Chemistry of Renieramycins. Part 4. Synthesis of a Simple Natural Marine Product, 6-Hydroxy-7-methoxyisoquinolinemethanol

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6-Hydroxy-7-methoxyisoquinolinemethanol (15) and mimosamycin (1) were recently isolated from a marine sponge, *Haliclona* sp. The former was prepared in ten steps from vanillin (22) in 26% overall yield using an isopropyl for phenol protection.

Key words Pomeranz–Fritsch synthesis; phenol; marine natural product; isoquinoline; isopropyl protecting group

During the past two decades, mimosamycin (**1**) and renierone (**2**) and its derivatives (**3**—**14**) have been isolated from marine sponges belonging to genera *Reniera*,[1—3] *Xestospongia*,[4—7] *Cribrochalina*,[8,9] *Haliclona*,[10—12] and *Petrosia*,[13,14] as well as a nudibranch, *Jorunna funebris*.[15—17] Recently, **1** and 6-hydroxy-7-methoxyisoquinolinemethanol (**15**) were isolated from the cytotoxic fractions of an aqueous extract of a marine sponge *Haliclona* sp., and the structure of **15** was established by conventional spectroscopic methods, particularly, nuclear Overhauser enhancement (NOE) experiments.[12] In the course of our chemical studies of these natural marine products, we have been interested in the structure of **15** because the biosynthetic pathway of this natural product may be different from those of **2**—**14**. We describe herein the five-steps synthesis of **15** from known compound **16**.[18]

To establish the practical synthesis of **15**, it is important to select a protecting group for the phenol. We chose an isopropyl group to protect the phenolic function because selective deprotection could be achieved by using $TiCl_4$ at room temperature, leaving methoxyl-substituted arenas unaffected.[19,20] According to the procedure of Rozwadowska and Brozda,[21] a two-phase system composed of the starting material **16** with potassium cyanide and benzoyl chloride in dichloromethane and water gave the Reissert compound **17** in 75% yield, which, upon treatment with formalin in the presence of a phase transfer catalyst, benzyltriethylammonium chloride (TEBA), in 50% aqueous NaOH and acetonitrile at room temperature afforded [7-methoxy-6-(1-methylethoxy)-1-isoquinolyl]methanol (**18**) in 91% yield.

The direct conversion of **18** into the final goal **15** under a variety of conditions was unsuccessful. It was difficult to remove the inorganic materials from the crude products because of the poor solubility of **15** in organic solvents. Accordingly, a sequence of reactions was examined. Treatment of **18** with acetic anhydride and triethylamine in dichloromethane afforded acetate **19** in quantitative yield,

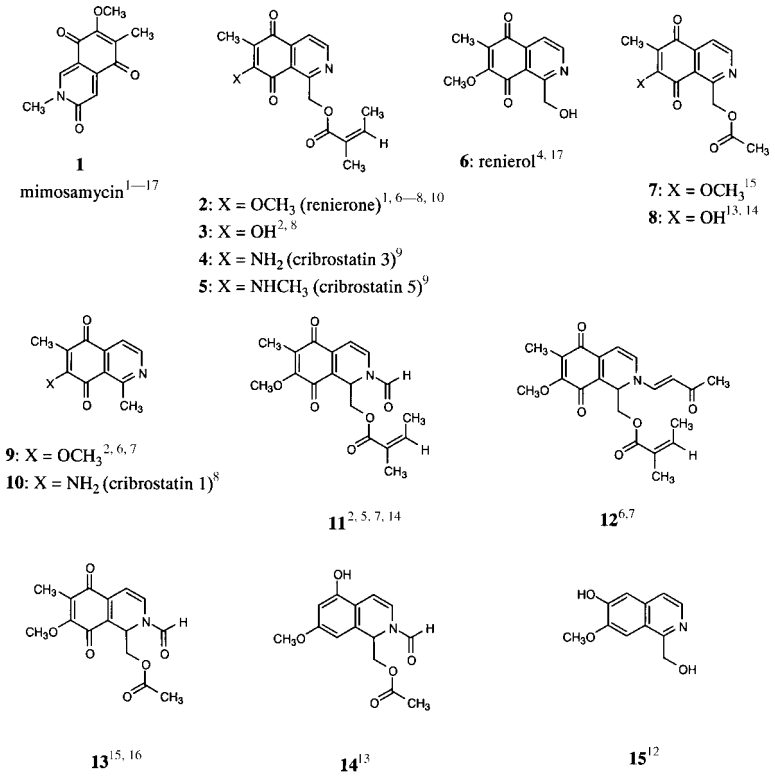

Fig. 1

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Table 1. NMR Data for Diacetates **21** and **27**

