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Synthesis of 5,8-Dihydroxy-3,4-dihydrocarbostyril

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5,8-Dihydroxy-3,4-dihydrocarbostyril, a key intermediate for the synthesis of β_1-selective 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril hydrochloride (opc-1427) was prepared from 2,5-dimethoxyaniline.

Keywords——5,8-dihydroxy-3,4-dihydrocarbostyril; intermediate; 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril; opc-1427; cyclization; 2,5-dimethoxyaniline

Previously, the authors[1] reported the synthesis of 5,8-dihydroxy-3,4-dihydrocarbostyril, which is an intermediate in the synthesis of 5-(3-*tert*-butylamino-2-hydroxypropoxy)-8-hydroxy-3,4-dihydrocarbostyril (8-hydroxy-carteolol) from 5-hydroxy-3,4-dihydrocarbostyril.[2] However, the reported method did not give a satisfactory yield. Thus, we investigated three routes to 5,8-dihydroxy-3,4-dihydrocarbostyril (I) from 2,5-dimethoxyaniline as a starting material, *via* the cyclization of 2,5-dimethoxycarboxyacetanilide (III), 2,5-dimethoxy-β-alkoxyacryloanilide (X) and 2,5-dimethoxy-β,β-dimethoxypropioanilide (XI).

First, heating of 2,5-dimethoxyaniline and diethyl malonate under reduced pressure gave 2,5-dimethoxy-ethoxycarbonylacetanilide (II) (89%), which was hydrolyzed to 2,5-dimethoxy-carboxyacetanilide (III) (82%). Cyclization of III by heating with $POCl_3$ gave 2,4-dichloro-5,8-dimethoxyquinoline (IV) in 70% yield. Treatment of IV with KOBu^t followed by hydrolysis of the resulting 2-*tert*-butoxy-4-chloro-5,8-dimethoxyquinoline (V) with conc. HCl gave 4-chloro-5,8-dimethoxycarbostyril (VI) in 79% yield. Catalytical hydrogenation of VI gave

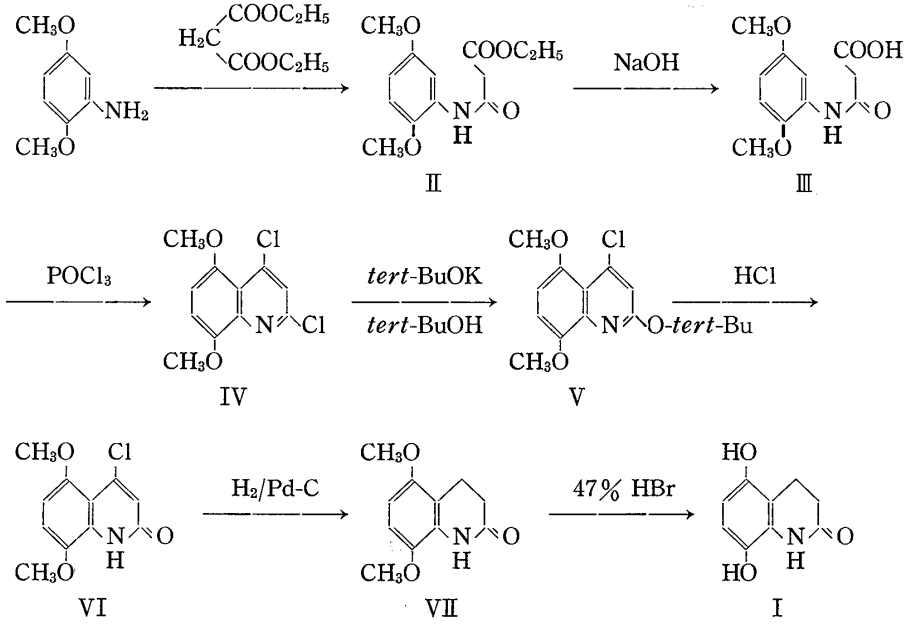

Chart 1

5,8-dimethoxy-3,4-dihydrocarbostyril (VII) (74%). Compound VII was easily hydrolyzed to 5,8-dihydroxy-3,4-dihydrocarbostyril (I) (81%) (Chart 1). The structures of VI and V were confirmed by the appearance of amide absorption at 1650 cm^{-1} in the IR spectrum of VI, and by the chemical transformation of VI to I.

