Synthesis of 1,2,3,4-Tetrahydroisoquinoline-2-sulfonic Acids

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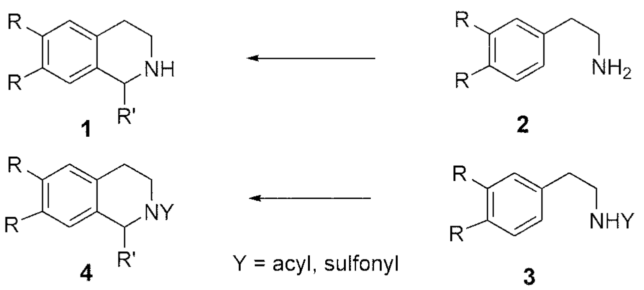
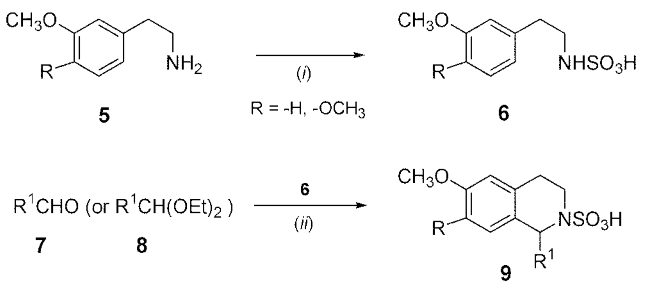
Received May 7, 2003

Key Words : Tetrahydroisoquinoline, Sulfamic acid, Iminium ion

The 1,2,3,4-tetrahydroisoquinoline (THIQ) alkaloids **1**, which are widely distributed in plant and animal kingdoms, have received much attention because of their important biological activities.[1] For example, 1-aryl- or 1-alkyl-1,2,3,4-tetrahydroisoquinolines present in mammalian brain play a major role in therapy of variety of neurological disorders.[2]



Two general, acid mediated procedures have been reported for the preparation of THIQ ring system. The first entails the Pictet-Spengler reaction of a 2-arylethylamine **2** with aldehyde.[3] The second method requires the treatment of a *N*-substituted-2-arylethylamine **3** (*i.e.*, *N*-acyl[4] and *N*-sulfonyl group[5] on the nitrogen) with carbonyl compound (*i.e.*, aldehyde, and the corresponding acetal). In these processes, introduction of an electron withdrawing substituents on nitrogen is to increase the electrophilicity of iminium intermediate. Previously, we demonstrated the intramolecular- and intermolecular α-sulfamidoalkylation transformation proceeding through the intermediacy of an iminium ion provide an expeditious route for the preparation of cyclic sulfamides containing THIQ ring.[6] The sulfamic acid also have a sulfonic acid group as an electron withdrawing group on the nitrogen atom and is readily hydrolyzed to the corresponding amines.[7]



Scheme 1. Synthesis of **8**. Reagents and coditions: (i) 1) $ClSO_3H$-Et_3N, -5-0 °C, 2) *c*-HCl; (ii) HCO_2H.

In this present study, we report on the reaction of *N*-(2-arylethyl)sulfonic acids **6** with aldehydes **7** (or the corresponding acetals **8**) in formic acid for generation of 1,2,3,4-tetrahydroisoquinoline-2-sulfonic acids **9**.

The starting sulfamic acid **6** were prepared according to established synthetic protocols.[8] When amine **5** was reacted with $ClSO_3H$-Et_3N in chloroform, followed by treatment with hydrochloric acid, sulfamic acid **6** was formed in 60-70 % yield. Intramolecular cyclization of **6** with **7** or **8** in fomic acid (96% in H_2O) gave the desired product **9** in good yield. Identification of all the isolated products **9** was accomplished with the aid of infrared, ^{1}H and ^{13}C NMR, and mass