C no.	Compound **21**				Compound **27**			
	^{13}C	^{1}H mult., *J* (Hz)	HMBC	NOESY	^{13}C	^{1}H mult., *J* (Hz)	HMBC	NOESY
1	152.6 s				153.6 s			
3	140.7 d	8.44 d (5.6)	C-1, C-4, C-10	4-H	142.5 d	8.45 d (5.6)	C-1, C-4, C-10	4-H
4	120.8 d	7.56 d (5.6)	C-3, C-5, C-9	3-H	120.2 d	7.55 d (5.6)	C-3, C-5, C-9	3-H, 5-H
5	119.9 d	7.52 s	C-4, C-6, C-7, C-9		106.3 d	7.18 s	C-4, C-6, C-7, C-9	4-H, OCH_3
6	144.1 s				153.8 s			
7	151.5 s				141.5 s			
8	104.2 d	7.48 s	C-1, C-6, C-7, C-10	OCH_3, 11-H_2	117.8 d	7.77 s	C-6, C-7, C-10	11-H_2
9	126.0 s				122.1 s			
10	132.1 s				136.6 s			
11	65.5 t	5.70 s	C-1, C-9, C-13	8-H	65.5 t	5.61 s	C-1, C-9, C-13	8-H
13	170.8 s				170.7 s			
14	20.9 q	2.16 s	C-13		20.9 q	2.15 s	C-13	
16	168.6 s				168.9 s			
17	20.6 q	2.39 s	C-16		20.6 q	2.39 s	C-16	
OCH_3	56.1 q	3.98 s	C-6	8-H	56.6 q	3.98 s	C-6	5-H

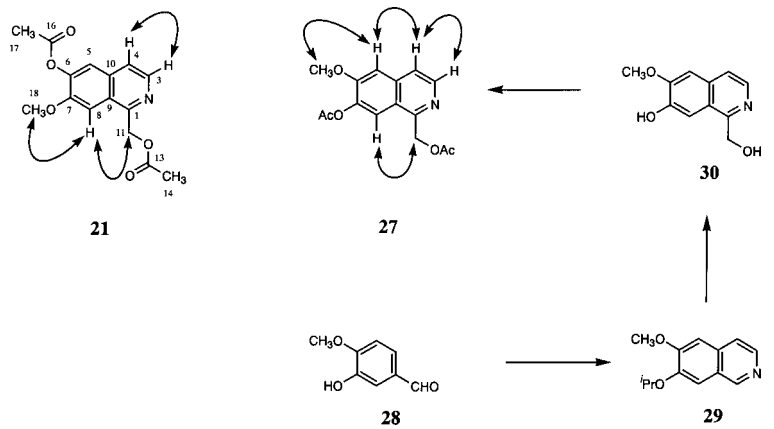

Fig. 2

which upon treatment with $TiCl_4$ gave phenol **20** in 67% yield. After hydrolyzing **20** with 10% aqueous LiOH and chloroform, the pH of the mixture was brought to 6—7 using acetic acid, and the reaction mixture was concentrated *in vacuo* to give a residue that was subjected to purification by silica gel column chromatography to afford a solid, the recrystallization of which from ethanol gave 6-hydroxy-7-methoxyisoquinolinemethanol (**15**) in 73% yield. Thus, we succeeded in preparing the structure reported for the natural product, but the properties of the ^{1}H- and ^{13}C-NMR spectrum could not be identical with those reported in the literature. All the proton and carbon 13 signals of **15** reported by Rashid and co-workers[12] revealed a distinct upfield shift comparable to synthetic **15**. However, the spectral data of synthetic **15** in dimethylsulfoxide (DMSO)-d_6 with two drops of trifluoroacetic acid (TFA)-*d* was in excellent agreement with the reported data of **15**. This result indicates that the reported sample may be produced in the form of a salt during the extraction and isolation procedure.[22]

Finally, the fully assigned ^{13}C-NMR signals for diacetates **21** and **27**[23] that were obtained by acetylation of **15** and **30** with acetic anhydride in pyridine were recorded (Table 1). Unambiguous assignment was made possible by long-range ^{1}H–^{13}C connectivity, which was determined through a series of ^{1}H detected two-dimensional heteronuclear multiple bond correlation (HMBC) NMR experiments and NOE (Fig. 2). These spectra clearly showed that acetates 21 and 27 were identical.

