LEAD TETRAACETATE OXIDATION OF (±)-*N*-ACYL-NORAPORPHINES: FACILE SYNTHESIS OF 4α-HYDROXY-NORAPORPHINES AND 4α-HYDROXYAPORPHINES‡

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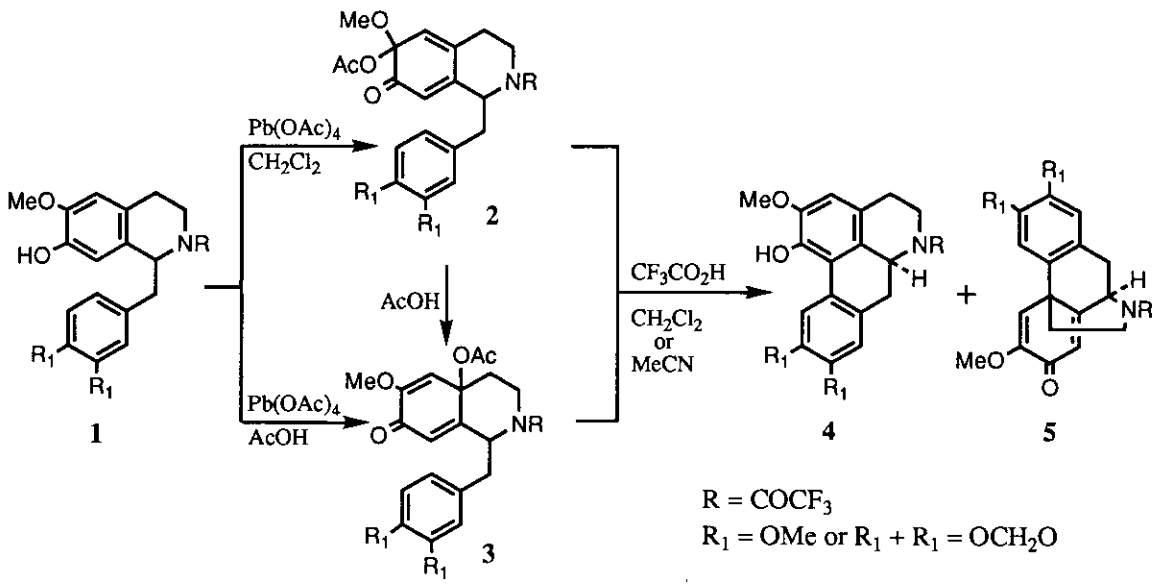
Abstract-Lead tetraacetate oxidation of *N*-trifluoroacetylwilsonirine (**4a**) and -nordomesticine (**4b**) in acetic acid at room temperature gave exclusively 4α-acetoxy-*N*-trifluoroacetylwilsonirine (**7a**) and -nordomesticine (**7b**), which were also obtained in good yield by oxidation in dichloromethane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

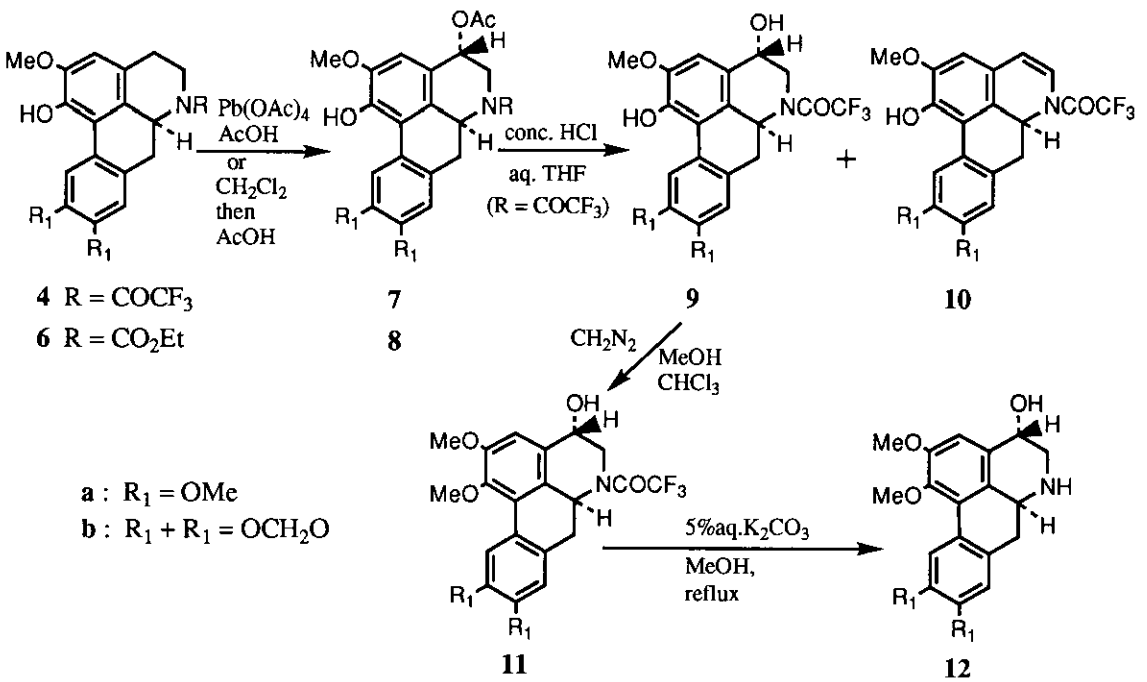
We have recently reported that lead tetraacetate (LTA) oxidation of 1-arylmethyl-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinolin-7-ols (**1**) in dichloromethane (CH_2Cl_2) or AcOH produces stable *o*-quinol acetates (*o*-QAs)(**2**)[1a,b] or *p*-QAs (**3**),[1c] treatment of which with trifluoroacetic acid in CH_2Cl_2[1] 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 4α-acetoxy-*N*-acylnoraporphines (**7** and