Table 1. Reaction condition, mp, and yield of product **9**

Entry	No.	R¹	R	Reaction conditions: Temp. (°C)	Time (h)	mp (°C)[a]	Yield (%)[b]
1	**9a**	H	H	rt	1	200-213	81
2	**9b**	H	OMe	rt	1	172-200	65
3	**9c**	CH_2Cl	H	rt	12	75-80	74
4	**9d**	CH_2Cl	OMe	rt	0.5	174-176	92
5	**9e**	CH_2CN	H	rt	24	205-215	65
6	**9f**	CH_2CN	OMe	rt	1	194-195	68
7	**9g**	COOEt	H	rt	48	104-108	58
8	**9h**	COOEt	OMe	rt	48	170-171	67
9	**9i**	Benzyl	H	rt	24	142-145	84
10	**9j**	Benzyl	OMe	rt	48	150-152	73
11	**9k**	Phenyl	H	50	24	169-171	65
12	**9l**	Phenyl	OMe	50	24	172-176	78
13	**9m**	3-methoxy-4-hydroxyphenyl	H	50	24	117-119	62
14	**9n**	3-methoxy-4-hydroxyphenyl	OMe	50	24	76-99	71
15	**9o**	3,4,5-trimethoxy-phenyl	H	rt	48	159-160	66
16	**9p**	3,4,5-trimethoxy-phenyl	OMe	50	24	169-176	68
17	**9q**	2-furyl	H	rt	48	180-188	70
18	**9r**	2-furyl	OMe	rt	48	134-140	74
19	**9s**	2-thiophenyl	H	rt	24	186-190	70
20	**9t**	2-thiophenyl	OMe	rt	24	230-238	76

[a]Isolated yields. [b]Melting points are uncorrected.

spectroscopy. In the infrared spectrum, the compound **9** exhibited characteristic absorption bands at 1246-1277 and 1016-1119 cm^{-1} for the sulfonyl group.[9] Diagnostic signals of compounds **9** were observed at 4.38-6.13 ppm in the ^1H NMR spectra and at 48.5-60.8 ppm in the ^{13}C NMR spectra for the methine (C-1) unit furnished by aldehdes **7** (or acetals **8**).

In conclusion, we have developed a general and versatile method for the synthesis of 1, 2, 3, 4-tetrahydroisoquinoline-2-sulfonic acids, by the reaction of *N*-(2-arylethyl)sulfamic acids with aldehydes (or acetals).

Experimental Section

Typical experimental procedure for synthesis of *N*-arylethylsulfamic acid 6. A solution of arylethylamine **5** (10 mmol) and triethylamine (12 mmol) in 30 mL of $CHCl_3$ was stirred at -5-0 °C and chlorosulfonic acid (10 mmol) was added dropwise so as to maintain the temperature below 0 °C. The solution was acidified with 1 *N* HCl solution to pH 2. The solid that precipitated was filtered to give the desired products **6**.

2-(3-Methoxyphenyl)ethylsulfamic acid (**6a**): Beginning with 3-methoxyphenethylamine (1.51 g), compound **6a** was obtained in 55% yield (1.27 g): mp 144-146 °C; IR (KBr) 3180 (NH), 1288, 1063 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.87 (t, *J* = 8.3 Hz, 2H), 3.21 (t, *J* = 8.3 Hz, 2H), 3.75 (s, 3H), 6.79-6.82 (m, 3H), 7.22-7.25 (m, 1H), 10.18 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 32.5, 45.6, 55.5, 112.9, 114.7, 121.3, 130.2, 139.4, 160.0 ppm; LR FBA MS: calcd for $[M-1]^-$ 230.1, found 230.2.

2-(3,4-Dimethoxyphenyl)ethylsulfamic acid (6b): Beginning with 3,4-dimethoxyphen-ethylamine (1.81 g), compound **6b** was obtained in 67% yield (1.75 g): mp 164-170 °C; IR (KBr) 3146 (NH), 1259, 1072 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.82 (t, *J* = 8.3Hz, 2H), 3.19 (t, *J* = 8.3 Hz, 2H), 3.71 (s, 3H), 3.75 (s, 3H), 6.73 (dd, *J* = 1.8 Hz and *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 1.8 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 10.18 (br s, 1H) ppm; ^{13}C NMR (DMSO-d_6) δ 32.1, 45.9, 56.0, 56.1, 112.6, 113.0, 121.0, 130.2, 184.2, 149.4 ppm; LR FBA MS: calcd for $[M-1]^-$ 260.1, found 260.2.

Typical experimental procedure for synthesis of 1,2,3, 4-tetrahydroisoquinoline-2-sulfonic acid 9. A formic acid (96% in H_2O, 20 mL) solution of arylethylsulfamic acids **6** (2.0 mmol) and aldehydes **7** (or acetals **8**) (2.0 mmol) was stirred, and then the solution was quenched with 1 *N* HCl (50 mL). The solid that precipitated was filtered and then recrystallized from methanol-chloroform to give the desired products **9** (Table 1).