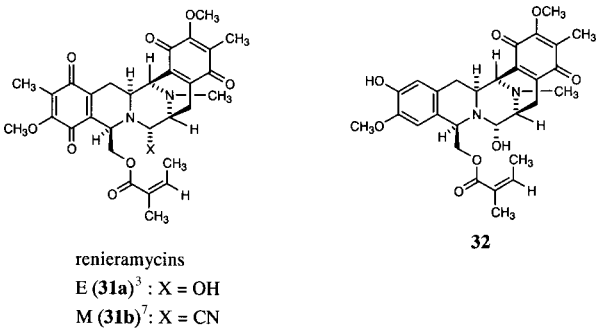

Fig. 3

In summary, we succeeded in the practical synthesis of a simple natural marine product **15** from vanillin (**22**) in 26% overall yield. There are scant data on the biosynthesis of simple natural marine products **3**—**14**; however, it is interesting that they have often been isolated, together with their dimeric analogues. He and Faulkner suggested that renieramycin-type compounds (such as **31a**) underwent oxidative cleavage degradation to give mimosamycin (**1**) and renierone (**2**).[3]

Thus, we believe that it may be possible to discover a new type of renieramycin compound, such as **32**.

Experimental

All melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were obtained with a Hitachi 260-10 IR Fourier-transform spectrometer. ^{1}H-NMR spectra were recorded at 270 MHz on a JEOL JNM-EX 270 spectrometer and at 300 MHz on a JEOL-AL300 spectrometer. ^{13}C-NMR spectra were recorded at 67.5 MHz [multiplicity determined from off-resonance decoupled or distortionless enhancement by polarization transfer (DEPT) spectra]. NMR spectra were measured in $CDCl_3$, and chemical shifts were recorded in δ_H values relative to $(CH_3)_4Si$ as the internal standard. Mass spectra were recorded on a JMS-700 instrument with a direct inlet system operating at 70 eV. Elemental analyses were conducted on YANACO MT-6 CHN CORDER elemental analyzers.

***N*-Benzoyl-1-cyano-7-methoxy-6-(1-methylethoxy)-1,2-dihydroisoquinoline (17)** Benzoyl chloride (3.48 ml, 30 mmol) was added dropwise for 5 min to a stirred solution of **16** (1.09 g, 5 mmol) in dichloromethane (10 ml) and KCN (2.61 g, 40 mmol) in water (10 ml). The mixture was stirred for an additional 2 h, diluted with water (30 ml), and extracted with chloroform (30 ml×3). The combined extracts were washed with brine (30 ml), dried, and concentrated *in vacuo* to give a residue, the recrystallization of which from ethyl acetate–ether gave **17** (1.30 g, 74.7%) as colorless prisms, mp 131—134 °C. ^{1}H-NMR δ: 1.39 (6H, d, J=5.9 Hz, CH(C<u>H</u>$_3$)$_2$), 3.90 (3H, s, OCH_3), 4.56 (1H, sept, J=5.9 Hz, OCH), 5.96 (1H, d, J=7.6 Hz, 3-H), 6.50 (2H, br s, 1-H and 4-H), 6.74, 6.86 (each 1H, s, ArH), 7.43—7.75 (5H, m). ^{13}C-NMR δ: 21.9 (q, CH(C<u>H</u>$_3$)$_2$), 44.8 (d, 1-H), 56.2 (q, OCH_3), 71.7 (d, OCH), 110.3 (d), 112.8 (d), 116.6 (s, CN), 123.3 (s), 124.2 (d), 128.6 (d), 128.8 (d), 129.1 (d), 130.5 (s), 131.8 (d), 148.6 (s), 150.5 (s), 168.7 (s, CO). IR (KBr) cm^{-1}: 1680, 1640, 1520, 1450, 1350, 1240, 1110. MS *m/z* (%): 348 (M^+, 2), 217 (33), 176 (11), 175 (100), 160 (24), 132 (30), 131 (15), 105 (27), 77 (14). High-resolution MS Calcd for $C_{21}H_{20}N_2O_3$: 348.1479. Found: 348.1474.