Compound III was also cyclized to 2,4-dihydroxy-5,8-dimethoxyquinoline (VIII) by heating with PPA, which was easily converted to VII (70%) by tosylation, followed by hydrogenation. Methanesulfonation was also tried for this conversion, but the yield was only 22% (Chart 2).

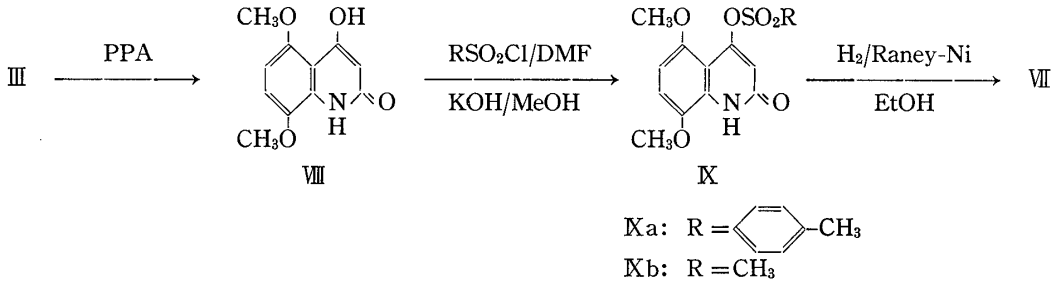

Chart 2

Second, a solution of 2,5-dimethoxyaniline, β-ethoxyacrylic acid chloride[3] and triethylamine was stirred under reflux to give 2,5-dimethoxy-β-ethoxyacryloanilide (Xa) in 51% yield. In the same manner, 2,5-dimethoxy-β-isobutoxyacryloanilide (Xb) was obtained in 75% yield. Cyclization of Xa with conc. HCl[4] gave 5,8-dimethoxycarbostyril (XII) (86%), which was hydrogenated to give VII in 92% yield (Chart 3).

Third, acylation of 2,5-dimethoxyaniline with 3,3-dimethoxypropionic and ethylcarbonic mixed anhydride gave 2,5-dimethoxy-β,β-dimethoxypropioanilide (XI) in 25% yield. Cyclization of XI with conc. H_2SO_4 gave XII in 73% yield (Chart 3).

In conclusion, it is considered that the most suitable procedure for industrial production is to synthesize I from 2,5-dimethoxyaniline *via* 2,5-dimethoxy-β-isobutoxyacryloanilide.

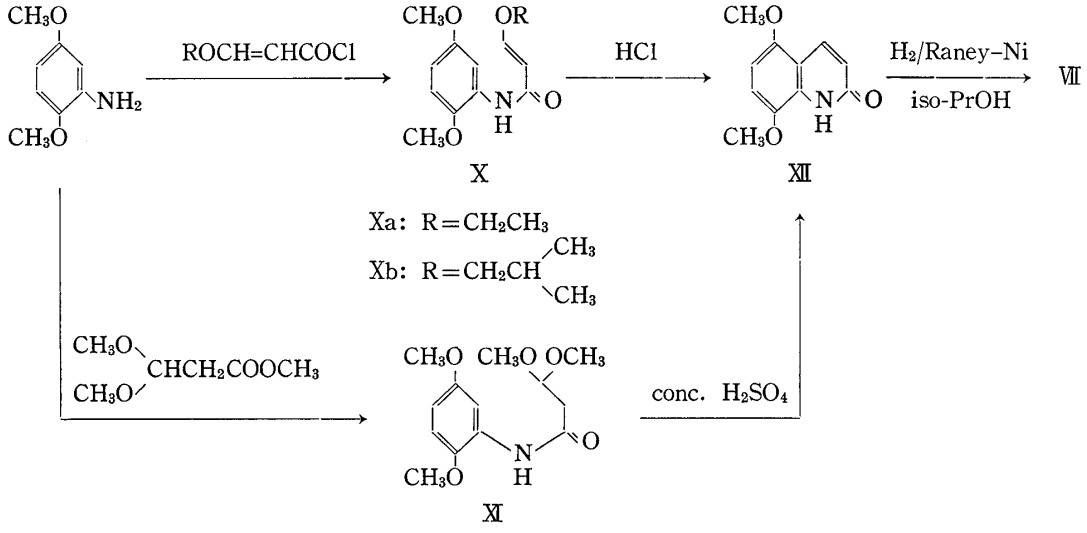

Chart 3

Experimental

All melting points are uncorrected. NMR spectra were recorded on a Varian EM-390 NMR spectrometer using 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS) or tetramethylsilane as an internal standard. IR spectra were measured on a Nihon-Bunko Jasco IRA-2.

