Studies on *Aconitum* Species. XV. Deoxygenation Reaction of Aconitine Type Alkaloids

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Mesaconitine (1) in tetrahydrofuran reacted with sodium hydride, a catalytic amount of imidazole, carbon disulfide and methyl iodide at room temperature to give the di-*O*-(*S*-methyl)thiocarbonate (5). The reductive cleavage of 5 with tri-*n*-butyltin hydride gave isodelphinine (3) in a high yield of 83%. The exact same reactions of aconitine (2) and jesaconitine (6) gave penduline (4) and 3,13-dideoxyjesaconitine (7) in 85 and 86% yields, respectively. The same reactions in diethylether, in place of tetrahydrofuran, gave the 3-deoxy compounds, hypaconitine (9), deoxyaconitine (10) and deoxyjesaconitine (11), in yields of 87, 88 and 85%, respectively. When the same reaction as used for the syntheses of the 3,13-dideoxy compounds was done at refluxing temperature, 3,13,15-trideoxy compounds, that is, 3,13,15-trideoxymesaconitine, 3,13,15-trideoxyaconitine and 3,13,15-trideoxyjesaconitine, were obtained in yields of 83, 83 and 88%, respectively.

Keywords aconitine; deoxygenation; mesaconitine; jesaconitine; hypaconitine

Aconitine type alkaloids are highly oxygenated compounds and studies on the reactivity of their oxygen functions, as well as chemical correlations and structure–activity relationships, are important in order to understand their potent biological activities.

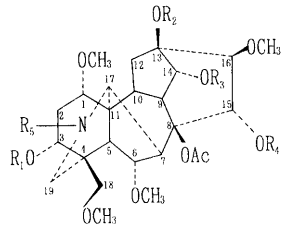
In 1988, Kulanthaivel and Pelletier[1] reported on the deoxygenation of several C19 diterpenoid alkaloids by using reductive cleavage of imidazolylthiocarbonylester with tri-*n*-butyltin hydride (*n*-Bu_3SnH). However, there have been few reports of deoxygenation reactions of aconitine-type alkaloids. We reported previously on the transformation of mesaconitine (**1**) and aconitine (**2**) into isodelphinine (**3**) and penduline (**4**), respectively, by deoxygenation of a C13-*O*-triflate by means of photochemical cleavage.[2–4] But the yield of the photochemical deoxygenation was low. Further, synthesis of compounds deoxygenated at C3, C13 and C15 is necessary to investigate the structure–activity relationships.

In this paper, we present high-yield deoxygenations at C3, C13 and C15 of aconitine-type alkaloids according to Barton and McCombic.[5]

Treatment of **1** with sodium hydride (NaH) in the presence of a catalytic amount of imidazole in tetrahydrofuran (THF), followed by the addition of carbon disulfide (CS_2) and methyl iodide (CH_3I) at room temperature, gave 3,13-di-*O*-(*S*-methyl)thiocarbonate (**5**) in 96% yield. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **5** revealed the presence of two *S*-methyl groups, at δ 2.57 and 2.46. The signal at δ 5.70 (1H, J = 12.7, 5.5 Hz) assignable to C3-β-H suggested the presence of a thiocarbonyloxy group at C3, and the ^{13}C-nuclear magnetic resonance (^{13}C-NMR) spectrum suggested the presence of another thiocarbonyloxy group at C13. The other signals and the mass (MS) spectrum were in agreement with the assigned structure. The reductive cleavage of **5** with *n*-Bu_3SnH gave **3** in a yield of 83%. This product was identical with an authentic sample[2] in terms of melting point and (NMR), infrared (IR), and MS spectra.

Application of this methodology to **2** gave **4** in a yield of 85%. This product was identical with an authentic sample[3] in terms of melting point and NMR, IR and MS spectra.

