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Synthesis of Optically Active Aporphine and Morphinandienone Alkaloids via *p*-Quinol Esters

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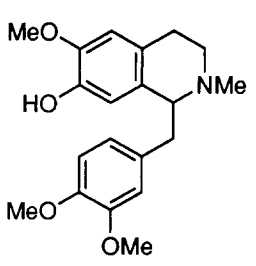
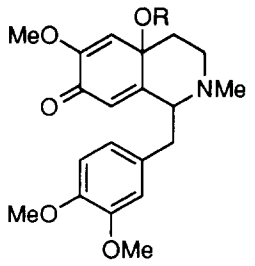
Abstract: Lead tetraacetate oxidation of *N*-trifluoroacetylnorcodamine (**5**) in (*S*)-(+)-2-phenylpropionic acid gave a diastereomeric mixture of two *p*-quinol acylates, which were easily separated to enantiomerically pure **6a** and **6b**. Treatment of the chiral quinol acylates (**6a**) and (**6b**) with trifluoroacetic acid in CH_2Cl_2 at room temperature afforded (1*R*)-(-)-6-trifluoroacetylwilsonirine (**7a**) and (1*S*)-(+)-(**7b**), respectively. Saponification of **7a** and **7b** gave rise to (-)-wilsonirine (**8a**) and its enantiomer (**8b**), respectively. Similarly, (-)-nordomesticine (**12a**) and (+)-(**12b**) were synthesized in enantiomerically pure form from **10a** and **10b**. On the other hand, acid treatment of **6a** and **6b** in CH_3CN at lower temperature (-30 °C) followed by *N*-deprotection gave the corresponding normorphinandienones (**15a** and **15b**) as major products, which were transformed to enantiomerically pure (-)-**16a** and (+)-sebiferine (**16b**). In a similar sequence of reactions, (+)-amurine (**19a**) and its enantiomer (**19b**) were synthesized.

A number of aporphine alkaloids have been isolated and characterized.[1] Although there are various enantio- or diastereo-selective synthesis of optically active 1-substituted tetrahydroisoquinolines,[2] few procedures for the synthesis of homochiral aporphines have been reported.[3] We have already developed a facile method[4] for synthesis of racemic aporphine (**3**) *via* the reactive intermediate, *p*-quinol acetate (**2**), which is readily derived from tetrahydroisoquinolin-7-ol (**1**) bearing an activated benzyl group at the 1-position by lead tetraacetate (LTA) oxidation. We were encouraged to prepare optically active *p*-quinol esters which hold great promise as precursors of tetracyclic alkaloids. We describe here a synthesis of enantiomerically pure aporphines and morphinandienones in a new synthetic manner including LTA oxidation in a chiral acid.

First of all, a readily available chiral acid was sought for formation of chiral *p*-quinol acylates which could be separated into two diastereoisomers. After careful exploration,[5] (*S*)-(+)-2-phenylpropionic acid was found to be adequate for the formation of stable *p*-quinol esters. However, when (±)-codamine (**1**) was submitted to LTA oxidation in the acid, formation of four diastereomers of *p*-quinol esters (**4**), consisting of two pairs of 1,4a-*cis* and *trans* isomers, was observed on thin layer chromatography. Separation of the mixture is bothersome and it forced us to choose the *N*-acyl analogue (**5**) as a starting compound, because it has a quasi-axially oriented

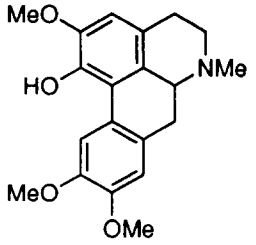


1

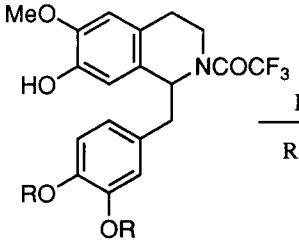


2: R=Ac
4: R=COR*

R*=CH(Me)Ph (*S*)