2,5-Dimethoxy-ethoxycarbonylacetanilide (II)——A mixture of 200 g of 2,5-dimethoxyaniline and 1.5 l of diethyl malonate was heated at 140—150°C for 2 h, while N_2 gas was bubbled through the solution. After removal of about 60 ml of EtOH, the excess diethyl malonate was removed under reduced pressure. The residue was recrystallized from iso-PrOH to give II (310 g, 88.8%) as colorless leaflets, mp 68—69°C. IR (KBr) cm^{-1}, 1725 ($COOC_2H_5$), 1680 (CONH). NMR ($CDCl_3$) ppm: 1.31 (3H, t, $J=7$ Hz, $-COOCH_2CH_3$), 3.42 (2H, s, $-COCH_2COO-$), 3.77, 3.86 (each 3H, s, $2\times-OCH_3$), 4.22 (2H, q, $J=7$ Hz, $-COOCH_2CH_3$), 6.57 (1H, dd, $J_1=3$ Hz, $J_2=9$ Hz, C_4-aromatic H), 6.83 (1H, d, $J=9$ Hz, C_3-aromatic H), 8.08 (1H, d, $J=3$ Hz, C_6-aromatic H), 9.40 (1H, z, $-NHCO-$). *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.42; N, 5.24. Found: C, 58.42; H, 6.46; N, 5.26.

2,5-Dimethoxy-carboxyacetanilide (III)——A solution of 160 g of II in 1.5 l of 5% NaOH was stirred at 55—60°C for 1 h. After cooling, the reaction mixture was acidified with 250 ml of conc. HCl and the crystalline precipitate was removed by filtration. Recrystallization from iso-PrOH gave III (118 g, 82.4%) as colorless crystals, mp 141—142.5°C. IR(KBr) cm^{-1}: 1727 (COO), 1634 (CONH), 1605 (aroma). NMR ($CDCl_3$) ppm: 3.52 (2H, s, $-CH_2COOH$), 3.69, 3.79 (each 3H, s, $2\times-OCH_3$), 6.65 (1H, dd, $J_1=3$ Hz, $J_2=9$ Hz, C_4-aromatic H), 6.96 (1H, d, $J=9$ Hz, C_3-aromatic H), 7.82 (1H, d, $J=3$ Hz, C_6-aromatic H), 9.54 (1H, s). *Anal.* Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.23; H, 5.50; N, 5.88.

2,4-Dichloro-5,8-dimethoxyquinoline (IV)——A mixture of 60 g of III and 300 ml of $POCl_3$ was heated under reflux for 2 h. The excess $POCl_3$ was removed under reduced pressure. The residual oil was poured into ice-water. The crystalline precipitate was collected by filtration and washed with water. Recrystallization from EtOH gave IV (45 g, 69.5%) as pale yellow needles, mp 129—130°C. NMR ($CDCl_3$) ppm: 3.85, 3.96 (each 3H, s, $2\times-OCH_3$), 6.81, 6.96 (each 1H, d, $J=9$ Hz, $2\times$aromatic H), 7.40 (1H, s, C_3-aromatic H). *Anal.* Calcd for $C_{11}H_9Cl_2NO_2$: C, 51.19; H, 3.51; N, 5.43. Found: C, 51.25; H, 3.64; N, 5.45.

2-*tert*-Butoxy-4-chloro-5,8-dimethoxyquinoline (V)——A mixture of 28 g of IV and 165 g of $KOBu^t$ in 300 ml of *tert*-BuOH was refluxed under a nitrogen atmosphere for 3 h. The reaction mixture was poured into 2 l of ice-water. The crystalline precipitate was collected by filtration to give crude V. An analytical sample, mp 119—119.5°C, was obtained as colorless needles by recrystallization from iso-PrOH. IR(KBr) cm^{-1}: 1620, 1597, 1399, 1365, 1320, 1226, 1170, 1000. NMR ($CDCl_3$) ppm: 1.65 (9H, s, $-OC(CH_3)_3$), 3.82, 3.90 (each 3H, s, $2\times-OCH_3$), 6.64, 6.91 (each 1H, d, $J=9$ Hz, aromatic H), 6.87 (1H, s, C_3-aromatic H). *Anal.* Calcd for $C_{15}H_{18}ClNO_3$: C, 60.92; H, 6.13; N, 4.72. Found: C, 60.81; H, 5.96; N, 4.69.

