A Convenient Synthesis of 1,1-Disubstituted 1,2,3,4-Tetrahydroisoquinolines *via* Pictet–Spengler Reaction Using Titanium(IV) Isopropoxide and Acetic-Formic Anhydride

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A synthesis of 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines (6) was achieved in a highly efficient manner *via* Pictet–Spengler reaction of arylethylamines (1) and acyclic and cyclic ketones (2) using titanium (IV) isopropoxide and acetic-formic anhydride. The cyclization of the *in situ* formed acyliminium ion (4) to *N*-formyl 1,2,3,4-tetrahydroisoquinoline (5) was greatly facilitated by using trifluoroacetic acid as an additional reagent. The Pictet–Spengler reaction was carried out by one pot procedure, providing a convenient and effective method for preparing various 1,2,3,4-tetrahydroisoquinolines.

Key words Pictet–Spengler reaction; titanium(IV) isopropoxide; 1,2,3,4-tetrahydroisoquinoline; *N*-formylation; acyliminium ion

The Pictet–Spengler reaction is one of the key reactions for construction of the isoquinoline skeleton, which constitutes an important class of naturally occurring bioactive substances.[1] The reaction utilizes an acid-catalyzed cyclization of the intermediate imine formed by condensation of arylethylamine with a carbonyl compound. Aldehydes or activated ketone such as a 1,2-carbonyl compound are preferred for the carbonyl compound. Generally speaking, the Pictet–Spengler reaction of simple ketones using as the carbonyl compounds is known to be difficult.[2] This retardation of the reaction can be ascribed to the difficulty in the formation of imines by conventional methods, and also to the steric inhibition in the cyclization of the imine, which produces a congested quarternary carbon at C1 of the isoquinoline skeleton.

Recently, Bhattacharyya *et al.*[3] reported that titanium(IV) isopropoxide is an excellent reagent that catalyzes the condensation reaction of ketones with amines. They successfully applied this reaction to the preparation of higher various amines in a highly effective manner through the reduction of intermediary formed imines. This and also our experiments[4] of the reductive amination reaction using the titanium reagent demonstrates that the imines, although not isolable from the reaction mixture, are quantitatively produced from ketones. In this paper we describe the Pictet–Spengler reaction of the imines formed by the condensation of arylethylamines with various ketones using the titanium reagent. This reaction should provide a general and convenient method for preparing 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines including 1-methyl-1-phenyl derivatives (**6a**, **b**), non-competitive *N*-methyl-D-aspartate (NMDA) antagonists.[5,6]

Results and Discussion

The condensation reaction of arylethylamines (**1**) and ketones (**2**) to imines (**3**) was carried out by heating in titanium(IV) isopropoxide without using any solvent. Although the isolation of **3** from the reaction mixture was unsuccessful, this condensation was proved to proceed quantitatively as shown by the following experiment: A mixture of 2-(3,4-dimethoxyphenyl)ethylamine (**1a**) (1.2 eq), acetophenone (**2a**) (1 eq) and titanium(IV) isopropoxide (1.5 eq) was heated at 80 °C for 3 h and then treated with sodium borohydride to yield the secondary amine (**7**) in 99% yield.

Then, we found that the imines (**3**) thus formed *in situ*, on heating in a solution of acetic-formic anhydride, induced the Pictet–Spengler cyclization (Table 1). For example, a solution containing 10 eq of acetic-formic anhydride which was prepared from 10 eq of acetic anhydride and 30 eq of formic acid (the ratio of Ac_2O and HCOOH = 1 : 3), was added to the titanium(IV) isopropoxide solution of **3a**. The mixture was then heated at 70 °C for 3 h to yield two products, the desired *N*-formyl tetrahydroisoquinoline (**5a**) in 12% yield and the uncyclized *N*-formyl enamine (**8**) in 8% yield (run 1). On the other hand, the Pictet–Spengler cyclization did not occur when a solution of acetic-formic anhydride prepared from the equimolar amount of Ac_2O (10 eq) and HCOOH (10 eq) was used. The reaction gave only the uncyclized **8** in 16% yield (run 2). The difference between the two reactions (runs 1, 2) is the amount of formic acid used. The reaction of run 1, where the acetic formic anhydride solution contains double the excess of formic acid of acetic-formic anhydride, caused the cyclization. This result suggested that the cyclization of **3a** to **5a** required the increased acidity in the reaction medium. However, the concomitant use of *p*-toluenesulfonic acid (1 eq) and acetic-formic anhydride (10 eq) produced **5a** only in 7% yield (run 3). This result was very poor when compared with the fact that the treatment of **8** with *p*-toluenesulfonic acid in boiling benzene for 30 min produced **5a** in 72% yield. The longer reaction time (48 h) slightly improved the yield of the cyclized **5a** (21%) (run 4).

Judging from the results described above, this Pictet–Spengler cyclization might be improved by using a large excess amount of a solution of acetic-formic anhydride containing an excess of formic acid. Recently, T. Ohwada and his colleagues[7] clearly demonstrated in their investigations of dication chemistry that the Pictet–Spengler cyclization was enormously facilitated by increasing acidity in the reaction media. Thus, the imine (**3a**) prepared in neat titanium(IV) isopropoxide was treated with 100 eq of acetic-formic anhydride containing 200 eq of formic acid under heating at 70 °C for 18 h. This reaction produced **5a** in 56% yield (run 5).

