A SYNTHETIC APPROACH TO (±)-*O*-METHYLCLAVIZEPINE: AN ALTERNATIVE SYNTHESIS OF *C*-NORCULARINE§

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Abstract --- *C*-Norcularine (**2**) was synthesized stepwise *via* the xanthone (**3**) or by intramolecular Pictet-Spengler reaction directly from the amino aldehyde (**10**).

(-)-Clavizepine (**1a**), a unique dibenzopyranazepine alkaloid, has been isolated from *Corydalis claviculata* (L).[1] From the view of the novel structure and pharmacological activities[2] of 1-aryl-3-benzazepine, which is a seco-compound of **1**, **1a** is an attractive target for total synthesis. Since structure of *O*-methylclavizepine (**1b**) is closely related to *C*-norcularine (**2**), skeleton of **1** might be constructed from **2** by expansion of B ring. However no synthetic study on **1a** and **1b** has been performed so far. The novel transformation of **2** to **1b**, therefore, seems to be developed by efficient synthesis of **2**. Although *C*-norcularine (**2**)[3] is synthesized *via* dehydro-*C*-norcularine by intramolecular Pictet-Spengler reaction of the amide aldehyde, we planed to synthesize **2** through xanthones (**3**), which might be also converted to **1b**.[4] Here we wish to describe an alternative

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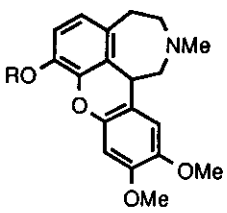
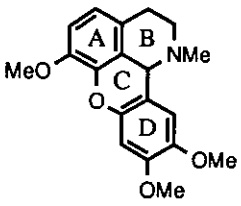
§ Dedicated to Professor Emeritus Masatomo Hamana on the occasion of his 75th birthday.



1

1a : R=H

1b : R=Me



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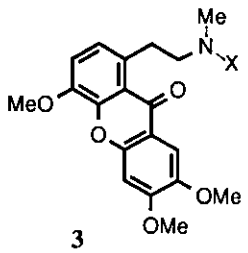
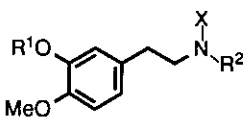


3

3a : X=$COCF_3$

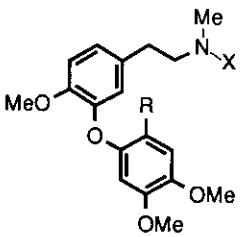
3b : X=H



4 : R^1=H, R^2=Me, X=$COCF_3$

5 : R^1=CH_2Ph, R^2=X=H

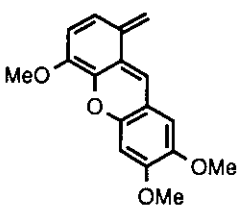
6 : R^1=CH_2Ph, R^2=H, X=CHO



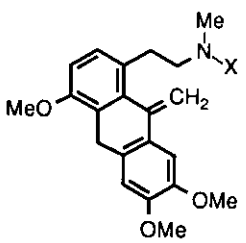
7 : R=CHO, X=$COCF_3$

8 : R=COOH, X=$COCF_3$

10 : R=CHO, X=H



9 $(M-43)^+$



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synthesis of *C*-norcularine (**2**) from **3a**.