[7-Methoxy-6-(1-methylethoxy)-1-isoquinolyl]methanol (18) Formalin (1.04 ml) was added dropwise for 5 min to a stirred solution of **17** (1.392 g, 4 mmol), TEBA (120 mg, 0.528 mmol), and 50% aqueous NaOH (2 ml) in acetonitrile (28 ml), and the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with dichloromethane (100 ml) and extracted with 1% HCl solution (100 ml×3). The combined aqueous layer was rendered alkaline with NH_4OH, and extracted with chloroform (150 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a solid (950 mg), the recrystallization of which from ethyl acetate gave **18** (895.4 mg, 90.6%) as colorless prisms, mp 109—112 °C. ^{1}H-NMR δ: 1.48 (6H, d, J=6.3 Hz, CH(C<u>H</u>$_3$)$_2$), 3.40—3.80 (1H, br s, OH), 4.00 (3H, s, OCH_3), 4.78 (1H, sept, J=6.3 Hz, OCH), 5.13 (2H, s, C<u>H</u>$_2$OH), 7.06, 7.11 (each 1H, s, ArH), 7.43 (1H, d, J=5.9 Hz, 4-H), 8.31 (1H, d, J=5.9 Hz, 3-H). ^{13}C-NMR δ: 21.7 (q, CH(C<u>H</u>$_3$)$_2$), 56.1 (q, OCH_3), 61.3 (t, CH_2), 71.1 (d, OCH), 101.6 (d), 107.5 (d), 119.1 (d), 120.4 (s), 132.8 (s), 139.0 (d), 151.2 (s), 151.4 (s), 154.7 (s). IR (KBr) cm^{-1}: 3250, 3000, 1480, 1280, 1240, 1210, 1170. MS *m/z* (%): 247 (M^+, 70), 205 (43), 204 (100), 190 (36), 176 (77), 175 (2), 174 (11), 162 (15), 161 (18), 133 (14). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.74; H, 6.92; N, 5.37.

[7-Methoxy-6-(1-methylethoxy)-1-isoquinolyl]methyl Acetate (19) Acetic anhydride (189 μl, 2 mmol) was added to a stirred solution of **18** (247 mg, 1 mmol) and triethylamine (278 ml, 2 mmol) in dry dichloromethane (10 ml), and the mixture was stirred for 4 h at room temperature. The mixture was diluted with brine (30 ml), then extracted with dichloromethane (30 ml×3). The combined extracts were washed with 5% aqueous $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (348.1 mg). Chromatography on a silica gel (10 g) column with hexane–ethyl acetate (2 : 1) as the eluent gave **19** (288.6 mg, 100%) as a solid. When this sample was left to stand in a refrigerator for a couple of days, colorless crystals were obtained, mp 68.5—69 °C. ^{1}H-NMR δ: 1.48 (6H, d, J=5.9 Hz, CH(C<u>H</u>$_3$)$_2$), 2.15 (3H, s, $COCH_3$), 4.00 (3H, s, OCH_3), 4.78 (1H, sept, J=5.9 Hz, OCH), 5.66 (2H, s, C<u>H</u>$_2$OH), 7.09, 7.36 (each 1H, s, ArH), 7.48 (1H, d, J=5.6 Hz, 4-H), 8.36 (1H, d, J=5.6 Hz, 3-H). ^{13}C-NMR δ: 20.9 (q, CO<u>C</u>H$_3$), 21.7 (q, CH(C<u>H</u>$_3$)$_2$), 56.1 (q, OCH_3), 65.7 (t, CH_2), 71.1 (d, OCH), 103.1 (d), 107.2 (d), 120.1 (d), 122.6 (s), 133.4 (s), 140.8 (d), 151.3 (s), 151.8 (s), 151.8 (s), 170.9 (s, CO). IR (KBr) cm^{-1}: 1720. MS *m/z* (%): 289 (M^+, 24), 246 (17), 205 (24), 204 (100). *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.32; H, 6.70; N, 4.57.

