Flow Thermolysis Rearrangements in the Indole Alkaloid Series: Strictamine and Akuammicine Derivatives. The Absolute Configurations of Ngouniensine and *epi*-Ngouniensine

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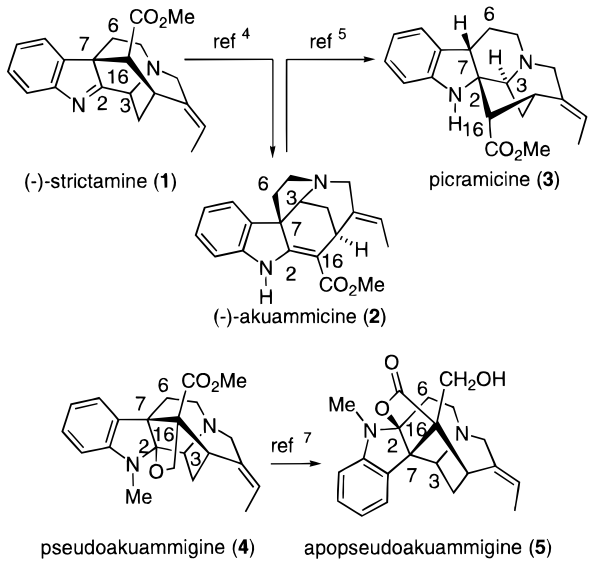
Flow thermolysis of strictamine (**1**) generated two of the predictable rearrangement products, resulting from [1,5]-sigmatropic shifts: akuammicine (**2**) and indolenine **9**. Besides formation of these two compounds, a quite different pathway gave rise to a novel rearrangement leading to indole **6**, with the framework of the natural alkaloid ngouniensine (**19**). Rearrangement to the ngouniensine skeleton became the major pathway when the akuammicine derivatives **10**, **12**, and **17** were submitted to thermolysis, generating compounds **11**, **13** + **15**, and **18**, respectively. These results allowed us to assign the absolute configuration of (−)-ngouniensine (**19**) (3*R*,20*R*) and that of (−)-epingouniensine ((−)-**21**) (3*R*,20*S*).

Introduction

(−)-Strictamine (**1**, "desacetyldesformoakuammiline"[1]) and (−)-akuammicine (**2**)[2] (Scheme 1) are two isomeric indole alkaloids whose structures only differ in the junctions of the indolic carbon atoms 2 and 7[3] with the terpenic carbon atoms 3 and 16. Chemical correlations have been performed through base-catalyzed rearrangements of strictamine (**1**) and congeners to compounds with the akuammicine skeleton.[4] Furthermore, akuammicine (**2**) has been reductively rearranged[5] to picramicine (**3**), whereas pseudoakuammigine (**4**)[6,7] (an alkaloid with the strictamine skeleton) has also been rearranged[7] by acid treatment to apopseudoakuammigine (**5**), through redistribution of the junctions of carbon atoms 3,6, and 16 with the indole nucleus.

In light of our previous studies on the thermal rearrangements of natural indolenines (3*H*-indoles) in the *Aspidosperma* series,[8] it seemed to us that flow thermolysis of compounds with the strictamine or akuammicine skeleton might induce a similar scrambling of the bonds between carbon atoms 2 and 7 and carbon atoms 3, 6, and 16 via [1,5] sigmatropic shifts, as tentatively predicted in Scheme 2. Thus, starting from a compound with skeleton **A1** or **A2** one could expect formation of either of the other two compounds among **A1**−**3** that equilibrate with the *o*-quinoid intermediates [**B1,3**], while

Scheme 1



indoles **I1** or **2** might constitute irreversible end points of the rearrangement. For permutational reasons, structures located at opposite positions in Scheme 2 obviously derive one from the other through turning the indole ring upside down (reverse skeletons) so that the shapes of their aliphatic parts are largely comparable.

Results and Discussion

Flow thermolysis of strictamine (**1**) at 475 ± 5 °C yielded akuammicine (**2**) (∼ 3%), indole **6** (9%), and indolenine **9** (32%) and some recovered starting material (17%) (Scheme 3).

Compound **9** was obtained as the unique product when the oven temperature was raised to 490°C. Its structure was confirmed as follows, indicating an apopseudoakuammigine (**A3**) skeleton: the indolenine ring system was identified by both the UV spectrum and the ^{13}C NMR chemical shift of C-2 at 184.5 ppm while the respective connections of carbon atoms 3, 6, and 16 with C-2 and C-7 were unequivocally established by HMQC and HMBC experiments (Table 1). Indole **6** appeared to possess nei-

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(1) Schnoes, H. K.; Biemann, K.; Mokry, J.; Kompis, I.; Chatterjee, A.; Ganguli, G. *J. Org. Chem.* **1966**, *31*, 1141.

(2) (a) Robinson, R.; Aghoramurthy, D. Tetrahedron, **1957**, *1*, 172. (b) Bernauer, K.; Arnold, W.; Weissmann, C.; Schmid, H; Karrer, P. *Helv. Chim. Acta* **1960**, *43*, 717. (c) Lévy, J., Le Men, J., Janot, M.-M. *Bull. Soc. Chim. Fr.* **1960**, 979. (d) Edwards, P. N., Smith, G. F. *J. Chem. Soc.* **1961**, 152.

(3) Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(4) Pousset, J. L.; Poisson, J.; Olivier, L.; Le Men, J.; Janot, M.-M. C. R. *Acad. Sci.* **1965**, 5538.

(5) Hinshaw, W. B., Jr.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1971**, *15*, 995.

(6) (a) Robinson, R.; Thomas, A. F. *J. Chem. Soc.* **1954**, 3522. (b) Olivier, L.; Lévy, J.; Le Men, J.; Janot, M.-M.; Djerassi, C.; Budzikiewicz, H.; Wilson, J. M.; Durham, L. J. *Bull. Soc. Chim. Fr.* **1963**, 646.

