

LEAD TETRAACETATE OXIDATION OF ($\pm$)-*N*-ACYL-NORAPORPHINES: FACILE SYNTHESIS OF 4 α -HYDROXY-NORAPORPHINES AND 4 α -HYDROXYAPORPHINES $\ddagger$

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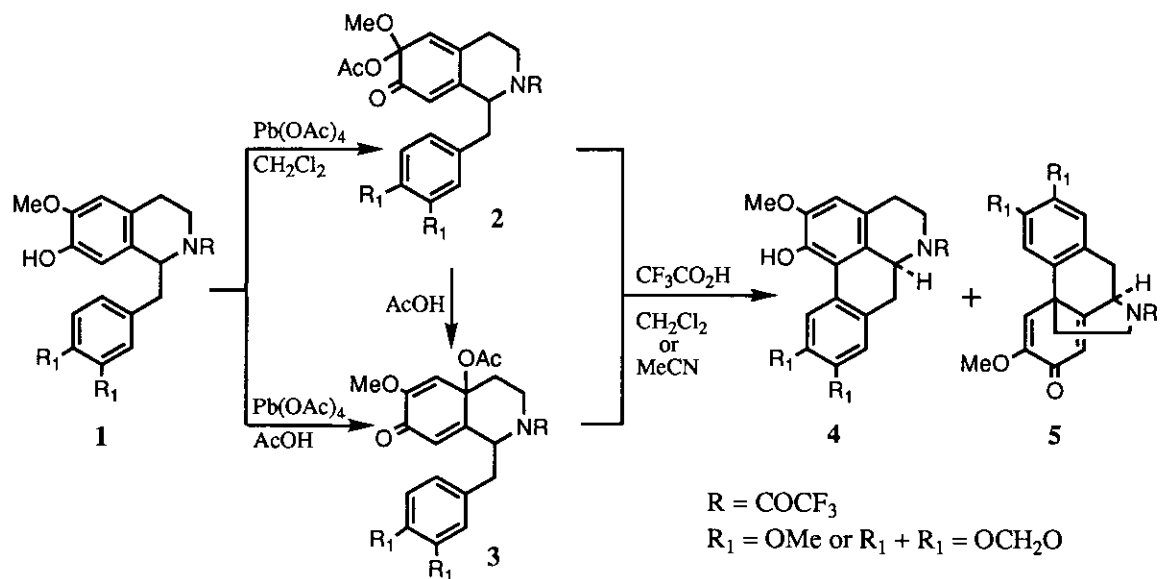
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Abstract-Lead tetraacetate oxidation of *N*-trifluoroacetylwilsonirine (4a) and -nordomesticine (4b) in acetic acid at room temperature gave exclusively 4 α -acetoxy-*N*-trifluoroacetylwilsonirine (7a) and -nordomesticine (7b), which were also obtained in good yield by oxidation in dichloromethane at 0 °C and successive treatment with acetic acid. *N*-Ethoxy-carbonylwilsonirine (6a) was converted into 4 α -hydroxyglaucone (epicataline)(15a) by the present methodology.

