Selective Demethylation of Some Aconitine-Type Norditerpenoid Alkaloids

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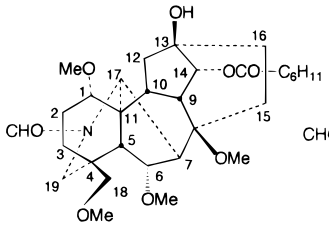
Demethylation of some aconitine-type norditerpenoid alkaloids was carried out with trimethylsilyl iodide and with HBr in glacial AcOH. Aconitine (**10**), cammaconine (**23**), delphinine (**3**), falconerine (**18**), lappaconitine (**22**), and talatizamine (**24**) afforded partially demethylated products. When methoxyl groups are present at the C-16 and C-18 positions, these are demethylated, and the methoxyl group at the C-1 position underwent demethylation in none the alkaloids studied except falconerine (**18**). With HBr−AcOH, in the case of alkaloids possessing a C-3 hydroxyl group, the methoxymethyl at C-18 formed a tetrahydrofuran, cyclizing at the C-6 position. Detailed NMR spectral studies (^{1}H, ^{13}C, ^{1}H homonuclear COSY, HETCOR, and selective INEPT) carried out on the demethylation products have enabled accurate chemical shift assignments to be made for the demethylated alkaloids.

Most of the aconitine-type norditerpenoid alkaloids (C_{19}) possess an oxygen function at C-1, C-8, C-14, C-16 and in some cases at the C-3, C-6, C-13, C-15, C-18 positions, opposed to the diterpenoid alkaloids (C_{20}), which lack a methoxyl function in the main skeleton. Although the structure determination of the norditerpenoid alkaloids has become considerably simplified because of the advent of ^{13}C-NMR spectroscopy,[1,2] selective demethylations would be useful in facilitating the structure elucidation of newly isolated norditerpenoid alkaloids. The first investigation of the demethylation of norditerpenoid alkaloids with HI and phosphorus or with $AlCl_3$ was carried out by Jacobs *et al.*[3] Some alkaloids were partially demethylated with HCl and with HNO_3.[4] Treatment of octahydroisopyro-α-oxodelphinine (**1**) with aqueous $ZnCl_2$ and 5% HCl gave the furan **2**.[3] Similar demethylations to afford cyclic ethers were carried out on neoline and *N*-acetyl-*N*-deethylisopyrochasmanine.[5−7] We had previously reported the demethylation of some diterpenoid alkaloids using HBr in AcOH and discussed the efficacy of this method.[8] We now report further examination of this method for the demethylation of aconitine-type nordiiterpenoid alkaloids and also the application of trimethylsilyl iodide (TMS-I) as a demethylating agent.



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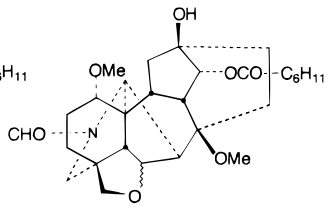

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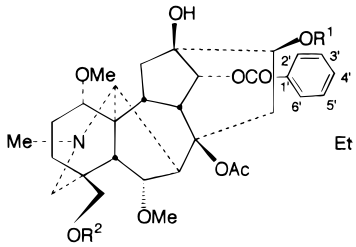
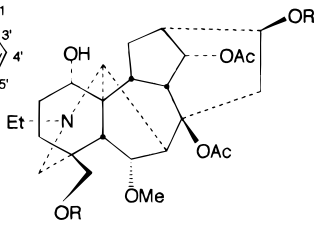
Results and Discussion

The aconitine-type alkaloid delphinine (**3**), when treated with HBr−AcOH, gave a mixture of the demethylated and acetylated alkaloids (**4** and **5**), and delphisine (**6**) gave compound **7**. In the aconitine-type alkaloids, the C-18 methoxyl group is preferentially demethylated, and the next methoxyl group to be demethylated is the one at C-16. In these alkaloids, the conformation of the methoxyl group at C-6 is α. The methoxyls at C-1 and C-6 are not demethylated under these conditions.

Demethylation of delphinine (**3**) with TMS-I in CH_2Cl_2 selectively demethylated first the 18-methoxyl group to afford **8** and 16,18-di-*O*-desmethyl delphinine (**9**). Both compounds are amorphous and exhibit NMR spectral data consistent with the proposed structures (Table 1). Alkaloid **8** was isolated earlier from *Delphinium staphisagria* L. and has been designated as delstaphigine.[9]