Next, we proved that this Pictet–Spengler cyclization pro-

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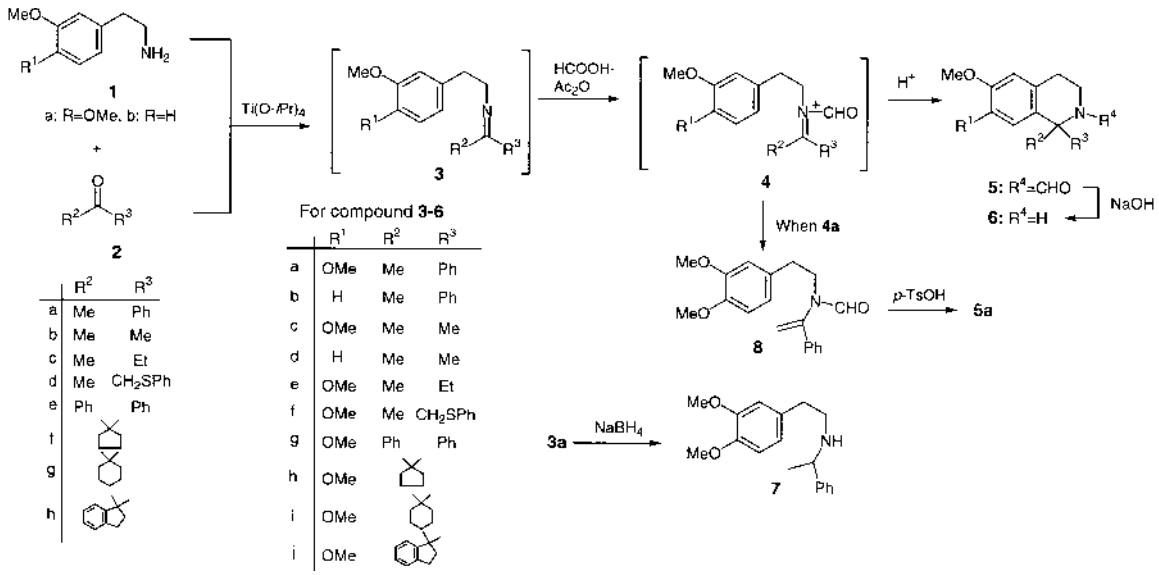

Chart 1

Table 1. Pictet–Spengler Reaction of **3a** under Various Conditions

	Reagents			Conditions		Products	
Run	Ac_2O (mol eq)	HCOOH (mol eq)	Other acid (mol eq)	Temp. (°C)	Time (h)	**5a** (yield %)	**8** (yield %)
1	10	30	—	70	3	12	8
2	10	10	—	70	18	—	16
3	10	30	*p*-TsOH (1)	70	18	7	—
4	10	30	—	70	48	21	—
5	100	300	—	70	18	56	—
6	—	300	—	70	18	—	—
7	—	—	CF_3COOH (300)	70	18	—	—
8	100	100	CF_3COOH (200)	70	18	99	—

Table 2. Synthesis of 1,1-Disubstituted 1,2,3,4-Tetrahydroisoquinolines (**6**)

		Pictet–Spengler reaction			Hydrolysis of **5**	
Arylamines	Ketones	Reagent[a)]	*N*-Formyl TIQ[b)] (**5**)	Yield (%)	TIQ[b)] (**6**)	Yield (%)
1a	**2a**	A	**5a**	56	**6a**	78
1a	**2a**	B	**5a**	99		
1b	**2a**	A	**5b**	34	**6b**	82
1b	**2a**	B	**5b**	99		
1a	**2b**	A	**5c**	55	**6c**	90
1a	**2b**	B	**5c**	96		
1b	**2b**	A	**5d**	38	**6d**	94
1b	**2b**	B	**5d**	73		
1a	**2c**	A	**5e**	48	**6e**	92
1a	**2c**	B	**5e**	92		
1a	**2d**	A	**5f**	51	**6f**	75
1a	**2d**	B	**5f**	76		
1a	**2f**	A	**5h**	53	**6h**	87
1a	**2f**	B	**5h**	92		
1a	**2g**	A	**5i**	20	**6i**	84
1a	**2g**	B	**5i**	87		
1a	**2h**	A	**5j**	11	**6j**	90
1a	**2h**	B	**5j**	60		

a) Reagent A: Ti(O-*iso*Pr)$_4$ (1.5 mol eq), Ac_2O (100 mol eq), HCOOH (300 mol eq), B: Ti(O-*iso*Pr)$_4$ (1.5 mol eq), Ac_2O (100 mol eq), HCOOH (100 mol eq) and CF_3COOH (200 mol eq). *b*) TIQ: 1,2,3,4-Tetrahydroisoquinoline.

ceeded *via* the acyliminium ion **4**, not the iminium ions produced by protonation of the imine **3**. That is, when a solution of **3a** in formic acid (run 6) or in trifluoroacetic acid (run 7) without acetic-formic anhydride was heated at 70 °C for 18 h, no cyclization occurred to any extent.

The Pictet–Spengler reaction of other acyclic ketones (**2b**—**d**) under conditions similar to those of the run 5 (method A) also provided the corresponding *N*-formyl 1,1-disubstituted 1,2,3,4-tetrahydroisoquinolines (**5c**, **e**, **f**) in moderate yields as shown in Table 2. The reaction of the cyclic ketones cyclopentanone (**2f**), cyclohexanone (**2g**), and 1-indanone (**2h**) yielded the corresponding 1-spirocycloalkylated 1,2,3,4-tetrahydroisoquinolines (**5h**—**j**), in 53, 20, 11% yields, respectively. This gradually decreased yields were observed in the reactions of cyclic ketones and suggesed that the cyclization, as anticipated, is sensitive to the steric congestion. In fact, the Pictet–Spengler reaction of benzophenone (**2e**) did not yield 1,1-diphenyl-1,2,3,4-tetrahydroisoquinoline (**5g**).