(7) Britten, A. Z.; Edwards, P. N.; Joule, J. A.; Smith, G. F.; Spiteller, G. *Chem. Ind.* **1963**, 799.

(8) (a) Hugel, G.; Lévy, J. *Tetrahedron* **1984**, *40*, 1067. (b) Hugel, G.; Royer, D.; Sigaut, F.; Lévy, J. *J. Org. Chem.* **1991**, *56*, 4631

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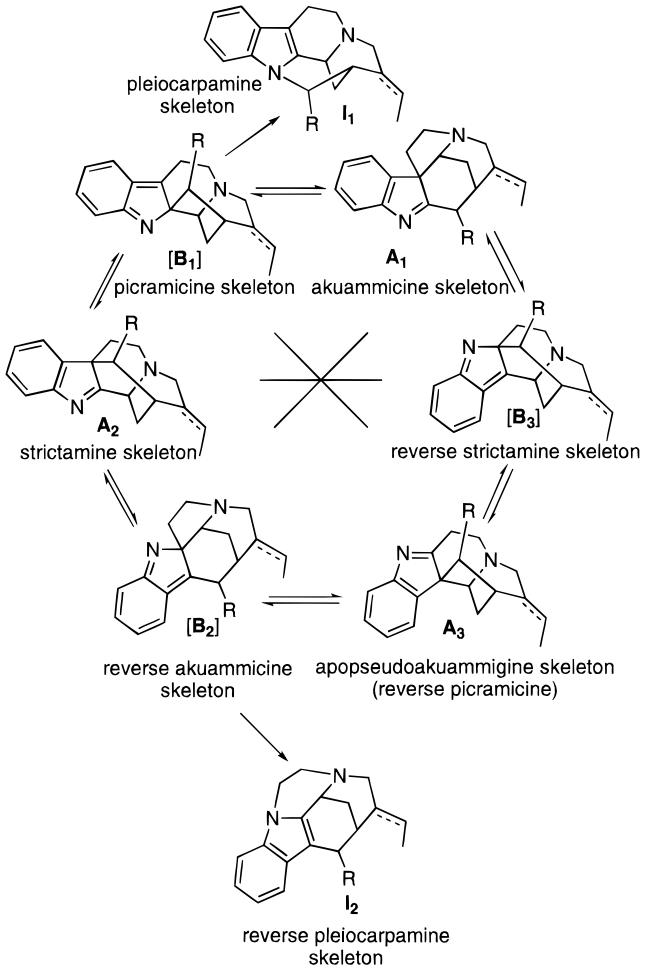
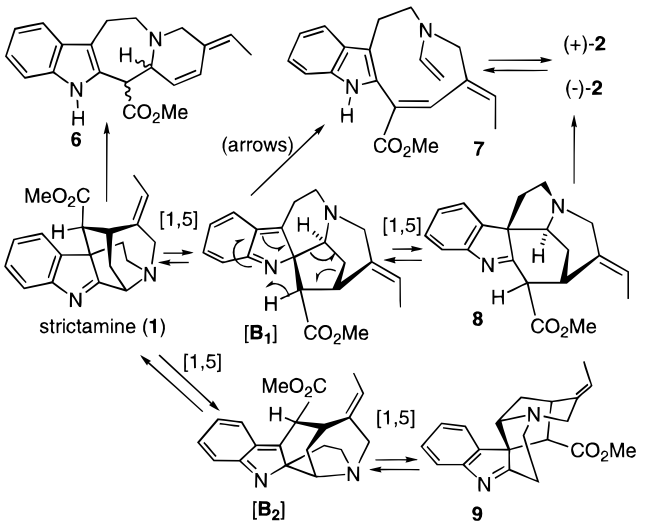
Scheme 2[a]



[a] The numbering of skeletons is used throughout the text.

Scheme 3



ther expected skeleton **I1** nor **I2** (R = CO_2Me, Scheme 2) but instead resulted from a completely different rearrangement. This labile compound was isolated in a minute amount, which impeded extensive HMBC and HMQC studies. Its proposed structure, while consistent with the spectroscopic data (^1H NMR, ^{13}C NMR), remains hypothetical since it is mainly deduced by analogy to some of the other rearrangement products discussed below.

Table 1. ^{13}C NMR[a] and HMBC[b] Data for Compound 9

C no.	^{13}C NMR	HMBC	C no.	^{13}C NMR	HMBC
3	74.3	7; 15, 21, 5	14	34.0	3, 15; 7, 16, 20; 2, 22
5	56.6	6; 2, 3, 21	15	39.9	20; 3, 19, 21; 7
6	29.8	2, 5; 7	16	56.4	7, 17, 22; 2, 8, 20
7	65.6		18	12.5	
8	144.6		19	116.9	
9	122.2		20	136.3	
10	124.6		21	50.4	20; 3, 15, 19
11	127.9		22 (C=O)	170.6	
12	120.1		CO_2Me	51.6	
13	154.2				

[a] ppm. [b] ^2J, ^3J, ^4J correlations.

Interestingly, the isolated akuammicine (**2**) had suffered partial racemization to (±)-akuammicine (pseudoakuammicine[9]) (ee = 38%). Formation of this (±)-akuammicine is thought to proceed through the achiral species **7** (Scheme 3), resulting itself from fragmentation of the **B1**-type intermediate, and a proportion of (−)-akuammicine itself would be formed through isomer **8** arising via the **B1**-type intermediate by successive [1,5] sigmatropic shifts. Not surprisingly, species **7** has been considered in the examination of the mass spectral fragmentation of akuammicine (**2**).[10] Cyclization of **7** to (±)-akuammicine would then parallel a strategy recently used by Kuehne[11] for the synthesis of (±)-**2**. These results shed some light on the thermal (sealed tube) epimerization of centers 3 and 15 of 19,20-dihydroakuammicine (**10**), which was reported by Scott two decades ago.[12] Apart from this racemization and the formation of **6**, the generation of akuammicine (**2**) and of indolenine **9** from strictamine (**1**) is in accordance with some of the assumptions presented in Scheme 2 and suggests the existence of intermediates [**B1**] leading to **2** *via* **7** or **8** and [**B2**] leading to **9**.

