Convenient Synthesis of 2,3,9,10-Tetraoxygenated Protoberberine Alkaloids and Their 13-Methyl Alkaloids[1,2)]

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New and convenient synthesis of 2,3,9,10-tetraoxygenated protoberberine alkaloids and their 13-methyl alkaloids through the same intermediates was developed. Acylation of the brominated benzylphenethylamine (13) with α-chloro-α-(methylthio)acetyl chloride, followed by cyclization with stannic chloride, furnished the key intermediates 4-methylthio-3-phenethylisoquinolin-3-ones (14), which were methylated to provide their methyl derivatives (17). Both isoquinolin-3-ones (14 , 17) were easily transformed into protoberberine alkaloids (16) and their 13-methyl alkaloids (21) in good yield.

Key words protoberberine alkaloid; 13-methylprotoberberine; isoquinolin-3-one; α-(methylthio)acetyl chloride; Bischler–Napieralski reaction

Protoberberine alkaloids (I)[3)] are representative isoquinoline alkaloids which possess physiological activities and have been shown to play important roles as biogenetic precursors of related isoquinoline alkaloids such as benzo[*c*]phenanthridine, spirobenzylisoquinoline, phthalideisoquinoline, protopine, and rhoeadine alkaloids. Therefore, many methods have been developed so far for the synthesis of protoberberine alkaloids.[3)] Among them, a method[4)] *via* the 2-phenethylisoquinolin-3-one (II) can be expected to be promising and practical, especially from a regioselective viewpoint, however, this method has only been applied to limited examples[5)] and lacks generality because the starting materials for II are not easily accessible.

We proposed that the key isoquinolin-3-one (II) might be simply obtained from secondary benzylphenethylamine (V), which could be smoothly derived from commercially or readily available benzaldehyde (VI) and phenethylamine (VII), through acylation and cyclization. Acylation with α-(methylthio)acetyl chloride or its derivative, developed by Tamura *et al*.,[6)] would be the best choice for our purpose, and subsequent cyclization of the intermediate amide (IV) would furnish the six-membered lactam (III) in preference to the seven-membered one.[7)] Desulfurization of III could give rise to II, which has been shown to be converted to protoberberine alkaloids (I) by a standard procedure.

Synthesis of 2,3,9,10-Tetraoxygenated Protoberberine Alkaloids According to our retrosynthesis, we first tried to establish a general synthesis of the abundant but synthetically rather difficult 2,3,9,10-tetraoxygenated protoberberine alkaloids.

Condensation of 3,4-dimethoxyphenethylamine (**1a**) with 2,3-dimethoxybenzaldehyde (**2**), followed by reduction with lithium aluminum hydride (LAH) afforded the secondary amine (**3a**) in 79% yield. Acylation of **3a** with α-(methylthio)acetyl chloride (**4**)[6)] in the presence of triethylamine in dichloromethane at 0 °C gave the amide (**5**, 73%), which was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to furnish the sulfoxide (**6**, 74%). Exposure of **6** to *p*-toluenesulfonic acid (*p*-TsOH) in refluxing carbon tetrachloride[6)] effected a Pummerer-type reaction resulting in the desired isoquinolin-3-one (**7a**) and the seven-membered lactam benzazepinone (**8a**) in 24 and 34% yields, respectively. Acidic treatment of **6** with methanesulfonic acid or trifluoroacetic acid instead of *p*-TsOH gave similar results (**7a**: 25 or 17% yield; **8a**: 41 or 47% yield, respectively). Contrary to our expectation, selective formation of the six-membered lactam (**7a**) could not be achieved.[7)]

On the other hand, **3a** was acylated with α-chloro-α-(methylthio)acetyl chloride (**9**)[6)] in the presence of triethylamine and then cyclized with stannic chloride in

