BIOMIMETIC SYNTHESIS OF *NAUCLEA* INDOLE ALKALOIDS, NAUCLEIDINAL, AND 3-*EPI*-NAUCLEIDINAL, BY STEREOSELECTIVE REARRANGEMENT OF STRICTOSAMIDE AND THE VINCOSIDE LACTAM AGLYCONES

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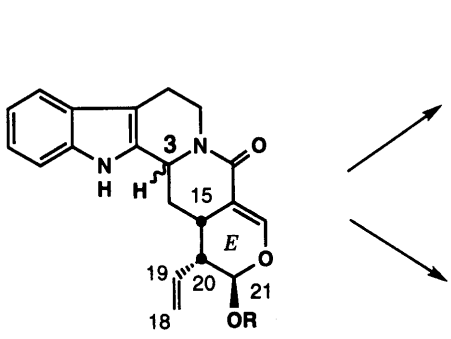
Based on a biogenetic consideration, a *Nauclea* alkaloid, naucleidinal (**6**), and its 3-epimer (**7**) were stereoselectively prepared from the aglycones of strictosamide and the vincoside lactam, and their absolute stereochemistry was confirmed.

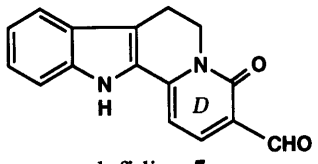
KEY WORDS biomimetic synthesis; *Nauclea* alkaloid; naucleidinal; 3-*epi*-naucleidinal; strictosamide; vincoside lactam

During the course of our research project on the chemical and pharmacological studies of *Mitragyna* indole alkaloids,[1] which have been found to exhibit potent analgesic and antinociceptive activities, we have had an opportunity to reexamine the structure of a simple *Nauclea* alkaloid, nauclefidine (**5**).[2] In this study, we have proposed a mode of biosynthesis of nauclefidine from strictosamide (**1**) and have succeeded in the realization of this hypothesis by chemical means.[2] Our interest next turned to the biogenetic pathway of another *Nauclea* alkaloid, naucleidinal (**6**), one of the constituents in *Nauclea latifolia* and *N. officinalis*.[3] It is conceivable that, in analogy with the biogenetic route of nauclefidine (**5**), alkaloid (**6**) would also arise from strictosamide through *E*-ring isomerization of its aglycone (**2**). Based on this working hypothesis, we examined the chemical transformation of strictosamide (**1**) into naucleidinal (**6**) as well as of the vincoside lactam (**3**) to 3-*epi*-naucleidinal (**7**), which we describe in this communication.

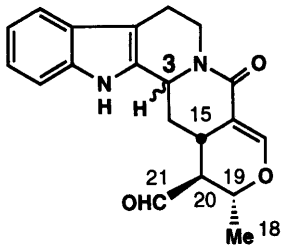
Rearrangement of the *E*-ring in strictosamide aglycone (**2**), *i.e.*, ring opening of the hemiacetal part, double-bond migration from the C18-19 to C19-20 positions, and subsequent Michael-type addition of the enol function to the resultant α,β-unsaturated aldehyde, which leads to a naucleidinal-type compound, could be anticipated. The reaction conditions, developed by Purdy and McLean[4] for the transformation of



R=Glc, 3-Hα: strictosamide **1**
R=H, 3-Hα: **2**
R=Glc, 3-Hβ: vincoside lactam **3**
R=H, 3-Hβ: **4**



nauclefidine **5**



3-Hα: naucleidinal **6**
3-Hβ: 3-*epi*-naucleidinal **7**

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secoiridoid, sweroside, to naucledal, were then applied to the rearrangement of strictosamide aglycone (**2**), which was prepared from strictosamide (**1**) by enzymatic hydrolysis using β-D-glucosidase. Thus, **2** was treated with 10% aqueous pyridine at 110°C for 5 h to afford a rearrangement product in 52% yield after SiO_2 column chromatography. The identity of the semisynthetic compound and natural naucleidinal (**6**) was fully confirmed by comparison of their chromatographic behavior and UV, MS, high-resolution MS, CD, and ^{1}H-NMR spectra.[5] Among these, the key data were the coupling constants between the protons at C19, 20, and 15, and the observed NOE in the ^{1}H-NMR spectra of **6**, which clarified the stereochemistry at the newly formed stereocenter of the C19 and C20 positions. The *J* values between H-19 and H-20 and between H-20 and H-15 are, respectively, 10.0 and 10.3 Hz, indicating that both the methyl and aldehyde groups have an equatorial orientation. Furthermore, an extensive NOE (6.1%) observed between H-19 and H-15 demonstrated their 1,3-*cis* diaxial relationship. The CD spectrum of the rearrangement product **6** showed a positive Cotton effect at the longest wavelength absorption at 268 nm. This observation, together with the fact that the absolute stereochemistry of the starting material (**1**) is established,[6] proves the α-H configuration at C3 in **6**. From these data, the stereochemistry including the absolute configuration of naucleidinal was confirmed.

