

ISOLATION, PARTIAL SYNTHESIS AND STEREOCHEMICAL  
STUDY OF 10-HYDROXYSTRICTOSAMIDE, A CONSTITUENT OF  
*NAUCLEA ORIENTALIS* IN THAILAND

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**Abstract** - From the Rubiaceous plant, *Nauclea orientalis*, in Thailand, seven non-alkaloidal and two glycosidic indole compounds were isolated. 10-Hydroxystriostosamide (**5**) and its pentaacetyl derivative (**11**) were prepared to determine the C3 stereochemistry.

Presently, more than forty monoterpenoid indole alkaloids have been found from the *Nauclea* plants. In our previous papers, we described the synthesis of *Nauclea* indole alkaloids, nauclefidine<sup>1</sup> and naucleidinal,<sup>2</sup> the former of which was isolated from *Nauclea officinalis*<sup>3</sup> and the latter was found in *N. latifolia*<sup>4</sup> and *N. officinalis*.<sup>3</sup> In turn, by recent chemical and biological studies on the components of *Nauclea orientalis* native to Papua New Guinea, several monoterpenoid indole alkaloids were isolated,<sup>5</sup> some of which have an angustine skeleton exhibiting antiproliferative activity.<sup>6</sup> Since the *Nauclea* plants are potentially valuable as candidates of new medicinal resources, we have been interested in the chemical components of *Nauclea orientalis* growing in Thailand. In this paper, we describe the constituents in the leaves of *N. orientalis* as well as the partial synthesis and stereochemical study of 10-hydroxystriostosamide, one of the alkaloidal constituents in this plant.

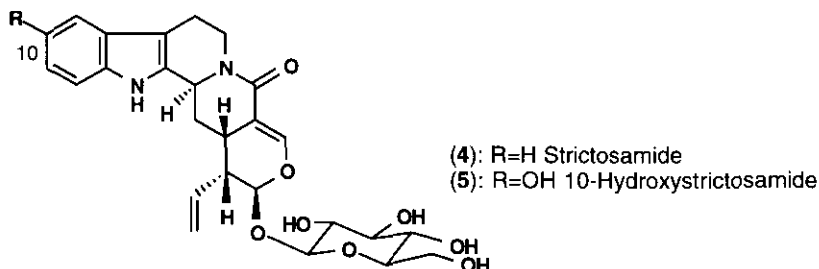
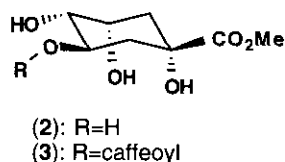
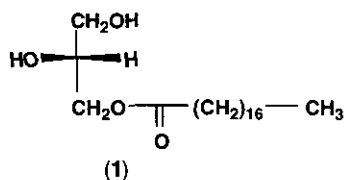
The plant material was collected at Chiang Rai Province of Thailand in December in 1994. The dried powdered leaves (2.9 kg) of the plant were extracted with MeOH (5x3 liters) at room temperature and then filtered. The filtrate was evaporated to give a syrupy mass (517 g), a portion (241 g) of which was partitioned with CHCl<sub>3</sub>-H<sub>2</sub>O. By evaporation of the CHCl<sub>3</sub> layer, the crude CHCl<sub>3</sub> extract (4.9 g) was obtained. The aqueous layer was extracted with *n*-BuOH to yield the extract (28.9 g) after evaporation. The CHCl<sub>3</sub> and *n*-BuOH extracts were respectively purified by a combination of SiO<sub>2</sub> column chromatography,

preparative TLC and medium pressure liquid chromatography.

From the  $\text{CHCl}_3$  extract, five known non-alkaloidal compounds, *i.e.*, scopoletin (22 mg),  $\beta$ -sitosterol (30 mg), pomolic acid (2.4 mg),  $\alpha$ -tocopherol (5.7 mg), and (-)-glycerol 1-octadecanate (**1**) (3.1 mg),<sup>7</sup> previously isolated from a fungus, *Penicillium* species, were obtained.