(6-Hydroxy-7-methoxy-1-isoquinolyl)methanol Acetate (20) A stirred solution of **19** (578.0 mg, 2 mmol) in dry dichloromethane (4 ml) was cooled in ice water and a dichloromethane solution of $TiCl_4$ (1.0 M, 6 ml, 6 mmol) was added dropwise for 5 min. This mixture was then stirred at room temperature for 68 h. The reaction mixture was poured into water (100 ml), and the pH was brought to 6—7 with 5% $NaHCO_3$ solution. Then, the mixture was extracted with chloroform (100 ml×3). The combined extracts were washed with brine (100 ml), dried, and concentrated *in vacuo* to give a solid (406 mg), the recrystallization of which from acetone gave **20** (327.6 mg, 66.5%) as colorless prisms, mp 192—193 °C. ^{1}H-NMR δ: 2.14 (3H, s, $COCH_3$), 4.05 (3H, s, OCH_3), 5.69 (2H, s, C<u>H</u>$_2$OH), 7.25, 7.40 (each 1H, s, ArH), 7.49 (1H, d, J=5.6 Hz, 4-H), 8.36 (1H, d, J=5.6 Hz, 3-H). ^{13}C-NMR δ: 20.9 (q, CO<u>C</u>H$_3$), 56.1 (q, OCH_3), 65.5 (t, CH_2), 102.5 (d), 108.7 (d), 120.3 (d), 122.6 (s), 134.0 (s), 140.4 (d), 148.7 (s), 150.0 (s), 151.9 (s), 170.9 (s, CO). IR (KBr) cm^{-1}: 3200, 1740. MS *m/z* (%): 247 (M^+, 24), 205 (22), 204 (100), 190 (9). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.37; H, 5.49; N, 5.37.

6-Hydroxy-7-methoxyisoquinolinemethanol (15) A 10% aqueous LiOH solution (0.5 ml) was added to a stirred solution of **20** (74.1 mg,

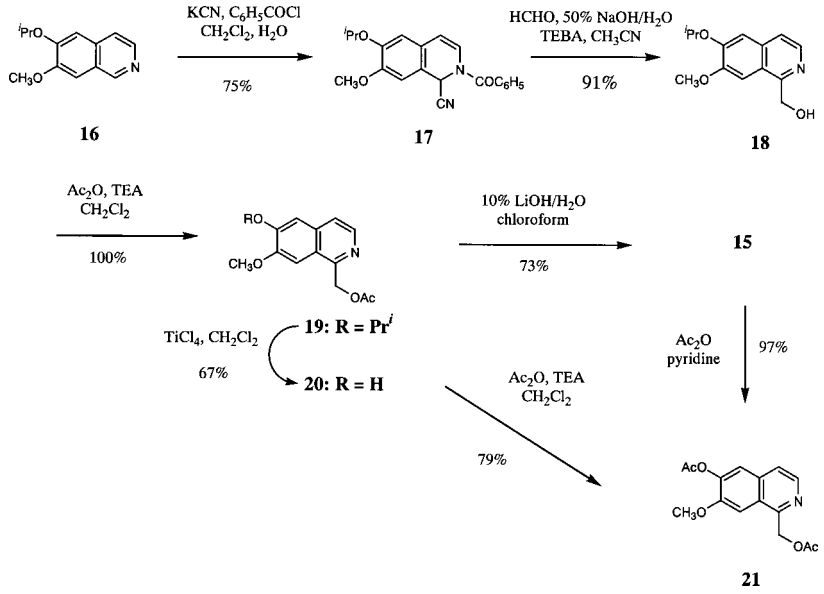

Chart 1

0.3 mmol) in chloroform (5 ml), and the mixture was stirred at room temperature for 2 h. After the pH of the mixture was brought to 6—7 with acetic acid, the mixture was concentrated *in vacuo* to give a residue (151.3 mg). Chromatography on a silica gel (4 g) column with chloroform–methanol (40 : 1) as the eluent gave **1a** (44.7 mg, 72.7%) as a white powder, the recrystallization of which from ethanol gave **15** as colorless needles, mp 202—204 °C. ^{1}H-NMR δ (DMSO-d_6): 3.94 (3H, s, OCH_3), 4.95 (2H, s, CH_2OH), 7.17 (1H, s, ArH), 7.44 (1H, d, J=5.6 Hz, 4-H), 7.52 (1H, s, ArH), 8.14 (1H, d, J=5.6 Hz, 3-H). ^{13}C-NMR δ (DMSO-d_6): 55.6 (q, OCH_3), 63.3 (t, CH_2), 103.9 (d, C-8), 108.4 (d, C-5), 118.5 (d. C-4), 121.0 (s, C-9), 133.0 (s, C-10), 139.2 (d. C-3), 149.8 (s, C-1), 151.6 (s, C-7), 156.7 (s, C-6). . ^{1}H-NMR δ (DMSO-d_6+two drops of TFA-d): 4.02 (3H, s, OCH_3), 5.38 (2H, s, CH_2OH), 7.52 (1H, s, 5-H), 7.60 (1H, s, 8-H), 8.04 (1H, d, J=5.9 Hz, 4-H), 8.20 (1H, d, J=5.9 Hz, 3-H). ^{13}C-NMR δ (DMSO-d_6+two drops of TFA-d): 56.4 (q, OCH_3), 58.4 (t, CH_2), 104.9 (d, C-8), 109.3 (d, C-5), 119.0 (s, C-9), 121.2 (d. C-4), 128.7 (d. C-3), 135.9 (s, C-10), 152.0 (s, C-7), 154.7 (s, C-1), 157.0 (s, C-6). IR (KBr) cm^{-1}: 3400, 3050, 1625, 1575, 1470, 1455, 1440, 1380, 1325, 1255, 1215. MS *m/z* (%): 205 (M^+, 100), 204 (76), 190 (24), 176 (59), 175 (20), 174 (13), 162 (20), 161 (30), 160 (11), 133 (21), 132 (19). High-resolution MS Calcd for $C_{11}H_{11}NO_3$: 205.0739. Found: 205.0741.