Next, we found that the use of trifluoroacetic acid as an additional reagent greatly improved the yields of the cyclized **5**. That is, 200 eq of trifluoroacetic acid was added to the acyliminium ion (**4a**) *in situ* prepared from **3a** in a solution containing 100 eq of acetic-formic anhydride prepared from Ac_2O (100 eq) and HCOOH (100 eq). Then, the reaction mixture was heated at 70 °C for 18 h. This treatment caused the cyclization quantitatively, thus producing **5a** in 99% yield (run 8). The reaction of other acyclic ketones (**2b**—**d**) and cyclic ketones (**2f**—**h**) by this treatment (method B) also provided the tetrahydroisoquinolines (**5c**, **e**, **f**) and (**5h**—**j**) in excellent yields. The results are summarized in Table 2.

Finally, we wish to note that this Pictet–Spengler reaction, as generally observed in the conventional Pictet–Spengler reaction,[7] requires electron-rich aromatics of the arylethyl moiety. Thus, the reaction of 2-(3-methoxyphenyl)ethylamine (**1b**) with **2a** or **2b** under the conditions using a large excess of acetic-formic anhydride and trifluoroacetic acid afforded the corresponding *N*-formyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (**5b**, **d**) in 99% and 73% yield, respectively. The reaction of 2-(4-methoxyphenyl)ethylamine and phenylethylamine in which the nucleophilic center is not electronically activated, induced no expected cyclizations, however.

Alkaline hydrolysis of the *N*-formyl-1,2,3,4-tetrahydroisoquinoline (**5**) afforded the 1,1-disubstituted 1,2,3,4-tetrahydroisoquinoline (**6**) in good yields as shown in Table 2.

Thus, the Pictet–Spengler reaction of arylethylamines and ketones using titanium(IV) isopropoxide and acetic-formic anhydride provides a convenient method of synthesizing various 1,1-disubstitued 1,2,3,4-tetrahydroisoquinolines. This method is particularly highly effective when trifluoroacetic acid is used as an additional reagent for the cyclization.

Experimental

Unless otherwise stated, the following procedures were adopted. All melting points were measured on a Yanagimoto micro hot-stage melting point apparatus (Yanagimoto MP type) and are uncorrected. IR spectra were measured with a HORIBA FT-710 as KBr disks and values are given in cm^{-1}. NMR spectra were recorded on a JNM-AL300 (^1H, 300 MHz; ^{13}C, 75 MHz) NMR spectrometer in $CDCl_3$ solution using tetramethylsilane (TMS) as an internal standard. Low-resolution MS spectra (LR-MS) were taken on a JMS-AM20, and high-resolution MS spectra (HR-MS) was taken on a JMS-D300 spectrometer at 70 eV or at 270 eV [chemical ionization MS (CI-MS), reactant gas: iso-butane] using a direct inlet system. Elemental analyses were recorded on a Yanaco CHN-corder MT-3. For column chromatography, silica gel (Mallinckrodt type 150A or Wako-Gel C-200) was used.

Reductive Amination of 2-(3,4-Dimethoxyphenyl)ethylamine (1a) and Acetophenone (2a) A mixture of **1a** (1 g, 5.52 mmol), **2a** (552 mg, 4.60 mmol) and Ti(O-*iso*Pr)$_4$ (1.96 g, 6.9 mmol) was heated at 80 °C for 3 h under an argon atmosphere. The reaction mixture was diluted with MeOH (100 ml), and $NaBH_4$ (0.3 g, 8 mmol) was added slowly at 0 °C and stirred for 1 h at room temperature Water (10 ml) was added to the reaction mixture. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$, washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residual oil was chromatographed over SiO_2 (hexane/ethyl acetate 1 : 1) to give *N*-(1-phenylethyl)-2-(3,4-dimethoxyphenyl)ethylamine (**7**) (1.3 g, 99%) as a pale yellow gum. IR: 2830, 2364, 1591, 1516. ^1H-NMR: 1.32 (3H, d, J=7 Hz, CH_3), 2.68—2.75 (4H, m, NCH_2CH_2), 3.73—3.79 (1H, m, C<u>H</u>CH_3), 3.83 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.67—6.80 (3H, m, Ar-H), 7.23—7.33 (5H, m, Ph). ^{13}C-NMR: 24.1 (CH_3), 35.7 (C2), 48.7 (C1), 55.5 (OCH_3), 55.6 (OCH_3), 58.0 (C1′), 111.6 (C2″ and C5″), 120.4 (C6″), 128.6 (2×PhCH), 126.3 (2×PhCH), 126.6 (PhCH), 128.2 (2×PhCH), 132.4 (PhC), 145.4 (C1″), 147.1 (C3″ or C4″), 148.6 (C3″ or C4″). LR-MS *m*/*z*: 285 (M^+). HRMS *m*/*z* Calcd for $C_{18}H_{23}NO_2$: 285.1729. Found: 285.1765.