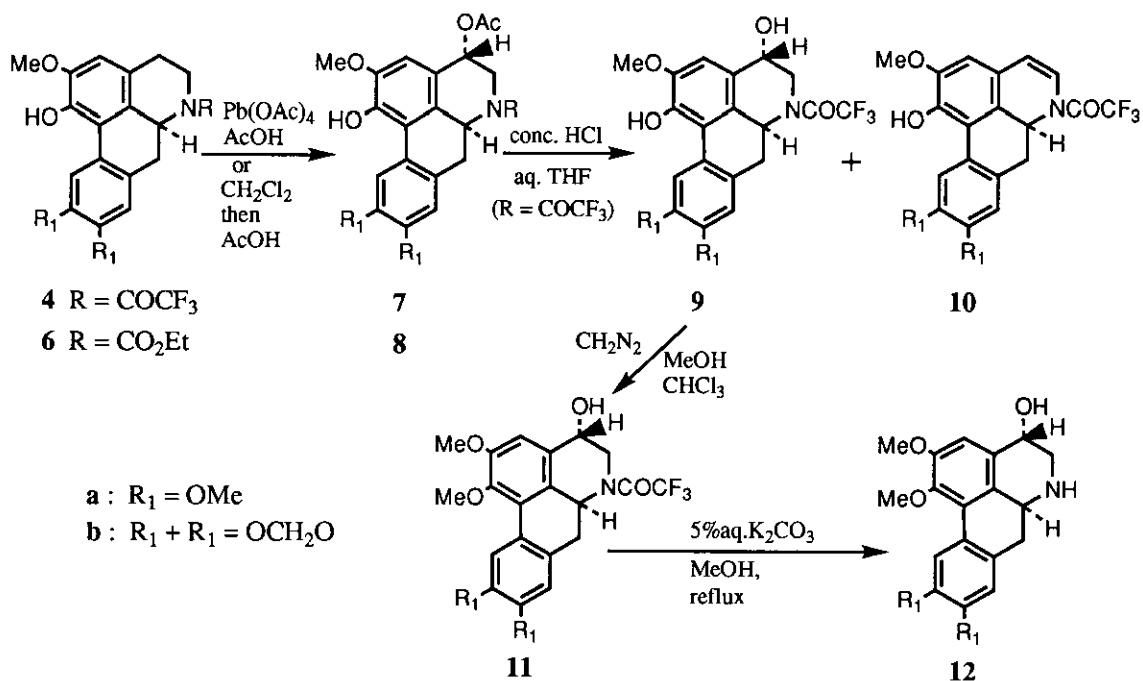
We have recently reported that lead tetraacetate (LTA) oxidation of 1-arylmethyl-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-ols (1) in dichloromethane (CH₂Cl₂) or AcOH produces stable *o*-quinol acetates (*o*-QAs)(2)^{1a,b} or *p*-QAs (3),^{1c} treatment of which with trifluoroacetic acid in CH₂Cl₂¹ or MeCN^{1b,c} leads to noraporphines (4) and normorphinandienones (5), respectively (Scheme 1).

In our continuing studies on LTA oxidation of *N*-acyltetrahydroisoquinolinols, we found that *N*-acylnoraporphines (4 and 6) produced exclusively 4 α -acetoxy-*N*-acylnoraporphines (7 and

$\ddagger$ This paper is dedicated to Professor Koji Nakanishi, Columbia University, on the occasion of his 75th birthday.



Scheme 1



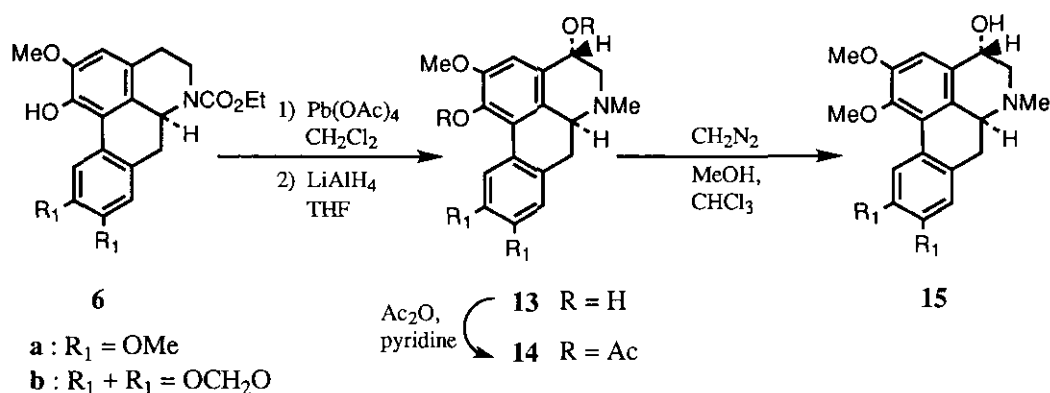
Scheme 2

8). The present paper describes LTA oxidation of *N*-acetylnoraporphines (**4**) leading to 4 α -acetoxy-*N*-acetylnoraporphines (**7**) and synthesis of 4 α -hydroxy-*N*-noraporphines (**9**, **11**, **12**) and 4 α -hydroxyaporphines (**13-15**) including epicataline (**15a**) from **4** and **6** by way of **7** and **8**.

