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DEOXYGENATION REACTIONS OF C_{19}-DITERPENOID ALKALOIDS

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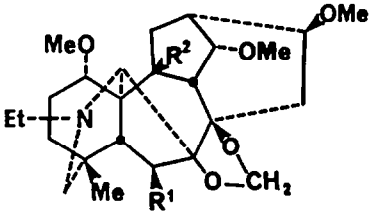
Abstract: Efficient methods for deoxygenation of secondary and tertiary alcohols of some C_{19}-diterpenoid alkaloids are presented. Delphisine (**12**) was converted to 1-deoxydelphisine (**19**) *via* either 1,2-pyrodelphisine (**17**) or phenyl thionocarbonate **20**. The following alkaloids were deoxygenated *via* their thiocarbonylimidazolyl derivatives: 14-acetyldelcosine (**13**) to 14-acetyl-1-deoxydelcosine (**22**); alkaline hydrolysis of **22** gave 1-deoxydelcosine (**23**); aconitine (**24**) to 3-deoxyaconitine (**27**); yunaconitine (**25**) to crassicauline A (**28**). Deoxygenation of 14-acetyldictyocarpine (**30**) *via* the chloro-derivative **31** gave 14-acetyl-10-deoxydictyocarpine (**34**). Reduction of **31** with $LiAlH_4$ gave the unusual elimination product **32**. An improved partial synthesis of hypaconitine (**35**) from aconitine (**24**) is also presented.

Deoxygenation is an important synthetic reaction in many areas of natural products chemistry, especially sugars and aminoglycoside antibiotics.[1] Surprisingly very little is known about the deoxygenation of diterpenoid alkaloids, perhaps because of the complex nature of these compounds. Because C_{19}-diterpenoid alkaloids are often highly oxygenated at various positions of the nucleus[2] methods for selective conversion of ROH to RH are essential for structure correlation among these alkaloids.

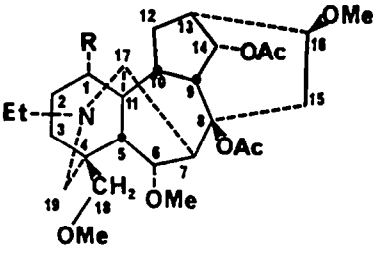
In 1958 Carmack[3] studied the conversion of deltaline (**1**) to delpheline (**2**) by the nucleophilic replacement of OH with chlorine followed by reductive dehalogenation with $LiAlH_4$. The disadvantage of this method is the nonselectivity which resulted in the hydrogenolysis of the acetate function at C-6. During a reinvestigation of the above conversion, we have observed that reduction of intermediate **3** gave an unusual elimination product (**4**) as a minor side product.[4] Product **4** was formed in a yield of 60% along with chloro compound **5** (16%) when crude **3** was reduced with $LiAlH_4$[4] (see Experimental). In a preliminary communication we described efficient methods for selective deoxygenation of tertiary and secondary alcohols of some C_{19}-diterpenoid alkaloids.[4] Thus, deltaline (**1**) was deoxygenated in almost quantitative yield to 10-deoxydeltaline (**6**) by the reduction of the intermediate **3** with *n*-Bu_3SnH. Reaction of deltamine (**7**) with CS_2 and CH_3I in NaOH solution gave the *S*-methyl dithiocarbonate **8** in good yield. Under similar conditions delpheline (**2**) gave the corresponding intermediate **9** in a yield of only 15%. However, **9** was prepared in high yield by the reaction of delpheline with NaH and a catalytic amount of imidazole followed by addition of CS_2 and CH_3I. Reduction of **8** and **9** with *n*-Bu_3SnH[5] furnished the deoxy compounds **10** and **11**, respectively. The results are shown in Table 1. Herein we describe in detail several examples of selective deoxygenation of C_{19}-diterpenoid alkaloids.

Deoxygenation of delphisine (**12**) and 14-acetyldelcosine (**13**): Our initial attempts to prepare the thioacyl intermediate **14** from delphisine according to the above mentioned procedures were unsuccessful. Thus, no reaction was observed when **12** was treated with CS_2 and CH_3I in NaOH solution. On the other hand, use of NaH as a base resulted in the transesterification of the secondary acetate and partial hydrolysis of the tertiary acetate to give products such as **15** and **16** in poor yields. In an alternative approach treatment of delphisine (**12**) with $SOCl_2$ gave 1,2-pyrodelphisine (**17**) and the chloro derivative **18**. Compound **17** was the only

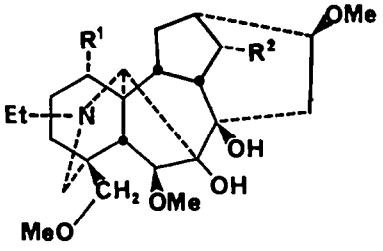
product when the reaction was carried out on a smaller scale. Catalytic hydrogenation of 17 afforded 1-deoxydelphisine (19) in 80% yield. 1-Deoxydelphisine has not been described previously and was characterized by physical and spectral data (see Experimental). The significant feature in the ^{13}C NMR spectrum is that the signal at 73.1 ppm of delphisine is replaced by the signal at 37.3 ppm (C-1) in 19. The C-2 also showed an upfield shift (Δ 8.6 ppm) as a result of removal of the hydroxyl group.