Jesaconitine (**6**) gave 3,13-dideoxyjesaconitine (**7**) by the above method in an 86% overall yield. Synthesis of the 3,13-dideoxy compound has not previously been reported,



1: R_1=H, R_2=H, R_3=Bz, R_4=H, R_5=CH_3
2: R_1=H, R_2=H, R_3=Bz, R_4=H, R_5=CH_2CH_3
5: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=Bz, R_4=H, R_5=CH_3
6: R_1=H, R_2=H, R_3=As, R_4=H, R_5=CH_2CH_3
8: R_1=$CS(SCH_3)$, R_2=H, R_3=Bz, R_4=H, R_5=CH_3
12: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=As, R_4=$CS(SCH_3)$, R_5=CH_2CH_3
14: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=Bz, R_4=H, R_5=CH_2CH_3
15: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=As, R_4=H, R_5=CH_2CH_3
16: R_1=$CS(SCH_3)$, R_2=H, R_3=Bz, R_4=H, R_5=CH_2CH_3
17: R_1=$CS(SCH_3)$, R_2=H, R_3=As, R_4=H, R_5=CH_2CH_3
18: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=Bz, R_4=$CS(SCH_3)$, R_5=CH_2CH_3
20: R_1=$CS(SCH_3)$, R_2=$CS(SCH_3)$, R_3=Bz, R_4=$CS(SCH_3)$, R_5=CH_3

Chart 1

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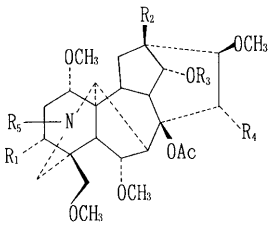

3: $R_1=H$, $R_2=H$, $R_3=Bz$, $R_4=OH$, $R_5=CH_3$
4: $R_1=H$, $R_2=H$, $R_3=Bz$, $R_4=OH$, $R_5=CH_2CH_3$
7: $R_1=H$, $R_2=H$, $R_3=As$, $R_4=OH$, $R_5=CH_2CH_3$
9: $R_1=H$, $R_2=OH$, $R_3=Bz$, $R_4=OH$, $R_5=CH_3$
10: $R_1=H$, $R_2=OH$, $R_3=Bz$, $R_4=OH$, $R_5=CH_2CH_3$
11: $R_1=H$, $R_2=OH$, $R_3=As$, $R_4=OH$, $R_5=CH_2CH_3$
13: $R_1=H$, $R_2=H$, $R_3=As$, $R_4=H$, $R_5=CH_2CH_3$
19: $R_1=H$, $R_2=H$, $R_3=Bz$, $R_4=H$, $R_5=CH_2CH_3$
21: $R_1=H$, $R_2=H$, $R_3=Bz$, $R_4=H$, $R_5=CH_3$

Chart 2

and its structure was determined by analysis of the spectral data (see Experimental).

These results indicate that the deoxygenation procedure leads to the production of 3,13-dideoxygenated derivatives in considerable yield. Meanwhile, deoxygenation at C3 alone could also be performed by using diethyl ether instead of THF as a reaction solvent to give the 3-*O*-(*S*-methyl)thiocarbonate (**8**) of **1** in a yield of 93%. The ^{1}H-NMR spectrum of **8** showed a signal at δ 5.72 (dd, $J=12.7$, 5.4 Hz) assignable to C3-β-H. Other NMR and MS signals of **8** were in agreement with the assigned structure. Reductive cleavage of **8** with *n*-Bu_3SnH gave hypaconitine (**9**) in a yield of 87%. This product was identical with an authentic sample in terms of melting point and NMR, IR and MS spectra.

Application of the deoxygenation sequence to **2** and **6** gave deoxyaconitine (**10**) and deoxyjesaconitine (**11**) in overall yields of 88 and 85%, respectively. These transformation processes occur in considerably superior yields to those previously obtained.[7]

Lastly, deoxygenation at C3, C13 and C15 was achieved as follows.

A hydroxy group at C15 in aconitine-type alkaloids generally resists acylation, since the hydroxy group is shielded by the aroyl group at C14 and the acetyl group at C8. A mixture of **6** with NaH and a catalytic amount of imidazole in THF was stirred for 0.5 h, followed by the addition of CS_2 and CH_3I at room temperature. The reaction mixture was refluxed for 1.5 h to give the 3,13,15-tri-*O*-(*S*-methyl)thiocarbonate (**12**) in a yield of 93%. In the ^{1}H-NMR spectrum of **12**, three *S*-methyl signals were apparent, at δ 2.46, 2.57 and 2.66. Three (*S*-methyl)thiocarbonyloxy groups were concluded to be present at C3, C13 and C15 on the basis of the other ^{1}H-NMR signals and ^{13}C-NMR chemical shifts (see Experimental).