3 Delphinine: R^1, R^2 = Me
4 R^1 = Me; R^2 = Ac
5 R^1, R^2 = Ac
8 Delstaphigine: R^1 = Me; R^2 = H
9 R^1, R^2 = H



6 Delphisine: R = Me
7 R = Ac

We have carried out the demethylation of aconitine (**10**) with HBr−AcOH. The ^{1}H- and ^{13}C-NMR spectra, the microanalytical results, and the EIMS data for the demethylated product are not in accord with the expected 18-acetyl-18-*O*-desmethylaconitine (**11**) or 16-acetyl-16-*O*-desmethylaconitine (**12**) ($C_{35}H_{47}NO_{12}$). The demethylation of aconitine (**10**) with HBr−AcOH essentially gave **13** and **14**. This was an unexpected result, as the alkaloid is closely related to delphinine, except for the hydroxyl groups at C-3 and C-15 positions and an *N*-ethyl instead of an *N*-methyl group. A HRMS *m/z*, $[M + H]^+$ 642, and another mass spectrum (electrospray) (M^+, 641), for the demethylated alkaloid (**13**) and the micro-analytical results confirm the molecular formula $C_{34}H_{43}NO_{11}$. We have carried out ^{1}H, ^{13}C, ^{1}H−^{1}H COSY, HETCOR, and selective INEPT NMR experiments on **13**. The mass-spectral fragment ions indicated *m/z* 610 $[M - OMe]^+$, 582 $[M - OCOMe]^+$, 522 $[582 - MeCO_2H]^+$, suggesting the presence of a C-1 α

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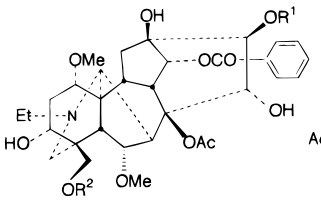
Table 1. ^{13}C-NMR (250 MHz) Spectral Data for **8**, **9**, **25**, **27**, **14**, **20**, and **21**

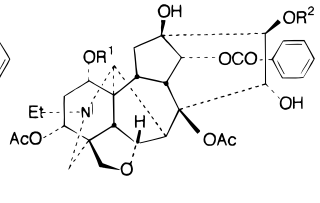
C	8	9	25	27	14	20	21
1	84.6 (d)	84.7 (d)	83.8 (d)	85.4 (d)	84.1 (d)	79.2 (d)	77.8 (d)
2	26.4 (t)	26.3 (t)	25.6 (t)	26.0 (t)	33.4 (t)	34.1 (t)	40.7 (t)
3	35.3 (t)	35.4 (t)	31.7 (t)	38.4 (t)	72.7 (d)	72.5 (d)	72.0 (d)
4	39.6 (s)	39.7 (s)	84.4 (s)	38.4 (s)	48.1 (s)	48.1 (s)	48.1 (s)
5	49.9 (d)	49.8 (d)	48.1 (d)	37.6 (d)	56.7 (d)	56.7 (d)	56.4 (d)
6	82.5 (d)	82.5 (d)	26.6 (t)	24.8 (t)	76.3 (d)	75.4 (d)	75.3 (d)
7	47.2 (d)	47.2 (d)	49.6 (d)	45.7 (d)	45.2 (d)	55.0 (d)	53.8 (d)
8	85.5 (s)	85.5 (s)	74.8 (s)	73.4 (s)	89.5 (s)	73.3 (s)	73.3 (s)
9	44.8 (d)	45.2 (d)	78.3 (s)	46.1 (d)	43.2 (d)	45.5 (d)	45.3 (d)
10	41.0 (d)	41.2 (d)	38.5 (d)	45.1 (d)	40.3 (d)	43.4 (d)	43.0 (d)
11	50.1 (s)	50.2 (s)	50.9 (s)	48.6 (s)	46.4 (s)	46.1 (s)	47.0 (s)
12	35.3 (t)	35.4 (t)	23.8 (t)	28.0 (t)	36.5 (t)	27.5 (t)	27.1 (t)
13	74.8 (s)	74.9 (s)	50.2 (d)	44.6 (d)	75.1 (s)	39.9 (d)	40.4 (d)
14	78.7 (d)	79.6 (d)	82.4 (d)	73.6 (d)	78.8 (d)	74.2 (d)	74.4 (d)
15	39.3 (t)	41.7 (t)	41.8 (t)	39.9 (t)	77.4 (d)	41.4 (t)	41.7 (t)
16	83.5 (d)	74.4 (d)	74.8 (d)	76.4 (d)	81.6 (d)	75.8 (d)	73.7 (d)
17	63.6 (d)	63.6 (d)	61.3 (d)	62.1 (d)	61.7 (d)	62.2 (d)	61.3 (d)
18	71.3 (t)	71.3 (t)		79.3 (t)	75.9 (t)	75.7 (t)	76.1 (t)
19	56.5 (t)	56.5 (t)	55.4 (t)	53.0 (t)	51.0 (t)	51.7 (t)	51.8 (t)
N-CH_2CH_3			48.9 (t)	49.3 (t)	49.7 (t)	49.6 (t)	49.1 (t)
	42.6 (q)	42.6 (q)	13.4 (q)	13.5 (q)	13.0 (q)	13.0 (q)	13.1 (q)
1-OCH_3	56.1 (q)	56.1 (q)	56.4 (q)	56.1 (q)	57.3 (q)		
1-OC(O)CH_3						170.2 (s)	
						21.0 (q)	
3-OC(O)CH_3					170.6 (s)	170.4 (s)	170.3 (s)
					21.1 (q)	21.1 (q)	21.0 (q)
6-OCH_3	57.4 (q)	57.4 (q)					
14-OC(O)CH_3	166.3 (s)	166.6 (s)	171.8 (s)	170.2 (s)	166.0 (s)	165.7 (s)	165.7 (s)
			21.2 (q)	21.3 (q)			
16-OCH_3/OC(O)CH_3	58.7 (q)						
			170.1 (s)	170.1 (s)	170.2 (s)	170.6 (s)	170.5 (s)
			21.2 (q)	21.2 (q)	21.1 (q)	21.5 (q)	21.1 (q)
18-OCH_3				59.4 (q)			
8-C(O)CH_3	170.0 (s)	169.9 (s)			171.2 (s)		
	21.6 (q)	21.2 (q)			21.2 (q)		
OCO			167.3 (s)				
1′	130.1 (s)	130.1 (s)	115.6 (s)		129.5 (s)	122.4 (s)	122.4 (s)
2′	128.5 (d)	129.6 (d)	141.6 (s)		129.5 (d)	110.3 (d)	110.3 (d)
3′	129.7 (d)	128.7 (d)	120.2 (d)		128.7 (d)	148.7 (s)	148.7 (s)
4′	133.1 (d)	133.4 (d)	134.4 (d)		133.5 (d)	153.1 (s)	153.1 (s)
5′	129.7 (d)	128.7 (d)	122.3 (d)		128.7 (d)	112.0 (d)	112.0 (d)
6′	128.5 (d)	129.6 (d)	130.9 (d)		129.5 (d)	123.5 (d)	123.5 (d)
			169.1 (s)	NHCO			
			25.5 (q)	CH_3			
Ar-OMe						55.9 (q)	55.9 (q)
						56.0 (q)	56.0 (q)