The other starting materials used in this study were obtained from (−)-akuammicine ((−)-**2**).[13] Stereospecific catalytic hydrogenation gave 19,20-dihydroakuammicine (**10**);[2c,14] hydrolysis and decarboxylation[2abc] of **10** and (−)-**2** gave tubifoline (**12**)[15] and 19,20-dehydrotubifoline (**17**),[2a] respectively (see Schemes 4 and 5 for structures).

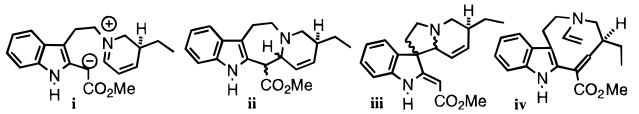
Flow thermolysis of 19,20-dihydroakuammicine (**10**) at 450 ± 5 °C resulted in the isolation of aldehyde **11** (11%) (Scheme 4), recovery of some starting material (38%), and formation of decomposition products. The highly conjugated chromophore of **11** was responsible for a long-wave

(9) (a) Boonchuay, W.; Court, W. E. *Planta Med.* **1976**, *29*, 380. (b) Edwards, P. N.; Smith, G. F. *Proc. Chem. Soc. (London)* **1960**, 215.

(10) Budzikiewicz, H.; Djerassi, C.; Williams, D. H. *Structure Elucidation of Natural Products by Mass Spectrometry, Vol. 1: Alkaloids*; Holden-Day: San Francisco, 1964, p 135.

(11) Kuehne, M. E.; Frasier, D. A.; Spitzer, T. D. *J. Org. Chem.* **1991**, *56*, 2696

(12) Scott, A. I.; Yeh, C. L. *J. Am. Chem. Soc.* **1974**, *96*, 2273−74. The authors postulated the ionic intermediate **i**, which seems more prone to cyclization to **ii** (ngouniensine skeleton) or to the anilinoacrylic ester **iii** than to reversal to the akuammicine skeleton. Most probably the reaction proceeds through the thermally produced nonionic intermediate **iv**.



(13) the optical purity of the alkaloid (−)-**2** was checked: $[\alpha]_D$ −735 (EtOH).[2c]

(14) Weissmann, C.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1961**, *44*, 1877.

(15) Bernauer, K.; Arnold, W.; Weissmann, C.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1960**, *43*, 717. (b) Kump, W. G.; Patel, M. B.; Rowson, J. M.; Schmid, H. *Helv. Chim. Acta* **1964**, *47*, 1497.

Scheme 4

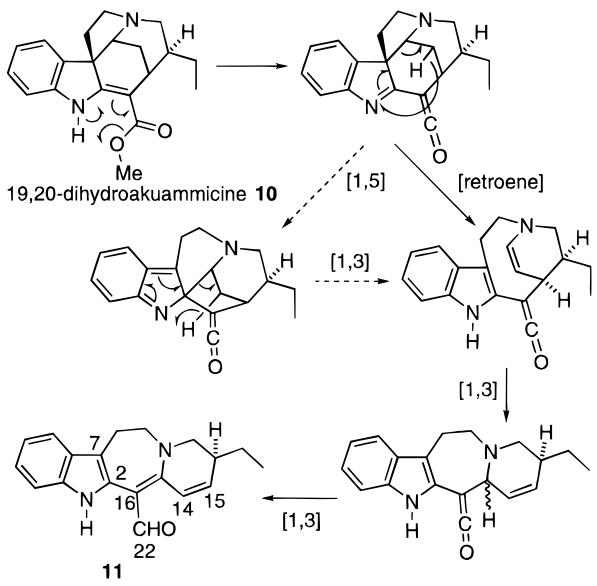


Table 2. ^{13}C NMR Data for Compounds 11, 13−16, and 18

C no.	11	13	14	15	16	18
2	131.8	135.0	135.1	135.1	135.7	134.6
3	160.0	58.5	56.8	62.4	62.2	61.3
5	57.3	57.5	56.8	60.1[a]	58.2	58.4
6	26.4	22.6	20.7	25.2	21.4	23.9
7	108.7	113.6	113.1	113.1	113.4	113.5
8	127.4	128.6	129.0	128.7	128.3	128.6
9	117.0	117.6	117.4	117.6	117.5	117.6
10	118.7	119.2	119.1	119.2	119.2	119.3
11	121.1	121.0	120.9	120.9	120.8	121.1
12	110.7	110.3	110.1	110.3	110.4	110.4
13	134.0	134.7	134.7	134.6	134.6	134.7
14	122.4	129.7	32.1	129.9	34.4	132.2[b]
15	138.5	130.5	26.3	130.8	30.9	122.6
16	104.7	31.1	28.6	36.6	35.1	34.1
18	11.2	11.6	11.5	11.3	11.4	12.5
19	24.8	26.7	27.2	26.5	27.2	120.9
20	35.9	37.7	38.5	37.6	38.1	132.4[b]
21	55.6	52.6	51.5	60.2[a]	63.0	58.3
22	187.1					

[a] Labeled values may be interchanged. [b] From ^{13}C NMR (CD_3OD).