The Pictet–Spengler Reaction of 2-(3,4-Dimethoxyphenyl)ethylamine (1a) with Acetophenone (2a) A mixture of **1a** (1 g, 5.52 mmol), **2a** (0.552 g, 4.60 mmol) and Ti(O-*iso*Pr)$_4$ (1.96 g, 6.90 mmol) was heated at 80 °C for 3 h under an argon atmosphere. To the reaction mixture was added a solution of acetic-formic anhydride [prepared from HCOOH (6.35 g, 0.138 mol) and Ac_2O (4.7 g, 46 mmol)] at 0 °C, then the mixture was heated at 70 °C for 3 h. The reaction mixture was diluted with MeOH (100 ml) and passed through a short SiO_2 column chromatography ($CHCl_3$–MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca.* 50 ml and diluted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by chromatography over SiO_2 (hexane/ethyl acetate 1 : 1) to give **5a** (205 mg, 12%) and **8** (137 mg, 8%). Other reaction conditions and results are summarized in Table 1.

2-Formyl-6,7-dimethoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5a**): Pale yellow needles, crystallized from MeOH–hexane, mp 100—101 °C. IR: 2935, 1664, 1612, 1515 cm^{-1}. ^1H-NMR: 2.04 (3H, s, CH_3), 2.80—2.97 (2H, m, 4-H), 3.54—3.60 (1H, m, 3-H), 3.64 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 4.11—4.22 (1H, m, 3-H), 6.26 (1H, s, 8-H), 6.62 (1H, s, 5-H), 7.2—7.4 (5H, m, Ph), 8.10 (1H, s, CHO). ^{13}C-NMR: δ 28.5 (C4), 29.2 (CH_3), 36.0 (C3), 55.8 (OCH_3), 56.0 (OCH_3), 62.7 (C1), 110.7 (C5), 110.9 (C8), 126.4 (C4a), 127.3 (C2′ and C6′), 127.6 (C4′), 128.7 (C3′ and C5′), 133.4 (C8a), 145.5 (C1′), 147.7 (C6 or C7), 147.8 (C6 or C7), 163.0 (CHO). LR-MS *m*/*z*: 311 (M^+, base peak). HR-MS *m*/*z* Calcd for $C_{19}H_{21}NO_3$: 311.1522. Found: 311.1552. *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.88; N, 4.30.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-(1-phenylvinyl)formamide (**8**): A pale yellow gum. IR: 2935, 1676, 1610, 1516. ^1H-NMR: 2.75 (2H, t, J=8 Hz, 2-H), 3.68 (2H, t, J=8 Hz, 1-H), 3.81 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.92 (1H, s, 2′-H), 5.20 (1H, s, 2′-H), 6.62—6.75 (3H, m, Ar-H), 7.3—7.4 (5H, m, Ph), 8.35 (1H, s, CHO). ^{13}C-NMR: 33.1 (C2), 44.3 (C1), 55.6 (OCH_3), 55.7 (OCH_3), 108.7 (C2″), 110.9 (C5″), 120.6 (C6″), 128.6 (2×PhCH), 128.6 (2×PhCH), 129.1 (PhCH), 130.6 (C1′), 135.3 (PhC), 145.9 (C1″), 147.3 (C3″ or C4″), 148.6 (C3″ or C4″), 162.3 (CHO). LR-MS *m*/*z*: 311 (M^+). HR-MS *m*/*z* Calcd for $C_{19}H_{21}NO_3$: 311.1521. Found: 311.1526.

Cyclization Reaction of 8 A solution of **8** (218 mg, 0.7 mmol) and *p*-TsOH (360 mg, 2.1 mmol) in benzene (20 ml) was refluxed for 30 min. The reaction mixture was diluted with benzene (50 ml) and washed with 5% NaOH and H_2O. After removal of the solvent *in vacuo*, the product was purified by column chromatography over SiO_2 (ethyl acetate/hexane 1 : 1) to give **5a** (164 mg, 75%).

The Pictet–Spengler Reaction of Arylethylamines (1) with Ketones (2). General Procedure i) Method A: A mixture of **1** (5.52—9.20 mmol), **2** (4.60 mmol) and Ti(O-*iso*Pr)$_4$ (6.90 mmol) was heated at 80 °C for 3 h under an argon atmosphere. To this reaction mixture a solution of acetic-formic anhydride [prepared from HCOOH (63.6 g, 1.38 mol) and Ac_2O (47 g, 0.46 mol)] was added at 0 °C and the mixture was heated at 70 °C for 18 h. The work-up of the reaction mixture as described above gave **5**.

Method B: A mixture of **1** (5.52—9.20 mmol), **2** (4.60 mmol) and Ti(O-*iso*Pr)$_4$ (6.90 mmol) was heated at 80 °C for 3 h under an argon atmosphere. To this reaction mixture acetic-formic anhydride [prepared from HCOOH (21.2 g, 0.46 mol) and Ac_2O (47 g, 0.46 mol)] was added at 0 °C and heated

at 70 °C for 2 h. To this reaction mixture CF_3COOH (105 g, 0.92 mol) was added and heated at 70 °C for 18 h. The work-up of the reaction mixture as described above gave **5**. Yields are summarized in Table 1.