9a: IR (KBr) 1269, 1063 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.13 (t, *J* = 6.4 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 4.39 (s, 2H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.78 (dd, *J* = 2.3 Hz and *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 26.3, 45.9, 48.5, 54.9 113.1, 113.4, 120.8, 128.1, 133.1, 159.3 ppm; LR FBA MS: calcd for $[M-1]^-$ 242.1, found 242.7.

9b: IR (KBr) 1258, 1057 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.07 (t, *J* = 6.4 Hz, 2H), 3.59 (t, *J* = 6.4 Hz, 2H), 3.74 (s, 6H), 4.38 (s, 2H), 6.77 (s, 1H), 6.79 (s, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 25.6, 46.1, 48.5, 55.4, 55.5, 109.8, 111.5, 120.5, 123.8, 148.2, 148.7 ppm; LR FBA MS: calcd for $[M-1]^-$ 272.1, found 272.7.

9c: IR (KBr) 1265, 1047 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.05 (ddd, *J* = 5.5 Hz, *J* = 5.5 Hz, and *J* = 17.6 Hz, 1H), 3.18 (ddd, *J* = 5.5 Hz, *J* = 8.3 Hz, and *J* = 17.6 Hz, 1H), 3.45 (ddd, *J* = 5.5 Hz, *J* = 8.3 Hz, and *J* = 13.2 Hz, 1H), 3.69 (ddd, *J* = 5.5 Hz, *J* = 5.5 Hz, and *J* = 13.2 Hz, 1H), 3.74 (s, 3H), 4.18 (dd, *J* = 7.1 Hz and *J* = 12.8 Hz, 1H), 4.29 (dd, *J* = 3.4 Hz and *J* = 12.8 Hz, 1H), 4.94 (dd, *J* = 3.4 Hz and *J* = 7.1 Hz, 1H), 6.79 (d, *J* = 2.7 Hz, 1H), 6.83 (dd, *J* = 2.7 Hz and *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 25.3, 40.0, 44.6, 55.1, 55.7, 113.7, 113.8, 120.7, 127.9, 134.5, 159.5 ppm; LR FBA MS: calcd for $[M-1]^-$ 290.0, found 290.2.

9d: IR (KBr) 1273, 1071 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.03 (ddd, *J* = 5.5 Hz, *J* = 5.8 Hz, and *J* = 17.1 Hz, 1H), 3.14 (ddd, *J* = 5.5 Hz, *J* = 7.6 Hz, and *J* = 17.1 Hz, 1H), 3.50 (ddd, *J* = 5.8 Hz, *J* = 7.6 Hz, and *J* = 12.5 Hz, 1H), 3.74 (ddd, *J* = 5.5 Hz, *J* = 5.5 Hz, and *J* = 12.5 Hz, 1H), 3.78 (s, 6H), 4.25 (dd, *J* = 7.3 Hz and *J* = 12.9 Hz, 1H), 4.38 (dd, *J* = 3.6 Hz and *J* = 12.9 Hz, 1H), 4.97 (dd, *J* = 3.6 Hz and *J* = 7.3 Hz, 1H), 6.83 (s, 1H), 7.01 (s, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 24.6, 40.1, 44.7, 55.3, 55.6, 55.8, 109.7, 112.0, 120.4, 125.3, 148.6, 149.5 ppm; LR FBA MS: calcd for $[M-1]^-$ 320.0, found 320.2.

9e: IR (KBr) 1251, 1049 cm^{-1}; ^1H NMR (methanol-d_3) δ 3.10 (ddd, *J* = 6.4 Hz, *J* = 6.4 Hz, and *J* = 17.5 Hz, 1H), 3.18 (ddd, *J* = 6.4 Hz, *J* = 7.1 Hz, and *J* = 17.5 Hz, 1H), 3.36 (dd, *J* = 5.0 Hz and *J* = 17.6 Hz, 1H), 3.40 (dd, *J* = 6.1 Hz and *J* = 17.6 Hz, 1H), 3.48 (ddd, *J* = 6.4 Hz, *J* = 6.4 Hz, and *J* = 13.0 Hz, 1H), 3.64 (ddd, *J* = 5.5 Hz, *J* = 7.1 Hz, and *J* = 13.0 Hz, 1H), 3.80 (s, 3H), 4.89 (dd, *J* = 5.0 Hz and *J* = 6.1 Hz, 1H), 6.84 (d, *J* =2.3 Hz, 1H), 6.91 (dd, *J* = 2.3 Hz and *J* = 8.7 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (methanol-d_3) δ 22.0, 24.9, 39.6, 51.1, 54.6, 113.5, 113.8, 115.8, 121.1, 127.6, 133.3, 160.2 ppm; LR FBA MS: calcd for $[M-1]^-$ 281.1, found 281.7.