UV absorption up to 439 nm. The ^{1}H NMR spectrum revealed two singlets at 11.60 ppm (NH indole) and at 9.83 ppm (aldehydic proton). The olefinic protons H-14 and H-15 gave signals at 6.72 and 6.36 ppm. Apart from the aromatic indole system and carbon C-22 at 187.1 ppm (aldehyde), lower field signals in the ^{13}C NMR spectrum were ascribed to the tertiary carbons C-14 (122.4 ppm) and C-15 (138.5 ppm) and to the two quaternary carbons C-3 (160.0 ppm) and C-16 (104.7 ppm). HMQC and HMBC experiments further settled the structure (see Tables 2 and 3). A plausible mechanism for the formation of aldehyde **11** is depicted on Scheme 4. The enamino ester **10** would first undergo elimination of methanol leading to an iminoketene, followed by a retroene fragmentation and two successive [1,3] shifts. An intermediate *o*-quinoid azadiene (dotted arrows on Scheme 4) might possibly be involved.

Thermolysis of tubifoline (**12**) at 490 ± 5 °C was more efficient, producing in addition to recovered **12** (23%) two diastereomeric indoles **13** and **15** (1.6:1; total yield, 60%) (Scheme 5). The structures of **13** and **15** were again deduced from NMR studies, with regard to the known 20-*S* configuration of C-20 in tubifoline (**12**). Thus, H-3 in **13** was equatorially oriented on the piperideine ring, as evidenced by the ^{1}H NMR signal at 3.69 ppm and the ^{13}C NMR signal of C-3 at 58.5 ppm, indicating its *cis* relationship with H-20, whereas the (axial) H-3 and C-3 in **15** resonated at ~3.00 ppm and 62.4 ppm, respectively. Catalytic hydrogenation of **13** and **15**, respectively, gave (−)-**14** and (−)-**16**, whose structures and relative configurations were deduced from the NMR data with reference to those of natural ngouniensine (**19**)[16a,b] (Table 1). Ngouniensine is the major alkaloid of *Strychnos ngouniensis*. Its structure has been confirmed by synthesis,[17] but its absolute configuration had not been determined until now. Isolation of compounds (−)-**14** and (−)-**16** of known absolute configuration (based on the stereospecific hydrogenation of the 19,20 double bond of akuammicine) then called for a chemical correlation in order to solve the problem. The fact that two C-3 epimeric compounds **13** and **15** (**13** being the major isomer) were obtained from tubifoline (**12**) may be ascribed to an intermediate (**J**) (Scheme 5) evolving along two different pathways: a concerted [1,3] shift leading to **13** and a nonconcerted pathway through homolytic breaking of the 15,16-bond leading nonselectively to **13** and **15**. The following results on the thermolysis of 19,-20-dehydrotubifoline (**17**) indeed indicate that the difference in the yields of **13** and **15** is not due to partial asymmetric induction originating from C-20, but instead is linked to the original configuration of C-15. Thus, thermolysis of 19,20-dehydrotubifoline (**17**) gave indole **18** (20%), which proved to be only partially racemic, as its catalytic hydrogenation yielded unequal quantities of compounds identified as **14** (49%) and **16** (37%), with low $[\alpha]_D$ values (owing to the nonstereospecific hydrogenation).

Attempts at oxidation of indoles **14** and **15** with selenium dioxide using Cook's method[18] failed. Potassium permanganate oxidation of (−)-ngouniensine (**19**) in the presence of either triethylbenzylammonium chloride[19] or 18-crown-6 yielded ketone **20** (11%) (Scheme 6), which was further reduced with $LiAlH_4$ to a compound that was shown to be (+)-**14**, as indicated by the identity of its NMR, MS, and TLC data with those of (−)-**14**, and by the opposite signs of its $[\alpha]_D$ and CD maxima. The absolute configuration of (−)-ngouniensine is therefore 3*R*, 20*R*. In as much as natural (−)-ngouniensine (**19**) is enantiomerically pure, the antipodal correlation further ascertains the full retention of configuration at C-20 during thermolysis of tubifoline (**12**), a fact that had been implicitly postulated in the above discussion, in agreement with previous findings by Schmid.[20]

Separately flow thermolysis of (−)-ngouniensine (**19**) at 610 ± 5 °C allowed recovery of 52% starting material and isolation of (+)-**21** (15%), which proved to be enantiomeric with natural[16b] (−)-*epi*ngouniensine ((−)-**21**). Thus, (−)-*epi*-ngouniensine ((−)-**21**) is 3*R* ,20*S*, and it is epimeric at C-20 with (−)-ngouniensine (**19**). Epimerization at C-3 during thermolysis of ngouniensine could be due to an exo/endo equilibrium of the double bond

(16) (a) Massiot, G.; Zèches, M.; Thépenier, P.; Jacquier, M. J.; Le Men-Olivier, L.; Delaude, C. *J. Chem. Soc., Chem. Commun.* **1982**, 768. (b) Massiot, G.; Thépenier, P.; Jacquier, M. J.; Lounkokobi, J.; Mirand, C.; Zèches, M.; Le Men-Olivier, L. *Tetrahedron* **1983**, *39*, 3645.

(17) Bosch, J.; Bennasar, M.-L.; Zulaica, E.; Massiot, G.; Massoussa, B. *Tetrahedron Lett.* **1987**, *28*, 231.

(18) Cain, M.; Campos, O.; Guzman, F.; Cook, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 907.

(19) Starks, C. M. *J. Am. Chem. Soc.* **1971**, *93*, 195.