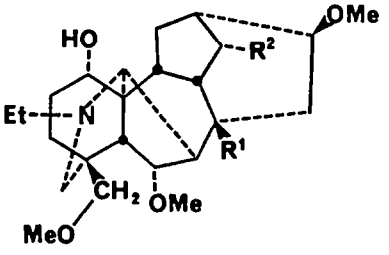


1 R^1 = OAc; R^2 = OH
2 R^1 = OH; R^2 = H
5 R^1 = OH; R^2 = Cl
6 R^1 = OAc; R^2 = H
7 R^1 = R^2 = OH
8 R^1 = OCS(SMe); R^2 = OH
9 R^1 = OCS(SMe); R^2 = H
10 R^1 = H; R^2 = OH
11 R^1 = R^2 = H



12 R = OH
14 R = OCS(SMe)
18 R = Cl
19 R = H
20 R = OCSO-





13 R^1 = OH; R^2 = OAc
21 R^1 = OCS-N ; R^2 = OAc
22 R^1 = H; R^2 = OAc
23 R^1 = H; R^2 = OH

15 R^1 = OAc; R^2 = OCS(SMe)
16 R^1 = OH; R^2 = OCS(SMe)

The thiocarbonyl reagents, phenyl chlorothionocarbonate[6] and *N-N'*-thiocarbonyldiimidazole (TCDI)[7], have been reported for the preparion of thioacyl intermediates in high yields under mild acylation conditions. Reductive cleavage of the thioesters with *n*-Bu_3SnH[5] gives deoxy compounds in excellent yield. In our hands these reagents have proven suitable for reduction of substrates bearing ester functions, such as delphisine. Thus, treatment of delphisine (12) with phenyl chlorothionocarbonate in the presence of 4-dimethylaminopyridine gave the thionocarbonate 20 in 80% yield. The thionocarbonate 20 was identified through its ^1H and ^{13}C NMR spectral data. The ^{13}C NMR spectrum showed a low-field signal (87.7 ppm) for the carbon bearing

Table 1. Deoxygenation of C_{19} Diterpenoid Alkaloids

Substrate	Intermediate	Yield (%)*	Product	Yield*(%)
1	3	98	6	90
2	9	84	11	78
7	8	97	10	74
12	17	63	19	80
12	20	80	19	97
13	21	98	22	87
24	26	96	27	84
25	28	89	29	85
30	31	97	32	60
	31		34	84
37	39	97	35	92

*Isolated yield

the thionosubstituent and a thiocarbonyl absorption at 193.4 ppm. Accordingly the ^1H NMR spectrum showed a downfield signal (δ 5.36) for the proton attached to the carbon bearing the thiono substituent. Reduction of **20** with *n*-Bu_3SnH in refluxing benzene gave 1-deoxydelphisine (**19**) which was identical in all respects with the substance prepared by the catalytic hydrogenation of **17**.

Heating 14-acetyldelcosine (**13**) with *N*-*N*'-thiocarbonyldiimidazole (TCDI) in refluxing 1,2-dichloroethane gave the imidazolide **21** in 98% yield. This compound was characterized by the presence of the thiocarbonyl (183.1 ppm) and three imidazolyl protons (δ 8.31, 7.62 and 7.06) in the ^{13}C and ^1H NMR spectra, respectively. Reduction of **21** with *n*-Bu_3SnH afforded 14-acetyl-1-deoxydelcosine (**22**) in 87% yield. Alkaline hydrolysis of **22** furnished 1-deoxydelcosine (**23**) in 92% yield. Alkaloids **22** and **23** are new and were characterized through spectral data (see Experimental).

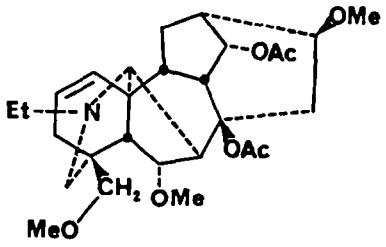
Deoxygenation of aconitine (**24**) and yunaconitine (**25**): Treatment of aconitine (**24**) with TCDI gave 3-*O*-(imidazolylthiocarbonyl)-aconitine (**26**) in 96% yield. Even though aconitine has secondary OH groups at C-3 and C-15, the ester was introduced only at C-3. This was apparent from the downfield shift of C-3 (Δ 11.3 ppm) and characteristic upfield shift of C-18 (Δ5.6 ppm) in the ^{13}C NMR spectrum of **26** when compared with that of aconitine. Reduction of **26** with *n*-Bu_3SnH furnished 3-deoxyaconitine (**27**) in 84% yield. The synthetic alkaloid was identical with that of the natural substance in all respects (IR, ^1H and ^{13}C NMR).[8,9] Application of an analogous deoxygenation sequence to yunaconitine (**25**) gave crassicauline A (**28**) *via* the intermediate **29**. The synthetic and natural crassicauline A showed identical m.p., IR, ^1H and ^{13}C NMR data.[10,11]

Deoxygenation of 14-acetyldictyocarpine (**30**): We have reported an unusual elimination product **4** when the chloro-derivative **3** was reduced with $LiAlH_4$.[4] In order to confirm the consistency of this unique example, we have selected the congener alkaloid **30** for deoxygenation. Reaction of **30** with $SOCl_2$ produced 14-acetyl-10-chloro-10-dehydroxydictyocarpine (**31**). $LiAlH_4$ reduction of **31** gave the elimination product **32** in 60% yield. Contrary to the previous example[4] the diol **33**, analogous to delpheline which was the major product, was not detected. The structure **32** for the elimination product was assigned by analogy with **4**.[4] A possible mechanism of formation of **4** and **32** from **3** and **31**, respectively, is as shown below. As expected, reduction of **31** with *n*-Bu_3SnH gave 14-acetyl-10-deoxydictyocarpine (**34**).