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



Scheme 1



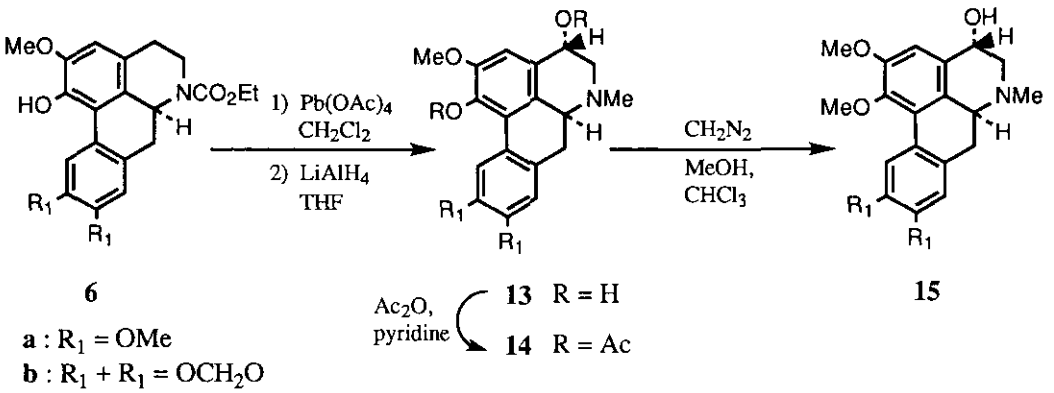
Scheme 2

8). The present paper describes LTA oxidation of *N*-acylnoraporphines (**4**) leading to 4α-acetoxy-*N*-acylnoraporphines (**7**) and synthesis of 4α-hydroxy-*N*-noraporphines (**9**, **11**, **12**) and 4α-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 CH_2Cl_2 at 0 °C followed by treatment with AcOH at room temperature. Its ^{1}H 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-$CHCl_3$ 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 ^{1}H 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 4α-acetoxynoraporphine (**7b**) in 42% yield, which was transformed to 4α-hydroxynornantenine (**12b**) from **9b** by way of **11b**.

In order to absolutely determine stereostructure of 4α-acetoxynoraporphine, transformation of **6b** to 4α-acetoxy-*O*-acetyldomesticine.[2] Namely, oxidation of **6b**[4] under the reaction conditions similar to those noted for **4** and in succession $LiAlH_4$ reduction gave 4-hydroxy-aporphine in 53% yield by purification using preparative TLC. The ^{1}H 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 4α-hydroxydomesticine (**13b**) by the spectral (^{1}H NMR, MS) evidence and its conversion to the known 4α-acetoxy-*O*-acetyldomesticine.[2] Analogously, dimethoxy derivative[5] (**6a**) gave **13a** in 54% yield by way of **8a** in a manner similar to that noted for **6b** (Scheme 3).

Finally, methylation of 4α-hydroxyaporphines (**13**) with diazomethane-ether in MeOH-$CHCl_3$ at room temperature afforded epicataline[6] (**15a**) and 4α-hydroxynantenine (**15b**), respectively (Scheme 3).