[α] δ in $CDCl_3$.

methoxyl and two acetate groups.[10] A detailed analysis of the selective INEPT and COSY NMR data are in conformity with structure **13** for this demethylation product.



10 Aconitine: R^1, R^2 = Me
11 R^1 = Me; R^2 = Ac
12 R^1 = Ac; R^2 = Me
16 R^1 = Me; R^2 = H
17 R^1, R^2 = H



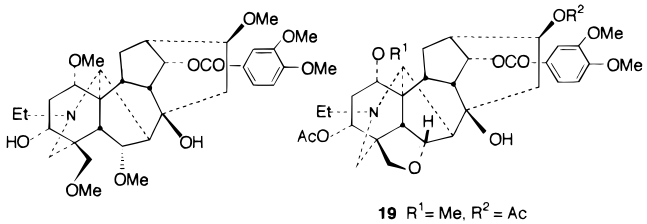
13 R^1, R^2 = Me
14 R^1 = Me, R^2 = Ac
15 R^1, R^2 = Ac

In the ^{1}H-NMR spectrum of aconitine, H-3 appears at δ 3.77,[11] and in **13**, this proton is observed at δ 4.82, indicating that the C-3 hydroxyl group is acetylated. In aconitine, H-6 appears at δ 4.04,[11] and this is shifted downfield by 0.43 ppm to δ 4.47 in the demethylation product. This small shift suggests that C-6 does not bear an acetate group, confirming that this compound is not 6-acetyl-6-*O*-desmethylaconitine.

The second demethylation product **14** of aconitine showed a molecular ion m/z $[M + H]^+$ at 670 suggestive of the molecular formula $C_{35}H_{43}NO_{12}$. The ^{1}H-NMR spectrum of this compound showed the H-3 proton at δ 4.82, again indicating an acetoxyl group at the C-3 position. H-6 appeared at δ 4.50, which is a small shift from δ 4.04 in **10**, not indicative of an acetoxyl at C-6. The H-16 proton in aconitine is observed at δ 3.33,[11] and this is shifted downfield to δ 5.11 in **14**. These results and all other spectral data (Table 1) are in conformity with the proposed structure for this demethylation product. This differs from the tetraacetate **15** obtained by Blagbrough *et al.*[12] in which the C-1 methoxyl group has been demethylated and acetylated. In our experiments, we did not observe demethylation of the C-1 methoxyl with HBr−AcOH. Blagbrough *et al.* have commented on the formation of the furan in the demethylation with HBr−AcOH of aconitine and not delphinine. They propose that the C-3 hydroxyl group present in **10**, but not in **3**, undergoes ready acetylation in HBr in HOAc and that this acetate promotes an intramolecular displacement of the 18-methoxyl group by the oxygen atom of the *O*-methyl ether at C-6. The C-3 acetate appears to be a part of the displacement process probably by the formation of a six-membered

acetal; however, we believe that the C-18 methoxyl is initially demethylated and gets converted to the C-18-*O*-acetate (as observed in other demethylations) and is a better leaving group. The oxygen atom of C-6-*O*-methyl ether forms the furan ring with retention of configuration at C-6. Demethylation of **10** with TMS-I gave a mixture of 18-des-*O*-methyl- (**16**) and 16,18-di-*O*-desmethyl aconitines (**17**), as also reported earlier.[12]

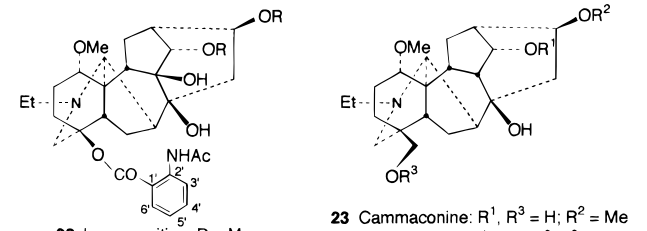
Demethylation with HBr−AcOH of falconerine [13] (**18**) possessing an OH group at C-3 takes a similar course as in aconitine to afford the tetrahydrofurans **19**−**21**. The structure of demethylation product **19** was based on detailed ^{1}H- and ^{13}C-NMR spectral data.