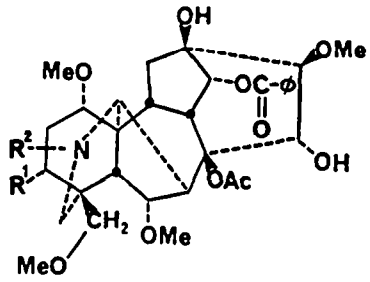
Partial synthesis of hypaconitine (**35**) from aconitine (**24**): Several years ago Marion[12] reported the synthesis of hypaconitine (**35**) from aconitine (**24**) in an overall yield of 7.7% by the reaction sequence outlined below:

Aconitine (24) $\xrightarrow[KMnO_4]{\text{aq. acetone}}$ *N*-Desethylaconitine (36) 22% $\xrightarrow[CaCO_3,CH_3I]{MeOH\text{-}Et_2O}$ Mesaconitine (37) 94% $\xrightarrow{SOCl_2}$ Anhydromesaconitine (38) 91.5% $\xrightarrow[H_2/PtO_2/EtOH]{}$ Hypaconitine (35) 40.5%

The present synthesis involving a high-yield deoxygenation sequence, furnishes **35** in an overall yield of 49%. The yield of *N*-desethylaconitine (**36**) was improved to 61% with alkaline $KMnO_4$ instead of neutral $KMnO_4$ solution. Methylation of **36** with CH_3I gave mesaconitine (**37**) in 90% yield. Reaction of **37** with TCDI gave **39** (97%), which upon reduction with *n*-Bu_3SnH furnished hypaconitine (**35**) in 92% yield.



17



24 R^1 = OH; R^2 = Et

26 R^1 = OCS-(N-heterocycle); R^2 = Et

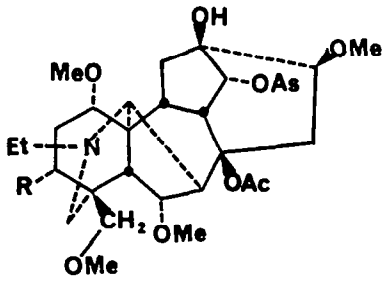
27 R^1 = H; R^2 = Et

35 R^1 = H; R^2 = Me

36 R^1 = OH; R^2 = H

37 R^1 = OH; R^2 = Me

39 R^1 = OCS-(N-heterocycle); R^2 = Me

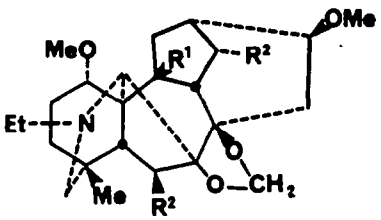


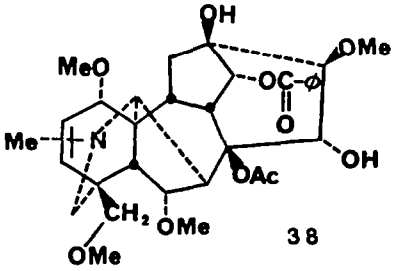
As = CO-(C$_6$H$_4$)-OMe

25 R = OH

28 R = H

29 R = OCS-(N-heterocycle)



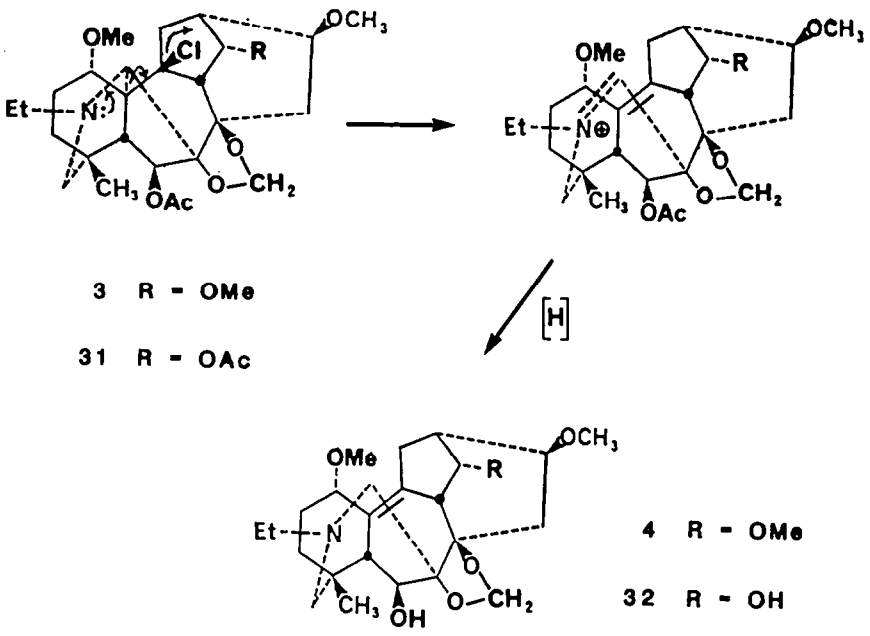


38

30 R^1 = OH; R^2 = OAc

33 R^1 = H; R^2 = OH

34 R^1 = H; R^2 = OAc



3 R = OMe

31 R = OAc

4 R = OMe

32 R = OH

EXPERIMENTAL

General Experimental Procedures: Melting points are corrected and were determined on a Thomas-Kofler hot stage equipped with a microscope and polarizer. Spectroscopic measurements were carried out on the following instruments: IR: Perkin Elmer Model 1420 Spectrophotometer; ^{1}H NMR: JEOL FT Model FX-90Q; ^{13}C NMR: JEOL FT Model FX-90Q at 22.49 MHz and Model FX-60 at 15.03 MHz; MS: Finnegan Quadrupole 4023 Spectrometer. Centrifugal chromatography[13,14] was carried out on a "Chromatotron" Model 7924T (Harrison Research, Palo Alto, CA, U.S.A.) with 1 mm adsorbent thickness. All the substrates used in this study were isolated and carefully identified by ^{1}H and ^{13}C NMR spectroscopy.