Reductive cleavage of **12** with *n*-Bu_3SnH furnished 3,13,15-trideoxyjesaconitine (**13**) in a yield of 88%. Its melting point and spectral data were identical with those of foresaconitine isolated from *Aconitum forrestii*.[10,11] Application of the same deoxygenation sequence to **1** and **2** also gave the 3,13,15-trideoxycompounds (**21**, **19**).

Experimental

All melting points are uncorrected. IR spectra were taken in KBr disks with a JASCO FT/7000 spectrometer, and ultraviolet (UV) spectra were measured in EtOH solution with a Shimadzu UV 240 spectrophotometer. NMR spectra were measured in $CDCl_3$ solution with a JEOL GX-270, using tetramethylsilane as an internal standard. MS and high resolution mass spectra (HR-MS) were measured with a Hitachi M-2000 spectrometer. Column chromatography was performed on silica gel (0.06—0.200 mm, Merck). Preparative thin layer chromatography (TLC) was performed on Silica gel F_{254} (thickness 1 mm, Merck).

3,13-Di-*O*-(*S*-methyl)thiocarbonylmesaconitine (5) A mixture of **1** (50 mg), dry THF (6 ml), imidazole (1.3 mg) and NaH (116 mg) was stirred at 0 °C for 30 min, then CS_2 (1.2 ml) and CH_3I (0.9 ml) were added dropwise. The mixture was stirred for 1.5 h at room temperature, then the reaction was quenched with ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, then dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with Et_2O saturated with 28% ammonia water–hexane (3:2) as an eluting solvent to yield **5** (60 mg, 96%, amorphous). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1715 (C=O). ^{1}H-NMR δ: 1.41 (3H, s, $OCOCH_3$), 2.38 (3H, s, NCH_3), 2.46 (3H, s, SCH_3), 2.57 (3H, s, SCH_3), 3.18 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 5.24 (1H, d, $J=5.1$ Hz, C14-β-H), 5.70 (1H, dd, $J=12.7$, 5.5 Hz, C3-β-H), 7.43—8.09 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.8 and 19.4 (SCH_3 ×2), 81.9 (C3), 88.4 (C13), 213.9 and 214.9 (C=S ×2). MS *m/z*: 811 (M^+), 780 (M^+-OCH_3, base peak), 720 ($M^+-OCH_3-CH_3COOH$).

Isodelphinine (3) A solution of **5** (20 mg) in 1 ml of dry benzene was refluxed with *n*-Bu_3SnH (0.15 ml) in dry benzene (0.5 ml) for 2 h. The reaction mixture was concentrated *in vacuo*, then the residue was chromatographed on silica gel with Et_2O saturated with 28% ammonia water–hexane (4:1) as an eluting solvent and crystallized from Et_2O–hexane to give **3** (12.3 mg, 83% yield): mp 159—161 °C (lit.[4] 158—160 °C). IR ν_{max}^{KBr} cm^{-1}: 3500, 1720 and 1705 (C=O). ^{1}H-NMR δ: 1.43 (3H, s, $OCOCH_3$), 2.35 (3H, s, NCH_3), 3.18 (3H, s, OCH_3), 3.28 (6H, s, OCH_3), 3.52 (3H, s, OCH_3), 5.05 (1H, t, $J=4.3$ Hz, C14-β-H), 7.40—8.05 (5H, m, benzoyl group). MS *m/z*: 599 (M^+), 568 (M^+-OCH_3), 508 ($M^+-OCH_3-CH_3COOH$, base peak). The NMR and MS spectra of **3** were identical to those of an authentic sample.

