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TOTAL SYNTHESIS OF LENNOXAMINE AND CHILENINE *VIA* RING-EXPANSION OF ISOINDOLOISOQUINOLINE TO ISOINDOLOBENZAZEPINE[#]

Yuji Koseki, Shinya Katsura, Shuichi Kusano, Harumi Sakata, Hiroto Sato, Yoshinori Monzene, and Tatsuo Nagasaka*

Tokyo University of Pharmacy and Life Science, School of Pharmacy, 1432 Horinouchi, Hachiouji, Tokyo 192-0392, Japan, E-mail: nagasaka@ps.toyaku.ac.jp

Abstract– Convenient synthesis of the benzazepine alkaloids, lennoxamine (**1**) and chilenine (**2**), is described. The key steps are conversion of methylenelactam (**5**) to an *N*-tertiary acyliminium ion precursor (**16**) and a novel expansion of the six-membered ring of **4** to a benzazepine ring system (**3b**), which could be transformed into lennoxamine (**1**) and chilenine (**2**).

Lennoxamine (**1**) and chilenine (**2**), isolated from the Chilean barberries *Berberis darwinii* and *Berberis empetrifolia*, respectively, are grouped into isoindolobenzazepine alkaloids.[1]

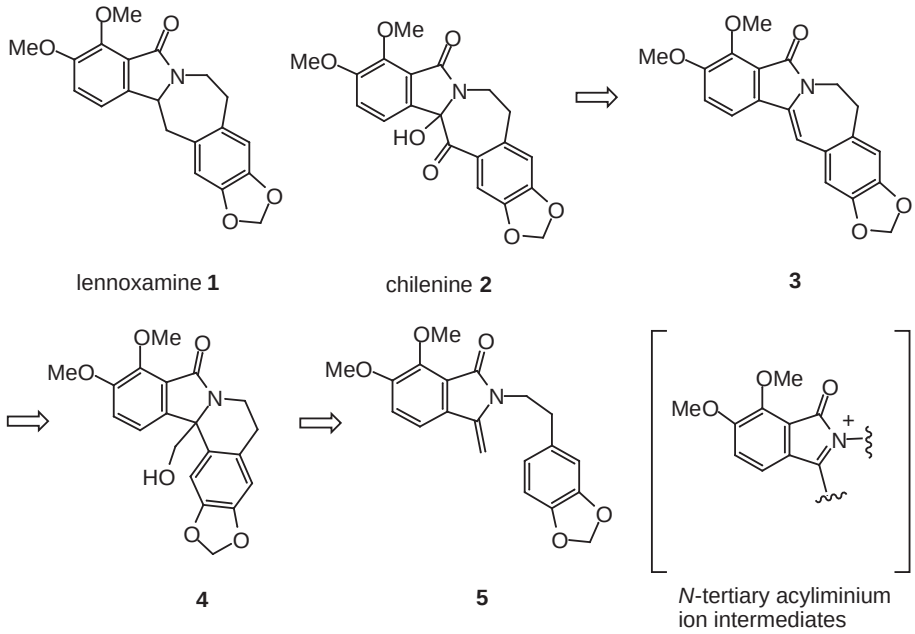
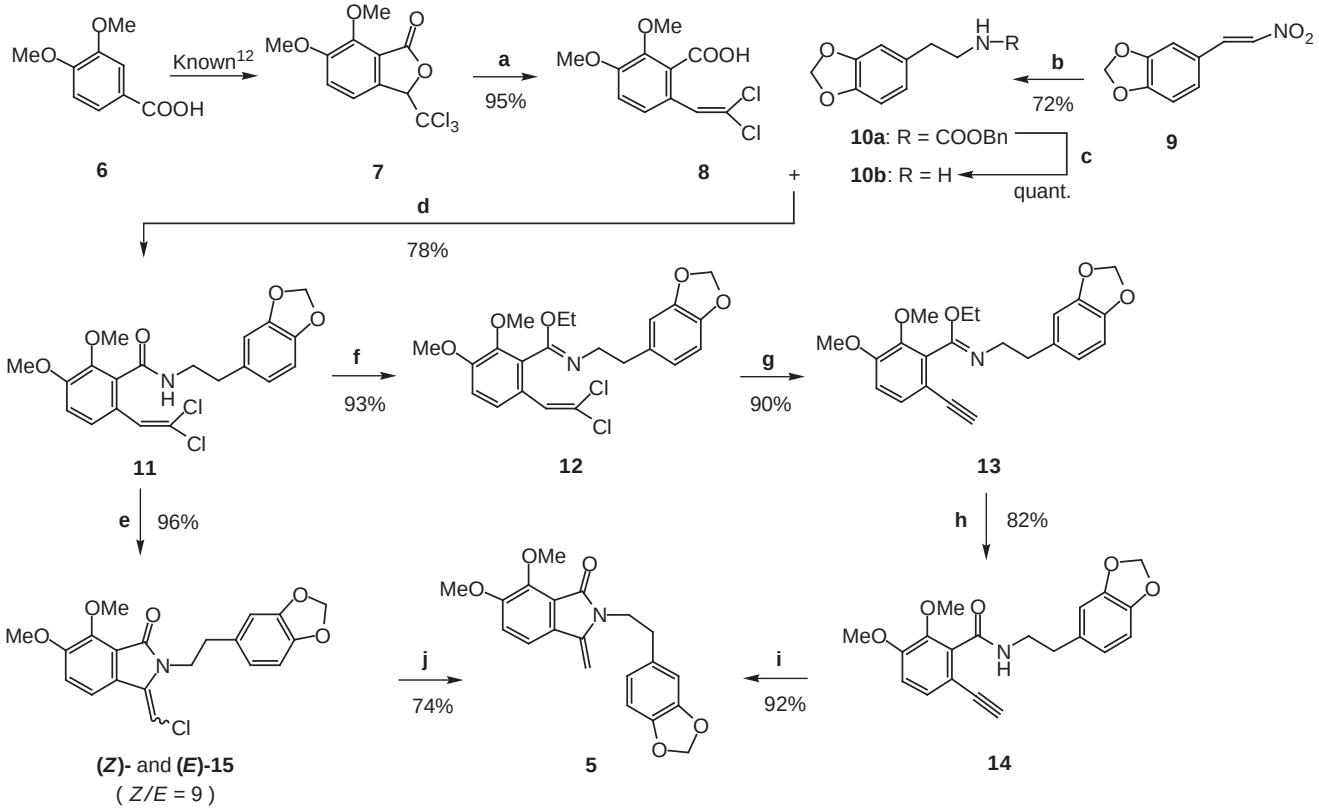