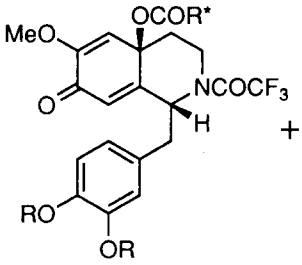


3



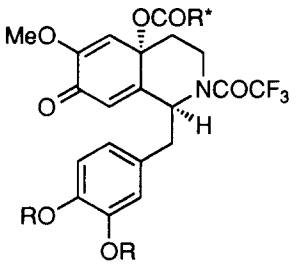
5: R=Me
9: R+R=CH_2

LTA
R*COOH



6a: R=Me
10a: R+R=CH_2

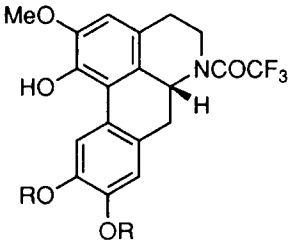
+



6b: R=Me
10b: R+R=CH_2

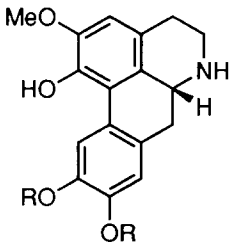
6a
10a

TFA
CH_2Cl_2



7a: R=Me
11a: R+R=CH_2

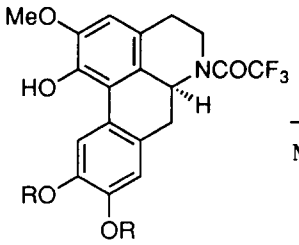
K_2CO_3
MeOH-H_2O



8a: R=Me
12a: R+R=CH_2

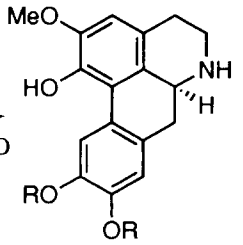
6b
10b

TFA
CH_2Cl_2



7b: R=Me
11b: R+R=CH_2

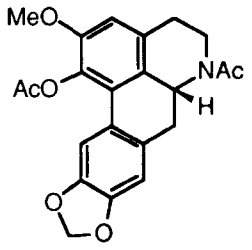
K_2CO_3
MeOH-H_2O



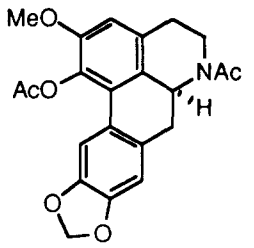
8b: R=Me
12b: R+R=CH_2

arylmethyl group and could be attacked by the acid only from a side opposite to the substituent. Actually, oxidation of (±)-*N*-trifluoroacetyl-1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-1-veratrylisoquinoline (**5**)[6] by LTA (1.2 eq.) in (*S*)-(+)-2-phenylpropionic acid at room temperature for 4.5 h gave a mixture of two diastereomers, which were easily separated by medium pressure liquid chromatography to the *p*-quinol esters (**6a**)[7] [35%, IR ($CHCl_3$), cm^{-1}: 1735 (ester), 1685, 1650, 1625 ($NCOCF_3$ and dienone)] and (**6b**)[7] [29%, IR ($CHCl_3$), cm^{-1}: 1735 (ester), 1685, 1650, 1625 ($NCOCF_3$ and dienone)]. The absolute configuration of both compounds was determined by transformation of **6b** into the natural alkaloid (**8b**) as described below. Treatment of **6a** with trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) afforded an optically active aporphine (**7a**) (64%), the enantiomeric excess (ee) of which was estimated to be 84% by HPLC analysis using a chiral column (DAICEL CHIRALCEL OJ). Enantiomerically pure **7a** was prepared in the following manner. The product was dissolved in hot CH_2Cl_2 and then after cooling to room temperature the resulting precipitate (mp 188-188.5 °C, 5.7%, 7.1% ee) was removed by filtration. Evaporation of the solvent gave homochiral (*R*)-(-)-6-trifluoroacetylwilsonirine (**7a**) as an amorphous mass, mp 88-89 °C, (48%, 100% ee). Similar treatment of the *p*-quinol acylate (**6b**) provided (*S*)-(+)-6-trifluoroacetylwilsonirine (**7b**) (an amorphous mass, mp 87-89°C, 96.4% ee) in 33.2% yield. Each amide (**7a** or **7b**) was refluxed in 4.3% aqueous K_2CO_3-MeOH (1:10) for 5-6 h to give the corresponding (*R*)-(-)-wilsonirine (**8a**) (mp 106-108 °C, 23%, 100% ee) or (*S*)-(+)-wilsonirine (**8b**) (mp 107-109 °C, 39%, 95.9% ee) as colorless crystals, respectively. The physical data of the latter product (**8b**) were consistent with those of natural wilsonirine.[8]

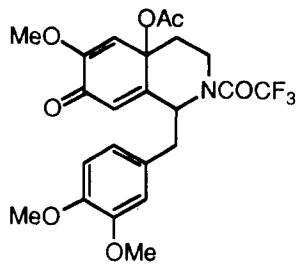
Then this methodology was applied to synthesis of homochiral 9,10-methylenedioxyaporphine, (*S*)-(+)-nordomesticine and its enantiomer. Oxidation of racemic 1-piperonyltetrahydroisoquinolin-7-ol (**9**)[6] afforded two separable *p*-quinol acylates, **10a** (43%) and **10b** (29%). Acid treatment of **10a** and **10b** followed by similar purification as described above gave (*R*)-(-)- (**11a**) (mp 243-244 °C, 32%, 95.3% ee) and (*S*)-(+)-6-trifluoroacetylnordomesticine (**11b**) (mp 244-245 °C, 23%, 94.7% ee), respectively. Alkaline hydrolysis of the trifluoroacetamides (**11a** and **11b**) yielded (*R*)-(-)-nordomesticine (**12a**) (oil, 55%, 100% ee) and (*S*)-(+)-(**12b**) (oil, 70%, 99% ee). ^{1}H-NMR and high resolution mass spectra of products (**12a** and **12b**) and their diacetates (**13a** and **13b**)[9] supported the structure assignment.



13a



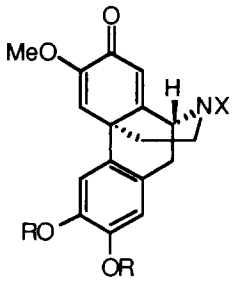
13b



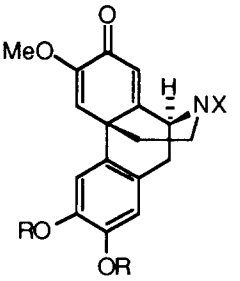
20

Recently, formation of the morphinandienone skeleton from racemic *N*-trifluoroacetyl-*p*-quinol acetate (**20**) was established in our laboratory.[10] Thus, these reaction conditions were adapted to the reaction of the chiral *p*-quinol acylates in hand. Namely, the reaction of the quinol acylate (**6a**) with TFA in CH_3CN at -30°C gave an

expected normorphinandienone (**14a**) (35%) together with the noraporphine (**7a**) (16%) and the starting compound (**6a**) (28%). Prolongation of the reaction time did not increase the yield of **14a**.