3,13-Di-*O*-(*S*-methyl)thiocarbonylaconitine (14) Compound **14** was prepared from **2** in 93% yield in the same manner as used for the synthesis of compound **5**: amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3420 (OH), 1717 (C=O). ^{1}H-NMR δ: 1.12 (3H, t, $J=7.1$ Hz, NCH_2CH_3), 1.41 (3H, s, $OCOCH_3$), 2.45 (3H, s, SCH_3), 2.57 (3H, s, SCH_3), 3.18 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 5.24 (1H, d, $J=5.1$ Hz, C14-β-H), 5.71 (1H, dd, $J=12.3$, 5.5 Hz, C3-β-H), 7.45—8.07 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.9 and 19.3 (SCH_3 ×2), 81.6 (C3), 88.3 (C13), 213.9 and 215.0 (C=S ×2). MS *m/z*: 825 (M^+), 794 (M^+-OCH_3, base peak), 734 ($M^+-OCH_3-CH_3COOH$).

Penduline (4) Compound **4** was prepared from **14** in 91% yield in the same manner as used for the synthesis of compound **3**: mp 165—166 °C (acetone–hexane) (lit.[4] 166—167 °C). IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1715 (C=O). ^{1}H-NMR δ: 1.06 (3H, t, $J=7.0$ Hz, NCH_2CH_3), 1.43 (3H, s, $OCOCH_3$), 3.18 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.52 (3H, s, OCH_3), 5.05 (1H, t, $J=4.5$ Hz, C14-β-H), 7.38—8.14 (5H, m, benzoyl group). MS *m/z*: 613 (M^+), 582 (M^+-OCH_3), 522 ($M^+-OCH_3-CH_3COOH$, base peak). The NMR and MS spectra of **4** were identical to those of an authentic sample.

3,13-Di-*O*-(*S*-methyl)thiocarbonyljesaconitine (15) Compound **15** was prepared from **6** in 96% yield in the same manner as used for the synthesis of compound **5**: amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1717 (C=O). ^{1}H-NMR δ: 1.12 (3H, t, $J=7.1$ Hz, NCH_2CH_3), 1.42 (3H, s, $OCOCH_3$), 2.46 (3H, s, SCH_3), 2.56 (3H, s, SCH_3), 3.18 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.25 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.87 (3H, s, OCH_3 of anisoyl group), 5.21 (1H, d, $J=5.1$ Hz, C14-β-H), 5.71 (1H, dd, $J=12.7$, 7.8 Hz, C3-β-H), 6.94 and 8.03 (each 2H, d, $J=9.1$ Hz, anisoyl group). ^{13}C-NMR δ: 18.8 and 19.4 (SCH_3 ×2), 81.6 (C3), 88.4 (C13), 213.9 and 214.7 (C=S ×2). MS *m/z*: 855 (M^+), 824 (M^+-OCH_3, base peak), 764 ($M^+-OCH_3-CH_3COOH$).

3,13-Dideoxyjesaconitine (7) Compound **7** was prepared from **15** in 89% yield in the same manner as used for the synthesis of compound **3**: amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3425 (OH), 1711 (C=O). ^{1}H-NMR δ: 1.11 (3H, t, $J=7.1$ Hz, NCH_2CH_3), 1.42 (3H, s, $OCOCH_3$), 3.19 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.58 (3H, s, OCH_3), 3.87 (3H, s, OCH_3 of anisoyl group), 5.06 (1H, t, $J=4.5$ Hz, C14-β-H), 6.96 and 8.05 (each 2H, d, $J=9.0$ Hz, anisoyl group). ^{13}C-NMR δ: 85.1 (C1), 26.4 (C2), 34.8 (C3), 39.0 (C4), 49.0 (C5), 83.5 (C6), 44.3 (C7),

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92.0 (C8), 45.3 (C9), 38.6 (C10), 50.0 (C11), 28.8 (C12), 44.5 (C13), 76.1 (C14), 75.4 (C15), 89.3 (C16), 61.5 (C17), 80.3 (C18), 53.2 (C19), 49.1 (NCH_2CH_3), 13.5 (NCH_2CH_3), 56.1 (C1′), 57.7 (C6′), 57.9 (C16′), 59.0 (C18′), 55.3 ($COC_6H_4OCH_3$), 172.2 ($COCH_3$), 21.3 ($COCH_3$), 166.0 ($COC_6H_4OCH_3$), 122.4, 131.6, 113.5 and 163.2 ($COC_6H_4OCH_3$). MS *m/z*: 643 (M^+), 612 (M^+-OCH_3, base peak), 552 ($M^+-OCH_3-CH_3COOH$). *Anal.* Calcd for $C_{35}H_{49}NO_{10}$: C, 65.30; H, 7.67; N, 2.18. Found: C, 65.57; H, 7.84; N, 2.23.