N-Trifluoroacetylwilsonirine (**4a**)^{1a,c} was oxidized with LTA in AcOH at room temperature for 1 h to afford in 71% yield acetoxy-*N*-trifluoroacetylwilsonirine as a sole product, which was also formed in 55% yield by oxidation in CH₂Cl₂ at 0 °C followed by treatment with AcOH at room temperature. Its ¹H NMR spectrum showed three protons singlet due to an acetoxyl group at δ 2.04 and one proton multiplet (w1/2 = 5.7 Hz) due to 4-H at δ 5.84. This spectral data suggested that an acetoxyl group was introduced at the 4-position. Stereochemistry of the acetoxyl group was deduced as follows. The 4-acetoxy product was treated with concentrated HCl in aq. THF at room temperature for 24 h to give *N*-trifluoroacetyl-4-hydroxywilsonirine (**9a**) together with *N*-trifluoroacetyl-4,5-dehydrowilsonirine (**10a**). Methylation of the former (**9a**) with diazomethane-ether in MeOH-CHCl₃ gave *N*-trifluoroacetyl-4-hydroxynorglaucine (**11a**), hydrolysis of which with 5% aq. potassium carbonate in boiling MeOH produced 4-hydroxynorglaucine (**12a**) in 32% overall yield (from **9a**)(Scheme 2). The ¹H NMR spectral data were closely resemble to those for epicataline described in a literature.³ Thus stereochemistry of the 4-hydroxy group was assumed to be α -oriented. Similarly, oxidation of methylenedioxy congener (**4b**)^{1c} afforded the corresponding 4 α -acetoxynoraporphine (**7b**) in 42% yield, which was transformed to 4 α -hydroxynornantenine (**12b**) from **9b** by way of **11b**.

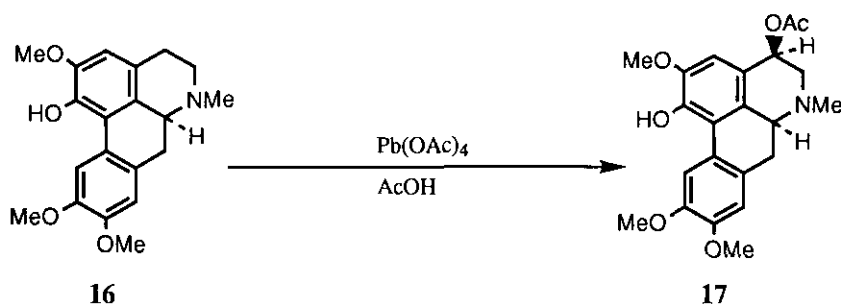
In order to absolutely determine stereostructure of 4 α -acetoxynoraporphine, transformation of **6b** to 4 α -acetoxy-*O*-acetyl domesticine.² Namely, oxidation of **6b**⁴ under the reaction conditions similar to those noted for **4** and in succession LiAlH₄ reduction gave 4-hydroxyaporphine in 53% yield by purification using preparative TLC. The ¹H NMR spectrum showed three protons singlet assignable to *N*-methyl group at δ 2.56 and disappearance of an acetyl group. As expected, the structure of the hydroxyaporphine was confirmed to be 4 α -hydroxy domesticine (**13b**) by the spectral (¹H NMR, MS) evidence and its conversion to the known 4 α -acetoxy-*O*-acetyl domesticine.² Analogously, dimethoxy derivative⁵ (**6a**) gave **13a** in 54% yield by way of **8a** in a manner similar to that noted for **6b** (Scheme 3).

Finally, methylation of 4 α -hydroxyaporphines (**13**) with diazomethane-ether in MeOH-CHCl₃ at room temperature afforded epicataline⁶ (**15a**) and 4 α -hydroxynantenine (**15b**), respectively (Scheme 3).



Scheme 3

Thus, it was proved unequivocally that stereochemistry of the acetoxyl group newly introduced at the 4-position was α -oriented. And epicataline (**15a**) and 4 α -hydroxynantenine (**15b**) were also synthesized starting with **6** by the present methodology. Previously, we have reported that LTA oxidation of thaliporphine (**16**) in AcOH provides the 4 β -acetoxythaliporphine⁷ (**17**) (Scheme 4). The present finding is quite different from that



Scheme 4

obtained for **16**. Although it is noted that LTA oxidation of *N*-acylnoraporphines (**4**, **6**) and *N*-methylaporphine (**16**) gave 4 α - and 4 β -acetoxyaporphines (each acetoxyl group at the 4-

position has opposite stereochemistry), respectively, the reason why oxidation of *N*-acylnoraporphines gives exclusively 4 α -acetoxyaporphines can not be explained at this stage. Further investigation on mechanism of the oxidation is now in progress.