14a: R=Me, X=$COCF_3$
15a: R=Me, X=H
16a: R=X=Me
17a: R+R=CH_2, X=$COCF_3$
18a: R+R=CH_2, X=H
19a: R+R=CH_2, X=Me



14b: R=Me, X=$COCF_3$
15b: R=Me, X=H
16b: R=X=Me
17b: R+R=CH_2, X=$COCF_3$
18b: R+R=CH_2, X=H
19b: R+R=CH_2, X=Me

Similarly, enantiomeric normorphinandienone (**14b**) (31%) and noraporphine (**7b**) (16%) were furnished by treatment of **6b** under the conditions similar to those noted above. IR and ^{1}H-NMR spectral data of both normorphinandienones (**14a** and **14b**) were completely consistent with those of each authentic racemate.[10] The enantiomeric purity of **14a** and **14b** was estimated after recrystallization to be 92 and 98% ee by HPLC analysis, respectively. Hydrolysis of **14b** with K_2CO_3 in aqueous MeOH yielded (+)-norsebiferine (**15b**), which was converted by *N*-methylation into (+)-sebiferine (**16b**)[11] (an amorphous mass; 53% from **14b**). The specific rotation ($[\alpha]_D^{24}$) of **16b** (97% ee) was measured to be +12 consistent with the value ($[\alpha]_D^{20}$ = +13) for the natural alkaloid.[11] Through the same processes as above, the enantiomer {(-)-**16a**; $[\alpha]_D^{24}$ = -13} was synthesized from **14a**. The tactics were applied to the methylenedioxy congeners (**10a** and **10b**). Thus, acid treatment of the *p*-quinol acylate (**10a**) gave an *N*-trifluoroacetylnormorphinandienone (**17a**), which was successively hydrolyzed and *N*-methylated to afford (+)-amurine (**19a**) (mp 203-205 °C, 99% ee, $[\alpha]_D^{27}$ = +10.7); (lit.[12] $[\alpha]_D^{27}$ = +11). Its enantiomer {(-)-**19b**, mp 200-203 °C, $[\alpha]_D^{27}$ = -13.5} was also prepared from **10b** through the same sequence of reactions. ^{1}H-NMR spectra of both normorphinandienones (**19a** and **19b**) were superimposable on each other.

Although the present methodology serves effectively for synthesis of optiically active aporphine and morphinandienone, partial racemization can not be prevented because of the following possibility; (1) acid treatment of some kinds of 1-alkyltetrahydroisoquinolines[13] causes racemization at the 1-position and (2) a proton at the 1-position in *N*-acyl-*p*-quinol acylates (**6** and **10**) seems to be enolizable because of the presence of the conjugated enone, resulting in a little bit of racemization.

In conclusion, we have developed a novel methodology *via* optically active *p*-quinol esters for the synthesis of homochiral aporphine and morphinandienone alkaloids. (*S*)-(+)-2-Phenylpropionic acid employed in the reaction was completely recovered without loss of enantiomeric purity. Further application of the procedure to asymmetric synthesis of 1-phenyl- and 1-phenethyl-tetrahydroisoquinoline alkaloids is now in progress.

EXPERIMETAL

All melting points were measured on a Büchi melting point apparatus and are uncorrected. IR spectra were taken with a Hitachi model 260-10 spectrometer in $CHCl_3$ solution. ^{1}H-NMR spectra were recorded on a JEOL model FX-100 spectrometer in $CDCl_3$ solution using tetramethylsilane as internal standard. Mass spectra (MS) were obtained on a Hitachi model M-60 spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. Ee values were estimated by HPLC analysis with chiral column (DAICEL CHIRALCEL OC, OD, or OJ). Preparative thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck Kieselgel 60 F_{254}).

Preparation of *p*-Quinol Acylates (6 and 10)

Oxidation was carried out according to a procedure similar to that previously reported except using (*S*)-(+)-2-phenylpropionic acid instead of acetic acid.[4] Usual work-up of the reaction mixture gave yellowish brown oil, which was purified by medium pressure liquid chromatography on silica gel.

From (±)-**5** : A mixture of (±)-**5** (200 mg, 0.47 mmol) and LTA (250 mg, 0.56 mmol) in (*S*)-(+)-2-phenylpropionic acid (3 ml) was stirred for 4 h. Elution of the residue (317 mg) with hexane-AcOEt (55 : 45) gave two *p*-quinol acylates (**6a** and **6b**, polarity; **6a** < **6b**). *(1R, 4aR, 2'S)-1,2,3,4,4a,7-Hexahydro-7-oxo-4a-(2'-phenylpropionyloxy)-2-trifluoroacetyl-1-veratrylisoquinoline* (**6a**) (oil, 94 mg, 35%); ^{1}H-NMR δ: 1.50 [3H, d, J = 7 Hz, OCOCH(*CH*$_3$)Ph], 3.64, 3.83, 3.84 (each 3H, s, OCH_3); IR cm^{-1}: 1735 (ester), 1685, 1650, 1625 (dienone and $NCOCF_3$). *(1S, 4aS, 2'S)-1,2,3,4,4a,7-Hexahydro-7-oxo-4a-(2'-phenylpropionyloxy)-2-trifluoroacetyl-1-veratrylisoquinoline* (**6b**) (oil, 78 mg, 29%); ^{1}H-NMR δ: 1.53 [3H, d, J = 7 Hz, OCOCH(*CH*$_3$)Ph], 3.64, 3.76, 3.82 (each 3H, s, OCH_3); IR cm^{-1}: 1735 (ester), 1685, 1650, 1625 (dienone and $NCOCF_3$).