18 Falconerine

19 R^1 = Me, R^2 = Ac
20 R^1, R^2 = Ac
21 R^1 = H, R^2 = Ac

The demethylation of other aconitine-type alkaloids, lappaconitine (**22**), cammaconine (**23**), and talatizamine (**24**) with HBr−AcOH has also been investigated. On the basis of NMR spectral data, the demethylation product of lappaconitine (**22**) has been assigned the structure 14,16-di-*O*-desmethyl-14,16-diacetyllappaconitine (**25**). The demethylation product of cammaconine (**23**) and one of those from talatizamine (**24**) have been shown to be identical with structure **26**. A second product isolated in the demethylation of talatizamine **24** has been assigned structure **27** (Table 1). The structure assignment of **26** was consistent with the detailed NMR spectral studies. Talatizamine was first isolated from *Aconitum talassicum* by Konovalova and Orekhov,[14] and its structure was established by Yunusov and Yunusov[15] from a study of the pyrolysis products, ^{1}H-NMR, and MS data. ^{13}C-NMR chemical shift assignments for **24** made by Konno *et al.*[16] were not rigorous and were probably made on the basis of application of rules of chemical shifts for different substituent groups and comparison of spectra of closely related compounds. We therefore carried out detailed ^{1}H- and ^{13}C-NMR analysis of talatizamine (**24**), which happens to be a sparsely substituted norditerpenoid alkaloid. Lappaconitine (**22**), when treated with TMS-I, gave the polar compound 14,16-di-*O*-desmethyllappaconitine, which was difficult to purify by chromatography; it was therefore acetylated to afford **25**.



22 Lappaconitine: R = Me

25 R = Ac

23 Cammaconine: R^1, R^3 = H; R^2 = Me
24 Talatizamine: R^1 = H; R^2, R^3 = Me
26 R^1, R^2, R^3 = Ac
27 R^1, R^2 = Ac; R^3 = Me

Experimental Section

General Experimental Procedures. Mps are corrected and were determined on a Thomas-Kofler hot stage equipped with a microscope and a polarizer. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. IR spectra were recorded on a Perkin-Elmer model 1420 spectrophotometer. ^{1}H-, ^{13}C-, and 2D-NMR spectra were recorded in $CDCl_3$ on Bruker AC-250 and Bruker AC-300 spectrometers. Electrospray mass spectra (ESIMS) were recorded on a Perkin-Elmer SCIEX API-1 mass spectrometer. For chromatographic separation on a Chromatotron, rotors were coated with 1-mm thick Al_2O_3, 60PF 254+366 (Type E, EM Art, 1104). The alkaloids used in the demethylation experiments were obtained as follows: aconitine from "Merck Aconitine",[17] cammaconine and talatizamine from *A. columbianum*,[18] delphinine from the seeds of *D. staphisagria*,[19] falconerine from *A. falconeri*,[13] and lappaconitine from *A. septentrionale*.[20]

General Procedure for Demethylation Reactions with HBr−AcOH. To a solution of the substrate in AcOH, HBr (30% solution in AcOH, Aldrich) was added and the solution kept at room temperature for 4−7 days in a glass-stoppered flask. The progress of the reaction was monitored by TLC. The TLC plates were first exposed to aqueous NH_4OH (3 min) in a separate chamber and then developed in an appropriate solvent along with the starting material. When the spot corresponding to the starting material disappeared, the reaction mixture was diluted with H_2O (2−3-fold) and cooled in an ice bath. The reaction mixture was basified to pH 10 (at 0−5 °C) with saturated Na_2CO_3 solution. The basic reaction mixture was then repeatedly extracted with $CHCl_3$. Separation of the reaction products was carried out on an Al_2O_3 rotor.[21,22]

Tables 2−5 have been provided for the compounds **13**, **19**, **26**, and **24** giving ^{1}H, ^{13}C, COSY and SINEPT (^{1}H→^{13}C) data as Supporting Information.