10-Chloro-10-dehydroxydeltaline (3): Deltaline (1) (238 mg) in 10 ml of dry benzene was stirred with 1.5 ml of freshly distilled $SOCl_2$ at room temperature for 20 h. Benzene and excess $SOCl_2$ were evaporated *in vacuo* and the product was purified by centrifugal chromatography (basic Al_2O_3) to give 3 in 98% yield. M.p. 171-172°C; $[\alpha]_D^{25}$ -40.7° (c 0.16, $CHCl_3$); EIMS: m/z 525 (M^+, $C_{27}H_{40}NO_7{}^{35}Cl$) and 527 ($M^+$, $C_{27}H_{40}NO_7{}^{37}Cl$).[4]

10-Deoxydeltaline (6): To a refluxing solution of 3 (79 mg) in 6 ml of dry benzene under N_2 was added dropwise 294 mg of *n*-Bu_3SnH in 1 ml of benzene. After being refluxed for 24 h, the product was purified by centrifugal chromatography on basic Al_2O_3 and silica rotors to afford 10-deoxydeltaline (6, 90%). M.p. 124-126°C; $[\alpha]_D^{27}$ -31.7° (c 0.37, EtOH); EIMS: m/z 491 (M^+, $C_{27}H_{41}NO_7$).[4]

Delpheline 2 and 4: To a refluxing solution of 3 (34 mg) in 5 ml of anhydrous ether under N_2 was added an ethereal solution of $LiAlH_4$ (55 mg). After 4 h, excess $LiAlH_4$ was decomposed with ether and water. The mixture was diluted with 60 ml of CH_2Cl_2. Filtration and removal of solvent *in vacuo* and subsequent purification of the resulting residue by centrifugal chromatography (basic Al_2O_3) gave delpheline (2) (23 mg, 80%) and 4 (2.5 mg, 9%). 4: m.p. 214-216°C; $[\alpha]_D^{27}$ -6.3° (c 0.27, $CHCl_3$); EIMS: m/z 449 (M^+, $C_{25}H_{39}NO_6$).[4]

Compound 4 and 5: Compound 3 (62 mg) obtained from $SOCl_2$ reaction (without purification) was reduced with $LiAlH_4$ as detailed above to yield 32 mg of 4 (60%) and 9 mg of 5 (16%). 5: m.p. 195.5-197°C (decom.); $[\alpha]_D^{25}$ -13.6° (c 0.35, $CHCl_3$); EIMS: m/z 483 (M^+, $C_{25}H_{38}NO_6{}^{35}Cl$) and 485 ($M^+$, $C_{25}H_{38}NO_6{}^{37}Cl$).[4]

S-Methyl-6-*O*-deltaminedithiocarbonate (8): A mixture[15] of deltamine (7) (100 mg), 1.5 ml of DMSO, 1 ml of CS_2 and 0.4 ml of 5N NaOH was stirred at 0°C for 45 min. To this mixture was added dropwise 1 ml of CH_3I. After stirring for 2 h at 0°C, the mixture was quenched with 20 ml of water and extracted with $CHCl_3$ (3 x 25 ml). Removal of $CHCl_3$ left a yellow residue, which upon purification by centrifugal chromatography (basic Al_2O_3) furnished 8 (116 mg, 97%). Amorphous; $[\alpha]_D^{25}$ -19.8° (c 0.28, $CHCl_3$); EIMS: m/z 555 (M^+, $C_{27}H_{41}NO_7S_2$).[4]

6-Deoxydeltamine (10): Reduction of 8 (94 mg) with *n*-Bu_3SnH[5] in refluxing benzene for 6 h and usual purification gave 10 (58 mg, 74%) and unreacted 8 (14 mg, 15%). 10: m.p. 173-175°C; $[\alpha]_D^{25}$ -31.2° (c 0.18, $CHCl_3$); EIMS: m/z 449 (M^+, $C_{25}H_{39}NO_6$).[4]

S-Methyl-6-*O*-delphelinedithiocarbonate (9). Method A: Delpheline (2) (39 mg) under the reaction conditions detailed for 7 gave 9 (6.2 mg, 13%) and unreacted 2 (30 mg, 77%).

Method B:[5] Delpheline (2) (82 mg) in 10 ml of dry THF and 5 mg of imidazole was stirred with 195 mg of NaH (50% dispersion) for 2 h at room temperature under N_2. CS_2 (2 ml) and CH_3I (1.5 ml) was added at an interval of 30 min. The mixture was quenched with 40 ml of water and extracted with $CHCl_3$ (3 x 40 ml). Evaporation of solvent and purification as usual furnished 83 mg of **9** (84%). Amorphous; $[\alpha]_D^{27}$ -13.3°C (c 0.51, $CHCl_3$); EIMS: m/z 508 (M^+ -31, $C_{27}H_{41}NO_6S_2$).[4]

6-Deoxydelpheline (11): Reduction of **9** (64 mg) as detailed for **8** for 24 h gave after usual purification 48 mg of **11** (78%). M.p. 119.5-120.5°C; $[\alpha]_D^{28}$ -40.5 (c 0.64, $CHCl_3$); EIMS: m/z 433 (M^+, $C_{25}H_{39}NO_5$).[4]