From (±)-**9** : A mixture of (±)-**9** (600 mg, 1.47 mmol) and LTA (840 mg, 1.88 mmol) in (*S*)-(+)-2-phenylpropionic acid (9 ml) was stirred for 4.5 h. Elution of the residue (938 mg) with hexane-AcOEt (65 : 35) gave two *p*-quinol acylates (**10a** and **10b**, polarity; **10a** < **10b**). *(1R, 4aR, 2'S)-1,2,3,4,4a,7-Hexahydro-7-oxo-4a-(2'-phenylpropionyloxy)-2-trifluoroacetyl-1-piperonylisoquinoline* (**10a**) (oil, 346 mg, 42%); ^{1}H-NMR δ: 1.50 [3H, d, J = 7.1 Hz, OCOCH(*CH*$_3$)Ph], 3.66 (3H, s, OCH_3), 5.91 (2H, s, OCH_2O); IR cm^{-1}: 1730 (ester), 1665, 1650, 1625 (dienone and $NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{29}H_{26}F_3NO_7$; 557.1660. Found; 557.1690. *(1S, 4aS, 2'S)-1,2,3,4,4a,7-Hexahydro-7-oxo-4a-(2'-phenylpropionyloxy)-2-trifluoroacetyl-1-piperonylisoquinoline* (**10b**) (oil, 233 mg, 29%); ^{1}H-NMR δ: 1.53, [3H, d, J = 7.1 Hz, OCOCH(*CH*$_3$)Ph], 3.90 (3H, s, OCH_3), 5.90 (2H, s, OCHO); IR cm^{-1}: 1740 (ester), 1690, 1655, 1630 (dienone and $NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{29}H_{26}F_3NO_7$; 557.1658. Found; 557.1658.

Treatment of *p*-Quinol Acylates (6 and 10) with TFA in CH_2Cl_2 or CH_3CN

Acid treatment of *p*-quinol acylates (**6** and **10**) was carried out according to the procedures similar to those (in CH_2Cl_2[4] and CH_3CN[10]) previously reported. Usual work-up of the reaction mixture gave an oily residue, which was separated by preparative TLC.

a) In CH_2Cl_2. From **6a** : A mixture of **6a** (280 mg, 0.49 mmol) and TFA (1.5 ml) in CH_2Cl_2 (30 ml) was stirred for 3.5 h. Preparative TLC of the yellowish brown oil (209 mg) with $CHCl_3$ afforded *(R)-(-)-6-trifluoroacetylwilsonirine* (**7a**) as an amorphous mass (132 mg, 64%, 84% ee). The solid was dissolved in boiling CH_2Cl_2 and colorless crystals (11 mg, 5.7%, 7.1% ee, mp 188-188.5 °C) were precipitated from the

cooled solution. Evaporation of filtrate *in vacuo* gave optically pure (-)-**7a** [100 mg, 48%, 100% ee (OJ; *i*-PrOH : hexane = 9 : 1)] as an amorphous mass; mp 87-89 °C; $[\alpha]_D^{24}$ -234.3 (c = 1.0, $CHCl_3$); ^{1}H-NMR δ: 3.89 (3H, s, OCH_3), 3.93 (6H, s, 2xOCH_3), 6.55 (1H, s, 3-H), 6.75 (1H, s, 8-H), 8.09 (1H, s, 11-H); IR cm^{-1}: 1685 ($NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{21}H_{20}F_3NO_5$: 423.1291. Found: 423.1284.

From **6b** : A mixture of **6b** (200 mg, 0.35 mmol) and TFA (1 ml) in CH_2Cl_2 (20 ml) was stirred for 4.5 h. Preparative TLC of the yellowish brown oil (150 mg) with $CHCl_3$ afforded *(S)-(+)-6-trifluoroacetylwilsonirine* (**7b**) as an amorphous mass (112 mg, 77%, 85% ee). A manner similar to that noted for **7a** gave colorless crystals (3.2 mg, 2.2%, 3.5% ee, mp 190-191 °C) and (+)-**7b** [49 mg, 33%, 96.4% ee (OJ; *i*-PrOH : hexane = 9 : 1)] as an amorphous mass; mp 87-89 °C; $[\alpha]_D^{24}$ +253.1 (c = 0.7, $CHCl_3$); ^{1}H-NMR δ: 3.89 (3H, s, OCH_3) 3.93 (6H, s, 2xOCH_3), 6.55 (1H, s, 3-H), 6.75 (1H, s, 8-H), 8.09 (1H, s, 11-H); IR cm^{-1}: 1685 ($NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{21}H_{20}F_3NO_5$: 423.1292. Found: 423.1280.

From **10a** : A mixture of **10a** (346 mg, 0.62 mmol) and TFA (1.7 ml) in CH_2Cl_2 (35 ml) was stirred for 4 h. Preparative TLC of the yellowish brown oil (256 mg) with $CHCl_3$ gave *(R)-(-)-6-trifluoroacetylnordomesticine* (**11a**) as an amorphous mass (103 mg, 41%, 94.7% ee). A manner similar to that noted for **7a** gave colorless crystals (17 mg, 6.7%, 79.6% ee, mp 256-257 °C) and (-)-**11a** [82 mg, 32%, 95.3% ee (OD; *i*-PrOH : hexane = 9 : 1)]as an amorphous mass; mp 243-244 °C; $[\alpha]_D^{21}$ -259.4 (c = 0.1, $CHCl_3$); ^{1}H-NMR δ: 3.91 (3H, s, OCH_3) 5.96 (2H, s, OCH_2O), 6.55 (1H, s, 3-H), 6.73 (1H, s, 8-H), 7.99 (1H, s, 11-H); IR cm^{-1}: 1685 ($NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{20}H_{16}F_3NO_5$: 407.0978. Found: 407.0972.