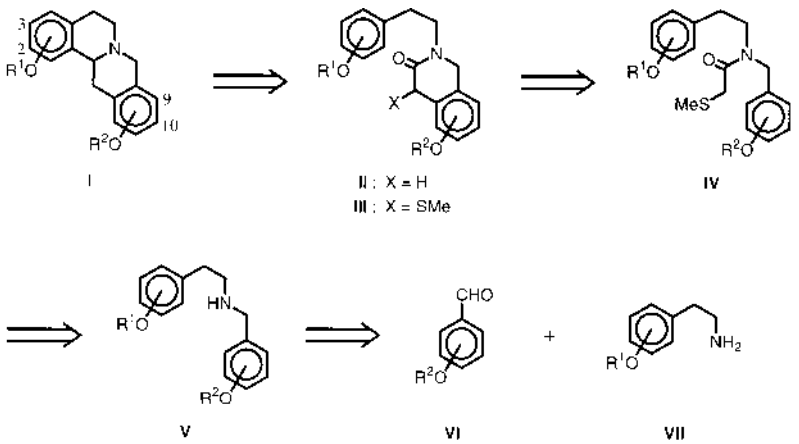

Chart 1

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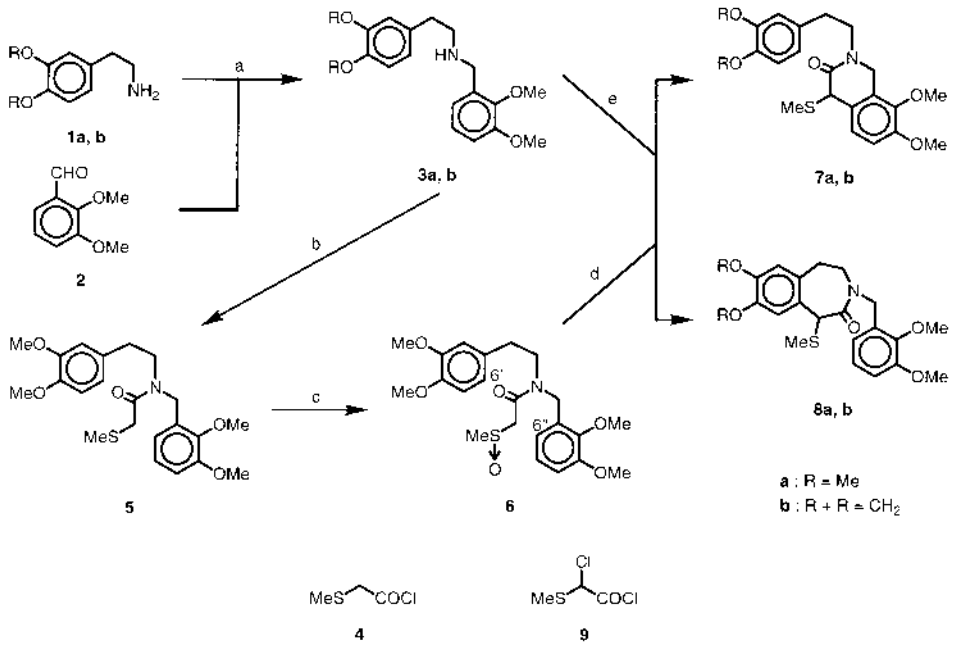
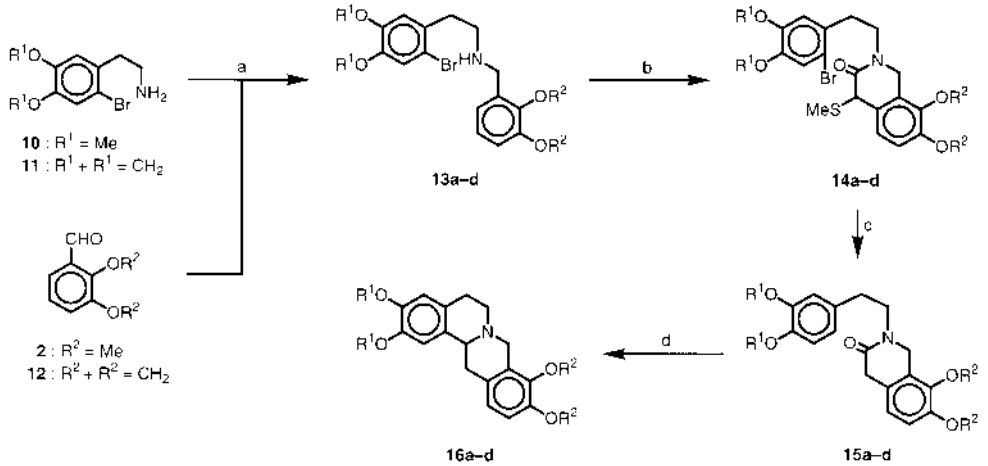