Action of TMS-I on Delphinine (3). To a solution of delphinine (**3**, 1 g) in CH_2Cl_2 (20 mL) was added a solution of fresh TMS-I (0.5 mL) in CH_2Cl_2 (0.5 mL) and TMS-I (0.5 mL) in CH_2Cl_2 (0.5 mL) after 74 h. The mixture was kept at room temperature for 5 days. TLC of the reaction mixture showed no spot of **3**. MeOH (7 mL) was added and the solvent evaporated *in vacuo* to afford a crude demethylation product (950 mg). Part of this (500 mg) was dissolved in CH_2Cl_2 (10 mL) and chromatographed on an Al_2O_3 rotor. Twenty fractions (20 mL each) were collected by gradient elution with hexane, ether, and an increasing percentage of MeOH. Fractions 9−13 (ether−10% MeOH) gave **8** (50 mg) and fractions 14−17 (ether−30% MeOH) afforded **9** (20 mg). The compound **8** was amorphous and showed ESIMS: *m*/*z* 586 ($C_{32}H_{43}NO_9$, MW 585) $[M + H]^+$, (100%); IR (nujol), ν_{max} 3450, 2910, 1730, 1712, 1450, 1370, cm^{-1}; ^{1}H NMR δ 8.03 (2H, d, J = 7.5 Hz, ArH-2′,6′), 7.54 (1H, dd, J = 7.5, 7.3 Hz, ArH-4′), 7.41 (2H, t, J = 7.5 Hz, ArH-3′,5′), 4.87 (1H, d, J = 5.1 Hz, H-14), 3.50, 3.25, 3.24 (each 3H, s, OMe), 2.34 (3H, s, *N*Me), 1.26 (3H, s, OAc); for ^{13}C-NMR data, see Table 1.

Compound **9** was amorphous and showed ESIMS: *m*/*z* 572 ($C_{31}H_{41}NO_9$, MW 571), $[M + H]^+$,(100%); IR (nujol) ν_{max} 3400, 1730, 1712, 1450, 1372, 1280, 710 cm^{-1}; ^{1}H NMR δ 8.01 (2H, d, J = 7.5 Hz, ArH-2′,6′), 7.55 (1H, dd, J = 7.3 Hz, ArH-4′), 7.43 (2H, t, J = 7.5, 7.3 Hz, ArH-3′, ArH-5′), 4.97 (1H, d, J = 5.05 Hz, H-14), 3.22, 3.14 (each 3H, s, OMe), 2.38 (3H, s, *N*Me), 1.32 (3H, s, OAc); for ^{13}C NMR data, see Table 1.

Action of TMS-I on Lappaconitine (22). To a solution of lappaconitine (**22**, 200 mg) in CH_2Cl_2 (20 mL) was added, while being stirred at 5 °C, a solution of fresh TMS-I (0.6 mL) in CH_2Cl_2 (0.5 mL) in a stoppered flask. After 25 h, MeOH (5 mL) was added and the reaction mixture evaporated and dried *in vacuo* to give a yellowish residue. To the residue, pyridine (3 mL) and Ac_2O (3 mL) were added and kept at room temperature for 32 h. The reaction mixture was poured into iced H_2O, and the solution was basified with Na_2CO_3 to pH 10. The basic solution was extracted with $CHCl_3$ (100 mL × 4), the extract dried over anhydrous Na_2SO_4, and the solvent evaporated *in vacuo* to give a residue (187 mg). This was dissolved in CH_2Cl_2 (10 mL), chromatographed on an Al_2O_3 rotor, and eluted with hexane, and increasing percentages of $CHCl_3$, and 50 mL fractions were collected. Fraction 26 (hexane−64% $CHCl_3$) gave an amorphous solid (45 mg). ^{1}H- and ^{13}C-NMR spectra of this compound were found to be identical with 14,-16-di-*O*-desmethyl-14,16-diacetyllappaconitine (**25**). For the ^{1}H-NMR data of **25** (see below) and ^{13}C-NMR data, see Table 1.

Action of HBr−AcOH on Aconitine (10). To a solution of aconitine (**10**, 150 mg) in AcOH (3 mL) a solution of HBr in AcOH (0.6 mL) was added and the mixture stirred for 4 days at room temperature. Usual workup and purification on an Al_2O_3 rotor gave two homogeneous products: **13** (6 mg) and **14** (42 mg). Compound **13**: mp 145−149 °C, $[\alpha]^{25}_D$ +2.7° (*c* 0.2885, $CHCl_3$); *anal.* C 62.20%, H 6.84%, calcd for $C_{34}H_{44}NO_{11}$, C 63.65%, H 6.71%; ESIMS, *m/z* 642 ($C_{34}H_{43}NO_{11}$, MW 641), $[M + H]^+$, (100); IR (Nujol) ν_{max} 3478, 1730, 1722, 1712, 1280, 1270, 1258 cm^{-1}; ^{1}H NMR δ 3.29 (1H, m, H-1), 2.30 (1H, m, H-2α), 2.40 (1H, m, H-2*β*). 4.82 (1H, m, H-3), 1.94 (1H, d, *J* = 6.7 Hz, H-5), 4.47 (1H, d, *J* = 6.7 Hz, H-6), 3.03 (1H, s, H-7), 2.71 (1H, m, H-9), 2.71 (1H, m, H-10), 2.20, 2.60 (2H, m, H-12), 4.86 (1H, d, *J* = 4.7 Hz, H-14), 4.45 (1H, d, *J* = 7.0 Hz, H-15), 3.35 (1H, d, *J* = 7.0 Hz, H-16), 3.03 (1H, s, H-17), 3.32 (2H, m, H-18), 2.02, 3.32 (2H, m, H-19), 2.40, 2.72 (each 1H, d, *NCH*$_2$), 1.01 (3H, t, *NCH*$_2$*CH*$_3$), 3.32 (3H, s, 1-OMe), 3.78 (3H, s, 16-OMe), 2.06 (3H, s, 8-OAc), 8.01 (2H, d, *J* = 7.3 Hz, H-2′, H-6′), 7.45 (2H, dd, *J* = 7.3 Hz, H-3′, H-5′), 7.56 (1H, d, *J* = 7.3 Hz, H-4′); ^{13}C NMR δ 84.2 (d, C-1), 33.4 (t, C-2), 72.7 (d, C-3), 48.0 (s, C-4), 56.7 (d, C-5), 77.4 (d, C-6), 45.0 (d, C-7), 90.1 (s, C-8), 42.8 (d, C-9), 40.0 (d, C-10), 46.3 (s, C-11), 35.4 (t, C-12), 74.7 (s, C-13), 78.8 (d, C-14), 78.9 (d, C-15), 90.1 (d, C-16), 61.8 (d, C-17), 75.8 (t, C-18), 51.1 (t, C-19), 49.7 (t, *N-CH*$_2$), 13.0 (q, *N*-CH$_2$*CH*$_3$), 57.6 (q, C-1 OMe), 61.3 (q, C-16 OMe), 170.7 (s, 3-O*C*OCH$_3$), 21.2 (q, 3-OCO*CH*$_3$), 172.3 (s, 8-OCO*CH*$_3$), 21.2 (q, 8-OCO*CH*$_3$),166.0 (s, 14-OCO), 129.8 (s, C-1′), 129.9 (d, C-2′, C-6′), 128.6 (d, C-3′, C-5′), 133.4 (d, C-4′).