S-Methyl-1-*O*-delphisinedithiocarbonate (14). Method A: Delphisine (12) (16 mg) under the reaction conditions reported for **7** gave only the starting material. Method B: Delphisine (31 mg) under the reaction conditions as detailed for **2** (Method B) gave a mixture of two compounds. Purification by preparative TLC (silica, 1 mm, $CHCl_3$-MeOH, 15:1) gave 3 mg of **15** and 5 mg of **16** in amorphous forms. **15**: ^1H NMR ($CDCl_3$): δ 5.60 (t, J = 4.5 Hz, H-14β), 4.06 (dd, J = 7,1 Hz, H-6β), 3.32 (6H), 3.29 (3H) (each s, OMe), 2.55 (s, S-Me), 2.28 (s, OAc) and 1.15 (t, J = 7 Hz, *N*-CH_2-CH_3). **16**: ^1H NMR ($CDCl_3$): δ 5.64 (t, J = 4.5 Hz, H-14β), 4.11 (dd, J = 7,1 Hz, H-6β), 3.35, 3.33 and 3.29 (each s, OMe), 2.59 (s, S-Me) and 1.15 (t, J = 7 Hz, *N*-CH_2-CH_3).

1,2-Pyrodelphisine (17): A mixture of delphisine (12) (122 mg), 5 ml of dry benzene and 1.5 ml of freshly distilled $SOCl_2$ was stirred at room temperature for 3 days. Benzene and $SOCl_2$ were evaporated *in vacuo* and the resulting residue was purified by centrifugal chromatography (basic Al_2O_3) to give **17** (77 mg, 65%) and **18** slightly contaminatd with **17** (38 mg). **17**: Amorphous; $[\alpha]_D^{26}$ -16.2° (c 0.46, $CHCl_3$); IR (nujol): 1735 cm^{-1}; EIMS: m/z 503 (M^+, $C_{28}H_{41}NO_7$) and ^1H NMR ($CDCl_3$): δ 5.97 (ddd, J = 10.5, 4.4, 2.6 Hz, H-2), 5.34 (dbr, J = 10.5 Hz, H-1), 4.85 (t, J = 4.5 Hz, H-14β), 4.11 (dbr, J = 7 Hz, H-6β), 3.30, 3.29 and 3.26 (each s, OMe), 2.04 and 1.98 (each s, OAc) and 1.06 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2. **18**: m.p. 157-161°C; EIMS: m/z 504 (M^+ -Cl) and ^1H NMR ($CDCl_3$): δ 4.87 (t, J = 4.5 Hz, H-14β), 4.48 (m, H-1β), 4.01 (dd, J = 6,1 Hz, H-6β), 3.32, 3.31 and 3.27 (each s, OMe), 2.05 and 1.99 (each s, OAc) and 1.06 (t, J = 7 Hz, *N*-CH_2-CH_3).

1-Deoxydelphisine (19): Compound **17** (30 mg) in 10 ml of absolute EtOH was shaken with 10% Pd/C (55 mg) in an atmosphere of H_2 (20 lbs) for 4 h. Filtration and removal of solvent *in vacuo* gave a residue which upon purification by centrifugal chromatography (basic Al_2O_3) furnished **19** (24 mg, 80%). Amorphous; $[\alpha]_D^{27.5}$ -4.1° (c 0.63, $CHCl_3$); IR (nujol): 1740 cm^{-1}; EIMS: m/z 505 (M^+, $C_{28}N_{43}NO_7$) and ^1H NMR ($CDCl_3$): δ 4.82 (t, J = 4.5 Hz, H-14β), 4.06 dbr (J = 7 Hz, H-6β), 3.32, 3.31 and 3.26 (each s, OMe), 2.05 and 1.98 (each s, OAc) and 1.07 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

Phenyl-1-*O*-delphisinethionocarbonate (20): A mixture of delphisine (12) (24 mg), 2 ml of CH_3CN, 7 mg of 4-dimethylaminopyridine and 0.1 ml of phenyl chlorothionocarbonate was stirred at room temperature for 16 h. TLC indicated a small percentage of unreacted **12**. An additional 0.1 ml of the acylating agent was added and after being stirred for 24 h, the TLC profile remained the same. The mixture was then kept at 55°C for 2 h. No change in the product composition was observed. In another experiment a mixture of delphisine (101 mg), 7 ml of CH_3CN, 37 mg of 4-dimethylaminopyridine and 0.4 ml of phenyl chlorothionocarbonate was stirred at room temperature for 26 h. The above two reaction mixtures were combined and purified by centrifugal chromatography (basic Al_2O_3) to furnish **20** (125 mg, 80%) and unreacted **12** (21 mg, 17%). **20**: m.p. 150-151°C; $[\alpha]_D^{29.5}$ -42.3° (c, 0.699, $CHCl_3$); IR (nujol): 1735 cm^{-1}; EIMS: m/z 657 (M^+-HO(CS)OPh) and ^1H NMR ($CDCl_3$): δ 7.47-7.30 (m, 3H), 7.07 m (2H) (aromatic protons), 5.36 (dd, J = 10.5, 6.6 Hz, H-1β), 4.78 (t, J = 4.5 Hz, H-14β), 4.09 (dbr, J = 7 Hz, H-6β), 3.31, 3.30 and 3.27 (each s, OMe), 2.04 and 1.99 (each s, OAc) and 1.08 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

1-Deoxydelphisine (19): A solution of **20** (44 mg) in 4 ml of dry benzene was refluxed with 6 mg of AIBN and 247 mg of *n*-Bu_3SnH for 4 h under N_2. Usual workup and purification yielded **19** (33 mg, 97%). The ^1H and ^{13}C NMR spectra of this material were identical with those of **19** prepared from catalytic hydrogenation of **17**.