From **10b**: A mixture of **10b** (233 mg, 0.57 mmol) and TFA (1.1 ml) in CH_2Cl_2 (23 ml) was stirred for 4 .5 h. Preparative TLC of the yellowish brown oil (171 mg) with $CHCl_3$ gave *(S)-(+)-6-trifluoroacetylnordomesticine* (**11b**) as an amorphous mass (79 mg, 47%, 93.1% ee). A manner similar to that noted for **7a** gave colorless crystals (36 mg, 21%, 92.5% ee, mp 244-245 °C) and (+)-**11b** [39 mg, 23%, 94.7% ee[14] (OD; *i*-PrOH : hexane = 9 : 1)] as an amorphous mass; mp 244-245 °C; $[\alpha]_D^{21}$ +262.3 (c = 0.1, $CHCl_3$); ^{1}H-NMR δ: 3.92 (3H, s, OCH_3), 5.96 (2H, s, OCH_2O), 6.55 (1H, s, 3-H), 6.73 (1H, s, 8-H), 7.99 (1H, s, 11-H); IR cm^{-1}: 1685 ($NCOCF_3$). High resolution MS (*m/z*) Calcd for $C_{20}H_{16}F_3NO_5$: 407.0979. Found: 407.0995.

b) In CH_3CN. From **6a** : A mixture of **6a** (316 mg, 0.55 mmol) and TFA (1.5 ml) in CH_3CN (30 ml) was stirred at -30 °C for 7.5 h. Preparative TLC of the yellowish brown oil (277 mg) with $CHCl_3$-acetone (35 : 1) gave aporphine (**7a**) {37 mg (16%), an amorphous mass, mp 162-168 °C, $[\alpha]_D^{26}$ -213.3 (c = 0.3, $CHCl_3$) (84% ee)}, the starting *p*-quinol acylate (**6a**) (89 mg, 28%), and *(9R)-(-)-N–trifluoroacetylnorsebiferine* (**14a**) (81 mg, 35%) (porality ; **7a** < **6a** < **14a**). The former two compounds were spectroscopically identified against authentic specimens. Crystallization of the latter product (**14a**) from ether afforded colorless crystals, mp 202-203.5 °C. $[\alpha]_D^{25}$ -59.1 (c = 0.4, $CHCl_3$) [92% ee (OC; EtOH : hexane = 7 : 1)]; ^{1}H-NMR δ: 3.80, 3.85, 3.89 (each 3H, s, OCH_3), 6.32 (1H, s, 5-H), 6.34, 6.39 (1H, each s, 8-H), 6.60 (1H, s, 1-H), 6.82 (1H, s, 4-H); IR cm^{-1}: 1690, 1680, 1655, 1628 ($NCOCF_3$ and dienone). High resolution MS (*m/z*) Calcd for $C_{21}H_{20}F_3NO_5$: 423.1292. Found: 423.1289.

From **6b** : A mixture of **6b** (175 mg, 0.3 mmol) and TFA (0.85 ml) in CH_3CN (19 ml) was stirred at -30 °C for 7.5 h. Preparative TLC of the yellowish brown oil (141 mg) with $CHCl_3$-acetone (35 : 1) gave noraporphine (**7b**) {21 mg (16%), an amorphous mass, mp 156-159 °C, $[\alpha]_D^{25}$ +214 (c = 0.3, $CHCl_3$) (86.6% ee)}, the starting *p*-quinol acylate (**6b**) (57 mg, 31%), and *(9S)-(+)-N–trifluoroacetylnorsebiferine* (**14b**) (41 mg, 31%) (porality ; **7b** < **6b** < **14b**). The former two compounds were spectroscopically identified with authentic specimens, respectively. Crystallization of the latter product (**14b**) from ether afforded colorless crystals, mp

203-204 °C. $[\alpha]_D^{25}$ +60.7 (c = 0.4, $CHCl_3$) [98.1% ee (OC; EtOH : hexane = 7 : 1)]; ^{1}H-NMR δ: 3.80, 3.85, 3.89 (each 3H, s, OCH_3), 6.32 (1H, s, 5-H), 6.34, 6.39 (1H, each s, 8-H), 6.60 (1H, s, 1-H), 6.82 (1H, s, 4-H); IR cm^{-1}: 1690, 1680, 1655, 1628 ($NCOCF_3$ and dienone). High resolution MS (*m/z*) Calcd for $C_{21}H_{20}F_3NO_5$: 423.1292. Found: 423.1295.

From **10a** : A mixture of **10a** (302 mg, 0.54 mmol) and TFA (1.5 ml) in CH_3CN (30 ml) was stirred at -30 °C for 4 h. Preparative TLC of the yellowish brown oil (268 mg) with hexane-AcOEt (1 : 1) gave the noraporphine (**11a**) {13 mg (6%), an amorphous mass, mp 234-237 °C, $[\alpha]_D^{26}$ -211.4 (c = 0.3, $CHCl_3$) (93.5% ee)}, the starting *p*-quinol acylate (**10a**) (109 mg, 36%), and *(9R)-(-)-N–trifluoroacetylnoramurine* (**17a**) (59 mg, 27%) (porality ; **11a** < **10a** < **17a**). The former two compounds were spectroscopically identified by comparison with authentic specimens. Crystallization of the latter product (**17a**) from ether afforded a small amount of colorless crystals (0.7 mg, mp 206-207 °C, 9.6% ee). Evaporation of the filtrate under reduced pressure gave an amorphous mass (**17a**) {42 mg (19%), mp 102-105 °C; $[\alpha]_D^{27}$ -31.6 (c = 0.4, $CHCl_3$) [94.9% ee (OJ; EtOH : hexane = 1 : 1)]; ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 5.93 (2H, AB type, OCH_2O), 6.28 (1H, s, 5-H), 6.34, 6.37 (1H, each s, 8-H), 6.58 (1H, s, 1-H), 6.86 (1H, s, 4-H); IR cm^{-1}: 1690, 1680, 1660, 1630 ($NCOCF_3$ and dienone). High resolution MS (*m/z*) Calcd for $C_{20}H_{16}F_3NO_5$: 407.0979. Found: 407.0976.