Compound **14**: mp 195−197 °C: $[\alpha]^{25}_D$ −21.0° (*c* 0.813, $CHCl_3$); ESIMS *m/z* 670 ($C_{35}H_{43}NO_{12}$, MW 669), $[M + H]^+$, (100); IR (Nujol) ν_{max} 3435, 1730, 1725, 1713, 1280, 1237, 1110, 1090 cm^{-1}; ^{1}H NMR δ 8.03 (2H, d, *J* = 7.2 Hz, ArH-2′,6′), 7.57 (1H, d, *J* = 7.2 Hz, ArH-4′), 7.06 (2H, dd, *J* = 7.2 Hz, ArH-3′, 5′), 5.11 (1H, d, *J* = 6.5 Hz, H-16), 4.95 (1H, d, *J* = 4.8 Hz, H-14), 4.82 (1H, dd, *J* = 4.5 Hz, H-6), 4.50 (1H, m, H-6), 4.42 (1H, br d, *J* = 6.5 Hz, H-15), 4.27 (1H, d, *J* = 2 Hz, 15-OH), 3.30 (1H, m, H-1), 3.30 (3H, s, 1-OMe), 3.08 (1H, s, H-17), 3.04 (1H, s, H-7), 2.88 (1H, s, 13-OH), 2.75 (1H, m, H-9), 2.05, 2.41 (2H, m, H-2), 2.20 (3H, s, 3-OAc), 2.19 (1H, m, H-10), 2.13, 2.80 (2H, m, H-12), 2.05 (3H, s, 16-OAc), 1.95 (1H, m, H-5), 1.45 (3H, s, 8-OAc), 1.07 (3H, t, *J* = 7.0 Hz, *NCH*$_2$*CH*$_3$); for ^{13}C-NMR data of **14**, see Table 1.

Action of HBr−AcOH on Lappaconitine (22). To a solution of lappaconitine (**22**, 300 mg) in AcOH (5 mL), a solution of HBr in AcOH (0.6 mL) was added, and the mixture was kept at room temperature for 5 days. Workup and purification of the product on a basic Al_2O_3 rotor gave **25** as a homogeneous amorphous product (133 mg): mp 112−114 °C; $[\alpha]^{25}_D$ +20.2° (*c* 1.201 $CHCl_3$); ESIMS *m/z* 641 ($C_{34}H_{45}N_2O_{10}$, MW 640), $[M + H]^+$, (100), IR (Nujol) ν_{max} 3435, 1740, 1730, 1713, 1602, 1585, 1522, 1515, 1235, 1080, 1020 cm^{-1}; ^{1}H NMR δ 11.05 (1H, s, NH), 8.63 (1H, dd, *J* = 7.5, 1 Hz, ArH-3′), 7.90 (1H, dd, *J* = 7.5 Hz, ArH-6′), 7.47 (1H, ddd, *J* = 7.6, 7.5, 1 Hz, ArH-4′), 7.00 (1H, ddd, *J* = 7.7, 7.6, 1 Hz, ArH-5′), 4.83 (1H, t, *J* = 7.5 Hz, H-16), 4.70 (1H, d, *J* = 7.4 Hz, H-14), 2.50, 3.55 (each 1H, d, J_{gem} = 12.5 Hz, H-19), 3.26 (3H, s, OCH$_3$), 2.21 (3H, s, NHAc), 2.12 (3H, s, OAc), 2.00 (3H, s, OAc), 1.11 (3H, t, *J* = 7.3 Hz, CH$_2$C*H*$_3$); for ^{13}C-NMR data of **25**, see Table 1.