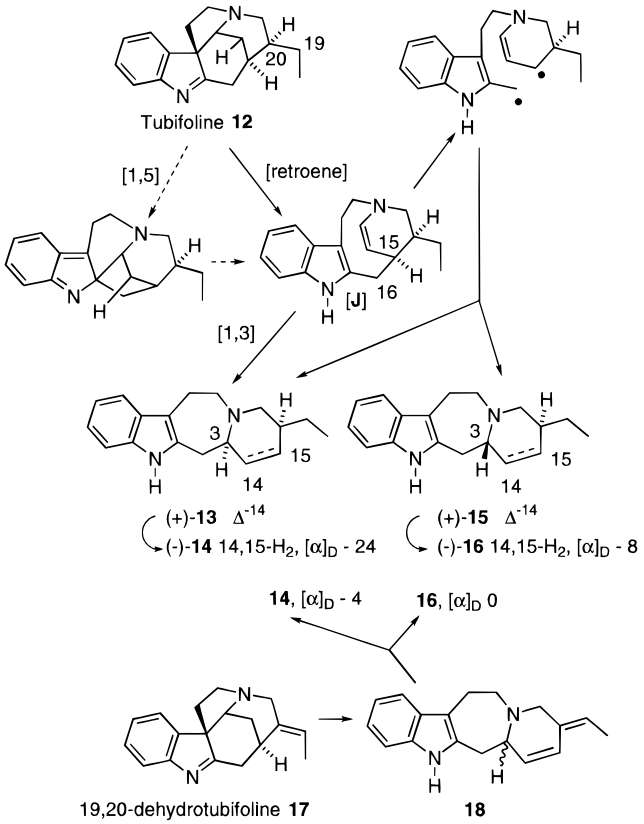
(20) Schumann, D.; Schmid., H. *Helv. Chim. Acta* **1963**, *46*, 1996.

Table 3. Main HMBC[a] Data for Compounds 11, 13−16, and 18

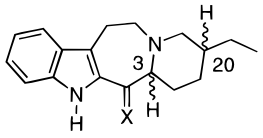
position	11	13	14	15	16	18
3		14	5	5, 15, 21		5
5	6; 3, 7, 21	6; 3, 7, 21	6; 3, 7, 21	6; 3, 7, 21	6; 3, 7, 21	6; 3, 7, 21
6	5, 7; 2, 8	5, 7; 2	5, 7; 2, 8	7; 2, 8	5, 7; 2, 8	5, 7; 2, 8
14	3; 20	3; 20		3, 15; 20		3; 16, 20
15	14, 20; 3, 19, 21	20; 3		14, 20; 3, 19, 21		19, 20; 3, 21
16		2, 3; 7, 14	2,3; 7, 14	2, 3; 7, 14	2, 3; 7, 14	2, 3; 7, 14
17	19; 20					
19	18, 20; 15, 20					18; 15, 21
21	20; 3, 5, 15, 19	20; 3, 5, 15, 19				20; 3, 15, 19
22	16; 2					

[a] ^2J, ^3J correlations.

Scheme 5



Scheme 6

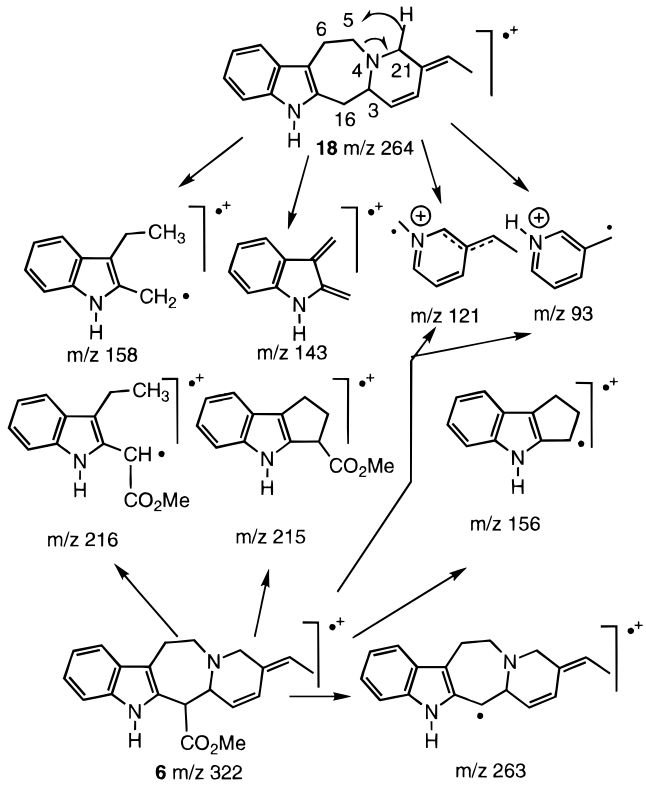


	X	H-3	H-20	$[\alpha]_D$ (MeOH)	
(-)-**19**	CH_2	β	β	- 89	nat. ngouniensine
20	O	β	β	-	
(+)-**14**	H_2	β	β	+ 23	
(+)-**21**	CH_2	α	β	+ 32	
(-) -**21**	CH_2	β	α	− 32	nat. epingouniensine

promoted by reversible [1,3] H-shifts. (+)-*epi*-Ngouniensine ((+)-**21**) was also isolated upon heating (−)-ngouniensine methiodide at 110 °C for 3 days in the presence of tri-*n*-butylphosphine.

Incidentally, the unambiguously established structure of indole **18** strengthens arguments in favor of the

Scheme 7



postulated structure of compound **6**, as comparison of their respective mass spectra showed significant similarities (Scheme 7). The mass spectral fragmentation of **18** was dominated by cleavage of the 3−16, 4−5, and 5−6 bonds along with possible transfer of H-21 that was driven by aromatization of the piperidine nucleus. Thus were generated the indolyl ions at *m*/*z* 158 (base peak) and m/z 143 (13) and the pyridinyl ions at *m*/*z* 121 (67) and *m*/*z* 93 (48). In the mass spectrum of **6**, the pyridinyl ions at *m*/*z* 121 (base peak) and *m*/*z* 93 (30) were significantly present. Appendage of the methoxycarbonyl group on C-16 was indicated by a peak at *m*/*z* 263 (12, $M^{\bullet+} - CO_2Me$) and by ions at *m*/*z* 215 (22) and 216 (22, 158 + CO_2Me). Finally, a peak at *m*/*z* 156 (78), that is 2 Da less than the *m*/*z* 158 ion of **18**, further confirmed substitution of C-16 in **9**.