At first, an *N*-protected hydroxyphenethylamine (**4**), a part for the Ullmann connection, was prepared. Treatment of a known phenethylamine (**5**)[8] with ethyl formate gave an *N*-formate (**6**), reduction of which with lithium aluminum hydride ($LiAlH_4$) followed by *N*-trifluoroacetylation and subsequent debenzylation yielded a phenolic phenethylamine (**4**). The Ullmann reaction of **4** with 6-bromoveratraldehyde in the presence of copper catalyst[9] afforded a biaryl ether (**7**), mp 111-113°C, in 63% yield. ^{1}H-Nmr spectrum of **7** showed three singlets (δ 3.77, 3.82, 3.90) due to three methoxyl groups to prove formation of ether linkage. The aldehyde (**7**) was oxidized with potassium permanganate ($KMnO_4$) under neutral conditions[10] to give a carboxylic acid (**8**), mp 163-165°C, which was cyclized by polyphosphoric acid (PPA) to yield the desired xanthone (**3a**), mp 178°C, in 82% yield from **7**. In ir spectrum of **3a** a carbonyl absorption appears at 1640 cm^{-1} showing characteristic conjugation of the carbonyl group with two aryls. The xanthone (**3a**) was treated with aqueous potassium carbonate (aq. K_2CO_3) to give an amino ketone (**3b**), sodium borohydride ($NaBH_4$) reduction of which produced directly the tetracyclic compounds (**2**), mp 164-165°C,[11] in 56% yield from **3a**. In mass spectrum of **2**, two peaks of molecular ion (*m/z*: 327) and retro-Diels-Alder fragment ion (**9**) [*m/z*: 284 (M^+-43)] exist, and a singlet of 6a-proton (δ 5.14) appears in ^{1}H-nmr spectrum. Those spectral data supported the structure to be **2**. To confirm the structure, an authentic sample was prepared through a modified Kametani's procedure.[3] Deprotection of the amide (**7**) with aq. K_2CO_3 yielded the secondary amine (**10**), which without purification was subjected to intramolecular Pictet-Spengler reaction. Thus, stirring of the mixture of **10** and conc. hydrochloric acid (c. HCl) at room temperature for 5 days formed sluggishly *C*-norcularine (**2**), mp 164-165°C, in 60% yield (from **7**). This authentic sample was identical in all respects with the tetracyclic compound (**2**) described above.

In conclusion, synthesis of *C*-norcularine was accomplished by the alternative route. Transformation of *C*-norcularine (**2**) to *O*-methylclavizepine (**1b**) by the Stevens-type rearrangement[12] is now in progress.

ACKNOWLEDGEMENT

The authors are indebted to Takasago Perfumery Co., Ltd. for the supply of vanillin and to Sankyo Co., Ltd. for elemental analyses. Thanks are also to Miss N. Sawabe and Mrs. F. Hasegawa of this Faculty for nmr and mass spectral measurements.

EXPERIMENTAL

All melting points were measured on a Büchi melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were taken with a JEOL model GSX-500 (500 MHz) and FX-100 (100 MHz) in $CDCl_3$ solution with Me_4Si as an internal standard. Ir spectra were run on a Hitachi model 260 spectrophotometer in $CHCl_3$ solution. Mass spectra were measured on a Hitachi model M-80A mass spectrometer. Preparative thin layer chromatography (tlc) was performed on silica gel 60 F_{254} plates (Merck; 2.0 mm thick).

***N*-Formyl-3-benzyloxy-4-methoxyphenethylamine (6)**

A mixture of 3-benzyloxy-4-methoxyphenethylamine (**5**)[8] (5.67 g, 0.22 mol) and ethyl formate (50 ml, 0.62 mol) was heated to reflux for 6 h. Evaporation of excess ethyl formate under reduced pressure gave pale yellow crystals (6.53 g, quantitative), which were recrystallized from hexane to afford **6** as colorless crystals(5.81 g, 89%), mp 96-97°C. High resolution ms Calcd for $C_{17}H_{19}NO_3$: 285.1364. Found: 285.1365. ^{1}H-Nmr δ: 3.85 (3H, s, OMe), 5.13 (2H, s, PhCH_2O), 7.96 (1H, s, CHO). Ir (cm^{-1}): 3450 (NHCO), 1690 (NHCO).