a) 1) CH_2Cl_2, r.t.; 2) LAH, THF, r.t.; b) **4**, Et_3N, CH_2Cl_2, 0 °C; c) *m*CPBA, CH_2Cl_2, 0 °C; d) *p*-TsOH, CCl_4, reflux; e) 1) **9**, Et_3N, CH_2Cl_2, 0 °C; 2) $SnCl_4$, 0 °C.

Chart 2



a : $R^1 = R^2$ = Me, **b** : R^1 = Me, $R^2 + R^2 = CH_2$, **c** : $R^1 + R^1 = CH_2$, R^2 = Me, **d** : $R^1 + R^1 = R^2 + R^2 = CH_2$

a) 1) CH_2Cl_2, r.t.; 2) LAH, THF, r.t.; b) 1) **9**, Et_3N, CH_2Cl_2, 0 °C; 2) $SnCl_4$, 0 °C; c) Raney Ni, EtOH, reflux; d) 1) $POCl_3$, K_2CO_3, CH_3CN, 60 °C; 2) $NaBH_4$, MeOH, reflux.

Chart 3

dichloromethane at 0 °C to provide **7a** and **8a** in 29 and 43% yields, respectively. The procedure with **9** was found to be superior to that with **4** in manipulation. Cyclization with $SnCl_4$ under various conditions (temperature: −30—0 °C, solvent: chloroform or benzene) or that with $TiCl_4$ (0 °C, dichloromethane) was not able to affect the product ratio. Changing the oxygenated substituents on the phenethyl part from the dimethoxy to methylenedioxy group again did not alter the cyclization selectivity. Namely, the secondary amine (**3b**, 62%), derived from 3,4-methylenedioxyphenethylamine (**1b**), was acylated with **9** and then cyclized with $SnCl_4$ to afford the isoquinolin-3-one (**7b**) and the benzazepinone (**8b**) in 30 and 41% yields, respectively. Preferential cyclization to the seven-membered lactam in the above electrophilic cyclization reactions would be due to higher electron density at C-6′ on the aromatic ring of phenethyl part in comparison with that at C-6″ on the aromatic ring of benzyl part.[8)]

In order to prevent the formation of the seven-membered lactam, benzazepinone, a bromine atom was introduced to the phenethyl part of **3** as a blocking group. Acylation of the brominated amine (**13a**, 85%), prepared from brominated phenethylamine (**10**)[9)] and **2**, with acyl chloride (**9**), followed by treatment with $SnCl_4$ afforded the isoquinolin-3-one (**14a**) in 78% yield as a sole product, as expected. Concurrent reductive removal of both the bromine atom and the methylthio group was realized by the exposure of **14a** to Raney Ni in refluxing ethanol, providing the desired isoquinolin-3-one (**15a**, 88%), which was also obtained from **7a** by a similar

procedure in 90% yield. The Bischler–Napieralski reaction of **15a** in acetonitrile with phosphorus oxychloride in the presence of potassium carbonate[10] and subsequent reduction with sodium borohydride provided (±)-tetrahydropalmatine (**16a**), mp 150—152 °C, in 76% yield. Similarly, (±)-sinactine (**16b**), mp 169—171 °C, (±)-canadine (**16c**), mp 172—174 °C, and (±)-stylopine (**16d**), mp 198—200 °C, were synthesized starting from the corresponding phenethylamine (**10** or **11**) and the benzaldehyde (**2** or **12**) *via* the secondary amine (**13**) and the isoquinolin-3-ones (**14** and **15**). The results are summarized in Table 1. The synthetic alkaloids obtained above were proven to be identical with the corresponding authentic samples (see Experimental). Thus, we have developed a convenient, general, and practical synthetic method for 2,3,9,10-tetraoxygenated protoberberine alkaloids.