From **10b** : A mixture of **10b** (226 mg, 0.4 mmol) and TFA (1 ml) in CH_3CN (20 ml) was stirred at -30 °C for 5 h. Preparative TLC of the yellowish brown oil (190 mg) with hexane-AcOEt (1 : 1) gave aporphine (**11b**) {28 mg (17%), an amorphous mass, mp 198-206 °C, $[\alpha]_D^{26}$ +107.4 (c = 0.2, $CHCl_3$) (83.1% ee)}, the starting the *p*-quinol acylate (**10b**) (104 mg, 46%), and *(9S)-(+)-N–trifluoroacetylnoramurine* (**17b**) (36 mg, 22%) (porality ; **11b** < **10b** < **17b**). The former two compounds were spectroscopically identified by comparison with authentic specimens. Crystallization of the latter product (**17b**) from ether afforded a small amount of colorless crystals (1.4 mg, mp 205-206 °C, 6.6% ee). Evaporation of the filtrate under reduced pressure gave an amorphous mass (**17b**) {25 mg (15%), mp 107-117 °C; $[\alpha]_D^{27}$ +37.1 (c = 0.5, $CHCl_3$) [95.2% ee (OJ; EtOH : hexane = 1 : 1)]; ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 5.93 (2H, AB type, OCH_2O), 6.28 (1H, s, 5-H), 6.34, 6.37 (1H, each s, 8-H), 6.58 (1H, s, 1-H), 6.86 (1H, s, 4-H). IR cm^{-1}: 1690, 1680, 1660, 1630 ($NCOCF_3$ and dienone). High resolution MS (*m/z*) Calcd for $C_{20}H_{16}F_3NO_5$: 407.0978. Found: 407.0971.

General Procedure for Hydrolysis of 7, 12, 14, and 17

A solution of **7, 12, 14,** and **17** and 4.3 % aqueous K_2CO_3 in MeOH was refluxed. Usual work-up of the reaction mixture gave an oily residue, which was purified by crystallization or preparative TLC.

(*R*)-(-)-Wilsonirine (8a) : A mixture of (-)-**7a** (108 mg, 0.25 mmol), aqueous K_2CO_3 (2 ml) and MeOH (20 ml) was refluxed for 5 h. A yellowish brown oil (83 mg), which was crystallized from acetone to give (-)-**8a** [19 mg, 23%, 100% ee (OD; *i*-PrOH : hexane = 9 : 1)] as colorless crystals; mp 106-108 °C, $[\alpha]_D^{24}$ -53.9 (c = 0.2, MeOH); ^{1}H-NMR δ: 3.89 (9H, s, 3xOCH_3), 6.53 (1H, s, 3-H), 6.72 (1H, s, 8-H), 8.03 (1H, s, 11-H). High resolution MS (*m/z*) Calcd for $C_{19}H_{21}NO_4$: 327.1469. Found: 327.1465.

(*S*)-(+)-Wilsonirine (8b) : A mixture of (+)-**7b** (76 mg, 0.18 mmol), aqueous K_2CO_3 (1.5 ml) and MeOH (15 ml) was refluxed for 6 h. A yellowish brown oil (63 mg), which was crystallized from acetone to give (+)-**8b** [23 mg, 39%, 95.9% ee (OD; *i*-PrOH : hexane = 9 : 1)] as colorless crystals; mp 107-109 °C, $[\alpha]_D^{24}$ +54.8 (c = 0.1, MeOH) (lit.[8] mp 108-110 °C, $[\alpha]_D^{24}$ +47); ^{1}H-NMR δ: 3.89 (9H, s, 3xOCH_3), 6.53 (1H, s, 3-H), 6.72 (1H, s, 8-H), 8.03 (1H, s, 11-H). High resolution MS (*m/z*) Calcd for $C_{19}H_{21}NO_4$: 327.1468. Found: 327.1456.

(*R*)-(-)-Nordomesticine (12a) : A mixture of (-)-**11a** (46 mg, 0.15 mmol), aqueous K_2CO_3 (1.5 ml) and MeOH (15 ml) was refluxed for 5 h. Preparative TLC of the yellowish brown oil (48 mg) with $CHCl_3$-MeOH (5 : 1) gave (-)-**12a** [20 mg, 55%, 100% ee (OJ; *i*-PrOH : hexane = 9 : 1)] as an oil; ^{1}H-NMR δ 3.89 (3H, s, OCH_3), 5.93 (2H, s, OCH_2O), 6.53 (1H, s, 3-H), 6.70 (1H, s, 8-H), 7.94 (1H, s, 11-H). High resolution MS (*m/z*) Calcd for $C_{18}H_{17}NO_4$: 311.1156. Found: 311.1162. *(R)-(-)-N,O-Diacetylnordomesticine* (**13a**), mp 235-238 °C. $[\alpha]_D^{22}$ -319.3 (c = 0.4, $CHCl_3$) [97% ee (OD; EtOH : hexane = 1 : 5)]; ^{1}H-NMR δ: 2.20, 2.33 (each 3H, s, $OCOCH_3$ and $NCOCH_3$), 3.83 (3H, s, OCH_3), 5.95 (2H, s, OCH_2O), 6.64 (1H, s, 3-H), 6.73 (1H, s, 8-H), 7.36 (1H, s, 11-H). IR cm^{-1}: 1770 ($OCOCH_3$), 1635 ($NCOCH_3$). High resolution MS (*m/z*) Calcd for $C_{22}H_{21}NO_6$: 395.1367. Found: 395.1374.