14-Acetyl-1-*O*-(imidazolylthiocarbonyl)-delcosine (21): A solution of 14-acetyldelcosine (13) (92 mg) in 4 ml of 1,2-dichloroethane was stirred with 34 mg of *N*-*N'*-thiocarbonyldiimidazole (TCDI) at 80°C under N_2 for 2.5 h. Purification of the product by centrifugal chromatography (basic Al_2O_3) yielded **21** (110 mg, 98%). Amorphous; $[\alpha]_D^{26}$ +13.8° (c, 0.21, $CHCl_3$); IR (KBr): 3600, 1735 cm^{-1}; EIMS: m/z 477 (M^+ -$C_4H_4N_2OS$) and ^1H NMR ($CDCl_3$): δ 8.31, 7.62 and 7.06 (each br, imidazolyl protons), 5.53 (t, J = 8.8 Hz, H-1β), 4.71 (t, J = 4.5 Hz, H-14β), 3.44, 3.31 and 3.22 (each s, OMe), 2.02 (s, OAc) and 1.12 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

14-Acetyl-1-deoxydelcosine (22): Reductive cleavage of **21** (97 mg) with *n*-Bu_3SnH under usual conditions for 3 h furnished **22** (71 mg, 87%), m.p. 51-53°C; $[\alpha]_D^{24}$ +25.7° (c 0.285, $CHCl_3$); IR (nujol): 3460, 3390 and 1740 cm^{-1}; EIMS: m/z 479 (M^+, $C_{26}H_{41}NO_7$) and ^1H NMR ($CDCl_3$): 4.73 (t, J = 4.5 Hz, H-14β), 3.34, 3.27 and 3.26 (each s, OMe), 2.00 (s, OAc), 1.00 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

1-Deoxydelcosine (23): A mixture of **22** (52 mg), 2 ml of MeOH and 60 mg of K_2CO_3 in 1 ml of water was stirrd at room temperature under N_2 for 44 h. Workup and usual purification furnished **23** (44 mg, 92%), m.p. 161-162°C; $[\alpha]_D^{25}$ +42° (c 0.22, $CHCl_3$); IR (KBr): 3520, 3420 and 3380 cm^{-1}; EIMS: m/z 437 (M^+, $C_{24}H_{39}NO_6$) and ^1H NMR ($CDCl_3$): δ 4.07 (m, H-14β), 3.38, 3.34 and 3.30

(each s, OMe), 1.03 (t, J = 7 Hz, *N*-CH_2-CH_3), (C_6D_6): δ 4.09 (m, H-14β), 3.08, 2.99 and 2.96 (each s, OMe), 1.11 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

3-*O*-(Imidazolylthiocarbonyl)-aconitine (26): The title compound was prepared from aconitine (139 mg) in a manner analogous to the previous procedure in a yield of 96%, m.p. 209.5-211°C; $[\alpha]_D^{29}$ +16.2° (c 0.455, $CHCl_3$); IR (nujol): 3450 and 1720 cm^{-1}; EIMS: m/z 628 (M^+ - $C_4H_3N_2OS$) and ^1H NMR ($CDCl_3$): δ 8.33, 7.63 and 7.06 (each br, imidazolyl protons), 8.05 (m, 2H) and 7.65-7.43 (m, 3H) (benzoyl protons), 5.66 (dd, J = 11.7, 6.6 Hz, H-3β), 4.90 (d, J = 5 Hz, H-14β), 4.49 (d, J = 5 Hz, H-15β), 3.76, 3.29, 3.22 and 3.17 (each s, OMe), 1.41 (s, OAc) and 1.15 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

3-Deoxyaconitine (27): Reduction of 94 mg of **26** with *n*-Bu_3SnH according to the normal procedure and usual purification gave **27** (66 mg, 84%). The synthetic alkaloid was identical with that of the natural substance in all respects (m.p., IR, ^1H and ^{13}C NMR).[8,9]

3-*O*-(Imidazolylthiocarbonyl)-yunaconitine (29): A mixture of yunaconitine (**25**) (71 mg), 4 ml of 1,2-dichloroethane and 70 mg of TCDI was stirred as described previously. The usual workup gave 74 mg of **29** (89%), m.p. 173-176°C; $[\alpha]_D^{25}$ +26.6° (c 0.305, $CHCl_3$); IR (KBr): 3500 br, 1730 and 1710 cm^{-1}; EIMS: m/z 642 (M^+ - $C_4H_3N_2OS$) and ^1H NMR ($CDCl_3$): δ 8.28, 7.57 and 7.00 (each br, imidazolyl protons), 7.97 and 6.88 (each 2H, dbr, J = 8.8 Hz, anisoyl protons), 5.59 (dd, J = 11.7, 6.6 Hz, H-3β), 4.85 (d, J = 5 Hz, H-14β), 3.50, 3.22, 3.15 and 3.10 (each s, OMe), 1.31 (s, OAc), 1.10 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

Crassicauline A (28): Compound **29** (68 mg) was reduced according to the general procedure to yield 50 mg of crassicauline A (85%). The synthetic alkaloid had identical m.p., ^1H and ^{13}C NMR with those of the natural substance.[10,11]