2-Formyl-6-methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoloine (**5b**) was obtained from 2-(3-methoxyphenyl)ethylamine (**1b**) (830 mg, 5.52 mmol) and **2a** (552 mg, 4.60 mmol) as a pale yellow gum. IR: 1664, 1610 cm^{-1}. ^{1}H-NMR: 2.02, 2.04 (total 3H, each s, CH_3), 2.86—2.96 (2H, m, 4-H), 3.58—3.67 (1H, m, 3-H), 3.77 (3H, s, OCH_3), 4.11—4.18 (1H, m, 3-H), 6.66—6.78 (3H, s, Ar-H), 7.2—7.4 (5H, m, Ph), 8.12 (s, 1H, CHO). ^{13}C-NMR: 29.2 (C4), 29.5 (CH_3), 36.1 (C3), 55.2 (OCH_3), 62.7 (C1), 113.0 (C7), 113.1 (C5), 127.3 (C3′ and C5′), 127.5 (C4′), 128.7 (C2′ and C6′), 128.9 (C8), 134.0 (C1′), 135.4 (C4a), 145.8 (C7a), 158.0 (C6), 163.0 (CHO). LR-MS *m/z*: 281 (M^+), 266 (base peak). HR-MS *m/z* Calcd for $C_{18}H_{19}NO_3$: 281.1416. Found: 281.1423.

2-Formyl-6,7-dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (**5c**) was obtained from **1a** (1 g, 5.52 mmol) and **2b** (267 mg, 4.6 mmol) as pale yellow plates, crystallized from MeOH–hexane, mp 96—98 °C. IR: 1653, 1517 cm^{-1}. ^{1}H-NMR: 1.73 (3H, s, CH_3), 1.81 (3H, s, CH_3), 2.75 (1H, t, *J*=6Hz, 4-H), 2.81 (1H, t, *J*=6Hz, 4-H), 3.49 (1H, t, *J*=6Hz, 3-H), 3.83 (1H, t, *J*=6 Hz, 3-H), 3.87 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.58 (1H, s, 5-H), 6.72 (1H, s, 8-H), 8.21, 8.62 (total 1H, each s, CHO). ^{13}C-NMR: 29.0 (C4), 31.1 (2×CH_3), 35.2 (C3), 55.8 (OCH_3), 56.1 (OCH_3), 57.4 (C1), 108.8 (C5), 111.3 (C8), 126.6 (C4a), 133.4 (C8a), 147.7 (C6 and C7), 160.1 (CHO). LR-MS *m/z*: 249 (M^+), 234 (base peak). HR-MS *m/z* Calcd for $C_{14}H_{19}NO_3$: 249.1362. Found: 249.1351. *Anal.* Calcd for $C_{14}H_{19}NO_3$: C, 69.45; H, 7.68; N, 5.62. Found: C, 67.37; H, 7.81; N, 5.43.

2-Formyl-6-methoxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (**5d**) was obtained from **1b** (692 mg, 5.52 mmol) and **2b** (266 mg, 4.60 mmol) as a pale yellow gum. IR: 1630, 1548 cm^{-1}. ^{1}H-NMR: 1.71 (3H, s, CH_3), 2.80 (2H, t, *J*=6Hz, 4-H), 3.79 (3H, s, OCH_3), 3.83 (2H, t, *J*=6Hz, 3-H), 6.62 (1H, d, *J*=3 Hz, 5-H), 6.80 (1H, dd, *J*=9, 3 Hz, 7-H), 7.18 (1H, d, *J*=9 Hz, 8-H), 8.61 (1H, s, CHO). ^{13}C-NMR: 29.8 (C4), 31.3 (2×CH_3), 35.2 (C3), 55.3 (OCH_3), 57.5 (C1), 111.3 (C8), 113.2 (C5), 126.8 (C7), 134.0 (C4a), 135.7 (C8a), 157.9 (C6), 160.7 (CHO). LR-MS *m/z*: 219 (M^+), 204 (base peak). HR-MS *m/z* Calcd for $C_{13}H_{17}NO_2$: 219.1259. Found: 219.1230.

1-Ethyl-2-formyl-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**5e**) was obtained from **1a** (1 g, 5.52 mmol) and **2c** (331 mg, 4.60 mmol) as a pale yellow gum. IR: 1678, 1626, 1514 cm^{-1}. ^{1}H-NMR: 0.47, 0.61 (total 3H, each t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.59, 1.66 (total 3H, each s, CH_3), 1.80—2.04, 3.06—3.13 (2H, m, –$C\underline{H}_2CH_3$), 2.62—2.74 (2H, m, 4-H), 3.59—3.67, 3.72—3.79 (2H, m, H-3), 3.78 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.51 (1H, s, 5-H), 6.60 (1H, s, 8-H), 8.14, 8.43 (1H, s, CHO). ^{13}C-NMR: 7.6 ($CH_2\underline{C}H_3$), 28.6 (C4), 29.9 (CH_3), 35.1 ($\underline{C}H_2CH_3$), 35.4 (C3), 55.5 (OCH_3), 55.9 (OCH_3), 60.4 (C1), 108.4 (C5), 110.9 (C8), 127.5 (C4a), 131.9 (C8a), 147.4 (C6), 147.7 (C7), 161.0 (CHO). LR-MS *m/z*: 263 (M^+), 234 (base peak). HR-MS *m/z* Calcd for $C_{15}H_{21}NO_3$: 263.1519. Found: 263.1496.