In conclusion, LTA oxidation of *N*-acylnoraporphines was found to produce exclusively 4 α -acetoxy-*N*-acylnoraporphines, which were converted into 4 α -hydroxynoraporphines (**11**, **12**) and 4 α -hydroxyaporphines (**13-15**) including epicataline (**15a**).

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points were measured on a Büchi melting point measuring apparatus and are uncorrected. IR spectra were taken with a Hitachi model 260 spectrophotometer on KBr disk, unless otherwise noted. ^1H NMR spectra were measured on a JEOL FX-100 (100 MHz) or EX-270 (270 MHz) spectrometer in CDCl_3 using TMS as an internal standard, unless otherwise noted. MS spectra were recorded on a Hitachi model M-80A instrument. CH_2Cl_2 for reaction solvent was distilled and passed through basic alumina. Column chromatography was carried out on silica gel. Preparative TLC was performed on plates (20 x 20 cm) coated with 0.5 mm thickness of Merck Kieselgel 60 containing F-254 indicator.

4 α -Acetoxy-*N*-trifluoroacetylwilsonirine (7a). (1) In AcOH. LTA (251 mg, 0.57 mmol) was added in one portion to a water-cold, stirred solution of **4a**^{1a,c} (200 mg, 0.47 mmol) in AcOH (20 mL) and the whole mixture was stirred at rt for 1 h. The reaction mixture was carefully basified with saturated aq. NaHCO_3 . The product was taken up in CH_2Cl_2 and dried over K_2CO_3 . Usual work-up gave a residue (231 mg), which was purified by column chromatography (CHCl_3) to produce the title compound (**7a**, 160.6 mg, 71%), mp 181-183 °C (ether). Anal. Calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_7\text{F}_3$: C, 57.38; H, 4.61; N, 2.91. Found: C, 57.38; H, 4.69; N, 2.99. MS m/z : 481(M⁺). IR 3450, 1745, 1690 cm^{-1} . ^1H NMR δ : 2.04 (3H, s, OAc), 3.91, 3.92, 3.96 (9H, each s, OCH_3), 5.18 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 5.84 (1H, m, $w_{1/2} = 5.7$

Hz, 4-H), 6.76, 6.81 (each 1H, s, arom-H), 8.05 (1H, s, 11-H).

(2) In CH_2Cl_2 . A mixture of **4a** (590 mg, 1.39 mmol) and LTA (741 mg, 1.67 mmol) in CH_2Cl_2 (30 mL) was stirred at 0 °C for 40 min. Work-up as described above gave a residue, which was treated with AcOH at rt for 2 h to leave an amorphous mass (398 mg). Purification by column chromatography (CH_2Cl_2) provided a solid, which was recrystallized from ether-hexane to afford **7a** (368.5 mg, 55%). It was identical with the product obtained in (1).

***N*-Trifluoroacetyl-4 α -acetoxynordomesticine (7b).** (1) In AcOH. A mixture of **4b**^{1c} (30 mg, 0.074 mmol) and LTA (39 mg, 0.088 mmol) in AcOH (5 mL) was stirred at rt for 50 min. Work-up similar to that described for **7a** gave a residue (35.3 mg), which was purified by preparative TLC (CHCl_3) to leave the title compound (**7b**, 14.4 mg, 42%), mp 237-240 °C (hexane-benzene). Anal. Calcd for $\text{C}_{22}\text{H}_{18}\text{NO}_7\text{F}_3$: C, 56.78; H, 3.90; N, 2.91. Found: C, 56.94; H, 3.81; N, 3.28. MS m/z : 465 (M^+). IR 3450, 1750, 1735, 1685 cm^{-1} . ^1H NMR δ : 2.03 (3H, s, OAc), 3.96 (3H, s, OMe), 5.15 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 5.84 (1H, m, $w_{1/2} = 5.7$ Hz, 4-H), 5.96 (2H, s, OCH_2O), 6.74, 6.80 (each 1H, s, arom-H), 7.95 (1H, s, 11-H).

(2) In CH_2Cl_2 . A mixture of **4b** (30 mg, 0.074 mmol) and LTA (39 mg, 0.088 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 15 min. Work-up similar to that described above gave an oily residue (39 mg), which was treated with AcOH (5 mL) at rt for 30 min to afford a solid. Purification by preparative TLC (CH_2Cl_2) provided **7b** (14 mg, 41%). It was identical with the product obtained in (1).