9f: IR (KBr) 1271, 1071 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.05-3.09 (m, 2H), 3.38 (dd, *J* = 5.0 Hz and *J* = 17.9 Hz, 1H), 3.54 (dd, *J* = 5.5 Hz and *J* = 17.9 Hz, 1H), 3.54 (ddd, *J* = 5.0 Hz, *J* = 5.7 Hz, and *J* = 12.7 Hz, 1H), 3.69 (ddd, *J* = 5.5 Hz, *J* = 7.3 Hz, and *J* = 12.7 Hz, 1H), 3.76 (s, 3H), 3.77 (s, 3H), 4.97 (dd, *J* = 5.0 Hz and *J* = 5.5 Hz, 1H), 6.82 (s, 1H), 6.96 (s, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 22.7, 24.3, 39.5, 50.6, 55.4, 55.6, 109.5, 111.9, 116.8. 120.9, 124.7, 148.4, 149.5 ppm; LR FBA MS: calcd for $[M-1]^-$ 311.1, found 311.7.

9g: IR (KBr) 1248, 1016 cm^{-1}; ^1H NMR (acetone-d_6) δ 1.29 (t, *J* = 7.1 Hz, 3H) 3.14 (ddd, *J* = 5.5 Hz, *J* = 5.7 Hz, and *J* = 17.2 Hz, 1H), 3.24 (ddd, *J* = 5.5 Hz, *J* = 8.7 Hz, and *J* = 17.2 Hz, 1H), 3.67 (ddd, *J* = 5.5 Hz, *J* = 5.7 Hz, and *J* = 12.3 Hz, 1H), 3.77-3.81 (m, 1H), 3.80 (s, 3H), 4.31 (q, *J* = 7.1 Hz, 2H), 5.45 (s, 1H), 6.85 (d, *J* = 2.7 Hz, 1H), 6.89 (dd, *J* = 2.7 Hz and *J* = 8.7 Hz, 1H), 7.46 (d, *J* = 8.7 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 13.4, 25.0, 39.9, 54.9, 55.7, 62.8, 113.4, 113.7, 117.9, 129.1, 134.1, 160.0, 167.6 ppm; LR FBA MS: calcd for $[M-1]^-$ 315.1, found 315.7.

9h: IR (KBr) 1273, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.33 (t, J = 7.3 Hz, 3H) 2.96 (ddd, J = 3.2 Hz, J = 3.2 Hz, and J = 16.5 Hz, 1H), 3.14 (ddd, J = 4.1 Hz, J = 12.4 Hz, and J = 16.5 Hz, 1H), 3.45 (ddd, J = 3.2 Hz, J = 12.4 Hz, and J = 12.4 Hz, 1H), 4.21 (ddd, J = 3.2 Hz, J = 3.2 Hz, and J = 12.4 Hz, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 4.35 (q, J = 7.3 Hz, 2H), 5.43 (s, 1H), 6.65 (s, 1H), 6.93 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.1, 26.2, 45.9, 56.1, 56.2, 60.8, 64.3, 109.7, 111.2, 124.8, 148.8, 149.8, 149.7, 169.0 ppm; LR FBA MS: calcd for $[M-1]^-$ 344.1, found 344.7 .

