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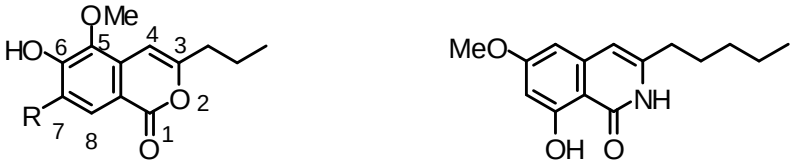
SYNTHESIS AND EVALUATION OF PHOSPHODIESTERASE IV INHIBITORY POTENCY OF ISOCARBOSTYRIL DERIVATIVES OF NATURALLY OCCURRING ISOCOUMARINS, SCOPARINES A AND B

Kumiko Taguchi,[†] Koichi Kobayashi,[‡] Keiko Ishida,[†] Katsuo Kamata,[†] and Toshio Honda[‡]*

[†]Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan; [‡]Faculty of Pharmaceutical Sciences, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142-8501, Japan

Abstract – Eight isocarbostyril derivatives bearing *n*-propyl substituent at the 3-position were prepared from the naturally occurring isocoumarins, scoparines A and B. Their phosphodiesterase IV (PD-4) inhibitory potency were evaluated by the vascular relaxation response in the mesenteric artery. Eight derivatives showed vascular relaxation response, probably relating with PD-4 inhibitory. However, these responses were weaker than the known PD-4 inhibitor (Ro201724).

The isocoumarins, naturally occurring lactones with a wide range of biological activities,[1,2] have drawn the attention of medicinal chemists because of their attractive potency for medicinal purpose. Their nitrogen analogues, isocarbostyril derivatives, are recognized as bioactive natural products,[3] and also as potential medicinal compounds.[4]



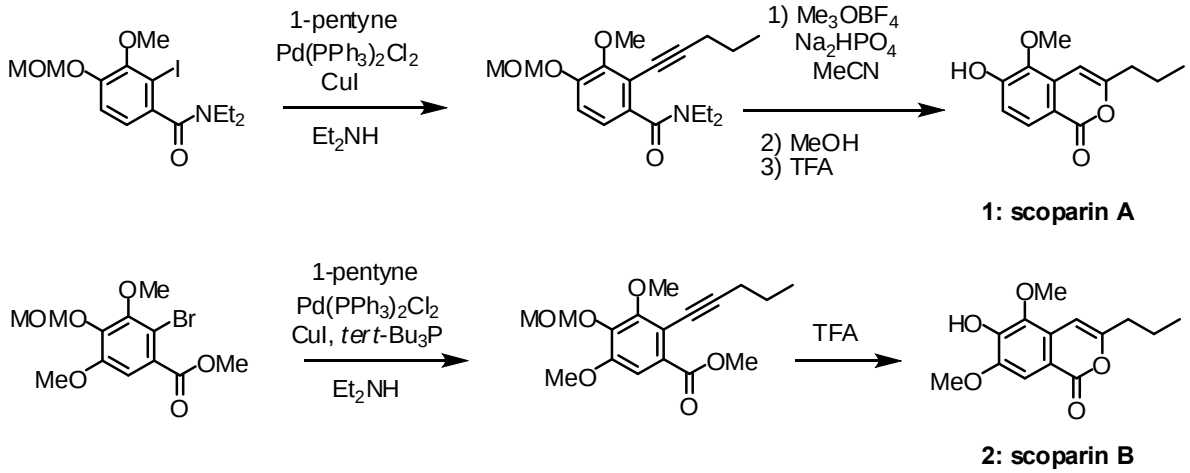
scoparine A (**1**): R = H
scoparine B (**2**): R = OMe

ruprechstyril (**3**)

Figure 1. **Structures of scoparines A and B, and ruprechstyril**

Recently, we have established[5] the first syntheses of natural isocoumarins, scoparines A and B, and an

isocarbostyril, ruprechstyril, respectively, where the Sonogashira coupling[6] of aromatic halides and alkynes, followed by regioselective 6-*endo*-dig cyclization[7] of oxygen functions to carbon-carbon triple bonds were involved as key steps, as shown in Scheme 1.



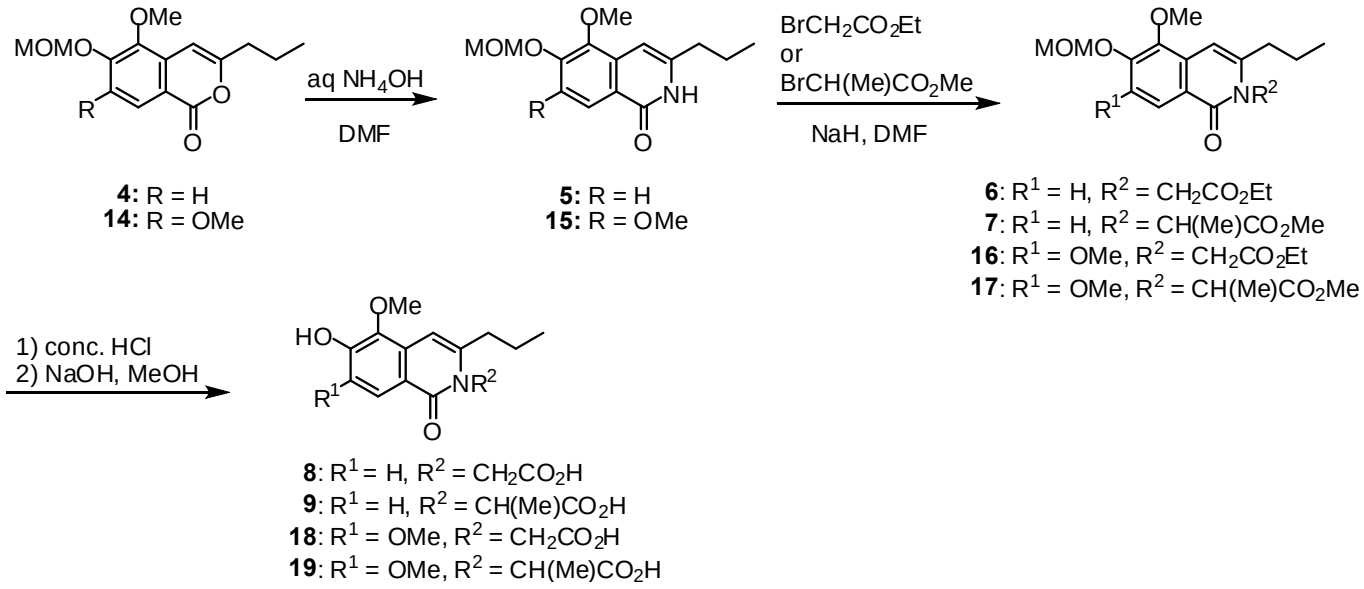
Scheme1. Previous synthesis of natural isocoumarins, scoparines A and B