Acid Hydrolysis of 4 α -Acetoxy-*N*-trifluoroacetyl noraporphines (7). From **7a**. A solution of **7a** (164 mg, 0.34 mmol), concentrated HCl (2 mL), and THF (10 mL)-water (2 mL) was stirred at rt for 24 h. The reaction mixture was diluted with water and the product was taken up in CH_2Cl_2 . Usual work-up of the organic layer afforded a solid (151 mg), which was purified by preparative TLC [CHCl_3 : MeOH (20:1) as developing solvent] to leave *N*-trifluoroacetyl-4 α -hydroxywilsonirine (**9a**) (72 mg, 48%) and *N*-trifluoroacetyl-4,5-dehydrowilsonirine (**10a**) (23 mg, 16%). **9a**: mp 198-200 °C (benzene). ^1H NMR δ : 3.90, 3.92, 3.96 (each 3H, s, OMe), 4.72 (1H, m, $w_{1/2} = 5.7$ Hz, 4-H), 5.13 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 6.35, 6.76 (each 1H, s, arom-H), 8.06 (1H, s, 11-H); IR 3540 cm^{-1} . MS m/z : 439 (M^+). Anal.

Calcd for $C_{21}H_{20}NO_6F_3$: C, 57.41; H, 4.59; N, 3.91; F, 12.97. Found: C, 57.54; H, 4.80; N, 3.20; F, 12.81. **10a**: mp 164-166 °C (EtOH). 1H NMR δ : 2.78 (1H, dt, $J = 0.9, 12.9$ Hz), 3.90 (3H, s, OMe), 3.93 (each 3H, s, OMe), 5.24 (1H, dd, $J = 3.6, 12.9$ Hz), 5.66 (1H, d, $J = 8.6$ Hz), 6.24, 6.47, 6.78 (each 1H, s), 6.63, 6.64 (1H, each d, $J = 8.6$ Hz), 7.99 (1H, 11-H). IR 3520, 1685, 1655 cm^{-1} . MS m/z : 421 (M^+). HRMS Calcd for $C_{21}H_{18}NO_5F_3$ (M^+): 421.1135. Found: 421.1134.

From **7b**. *N*-Trifluoroacetyl-4 α -hydroxynordomesticine (**9b**)(14.2 mg, 52%) and *N*-trifluoroacetyl-4,5-dehydronordomesticine (**10b**)(5.2 mg, 20%) were obtained by the reaction of **7b** (30 mg, 0.06 mmol) with concentrated HCl (1 mL) and THF (5 mL)-water (1 mL) in a way similar to that noted for **7a**. **9b**: mp 265-274 °C ($CHCl_3$ -MeOH). 1H NMR ($DMSO-d_6$) δ : 3.85 (3H, s, OMe), 4.64 (1H, m, $w_{1/2} = 5.7$ Hz, 4-H), 4.82 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 6.00 (2H, s, OCH_2O), 6.88, 6.92 (each 1H, s, arom-H), 7.92 (1H, s, 11-H). IR 3560, 3430, 1680 cm^{-1} . MS m/z : 423 (M^+). **10b**: oil. 1H NMR δ : 3.73 (1H, t, $J = 12.9$ Hz), 3.37 (1H, dd, $J = 3.4, 12.9$ Hz), 3.90 (3H, s, OMe), 5.19 (1H, dd, $J = 3.4, 12.9$ Hz), 5.64 (1H, d, $J = 8.6$ Hz), 5.96 (2H, s, OCH_2O), 6.20, 6.47 (each 1H, s), 6.57, 6.70 (1H, each d, $J = 8.6$ Hz), 6.75 (1H, s), 7.87 (1H, s, 11-H). IR ($CHCl_3$) 3450, 1680, 1645 cm^{-1} . MS m/z : 405 (M^+).

