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 McLean⁴⁾ for the transformation of

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secoiridoid, sweroside, to naucleal, 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 SiO₂ 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 ¹H-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 ¹H-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). ¹H-NMR (400 MHz, CDCl₃) 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). ¹³C-NMR (100 MHz, CDCl₃) 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 × 10⁻³, MeOH) Δε^{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 C₂₀H₂₀N₂O₃: 336.1431. Found: 336.1451. ¹H-NMR (400 MHz, CDCl₃ + 1 drop of CD₃OD) 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, H₂-6), 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). ¹³C-NMR (100 MHz, CDCl₃ + 1 drop of CD₃OD) 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 × 10⁻³, MeOH) Δε^{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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