14-Acetyl-10-chloro-10-dehydroxydictyocarpine (31): A solution of 14-acetyldictyocarpine (**30**) (107 mg) in 5 ml of dry benzene was stirred with 1.5 ml of $SOCl_2$ for 42 h. The usual workup and purification afforded **31** (111 mg). Amorphous; $[\alpha]_D^{21}$ -43.5° (c 0.348, $CHCl_3$); IR (nujol): 1740 and 1715 cm^{-1}; EIMS: m/z 553 (M^+, $C_{28}H_{40}NO_8{}^{35}Cl$) and 555 ($M^+$, $C_{28}H_{40}NO_8{}^{37}Cl$) and ^1H NMR ($CDCl_3$): δ 5.43 (br, H-6α), 5.43 (t, J = 4.5 Hz, H-14β), 3.28 (s, 6H, OMe), 4.97 and 4.88 (each s, OCH_2O), 2.07 (s, OAc), 1.06 (t, J = 7 Hz, *N*-CH_2-CH_3) and 0.90 (s, CH_3-18). The ^{13}C NMR data are in Table 2.

14-Acetyl-10-deoxydictyocarpine (34): Compound **31** (105 mg) was reduced with *n*-Bu_3SnH according to the general procedure to yield **34** (82 mg, 84%). Amorphous; $[\alpha]_D^{25}$ -60.6° (c 0.459, $CHCl_3$); IR (nujol): 1740 cm^{-1}; EIMS: m/z 519 (M^+, $C_{28}H_{41}NO_8$) and ^1H NMR ($CDCl_3$): δ 5.31 (br, H-6α), 4.77 (t, J = 4.5 Hz, H-14β), 4.86 and 4.81 (each s, OCH_2O), 3.27 and 3.22 (each s, OMe), 2.00 (s, 6H, OAc), 1.00 (t, J = 7 Hz, *N*-CH_2-CH_3) and 0.80 (s, CH_3-18). The ^{13}C NMR data are in Table 2.

Compound 32[16]: A solution of **31** (83 mg) in 20 ml of anhydrous ether was refluxed with 100 mg of $LiAlH_4$ in the usual way. Normal workup gave 42 mg of **32** (64%). Amorphous; $[\alpha]_D^{28}$ +35.3° (c 0.455, $CHCl_3$); IR (nujol): 3450 cm^{-1}; EIMS: m/z 435 (M^+, $C_{24}H_{37}NO_6$) and ^1H NMR ($CDCl_3$): δ 5.16 and 4.79 (each s, OCH_2O), 4.82 (br, H-6α), 3.40 and 3.22 (each s, OMe), 1.14 (s, CH_3-18) and 0.97 (t, J = 7 Hz, *N*-CH_2-CH_3). The ^{13}C NMR data are in Table 2.

Synthesis of hypaconitine (35) from aconitine (24): *N*-desethylaconitine (36): To a solution of aconitine (297 mg) in 30 ml of acetone was added 400 mg of $KMnO_4$ in 15 ml of water and 250 mg of K_2CO_3 in 2 ml of water at room temperature. After 30 min acetone was evaporated *in vacuo* and MnO_2 was decomposed with 15 ml of ice-cold 1.5% H_2SO_4 and 400 mg of $NaHSO_3$ in 10 ml of water. The aqueous solution was extracted with $CHCl_3$ (3 x 40 ml). Evaporation of $CHCl_3$ left a residue (72 mg) which showed several spots on TLC. The remaining aqueous solution was cooled, basified with solid Na_2CO_3 to pH 8.5 and extracted with $CHCl_3$ (5 x 40 ml). Evaporation of $CHCl_3$ and usual purification of the resulting residue gave **36** (174 mg, 61%), m.p. 175-178°C; ^1H NMR ($CDCl_3$): δ 8.02 (m, 2H) and 7.60-7.40 (m, 3H) (benzoyl protons), 4.87 (d, J = 5 Hz, H-14), 3.72, 3.29, 3.28 and 3.15 (each s, OMe), 1.35 (s, OAc). The ^{13}C NMR data are in Table 2.

Mesaconitine (37): A mixture of **36** (114 mg) in 5 ml of MeOH-ether (1:1), 150 mg of $CaCO_3$ and 0.4 ml of freshly distilled CH_3I was refluxed for 2 h. Purification of the product by centrifugal chromatography (basic Al_2O_3) gave 105 mg of **37** (90%), m.p. 202-204°C. The synthetic material was identical (IR, ^1H and ^{13}C NMR) with the natural product.[17,18]

3-*O*-(Imidazolylthiocarbonyl)-mesaconitine (39): The title compound **39** was prepared from **37** (74 mg) in the usual manner in a yield of 97%, m.p. 195-197.5°C; $[\alpha]_D^{26}$ +14.2° (c 0.15, $CHCl_3$); IR (KBr): 3460 br and 1720 cm^{-1}; EIMS: m/z 614 (M^+ - $C_4H_3N_2OS$) and ^1H NMR ($CDCl_3$): δ 8.34, 7.62 and 7.05 (each br, imidazolyl protons), 8.04 (m, 2H) and 7.65-7.42 (m, 3H) (benzoyl protons), 5.64 (dd, J = 11.7, 6.6 Hz, H-3β), 4.90 (d, J = 5 Hz, H-14β), 4.49 (d, J = 5 Hz, H-15β), 3.75, 3.31, 3.21 and 3.15 (each s, OMe), 2.41 (s, *N*-CH_3) and 1.40 (s, OAc). The ^{13}C NMR data are in Table 2.