(6-Acetyloxy-7-methoxy-1-isoquinolyl)methanol Acetate (21) From **15**: Acetic anhydride (0.2 ml, 2.12 mmol) was added to a stirred solution of **15** (52.6 mg, 0.257 mmol) in dry pyridine (1.0 ml), and the mixture was stirred for 2 h at room temperature. After dilution with water (10 ml), the mixture was extracted with chloroform (10 ml×3). The combined extracts were washed with 5% $NaHCO_3$ (10 ml), dried, and concentrated *in vacuo* to give a residue (80.0 mg), the recrystallization of which from ethyl acetate gave **21** (72.0 mg, 97.0%) as colorless prisms. From **20**: Acetic anhydride (76 μl, 0.8 mmol) was added to a stirred solution of **20** (98.8 mg, 0.4 mmol) and triethylamine (111 ml, 0.8 mmol) in dry dichloromethane (4 ml), and the mixture was stirred for 15 h at room temperature. The mixture was diluted with brine (20 ml) and extracted with dichloromethane (20 ml×3). The combined extracts were washed with 5% aqueous $NaHCO_3$, dried, and concentrated *in vacuo* to give a residue (120.0 mg), the recrystallization of which from ethyl acetate–ether gave **21** (90.8 mg, 78.5%) as colorless prisms, mp 95—96.5 °C. ^{1}H-NMR ($CDCl_3$) and ^{13}C-NMR ($CDCl_3$): see Table 1. ^{1}H-NMR δ ($CDCl_3$+CF_3COOD): 2.28 (3H, s, $COCH_3$), 2.42 (3H, s, $COCH_3$), 4.05 (3H, s, OCH_3), 6.00 (2H, s, CH_2), 7.60 (1H, s), 7.75 (1H, s), 7.97 (1H, d, J=5.6 Hz), 8.60 (1H, d, J=5.6 Hz). IR (KBr) cm^{-1}: 1760. 1740. MS *m/z* (%): 289 (M^+, 20), 247 (15), 246 (11), 205 (33), 204 (100), 190 (6). *Anal.* Calcd for $C_{15}H_{15}NO_5 \cdot 1/4H_2O$: C, 61.32; H, 5.32; N, 4.77. Found: C, 61.29; H, 5.18; N, 4.53.

7-Methoxy-6-(1-methylethoxy)isoquinoline (16) (Modified Pomeranz–Fritsch Isoquinoline Synthesis) 1) A mixture of vanillin (**22**) (15.2 g, 0.1 mol), isopropyl bromide (14.1 ml, 0.15 mol), and anhydrous K_2CO_3 (20.7 g, 0.15 mol) in DMF (100 ml) was heated at 80 °C for 1 h. The reaction mixture was diluted with water (200 ml) and extracted with ether (200 ml×3). The combined extracts were washed with brine (200 ml) and concentrated *in vacuo* to give a residue (26.7 g), the chromatography of which on a silica gel (200 g) column with hexane–ethyl acetate as an eluent gave 4-isopropyl-3-methoxybenzaldehyde (**23**) (19.4 g, 100%) as a colorless oil. ^{1}H-NMR δ: 1.43 (6H, d, J=6.3 Hz, $CH(C\underline{H}_3)_2$), 3.92 (3H, s, OCH_3), 4.69 (1H, sept, J=6.3 Hz, OCH), 6.98 (1H, d, J=7.9 Hz, 5-H), 7.41 (1H, d, J=2 Hz, 2-H), 7.43 (1H, dd, J=7.9, 2.0 Hz, 6-H), 9.84 (1H, s, CHO). IR (neat) cm^{-1}: 1670. MS *m/z* (%): 194 (M^+, 26), 152 (100), 151 (95). High-resolution MS Calcd for $C_{11}H_{14}O_3$: 194.0934. Found: 194.0941.