2-Formyl-6,7-dimethoxy-1-methyl-1-phenylsulfanylmethyl-1,2,3,4-tetrahydroisoquinoline (**5f**) was obtained from **1a** (1.2 g, 5.52 mmol) and **2d** (763 mg, 4.60 mmol) as pale yellow plates, crystallized from MeOH–hexane, mp 86—88 °C. IR: 1657, 1518 cm^{-1}. ^{1}H-NMR: 1.80, 1.83 (total 3H, each s, CH_3), 2.63—2.79, 2.98—3.07 (2H, m, 4-H), 3.36—3.57 (2H, m, 3-H), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.55, 6.57 (total 1H, each s, 5-H), 6.60, 6.65 (total 1H, each s, 8-H), 7.1—7.3 (5H, m, Ar-H), 8.16, 8.59 (total 1H, each s, CHO). ^{13}C-NMR: 26.4, 27.0 (CH_3), 28.6, 30.0 (C4), 34.9, 44.4 (C3), 44.6, 47.6 ($\underline{C}H_2$–S–), 55.6 (OCH_3), 55.8, 56.0 (OCH_3), 60.1, 61.7 (C1), 108.3, 108.6 (C5), 110.6, 111.3 (C8), 125.8, 126.8 (C4″), 127.3, 127.7 (C4a), 128.3, 128.8 (C3″ and C5″), 129.9, 130.9 (C2″ and C6″), 130.0, 131.5 (C8a), 133.6, 136.5 (C1″), 147.5, 147.6 (C6 or C7), 147.8, 148.0 (C6 or C7), 160.8, 162.6 (CHO). LR-MS *m/z*: 357 (M^+, base peak). HR-MS *m/z* Calcd for $C_{20}H_{23}NO_3S$: 357.1399. Found: 357.1427. *Anal.* Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 66.94; H, 6.43; N, 3.75.

2-Formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spirocyclopentane (**5h**) was obtained from **1a** (2 g, 11 mmol) and **2f** (462 mg, 5.5 mmol) as pale yellow plates crystallized from MeOH–hexane, mp 75—78 °C. IR: 1639, 1517. ^{1}H-NMR: 1.8—2.3 (8H, m, 2′-H, 3′-H, 4′-H and 5′-H), 2.77 (2H, t, *J*=6 Hz, 4-H), 3.82 (2H, t, *J*=6 Hz, 3-H), 3.86 (3H, s, OCH_3), 3.88 (3H, s, –OCH_3), 6.57 (1H, s, 5-H), 6.70 (1H, s, 8-H), 8.36 (1H, s, CHO). ^{13}C-NMR: 24.0 (C3′ and C4′), 28.8 (C4), 35.9 (C3), 40.8 (C2′ and C5′), 55.7 (OCH_3), 56.1 (OCH_3), 69.1 (C1), 108.5 (C5), 111.2 (C8), 127.6 (C4a), 132.0 (C8a), 147.58 (C6 or C7), 147.64 (C6 or C7), 160.2 (CHO). LM-RS: 275 (M^+), 205 (base peak). HM-RS *m/z* M^+ Calcd for $C_{16}H_{21}NO_3$: 275.1521. Found: 275.1559.

2-Formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spirocyclohexane (**5i**) was obtained from **1a** (2 g, 11 mmol) with **2g** (528 mg, 5.5 mmol) as colorless prisms, crystallized from MeOH–hexane, mp 123—126 °C. IR: 1641, 1523. ^{1}H-NMR: 1.42—1.99 (8H, m, 3′-H, 4′-H, 5′-H, 6′-H), 2.29 (2H, d, *J*=14 Hz, 2′-H), 2.82 (2H, t, *J*=6 Hz, 4-H), 3.82 (2H, t, *J*=6 Hz, H-3), 3.84 (3H, s, OCH_3), 3.89 (3H, s, –OCH_3), 6.55 (1H, s, 5-H), 6.75 (1H, s, 8-H), 8.54 (1H, s, CHO). ^{13}C-NMR: 21.8 (C3′ and C5′), 25.6 (C4), 27.9 (C4′), 34.3 (C3), 36.1 (C2′ and C6′), 55.7 (OCH_3), 56.2 (OCH_3), 59.8 (C1), 108.1 (C5), 111.8 (C8), 126.7 (C4a), 135.2 (C8a), 147.1 (C6 or C7), 147.8 (C6 or C7), 162.4 (CHO). LM-RS: 289 (M^+), 205 (base peak). HM-RS *m/z* M^+ Calcd for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1683.

2-Formyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-1′-indane (**5j**) was obtained from **1a** (2 g, 11 mmol) and **2h** (660 mg, 5.5 mmol) as colorless prisms, crystallized from MeOH–hexane, mp 124—127 °C. IR: 1646, 1521. ^{1}H-NMR: 2.43, 2.48 (total 1H, each t, *J*=8 Hz, 3′-H), 2.60, 2.65 (total 1H, each t, *J*=8 Hz, 3′-H), 2.75, 2.80 (total 1H, each t, *J*=3 Hz, 4-H), 2.96, 3.70 (total 3H, each dd, *J*=5, 12Hz, 3-H, 4-H), 3.21, 3.25 (total 1H, each dd, *J*=3, 8 Hz, 2′-H), 3.60 (3H, s, OCH_3), 3.88 (3H, s, –OCH_3), 4.64, 4.69 (total 1H, each q, *J*=3 Hz, 2′-H), 6.16 (1H, s, 5-H), 6.63 (1H, s, 8-H), 6.87 (1H, d, *J*=8 Hz, 4′-H), 7.19—7.37 (3H, m, 5′-H, 6′-H, 7′-H), 7.51 (1H, s, CHO). ^{13}C-NMR: 28.6 (C4), 29.8 (C3′), 36.5 (C3), 43.8 (C2′), 55.8 (OCH_3), 56.0 (OCH_3), 71.8 (C1), 110.59 (C5), 110.61 (C8), 125.0 (C4′), 126.2 (C5′), 127.4 (C6′), 127.7 (C7a′), 129.1 (C7′), 132.5 (C3a′), 143.9 (C4a), 145.1 (C8a), 147.6 (C6 or C7), 148.0 (C6 or C7), 161.3 (CHO). LM-RS: 323 (M^+), 278 (base peak). HM-RS *m/z* M^+ Calcd for $C_{20}H_{21}NO_3$: 323.1521. Found: 323.1526.