3-*O*-(*S*-Methyl)thiocarbonylmesaconitine (8) A mixture of **1** (50 mg), dry Et_2O (6 ml), imidazole (3 mg) and NaH (116 mg) was stirred at 0 °C for 30 min, then CS_2 (1.2 ml) and CH_3I (0.9 ml) were added dropwise. The mixture was stirred for 2 h at room temperature, then the reaction was quenched with ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, then dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with Et_2O saturated with 28% ammonia water–hexane (3:2) as an eluting solvent to yield **8** (53 mg, 93%): amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3370 (OH), 1710 (C=O). ^{1}H-NMR δ: 1.40 (3H, s, $OCOCH_3$), 2.44 (3H, s, NCH_3), 2.57 (3H, s, SCH_3), 3.18 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.88 (1H, d, J=5.3 Hz, C14-β-H), 5.72 (1H, dd, J=12.7, 5.4 Hz, C3-β-H), 8.05—7.43 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.5 (SCH_3), 81.7 (C3), 214.9 (C=S). MS *m/z*: 721 (M^+), 690 (M^+-OCH_3, base peak), 630 ($M^+-OCH_3-CH_3COOH$).

Hypaconitine (9) A solution of **8** (20 mg) in 1 ml of dry benzene was refluxed with n-Bu_3SnH (0.15 ml) in dry benzene (0.5 ml) for 2 h. The reaction mixture was concentrated *in vacuo*, then the residue was chromatographed on silica gel with Et_2O saturated with 28% ammonia water–hexane (4:1) as an eluting solvent and crystallized from MeOH to give **9** (16 mg, 94% yield): mp 189—190 °C. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1730 (C=O). ^{1}H-NMR δ: 1.39 (3H, s, $OCOCH_3$), 2.35 (3H, s, NCH_3), 3.18 (3H, s, OCH_3), 3.33 (6H, s, $OCH_3\times2$), 3.75 (3H, s, OCH_3), 4.87 (1H, d, J=5.0 Hz, C14-β-H), 8.05—8.12 (5H, m, benzoyl group). MS *m/z*: 615 (M^+), 584 (M^+-OCH_3, base peak), 524 ($M^+-OCH_3-CH_3COOH$). *Anal.* Calcd for $C_{33}H_{45}NO_{10}$: C, 64.37; H, 7.37; N, 2.27. Found: C, 64.49; H, 7.42; N, 2.26. The NMR and MS spectra of **9** were identical to those of an authentic sample.

3-*O*-(*S*-Methyl)thiocarbonylaconitine (16) Compound **16** was prepared from **2** in 92% yield in the same manner as used for the synthesis of compound **8**: amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1725 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.39 (3H, s, $OCOCH_3$), 2.56 (3H, s, SCH_3), 3.19 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.88 (1H, d, J=4.9 Hz, C14-β-H), 5.71 (1H, dd, J=12.1, 6.8 Hz, C3-β-H), 7.4—8.02 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.7 (SCH_3), 81.6 (C3), 214.7 (C=S). MS *m/z*: 735 (M^+), 704 (M^+-OCH_3, base peak), 644 ($M^+-OCH_3-CH_3COOH$).

Deoxyaconitine (10) Compound **10** was prepared from **16** in 96% yield in the same manner as used for the synthesis of compound **9**: colorless needles (MeOH), mp 169.5—170.5 °C (lit.[6] 168—170 °C). IR ν_{max}^{KBr} cm^{-1}: 3550 (OH), 1730 and 1715 (C=O). ^{1}H-NMR δ: 1.07 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.37 (3H, s, $OCOCH_3$), 3.15 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.87 (1H, d, J=5.0 Hz, C14-β-H), 7.32—8.12 (5H, m, benzoyl group). MS *m/z*: 629 (M^+), 598 (M^+-OCH_3), 538 ($M^+-OCH_3-CH_3COOH$, base peak). *Anal.* Calcd for $C_{34}H_{47}NO_{10}$: C, 64.84; H, 7.52; N, 2.22. Found: C, 64.69; H, 7.69; N, 2.23. NMR and MS spectra of **10** were identical with those of an authentic sample reported by Takayama *et al.*[6]