***N*-Methyl-*N*-trifluoroacetyl-3-hydroxy-4-methoxyphenethylamine (4)**

A solution of the formamide (**6**) (396 mg, 1.43 mmol) in anhydrous THF (5 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (212 mg, 5.6 mmol) in dry ether (6.5 ml) under ice cooling. After stirring for 20 min at room temperature, the reaction mixture was heated at 50°C (bath temperature) for 6 h. After decomposition of the excess reductant, the mixture was filtered. The filtrate was dried over anhydrous K_2CO_3 and evaporated under reduced pressure to give *N*-methyl-3-benzyloxy-4-methoxyphenethylamine as a pale yellow oil (382 mg) [^{1}H-nmr δ: 2.35 (3H, s, N*Me*), 3.84 (3H, s, O*Me*), 5.11 (2H, s, PhCH_2O)]. To a stirred mixture of the crude secondary amine (382 mg, 1.4 mmol), anhydrous K_2CO_3 (292 mg, 2.1 mmol), and dichloromethane (10 ml), was added dropwise trifluoroacetic anhydride (0.3 ml, 2.1 mmol) under ice cooling. Then the mixture was stirred at room temperature for 1 h. The reaction mixture was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave *N*-methyl-*N*-trifluoroacetyl-3-benzyloxy-4-methoxyphenethylamine as colorless crystals, mp 47-49°C (427 mg, 83% from **6**) [high resolution ms Calcd for $C_{19}H_{20}NO_3F_3$:367.1393. Found: 367.1383; ^{1}H-nmr δ: 3.84 (3H, s, O*Me*), 5.11 (2H, s, PhCH_2O); ir (cm^{-1}): 1690 (-NCOCF_3)]. A mixture of the trifluoroacetamide (427 mg, 1.16 mmol), 2% $PdCl_2$ solution (0.45 ml), active carbon (90 mg) and MeOH (8 ml) was hydrogenated under atmospheric pressure until uptake of hydrogen ceased. The mixture was filtrated and the filtrate was concentrated to give a residue, which was dissolved into $CHCl_3$. The solution was washed with brine and dried over anhyrous Na_2SO_4. Evaporation of the solvent gave the phenolic amide (**4**) as a pale brown oil (278 mg, 85%). High resolution ms Calcd for $C_{12}H_{14}NO_3F_3$: 277.0924. Found: 277.0961. ^{1}H-Nmr δ: 2.90-3.06 (3H, m, N*Me*), 3.85 (3H, s, O*Me*). Ir (cm^{-1}): 3540 (OH), 1690 (NCOCF_3).

6-[5-ß-(*N*-Methyl-*N*-trifluoroacetylamino)ethyl-2-methoxy]phenyloxy-veratraldehyde (7)

A mixture of the phenolic amide (**4**) (5.44 g, 20 mmol), 6-bromoveratraldehyde (5.51 g, 23 mmol), anhydrous K_2CO_3 (3.11 g, 23 mmol), finely powdered CuO[9] (1.87 g, 24 mmol) and pyridine (50 ml) was heated to reflux under Ar atmosphere for 13 h. After cooling, the reaction mixture was filtered and the collected solid was thoroughly washed with ether. Usual work-up of the combined filtrate gave an oily product, which was purified by silica gel column chromatography with $CHCl_3$-MeOH (50:1) as eluant to afford the title compound (**7**) as pale yellow crystals. Recrystallization from benzene-hexane gave colorless crystals, mp 111-113°C (4.23 g, 49%). *Anal.* Calcd for $C_{21}H_{22}NO_6F_3$: C, 57.14; H, 5.02; N, 3.17; F, 12.91. Found: C, 57.37; H, 4.98; N, 3.26; F, 12.84. ^{1}H-Nmr δ: 3.77, 3.82, 3.90 (each 3H, s, OMe), 6.28 (1H, d, *J*=2.9 Hz, 6'-*H*), 6.66-6.80 (1H, m, Ar*H*), 6.81-6.97 (2H, m, Ar*H*), 7.34 (1H, s, 2-*H*), 10.36 (1H, s, C*H*O). Ir (cm^{-1}): 1695 (N*COCF*$_3$, CHO).