***N*-Trifluoroacetyl-4 α -hydroxynorglaucine and *N*-Trifluoroacetyl-4 α -hydroxynornantenine (**11a** and **11b**)**. From **9a**. A solution of **9a** (40.2 mg, 0.09 mmol) and CH_2N_2 -ether (20 mL) in MeOH (20 mL)- $CHCl_3$ (10 mL) was allowed to stand at rt for 12 h. Usual work-up of the reaction mixture gave the title compound (**11a**)(22 mg, 42%), mp 196-197 °C ($CHCl_3$ -hexane). 1H NMR δ : 3.68 (3H, s, OMe), 3.91 (9H, s, OMe), 4.73 (1H, br s, $w_{1/2} = 5.7$ Hz, 4-H), 5.08 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 6.76, 6.80 (each 1H, s, arom-H), 8.08 (1H, s, 11-H). IR 3490, 1680 cm^{-1} . MS m/z : 453 (M^+). HRMS m/z Calcd for $C_{22}H_{22}NO_6F_3$ (M^+): 453.1396. Found: 453.1396.

From **9b**: The title compound (**11b**)(131 mg, 63.4%) was obtained by the reaction of **9b** (200 mg, 4.7 mmol) and diazomethane-ether (10 mL) in MeOH (10 mL)- $CHCl_3$ (50 mL). **11b**: mp 188-190 °C (CH_2Cl_2 -hexane). 1H NMR δ : 3.67, 3.91 (each 3H, s, OMe), 4.72 (1H, br s, $w_{1/2} = 5.7$ Hz, 4-H), 5.04 (1H, dd, $J = 5.7, 12.9$ Hz, 6a-H), 5.98 (2H, s, OCH_2O), 6.74, 6.80 (each 1H, s, arom-H), 7.92 (1H, s, 11-H). IR 3500, 1680 cm^{-1} . MS m/z : 437 (M^+).

4 α -Hydroxynorglaucine and 4 α -Hydroxynornantenine (12a and 12b). From **11a**.

A solution of **11a** (50 mg, 0.11 mmol) and 5% aq. K₂CO₃ (1 mL) in MeOH (10 mL) was refluxed for 4 h. Usual work-up of the reaction mixture gave the title compound (**12a**) (29.6 mg, 75%), mp 204-207 °C (CHCl₃-hexane). ¹H NMR δ : 3.68 (3H, s, OMe), 3.90 (9H, s, OMe), 4.83 (1H, dd, J = 6.0, 9.1 Hz, 4-H), 6.71, 7.07 (each 1H, s, arom-H), 8.07 (1H, s, 11-H). IR 3250, 3150 cm⁻¹. MS m/z : 357 (M⁺). Anal. Calcd for C₂₀H₂₃NO₅: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.89; H, 6.58; N, 3.96.

From **11b**. Similar treatment of **11b** (50 mg, 0.11 mmol) gave the title compound (**12b**) (38.7 mg, 100%) as amorphous mass. ¹H NMR δ : 3.67, 3.89 (each 3H, s, OMe), 4.81 (1H, dd, J = 6.0, 9.1 Hz, 4-H), 5.95 (2H, s, OCH₂O), 6.79, 7.06 (each 1H, s, arom-H), 7.90 (1H, s, 11-H).

4 α -Hydroxythaliporphine and 4 α -Hydroxydomesticine (13a and 13b). From **6a**.⁵

Compound (**8a**) [prepared from **6a** (100 mg, 0.25 mmol) in a manner similar to that noted for **4**] was employed without further purification. A suspension of **8a** and LiAlH₄ (25 mg, 0.66 mmol) in THF (4 mL) was stirred at rt for 12 h. An excess of the reductant was decomposed by adding water and the product was taken up in CH₂Cl₂. Purification of the product by column chromatography (two times) [first, hexane : AcOEt (1 : 1); second, CHCl₃ : MeOH (100 : 1)] gave the title compound (**13a**, 48 mg, 54%) as crystals, mp 154-156 °C (decomp.) (ether). ¹H NMR (270 MHz) δ : 2.56 (3H, s, NMe), 3.92 (6H, s, OMe), 3.94 (3H, s, OMe), 4.95 (1H, br t, unresolved), 6.78, 7.34 (each 1H, s, arom-H), 8.04 (1H, s, 11-H). MS m/z : 357 (M⁺). HRMS Calcd for C₂₀H₂₃NO₅ (M⁺): 357.1574. Found: 357.1566.