3-*O*-(*S*-Methyl)thiocarbonyljesaconitine (17) Compound **17** was prepared from **6** in 92% yield in the same manner as used for the synthesis of compound **8**: amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1725 (C=O). ^{1}H-NMR δ: 1.11 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.39 (3H, s, $OCOCH_3$), 2.56 (3H, s, SCH_3), 3.18 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.87 (3H, s, OCH_3 of anisoyl group), 4.84 (1H, d, J=4.9 Hz, C14-β-H), 5.71 (1H, dd, J=12.7, 7.7 Hz, C3-β-H), 6.93 and 7.98 (each 2H, d, J=8.7 Hz, anisoyl group). ^{13}C-NMR δ: 18.8 (SCH_3), 81.7 (C3), 214.7 (C=S). MS *m/z*: 765 (M^+), 734 (M^+-OCH_3, base peak), 674 ($M^+-OCH_3-CH_3COOH$).

Deoxyjesaconitine (11) Compound **11** was prepared from **17** in 93% yield in the same manner as used for the synthesis of compound **9**: colorless needles (acetone), mp: 175—176 °C. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1715 and 1710 (C=O). ^{1}H-NMR δ: 1.08 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.43 (3H, s, $OCOCH_3$), 3.17 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.88 (3H, s, OCH_3 of anisoyl group), 4.83 (1H, d, J=5.0 Hz, C14-β-H), 6.92 and 7.97 (each 2H, d, J=8.0 Hz, anisoyl group). MS *m/z*: 659 (M^+), 628 (M^+-OCH_3, base peak), 568 ($M^+-OCH_3-CH_3COOH$). NMR and MS spectra of **11** were identical with those of an authentic sample.[7]

3,13,15-Tri-*O*-(*S*-methyl)thiocarbonyljesaconitine (12) A mixture of **6** (50 mg), dry THF (6 ml), imidazole (3 mg) and NaH (116 mg) was stirred at 0 °C for 30 min, then CS_2 (1.2 ml) and CH_3I (0.9 ml) were added dropwise. The mixture was refluxed for 1.5 h, then the reaction was quenched with ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, then dried over anhydrous sodium sulfate. The solvent was evaporated off and the residue was purified by column chromatography on silica gel with Et_2O saturated with 28% ammonia water–hexane (3:2) as an eluting solvent to yield **12** (65 mg, 93% yield): amorphous powder. IR ν_{max}^{KBr} cm^{-1}: 3450 (OH), 1715 (C=O). ^{1}H-NMR δ: 1.18 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.28 (3H, s, $OCOCH_3$), 2.46 (3H, s, SCH_3), 2.57 (3H, s, SCH_3), 2.66 (3H, s, SCH_3), 3.18, 3.19, 3.29, 3.38 (3H, s, OCH_3), 3.83 (3H, s, OCH_3 of anisoyl group), 4.18 (1H, d, J=5.8 Hz, C15-β-H), 5.30 (1H, d, J=5.4 Hz, C14-β-H), 5.73 (1H, dd, J=11.1, 7.4 Hz, C3-β-H), 6.95 and 8.21 (each 2H, d, J=9.1 Hz, anisoyl group). ^{13}C-NMR δ: 18.9, 19.4 and 19.7 ($SCH_3\times3$), 81.3 (C3), 88.2 (C13), 87.6 (C15), 214.0, 214.8 and 217.1 (C=S). MS *m/z*: 945 (M^+), 914 (M^+-OCH_3, base peak), 854 ($M^+-OCH_3-CH_3COOH$).