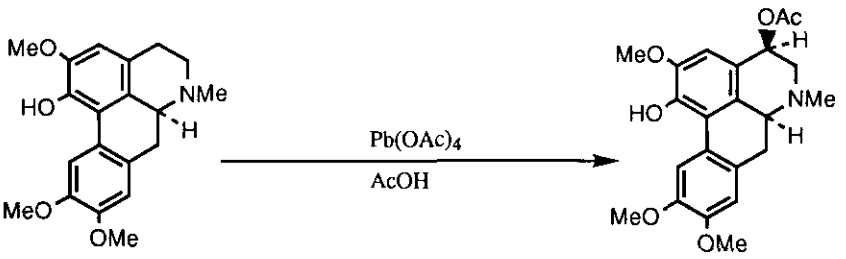
6

a : R_1 = OMe
b : $R_1 + R_1 = OCH_2O$

15

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 4α-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 4β-acetoxythaliporphine[7] (**17**)(Scheme 4). The present finding is quite different from that



16 **17**

Scheme 4

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

position has opposite stereochemistry), respectively, the reason why oxidation of *N*-acylnoraporphines gives exclusively 4α-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 4α-acetoxy-*N*-acylnoraporphines, which were converted into 4α-hydroxynoraporphines (**11**, **12**) and 4α-hydroxyaporphines (**13-15**) including epicataline (**15a**).

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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 disck, unless otherwise noted. ^{1}H 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.

4α-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 $C_{23}H_{22}NO_7F_3$: 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}. ^{1}H 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, w1/2 = 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-4α-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 $C_{22}H_{18}NO_7F_3$: 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, w1/2 = 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 4α-Acetoxy-*N*-trifluoroacetylnoraporphines (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-4α-hydroxywilsonirine (**9a**)(72 mg, 48%) and *N*-trifluoroacetyl-4,5-dehydro-wilsonirine (**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, w1/2 = 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). ^{1}H 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-4α-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). ^{1}H NMR (DMSO-d_6) δ: 3.85 (3H, s, OMe), 4.64 (1H, m, w1/2 = 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. ^{1}H 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-4α-hydroxynorglaucine and *N*-Trifluoroacetyl-4α-hydroxy-nornantenine (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). ^{1}H NMR δ: 3.68 (3H, s, OMe), 3.91 (9H, s, OMe), 4.73 (1H, br s, w1/2 = 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). ^{1}H NMR δ: 3.67, 3.91 (each 3H, s, OMe), 4.72 (1H, br s, w1/2 = 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$^+$).

4α-Hydroxynorglaucine and 4α-Hydroxynornantenine (12a and 12b). From **11a**. A solution of **11a** (50 mg, 0.11 mmol) and 5% aq. K_2CO_3 (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 ($CHCl_3$-hexane). ^{1}H 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 $C_{20}H_{23}NO_5$: 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. ^{1}H 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, OCH_2O), 6.79, 7.06 (each 1H, s, arom-H), 7.90 (1H, s, 11-H).

4α-Hydroxythaliporphine and 4α-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 $LiAlH_4$ (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 CH_2Cl_2. Purification of the product by column chromatography (two times) [first, hexane : AcOEt (1 : 1); second, $CHCl_3$: MeOH (100 : 1)] gave the title compound (**13a**, 48 mg, 54%) as crystals, mp 154-156 °C (decomp)(ether). ^{1}H 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 $C_{20}H_{23}NO_5$ (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 $LiAlH_4$ (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). ^{1}H 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, OCH_2O), 6.75, 7.04 (each 1H, s, arom-H), 7.93 (1H, s, 11-H). MS *m/z*: 341 (M^+). HRMS Calcd for $C_{19}H_{19}NO_5$ (M^+) : 341.1266. Found : 341.1264. 4α-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 sample[2] by comparison of each spectral data.

4α-Hydroxyglaucine (Epicataline)(15a) and 4α-Hydroxynantenine (15b). From **13a.** A solution of **13a** (15 mg, 0.04 mmol) and CH_2N_2-ether (6 mL) in $CHCl_3$ (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). ^{1}H 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 $C_{21}H_{25}NO_5$ (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). ^{1}H 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, OCH_2O), 6.75, 7.10 (each 1H, s, arom-H), 7.92 (1H, s, 11-H). MS *m/z*: 355 (M^+). HRMS Calcd for $C_{20}H_{21}NO_5$ (M^+) : 355.1417. Found : 355.1402.

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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. ^{1}H NMR spectral data for **15a** were almost identical with those for epicataline described in a literature[3] except *J* values due to the 4-H.
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