The vincoside lactam (**3**), the C3 epimer of strictosamide (**1**), was also converted to a naucleidinal-type compound (**7**) in 58% yield by employing the reaction conditions that were used in **1**. All of the data for the new rearrangement product support the structure of 3-*epi*-naucleidinal.[7] As shown in Fig. 1, compound (**7**) displays an opposite Cotton curve in the longest wavelength region compared with that of **6**. Alkaloid (**7**) has not been isolated from nature yet, but it is very possible that this will be found as a genuine natural product.

The stereochemical course of the rearrangement from **2** to **6** and from **4** to **7**, which proceeded in a stereoselective manner, can be best explained as follows. The double-bond migration from the vinyl-aldehyde **8** to the α,β-unsaturated aldehyde would proceed *via* [1,5]sigmatropic rearrangement to selectively yield the intermediary **9** possessing a *Z* configuration. The Michael-type addition of the hydroxyl function to **9** would occur through a chair-like transition state, resulting in the formation of a methyl group oriented at the α-equatorial position. Finally, under basic conditions, the aldehyde group settles into a thermodynamically stable equatorial configuration.

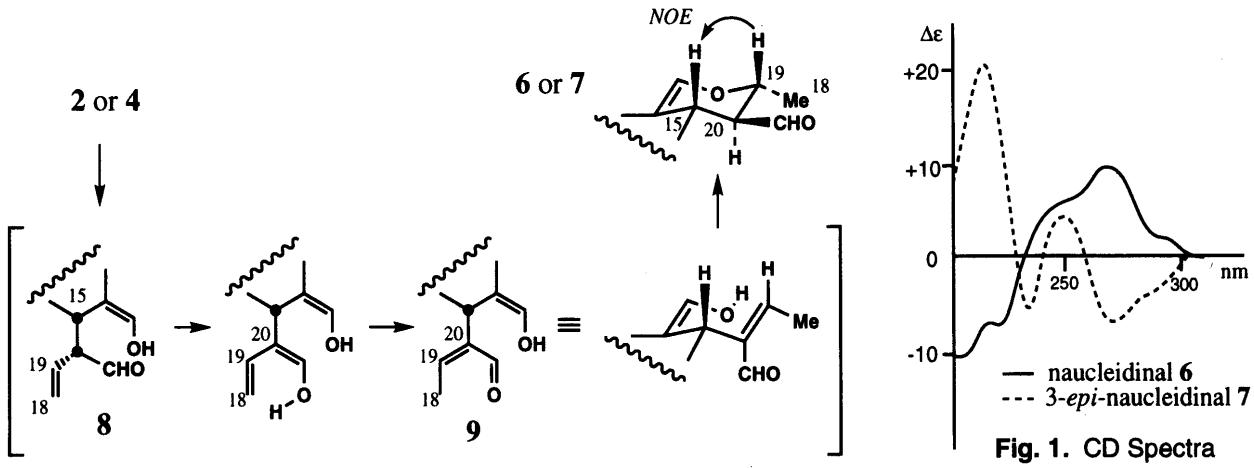

Fig. 1. CD Spectra

In conclusion, based on biogenetic considerations, a *Nauclea* alkaloid, naucleidinal (**6**), and its 3-epimer (**7**) could be stereoselectively obtained and their absolute stereochemistry was unambiguously established.