3,13,15-Trideoxyjesaconitine (13) A solution of **12** (30 mg) in dry benzene (1 ml) was refluxed with n-Bu_3SnH (0.2 ml) in dry benzene (0.5 ml) for 4 h. The reaction mixture was concentrated *in vacuo*, then the residue was chromatographed on silica gel with Et_2O saturated with 28% ammonia water–hexane (4:1) as an eluting solvent and crystallized from Et_2O–hexane to give **13** (18 mg, 88% yield), mp 151—152 °C (lit.[8] 153—154 °C). IR ν_{max}^{KBr} cm^{-1}: 1717 (C=O). $[\alpha]_D^{19}$ +29.8° (c=0.98, $CHCl_3$). ^{1}H-NMR δ: 1.08 (3H, t, J=7.1 Hz, NCH_2CH_3), 1.39 (3H, s, $OCOCH_3$), 3.17 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.38 (3H, s, OCH_3), 3.83 (3H, s, OCH_3 of anisoyl group), 5.03 (1H, t, J=4.8 Hz, C14-β-H), 6.91 and 8.01 (each 2H, d, J=8.9 Hz, anisoyl group). ^{13}C-NMR δ: 85.0 (C1), 26.3 (C2), 34.8 (C3), 39.2 (C4), 49.1 (C5), 82.8 (C6), 44.9 (C7), 85.8 (C8), 49.2 (C9), 43.9 (C10), 50.3 (C11), 28.9 (C12), 39.0 (C13), 75.8 (C14), 37.8 (C15), 83.3 (C16), 63.6 (C17), 80.4 (C18), 53.7 (C19), 49.1 (NCH_2CH_3), 13.4 (NCH_2CH_3), 56.5 (C1′), 57.8 (C6′), 56.0 (C16′), 59.0 (C18′), 55.3 ($COC_6H_4OCH_3$), 169.7 ($COCH_3$), 21.8 ($COCH_3$), 166.0 ($COC_6H_4OCH_3$), 163.3, 131.6, 122.8 and 113.6 ($COC_6H_4OCH_3$). MS *m/z*: 627 (M^+), 596 (M^+-OCH_3, base peak), 536 ($M^+-OCH_3-CH_3COOH$). HR-MS: Calcd for $C_{35}H_{49}NO_9$: 627.3407. Found: 627.3394. *Anal.* Calcd for $C_{35}H_{49}NO_9\cdot H_2O$: C, 65.10; H, 7.96; N, 2.17. Found: C, 65.11; H, 7.71; N, 2.16. NMR and MS spectra of **13** were identical with those of foresaconitine as reported by Chen and Breitmaier[8] and Yang *et al.*[9]

3,13,15-Tri-*O*-(*S*-methyl)thiocarbonylaconitine (18) Compound **18** was prepared from **2** in 83% yield in the same manner as used for the synthesis of compound **12**: colorless prism (Et_2O–hexane), mp 239—241 °C. IR ν_{max}^{KBr} cm^{-1}: 1717 (C=O). ^{1}H-NMR δ: 1.15 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.27 (3H, s, $OCOCH_3$), 2.45 (3H, s, SCH_3), 2.56 (3H, s, SCH_3), 2.66 (3H, s, SCH_3), 3.16 (3H, s, OCH_3), 3.18 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 5.31 (1H, d, J=5.3 Hz, C14-β-H), 5.73 (1H, dd, J=12.7, 5.4 Hz, C3-β-H), 7.45—8.20 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.9, 19.5 and 19.8 ($SCH_3\times3$), 81.3 (C13), 87.7 (C15), 214.1, 214.9 and 217.0 (C=S). MS *m/z*: 915 (M^+), 884 (M^+-OCH_3, base peak), 824 ($M^+-OCH_3-CH_3COOH$).