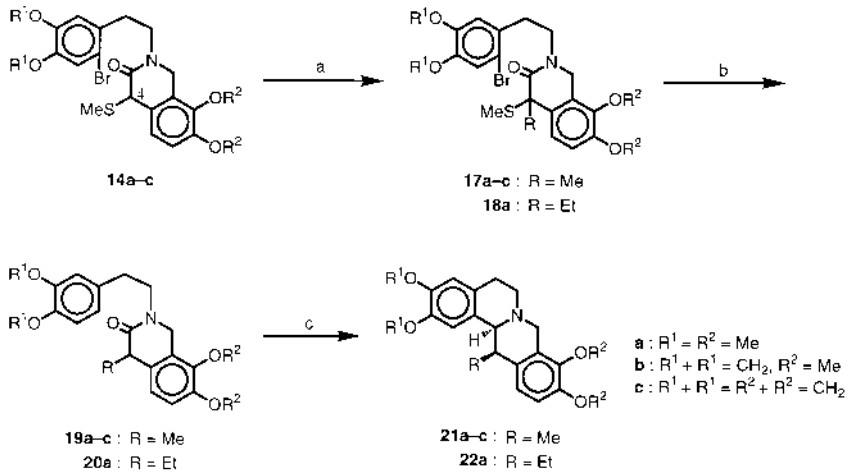
Synthesis of 13-Methyl-2,3,9,10-tetraoxygenated Protoberberine Alkaloids 13-Methylprotoberberine alkaloids[3] are a small group of protoberberine alkaloids having an extra methyl group at the C-13 position. They have been shown to be biogenetic precursors for 10-methyl-B/C-hexahydrobenzo[*c*]phenanethridine alkaloids.[3] Several synthetic methods for 13-methylprotoberberine alkaloids have been reported so far,[3,11,12] however, they are not necessarily satisfactory in generality. In the previous section, we developed a convenient synthesis of protoberberine alkaloids *via* 4-methylthio-2-phenethylisoquinolin-3-ones (**14**). The latter compounds also seem to be suitable intermediates for the synthesis of 13-methylprotoberberines because the C-4 position of **14** must be doubly activated by the carbonyl and methylthio group to be readily methylated. Our previous synthesis, therefore, should also open a new route to 13-methylprotoberberine alkaloids.

Table 1. Yield in the Synthesis of Protoberberine Alkaloids

Alkaloid	R^1, R^2	Yield (%)			
		16	**15**	**14**	**13**
(±)-Tetrahydropalmatine (**16a**)	$R^1=R^2=Me$	76	88	78	85
(±)-Sinactine (**16b**)	$R^1=Me$, $R^2+R^2=CH_2$	78	80	79	84
(±)-Canadine (**16c**)	$R^1+R^1=CH_2$, $R^2=Me$	68	77	72	88
(±)-Stylopine (**16d**)	$R^1+R^1=R^2+R^2=CH_2$	63	78	88	69

The 4-(methylthio)isoquinolin-3-one (**14a**) was exposed to lithium diisopropylamide at −78 °C and then to methyl iodide, affording the 4-methyl derivative (**17a**) in 80% yield. According to the conversion of **14** to **15**, treatment of **17a** with Raney Ni in refluxing ethanol effected the reductive removal of both the bromine and methylthio group to furnish the 4-methylisoquinolin-3-one (**19a**) in 88% yield. The Bischler–Napieralski reaction[10] of **19a** and subsequent $NaBH_4$ reduction provided (±)-corydaline (**21a**), mp 136—136.5 °C, in 61% yield. Similarly, 4-(methylthio)isoquinolin-3-one (**14b** or **14c**) was transformed into (±)-thalictricavine (**21b**), mp 208—209 °C, or (±)-tetrahydrocorysamine (**21c**), mp 203—204 °C, *via* **17b** or **17c**, and **19b** or **19c**, respectively, as summarized in Table 2. The synthetic alkaloids were proven to be identical with the corresponding authentic samples (see Experimental). Alkylation other than methylation was also possible. Ethylation of **14a** with ethyl iodide afforded the ethyl derivative (**18a**) in 74% yield. Sequential treatment of **18a** with Raney Ni in ethanol, $POCl_3$, and $NaBH_4$ provided (±)-13-ethyltetrahydropalmatine (**22a**, 63%) *via* **20a** (83%).