Figure 1

These alkaloids are biogenetically related to protoberberines, so their ring systems are accessible *in vivo and in vitro* by oxidation of berberine alkaloids.[2] Although these alkaloids do not appear to possess any useful pharmacological activities, their unique structural features include oxygenated substituents on the isoindolobenzazepine ring, which makes them attractive, synthetically challenging targets. Since chilenamine (Schopf's base IV) was first synthesized,[3] many groups have reported the total synthesis of

[#] Dedicated to Professor Yuichi Kanaoka on the occasion of his 75th birthday.

these alkaloids, especially lennoxamine (**1**),[4,5] chilenine (**2**)[5,6] and their derivatives.[7] In this paper, details of a novel and facile total synthesis of **1** and **2** starting from the commercially available **6** are described.[8] Our synthetic plan relied on the construction of an isoindolobenzazepine ring system (**3**) utilizing the ring-expansion[9,10] of isoindoloisoquinoline (**4**), which was obtained by cyclization of *N*-tertiary acyliminium ion intermediate[11] derived from methyleneisoindolone (**5**) (Figure 1). Scheme 1 depicts the synthesis of key building block (**5**) as an acyliminium ion precursor.



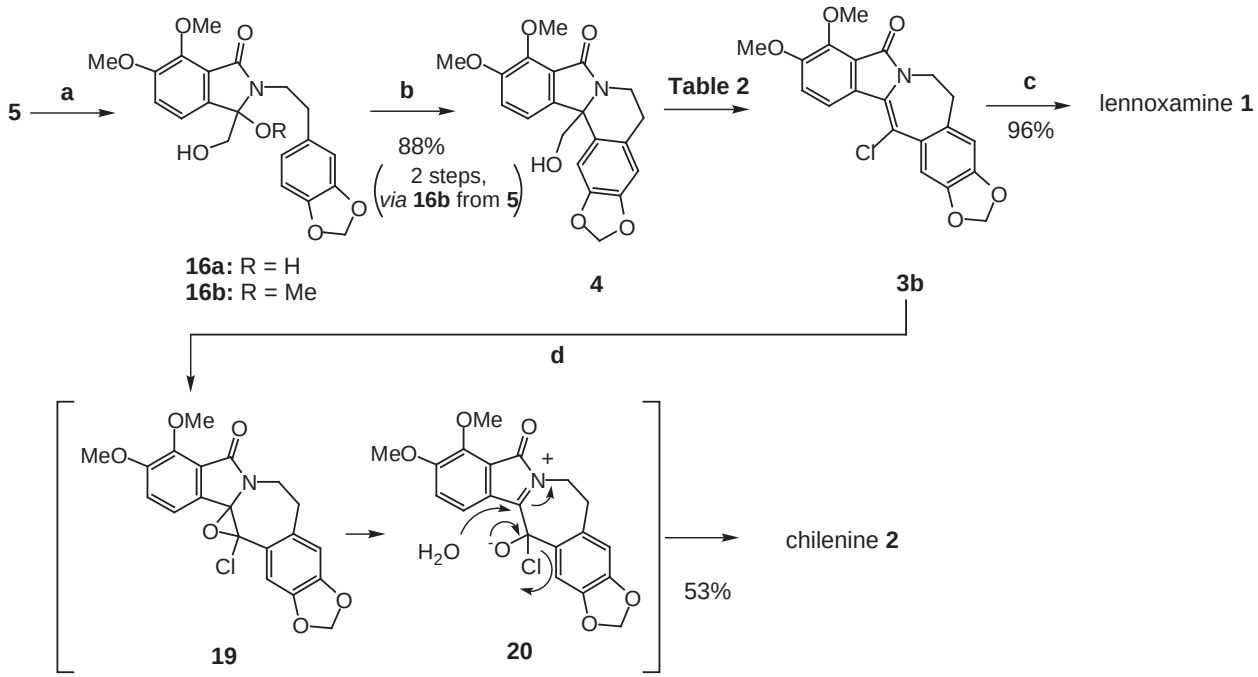
Reagents and conditions: **a**) Zn (3.2 equiv.), THF–AcOH, rt–65 °C; **b**) i) $LiAlH_4$ (4 equiv.), THF, ii) Cbz-Cl (1.4 equiv.), $NaHCO_3$ (2.5 equiv.), THF–H_2O; **c**) cat. 5% Pd–C, H_2, THF–MeOH; **d**) DEPC (1.1 equiv.), Et_3N (1.1 equiv.), THF, rt; **e**) LHMDS (1.0 equiv.), THF, -10 °C; **f**) $Et_3O^+ \cdot BF_4^-$ (2.1 equiv.), CH_2Cl_2, -10 °C–reflux; **g**) BuLi (2.1 equiv.), -10 °C; **h**) NaI (1.6 equiv.), TMSCl (1.6 equiv.), MeCN, -30 °C–rt; **i**) cat. LHMDS, THF, rt; **j**) Bu_3SnH (1.1 equiv.), AIBN (0.15 equiv.), hν (W-lump), toluene, 110 °C.