As an extension of this work, we are interested in the synthesis and the biological activity of isocarbostyril derivatives of the natural isocoumarins, scoparines A and B, since it is recognized that ruprechstyril-type compounds with a hydrophilic substituent at the 2-position inhibit phosphodiesterases, especially phosphodiesterase IV (PD-4), to be useful for treatment of asthma, bronchitis, angina pectoris, arrhythmia, allergy, rheumatism, etc.[4]

For the derivatization of scoparines A and B, we decided to introduce a hydrophilic substituent at the 2-position based on the consideration of the structural features of ruprechstyril-type compounds.[8] Thus, eight isocarbostyril derivatives of the natural isocoumarins, scoparines A and B, were prepared as follows.

Scoparine A methoxymethyl ether (**4**), derived from scoparine A,[5] was treated with ammonium hydroxide solution in DMF to give the corresponding isocarbostyril (**5**), which on alkylation with ethyl bromoacetate or methyl 2-bromopropionate in DMF in the presence of sodium hydride (50% in oil) afforded the *N*-alkylated products (**6**) and (**7**) in 49 and 80% yields, respectively. Deprotection of the methoxymethyl group at the 6-position of the former ester (**6**) with concentrated HCl and subsequent hydrolysis of the ester function with 15N NaOH in MeOH provided the phenolic acid (**8**) in 27% yield from **6**. The ester (**7**) was also transformed into the acid (**9**), in 66% yield from **7**, by the same procedures as described for the preparation of **8**. Next, we attempted to introduce a primary alcohol function at the 2-position as an alternative hydrophilic substituent. Treatment of **5** with 2-bromoethanol

tert-butyldimethylsilyl ether in DMF in the presence of NaH (50% in oil) gave the alkylation product (**10**) in 64% yield, which on hydrolysis with concentrated HCl furnished the desired alcohol (**12**) in 76% yield. Similar treatment of **5** with 3-bromopropanol *tert*-butyldimethylsilyl ether, and subsequent acid hydrolysis of the resulting ether (**11**) with concentrated HCl afforded **13** in 17% yield from **5**.



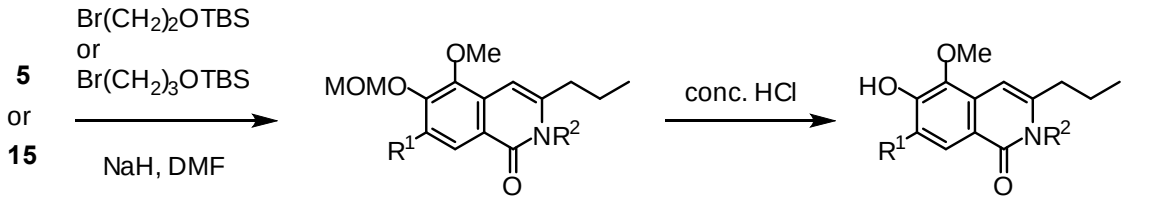
4: R = H
14: R = OMe

5: R = H
15: R = OMe

6: R^1 = H, R^2 = CH_2CO_2Et
7: R^1 = H, R^2 = $CH(Me)CO_2Me$
16: R^1 = OMe, R^2 = CH_2CO_2Et
17: R^1 = OMe, R^2 = $CH(Me)CO_2Me$

8: R^1 = H, R^2 = CH_2CO_2H
9: R^1 = H, R^2 = $CH(Me)CO_2H$
18: R^1 = OMe, R^2 = CH_2CO_2H
19: R^1 = OMe, R^2 = $CH(Me)CO_2H$

Scheme 2. Synthesis of isocarbostyril derivatives of scoparines A and B with an acid moiety



10: R^1 = H, R^2 = $(CH_2)_2OTBS$
11: R^1 = H, R^2 = $(CH_2)_3OTBS$
20: R^1 = OMe, R^2 = $(CH_2)_2OTBS$
21: R^1 = OMe, R^2 = $(CH_2)_3OTBS$

12: R^1 = H, R^2 = $(CH_2)_2OH$
13: R^1 = H, R^2 = $(CH_2)_3OH$
22: R^1 = OMe, R^2 = $(CH_2)_2OH$
23: R^1 = OMe, R^2 = $(CH_2)_3OH$

Scheme 3. Synthesis of isocarbostyril derivatives of scoparines A and B with a primary alcohol moiety

Applying the same synthetic strategy as above, scoparine B methoxymethyl ether (**14**), derived from scoparine B,[5] was first converted to the corresponding isocarbostyril (**15**), which was further transformed to the acids (**18** and **19**) via the esters (**16** and **17**), and the primary alcohols (**22** and **23**) via the silyl ethers (**20** and **21**), as shown in Schemes 2 and 3.