4-Chloro-5,8-dimethoxycarbostyril (VI)——A suspension of crude V in 100 ml of conc. HCl and 1.5 l of water was stirred at 60—70°C for 1 h, then cooled. The crystalline precipitate was collected by filtration and washed with water. Recrystallization from EtOH gave VI (20.7 g, 79.6% from IV) as pale yellow needles, mp 204—205°C. IR(IBr) cm^{-1}: 1650 (CONH). NMR ($CDCl_3$) ppm: 3.84, 3.89 (each 3H, s, $2\times-OCH_3$), 6.56, 6.91 (each 1H, d, $J=9$ Hz, aromatic H), 6.69 (1H, s, C_3-aromatic H), 9.11—9.55 (1H, br. s, $-NHCO-$). *Anal.* Calcd for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.04; H, 4.19; N, 5.87.

5,8-Dimethoxy-3,4-dihydrocarbostyril (VII)——(i) A mixture of 18 g of VI, 1.5 g of 10% palladium on charcoal in 300 ml of MeOH and 200 ml of water was hydrogenated at 65—70°C under 20 atm pressure of H_2. The mixture was cooled, and the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure, and allowed to cool. The resulting crystalline precipitate was collected by filtration. Recrystallization from iso-PrOH gave VII (11.5 g, 73.9%) as colorless needles, mp 106—107°C. IR(KBr) cm^{-1}: 1694 (CONH). NMR ($CDCl_3$) ppm: 2.36—3.04 (4H, m, $-CH_2CH_2-$), 3.74, 3.77 (each 3H, s, $2\times-OCH_3$), 6.44, 6.66 (each 1H, d, $J=9$ Hz, $2\times$aromatic H), 7.82 (1H, br. s, $-NHCO-$). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.61; H, 6.17; N, 6.74.

(ii) A mixture of 55 g of IXa, 25 g of Raney Ni in 800 ml of EtOH was stirred at 100°C under 6—7 atm pressure of H_2. The mixture was cooled, and the catalyst was removed by filtration. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 500 ml of $CHCl_3$ and the solution was washed with dil. HCl, 5% NaOH and water. The chloroform layer was dried over Na_2SO_4 and the solvent was evaporated off. The residue was recrystallized from iso-PrOH to give VII (26.5 g, 87.3%) as colorless needles, mp 105.5—107°C, which was identical with the sample obtained in (i) above.

5,8-Dihydroxy-3,4-dihydrocarbostyril (I)——A suspension of 5 g of VII in 50 ml of 47% HBr was heated under reflux for 2.5 h. The mixture was cooled and the resulting crystalline precipitate was collected by filtration and washed with water to give I (3.5 g, 80.9%) as colorless needles, mp 223—224.5°C (lit.[1] 228—230°C).

2,4-Dihydroxy-5,8-dimethoxyquinoline Hydrate (VIII)——III (36.7 g) was added to 220 g of polyphosphoric acid at 150°C and the mixture was allowed to stand at the same temperature for 30 min, then poured into ice-water. After the polyphosphoric acid had dissolved, the solution was neutralized with 4 N NaOH. The deposited solid was collected by filtration and washed with water. Recrystallization from MeOH gave VIII (33.0 g, 89.9%) as colorless needles, mp 187.5—189°C. NMR (DMSO-d_6) ppm: 3.88, 3.94 (each 3H, s, $2\times-OCH_3$), 5.75 (1H, s, C_3-aromatic H), 6.75, 7.13 (each 1H, d, $J=9$ Hz, $2\times$aromatic H). *Anal.* Calcd for $C_{11}H_{13}NO_5$: C, 55.22; H, 5.48; N, 5.84. Found: C, 54.97; H, 5.40; N, 5.77.