From the *n*-BuOH extract, two quinic acid derivatives, *i.e.*, quinic acid methyl ester (**2**) (19 mg) and 3-*O*-caffeoylquinic acid methyl ester (**3**) (88 mg), were isolated. It is interesting to note that potent inhibitory effect of caffeoylquinic acid derivatives on HIV-1 replication was recently reported.<sup>8</sup> Together with these non-alkaloidal compounds, two glycosidic indole alkaloids, strictosamide (**4**) (380 mg) and 10-hydroxystRICTOSAMIDE (**5**) (28 mg)<sup>4,9</sup> were found. Compound (**5**) was prepared<sup>10</sup> from 10-hydroxytryptamine hydrochloride (**7**) and secologanin (**8**) to confirm its structure. Thus, the Pictet-Spengler condensation and subsequent alkaline treatment yielded two C-3 epimeric products (**5** and **6**) in 33% total yield in the ratio of 1 to 4. The minor product was identical with the natural product from *N. orientalis*.

The stereochemistry at the C-3 position of semisynthetic compounds (**5** and **6**) was elucidated by comparison of their CD spectra, especially the Cotton curves around 270 nm<sup>10</sup> (see Figure), with those of **4** and **12**, and comparison of NMR data,<sup>9</sup> revealing the natural product to be 10-hydroxystRICTOSAMIDE having C-3(*S*) configuration. We recently demonstrated that the highly shifted acetyl NMR signal ( $\delta$  1.22 ppm) of strictosamide tetraacetate (**9**) is the acetyl group on C-2' in the sugar part and deduced that this high-field shift is caused by the shielding effect of the indole ring.<sup>11</sup> This unusual phenomenon is observed only in strictosamide tetraacetate (**9**) having 3*S* configuration, not in the vincoside lactam tetraacetate (**10**) having 3*R* configuration.<sup>12</sup> To compare the NMR spectra, then, 10-hydroxystRICTOSAMIDE (**5**) was acetylated with acetic anhydride in pyridine to give the pentaacetyl derivative (**11**).<sup>13</sup> As expected, the <sup>1</sup>H-NMR spectrum



of **11** exhibited an abnormal signal at  $\delta$  1.24 due to the C2' acetyl group, which was confirmed by the HH-COSY, HMQC and HMBC spectra. The present result supported the finding that the anomalous high-field chemical shift of the 2' acetyl group is generally applicable to the C3 stereochemical assignment of the strictosamide/vincoside lactam series of glycosidic indole alkaloids.

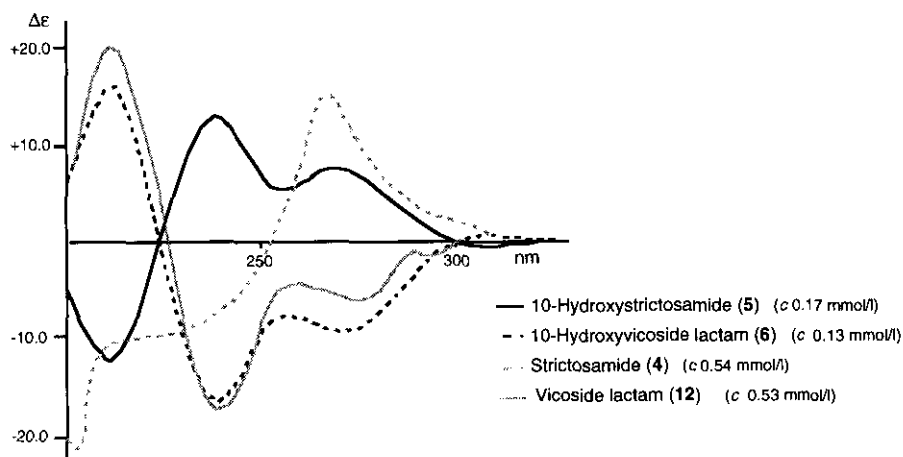
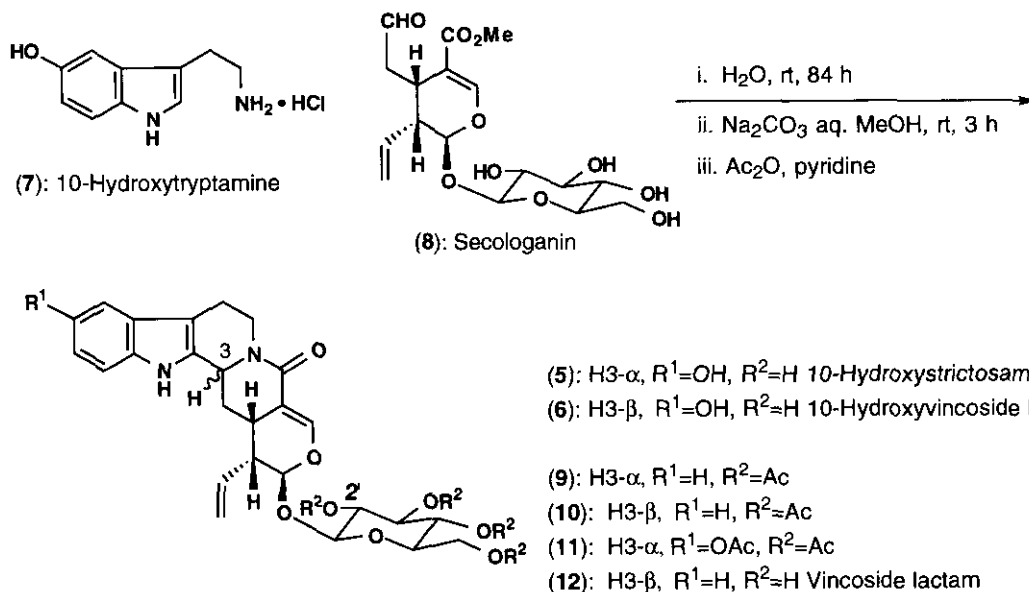