With the requisite materials available, a biological study on PD-4 inhibitory activity was carried out by the vascular relaxation response in the mesenteric artery of rats. In the vascular system, adenosine 3', 5'-cyclic monophosphate (cAMP) plays important roles in the regulation of vascular tone and the intracellular levels of cAMP are tightly regulated by rate of control of its hydrolysis (by cyclic nucleotide phosphodiesterases (PDs)); i.e. cAMP signaling in mammalian cells is terminated by cyclic nucleotide PDs, a multifamily class of enzymes that catalyze the hydrolysis of cyclic nucleotides to 5'-nucleotide monophosphates (which do not activate cAMP effector proteins).[9] Among the various PDs, the two of greatest are PD-3 and PD-4 because they preferentially hydrolyze cAMP.[10] Consequently, to investigate cAMP-mediated relaxation in the rat mesenteric artery, we tested Ro201724 (a specific PD-4 inhibitor), when it was added cumulatively to rings precontracted by phenylephrine (0.1 μM). Ro201724 caused concentration-dependent relaxations (ED_{50}; 215 nM). Next, to determine whether our synthesized compounds really did act as a PD-4 inhibitor, we performed experiments in which each compounds (1 nM to 10 μM) was added cumulatively to mesenteric artery rings. The results are summarized in Figure 2. Each compounds caused a concentration-dependent relaxation. But those compounds-induced relaxation responses were significantly decreased. However, the derivatives such as **12**, **13**, **22** and **23** were found to be more potent than those such as **8**, **9**, **18** and **19**. Moreover, the derivatives such as **22** and **23** were found to be more potent than those such as **12** and **13**.

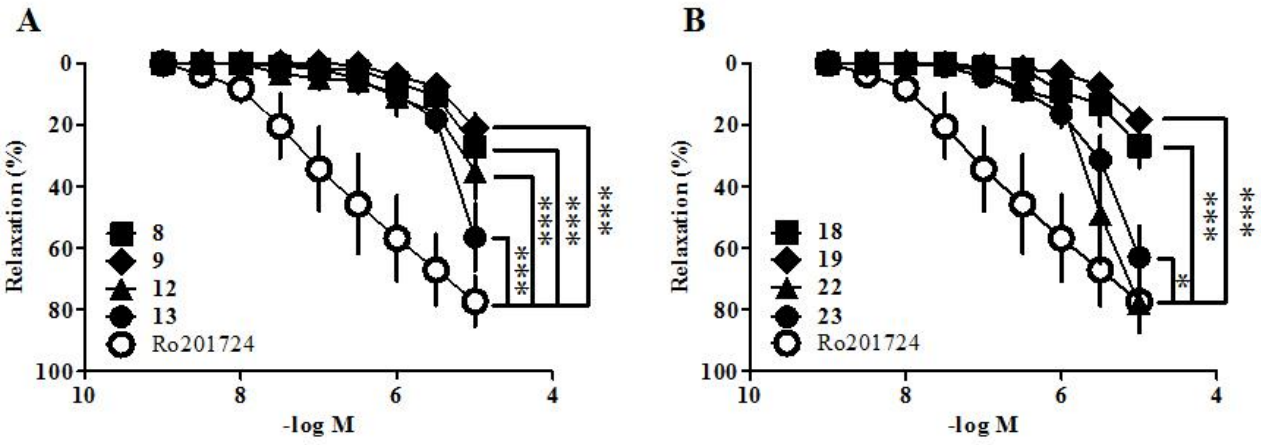


Figure 2. Concentration-response curves for the relaxations induced by Ro201724 (PD-4 inhibitor) and the synthesized compounds in isolated rings of superior mesenteric artery. Ordinate shows relaxation of the superior mesenteric artery as a percentage of the contraction induced by phenylephrine. Each data point represents the mean ± SE from 5 experiments. ***P<0.001 vs Ro201724

In conclusion, these results suggested that the synthesized compounds had the vasorelaxant effects. Among them, it was found that 7-methoxy derivatives (**22** and **23**)-induced maximal response almost

were no different to Ro201724, suggesting that those compounds might be PD-4 inhibitors. Furthermore, we found that 7-methoxy derivatives showed the stronger vasorelaxant activity than those of the corresponding 7-hydrogen derivatives, and the derivatives with a primary alcohol moiety at the 2-position showed stronger than those with a carboxylic acid moiety. Further studies on **22** or **23** are necessary to develop a novel PD-4 inhibitor with controlling vascular tone.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. IR spectra were obtained as thin films on sodium chloride plates using a JASCO FT/IR-200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on Bruker AV-400 (^{1}H NMR: 270 MHz, ^{13}C NMR: 67.8 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ scale from internal TMS. MS spectra were measured with a JEOL JMS-D 300 spectrometer. Elemental analyses were performed on a Yanaco-MT5.

Materials and methods

Reagents

Phenylephrine was purchased from Sigma Chemical Co. (St. Louis, MO, USA). 4-(3-Butoxy-4-methoxybenzyl)-2-imidazolidinone (Ro201724) was from Calbiochem-Novabiochem (La Jolla, CA). Drugs were dissolved in dimethyl sulfoxide except phenylephrine (which was dissolved in saline). All concentrations are expressed as the final molar concentration of the base in the organ bath.

Animals and experimental design

Male Wistar control rats were obtained at the age of 4 weeks (Clea, Tokyo, Japan). All animals were allowed a standard laboratory diet (MF; Oriental Yeast Industry, Tokyo, Japan) and water ad libitum in a controlled environment (room temperature 21-22 ˚C, room humidity 50 ± 5%) until they were 36-38 weeks old. This study was approved by the Hoshi University Animal Care and Use Committee, and all studies were conducted in accordance with *"Guide for the Care and Use of Laboratory Animals"* published by the US National Institutes of Health, and with *"Guide for the Care and Use of Laboratory Animals*" adopted by the Committee on the Care and Use of Laboratory Animals of Hoshi University (which is accredited by the Ministry of Education, Culture, Sports, Science, and Technology, Japan).

Measurement of isometric force

At 36-38 weeks of age, rats were anesthetized with diethyl ether, then euthanized by decapitation. The superior mesenteric artery was rapidly removed and immersed in oxygenated, modified Krebs-Henseleit solution (KHS). This solution consisted of (in mM) 118.0 NaCl, 4.7 KCl, 25.0 $NaHCO_3$, 1.8 $CaCl_2$, 1.2 NaH_2PO_4, 1.2 $MgSO_4$, and 11.0 glucose. The artery was carefully cleaned of all fat and connective tissue,

and ring segments 2 mm in length were placed in a bath containing 10 mL of KHS at 37 ˚C. The rings were stretched until an optimal resting tension of 1.0 g was loaded, and then allowed to equilibrate for at least 60 min. Force generation was monitored by means of an isometric transducer (model TB-611T; Nihon Kohden, Tokyo, Japan). For the relaxation studies, mesenteric rings were precontracted with an equally effective concentration of phenylephrine (0.1 μM). When the phenylephrine-induced contraction had reached a plateau level, Ro201724 or our new synthesized compounds (1 nM - 10 μM) was added in a cumulative manner.