9i: IR (KBr) 1246, 1059 cm^{-1}; ^{1}H NMR (methanol-d_3) δ 3.07 (ddd, J = 6.0 Hz, J = 6.9 Hz, and J = 16.3 Hz, 1H), 3.12 (dd, J = 8.2 Hz and J = 13.9 Hz, 1H), 3.16 (ddd, J = 6.0 Hz, J = 7.1 Hz, and J = 16.3 Hz, 1H), 3.33 (ddd, J = 6.0 Hz, J = 7.1 Hz, and J = 12.6 Hz, 1H), 3.49 (dd, J = 6.4 Hz and J = 13.8 Hz , 1H), 3.53 (ddd, J = 6.0 Hz, J = 6.9 Hz, and J = 12.6 Hz, 1H), 3.78 (s, 3H), 4.77 (dd, J = 6.4 Hz and J = 8.2 Hz, 1H), 6.79 (d, J = 2.3 Hz, 1H), 6.81 (dd, J = 2.3 Hz and J = 8.2 Hz, 1H), 7.05 (d, J = 8.2 Hz, 1H), 7.31-7.35 (m, 3H), 7.37-7.41 (m, 2H) ppm; ^{13}C NMR (methanol-d_3) δ 25.2, 39.2, 39.8, 54.5, 56.4, 113.1, 113.2, 123.4, 127.5, 127.9, 128.9, 129.4, 132.8, 135.3, 129.7 ppm; LR FBA MS: calcd for $[M-1]^-$ 332.1, found 332.7.

9j: IR (KBr) 1262, 1061 cm^{-1}; ^{1}H NMR (methanol-d_3) δ 3.04 (ddd, J = 3.9 Hz, J = 6.2 Hz, and J = 17.4 Hz, 1H), 3.09 (ddd, J = 6.0 Hz, J = 7.6 Hz, and J = 17.4 Hz, 1H), 3.18 (ddd, J = 3.9 Hz, J = 7.6 Hz, and J = 13.3 Hz, 1H), 3.36 (ddd, J = 6.0 Hz, J = 6.2 Hz, and J = 13.3 Hz, 1H), 3.42 (dd, J = 7.3 Hz and J = 13.7 Hz, 1H), 3.55 (dd, J = 7.4 Hz and J = 13.7 Hz , 1H), 3.67 (s, 3H), 3.81 (s, 3H), 4.74 (dd, J = 7.3 Hz and J = 7.3 Hz, 1H), 6.42 (s, 1H), 6.81 (s, 1H), 7.31-7.35 (m, 3H), 7.38-7.41 (m, 2H) ppm; ^{13}C NMR (methanol-d_3) δ 24.5, 39.1, 40.0, 53.8, 55.1, 55.3, 110.3, 111.8, 123.2, 124.0, 127.4, 129.0, 130.0, 135.9, 147.6, 149.0 ppm; LR FBA MS: calcd for $[M-1]^-$ 362.1, found 362.7.

9k: IR (KBr) 1269, 1067 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.15 (ddd, J = 5.5 Hz, J = 5.5 Hz, and J = 17.4 Hz, 1H), 3.30 (ddd, J = 6.5 Hz, J = 8.7 Hz, and J = 17.4 Hz, 1H), 3.47 (ddd, J = 5.5 Hz, J = 8.7 Hz, and J = 12.9 Hz, 1H), 3.53 (ddd, J = 5.5 Hz, J = 6.5 Hz, and J = 12.9 Hz, 1H), 3.80 (s, 3H), 5.66 (s, 1H), 6.72 (d, J = 8.7 Hz, 1H), 6.78 (dd, J = 2.8 Hz and J = 8.7 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 7.35-7.37 (m, 2H), 7.46-7.48 (m, 3H) ppm; ^{13}C NMR (acetone-d_6) δ 25.3, 40.0, 55.0, 59.2, 113.1, 113.6, 123.7, 129.1, 129.4, 129.6, 130.1, 134.2, 137.0, 159.3 ppm. LR FBA MS: calcd for $[M-1]^-$ 318.1, found 318.7.

9l: IR (KBr) 1262, 1063 cm^{-1}; ^{1}H NMR (methanol-d_3) δ 3.11 (ddd, J = 5.5 Hz, J = 6.0 Hz, and J = 17.4 Hz, 1H), 3.23 (ddd, J = 6.0 Hz, J = 6.4 Hz, and J = 17.4 Hz, 1H), 3.43 (ddd, J = 5.5 Hz, J = 7.3 Hz, and J = 13.0 Hz, 1H), 3.49 (ddd, J = 6.0 Hz, J = 6.4 Hz, and J = 13.0 Hz, 1H), 3.59 (s, 3H), 3.86 (s, 3H), 5.69 (s, 1H), 6.34 (s, 1H), 6.90 (s, 1H), 7.35-7.37 (m, 2H), 7.47-7.49 (m, 3H) ppm; ^{13}C NMR (methanol-d_3) δ 24.5, 39.5, 55.1, 55.3, 59.3, 110.7, 111.4, 122.9, 124.8, 129.1, 129.7, 129.8, 136.4, 148.3, 149.5 ppm; LR FBA MS: calcd for $[M-1]^-$ 348.1, found 348.7.