Action of HBr−AcOH on Cammaconine (23). To a solution of cammaconine (**23**, 300 mg) in AcOH (5 mL) a solution of HBr in AcOH (0.6 mL) was added and the mixture kept at room temperature for 4 days. Usual workup and purification of the product twice on an Al_2O_3 column gave **26** (83 mg) as an amorphous homogeneous compound: $[\alpha]^{25}_D$ +13.6° (*c* 1.595, $CHCl_3$); ESIMS *m/z* 520 ($C_{28}H_{41}NO_8$, MW 519), $[M + H]^+$, (100); IR (Nujol) ν_{max} 3550, 3438, 1742, 1730, 1712, 1642, 1252, 960, 760, 750 cm^{-1}; ^{1}H NMR δ 3.08 (1H, m, H-1), 2.00 (1H, m, H-2α), 2.26 (1H, m, H-2*β*), 1.32 (1H, m, H-3α), 1.75 (1H, m, H-3*β*), 2.10 (1H, m, H-5), 1.51, 1.90 (each 1H, m, H-6), 1.61 (1H, m, H-7), 1.79 (1H, m, H-9), 2.32 (1H, m, H-10), 2.00, 2.28 (2H, m, H-12), 2.50 (1H, m, H-13), 4.85 (1H, t, *J* = 4.5 Hz, H-14), 1.80, 2.50 (2H, m, H-15), 4.80 (1H, dd, *J* = 10.0, 2.0 Hz, H-16), 3.02 (1H, s, H-17), 3.02, 3.80 (each 1H, d, J_{gem} = 9.5 Hz, H-18), 2.02, 2.52 (2H, m, H-19), 2.41, 2.48 (each 1H, dq, *J* = 12.0, 7.5 Hz, *NCH*$_2$), 1.07 (3H, t, *J* = 7.5 Hz, *NCH*$_2$*CH*$_3$), 3.25 (3H, s, 1-OMe), 2.10 (3H, s, 14-OAc), 1.98 (3H, s, 16-OAc), 2.01 (3H, s, 18-OAc); ^{13}C NMR δ 85.0 (d, C-1), 25.7 (t, C-2), 35.3 (t, C-3), 37.5 (s, C-4), 46.2 (d, C-5), 24.9 (t, C-6), 45.8 (d, C-7), 73.3 (s, C-8), 44.6 (d, C-9), 45.0 (d, C-10), 48.6 (s, C-11), 27.9 (t, C-12), 37.6 (d, C-13), 76.2 (d, C-14), 39.8 (t, C-15), 73.5 (d, C-16), 61.9 (d, C-17), 69.9 (t, C-18), 52.6 (t, C-19), 49.2 (t, *NCH*$_2$), 13.4 (q, *NCH*$_2$*CH*$_3$), 56.1 (q, C-1 OMe), 170.2 (s, 14-O*C*OCH$_3$), 20.8 (q, 3-OCO*CH*$_3$), 170.2 (s, 16-OCO*CH*$_3$), 21.2 (q, 16-OCO*CH*$_3$), 171.1 (s, 18-O*C*OCH$_3$), 21.3 (q, 18-OCO*CH*$_3$).

Action of HBr−AcOH on Talatizamine (24). To a solution of talatizamine (**24**, 400 mg) in AcOH (3 mL) a solution of HBr in AcOH (1.25 mL) was added, and the reaction mixture was kept at room temperature for 5 days. Usual workup and purification of the product on Al_2O_3 rotors thrice gave two homogeneous products **26** (159 mg) and **27** (24 mg) along with trace of a minor compound. Compound **27**: amorphous product: $[\alpha]^{25}_D$ +17.3° (*c* 1.183, $CHCl_3$); ESIMS *m/z* 492 ($C_{27}H_{42}NO_7$, MW 491), $[M + H]^+$, (100); IR (Nujol) ν_{max} 3400, 1728, 1712, 1250, 1228 cm^{-1}. Talatizamine **24**: ^{1}H NMR δ 3.05 (1H, m, H-1), 1.93 (1H, m, H-2α), 2.19 (1H, m, H-2*β*), 1.31 (1H, m, H-3α), 1.71 (1H, m, H-3*β*), 1.80 (1H,

m, H-5), 1.41, 1.90 (each 1H, m, H-6), 2.05 (1H, m, H-7), 2.23 (1H, m, H-9), 1.80 (1H, m, H-10), 1.60, 1.79 (2H, m, H-12), 2.30 (1H, m, H-13), 4.08 (1H, t, J = 4.5 Hz, H-14), 2.01, 2.35 (2H, m, H-15), 3.36 (1H, m, H-16), 3.10 (1H, s, H-17), 3.00 (2H, m, H-18), 1.96, 2.46 (2H, m, H-19), 2.35, 2.45 (each 1H, m, *N*-CH_2), 1.00 (3H, t, J = 7.5 Hz, *N*CH_2CH_3), 3.21 (3H, s, 1-OMe), 3.29 (3H, s, 16-OMe), 3.25 (3H, s, 18-OMe), 4.75 (1H, br s, 14-OH); ^{13}C NMR δ 85.2 (d, C-1), 25.7 (t, C-2), 32.6 (t, C-3), 38.5 (s, C-4), 45.7 (d, C-5), 24.6 (t, C-6), 45.9 (d, C-7), 72.6 (s, C-8), 46.6 (d, C-9), 45.6 (d, C-10), 48.5 (s, C-11), 27.6 (t, C-12), 37.4 (d, C-13), 75.4 (d, C-14), 38.2 (t, C-15), 82.1 (d, C-16), 62.8 (d, C-17), 79.3 (t, C-18), 53.0 (t, C-19), 49.4 (t, *N*CH_2), 13.6 (q, *N*CH_2CH_3), 56.2 (q, C-1 OMe), 56.3 (q, C-16 OMe), 59.4 (q, C-18 OMe).