Conclusion

The rearrangement of strictamine **(1)** under flow thermolysis conditions mainly matched those of 1,2-dehydroaspidospermidine, in that [1,5] sigmatropic shifts were involved in both cases. In sharp contrast, indolenines in the akuammicine **(2)** series suffered quite different skeletal rearrangements, combined with some

racemization, which points to the influence of skeletal steric strain. This latter rearrangement performed for the first time a direct transformation of the *Strychnos* to the ngouniensine skeleton and thus allowed the first determination of the absolute configurations of (−)-ngouniensine and of (−)-*epi*-ngouniensine.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were measured on a Bruker AC300 spectrometer in $CDCl_3$ (unless specified otherwise). Coupling constants (*J*) are given in Hz. HMBC and HMQC[21] were measured in the reverse mode, ^{1}H pulses being emitted via the decoupler channel. Separations were carried out on TLC plates with Kieselgel 60 PF_{254} Merck, using CH_2Cl_2/MeOH and ether/MeOH as eluents. Flow thermolysis experiments were performed as previously described.[22]

Materials. Strictamine (**1**) and akuammicine (**2**) were isolated from *Alstonia plumosa* and from *Picralima nitida*, respectively, and their identity was carefully verified, including specific rotations. 19,20-Dihydroakuammicine (**10**) was prepared through catalytic hydrogenation of akuammicine[2c] and 19,20-dehydrotubifoline (**17**) and tubifoline (**12**) by refluxing **2** and **10**, respectively, in 10% aqueous HCl solution.[14,15]

Flow Thermolysis of Strictamine (1): Akuammicine (2), Indole 6, and Indolenine 9. Strictamine (**1**) (29 mg, 0.09 mmol) was dissolved in 30 mL of dry toluene, and the solution was passed through a vertical Pyrex column at 475 ± 5 °C under water pump vacuum. The effluent was condensed at the bottom of the column in a liquid nitrogen-cooled trap. The evaporated mixture was submitted to TLC (CH_2Cl_2/MeOH 95:5), allowing separation of akuammicine (**2**) (∼1 mg, 3%), recovered strictamine (**1**) (5 mg, 17%), indole **6** (2.5 mg, 9%), and indolenine **9** (9.5 mg, 32%). Akuammicine (**2**) was repurified on TLC before its $[\alpha]_D$ was measured. When the temperature of the oven was raised to 490 °C and above, only compound **9** was obtained (∼30%). Akuammicine (**2**): $[\alpha]_D$ −280 (*c* 0.1, EtOH) (lit.[2c] $[\alpha]_D$ −735 (EtOH)); R_f, UV, IR, and MS identical with those of an authentic sample. Indole **6**: $[\alpha]_D$ +13 (*c* 0.2, MeOH); UV (MeOH) λ_{max} 220, 278, 288 nm; ^{1}H NMR ($CDCl_3$) δ 1.73 (d, 2H, J = 6.8), 3.63 (s, 3H), 5.34 (q, 1H, $J \approx 5$), 5.90 (dt, 1H, $J \approx 9$, $J \approx 2.2$), 6.60 (dd, 1H, J = 9.0, $J \approx 2.2$), 7.86 (s, 1H); ^{13}C NMR δ 12.5, 28.2, 47.6, 51.6, 57.2, 59.3, 65.1, 110.5, 117.1, 115.7*, 119.7, 120.5, 121.2, 122.5, 128.5, 130.9, 131.5, 134.4, 138.2, 172.3* (* weak resonance); MS *m*/*z* 322 ($M^{\bullet+}$), 263, 156, 121; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, obsd 322.1676. Indolenine **9**: amorphous, $[\alpha]_D$ +101 (*c* 0.4, MeOH); IR (film) 2910, 2845, 1725 cm^{-1}; UV (MeOH) 208, 259 nm; ^{1}H NMR ($CDCl_3$) δ 1.68 (d, 3H, J = 6.8), 2.11 (d, 1H, J = 12.5), 2.52 (dt, 1H, J = 12.5, 5.0), 2.67 (td, 1H, J = 14.0, 4.5), 2.71 (dd, 1H, J = 14.0, 4.5), 3.05 (d, 1H, J = 5.0), 3.32 (m, 2H), 3.54 (s, 3H), 3.56 (d, 1H, J = 15.8), 3.70 (d, 1H, J = 15.8), 3.85 (d, 1H, J = 6.3), 3.92 (t, 1H, J = 6.3), 5.38 (q, 1H, J = 6.8), 7.21 (t, 1H, J = 7.7), 7.35 (m, 2H), 7.62 (d, 1H, J = 7.7); MS *m*/*z* 322 ($M^{\bullet+}$) 263, 241, 215, 156, 121; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, obsd 322.1651.