Scheme 1

After preparing **7** from 3,4-dimethoxybenzoic acid (**6**) according to Desai's method,[12] starting acid (**8**) was synthesized by subjecting **7** to reduction condition (zinc powder in THF–AcOH). The condensation of **8** with amine **10b**, prepared from the hydrogenolysis of **10a**, afforded dichlorovinylamide (**11**) in 78% yield. At this stage, condensation of **8** with amine (**10b**), prepared from the reduction[13] of nitro compound (**9**) with $LiAlH_4$, resulted in a moderate yield (50–60%). When compound (**11**) obtained in hand was subjected to strong basic conditions [e.g., 1 equiv. of lithium hexamethyldisilazide (LHMDS)], the cyclization proceeded smoothly to afford a 9:1 mixture of *Z*- and *E*-chloromethylenelactam (**15**) in high

yield. However, initial attempts to use it for obtaining the isoindolobenzazepine skeleton were unsuccessful.[14] Next, we planed to apply our method of the cyclization[14] of *o*-alkynylbenzamide derivatives to preparation of key compound (**5**). In order to convert **11** to alkynlamide (**14)** and not **15** under storong basic conditions (e.g. n-BuLi), protection of the amide moiety in **11** with Meerweine's reagent was necessary and carried out to afford imidate (**12**), which was converted to alkynylimidate (**13**) in good yield. Deprotection of resulting imidate (**13**) using the NaI–TMSCl–system in MeCN yielded the alkynylbenzamide (**14**) in satisfactory yield (82%).[14] Although the cyclization of alkynylamides, such as *o*-alkynylbenzamide (**14**), to the methyleneisoindolones under stoichiometric basic conditions (1 equiv. n-BuLi, LHMDS, etc) has been shown previously,[14,15] treatment of **14** with a catalytic amount of LHMDS (0.1 equiv.) was found to be equally effective (92%). However, the use of a catalytic amount of n-BuLi resulted in low yield (10%). On the other hand, the process from **15** to **5** appeared to give a shorter route. For this purpose, reductive dechlorinations of **15** to **5** utilizing the Bu_3SnH under a number of conditions were attempted.[16] After all, dechlorination of **15** with n-Bu_3SnH (1.1 equiv., 0.56 M) under irradiation proceeded smoothly to afford methylenelactam (**5**) in 74% yield. Although isolation of **5** from unreacted *E*-form (**15**) and other by-products was considerably troublesome in this reaction, this process provides a convenient method for preparing **5** from **11** in two steps.

The synthesis of **1** and **2** involving the construction of an isoindolobenzazepine ring system from methyleneisoindolone (**5**) is shown in Scheme 2.

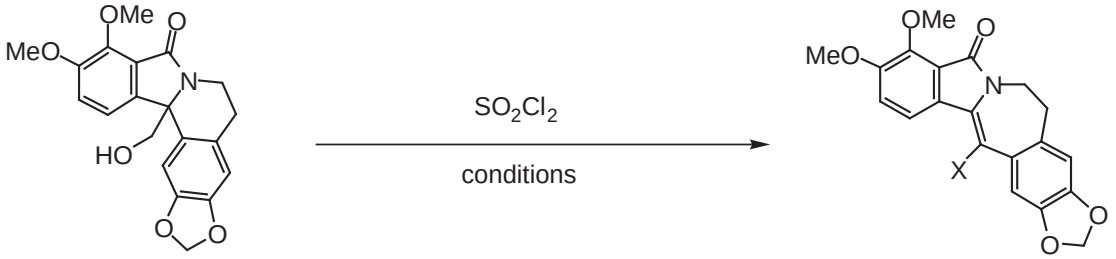


Reagents and conditions:
a) DMD, acetone, -78 °C– -35 °C (for **16a**); DMD, MeOH–acetone, -78 °C– -30 °C (for **16b**); **b**) $BF_3{\cdot}OEt_2$ (2 equiv.), CH_2Cl_2, -45 °C–0 °C; **c**) cat. 5% Pd–C, H_2, THF–MeOH; **d**) DMD, $CHCl_3$, -20 °C–rt

Scheme 2

Oxidation of **5** with *m*CPBA in CH_2Cl_2 yielded *N*-phenethylphthalimide unexpectedly.[17] Use of dimethyldioxirane (DMD) in acetone afforded the diol (**16a**) in quantitative yield, which was, however, unstable and insoluble in organic and aqueous solvents. Upon carrying out the reaction in the presence of methanol (MeOH–acetone = 2:1), slightly stable methoxylactam (**16b**) could be obtained.[18] When this crude material (**16b**) was treated with $BF_3{\cdot}Et_2O$ in CH_2Cl_2, cyclization of **16b** *via* an acyliminium ion intermediate proceeded smoothly to give 12b-(hydroxymethyl)isoindoloisoquinoline (**4**) in excellent yield (88% from **5**). For the rearrangement of **4** to **3**, a number of acidic conditions were attempted (e.g., HBr–AcOH, conc. H_2SO_4, polyphosphoric acid, CF_3SO_3H) at room and higher temperature conditions, but these conditions afforded no product having a seven-membered ring system. Based on a report by Yamauchi *et al*. of 1,2-aryl migration of 2-hydroxypropiophenone dimethyl acetals with SO_2Cl_2,[19] the ring-expansion reaction of **4** with SO_2Cl_2 was then investigated and the results were summarized in Table 1.

Table 1. Conversion of **4** into **3**



4 **3a:** X = H, **3b:** X = Cl

Entry	SO_2Cl_2 (equiv.)	Conditions[a)]	Product (%)	
			3a	**3b**
1	1.5	$CHCl_3$ / pyridine (1 : 1)	0	trace [b)]
2	1.5	DMF / Et_3N (1 : 1)	N.R	
3	3.0	$CHCl_3$ / Et_3N (4 : 1)	45	0 [c)]
4	3.0	$CHCl_3$ / pyridine (4 : 1), Et_3N (5 equiv.)	75	0 [c)]
5	3.0, then 1.3	$CHCl_3$ / pyridine (4 : 1), Et_3N (5 equiv.)	0	76[d)]

a) To the solution of **4** in mixed solvents was added dropwise SO_2Cl_2 at –78 °C and then the solution was warmed to rt, followed by standing overnight. **b**) A mixture of uncharacterizable products was formed and no starting material was detected. **c**) A varied amount of starting material was always recovered. **d**) After the disappearance of the starting material by TLC, further 1.3 equiv. of SO_2Cl_2 and then 2 equiv. of Et_3N were added dropwise.