5-Methoxymethylscoparine A (4). To a stirred solution of scoparine A (0.8 g 3.42 mmol) in CH_2Cl_2 (7 mL) in the presence of $^{i}Pr_2NEt$ (0.78 mL, 4.45 mmol) was added MOMCl (0.31 ml, 4.10 mmol) at 0 °C under argon. The mixture was stirred at the same temperature for 30 min, and then treated with saturated aqueous NH_4Cl solution. The mixture was extracted with $CHCl_3$, and the extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (5:1, v/v) gave the ether (**4**) (0.89 g, 94%) as a pale yellow oil. IR νmax: 2962, 1730, 1655, 1600 cm^{-1}; ^1H NMR δ: 1.01 (3H, t, *J* = 7.4 Hz), 1.70-1.80 (2H, m), 2.51 (2H, t, *J* = 7.4 Hz), 3.53 (3H, s), 3.92 (3H, s), 5.34 (2H, s), 6.54 (1H, s), 7.25 (1H, d, *J* = 8.9 Hz), 7.98 (1H, d, *J* = 8.9 Hz); ^{13}C NMR δ: 13.3, 20.1, 35.5, 56.4, 61.1, 94.6, 97.2, 114.6, 115.3, 126.3, 132.7, 142.3, 154.5, 158.1, 162.4; HRMS (EI) Calcd for $C_{15}H_{18}O_5$ (M^+) 278.1154. Found 278.1167.

5-Methoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (5). A mixture of the ether (**4**) (0.77 g, 2.8 mmol) and 25% NH_4OH (15 mL) in DMF (15 mL) was heated at 45 °C for 22 h. The mixture was concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (5:1, v/v) gave the amide (**5**) (0.63 g, 82%) as a colorless solid. Mp. 124-125 °C; IR νmax: 2961, 1656, 1638, 1604 cm^{-1}; ^1H NMR δ: 1.02 (3H, t, *J* = 7.3 Hz), 1.75-1.84 (2H, m), 2.64 (2H, *J* = 7.6 Hz), 3.55 (3H, s), 3.94 (3H, s), 5.34 (2H, s), 6.59 (1H, s), 7.28 (1H, d, *J* = 8.9 Hz), 8.12 (1H, d, *J* = 8.9 Hz), 11.23 (1H, br s); ^{13}C NMR δ: 13.6, 21.7, 35.6, 56.4, 61.2, 94.9, 98.0, 114.8, 119.9, 124.1, 134.3, 142.2, 142.7, 152.5, 164.3; HRMS (CI) Calcd for $C_{15}H_{20}NO_4$ ($M+H^+$) 278.1392. Found 278.1414. Anal Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.70; H, 6.86; N, 5.00.

Ethyl [5-methoxy-6-(methoxymethoxy)-1-oxo-3-propylisoquinolin-2(1*H*)-yl]acetate (6). To a stirred solution of isocarbostyril (**5**) (100 mg, 0.36 mmol) in DMF (1 mL) was added a suspension of NaH (50% in oil) (39.8 mg, 0.83 mmol) in DMF (1.0 mL) at 0 °C, and the resulting mixture was stirred at rt for 1 h. To this mixture was added a solution of ethyl bromoacetate (95.3 mg, 0.54 mmol) in DMF (0.5 mL) at rt, and the whole was stirred at the same temperature for 1 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O. The ethereal layer was washed with brine and dried over

Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (5:1, v/v) gave the ester (**6**) (63.8 mg, 49%) as a colorless solid. Mp. 99-100 °C; IR νmax: 2963, 1743, 1658, 1623 cm^{-1}: ^1H NMR δ: 1.05 (3H, t, *J* = 7.3 Hz), 1.29 (3H, t, *J* = 7.1 Hz), 1.67-1.74 (2H, m), 2.55 (2H, t, *J* = 7.5 Hz), 3.54 (3H, s), 3.93 (3H, s), 4.25 (2H, q, *J* = 7.1 Hz), 4.81 (2H, s), 5.32 (2H, s), 6.64 (1H, s), 7.26 (1H, d, *J* = 8.9 Hz), 8.09 (1H, d, *J* = 8.9 Hz); ^{13}C NMR δ: 13.7, 14.1, 21.6, 35.5, 45.0, 56.4, 61.2, 61.6, 88.9, 94.9, 99.3, 115.2, 119.6, 124.8, 132.3, 142.5, 152.4, 162.9, 168.7; HRMS (CI) Calcd for $C_{19}H_{25}NO_6$ (M^+) 363.1682. Found 363.1704.

Methyl 2-[5-methoxy-6-(methoxymethoxy)-1-oxo-3-propylisoquinolin-2(1*H*)-yl]propanoate (7). Alkylation of **5** (150 mg, 0.54 mmol) with methyl 2-bromopropanoate (542.8 mg, 3.25 mmol) and NaH (50% in oil) (57.2 mg, 1.19 mmol) in DMF (3.5 mL) was carried out by the same procedure as described for the preparation of **6** to give the ester (**7**) (157.4 mg, 80%) as a pale yellow oil. IR νmax: 2957, 1758, 1628 cm^{-1}; ^1H NMR δ: 0.93 (3H, t, *J* = 7.4 Hz), 1.70 (3H, d, *J* = 7.0 Hz), 1.71-1.79 (2H, m), 2.61-2.74 (2H, m), 3.55 (3H, s), 3.71 (3H, s), 3.96 (3H, s), 5.41 (2H, s), 5.44 (1H, q, *J* = 7.0 Hz), 7.26 (1H, s), 7.35 (1H, d, *J* = 9.1 Hz), 8.00 (1H, d, *J* = 9.1 Hz); ^{13}C NMR δ: 13.8, 17.6, 22.2, 39.8, 51.9, 56.4, 61.2, 70.2, 95.4, 106.6, 114.0, 116.6, 120.9, 135.0, 142.4, 150.0, 152.6, 158.6, 173.1; HRMS (EI) Calcd for $C_{19}H_{25}NO_6$ (M^+) 363.1682. Found 363.1657.