Flow Thermolysis of 19,20-Dihydroakuammicine 10: Aldehyde 11. Compound **10** (100 mg; 0.309 mmol) was dissolved in dry toluene (60 mL) and flow-thermolyzed at 450 ± 5 °C through a quartz column. TLC separation gave compound **11** (10 mg, 11%) and starting compound **10** (38 mg, 38%). Higher temperatures did not improve the yield but instead led to extensive decomposition of the starting material. The reaction was very sensitive to glass catalysis, and use of a new quartz column proved to be necessary. Aldehyde **11**: brown-orange compound; $[\alpha]_D$ +118 (*c* 0.04, MeOH); UV (MeOH) λ_{max}(log ϵ) 207 (4.26), 225 (4.15), 260 (4.06), 321 (4.09), 439 (3.74); ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, J = 7.5), 1.52 (m, 2H), 2.46 (m, 1H), 3.16 (m, 2H), 3.32 (dd, 1H, J = 12.8, 8.3), 3.57 (dd 1H, J = 12.8, 5.3), 3.70 (dd, 2H, J = 3.8, 5.3), 6.36 (dd, 1H, J = 10.5, 4.5), 6.72 (dd, 1H, J = 10.5, 1.5), ∼7.09 (m, 2H), 7.38 (d, 1H, J = 7.5), 7.43 (d, 1H, J = 7.5), 9.83 (s, 1H), 11.60 (s, 1H); MS *m*/*z* 292 ($M^{\bullet+}$) 264, 263, 156, 144; HRMS calcd for $C_{19}H_{20}N_2O_2$ 292.1574, obsd 292.1539.

Flow Themolysis of Tubifoline (12): Indoles 13 and 15. Tubifoline (**12**) (30 mg, 0.112 mmol) was dissolved in dry toluene (30 mL) and flow-thermolyzed at 490 ± 5 °C. TLC separations (three migrations: (1) CH_2Cl_2/MeOH 96:4, (2) and (3) CH_2Cl_2/MeOH 98.2) gave starting tubifoline (**12**) (7 mg, 23%) and the two indoles **13** (11 mg, 37%) and **15** (7 mg, 23%). Indole **13**: mp 50−55 °C; $[\alpha]_D$ +55 (*c* 0.8, MeOH); UV (MeOH) λ_{max} 227, 275, 283, 291 nm; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.5), 1.44 (m, 2H), 2.24 (m, 1H), 2.54 (dd, 1H, J = 1.5, 16.5), 2.60 (dd, 1H, J = 7.5, 12.0), 2.81 (dd, 1H, J = 12.0, 5.3) 2.87 (m, 1H), ∼3.10 (m, 4H), 3.69 (bd, 1H, $J \approx$ 10.5), 5.64 (dq, 1H, J = 1.7, 9.8), 5.76 (dt, 1H, J = 9.8, 2.3), 7.10 (m, 2H), 7.26 (m, 1H), 7.45 (m, 1H), 7.74 (s, 1H); MS *m*/*z* 266 ($M^{\bullet+}$), 166, 158, 143, 135, 123, 122, 107; HRMS calcd for $C_{18}H_{22}N_2$ 266.1783, obsd 266.1774. Indole **15**: mp 137−147 °C; $[\alpha]_D$ +41 (*c* 0.5, MeOH); UV (MeOH) λ_{max} 227, 275, 283, 291 nm; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3H, J = 7.5), 1.33 (m, 2H), 2.27 (t, 1H, J = 9.8), 2.38 (m, 1H), 2.67 (m, 2H), 3.00 (m, 5H), 3.16 (dt, 1H, J = 11.3, 3.8), 5.50 (dt, 1H, J = 9.8, 1.5), 5.75 (bd, 1H, J = 9.8), 7.10 (m, 2H), 7.27 (m, 1H), 7.46 (m, 1H), 7.73 (s, 1H); MS *m*/*z* 266 ($M^{\bullet+}$), 158, 143, 135, 123, 122, 107; HRMS calcd for $C_{18}H_{22}N_2$ 266.1783, obsd 266.1778.

Hydrogenation of Indoles 13 and 15: Indoles (−)-14 and (−)-16. A. A solution of the mixture of indoles **13** and **15** (40 mg, 0.150 mmol) in MeOH (10 mL) was hydrogenated for 12 h in the presence of PtO_2 (10 mg). Filtration followed by evaporation of the solvent and TLC separation gave indole (−)-**14** (21 mg, 52%) and indole (−)-**16** (19 mg, 47%). Indole (−)-**14**: mp 80−82 °C; $[\alpha]_D$ −24 (*c* 0.03, MeOH), −26 (*c* 0.4, MeOH); CD λ nm($\Delta\epsilon$) 245 (+1.38); IR (film) 3589, 3344, 2922, 2848, 1530 cm^{-1}; UV (MeOH) λ_{max} 228, 272, 283, 292 nm; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.5), ∼1.30 (m, 3H), 1.56 (m, 1H), 1.68 (m, 2H), 1.87 (m, 1H), 2.31 (dd, 1H, J = 1.8, 15.0), 2.70 (m, 3H), 3.05 (m, 1H), 3.24 (m, 2H), 3.45 (m, 1H), 3.72 (dd, 1H, J = 15.0, 11.3), 7.08 (m, 2H), 7.24 (m, 1H), 7.44 (m, 1H), 7.70 (s, 1H); MS *m*/*z* 268 ($M^{\bullet+}$), 156, 144, 124, 110; HRMS calcd for $C_{18}H_{24}N_2$ 268.1940, obsd 268.1956. Indole (−)-**16**: dble mp 74 °C, 136−8 °C; $[\alpha]_D$ −8 (*c* 0.2 MeOH), −10 (*c* 0.4 MeOH); IR (film) 3281, 2922, 2851, 1456 cm^{-1}; UV (MeOH) λ_{max} 227, 273, 283, 291 nm; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3H, J = 7.5, m, 1H), 1.24 (m, 2H), 1.57 (m, 2H), 1.73 (dq, 1H, J = 13.5, 3.8), 1.83 (bd, 1H, J = 13.5), 2.12 (t, 1H, J = 10.5), 2.41 (bt, 1H, J = 10.5), 2.62 (dd, 1H, J = 1.5, 15.1), 2.70−2.80 (m, 2H), 2.80−3.00 (m, 2H), 3.10 (dd, 1H, J = 10.5, 15.1), 3.39 (m, 1H), 7.10 (m, 2H), 7.25 (m, 1H), 7.44 (m, 1H), 7.72 (s, 1H); MS *m*/*z* 268 ($M^{\bullet+}$), 156, 144, 124, 110; HRMS calcd for $C_{18}H_{24}N_2$ 268.1938, obsd 268.1938. **B.** Indole **15** (4 mg, 0.015 mmol) dissolved in MeOH (1.5 mL) and in the presence of PtO_2 (4 mg) was hydrogenated during 8 h. Usual workup and TLC separation gave 4 mg of indole (−)-**16** (R_f, NMR, MS, $[\alpha]_D$).