2) Aminoacetaldehyde dimethylacetal (8.55 ml, 78.7 mmol) was added to a solution of **23** (14.02 g, 72.0 mmol) in benzene (500 ml). This mixture was refluxed in a Dean–Stark apparatus for 1 h. Removal of the solvent *in vacuo* gave the required Schiff's base **24** (21.2 g, 100%) as a pale yellow oil, which was used without further purification. ^{1}H-NMR δ: 1.39 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 3.42 (6H, s, $CH(OC\underline{H}_3)_2$), 3.75 (2H, d, J=5.3 Hz, $C\underline{H}_2CH$), 3.91 (3H, s, OCH_3), 4.60 (1H, sept, J=6.1 Hz, OCH), 4.67 (1H, t, J=5.3 Hz, $CH_2C\underline{H}$), 6.89 (1H, d, J=8.5 Hz, 5-H), 7.15 (1H, dd, J=8.5, 1.8 Hz, 6-H), 7.44 (1H, d, J=1.8 Hz, 2-H), 8.18 (1H, s, CH=N).

3) Schiff's base **24** (20.18 g, 72.0 mmol) was dissolved in methanol (500 ml), and $NaBH_4$ (2.99 g, 79.0 mmol) was added in portions with stirring. The mixture was stirred for 20 h, diluted with water (150 ml), and extracted with chloroform (300 ml×3). The combined extracts were washed with brine (300 ml), dried, and concentrated *in vacuo* to give am amine **25** (20.33 g, 100%), which was used without further purification. ^{1}H-NMR δ: 1.35 (6H, d, J=6.1 Hz, $CH(C\underline{H}_3)_2$), 2.75 (2H, d, J=5.5 Hz, $NC\underline{H}_2CH$), 3.37 (6H, s, $CH(OC\underline{H}_3)_2$), 3.74 (2H, s, $ArCH_2N$), 3.85 (3H, s, OCH_3), 4.48 (1H, sept, J=6.1 Hz, OCH), 4.49 (1H, t, J=5.5 Hz, $CH_2C\underline{H}$), 6.80 (1H, dd, J=8.1, 1.8 Hz, 6-H), 6.84 (1H, d, J=8.1 Hz, 5-H), 6.87 (1H, d, J=1.8 Hz, 2-H).

4) A solution of **25** (20.33 g, 72 mmol) and triethylamine (15.1 ml, 108 mmol) in dry dichloromethane (90 ml) was cooled with ice water, and a solution of *p*-toluenesulfonyl chloride (20.6 g, 108 mmol) in dry dichloromethane (60 ml) was added dropwise over 10 min. The mixture was stirred at room temperature for 20 h at room temperature. The organic layer was washed with 10% aqueous NaOH (300 ml), and then water (200 ml), dried, and concentrated *in vacuo* to give a residue (37.7 g). The chromatography of this residue on a silica gel (300 g) column with hexane–ethyl acetate (5 : 1) as the eluent gave **26** (31.43 g, 100%) as a colorless oil. ^{1}H-NMR δ: 1.34 (6H, d, J=5.9 Hz, $CH(C\underline{H}_3)_2$), 2.42 (3H, s, $ArCH_3$), 3.21 (2H, d, J=5.3 Hz, $NC\underline{H}_2CH$), 3.26 (6H, s, $CH(OC\underline{H}_3)_2$), 3.72 (3H, s, OCH_3), 4.36 (1H, t, J=5.3 Hz, $CH_2C\underline{H}$), 4.40 (2H, s, $ArCH_2N$), 4.48 (1H, sept, J=5.9 Hz, OCH), 6.67—6.71 (2H, m, 2-H, 6-H), 6.77 (1H, d, J=7.9 Hz, 5-H), 7.30, 7.74 (each 2H, d, J=8.3 Hz, CH_3–$C_6\underline{H}_4$–). IR (neat) cm^{-1}: 1345, 1170. MS *m/z* (%): 437 (M^+, 11), 282 (10), 179 (15), 137 (47), 75 (100). High-resolution MS Calcd for $C_{22}H_{31}NO_6S$: 437.1872. Found: 437.1877.