(6-Hydroxy-5-methoxy-1-oxo-3-propylisoquinolin-2(1*H*)-yl)acetic acid (8). A solution of the ester (**6**) (61.8 mg, 0.17 mmol) and conc. HCl (0.1 mL) in MeOH (1.5 mL) was stirred at rt for 17 h. After evaporation of the solvent, the residue was dissolved into MeOH (1.5 mL) and then treated with 15N NaOH solution (0.2 mL). The mixture was stirred at rt for further 1.5 h, and then concentrated in vacuo. The residue was dissolved into water, which was washed with Et_2O. The aqueous layer was acidified with 2N HCl and extracted $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was recrystallized from EtOH to give the acid (**8**) (27.1 mg, 55%). Mp. 271-273 °C; IR νmax: 3198, 2359, 1715, 1645, 1620, 1577 cm^{-1}; ^1H NMR δ: 1.07 (3H, t, *J* = 7.3 Hz), 1.70-1.76 (2H, m), 2.58 (2H, t, *J* = 7.7 Hz), 3.89 (3H, s), 4.81 (2H, s), 6.65 (1H, s), 7.02 (1H, d, *J* = 8.7 Hz), 7.96 (1H, d, *J* = 8.7 Hz); ^{13}C NMR δ: 11.5, 19.1, 32.5, 42.9, 58.4, 95.7, 114.7, 114.8, 122.0, 130.0, 137.5, 131.4, 150.8, 160.0, 168.3; HRMS (EI) Calcd for $C_{15}H_{17}NO_5$ (M^+) 291.1106. Found 291.1087. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.74; H, 6.12; N, 4.65.

2-(6-Hydroxy-5-methoxy-1-oxo-3-propylisoquinolin-2(1*H*)-yl)propanoic acid (9). The ester (**7**) (157.5 mg, 0.43 mmol) was hydrolyzed by the same procedure as described for the preparation of **8** to afford the acid as a colorless solid, which was recrystallized from benzene to provide the acid (**9**) (110 mg, 83%). Mp. 135-136 °C; IR νmax: 2961, 1724, 1626 cm^{-1}; ^1H NMR δ: 0.95 (3H, t, *J* = 7.4 Hz), 1.74 (3H, d, *J* =

6.9 Hz), 1.75-1.82 (2H, m), 2.75 (2H, t, *J* = 7.5 Hz), 3.94 (3H, s), 5.41 (1H, q, *J* = 6.9 Hz), 7.19 (1H, d, *J* = 8.9 Hz), 7.19 (1H, s), 7.99 (1H d, *J* = 8.9 Hz); ^{13}C NMR δ: 13.4, 17.2, 22.0, 39.5, 60.8, 70.3, 106.1, 112.4, 117.3, 121.2, 134.6, 138.9, 149.8, 152.2, 158.9, 174.9; HRMS (CI) Calcd for $C_{16}H_{20}NO_5$ ($M+H^+$) 306.1341. Found 306.1357. Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.05; H, 6.36; N, 4.55.

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-5-methoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (10). To a stirred solution of **5** (150 mg, 0.54 mmol) in DMF (1 mL) was added a suspension of NaH (50% in oil) (57.1 mg, 1.19 mmol) in DMF（1.0 mL）at 0 °C, and the mixture was stirred at rt for 1 h. To this mixture was added a solution of the bromide (777 mg, 3.25 mmol) in DMF (1.0 mL) at rt, and the whole was stirred at the same temperature for further 48 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (7:1, v/v) gave the ether (**10**) (149.8 mg, 64%) as a pale yellow oil. IR νmax: 2957, 1654, 1622, 1597 cm^{-1}; ^{1}H NMR δ: -0.10 (6H, s), 0.82 (9H, s), 1.26 (3H, t, *J*=7.1 Hz), 1.66-1.75 (2H, m), 2.81 (2H, t, *J* = 7.6 Hz), 3.54 (3H, s), 3.92 (3H, s), 3.94 (2H, t, *J* = 5.3 Hz), 4.22 (2H, t, *J* = 5.3 Hz), 5.32 (2H, s), 6.59 (1H, s), 7.24 (1H, d, *J* = 9.0 Hz), 8.10 (1H, d, *J* = 9.0 Hz); ^{13}C NMR δ: -5.7, 13.8, 18.1, 21.8, 25.7, 35.8, 45.7, 56.4, 61.12, 61.14, 94.9, 98.6, 114.9, 120.1, 124.5, 132.3, 142.2, 144.5, 152.1, 162.8; HRMS (CI) Calcd for $C_{23}H_{37}NO_5Si$ (M^+) 435.2441. Found 435.2464.

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-5-methoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (11). By the same procedure as described for the preparation of **10**, compound **5** (200 mg, 0.72 mmol) was alkylated with the bromide (1.1 g, 4.34 mmol) to give the ether (**11**) (66.4 mg, 21%). IR νmax: 2956, 1654, 1622, 1597 cm^{-1}; ^{1}H NMR δ: 0.08 (6H, s), 0.92 (9H, s), 1.06 (3H, t, *J*=7.4 Hz), 1.68-1.78 (2H, m), 1.89-1.95 (2H, m), 2.73 (2H, t, *J* = 7.6 Hz), 3.54 (3H, s), 3.72 (2H, t, *J* = 5.6 Hz), 3.92 (3H, s), 4.19 (2H, t, *J* = 7.7 Hz), 5.32 (2H, s), 6.59 (1H, s), 7.24 (1H, d, *J* = 9.0 Hz), 8.09 (1H, d, *J* = 9.0 Hz); ^{13}C NMR δ: -5.4, 13.8, 18.2, 22.4, 25.9, 31.8, 35.2, 41.1, 56.4, 60.5, 61.2, 95.0, 99.0, 115.1, 120.2, 124.5, 132.2, 142.2, 143.7, 152.0, 162.8; HRMS (CI) Calcd for $C_{24}H_{40}NO_5Si$ ($M+H^+$) 450.2675. Found 450.2666.