9m: IR (KBr) 1263, 1034 cm^{-1}; ^{1}H NMR (methanol-d_3) δ 3.12 (ddd, J = 5.5 Hz, J = 5.5 Hz, and J = 17.6 Hz, 1H), 3.30 (ddd, J = 6.2 Hz, J = 8.2 Hz, and J = 17.6 Hz, 1H), 3.46 (ddd, J = 5.5 Hz, J = 8.2 Hz, and J = 12.7 Hz, 1H), 3.53 (ddd, J = 5.5 Hz, J = 6.2 Hz, and J = 12.7 Hz, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 5.60 (s, 1H), 6.75 (d, J = 1.9 Hz and J = 8.3 Hz, 1H), 6.79 (s, 2H), 6.84 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 1.9 Hz 1H) ppm; ^{13}C NMR (methanol-d_3) δ 25.2, 39.8, 54.5, 55.2, 59.7, 112.7, 112.8, 113.5, 115.3, 122.7, 123.6, 127.5, 129.3, 133.5, 147.9, 148.2, 159.7 ppm LR FBA MS: calcd for $[M-1]^-$ 364.1, found 364.7.

9n: IR (KBr) 1260, 1059 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.08 (ddd, J = 6.0 Hz, J = 6.0 Hz, and J = 17.2 Hz, 1H), 3.20 (ddd, J = 6.4 Hz, J = 7.6 Hz, and J = 17.2 Hz, 1H), 3.42 (ddd, J = 6.0 Hz, J = 7.6 Hz, and J = 12.8 Hz, 1H), 3.49 (ddd, J = 6.0 Hz, J = 6.4 Hz, and J = 12.8 Hz, 1H), 3.62 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 5.61 (s, 1H), 6.39 (s, 1H), 6.76 (dd, J = 1.9 Hz and J = 8.0 Hz, 1H), 6.85 (d, J = 8.0 Hz,1H), 6.87 (s, 1H), 6.94 (d, J = 1.9 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 24.8, 4.04, 55.2, 55.4, 55.9, 59.5, 111.3, 111.6, 113.5, 114.9, 123.2, 123.6, 125.2, 128.0, 147.1, 147.9, 148.4, 149.6 ppm; LR FBA MS: calcd for $[M-1]^-$ 394.1, found 394.7.

9o: IR (KBr) 1277, 1057 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.13 (ddd, J = 5.0 Hz, J = 5.5 Hz, and J = 17.5 Hz, 1H), 3.41 (ddd, J = 6.0 Hz, J = 9.9 Hz, and J = 17.5 Hz, 1H), 3.55 (ddd, J = 5.5 Hz, J = 9.9 Hz, and J = 12.7 Hz, 1H), 3.68 (ddd, J = 5.0 Hz, J = 5.5 Hz, and J = 12.7 Hz, 1H), 3.71 (s, 3H), 3.73 (s, 6H), 3.80 (s, 3H), 6.03 (s, 1H), 6.62 (s, 2H), 6.80 (d, J = 2.8 Hz and J = 8.7 Hz, 1H), 6.87 (d, J = 2.8 Hz, 2H), 6.96 (d, J = 8.7 Hz 1H) ppm; ^{13}C NMR (acetone-d_6) δ 25.2, 40.6, 54.9, 55.9, 59.8, 59.9, 107.4, 113.1, 113.5, 123.6, 129.4, 132.3, 134.1, 138.8, 153.7, 159.4 ppm; LR FBA MS: calcd for $[M-1]^-$ 408.1, found 804.7.

9p: IR (KBr) 1261,1051 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.10 (ddd, J = 5.5 Hz, J = 5.7 Hz, and J = 17.4 Hz, 1H), 3.30 (ddd, J = 6.4 Hz, J = 8.0 Hz, and J = 17.4 Hz, 1H), 3.52 (ddd, J = 5.5 Hz, J = 8.0 Hz, and J = 13.8 Hz, 1H), 3.62 (ddd, J = 5.7 Hz, J = 6.4 Hz, and J = 13.8 Hz, 1H), 3.06 (s, 3H), 3.72 (s, 3H), 3.75 (s, 6H), 3.81 (s, 3H), 5.75 (s, 1H), 6.43 (s, 1H), 6.74 (s, 2H), 6.87 (s, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 25.0, 41.0, 54.8, 56.0, 56.2, 56.4, 60.4, 60.9, 107.2, 110.6, 111.2, 122.5, 124.7, 131.5, 138.8, 148.2, 149.3, 153.6 ppm. LR FBA MS: calcd for $[M-1]^-$ 438.1, found 438.7.