From **6b**.⁴ Compound (**8b**) [prepared from **6b** (100 mg, 0.26 mmol) in a manner similar to that noted for **4**] was employed without further purification. A suspension of **8b** and LiAlH₄ (25 mg, 0.66 mmol) in THF (4 mL) was stirred at rt for 12 h. Usual work-up of the reaction mixture gave, after purification by column chromatography [hexane : AcOEt (1 : 1)], the title compound (**13b**, 47 mg, 53%) as colorless crystals, mp 144-145 °C (ether). ¹H NMR (270 MHz) δ : 2.55 (3H, s, NMe), 3.95 (3H, s, OMe), 4.93 (1H, br s, unresolved), 5.96 (2H, dd, J = 1, 1.5 Hz, OCH₂O), 6.75, 7.04 (each 1H, s, arom-H), 7.93 (1H, s, 11-H). MS m/z : 341 (M⁺). HRMS Calcd for C₁₉H₁₉NO₅ (M⁺): 341.1266. Found: 341.1264. 4 α -Acetoxy-*O*-acetyl-domesticine (**14b**) [mp 204-206 °C (decomp.) (ether)] obtained from **13b** by acetylation in a

usual manner was identical to the authentic sample² by comparison of each spectral data.

4 α -Hydroxyglaucine (Epicataline)(15a) and 4 α -Hydroxynantenine (15b). From **13a**. A solution of **13a** (15 mg, 0.04 mmol) and CH₂N₂-ether (6 mL) in CHCl₃ (1 mL) and MeOH (3 mL) was allowed to stand at rt for 12 h. Usual work-up gave **15a**⁶ (9 mg, 58%), mp 187-189 °C (decomp)(ether-hexane). ¹H NMR (270 MHz) δ : 2.56 (3H, s, NMe), 3.67 (3H, s, 1-OMe), 3.91, 3.92, 3.93 (each 3H, s, OMe), 4.95 (1H, dd, J = 4.6, 6.2 Hz, 4-H), 6.67, 7.10 (each 1H, s, arom-H), 8.08 (1H, s, 11-H). MS m/z : 371 (M^+). HRMS Calcd for C₂₁H₂₅NO₅ (M^+): 371.1731. Found: 371.1743.

From **13b**: Similar methylation of **13b** (15 mg, 0.044 mmol) gave **15b** (8.3 mg, 53%), mp 206-208°C (decomp)(ether-hexane). ¹H NMR (270 MHz) δ : 2.53 (3H, s, NMe), 3.68 (3H, s, 1-OMe), 3.92 (3H, s, 2-OMe), 4.94 (1H, dd, J = 7.6, 8.6 Hz, 4-H), 5.98 (2H, dd, J = 1, 1.9 Hz, OCH₂O), 6.75, 7.10 (each 1H, s, arom-H), 7.92 (1H, s, 11-H). MS m/z : 355 (M^+). HRMS Calcd for C₂₀H₂₁NO₅ (M^+): 355.1417. Found: 355.1402.

REFERENCES AND NOTES

1. a) O. Hoshino, H. Ogasawara, M. Suzuki, and B. Umezawa, *Heterocycles*, 1987, **25**, 151.
b) O. Hoshino, H. Ogasawara, M. Suzuki, M. Arasawa, and B. Umezawa, *Heterocycles*, 1990, **30**, 385. c) O. Hoshino, H. Ogasawara, M. Arasawa, M. Suzuki, and K. Iijima, *Heterocycles*, 1993, **35**, 1005.
2. O. Hoshino, H. Hara, N. Serizawa, and B. Umezawa, *Chem. Pharm. Bull.*, 1975, **23**, 2048.
3. J. Hartenstein and G. Satzinger, *Angew. Chem., Int. Ed. Engl.*, 1977, **16**, 730.
4. *N*-Ethoxycarbonylnordomesticine (**6b**)(mp 240-241 °C) was prepared by LTA oxidation of *N*-ethoxycarbonyl-6-methoxy-1-(3,4-methylenedioxyphenylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (oil) in AcOH.
5. *N*-Ethoxycarbonylwilsonirine (**6a**)(mp 116-125 °C) was prepared by LTA oxidation of *N*-ethoxycarbonyl-6-methoxy-1-(3,4-dimethoxyphenylmethyl)-1,2,3,4-tetrahydroisoquinolin-7-ol (mp 162-164 °C) in AcOH.
6. ¹H NMR spectral data for **15a** were almost identical with those for epicataline described in a literature³ except J values due to the 4-H.
7. O. Hoshino, H. Hara, M. Ogawa, and B. Umezawa, *Chem. Pharm. Bull.*, 1975, **23**, 2578.