6-Hydroxy-2-(2-hydroxyethyl)-5-methoxy-3-propylisoquinolin-1(2*H*)-one (12). A solution of the ether (**10**) (141.0 mg, 0.32 mmol) in MeOH (2.0 mL) in the presence of conc. HCl (0.1 mL) was stirred at rt for 9 h. After concentration of the mixture, the residue was subjected to column chromatography on silica gel. Elution with hexane:AcOEt (1:1, v/v) gave a colorless solid, which was recrystallized from $CHCl_3$ to afford the alcohol (**12**) (52.5 mg, 76%). Mp. 187-189 °C; IR νmax: 3234, 2963, 1640, 1590 cm^{-1}; ^{1}H NMR δ: 1.07 (3H, t, *J* = 7.3), 1.68-1.77 (2H, m), 2.74 (2H, t, *J* = 7.6), 3.28 (2H, br s), 3.86 (2H,

t, *J* = 5.9 Hz), 3.88 (3H, s), 4.25 (2H, t, *J* = 5.9 Hz), 6.62 (1H, s), 7.02 (1H, d, *J* = 8.8 Hz), 7.98 (1H, d, *J* = 8.8 Hz); ^{13}C NMR δ: 13.3, 21.8, 35.1, 45.6, 60.2, 60.6, 99.8, 116.5, 117.4, 124.3, 132.1, 139.3, 143.2, 152.5, 163.8; HRMS (CI) Calcd for $C_{15}H_{19}NO_4$ (M^+) 277.1314. Found 277.1310. Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.80; H, 7.01; N, 5.07.

6-Hydroxy-2-(2-hydroxypropyl)-5-methoxy-3-propylisoquinolin-1(2*H*)-one(13). By the same procedure as described for the preparation of **12**, the ether (**11**) (66.4 mg, 0.15 mmol) was hydrolyzed with conc. HCl to give the alcohol (**13**) (35.5 mg, 82%) (recrystallized from AcOEt). Mp. 144-146 °C; IR νmax: 3220, 2961, 1638, 1587 cm^{-1}; ^{1}H NMR δ: 1.09 (3H, t, *J* = 7.3), 1.68-1.81 (2H, m), 1.88-1.94 (2H, m), 2.69 (2H, t, *J* = 7.5 Hz), 3.53 (2H, t, *J* = 5.3 Hz), 3.90 (3H, s), 4.31 (2H, t, *J* = 5.6 Hz), 4.31 (1H, br s), 6.46 (1H, br s), 6.56 (1H, s), 7.08 (1H, d, *J* = 8.8 Hz), 8.11 (1H, d, *J* = 8.8 Hz); ^{13}C NMR δ: 13.8, 22.5, 32.7, 34.9, 39.3, 58.1, 61.8, 99.7, 115.8, 118.2, 125.8, 131.3, 139.2, 143.4, 151.8, 164.0; HRMS (CI) Calcd for $C_{16}H_{21}NO_4$ (M^+) 291.1470. Found 291.1452. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.89; H, 7.35; N, 4.79.

6-Methoxymethylscoparine B (14). To a stirred solution of scoparine B (1.1 g, 4.02 mmol) in CH_2Cl_2 (8 mL) in the presence of ^{i}Pr$_2$NEt (1.13 mL, 6.43 mmol) was added MOMCl (0.45 ml, 6.03 mmol) at 0 °C under argon. The mixture was stirred at the same temperature for 30 min, and then treated with saturated aqueous NH_4Cl solution. The mixture was extracted with $CHCl_3$, and the extract was washed with brine and dried Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (6:1, v/v) gave the ether (**14**) (1.2 g, 94%) as a colorless oil. IR νmax: 2962, 1727, 1654, 1601 cm^{-1}; ^{1}H NMR δ: 1.00□ (3H, t, *J* = 7.4 Hz), 1.69-1.79 (2H, m), 2.52 (2H, t, *J* = 7.3 Hz), 3.61 (3H, s), 3.92 (3H, s), 3.94 (3H, s), 5.25 (2H, s), 6.48 (1H, s), 7.52 (1H, s); ^{13}C NMR δ: 13.5, 20.3, 35.5, 56.2, 57.4, 61.5, 97.3, 98.5, 106.3, 116.0, 127.2, 144.8, 147.5, 153.1, 156.5, 162.8; HRMS (CI) Calcd for $C_{16}H_{21}O_6$ ($M+H^+$) 309.1338. Found 309.1344.

5,7-Dimethoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (15). A mixture of the ether (**14**) (1.3 g, 4.1 mmol) and 25% NH_4OH (20 mL) in DMF (25 mL) was stirred at rt for 12 h and then at 95 °C for 12 h. The mixture was concentrated to leave a solid, which was recrystallized from EtOH to give the amide (**15**) (0.78 g, 62%) as a colorless solid. Mp. 159-160 °C; IR νmax: 2961, 1641, 1605, 1474 cm^{-1}: ^{1}H NMR δ: 1.01 (3H, t, *J* = 7.3 Hz), 1.68-1.80 (2H, m), 2.54 (2H, t, *J* = 7.7 Hz), 3.63 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 5.25 (2H, s), 6.52 (1H, s), 7.61 (1H, s); ^{13}C NMR δ: 13.6, 21.7, 35.5, 56.1, 57.3, 61.4, 98.1, 98.6, 103.7, 120.9, 128.5, 139.6, 143.1, 147.7, 152.3, 163.5; HRMS (EI) Calcd for $C_{16}H_{21}NO_5$ (M^+) 307.1419. Found 307.1422. Anal Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.36; H, 6.98; N, 4.62.