6-[5-ß-(*N*-Methyl-*N*-trifluoroacetylamino)ethyl-2-methoxy]phenyloxy-veratric acid (**8**)

1% Aqueous $KMnO_4$ solution (120 ml, 7.6 mmol) was added dropwise to a mixture of the diaryl ether (**7**) (845 mg, 1.9 mmol), anhydrous $MgSO_4$[10] (1.6 g, 13 mmol) and acetone (400 ml), and then the whole was refluxed with stirring for 3 h. After cooling, the precipitate was filtered off and the filtrate was concentrated. Saturated aq. $KHCO_3$ solution (80 ml) was added to the residue and the alkaline solution was washed with ether. Aqueous layer was acidified with c. HCl and then the product was extracted with a mixture of $CHCl_3$ and MeOH (5:1). The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the title compound (**8**) as pale yellow crystals (760 mg, 87%), which were recrystallized from benzene to afford colorless crystals (598 mg, 68%), mp 163-165°C. *Anal.* Calcd for $C_{21}H_{22}NO_7F_3$: C, 55.02; H, 5.06; N, 3.06; F, 12.43. Found: C,

55.31; H, 4.89; N, 3.12; F, 12.44. ^{1}H-Nmr δ: 3.72, 3.77, 3.91 (each 3H, s, OMe), 6.27 (1H, d, *J*=6 Hz, 3 -*H*), 6.71-7.10 (3H, m, Ar*H*), 7.59 (1H, s, 2-*H*). Ir (cm^{-1}): 3350 (COO*H*), 1730 (*C*OOH), 1695 (-N*C*O*C*F$_3$).

1-[ß-(*N*-Methyl-*N*-trifluoroacetylamino)ethyl]-4,6,7-trimethoxyxanthone (3a)

A mixture of the acid (**8**) (1.13 g, 2.5 mmol) and commercially available PPA (13.6 g) was heated at 60-80°C (bath temperature) for 3 h under Ar stream. To the reaction mixture was added ice-water and then the solution was neutralized with $KHCO_3$ (powder). The product was extracted with $CHCl_3$, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the xanthone (**3a**) as colorless crystals (929 mg), which were recrystallized from MeOH to afford colorless crystals (820 mg, 83%), mp 178°C. *Anal*. Calcd for $C_{21}H_{20}NO_6F_3$: C, 57.41; H, 4.59; N, 3.19; F, 12.97. Found: 57.30; H, 4.39; N, 3.18; F, 13.17. Ms: *m/z* 439 (M^+). ^{1}H-Nmr δ: 4.00 (9H, s, 3xOMe), 6.99, 7.12 (each 1H, d, *J*=8.3 Hz, 2- and 3-*H*), 7.00 (1H, s, 5-*H*), 7.58 (1H, s, 8-*H*). Ir (cm^{-1}): 1640 (Ar*C*OAr), 1695 (-N*C*O*C*F$_3$).

1-[ß-(*N*-Metylamino)ethyl]-4,6,7-trimethoxyxanthone (3b)

10% K_2CO_3 solution (2 ml, 1.45 mmol) was added to a mixture of the xanthone (**3a**) (38 mg, 0.087 mmol) and MeOH (10 ml), and the whole was refluxed with stirring for 20 min. Reaction mixture was concentrated and diluted with water. The product was extracted with $CHCl_3$, and then the organic layer was washed with brine and dried over anhydrous K_2CO_3. The solvent was evaporated under reduced pressure to give the title compound (**3b**) as a brown oil (28 mg). ^{1}H-Nmr δ: 2.44 (3H, s, N*M*e), 2.85 (2H, t, *J*=7.1 Hz, ArC*H*$_2$CH$_2$-N), 3.44 (2H, t, *J*=7.1 Hz, ArCH$_2$C*H*$_2$N), 3.95 (3H, s, O*M*e), 3.97 (6H, s, 2xO*M*e),

6.80-7.20 (3H, m, Ar*H*), 7.58 (1H, s, 8-*H*). Ir (cm^{-1}): 1640 (Ar*CO*Ar). This product was rather unstable and used for next reaction without purification.