Hydrolysis of 5. General Pocedure A solution of **5** (0.35 mmol) in EtOH (20 ml) and 20% NaOH (20 ml) was refluxed for 18 h. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with $CHCl_3$. The extract was washed with brine and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified by chromatography over SiO_2 (hexane/ethyl acetate 1 : 4) to give **6**. Yields are summarized in Table 2.

6,7-Dimethoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6a**): Colorless prisms, crystallized from ethyl acetate–hexane, mp 94—96 °C. [Hydrochloride salt: colorless prisms crystallized from MeOH–Et_2O, mp 220—221 °C (lit.,[6] mp 260—262 °C)]. IR: 2952, 1610, 1512 cm^{-1}. ^{1}H-NMR: 1.84 (3H, s, CH_3), 2.65—3.02 (4H, m, 3-H, 4-H), 3.75 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.54 (1H, s, 8-H), 6.62 (1H, s, 5-H), 7.2—7.3 (5H, m, Ph). ^{13}C-NMR: 29.6 (C4), 30.3 (CH_3), 39.0 (C3), 55.7 (OCH_3), 56.0 (OCH_3), 58.8 (C1), 110.9 (C5), 111.6 (C8), 126.4 (C4a), 127.1 (C2′ and C6′), 127.5 (C1′), 127.9 (C3′ and C5′), 133.9 (C4a), 147.0 (C8a), 147.6 (C6 or C7), 148.3 (C6 or C7). LR-MS *m/z*: 283 (M^+), 268 (base peak). HR-MS *m/z* Calcd for $C_{18}H_{21}NO_2$: 283.1572. Found: 283.1572.

6-Methoxy-1-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**6b**): A pale yellow gum. (lit.,[6] Hydrochloride salt, mp 284—286 °C). IR: 1608, 1577, 1500 cm^{-1}. ^{1}H-NMR: 1.82 (3H, s, CH_3), 2.67—3.04 (4H, m, 3-H, 4-H), 3.80 (3H, s, OCH_3), 6.67 (1H, d, *J*=3Hz, 5-H), 6.72 (1H, dd, *J*=9, 3 Hz, 7-H), 6.99 (1H, d, *J*=9 Hz, 8-H), 7.16—7.29 (5H, m, Ph). ^{13}C-NMR: 30.4 (C4), 30.5 (CH_3), 39.0 (C3), 55.1 (OCH_3), 58.7 (C1), 112.1 (C7), 113.4 (C5), 126.4 (C8), 127.1 (C2′ and C6′), 127.9 (C3′ and C5′), 128.9 (C4′), 134.4 (C1′), 136.5 (C4a), 149.0 (C8a), 157.7 (C6). LR-MS *m/z*: 253 (M^+, base peak). HR-MS *m/z* Calcd for $C_{17}H_{19}NO$: 253.1467. Found: 253.1475.

6,7-Dimethoxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (**6c**): A colorless gum. IR: 1620, 1579 cm^{-1}. ^{1}H-NMR: 1.48 (6H, s, 2×CH_3), 2.74 (2H, t, *J*=6 Hz, 4-H), 3.12 (2H, t, *J*=6 Hz, 3-H), 3.84 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.54 (1H, s, 8-H), 6.67 (1H, s, 5-H). ^{13}C-NMR: 29.7 (C4), 30.9 (2×CH_3), 38.8 (C3), 52.6 (C1), 55.5 (OCH_3), 55.8 (OCH_3), 108.8 (C5), 111.4 (C8), 125.9 (C4a), 135.5 (C8a), 147.0 (C6 and C7). LRMS *m/z*: 221 (M^+), 207 (base peak). HRMS *m/z* Calcd for $C_{13}H_{19}NO_2$: 221.1413. Found: 221.1410.

6-Methoxy-1,1-dimethyl-1,2,3,4-tetrahydroisoquinoline (**6d**): A pale yellow gum. IR: 1608, 1576, 1500 cm^{-1}. ^{1}H-NMR: 1.43 (6H, s, 2×CH_3), 2.75 (2H, t, *J*=6 Hz, 4-H), 3.12 (2H, t, *J*=6 Hz, 3-H), 3.77 (3H, s, OCH_3), 6.58 (1H, d, *J*=3 Hz, 5-H), 6.73 (1H, dd, *J*=9, 3 Hz, 7-H), 7.12 (1H, d, *J*=9 Hz, 8-H). ^{13}C-NMR: 31.1 (C4), 31.5 (2×CH_3), 39.1 (C3), 52.5 (C1), 55.1 (OCH_3), 112.4 (C7), 113.4 (C5), 127.0 (C8), 135.5 (C4a), 136.5 (C8a), 157.3 (C6). LR-MS *m/z*: 191 (M^+). HR-MS *m/z* Calcd for $C_{12}H_{17}NO$: 191.1310. Found: 191.1290.