(*S*)-(+)-Nordomesticine (12b) : A mixture of (+)-**11b** (37 mg, 0.092 mmol), aqueous K_2CO_3 (1.3 ml) and MeOH (12 ml) was refluxed for 5.5 h. Preparative TLC of the yellowish brown oil (34 mg) with $CHCl_3$-MeOH (5 : 1) gave (+)-**12b** [20 mg, 70%, 99% ee (OJ; *i*-PrOH : hexane = 9 : 1)] as an oil; ^{1}H-NMR δ: 3.89 (3H, s, OCH_3), 5.93 (2H, s, OCH_2O), 6.53 (1H, s, 3-H), 6.70 (1H, s, 8-H), 7.94 (1H, s, 11-H). High resolution MS (*m/z*) Calcd for $C_{18}H_{17}NO_4$: 311.1155. Found: 311.1155. *(S)-(+)-N,O-Diacetylnordomesticine* (**13b**), mp 235-236 °C (EtOH) (colorless crystals); $[\alpha]_D^{22}$ +326.4 (c = 0.4, $CHCl_3$) [99.4% ee (OD; EtOH : hexane = 1 : 5)]; ^{1}H-NMR δ: 2.20, 2.33 (each 3H, s, $OCOCH_3$ and $NCOCH_3$), 3.83 (3H, s, OCH_3), 5.95 (2H, s, OCH_2O), 6.64 (1H, s, 3-H), 6.73 (1H, s, 8-H), 7.36 (1H, s, 11-H); IR cm^{-1}: 1770 ($OCOCH_3$), 1635 ($NCOCH_3$). *Anal.* Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.83; H, 5.61; N, 3.62.

(9*R*)-(+)-Norsebiferine (15a) : A mixture of (-)-**14a** (21 mg, 0.05 mmol), aqueous K_2CO_3 (1.2 ml) and MeOH (6 ml) was refluxed for 5 h. Preparative TLC of the yellow oil (19 mg) with $CHCl_3$-MeOH-NH_4OH (100 : 5 : 0.1) gave (+)-**15a** [17 mg, 100%, 96.9% ee (OC; EtOH : hexane = 1 : 1)] as an oil; $[\alpha]_D^{25}$ +16.4 (c = 0.3, $CHCl_3$); ^{1}H-NMR δ: 3.80, 3.85, 3.87 (each 3H, s, OCH_3), 6.27 (1H, s, 5-H), 6.32 (1H, s, 8-H), 6.61 (1H, s, 1-H), 6.78 (1H, s, 4-H); IR cm^{-1}: 1670, 1645, 1625 (dienone). High resolution MS (*m/z*) Calcd for $C_{19}H_{21}NO_4$: 327.1469. Found: 327.1466.

(9*S*)-(-)-Norsebiferine (15b) : A mixture of (+)-**14b** (20 mg, 0.047 mmol), aqueous K_2CO_3 (1.2 ml) and MeOH (6 ml) was refluxed for 5 h. Preparative TLC of the yellow oil (20 mg) with $CHCl_3$-MeOH-NH_4OH (100 : 5 : 0.1) gave (-)-**15b** [17 mg, 100%, 99% ee (OC; EtOH : hexane = 1 : 1)] as an oil; $[\alpha]_D^{25}$ -14.5 (c = 0.3, $CHCl_3$); ^{1}H-NMR δ: 3.80, 3.85, 3.87 (each 3H, s, OCH_3), 6.27 (1H, s, 5-H), 6.32 (1H, s, 8-H), 6.61 (1H, s, 1-H), 6.78 (1H, s, 4-H); IR cm^{-1}: 1670, 1645, 1625 (dienone). High resolution MS (*m/z*) Calcd for $C_{19}H_{21}NO_4$: 327.1469. Found: 327.1454.

(9*R*)-(+)-Noramurine (18a) : A mixture of (-)-**17a** (46 mg, 0.11 mmol), aqueous K_2CO_3 (2.6 ml) and MeOH (13 ml) was refluxed for 2.5 h. Preparative TLC of the yellow oil (35 mg) with $CHCl_3$-MeOH-NH_4OH (100 : 5 : 0.1) gave (+)-**18a** [30 mg, 85%, 93.6% ee (OJ; EtOH : hexane = 9 : 1)] as an oil; $[\alpha]_D^{25}$ +29.6 (c = 0.3, $CHCl_3$); ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 5.91 (2H, AB type, OCH_2O), 6.26 (2H, s, olefinic H), 6.59 (1H, s, 1-H), 6.80 (1H, s, 4-H); IR cm^{-1}: 1670, 1645, 1625 (dienone). High resolution MS (*m/z*) Calcd for $C_{18}H_{17}NO_4$: 311.1156. Found: 311.1146.