The additive effect of the basic solvents (i.e., addition of Et_3N) suppressed the contamination of impurities (Entry 3 *vs* Entry 1) and pyridine facilitated this reaction (Entry 4 *vs* Entries 2 and 3). The best result was obtained using $CHCl_3$–pyridine (4:1) containing 5 equiv. of Et_3N from which **3a** was formed in 75% yield. After reaction of **4** with SO_2Cl_2, further addition of SO_2Cl_2 (1.3 equiv.) and Et_3N (2 equiv.) to the reaction mixture afforded the chlorinated enamide (**3b**) in 76% yield (Entry 5).

A plausible pathway for this ring-expansion reaction is shown in Figure 2. For the first step, chlorosulfonylation of a hydroxy group with SO_2Cl_2 afforded **17**, which underwent migration of the more electron-rich 3,4-methylenedioxyphenyl group to give **3a** *via* the most stable acyliminium ion (**18**).

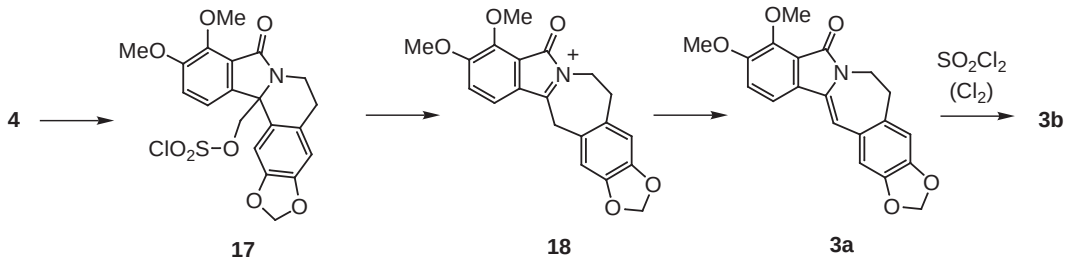


Figure 2

In the final step, catalytic hydrogenation (10% Pd–C, H_2, 3 atm, AcOH, 2 days) of **3a** afforded lennoxamine (**1**), but in unsatisfactory yield (38–51%).[20] In contrast, catalytic hydrogenation of chloroenamide (**3b**) progressed easily under hydrogen at atmospheric pressure to afford lennoxamine (**1**) in 96% yield (Scheme 2). Compound (**3a**) can be converted into **2** in a one-pot procedure (DMD and then aq. $NaHCO_3$, 38% yield) or in three steps utilizing twice OsO_4 oxidation procedures (40% yield) by Fang and Danishefsky.[6a] The exposure of chloroenamide (**3b**) to DMD in $CHCl_3$ afforded **2** in 53% yield. Thus, the chlorooxirane (**19**) formed initially, was attacked by water contained in the DMD–acetone solution to afford chilenine (**2**).

In conclusion, a novel synthesis of lennoxamine (**1**) and chilenine (**2**) using the oxidation of the methyleneisoindolone (**5**) with DMD to the alkoxylactam (**16**), an *N*-acyliminium ion equivalent, followed by the intramolecular cyclization of **16** to the isoindolisoquinoline (**4**) and the ring-expansion of **4** to isoindolobenzazepine (**3**) *via* successive *N*-acyliminium ion intermediates, was achieved.

EXPERIMENTAL

Melting points were determined on a Yanagimoto MP-S3 microscope plates and is uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 (300 MHz), Bruker DPX-400 (400 MHz) instruments. IR spectra were measured on a Hitachi M-260-10 spectrophotometer. The MS were recorded on a Hitachi M-80, VG Auto Spec instrument. Elemental analyses were taken with Perkin-Elmer 240B, Elemental Vavio EL. Column chromatography was performed on Fuji Silysia (BW 127 ZH, BW 300) or Wakogel (C-200, C-300) as a silica gel and Fuji Silysia (Chromatorex NH-silica gel) as a basic silica gel.

2-(2,2-Dichlorovinyl)-5,6-dimethoxybenzoic Acid (8). To a solution of **7**[12] (15.2 g, 49 mmol) in glacial acetic acid (240 mL) and THF (150 mL) was added zinc powder (10.2 g, 156 mmol) in three portions over a period of 1 h at 55 °C– 65 °C under Ar, and the mixture was stirred at the same temperature for 3 h. After the hot filtration, the filtrate was concentrated, and then coevaporated with toluene. Addition of ice-water to the residue gave a crude solid, which was recrystallized from benzene to give **8** (12.9 g, 95%) as colorless crystals. mp 135-137 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.94 (s, 3H), 3.99 (s, 1H), 7.07, (d, *J* = 8.6 Hz, 1H), 7.13, (s, 1H), 7.41 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.00, 62.03, 114.37, 121.93, 125.57, 126.12, 126.41, 129.00, 147.01, 152.43, 169.23; IR (KBr) cm^{-1}: 3000, 1700; MS *m/z*: 276 (M^+, ^{35}Cl), 278 (M^+, ^{37}Cl); *Anal*. Calcd for $C_{11}H_{10}O_4Cl_2$: C, 47.68; H, 3.64. Found: C, 47.98; H, 3.89.