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5) Naucleidinal (**6**); mp. 191-194°C (lit[3a] mp. 203°C, lit[3b] 192-194°C). ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.79 (1H, d, *J* = 2.5 Hz, H-21), 7.93 (1H, br s, NH), 7.51 (1H, d, *J* = 1.7 Hz, H-17), 7.48 (1H, d, *J* = 7.8 Hz, H-9), 7.39 (1H, dd, *J* = 7.6, 1.3 Hz, H-12), 7.20 (1H, td, *J* = 7.6, 1.3 Hz, H-11), 7.12 (1H, td, *J* = 7.6, 1.3 Hz, H-10), 5.08 (1H, m, H-5), 4.96 (1H, dd, *J* = 5.4, 2.0 Hz, H-3), 3.90 (1H, qd, *J* = 6.4, 10.0 Hz, H-19), 2.99-3.11 (2H, m, H-5, H-6), 2.73 (1H, m, H-15), 2.66 (1H, m, H-6), 2.47 (1H, ddd, *J* = 13.8, 3.6, 2.0 Hz, H-14), 2.34 (1H, ddd, *J* = 10.3, 10.0, 2.5 Hz, H-20), 1.87 (1H, ddd, *J* = 13.8, 13.6, 5.4 Hz, H-14), 1.47 (3H, d, *J* = 6.4 Hz, H-18). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 132.55 (C-2), 53.28 (C-3), 43.34 (C-5), 21.05 (C-6), 111.57 (C-7), 127.55 (C-8), 118.32 (C-9), 120.02 (C-10), 122.32 (C-11), 111.32 (C-12), 135.94 (C-13), 29.39 (C-14), 27.47 (C-15), 107.77 (C-16), 150.62 (C-17), 19.35 (C-18), 71.50 (C-19), 56.42 (C-20), 200.60 (C-21), 164.40 (C-22). CD (*c*=0.30 x 10^{-3}, MeOH) $\Delta\varepsilon^{20°}$ (nm): 0 (305), 2.24 (290), 6.31 (250), 9.98 (268), 0 (231), -7.13 (222).

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7) 3-*epi*-Naucleidinal (**7**); mp. 223-224°C, UV λ_{max}^{MeOH} nm (log ε): 225 (4.57), 283 (sh) (3.96), 290 (3.86). IR ν_{max}^{KBr} cm^{-1}: 1720, 1660, 1580. EI-MS m/z (%): 336 (100), 307 (15), 265 (23), 169 (38), 156 (44). HR-MS Calcd for $C_{20}H_{20}N_2O_3$: 336.1431. Found: 336.1451. ^{1}H-NMR (400 MHz, $CDCl_3$ + 1 drop of CD_3OD) δ: 9.86 (1H, d, *J* = 3.0 Hz, H-21), 8.71 (s, NH), 7.60 (1H, d, *J* = 1.7 Hz, H-17), 7.49 (1H, d, *J* = 7.5 Hz, H-9), 7.31 (1H, d, *J* = 7.5 Hz, H-12), 7.17 (1H, dd, *J* = 7.5, 7.5 Hz, H-11), 7.10 (1H, dd, *J* = 7.5, 7.5 Hz, H-10), 5.19 (1H, m, H-5), 4.82 (1H, br d, *J* = 12.4 Hz, H-3), 4.11 (1H, qd, *J* = 6.2, 9.9 Hz, H-19), 2.98 (1H, m, H-15), 2.80-2.90 (3H, m, H-5, H_2-6), 2.55 (1H, ddd, *J* = 12.7, 3.7, 3.7 Hz, H-14), 2.29 (1H, ddd, *J* = 10.2, 9.9, 2.9 Hz, H-20), 1.46 (3H, d, *J* = 6.2 Hz, H-18), 1.40 (1H, m, H-14). ^{13}C-NMR (100 MHz, $CDCl_3$ + 1 drop of CD_3OD) δ: 132.31 (C-2), 53.92 (C-3), 39.88 (C-5), 20.96 (C-6), 109.41 (C-7), 126.57 (C-8), 118.31 (C-9), 119.60 (C-10), 122.06 (C-11), 110.92 (C-12), 136.25 (C-13), 33.42 (C-14), 29.81 (C-15), 106.63 (C-16), 151.22 (C-17), 19.27 (C-18), 71.94 (C-19), 56.16 (C-20), 201.27 (C-21), 163.51 (C-22). CD (*c*=0.30 x 10^{-3}, MeOH) $\Delta\varepsilon^{20°}$ (nm): 0 (305), -6.92 (270), 0 (259), -9.98 (268), 4.28 (250), 0 (238), -3.87 (233), 0 (228), 20.78 (218).

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