6-[5-ß-(*N*-Methylamino)ethyl-2-methoxy]phenyloxyveratraldehyde (10)

A mixture of the diaryl ether (**7**) (220 mg, 0.5 mmol), 10% K_2CO_3 solution (5 ml, 4.3 mmol) and MeOH (20 ml) was heated to reflux for 30 min. After concentration, water was added to the residue and the product was extracted with $CHCl_3$. Organic layer was washed with brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave the title compound (**10**) as a brown oil (171 mg). ^{1}H-Nmr δ: 2.42 (3H, s, N*Me*), 3.77, 3.83, 3.91 (each 3H, s, O*Me*), 6.30 (1H, s, 5-*H*), 6.62-7.04 (3H, m, Ar*H*), 7.35 (1H, s, 3 -*H*), 10.37 (1H, s, C*HO*). Ir (cm^{-1}): 1670 (CHO).

***C*-Norcularine (2)**

(a) $NaBH_4$ (104 mg, 2.75 mmol) was added portion by portion to a solution of the aminoethylxanthone (**3b**) (28 mg, 0.082 mmol) in MeOH (10 ml) under ice cooling. The mixture was stirred at room temperature for 24 h, and then $NaBH_4$ (46 mg, 1.22 mmol) was added to the reaction mixture. The whole was further stirred for 5 h and concentrated under reduced pressure. The residue was diluted with water and extracted with $CHCl_3$. The organic layer was washed with brine and dried over anhydrous K_2CO_3. Evaporation of the solvent gave an oil (25 mg), which was purified by silica gel column chromatography [eluant: $CHCl_3$-MeOH (10:1)] to afford **2** (16 mg, 56% from **3a**) as brownish yellow crystals. which were recrystallized from acetonitrile to afford colorless crystals, mp 164-165°C. *Anal*. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.41; H, 6.43; N, 4.31. Ms: *m/z* 327 (M^+), 284 (M^+-43). ^{1}H-Nmr (500 MHz) δ: 2.17 (3H, s, N*Me*), 3.88, 3.91, 3.93 (each 3H, s, O*Me*), 5.14 (1H, s, 6a-*H*), 6.8048, 7.08 (each 1H, s, 7- and 10-*H*), 6.8051, 6.83 (each 1H, d, *J*=8.4 Hz, 2- and 3-*H*).

(b) A mixture of the amino aldehyde (**10**) (171 mg, 0.5 mmol) and c. HCl (10 ml, 100 mmol) was stirred at room temperarure for 24 h, and then c. HCl (2 ml, 20 mmol) was added to the mixture. The whole was stirred for 5 days at the same temperature. The reaction mixture was diluted with water and neutralized with Na_2CO_3 (powder) under ice cooling. The product was extracted with $CHCl_3$, and the organic layer was washed with brine and dried over anhydrous K_2CO_3. Evaporation of the solvent under reduced pressure gave a brown oil (182 mg), which was subjected to silica gel column chromatography to be separated to two compounds. First fraction [eluant: $CHCl_3$-MeOH (50:1)] gave *C*-norcularine (**2**) (98 mg, 60% from **7**) as brownish yellow crystals, which were recrystallized from acetonitrile to afford colorless crystals, mp 164-165°C. Starting amino aldehyde (**10**) (35 mg) was recovered from second fraction [eluant: $CHCl_3$-MeOH (10:1)]. Spectral data of the product were completely consistent with those of *C*-norcularine prepared from **3b**.

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11. The melting point of **2** was different from that (mp 137°C) reported in literature.[3] We thank Professor K. Fukumoto, Tohoku University, for his valuable suggestion, although direct comparison of each compound was not carried out.
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Received, 7th October, 1991