Benzyl *N*-[2-(Benzo[1,3]dioxol-5-yl)ethyl]carbamate (10a). To a suspension of $LiAlH_4$ (3.0 g, 78.1 mmol) in THF (25 mL) under Ar was added dropwise 3,4-methylenedioxy-(2-nitrovinyl)benzene (**9**)[13] (3.77 g, 19.5 mmol) in THF (51 mL) at -30 °C. After removal of the cooling bath, the mixture was stirred at rt for 3 h, and then heated at 65 °C –70 °C for 1 h. Ice was added to quench the reaction with the dry-ice bath, and then the mixture was stirred at rt for 30–40 min. After the resulting precipitate was removed by filtration with suction, the filtrate was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and then evaporated to give **10b**[13] as a dark brown oil in quantitative yield. To a solution of this crude oil in THF (23 mL) and H_2O (40 mL) were added Cbz-Cl (4.81 g, 26.8 mmol) and $NaHCO_3$ (4.09 g, 48.7 mmol) at 0 °C. After stirring at rt for 12 h, the mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, filtered, and then evaporated. The resulting residue was chromatographed (silica gel, hexane–$CHCl_3$–AcOEt = 10:5:1) to give **10a** (4.22 g, 72 %) as a white solid. Recrystallization of the resulting solid from *tert*-BuOMe afforded colorless crystals of **10a**: mp 83-84 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.73 (uneven t, *J* ≅ 7.2 Hz, 2H), 3.40 (uneven q, *J* ≅ 7.2 Hz, 2H), 4.67 (br, 1H), 5.09 (s, 2H), 5.92 (s, 2H), 6.67 (m, 3H), 7.34 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 35.72, 42.33, 66.59, 100.84, 108.31, 108.31, 109.03, 121.62, 128.06, 128.47, 132.37, 136.52, 146.14, 147.75, 156.23; IR (KBr) cm^{-1} 3320, 1670; MS *m/z*: 299 (M^+); *Anal*. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.14; H, 5.69; N, 4.56.

2-(Benzo[1,3]dioxol-5-yl)ethylamine (10b). A solution of **10a** (5.7 g, 19.2 mmol) in a mixture of MeOH (30 mL) and THF (8 mL) in the presence of 5% Pd-C (200 mg) was stirred at rt under an atmospheric pressure of hydrogen for 3 h, and then filtered. The filtrate was evaporated to afford the crude oil **10b** in quantitative yield. This crude oil was used for the next condensation without further purification.

***N*-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-2-(2,2-dichlorovinyl)-5,6-dimethoxybenzamide (11).** To a solution of **8** (5.31 g, 19.2 mmol) in THF (20 mL) under Ar were added a solution of **10b** (19.2 mmol) in THF (10 mL), the solution of diethyl phosphorocyanidate (DEPC) (3.43 g, 21.1 mmol) in THF (10 mL), and Et_3N (2.92 mL, 21.1 mmol) at 0 °C. After stirring at rt for 2 h, ice–water was added, and the mixture was extracted with $CHCl_3$. The extract was washed with 5% HCl, water, sat. Na_2CO_3, water, and brine, dried over $MgSO_4$, filtered, and the solvent was removed by evaporator. The crude solid was recrystallized from AcOEt–*i*Pr_2O to give **11** (5.5 g) as colorless crystals. The mother solution of recrystallization was concentrated by evaporator, and the resulting residue was chromatographed (basic silica gel, hexane–$CHCl_3$ = 3:1) to give **11** (0.78 g). The total yield of combined products was 6.28 g (78%). mp 125-128 °C (from AcOEt–hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.84 (t, *J* = 6.8 Hz, 2H), 3.68 (q, *J* = 6.8 Hz, 2H), 3.79 (s, 3H), 3.88 (s, 3H), 5.93 (s, 2H), 6.06 (br, 1H), 6.72 (m, 3H), 6.92 (d, *J* = 8.7 Hz, 1H), 6.93 (s, 1H), 7.45 (d, *J* = 8.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 35.35, 41.01, 55.85, 61.75, 100.86, 108.36, 108.97, 112.62, 121.23, 121.65, 124.30, 125.34, 125.99, 131.38, 132.33, 145.66, 146.20, 147.83, 152.48, 166.01; IR (KBr) cm^{-1}: 3220, 1623; MS *m/z*: 423 (M^+, ^{35}Cl), 425 (M^+, ^{37}Cl); *Anal*. Calcd for $C_{20}H_{19}NO_5Cl_2$: C, 56.61; H, 4.51; N, 3.30. Found: C, 56.43; H, 4.45; N, 3.32.

Ethyl *N*-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-2-(2,2-dichlorovinyl)-5,6-dimethoxybenzimidate (12). To a solution of **11** (2.05 g, 4.83 mmol) in CH_2Cl_2 (15 mL) under Ar was added dropwise $Et_3O^+ \cdot BF_4^-$ (*ca*. 1.5 M solution in CH_2Cl_2, 6.8 mL, 10.1 mmol) at -10 °C. After stirring at rt for 0.5 h, the mixture was refluxed overnight. After cooling at -15 °C, the mixture was neutralized with sat. $NaHCO_3$. The whole was extracted with CH_2Cl_2 and the organic layer was washed with brine, dried over $MgSO_4$, and then filtered. After evaporation of the solvent, the residue was purified by short column chromatography on silica gel (hexane–Et_2O = 4:1) to afford **12** (2.04 g, 93%) as a pale yellow oil: ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, *J* = 7.1 Hz, 3H), 2.74 (m, 2H), 3.08 (m, 1H), 3.26 (m, 1H), 3.80 (s, 3H), 3.89 (s, 3H), 4.30 (m, 2H), 5.89 (s, 2H), 6.36 (s, 1H), 6.58 (m, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 7.50 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 14.38, 37.51, 52.00, 55.78, 61.05, 61.31, 100.64, 107.97, 109.30, 112.37, 121.19, 121.64, 123.86, 124.53, 125.4, 128.29, 134.23, 145.43, 145.61, 147.27, 152.44, 157.28; IR (neat) cm^{-1}: 2950, 1670; MS *m/z*: 451 (M^+, ^{35}Cl), 453 (M^+, ^{37}Cl).