(9*S*)-(-)-Noramurine (18b) : A mixture of (+)-**17b** (28 mg, 0.069 mmol), aqueous K_2CO_3 (1.6 ml) and MeOH (8 ml) was refluxed for 4.5 h. Preparative TLC of the yellow oil (22 mg) with $CHCl_3$-MeOH-NH_4OH (100 : 5 : 0.1) gave (-)-**18b** [14 mg, 65%, 95.8% ee (OJ; EtOH : hexane = 9 : 1)] as an oil; $[\alpha]_D^{25}$ -33.3 (c = 0.3, $CHCl_3$); ^{1}H-NMR δ: 3.79 (3H, s, OCH_3), 5.91 (2H, AB type, OCH_2O), 6.26 (2H, s, olefinic H), 6.59

(1H, s, 1-H), 6.80 (1H, s, 4-H); IR cm^{-1}: 1670, 1645, 1625 (dienone). High resolution MS (*m/z*) Calcd for $C_{18}H_{17}NO_4$: 311.1157. Found: 311.1159.

General Procedure for Synthesis of (9*R*)-(-)- and (9*S*)-(+)-Sebiferine (16a and 16b) and (9*R*)-(+)- and (9*S*)-(-)-Amurine (19a and 19b)

A mixture of the amines (**15** and **18**), HCO_2H and formalin was heated on a boiling water bath. The reaction mixture was concentrated under reduced pressure. Then the residue was basified with saturated aqueous $NaHCO_3$ and the product was taken up in $CHCl_3$. Usual work-up of the $CHCl_3$ extract gave an oily residue, which was purified by preparative TLC with $CHCl_3$-MeOH (10 : 1).

(9*R*)-(-)-Sebiferine (16a) : A mixture of the amine (+)-(**15a**) (15 mg, 0.045 mmol), 85% HCO_2H (5.2 ml), and 35% formalin (2.6 ml) was heated for 10 h. Preparative TLC of the yellowish brown oil (17 mg) gave (-)-**16a** [6.7 mg, 44%, 97.1% ee (OJ; EtOH : hexane = 1 : 3)] as an amorphous mass; $[\alpha]_D^{24}$ -13 (c = 0.1, $CHCl_3$); ^{1}H-NMR δ: 2.49 (3H, s, NCH_3), 3.80, 3.85, 3.87 (each 3H, s, OCH_3), 6.31 (1H, s, 5-H), 6.33 (1H, s, 8-H), 6.61 (1H, s, 1-H), 6.79 (1H, s, 4-H); IR cm^{-1}: 1675, 1650, 1630 (dienone). High resolution MS (*m/z*) Calcd for $C_{20}H_{23}NO_4$: 341.1624. Found: 341.1622.

(9*S*)-(+)-Sebiferine (16b) : A mixture of the amine (-)-(**15b**) (16 mg, 0.048 mmol), 85% HCO_2H (5.6 ml), and 35% formalin (2.8 ml) was heated for 10 h. Preparative TLC of the yellowish brown oil (19 mg) gave (+)-**16b** [8.6 mg, 53%, 97% ee (OJ; EtOH : hexane = 1 : 3)] as an amorphous mass; $[\alpha]_D^{24}$ +12 (c = 0.2, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ +13 (c = 0.3, $CHCl_3$)]; ^{1}H-NMR δ: 2.49 (3H, s, NCH_3), 3.80, 3.85, 3.87 (each 3H, s, OCH_3), 6.31 (1H, s, 5-H), 6.33 (1H, s, 8-H), 6.61 (1H, s, 1-H), 6.79 (1H, s, 4-H); IR cm^{-1}: 1675, 1650, 1630 (dienone). High resolution MS (*m/z*) Calcd for $C_{20}H_{23}NO_4$: 341.1623. Found: 341.1634.

(9*R*)-(+)-Amurine (19a): A mixture of the amine (+)-(**18a**) (28 mg, 0.089 mmol), 98% HCO_2H (10 ml), and 35% formalin (5 ml) was heated for 6.5 h. Preparative TLC of the yellowish brown oil (25 mg) gave (+)-**19a** [7.3 mg, 25%, 99% ee (OJ; EtOH : hexane = 9 : 1)] as colorless crystals; mp 205-206 °C (lit.[12] 213-215 °C), $[\alpha]_D^{27}$ +10.7 (c = 0.2, $CHCl_3$) [lit.[12] $[\alpha]_D^{20}$ +11 (c = 0.2, $CHCl_3$)] ; ^{1}H-NMR δ: 2.47 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 5.91 (2H, AB type, OCH_2O), 6.26, 6.31 (each 1H, s, 5- and 8-H), 6.59 (1H, s, 1-H), 6.80 (1H, s, 4-H). High resolution MS (*m/z*) Calcd for $C_{19}H_{19}NO_4$: 325.1313. Found: 325.1314.

(9*S*)-(-)-Amurine (19b): A mixture of the amine (-)-(**18b**) (14 mg, 0.045 mmol), 98% HCO_2H (5 ml), and 35% formalin (2.5 ml) was heated for 7.5 h. Preparative TLC of the yellowish brown oil (15 mg) gave **19b** (7.8 mg, 53%) as an amorphous mass. Crystallization from $CHCl_3$-ether gave (-)-**19b** [1.5 mg, 10%, 99% ee (OJ; EtOH : hexane = 9 : 1)] as colorless crystals; mp 204-205 °C, $[\alpha]_D^{27}$ -13.5 (c = 0.1, $CHCl_3$) ; ^{1}H-NMR δ: 2.50 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 5.91 (2H, AB type, OCH_2O), 6.26, 6.31 (each 1H, s, 5- and 8-H), 6.59 (1H, s, 1-H), 6.80 (1H, s, 4-H). High resolution MS (*m/z*) Calcd for $C_{19}H_{19}NO_4$: 325.1312. Found: 325.1303.

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