5,8-Dimethoxy-4-*p*-tosyloxycarbostyril (IXa)——A solution of 26 g of *p*-toluenesulfonyl chloride in 30 ml of DMF was added dropwise to a solution of 15 g of VIII, 6.5 g of KOH in 150 ml of DMF and 67 ml of MeOH at 0—5°C. The reaction mixture was stirred at 50—55°C for 3 h and poured into ice-water. The

crystalline precipitate was collected by filtration and washed with water. Recrystallization from MeOH gave IXa (20.3 g, 79.8%) as colorless crystals, mp 175—176°C. IR(KBr) cm^{-1}: 1655 (CONH), 1380 (SO_2), 1175 (SO_2). NMR ($CDCl_3$) ppm: 2.48 (3H, s, $-SO_2-C_6H_4-CH_3$), 3.83 (3H, s, $-OCH_3$), 3.92 (3H, s, $-OCH_3$), 6.08 (1H, s, C_3-aromatic H), 6.57, 6.98 (each 1H, d, $J=9$ Hz, 2×aromatic H), 7.43, 7.90 (4H, dd, $J=8$ Hz, $-SO_2-C_6H_4-CH_3$, aromatic H), 9.41 (1H, s, -NHCO-). *Anal.* Calcd for $C_{16}H_{17}NO_6S$: C, 57.59; H, 4.57; N, 3.73. Found: C, 57.70; H, 4.42; N, 3.56.

5,8-Dimethoxy-4-mesyloxycarbostyril (IXb)——Methanesulfonyl chloride (5.2 g) was added to a solution of 5.0 g of VIII, 2.2 g of KOH in 100 ml of DMF and 20 ml of MeOH at 0—5°C. The reaction mixture was stirred at 50—55°C for 3 h and poured into ice-water. The crystalline precipitate was collected by filtration and washed with water. Recrystallization from DMF gave IXb (1.5 g, 22.0%), mp 199—200°C (dec.). *Anal.* Calcd for $C_{12}H_{13}NO_6S$: C, 48.16; H, 4.38; N, 4.68. Found: C, 48.45; H, 4.31; N, 4.60.

2,5-Dimethoxy-β-ethoxyacryloanilide (Xa)——A solution of 5.8 g of β-ethoxyacryl chloride in 20 ml of dry benzene was added dropwise to a solution of 5 g of 2,5-dimethoxyaniline and 5.3 ml of triethylamine in 100 ml of dry benzene. The reaction mixture was heated under reflux for 1 h. After cooling, the benzene layer was washed with water and dried over Na_2SO_4. The solvent was evaporated off. The residual oil was crystallized from ether–hexane. Recrystallization from acetone–H_2O gave Xa (9.2 g, 51.2%) as colorless crystals, mp 89—91°C. IR(KBr) cm^{-1}: 3300, 1665, 1606, 1540, 1488, 1205, 1170. NMR ($CDCl_3$) ppm: 1.33 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 3.74, 3.78 (each 3H, s, 2×$-OCH_3$), 3.89 (2H, q, $J=7$ Hz, $-OCH_2CH_3$), 5.35 (1H, d, $J=12$ Hz, -COCH=CH-), 6.50 (1H, dd, $J_1=3$ Hz, $J_2=9$ Hz, C_4-aromatic H), 6.73 (1H, d, $J=9$ Hz, C_3-aromatic H), 7.37—7.77 [2H, -NHCO-, 7.57 (1H, d, $J=12$ Hz, -COCH=CH-)], 8.15 (1H, d, $J=3$ Hz, C_6-aromatic H). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.97; H, 6.76; N, 5.48.