Ethyl *N*-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-2-ethynyl-5,6-dimethoxybenzimidate (13). To a solution of **12** (4.4 g, 9.72 mmol) in THF (43 mL) under Ar was added dropwise BuLi (1.38 M solution in hexane, 14.8 mL, 20.4 mmol) at -15 °C. After stirring at same temperature for 1 h, ice–water was added to quench the reaction. The mixture was extracted with Et_2O, and the extract was washed with brine, dried over $MgSO_4$, and filtered. After removal of the solvent by evaporator, the residue was purified by short

column chromatography on silica gel (hexane–Et_2O = 3:1) to afford **13** (3.53 g, 95%) as a dark brown oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, *J* = 7.1 Hz, 3H), 2.78 (m, 2H), 3.01 (s, 1H), 3.24 (m, 2H), 3.80 (s, 3H), 3.89 (s, 3H), 4.33 (m, 2H,), 5.88 (s, 2H), 6.64 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 1H); IR (neat) cm^{-1}: 2950, 1670.

***N*-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-2-ethynyl-5,6-dimethoxybenzamide (14).** To a suspension of **13** (3.11 g, 8.15 mmol) and NaI (1.47 g, 9.78 mmol) in MeCN (36 mL) under Ar was added dropwise a solution of TMSCl (1.06 g, 9.78 mmol) in MeCN (1 mL) at *ca*. -30 °C. The reaction mixture was allowed to warm to rt, and stirred for 15 h. When **13** was detected by TLC, the reaction mixture was cooled at *ca*. -30 °C again and NaI (0.49 g, 3.27 mmol) was added in one portion, and then a solution of TMSCl (0.35 g, 3.27 mmol) in MeCN (0.3 mL) was added dropwise. After stirring it until the disappearance of **13** by TLC, 10% $Na_2S_2O_3$ and sat. $NaHCO_3$ were added to quench the reaction under coolong at 0 °C, and then the mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and filtered. After removal of the solvent by evaporator, the resulting residue was chromatographed (silica gel, hexane–acetone = 3:1) to give **14** (2.35 g, 82%) as a white solid. Recrystallization from AcOEt–hexane gave a white brown powder of **14**: mp 119-120 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.86 (t, *J* = 6.8 Hz, 2H), 3.11 (s, 1H), 3.70 (uneven q, *J* ≅ 6.8 Hz, 2H), 3.83 (s, 3H), 3.88 (s, 3H), 5.92 (s, 2H), 5.95 (br, 1H), 6.75 (m, 3H), 6.86 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 35.22, 41.08, 55.84, 61.81, 79.30, 80.77, 100.78, 108.26, 109.11, 112.26, 112.67, 121.67, 129.64, 132.54, 134.90, 145.65, 146.03, 147.65, 153.42, 165.76; IR (KBr) cm^{-1}: 3270, 1640; MS *m/z*: 353 (M^+); *Anal*. Calcd for $C_{20}H_{19}NO_5$: C, 67.99; H, 5.38; N, 3.97. Found: C, 67.91; H, 5.50; N, 3.73.

2-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-6,7-dimethoxy-3-methylene-2,3-dihydro-1*H*-isoindol-1-one (5). (*by cyclization of 14 with LHMDS as the catalytic base*). To a solution of **14** (3.06 g, 8.66 mmol) in THF (30 mL) under Ar was added dropwise LHMDS (1.0 M solution in hexane, 0.86 mL, 0.86 mmol) at rt. After stirring for 2 h, ice–water was added to quench the reaction. The mixture was extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated. The residue was chromatographed (silica gel, hexane–AcOEt = 5:1) to give **5** (2.8 g, 92%) as an yellow solid. Recrystallization from toluene–*i*Pr_2O gave yellow crystals of **5**: mp113-114 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.87 (m, 2H), 3.89 (m, 2H), 3.92 (s, 3H), 4.10 (s, 3H), 4.69 (d, *J* = 2.2 Hz, 1H), 5.03 (d, *J* = 2.2 Hz, 1H), 5.93 (s, 2H), 6.72 (m, 3H), 7.10 (d, *J* = 8.3 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 34.12, 41.24, 56.64, 62.44, 86.38, 100.80, 108.29, 109.17, 115.18, 116.16, 121.16, 121.65, 129.99, 132.31, 141.00, 146.11, 146.57, 147.63, 153.55, 164.88; IR (KBr) cm^{-1}: 2900, 1690, 1630, 1490, 1450, 1400, 1250, 1120, 1020; MS *m/z*: 353 (M^+); *Anal*. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H,

5.42; N, 3.96. Found: C, 67.86; H, 5.49; N, 4.00.

(*by reductive dechlorination of 15 with Bu_3SnH*). To a solution of **15** (458 mg, 1.18 mmol) and azobisisobutyronitrile (29 mg, 0.17 mmol) in degassed toluene (2.3 mL) under Ar was added Bu_3SnH (0.35 mL, 1.29 mmol). The mixture was heated at 110 °C under irradiation with a 300 W-tangsten-lump for 6 h, and then concentrated under reduced pressur. The resulting residue was chromatographed (silica gel, hexane–acetone = 8:1) to give **5** (308 mg, 74%).

(*Z*)- and (*E*)-2-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-3-chloromethylene-6,7-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (15). To a solution of **11** (1.03 g, 2.42 mmol) in THF (12 mL) under Ar was added dropwise LHMDS (1.0 M solution in hexane, 2.42 mL, 2.42 mmol) at -10 °C. After stirring at -10 °C for 1 h, ice–water was added to quench the reaction. The mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, filtered, and the solvent was evaporated. The resulting residue (a mixture of *Z*- and *E*-isomer, *Z*/*E* = 9) was recrystallized from toluene–hexane to give **15** as an yellow solid (0.780 g). The mother solution of recrystallization was concentrated by evaporator, and the resulting residue was chromatographed (silica gel, hexane–acetone = 8:1) to give **15** (0.125 g). The total yield of **15** was 0.905 g (96%). Recrystallization from benzene–petroleum ether gave the major isomer, (*Z*)-**15** as yellow crystals: mp 156-157 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.92 (m, 2H), 3.92 (s, 3H), 4.08 (s, 3H), 4.29 (m, 2H), 5.93 (s, 2H), 6.10 (s, 1H), 6.76 (m, 3H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H); IR (KBr) cm^{-1}: 1720; MS *m/z*: 387 (M^+, ^{35}Cl), 389 (M^+, ^{37}Cl); *Anal*. Calcd for $C_{20}H_{18}NO_5Cl$: C, 61.94; H, 4.68; N, 3.61. Found: C, 62.19; H, 4.65; N, 3.70.