Flow Thermolysis of 19,20-Dehydrotubifoline (17): Indole 18. 19,20-Dehydrotubifoline (**17**) (70 mg, 0.265 mmol) dissolved in dry toluene (50 mL) was thermolyzed at 460 ± 5 °C. TLC allowed separation of compound **18** (14 mg, 20%) and of starting material **17** (12 mg, 17%). Two other minor, unstable compounds were not studied. Compound **18**: $[\alpha]_D$ +14 (*c* 1.4, MeOH); IR (film) 3400, 3220, 3040, 2910, 1460 cm^{-1}; UV(MeOH) λ_{max} 229, 272.5, 283, 291 nm; ^{1}H NMR ($CDCl_3$) δ 1.74 (d, 2H, J = 6.8), 2.70−3.60 (m, 8H), 5.40 (q, 1H, J = 6.8), 5.69 (dd, 1H, J = 9.0, ∼4.5), 6.54 (dd, 1H, J = 9, ∼4.5), 7.09 (m, 2H), 7.27 (m, 1H), 7.45 (m, 1H), 7.75 (s, 1H); MS *m*/*z* 264 ($M^{\bullet+}$), 158, 121, 93; HRMS calcd for $C_{18}H_{20}N_2$ 264.1625, obsd 264.1624.

Hydrogenation of Indole 18: Compounds 14 and 16. Indole **18** (16 mg, 0.060 mmol) dissolved in MeOH (5 mL) was hydrogenated during 8 h in the presence of PtO_2 (10 mg). The suspension was filtrated and the filtrate evaporated to dryness. TLC separation of the residue gave 8 mg of indole **14** (49%) and 6 mg of indole **16** (37%). Indole **14**: $[\alpha]_D$ −4 (*c* 0.8 MeOH).

(21) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093 (HMQC/HMBC: heteronuclear multiple quantum/multiple bond correlation).

(22) (a) Manisse, N.; Chuche, J. *Bull. Soc. Chim. Fr.* **1972**, 2422. (b) Coqueret, X.; Bourelle-Wargnier, F.; Chuche, J. *Tetrahedron* **1986**, *42*, 2263.

Indole **16**: $[\alpha]_D \pm 0$ (*c* 0.4 MeOH). The data (R_f, UV, MS, NMR) of compounds **14** and **16** were otherwise found to be identical with those of **14** and **16** as described above.

Preparation of (+)-*epi*-Ngouniensine ((+)-21). A. A solution of ngouniensine (**19**) (27 mg, 0.10 mmol) in 20 mL of toluene was flow-thermolyzed at 610 ± 5 °C. TLC separation allowed isolation of the starting (−)-ngouniensine (**19**) (14 mg, 52%), $[\alpha]_D$ −60 (*c* 0.8, MeOH), and 4 mg (15%) of (+)-*epi*-ngouniensine (**21**), $[\alpha]_D$ +32 ± 4 (*c* 0.3, MeOH); other data (R_f, UV, NMR) were identical with those of the natural product ($[\alpha]_D$ −32 (MeOH)).[16b]

B. A solution of ngouniensine methoiodide (110 mg, 0.26 mmol) in toluene (10 mL) and DMF (1 mL) was added with tri-*n*-butylphosphine (0.075 mL; 1 equiv) and the mixture heated at 110 °C for 3 days in a sealed tube under nitrogen. After evaporation of the solvent, two successive TLC separations gave (−)-ngouniensine (**19**) (35 mg, 48%) and (+)-*epi*-ngouniensine (**21**) (11 mg, 15%), $[\alpha]_D$ +34 (*c* 0.7, MeOH).

Indole (+)-14. Ngouniensine (**19**) (18 mg, 0.06 mmol) was dissolved in 2 mL of CH_2Cl_2, added with predried triethylbenzylammonium chloride (TEBA, 19 mg, 0.08 mmol) and $KMnO_4$ (10 mg, 0.06 mmol), and the mixture stirred during 30 min at rt. Direct purification of the reaction mexture by TLC (plate) gave separation of starting ngouniensine (**19**) (9 mg, 50%) and ketone **20** (2 mg, 11%). Ketone **20**: UV (MeOH) λ_{max} 204, 308 nm; MS *m*/*z* 282 ($M^{\bullet+}$, $C_{18}H_{22}N_2O$), 253, 225, 170, 143, 124, 112. Use of dried 18-crown-6 in place of TEBA gave the same yield of ketone **20**. To a solution of ketone **20** (3 mg, 0.011 mmol) in dry dioxane (4 mL) was added $LiAlH_4$ (30 mg), and the solution was refluxed for 6 h. The reaction mixture was cooled, and excess $LiAlH_4$ was destroyed by addition of wet diethyl ether. The resulting suspension was filtered and the filtrate evaporated to dryness. TLC separation gave indole (+)-**14** (2 mg, ∼70%). Indole (+)-**14**: $[\alpha]_D$ +23 (*c* 0.2, MeOH); CD λnm ($\Delta\epsilon$) 245 (−1.66); R_f, NMR, MS data were identical with those of (−)-**14** described above.

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Supporting Information Available: ^{1}H NMR spectra of **6**, **9**, **11**, **13**, **15**, and **18** and ^{13}C NMR spectra of **6**, **9**, **14**, **16**, and **18** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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