1-Ethyl-6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**6e**): A colorless gum. IR: 1520 cm^{-1}. ^{1}H-NMR: (3H, t, *J*=7 Hz, $CH_2C\underline{H}_3$), 1.39 (3H, s, CH_3), 1.59—1.75 (1H, m, $C\underline{H}_2CH_3$), 1.81—1.96 (1H, m, $C\underline{H}_2CH_3$), 2.621—2.77 (2H, m, H-4), 3.02—3.16 (2H, m, H-3), 3.85 (6H, s, 2×OCH_3), 6.54 (1H, s, H-5), 6.63 (1H, s, H-8). ^{13}C-NMR: 8.1 ($CH_2\underline{C}H_3$), 28.9 (CH_3), 30.1 (C4), 35.1 ($\underline{C}H_2CH_3$), 38.9 (C3), 55.2 (C1), 55.6 (OCH_3), 56.0 (OCH_3), 109.1 (C5), 111.5 (C8), 127.1 (C4a), 135.1 (C8a), 146.9 (C6), 147.1 (C7).

LR-MS *m/z* 235. HR-MS *m/z* Calcd for $C_{14}H_{21}NO_2$: 235.1572. Found 235.1545.

6,7-Dimethoxy-1-methyl-1-phenylsulfanylmethyl-1,2,3,4-tetrahydroisoquinoline (**6f**): A colorless gum. IR: 1582, 1574 cm^{-1}. ^{1}H-NMR: 1.51 (3H, s, CH_3), 2.66—2.75 (2H, m, 4-H), 3.00—3.04 (2H, m, 3-H). 3.25 (1H, d, J=13 Hz, SCH_2), 3.56 (1H, d, J=13 Hz, SCH_2), 3.81 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.55 (1H, s, 5-H), 6.60 (1H, s, 8-H), 7.1—7.4 (5H, m, SPh). ^{13}C-NMR: 28.6 (CH_3), 29.7 (C4), 38.6 (C3), 47.2 (SCH_2), 55.5 (OCH_3), 55.8 (OCH_3), 60.1 (C1), 108.7 (d, C5), 111.4 (C8), 125.8 (C4″), 127.1 (C1″), 128.6 (C2″ and C6″), 129.7 (C3″ and C5″), 133.1 (C4a), 137.0 (C8a), 146.9 (C6 or C7), 147.3 (C6 or C7). CIMS *m/z*: 330 (MH^+, base peak).

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spirocyclopentane (**6h**)[8]: A colorless gum. IR: 1508. ^{1}H-NMR: 1.85—1.96 (8H, m, 2′-H, 3′-H, 4′-H, 5′-H), 2.70 (2H, t, J=6 Hz, 4-H), 3.08 (2H, t, J=6 Hz, 3-H), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.52 (1H, s, 5-H), 6.66 (1H, s, 8-H). ^{13}C-NMR: 25.2 (C3′ and C4′), 29.9 (C4), 39.9 (C3), 43.0 (C2′ and C5′), 55.7 (OCH_3), 56.0 (OCH_3), 64.5 (C1), 108.9 (C5), 111.3 (C8), 127.2 (C4a), 135.4 (C8a), 147.0 (C6 or C7), 147.3 (C6 or C7). LR-MS *m/z*: 247 (M^+), 218 (base peak). HR-MS *m/z*: Calcd for $C_{15}H_{21}NO_2$ (M^+): 247.1571. Found: 247.1571.

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spirocyclohexane (**6i**)[8]: A colorless gum. IR: 1508. ^{1}H-NMR: 1.25 (1H, m, 2′-H), 1.60—1.76 (9H, m, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 2.69 (2H, d, J=14 Hz, 4-H), 3.04 (2H, t, J=6 Hz, 3-H), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.54 (1H, s, 5-H), 6.74 (1H, s, 8-H). ^{13}C-NMR: 21.6 (C3′ and C5′), 25.5 (C4), 30.2 (C4′), 37.7 (C2′ and C6′), 38.2 (C3), 54.2 (C1), 55.6 (OCH_3), 56.0 (OCH_3), 109.0 (C5), 111.4 (C8), 126.6 (C4a), 127.0 (C8a), 146.9 (C6 or C7), 147.0 (C6 or C7). LR-MS *m/z*: 261 (M^+), 218 (base peak). HR-MS *m/z*: Calcd for $C_{16}H_{23}NO_2$: 261.1726. Found: 261.1698.

6,7-Dimetoxy-1,2,3,4-tetrahydoisoquinoline-1-spiro-1′-indane (**6j**): A colorless gum. IR: 1508. ^{1}H-NMR: 2.3—2.5 (2H, m, 4-H), 2.74,(1H, dt, J=16, 4 Hz, 3′-H), 2.9—3.0 (2H, m, 2′-H, 3′-H), 3.1—3.2 (3H, m, 2′-H, 3-H), 3.62 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.28 (1H, s, 5-H), 6.60 (1H, s, 8-H), 6.90 (1H, d, J=8 Hz, 4′-H), 7.12 (1H, t, J=8 Hz, 5′-H), 7.22 (1H, t, J=8 Hz, 6′-H) ^{13}C-NMR: 29.7 (C3′), 29.9 (C2′), 40.2 (C4), 42.4 (C5), 55.7 (OCH_3), 55.8 (OCH_3), 68.3 (C1), 110.6 (C5), 110.9 (C8), 124.2 (C4′), 124.6 (C5′), 126.5 (C6′), 127.5 (C7′), 127.9 (C7a′), 133.5 (C3a′), 143.7 (C4a), 147.1 (C8a), 147.4 (C6 or C7), 150.1 (C6 or C7). LR-MS *m/z*: 295 (M^+), 295 (base peak). HR-MS *m/z*: Calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1578.

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