2-[2-(Benzo[1,3]dioxol-5-yl)ethyl]-3-hydroxymethyl-3,6,7-trimethoxy-2,3-dihydro-1*H*-isoindol-1-one (16b). To a DMD–acetone solution[21] (33 mL) was added dropwise a solution of **5** (610 mg, 1.73 mmol) in a mixed solution of MeOH (12 mL) and acetone (6 mL) at -78 °C. The reaction mixture was allowed to warm to -30 °C over 30 min, and kept for an additional 15 min at the same temperature. The reaction mixture was cooled to *ca*. -60 °C, and then quenched with 10% $Na_2S_2O_3$. The mixture was filtered, followed by dilution with MeOH (*ca*. 10 mL). The organic solvent was removed by evaporator under 40 °C. The residue was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and then concentrated under reduced pressure to give **16b** as a white powder (685 mg). This crude product was used in the next step immediately. Recrystallization from AcOEt gave colorless crystals of **16b**: mp 155-156 °C; ^{1}H-NMR (300 MHz, $CDCl_3$+ one drop of D_2O) δ: [1.72 (t, *J* = 7.0 Hz, 1H, D_2O exchageable)], 2.83 (s, 3H), 3.00 (m, 1H), 3.39 (m, 1H), 3.65 (m, 1H), 3.71 (d, *J* = 11.7 Hz, 1H), 3.84 (d, *J* = 11.7 Hz, 1H), 3.91 (s, 3H), 4.12 (s, 3H), 5.92 (d, *J* = 1.4 Hz, 1H), 5.93 (d, *J* = 1.4

Hz, 1H), 6.78 (m, 3H), 7.09 (d, *J* = 8.0 Hz), 7.17 (d, *J* = 8.0 Hz, 1H); IR (KBr) cm^{-1}: 3320, 2840, 1645; MS *m/z*: 401 (M^+); *Anal*. Calcd for $C_{21}H_{23}NO_7$: C, 62.83; H, 5.78; N, 3.49. Found: C, 62.68; H, 5.81; N, 3.51.

12b-Hydroxymethyl-9,10-dimethoxy-5,12b-dihydro-1,3-dioxolo[4,5-*g*]isoindolo[1,2-*a*]isoquinolin-8(6*H*)-one (4). The crude product (**16b**) was dissolved in dry CH_2Cl_2 (30 mL) under argon, and the solution was cooled at -40 °C– -50 °C. BF_3·OEt_2 (0.43 mL, 3.45 mmol) was added dropwise, and the reaction mixture was allowed to warm to 5 °C, and stirred an additional 1 h at the same temperature. The reaction mixture was cooled to -10 °C, neutralized with sat. $NaHCO_3$, and extracted with $CHCl_3$ (×7). The extract was washed with brine, dried over $MgSO_4$, filtered, and then concentrated. The residue was chromatographed (silica gel, $CHCl_3$–*i*PrOH = 30:1) to give **4** (563 mg, 88%) as a white solid. Recrystallization from MeOH gave colorless crystals of **4**: mp 238.5-240.0 °C; ^{1}H-NMR (300 MHz, $CDCl_3$+ one drop of D_2O) δ: [2.19 (br, 1H, D_2O exchageable)], 2.67 (ddd, *J* = 11.9, 4.4, 1.4 Hz, 1H), 2.97 (m, 1H), 3.48 (ddd, *J* = 13.4, 4.4, 1.4 Hz, 1H), 3.89 (s, 3H), 4.00 (d, *J* = 11.9 Hz, 1H), 4.05 (s, 3H), 4.08 (d, *J* = 11.9 Hz, 1H), 4.50 (ddd, *J* = 13.4, 6.4, 1.5 Hz, 1H), 5.90 (d, *J* = 1.4 Hz, 1H), 5.95 (d, *J* = 1.4 Hz, 1H), 6.59 (s, 1H), 7.12 (s, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.49 (d, *J* = 8.4 Hz, 1H); IR (KBr) cm^{-1}: 3230, 1660; MS *m/z*: 370 (M^++1), 338 (-CH_2OH); *Anal*. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 64.77; H, 5.34; N, 3.63.

9,10-Dimethoxy-5,6-dihydro-8*H*-1,3-dioxolo[4,5-*h*]isoindolo[1,2-*b*][3]benzazepim-8-one (3a). To a solution of **4** (110 mg, 0.298 mmol) in a mixed solvent of $CHCl_3$ (4 mL) and pyridine (1 mL) were added Et_3N (0.21 mL, 1.49 mmol) and then, dropwise, SO_2Cl_2 (0.072 mL, 0.893 mmol) at -78 °C under argon. The solution was allowed to warm to rt over 0.5 h and stirred overnight. The reaction was quenched with sat. $NaHCO_3$ solution, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, filtered, and then concentrated by evaporator. The residue was chromatographed (silica gel, $CHCl_3$) to give **3a** (78 mg, 75%) as an yellow solid: mp 213-214 °C (from AcOEt) (lit.,[5a] 209-211 °C) ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.02 (m, 2H), 3.75–4.25 (br, 2H), 3.93 (s, 3H), 4.10 (s, 3H), 5.96 (s, 2H), 6.32 (s, 1H), 6.66 (s, 1H), 6.79 (s, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 35.48, 41.81, 56.71, 62.45, 101.23, 104.93, 110.13, 110.25, 114.32, 116.33, 120.31, 127.78, 131.07, 133.24, 133.91, 146.55, 146.81, 146.88, 152.89, 163.65; IR (KBr) cm^{-1}: 1670, 1480; MS *m/z*: 351 (M^+); *Anal*. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.32; H, 4.96; N, 4.01.