3,13,15-Trideoxyaconitine (19) Compound **19** was prepared from **18** in 83% yield in the same manner as used for the synthesis of compound **13**: colorless needles (Et_2O–hexane). mp 150—151 °C (lit.[10] 148—150 °C). IR ν_{max}^{KBr} cm^{-1}: 1717 (C=O). ^{1}H-NMR δ: 1.10 (3H, t, J=7.0 Hz, NCH_2CH_3), 1.38 (3H, s, $OCOCH_3$), 3.17 (3H, s, OCH_3), 3.28 (6H, s, $OCH_3\times2$), 3.37 (3H, s, OCH_3), 5.05 (1H, d, J=5.0 Hz, C14-β-H), 7.39—8.02 (5H, m, benzoyl group). ^{13}C-NMR δ: 85.1 (C1), 26.5 (C2), 35.1 (C3), 39.1 (C4), 49.0 (C5), 82.9 (C6), 47.9 (C7), 85.8 (C8), 49.2 (C9), 38.8 (C10), 50.5 (C11), 28.9 (C12), 34.7 (C13), 75.5 (C14), 38.1 (C15), 85.3 (C16), 63.0 (C17), 80.2 (C18), 53.8 (C19), 49.0 (NCH_2CH_3), 13.3 (NCH_2CH_3), 56.6 (C1′), 57.8 (C6′), 56.2 (C16′), 59.1 (C18′), 169.8 ($COCH_3$), 21.6 ($COCH_3$), 166.0 (COC_6H_5), 128.3, 129.3 and 132.9 (COC_6H_5). MS *m/z*: 597 (M^+), 566 (M^+-OCH_3, base peak), 506 ($M^+-OCH_3-CH_3COOH$). *Anal.* Calcd for $C_{34}H_{47}NO_8$: C, 68.32; H, 7.92; N, 2.34. Found: C, 67.97; H, 8.03; N, 2.23. These spectral data was identical to those of crassicaudine.[10,11]

3,13,15-Tri-*O*-(*S*-methyl)thiocarbonylmesaconitine (20) Compound **20** was prepared from **1** in 83% yield in the same manner as used for the synthesis of compound **12**: colorless prisms (Et_2O–hexane), mp 233—234 °C. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). ^{1}H-NMR δ: 1.23 (3H, s,

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$OCOCH_3$), 2.47 (3H, s, NCH_3), 2.57 (3H, s, SCH_3), 2.58 (3H, s, SCH_3), 2.65 (3H, s, SCH_3), 3.17 (3H, s, OCH_3), 3.19 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.44 (3H, s, OCH_3), 5.35 (1H, d, J=5.3 Hz, C14-β-H), 5.72 (1H, dd, J=12.7, 5.4 Hz, C3-β-H), 7.45—8.28 (5H, m, benzoyl group). ^{13}C-NMR δ: 18.9, 19.5 and 19.8 ($SCH_3 \times 3$), 81.2 (C3), 88.2 (C13), 87.7 (C15), 214.1, 214.9 and 217.0 (C=S). MS m/z: 901 (M^+), 870 ($M^+ - OCH_3$, base peak), 810 ($M^+ - OCH_3 - CH_3COOH$).

3,13,15-Trideoxymesaconitine (21) Compound **21** was prepared from **20** in 83% yield in the same manner as used for the synthesis of compound **13**: colorless needles (Et_2O–hexane). mp 156—157 °C. IR ν_{max}^{KBr} cm^{-1}: 1715 (C=O). ^{1}H-NMR δ: 1.37 (3H, s, $OCOCH_3$), 2.31 (3H, s, NCH_3), 3.17 (3H, s, OCH_3), 3.28 (6H, s, $OCH_3 \times 2$), 3.38 (3H, s, OCH_3), 5.07 (1H, d, J=5.0 Hz, C14-β-H), 7.40—8.08 (5H, m, benzoyl group). ^{13}C-NMR δ: 85.0 (C1), 26.4 (C2), 37.8 (C3), 39.2 (C4), 48.5 (C5), 82.7 (C6), 48.1 (C7), 85.8 (C8), 44.9 (C9), 38.6 (C10), 50.4 (C11), 28.7 (C12), 34.6 (C13), 75.6 (C14), 38.9 (C15), 83.3 (C16), 63.2 (C17), 80.3 (C18), 56.1 (C19), 42.5 (NCH_3), 56.4 (C1′), 58.1 (C6′), 56.5 (C16′), 59.1 (C18′), 169.7 ($\underline{C}OCH_3$), 21.6 ($CO\underline{C}H_3$), 166.0 ($\underline{C}OC_6H_5$), 128.5, 129.5 and 133.0 ($CO\underline{C}_6H_5$). MS m/z: 583 (M^+), 552 ($M^+ - OCH_3$, base peak), 462 ($M^+ - OCH_3 - CH_3COOH$). *Anal.* Calcd for $C_{33}H_{45}NO_8$: C, 67.90; H, 7.77; N, 2.40. Found: C, 67.87; H, 7.82; N, 2.40.

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