Figure CD Spectra

## ACKNOWLEDGMENTS

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- 13 Spectral data of 10-hydroxystrictosamide pentaacetate (**11**); FAB-MS (NBA)  $m/z$ : 725 ( $MH^+$ ). High-resolution FAB-MS  $m/z$ : 725.2558 (calcd for  $C_{36}H_{41}N_2O_{14}$ : 725.2558). CD ( $c=0.37 \times 10^{-3}$  mol/L, MeOH, 18°C), 0 (320 nm), +13.9 (272), 0 (240), -16.0 (222), -13.5 (213), -15.2 (206).  $^1H$ -NMR (500 MHz,  $CDCl_3$ );  $\delta$ : 7.40 (s, 17-H), 7.28 (d,  $J=8.5$ , 12-H), 7.12 (d,  $J=2.2$ , 9-H), 6.88 (dd,  $J=8.5$ , 2.2, 11-H), 5.59 (dt,  $J=17.3$ , 9.8, 19-H), 5.33 (dd,  $J=17.3$ , 1.4, 18-H), 5.32 (dd,  $J=9.8$ , 1.4, 18-H), 5.28 (d,  $J=2.0$ , 21-H), 4.92 (m, 3-H), 4.99 (dd,  $J=14.2$ , 6.9, 5b-H), 2.98 (ddd,  $J=14.2$ , 12.5, 3.9, 5a-H), 2.94 (m, 6-H), 2.66 (m, 15-H), 2.62 (m, 6-H), 2.61 (m, 20-H), 2.15-2.00 (2H, m, 14- $H_2$ ), 5.13 (dd,  $J=9.8$ , 9.5, 3'-H), 4.99 (dd,  $J=9.8$ , 9.8, 4'-H), 4.78 (d,  $J=7.8$ , 1'-H), 4.77 (dd,  $J=7.8$ , 9.5, 2'-H), 4.26 (dd,  $J=12.4$ , 4.4, 6'-H), 4.10 (dd,  $J=12.4$ , 2.2, 6'-H), 3.69 (ddd,  $J=9.8$ , 4.4, 2.2, 5'-H), 2.30 (3H, s, 10-OAc), 2.00 (3H, s, 6'-OAc), 1.99 (3H, s, 4'-OAc), 1.90 (3H, s, 3'-OAc), 1.24 (3H, s, 2'-OAc).  $^{13}C$ -NMR (125 MHz,  $CDCl_3$ );  $\delta$ : 170.6 (6'-C=O), 170.4 (10-OCO), 169.9 (3'-C=O), 169.4 (4'-C=O), 169.1 (2'-C=O), 164.6 (C-22), 146.9 (C-17), 144.4 (C-10), 134.3 (C-2), 133.8 (C-13), 131.9 (C-19), 127.7 (C-8), 120.8 (C-18), 116.2 (C-11), 111.7 (C-12), 110.9 (C-7), 110.3 (C-9), 108.2 (C-16), 94.9 (C-21), 94.7 (C-1'), 72.1 (C-5'), 71.9 (C-3'), 70.0 (C-2'), 68.2 (C-4'), 61.6 (C-6'), 53.2 (C-3), 43.5 (C-5), 42.7 (C-20), 26.4 (C-14), 23.8 (C-15), 20.8 (C-6), 20.8 (6'-OAc), 20.6 (4'-OAc), 20.6 (3'-OAc), 19.2 (2'-OAc).