Ethyl [5,7-dimethoxy-6-(methoxymethoxy)-1-oxo-3-propylisoquinolin-2(1*H*)-yl]acetate (16). To a

stirred solution of **15** (134 mg, 0.44 mmol) in DMF (1 mL) was added a suspension of NaH (50% in oil) (42.0 mg, 0.87 mmol) in toluene (1 mL), and the resulting mixture was stirred at rt for 1 h. The mixture was treated with ethyl bromoacetate (119 mg, 0.71 mmol) and the whole was heated at 110 °C for 4 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (2:1, v/v) gave the ester (**16**) (148 mg, 86%) as a pale yellow oil. IR νmax: 2963, 1748, 1654, 1597 cm^{-1}; ^1H NMR δ: 1.05 (3H, t, *J* = 7.3 Hz), 1.30 (3H, t, *J* = 7.1 Hz), 1.64-1.76 (2H, m), 2.55 (2H, t, *J* = 7.6 Hz), 3.62 (3H, s), 3.95 (6H, s), 4.25 (2H, q, *J* = 7.1 Hz), 4.82 (2H, s), 5.24 (2H, s), 6.59 (1H, s), 7.61 (1H, s); ^{13}C NMR δ: 13.7, 14.1, 21.6, 35.3, 45.3, 56.1, 57.3, 61.4, 61.6, 98.6, 99.4, 104.4, 120.5, 126.6, 140.3, 143.0, 147.5, 152.4, 162.5, 168.6; HRMS (EI) Calcd for $C_{20}H_{27}NO_7$ (M^+) 393.1787. Found 393.1791.

Methyl 2-[5,7-dimethoxy-6-(methoxymethoxy)-1-oxo-3-propylisoquinolin-2(1*H*)-yl]propanoate (17). Alkylation of **15** (50.0 mg, 0.16 mmol) with methyl 2-bromopropanoate (40.6 mg, 0.24 mmol) and NaH (50% in oil) (15.6 mg, 0.32 mmol) was carried out by the same procedure as described for the preparation of **16** to give the ester (**17**) (56.4 mg, 89%) as a pale yellow oil. IR νmax: 2957, 1759, 1597 cm^{-1}; ^1H NMR δ: 0.92 (3H, t, *J* = 7.4 Hz), 1.72 (3H, d, *J* = 7.0 Hz), 1.69-1.81 (2H, m), 2.59-2.75 (2H, m), 3.63 (3H, s), 3.72 (3H, s), 3.98 (3H, s), 3.99 (3H, s), 5.25 (2H, s), 5.44 (1H, q, *J* = 7.0 Hz), 7.21 (1H, s), 7.38 (1H, s); ^{13}C NMR δ: 13.7, 17.6, 22.2, 39.6, 51.8, 56.0, 57.3, 61.4, 70.2, 98.7, 99.2, 106.8, 114.2, 130.2, 141.4, 147.1, 150.4, 152.2, 157.5, 173.2; HRMS (CI) Calcd for $C_{20}H_{28}NO_7$ ($M+H^+$) 394.1866. Found 394.1892.

(6-Hydroxy-5,7-dimethoxy-1-oxo-3-propylisoquinolin-2(1*H*)-yl)acetic acid (18). By the same procedure as described for the preparation of **8**, hydrolysis of **16** (98.3 mg, 0.25 mmol) with a trace amount of conc. HCl in MeOH (1.0 mL) was carried out to give the acid (**18**) (36.8 mg, 37%) (from AcOEt) as a colorless solid. Mp. 220-222 °C; IR νmax: 2959, 1726, 1691, 1588 cm^{-1}; ^1H NMR δ: 1.06 (3H, t, *J* = 7.3), 1.66-1.78 (2H, m), 2.60 (2H, t, *J* = 7.5 Hz), 2.97 (2H, br s), 3.94 (3H, s), 3.98 (3H, s), 4.83 (2H, s), 6.63 (1H, s), 7.56 (1H, s); ^{13}C NMR δ: 13.6, 21.5, 35.2, 45.2, 56.2, 61.0, 99.6, 103.3, 116.4, 127.0, 139.7, 140.5, 143.0, 147.7, 163.0, 170.4; HRMS (CI) Calcd for $C_{16}H_{20}NO_6$ ($M+H^+$) 322.1290. Found 322.1288. Anal Calcd for $C_{16}H_{19}NO_6$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.80; H, 6.01; N, 4.32.

2-(6-Hydroxy-5,7-dimethoxy-1-oxo-3-propylisoquinolin-2(1*H*)-yl)propanoic acid (19). Hydrolysis of **17** (62.8 mg, 0.16 mmol) was carried out by the same procedure as described for the preparation of **18** to give the acid (**19**) (18.1 mg, 34%) (from AcOEt) as a colorless solid. Mp. 156-157 °C; IR νmax: 3370, 2929, 1702, 1614 cm^{-1}; ^1H NMR δ: 0.87 (1H, br s), 0.94 (3H, t, *J* = 7.4 Hz), 1.28 (1H, br s), 1.76 (3H, d, *J* = 6.9 Hz), 1.71-1.82 (2H, m), 2.47 (2H, t, *J* = 7.5 Hz), 4.01 (3H, s), 4.04 (3H, s), 5.40 (1H, q, *J* = 6.9 Hz),

7.28 (1H, s), 7.30 (1H, s); ^{13}C NMR δ: 13.7, 17.2, 22.4, 39.1, 56.4, 61.1, 73.3, 98.2, 107.6, 111.4, 130.8, 139.0, 141.5, 147.9, 149.5, 159.0, 174.3; HRMS (EI) Calcd for $C_{17}H_{21}NO_6$ (M^+) 335.1369. Found 335.1380. Anal Calcd for $C_{17}H_{21}NO_6$: C, 60.89; H, 6.31; N, 4.18. Found: C, 60.87; H, 6.26; N, 4.20.