Hypaconitine (35): This compound was prepared from **39** in the usual manner in a yield of 92%, m.p. 185-187°C; $[\alpha]_D^{26}$ +25° (c 0.205, $CHCl_3$). This substance was identical (IR, ^1H and ^{13}C NMR) with the natural hypaconitine.[19]

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Table 2. ^{13}C NMR ($COCl_3$) spectra of 17, 19, 20, 21, 22, 23, 26, 29, 31, 32, 34, 36 and 39

Carbon	17	19	20	21	22	23a	26	29	31	32	34	36	39
1	125.3b	37.3	89.3	87.7	35.0	35.6	82.0	82.1	78.4	76.9	82.0	81.6	82.0
2	130.4b	20.9	26.4	26.0	20.5	21.2	30.5	30.6	27.0	21.8	26.7	34.9	30.6
3	38.0	31.4	34.8	32.1	31.6	32.1	81.3	81.2	36.3	30.8	36.5	71.0	81.6
4	38.5	39.2	39.0	38.2	38.1	38.6	42.9	43.3	33.8	35.8	33.7	43.8	43.4
5	46.2	48.9	49.8	50.1	45.9	46.1	45.7	46.6	52.2	48.1	55.5	51.4	45.3
6	83.4	84.0	83.2	90.0	90.9	91.3	83.4	83.2	78.4	71.6	78.1	83.4	83.4
7	47.3	48.6	49.4	88.6	88.2	89.0	45.3	45.0	91.2	87.6	91.6	43.6	44.4
8	86.2	86.1	85.4	77.2	78.1	78.0	91.6	85.2	83.4	83.5	82.9	91.6	91.6
9	42.8	44.8	44.4	45.0	48.9	49.4	44.4	48.8	51.6	42.2	47.6	47.3	44.6
10	41.4	43.6	43.7	42.7	42.9	46.5	40.3	40.3	81.5	131.5b	39.3	41.0	40.6
11	48.9	46.6	49.8	48.5	45.9	45.7	49.6	49.8	57.4	136.1b	50.2	49.4	49.8
12	30.8	30.4	29.4	28.2	30.1	29.3	36.2	35.5	36.3	29.5	27.4	34.9	36.2
13	38.5	38.5	38.3	37.3	38.1	39.3	74.0	74.8	41.3	36.9	37.8	74.1	74.1
14	75.4	75.5	c	75.2	76.2	76.0	78.7	78.4	74.2	76.2	75.5	78.9	78.8
15	38.5	38.1	37.6	33.9	33.9	35.2	78.7	39.2	34.7	30.5	34.0	78.9	78.8
16	82.8	83.1	82.8	82.9	83.2	82.9	90.1	83.7	81.2	81.3	81.2	89.9	90.3
17	61.0	63.6	61.3	65.5	66.9	67.9	60.9	61.3	64.1	69.6	64.2	55.7	62.0
18	79.4	80.4	79.9	77.7	78.4	78.6	71.6	71.8	25.3	30.3	25.3	77.0	71.3
19	56.8	53.8	53.9	53.0	53.4	53.9	47.8	48.2	56.5	54.1	56.6	40.7	50.6
N-CH_2	48.6	48.9	48.9	51.2	50.8	51.3	48.8	49.3	50.1	63.7	50.0	-	-
CH_3	12.9	13.4	13.4	14.3	14.0	14.4	13.2	13.3	13.7	12.8	13.8	-	42.3
1'	-	-	-	-	-	-	56.2	56.2	55.4	55.3	55.2	55.7	56.6
6'	57.8	57.8	58.2	57.6	57.1	57.1	58.2	58.7	-	-	-	57.6	58.2
16'	56.5	56.5	56.5	56.3	56.0	55.9	60.6	58.0	56.0	56.6	56.0	61.0	60.9
18'	58.9	59.0	59.1	59.1	59.0	58.8	58.7	58.7	-	-	-	59.1	58.8
-OCH_2O-	-	-	-	-	-	-	-	-	93.8	90.1	93.3	-	-
C=O	170.5	170.6	170.8	171.4	171.3	-	172.2	169.7	171.1	-	171.4	171.9	172.3
CH_3	22.2	22.3	22.4	21.3	21.3	-	21.2	21.5	21.5	-	21.5	21.3	21.3
C=O	169.3	169.4	169.5	-	-	-	-	-	169.9	-	170.0	-	-
CH_3	21.1	21.1	21.2	-	-	-	-	-	21.2	-	21.3	-	-
C=O							165.9	166.0	-	-	-	165.9	166.1
							129.8	122.6	-	-	-	129.9	129.9
							129.5	131.6	-	-	-	129.5	129.7
							128.5	113.8	-	-	-	128.6	128.6
							133.1	163.5	-	-	-	133.1	133.3
X							(X=H)	55.4	-	-	-	(X=H)	(X=H)
							-	(X=OCH_3)	-	-	-	-	-

^{13}C NMR shifts for R of 20: 193.5 (CS), 153.3 (C-1"), 122.1 (C-2" and C-6"), 129.5 (C-3" and C-5") and 126.5 (C-4").
^{13}C NMR shifts for R^1 of 21: 183.1 (CS), 136.6 (C-2"), 131.1 and 117.7 (C-4" and C-5").
^{13}C NMR shifts for R^1 of 26: 183.1 (CS), 136.5 (C-2"), 130.6 and 117.6 (C-4" and C-5").
^{13}C NMR shifts for R of 29: 183.1 (CS), 136.6 (C-2"), 130.7 and 117.7 (C-4" and C-5").
^{13}C NMR shifts for R^1 of 39: 183.3 (CS), 136.7 (C-2"), 130.8 and 117.7 (C-4" and C-5").
a In C_6D_6.
b Assignments in any vertical column may be exchanged.
c Obscured by solvent signal.

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