5) A solution of **26** (21.85 g, 50 mmol) in dioxane (500 ml) was treated with 6 N HCl (37 ml), then the mixture was heated under reflux for 1 h. The mixture was diluted with water (1000 ml), rendered alkaline with 4% NH_4OH solution, and extracted with ether (500 ml×3). The combined extracts were washed with brine (300 ml), dried, and concentrated *in vacuo* to give a solid, the recrystallization of which from ether gave **16** (7.06 g, 65.1%) as colorless prisms, mp 111—113 °C. ^{1}H-NMR δ: 1.48 (6H, d, J=5.9 Hz, $CH(C\underline{H}_3)_2$), 4.00 (3H, s, OCH_3), 4.77 (1H, sept, J=5.9 Hz, OCH), 7.05, 7.19 (each 1H, s, ArH), 7.47 (1H, d, J=5.6 Hz, 4-H), 8.36 (1H, d, J=5.6 Hz, 3-H), 9.02 (1H, s, 1-H). ^{13}C-NMR δ: 21.7 (q, $CH(\underline{C}H_3)_2$), 56.0 (q, OCH_3), 71.1 (d, OCH), 105.4 (d), 106.6 (d), 119.1 (d), 124.5 (s), 132.5 (s), 141.6 (d), 149.8 (d), 151.1 (s), 151.4 (s). IR (KBr) cm^{-1}: 1630, 1500, 1470, 1440, 1420, 1340, 1250, 1220, 1140, 1120, 930, 860. MS *m/z* (%): 217 (M^+, 11), 176 (11), 175 (100), 160 (24), 132 (30). *Anal.* Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.83; H, 7.01; N. 6.26.

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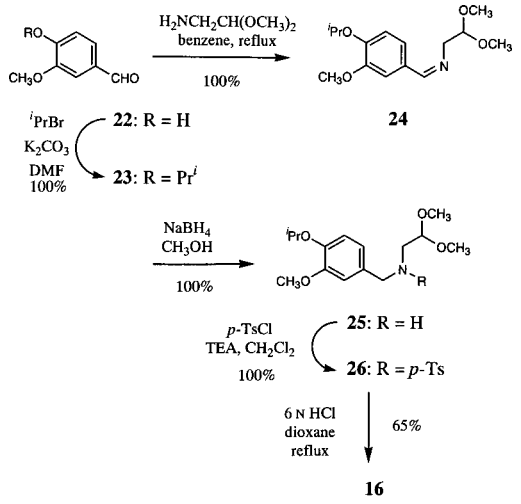
18) Compound **16** is already known, but details of the experiment could not be obtained from the literature [Servin A. L., Wicek D., Oryszczyn M. P., Jacquot C., Lussiana J. P., Christinaki H., Viel C., *Xenobiotica*, **17**, 1381—1391 (1987)]. Thus, according to modified Pomeranz–Fritsch isoquinoline synthesis,[24] compound **16** was prepared from vanillin (**22**) *via* 4-isopropyl-3-methylbenzaldehyde (**23**)[19] in five steps with 65% overall yield (see: Experimental).



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22) The crude fraction was separated and purified to obtain **15** by Sephadex LH 20 and C18 HPLC column using a methanol–water containing 0.1% TFA graduation. Furthermore, a sample of **21** could not be purified, because natural **15** was available only in minute quantities.[12] Therefore, the reported derivative **21** may also be retained in the form of a TFA salt.
23) In a similar way, (7-acetoxy-6-methoxy-1-isoquinolyl)methanol acetate (**27**) was prepared from isovanillin (**28**) *via* **29** and **30** in 11% overall yield. **30**: mp 181—183 °C (from acetone). ^{1}H-NMR δ (CD_3OD): 4.04 (3H, s, OCH_3), 5.09 (2H, s, CH_2), 7.13, 7.37 (each 1H, s, ArH), 7.54 (1H, d, J=5.0 Hz, 4-H), 8.17 (1H, d, J=5.0 Hz, 3-H). IR (KBr) cm^{-1}: 3250, 1480, 1420, 1340, 1280. MS *m/z* (%): 205 (M^+, 100), 204 (70), 176 (56), 175 (14), 161 (9). High-resolution MS Calcd for $C_{11}H_{11}NO_3$: 205.0739. Found: 205.0741. **27**: mp 114—115 °C (from ethyl acetate–ether). ^{1}H- and ^{13}C-NMR data: see Table 1. IR (KBr) cm^{-1}: 1760, 1730, 1370, 1270, 1210. MS *m/z* (%): 289 (M^+, 11), 247 (25), 205 (30), 204 (100). *Anal.* Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.09; H, 5.39; N, 4.75.
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