18 (m H14), 2.09 (m H14). CD spectrum: λ nm(Δε) in MeOH: 222(+17.49), 236(-30.36), 282(-1.32), 285(-0.66), 289(-1.98), 293(0).

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