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}ethyl)-5,7-dimethoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (20). To a stirred solution of **15** (100 mg, 0.33 mmol) in DMF:toluene (1:2, 1 mL) was added a solution of NaH (50% in oil) (34.3 mg, 0.72 mmol) in DMF (0.5 mL) at 0 °C, and the mixture was stirred at rt for 1 h. To this solution was added a solution of the bromide (311.0 mg, 1.3 mmol) in DMF (1.0 mL), and the resulting mixture was stirred at the same temperature for further 48 h. After treatment with saturated aqueous NH_4Cl solution, the mixture was extracted with Et_2O. The ethereal layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel. Elution with hexane:AcOEt (17:1, v/v) gave the ether (**20**) (71.8 mg, 47%) as a colorless solid. Mp. 99-100 °C; IR νmax: 2957, 1651, 1598 cm^{-1}; ^{1}H NMR δ: -0.09 (6H, s), 0.82 (9H, s), 1.06 (3H, t, *J* = 7.3 Hz), 1.65-1.74 (2H, m), 2.80 (2H, t, *J* = 7.6 Hz), 3.63 (3H, s), 3.93 (3H, s), 3.94 (2H, t, *J* = 5.4 Hz), 3.96 (3H, s), 4.24 (2H, t, *J* = 5.44 Hz), 5.25 (2H, s), 6.53 (1H, s), 7.61 (1H, s); ^{13}C NMR δ: -5.7, 13.8, 18.1, 21.9, 25.8, 35.6, 46.0, 56.1, 57.3, 61.1, 61.4, 98.6, 98.7, 104.1, 120.9, 126.6, 142.2, 142.7, 147.3, 152.2, 162.5; HRMS (CI) Calcd for $C_{24}H_{39}NO_6Si$ (M^+) 465.2546. Found 465.2541. Anal Calcd for $C_{24}H_{39}NO_6Si$: C, 61.90; H, 8.44; N, 3.01. Found: C, 61.78; H, 8.42; N, 3.03.

2-(2-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-5,7-dimethoxy-6-(methoxymethoxy)-3-propylisoquinolin-1(2*H*)-one (21). The ether (**21**) (66.4 mg, 21%), as a pale yellow oil, was obtained from **15** (200 mg, 0.72 mmol) and the bromide (1.1 g, 4.34 mmol) in DMF in the presence of NaH (50% in oil) (47.5 mg, 0.99 mmol) by using the same procedure as described for the preparation of **20**. IR νmax: 2957, 1650, 1598 cm^{-1}; ^{1}H NMR δ: 0.08 (6H, s), 0.92 (9H, s), 1.05 (3H, t, *J*=7.3 Hz), 1.67-1.76 (2H, m), 1.90-1.96 (2H, m), 2.71 (2H, t, *J* = 7.6 Hz), 3.62 (3H, s), 3.72 (2H, t, *J* = 5.6 Hz), 3.94 (3H, s), 3.95 (3H, s), 4.20 (2H, t, *J* = 7.6 Hz), 5.23 (2H, s), 6.55(1H, s), 7.62 (1H, s); ^{13}C NMR δ: -5.4, 13.8, 18.2, 22.4, 25.9, 31.8, 35.1, 41.4, 56.1, 57.3, 60.5, 61.4, 98.6, 99.1, 104.1, 121.0, 126.5, 141.4, 142.6, 147.3, 152.2, 162.4; HRMS (EI) Calcd for $C_{21}H_{33}NO_6Si$ (M^+-56(isobutene)) 423.2077. Found 423.2047.

6-Hydroxy-2-(2-hydroxyethyl)-5,7-dimethoxy-3-propylisoquinolin-1(2*H*)-one (22). A solution of the ether (**20**) (71.0 mg, 0.15 mmol) and a trace amount of conc. HCl in MeOH (2.0 mL) was stirred at rt for 5 h. After concentration of the mixture, the residual solid was recrystallized from AcOEt to give the alcohol (**22**) (29.8 mg, 64%). Mp. 144-146 °C; IR νmax: 3111, 2961, 1635, 1574 cm^{-1}; ^{1}H NMR δ: 1.06 (3H, t, *J* = 7.3 Hz), 1.67-1.76 (2H, m), 2.68 (2H, t, *J* = 7.8 Hz), 3.70 (1H, br s), 3.95 (3H, s), 3.98 (2H, t, *J* = 4.6 Hz), 4.00 (3H, s), 4.34 (2H, t, *J* = 4.4 Hz), 6.25 (1H, br s), 6.62 (1H, s), 7.57 (1H, s); ^{13}C NMR δ:

13.8, 22.1, 35.4, 46.7, 56.4, 61.1, 63.1, 100.0, 103.0, 117.1, 127.0, 139.5, 141.2, 142.5, 147.4, 164.3; HRMS (CI) Calcd for $C_{16}H_{21}NO_5$ (M^+) 307.1419. Found 307.1390. Anal Calcd for $C_{16}H_{21}NO_5$: C, 62.52; H, 6.88; N, 4.56. Found: C, 62.53; H, 7.08; N, 4.60.

6-Hydroxy-2-(2-hydroxypropyl)-5,7-dimethoxy-3-propylisoquinolin-1(2*H*)-one (23). Hydrolysis of the ether (**21**)（66.4 mg, 0.15 mmol）was carried out with conc. HCl by the same procedure as described for the preparation of **22** to afford the alcohol (**23**) (35.5 mg, 82%) (from AcOEt) as a colorless solid. Mp. 144-146 °C; IR νmax: 3306, 2961, 1640, 1587 cm^{-1}; ^{1}H NMR δ: 1.07 (3H, t, *J* = 7.3 Hz), 1.70-1.80 (2H, m), 1.89-1.95 (2H, m), 2.69 (2H, t, *J* = 7.5 Hz), 3.51 (2H, t, *J* = 5.4 Hz), 3.97 (3H, s), 4.00 (3H, s), 4.33 (2H, br s), 4.49 (1H, br s), 6.46 (1H, br s), 6.65 (1H, s), 7.61 (1H, s) ; ^{13}C NMR δ: 13.8, 22.5, 32.7, 34.7, 39.4, 56.4, 57.9, 61.0, 100.3, 103.3, 116.7, 126.9, 139.4, 141.0, 142.5, 147.4, 163.6; HRMS (CI) Calcd for $C_{17}H_{24}NO_5$ ($M+H^+$) 322.1654. Found 322.1655. Anal Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.41; H, 7.15; N, 4.30.

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