9q: IR (KBr) 1246, 1115 cm^{-1}; ^{1}H NMR (methanol-d_3) δ 3.17 (t, J = 6.4 Hz, 2H), 3.42-3.52 (m, 2H), 5.80 (s, 1H), 6.42 (d, J = 3.2 Hz, 1H), 6.49 (dd, J = 1.8 Hz and J = 3.2 Hz, 1H), 6.83 (dd, J = 2.3 Hz and J = 8.7 Hz, 1H), 6.86 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.7 Hz 1H), 7.63 (d, J = 1.8 Hz, 1H) ppm; ^{13}C NMR (methanol-d_3) δ 24.9, 39.0, 52.2, 54.8, 110.8, 112.9, 113.2, 113.6, 120.7, 128.9, 133.3, 144.7, 148.9, 159.8 ppm; LR FBA MS: calcd for $[M-1]^-$ 308.1, found 308.7.

9r: IR (KBr) 1265, 1119 cm^{-1}; ^{1}H NMR (methanol-d_3) δ

3.12 (t, J = 6.4 Hz, 2H), 3.41-3.50 (m, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 5.81 (s, 1H), 6.44 (d, J = 3.2 Hz, 1H), 6.50 (dd, J = 1.8 Hz and J = 3.2 Hz 1H), 6.57 (s, 1H), 6.87 (s, 1H), 7.65 (d, J = 1.8 Hz, 1H) ppm; ^{13}C NMR (methanol-d_3) δ 24.3, 38.3, 52.1, 55.3, 110.4, 110.8, 111.6, 113.0, 120.4, 124.5, 144.7, 148.4, 148.9, 149.7 ppm; LR FBA MS: calcd for $[M-1]^-$ 338.1, found 338.6.

9s: IR (KBr) 1269, 1055 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.17 (ddd, J = 6.4 Hz, J = 7.1 Hz, and J = 17.5 Hz, 1H), 3.23 (ddd, J = 5.9 Hz, J = 6.4 Hz, and J = 17.5 Hz, 1H), 3.48 (ddd, J = 6.4 Hz, J = 6.4 Hz, and J = 12.7 Hz, 1H), 3.54 (ddd, J = 5.9 Hz, J = 7.1 Hz, and J = 12.7 Hz, 1H), 3.80 (s, 3H), 6.06 (s, 1H), 6.82 (dd, J = 2.3 Hz and J = 8.7 Hz, 1H), 6.97 (d, J = 8.7 Hz, 1H), 7.12 (dd, J = 3.2 Hz and J = 5.4 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 7.58 (dd, J = 0.9 Hz and J = 5.4 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 25.1, 28.9, 53.5, 55.0, 113.1, 113.6, 123.5, 127.7, 128.5, 129.6, 130.6, 133.6, 139.6, 159.5 ppm; LR FBA MS: calcd for $[M-1]^-$ 324.0, found 324.2.

9t: IR (KBr) 1263, 1117 cm^{-1}; ^{1}H NMR (acetone-d_6) δ 3.16 (t, J = 6.4 Hz, 2H), 3.47-3.56 (m, 2H), 3.79 (s, 3H), 3.80 (s, 3H), 6.13 (s, 1H), 6.60 (s, 1H), 6.85 (s, 1H), 7.07 (dd, J = 3.2 Hz and J = 5.0 Hz, 1H), 7.35 (d, J = 3.2 Hz, 1H), 7.53 (dd, J = 0.9 Hz and J = 5.0 Hz, 1H) ppm; ^{13}C NMR (acetone-d_6) δ 24.3, 38.5, 53.2, 55.3, 55.4, 111.2, 111.5, 123.1, 124.7, 127.7, 128.5, 130.7, 139.7, 148.2, 149.7 ppm; LR FBA MS: calcd for $[M-1]^-$ 354.1, found 354.1.

Acknowledgements. This work was supported by grant No. R01-2001-000-00133-0 from the Korea Science & Engineering Foundation.

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