Action of HBr−AcOH on Falconerine (18). To a solution of falconerine (**18**, 110 mg) in AcOH (2 mL) a solution of HBr in AcOH (0.6 mL) was added, and the reaction mixture kept at room temperature for 7 days. Usual workup and purification of the product on a short Al_2O_3 column gave the homogeneous product **19** (29 mg) and a mixture of **20** and **21** (12 mg). Compound **19**: amorphous product: $[\alpha]^{25}_D$ +18.1° (*c* 0.7165, $CHCl_3$); ESIMS *m*/*z* 656 ($C_{35}H_{46}NO_{11}$, MW 655), $[M + H]^+$ (100); IR (Nujol) ν_{max} 3430, 1730, 1712, 1597, 1515, 1500, 1270, 1240, 1120, 1020 cm^{-1}; ^{1}H NMR δ 3.33 (1H, m, H-1), 2.25 (1H, m, H-2α), 2.41 (1H, m, H-2β), 4.83 (1H, m, H-3), 1.92 (1H, d, J = 6.3 Hz, H-5), 4.63 (1H, d, J = 6.6 Hz, H-6), 2.18 (1H, s, H-7), 2.30 (1H, m, H-9), 1.88 (1H, m, H-10), 2.21, 2.30 (2H, m, H-12), 2.50 (1H, m, H-13), 5.09 (1H, t, J = 4.8 Hz, H-14), 2.10 (2H, m, H-15), 4.80 (1H, m, H-16), 2.84 (1H, s, H-17), 3.35 (2H, m, H-18), 2.05, 3.20 (each 1H, d, J = 12.0 Hz, H-19), 2.35, 2.48 (each 1H, m, *N*CH_2), 1.09 (3H, t, J = 7.0 Hz, *N*CH_2CH_3), 3.28 (3H, s, 1-OMe), 2.03 (3H, s, 3-OAc), 1.74 (3H, s, 16-OAc), 7.56 (1H, d, J = 1.6 Hz, H-2′), 6.87 (1H, d, J = 8.5 Hz, H-5′), 7.65 (1H, dd, J = 8.5, 1.6 Hz, H-6′); ^{13}C NMR δ 84.3 (d, C-1), 33.5 (t, C-2), 72.8 (d, C-3), 48.1 (s, C-4), 56.8 (d, C-5), 77.8 (d, C-6), 54.8 (d, C-7), 73.3 (s, C-8), 45.4 (d, C-9), 43.8 (d, C-10), 46.8 (s, C-11), 27.8 (t, C-12), 40.1 (d, C-13), 75.8 (d, C-14), 41.3 (t, C-15), 74.3 (d, C-16), 62.1 (d, C-17), 75.7 (t, C-18), 51.5 (t, C-19), 49.5 (t, *N*CH_2), 12.9 (q, *N*CH_2CH_3), 57.4 (q, 1-OMe), 170.2 (s, 3-O*C*OCH_3), 21.0 (q, 3-OCO*C*H_3), 170.7 (s, 16-O*C*OCH_3), 21.1 (q, 16-OCO*C*H_3), 165.8 (14-OCO), 122.1 (s, C-1′), 110.3 (d, C-2′), 148.7 (s, C-3′), 153.4 (s, C-4′), 112.0 (d, C-5′), 123.5 (d, C-6′), 55.9, 56.0 (each q, OMe).

The compound eluted next appeared homogeneous on TLC, but its ^{1}H and ^{13}C NMR and ESIMS showed it to be a mixture of two compounds, **20** and **21**, in an approximate ratio of 4:3: ESIMS *m*/*z* 684 (for **20**, $C_{36}H_{46}NO_{12}$, MW 683), $[M + H]^+$, (100), *m*/*z* 642 (for **21**, $C_{34}H_{44}NO_{11}$, MW 641), $[M + H]^+$, (75); IR (Nujol) ν_{max} 3440, 1740, 1730, 1715, 1600, 1515, 1270, 1240, 1175, 1120, 1020 cm^{-1}; for ^{13}C NMR data, see Table 1.

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Supporting Information Available: Tables 2−5 containing ^{1}H and ^{13}C NMR, COSY, and SINEPT (^{1}H→^{13}C) data for compounds **13**, **19**, **26**, and **24** (7 pages). Ordering information is given on any current masthead page.

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