13-Chloro-9,10-dimethoxy-5,6-dihydro-8*H*-1,3-dioxolo[4,5-*h*]isoindolo[1,2-*b*][3]benzazepin-8-one

(3b). To a solution of **4** (150 mg, 0.406 mmol) in a mixed solvent of $CHCl_3$ (6 mL) and pyridine (1.5 mL) were added Et_3N (0.28 mL, 2.03 mmol) and then, dropwise, SO_2Cl_2 (0.1 mL, 1.21 mmol) at -78 °C under argon. The mixture was allowed to warm to rt over 0.5 h and stirred until the disappearance of the starting material by TLC. And then, the mixture was cooled to -78 °C again, more Et_3N (0.11 mL, 0.812 mmol) and SO_2Cl_2 (0.042 mL, 0.528 mmol) were added dropwise to the reaction mixture, which was stirred at rt for 10 h. The reaction was quenched with sat. $NaHCO_3$, and the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (silica gel, hexane–AcOEt = 4:1) to give **3b** (119 mg, 76%) as an yellow solid. Recrystallization from AcOEt gave yellow crystals of **3b**: mp 203-207 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.99 (m, 2H), 4.00–4.10 (br, 2H), 3.96 (s, 3H), 4.06 (s, 3H), 6.01 (s, 2H), 6.62 (s, 1H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.43 (s, 1H), 8.43 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 34.47, 45.25, 56.44, 62.27, 101.55, 108.20, 109.95, 114.21, 115.79, 121.70, 122.38, 129.28, 130.12, 131.88, 135.06, 146.82, 146.87, 147.92, 153.39, 163.59; IR (KBr) cm^{-1}: 1698; MS *m/z*: 385 (M^+, ^{35}Cl), 387 (M^+, ^{37}Cl); *Anal*. Calcd for $C_{20}H_{16}NO_5Cl$: C, 62.26; H, 4.18; N, 3.36. Found: C, 62.07; H, 4.39; N, 3.61.

Lennoxamine (1). Hydrogenation of **3b** (92 mg, 0.238 mmol) over 5% Pd-C (45 mg) in a mixted solution of MeOH (6 mL) and THF (6 mL) was carried out at rt for 6 h under an atmospheric pressure of hydrogen. After the catalyst was filtered off, the solvent was evaporated. The residue was chromatographed (silica gel, hexane–$CHCl_3$–AcOEt = 5:5:1) to give **1** (81 mg, 96%) as an white powder. Recrystallization from MeOH gave colorless crystals of **1**: mp 235-235.5 °C (lit.,[3a] 229-230 °C; lit.,[3c,4b] 228-229 °C; lit.,[1a,4f] 225 °C); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.83 (dd, *J* = 14.7, 10.4 Hz, 1H), 2.89 (m, 3H), 3.10 (dd, *J* = 14.7, 1.7 Hz, 1H), 3.92 (s, 3H), 4.11 (s, 3H), 4.30 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.75 (m, 1H). 5.95 (d, *J* = 1.4 Hz, 1H), 5.96 (d, *J* = 1.4 Hz, 1H), 6.71 (s, 1H), 6.78 (s, 1H), 7.13 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 35.90, 41.07, 42.67, 56.69, 60.12, 62.52, 101.01, 110.29, 110.29, 116.13, 117.05, 124.13, 130.90, 134.80, 138.14, 146.03, 146.30, 147.16, 152.58, 165.11; IR (KBr) cm^{-1}: 2860, 1681; MS *m/z*: 353 (M^+); *Anal*. Calcd for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42, N, 3.96. Found: C, 68.02, H, 5.40, N, 4.00.

Chilenine (2). To a DMD-acetone solution (16 mL) was added dropwise a solution of **3b** (325 mg, 0.848 mmol) in $CHCl_3$ (12 mL) at *ca.* -20 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h. The reaction mixture was cooled to *ca.* -20 °C and more DMD–acetone solution (10 mL) was added followed by stirring at rt for 1.5 h. The reaction was quenched with 10% $Na_2S_2O_3$, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, filtered, and then concentrated by evaporator. The residue was chromatographed (silica gel, toluene–AcOEt = 3:1) to give

2 (170 mg, 53%) as a white solid. Recrystallization from toluene–*i*Pr_2O gave a white powder of **2**: mp 157-158 °C (lit.,[2g] 152-153 °C, lit.,[6a] 154-156 °C, lit.,[2b] 155 °C); ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.11 (ddd, *J* = 15.6, 5.9, 4.2 Hz, 1H), 3.29 (ddd, *J* ≅ 15.6, *J* = 10.6, 5.9 Hz, 1H), 3.56 (ddd, *J* = 13.5, 5.9, 4.2 Hz, 1H), 3.87 (s, 3H), 4.00 (s, 3H), 4.09 (br, 1H, D_2O exchageable), 4.26 (ddd, *J* = 13.5, 10.6, 5.9 Hz, 1H), 5.94 (d, *J* = 1.2 Hz, 1H), 5.96 (d, *J* = 1.2 Hz, 1H), 6.66 (s, 1H), 6.71 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 30.98, 37.83, 56.34, 62.31, 90.42, 101.77, 108.66, 109.44, 116.25, 119.32, 122.61, 129.89, 133.75, 135.58, 145.84, 146.74, 151.35, 153.93, 166.12, 202.13; MS *m/z*: 383 (M^+); HRMS (EI) calcd for $C_{20}H_{17}NO_7$ 383.1005 (M^+), found 383.1008.

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