2,5-Dimethoxy-β-isobutyloxyacryloanilide (Xb)——This compound was prepared in the same manner as Xa from 1.1 g of 2,5-dimethoxyaniline, 1.17 ml of triethylamine, 1.3 g of β-isobutoxyacryl chloride and 70 ml of benzene, and was recrystallized from isopropyl ether to give Xb (1.5 g, 74.8%) as colorless crystals, mp 71—72.5°C. IR (KBr) cm^{-1}: 3375, 1661, 1615, 1430, 1220, 1204, 1165, 1140. NMR ($CDCl_3$) ppm: 0.95 (6H, d, $J=7$ Hz, $-OCH_2CH<^{CH_3}_{CH_3}$), 1.94 (1H, m, $-OCH_2CH(CH_3)_2$), 3.60 (2H, d, $J=7$ Hz, $-OCH_2CH(CH_3)_2$), 3.74, 3.78 (each 3H, s, 2×$-OCH_3$), 5.34 (1H, d, $J=13$ Hz, -COCH=CHO-), 6.50 (1H, dd, $J_1=3$ Hz, $J_2=9$ Hz, C_4-aromatic H), 6.74 (1H, d, $J=9$ Hz, C_3-aromatic H), 7.43—7.79 [2H, -NHCO-, 7.59 (1H, d, $J=13$ Hz, -COCH=CHO-)], 8.15 (1H, d, $J=3$ Hz, C_6-aromatic H). *Anal.* Calcd for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.54; H, 7.49; N, 4.97.

2,5-Dimethoxy-β,β-dimethoxypropioanilide (XI)——A mixture of a solution of 3.7 g of NaOH in 30 ml of MeOH and 17.3 g of methyl 3,3-dimethoxypropionate[5] was stirred at room temperature overnight. The solvent was evaporated off. The residue was washed with ether and the solid was suspended in 100 ml of CH_2Cl_2. Next, 11 ml of ethylcarbonate was added dropwise over a period of 30 min. The whole was stirred for 30 min, then 15.3 g of 2,5-dimethoxyaniline was added and the mixture was heated under reflux for 1 h. The mixture was then poured into ice-water. The CH_2Cl_2 layer was separated, washed with water, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on a column of silica gel using $CHCl_3$ as an eluent. After removal of the solvent, XI (6.6 g, 24%) was obtained as a colorless oil. NMR ($CDCl_3$) ppm: 2.69 (2H, d, $J=5$ Hz, $-COCH_2CH<$), 3.42 (6H, s, $-COCH_2CH(CH_3)_2$), 3.81, 3.75 (each 3H, s, 2×$-OCH_3$), 4.73 (1H, t, $J=5$ Hz, $-COCH_2CH<$), 6.49 (1H, dd, $J_1=3$ Hz, $J_2=9$ Hz, C_4-aromatic H), 6.77 (1H, d, $J=9$ Hz, C_3-aromatic H), 8.07 (1H, d, $J=3$ Hz, C_6-aromatic H), 8.68 (1H, br. s, -NHCO-).

5,8-Dimethoxycarbostyril (XII)——(i) Xa (2 g) was added slowly to 20 ml of conc. HCl with stirring at room temperature and the solution was stirred at room temperature for 30 min. The reaction mixture was neutralized with 10 N NaOH. The precipitated crystals were collected by filtration and washed with water. Recrystallization from iso-PrOH gave XII (1.4 g, 85.7%) as colorless needles, mp 153—154°C. IR(KBr) cm^{-1}: 1665 (CONH). NMR ($CDCl_3$) ppm: 3.82, 3.85 (each 3H, s, 2×$-OCH_3$), 6.42, 6.80 (1H, d, $J=9$ Hz, aromatic H), 6.65 (1H, d, $J=10$ Hz, -CH=CHCO-), 8.02 (1H, d, $J=10$ Hz, -CH=CHCO-), 9.47 (1H, br. s, -NHCO-). *Anal.* Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.39; H, 5.50; N, 6.82.

(ii) A solution of 1.0 g of XI in 1 ml of conc. H_2SO_4 was warmed at 60°C for 1 h. The reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from iso-PrOH to give XII (0.61 g, 76.3%) as colorless needles.

Acetylation of I——A mixture of 20 g of I, 2 drops of conc. HCl and 40 ml of Ac_2O was stirred at 70—80°C for 20 min, then poured into a large amount of ice-water. The precipitated crystals were collected by filtration and washed with water. Recrystallization from MeOH–$CHCl_3$ gave 5,8-diacetoxy-3,4-dihydrocarbostyril (24.5 g, 83.4%) as colorless crystals, mp 196—197°C. NMR ($CDCl_3$) δ: 2.29, 2.35 (each 3H, s, $-OCOCH_3$), 2.42—3.00 (4H, m, $-CH_2CH_2-$), 6.73, 7.01 (each 1H, d, $J=9$ Hz, 2×aromatic H), 9.15 (1H, br. s, -NHCO-). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.21; H, 4.93; N, 5.41.

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References and Notes

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