In conclusion, we developed a practical method for the



a) 1) LDA, THF, −78 °C; 2) MeI or EtI, r.t.; b) Raney Ni, EtOH, reflux; c) 1) $POCl_3$, K_2CO_3, CH_3CN, 60 °C; 2) $NaBH_4$, MeOH, r.t.

Chart 4

Table 2. Yield in the Synthesis of 13-Methylprotoberberine Alkaloids

Alkaloid	R, R^1, R^2	Yield (%)		
		21	**19**	**17**
(±)-Corydaline (**21a**)	$R=Me$, $R^1=R^2=Me$	61	88	80
(±)-Thalictricavine (**21b**)	$R=Me$, $R^1+R^1=CH_2$, $R^2=Me$	68	91	78
(±)-Tetrahydrocorysamine (**21c**)	$R=Me$, $R^1+R^1=R^2+R^2=CH_2$	55	95	81

synthesis of 2,3,9,10-tetraoxygenated protoberberine alkaloids as well as their 13-methyl alkaloids through the same intermediates, and the present method can be applied to the synthesis of a variety of protoberberine alkaloids.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Silica gel (Kieselgel 60, 70—230 mesh, Merck) and alumina (Aluminiumoxid 90, Aktivitätsstufe II—III, 70—230 mesh, Merck) were used for column chromatography. Organic extracts were dried over anhydrous Na_2SO_4. IR spectra were measured with a JASCO A-102 spectrometer in $CHCl_3$, MS with a Hitachi M-80 mass spectrometer, and ^{1}H-NMR spectra with a JEOL FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard.

General Procedure for Benzylphenethylamines A molecular sieve 4 Å (3.0 g) was added to a solution of phenethylamine derivative (**1**, **10**, or **11**, 18 mmol) and benzaldehyde derivative (**2** or **12**, 18 mmol) in CH_2Cl_2 (20 ml), and the mixture was stirred at room temperature for 24 h in a stream of nitrogen. The molecular sieve was filtered off and the filtrate was concentrated. A solution of the residue in tetrahydrofuran (THF) (20 ml) was added with stirring to a suspension of $LiAlH_4$ (90 mmol) in THF (100 ml), and the mixture was stirred at room temperature for 2 h. Water was added to the reaction mixture in order to destroy the excess $LiAlH_4$, and the precipitate was filtered off and washed with THF. The filtrate and washings were combined, dried, and concentrated to give the product.

N-(2,3-Dimethoxybenzyl)-3,4-dimethoxyphenethylamine (**3a**): Yield: 79%. Amorphous. IR cm^{-1}: 3300 (NH). ^{1}H-NMR δ: 7.1—6.7 (6H, m, Ar-H), 3.89 (9H, s, OMe×3), 3.82 (2H, s, NCH_2Ar), 3.78 (3H, s, OMe), 2.9—2.7 (4H, m, NCH_2CH_2Ar). MS *m/z* (%): 331 (M^+, 3), 181 (100), 152 (100). High-resolution (HR)-MS: Calcd for $C_{19}H_{25}NO_4$: 331.1860. Found: 331.1844.

N-(2,3-Dimethoxybenzyl)-3,4-methylenedioxyphenethylamine (**3b**): Yield: 62%. Amorphous. ^{1}H-NMR δ: 7.1—6.5 (7H, m, Ar-H×6, NH), 5.91 (2H, s, OCH_2O), 3.85, 3.79 (each 3H, each s, OMe×2), 3.80 (2H, s, NCH_2Ar), 2.80, 2.76 (4H, AB-q, J=4 Hz, NCH_2CH_2Ar). MS *m/z* (%): 315 (M^+, 0.6), 180 (99), 151 (100). HR-MS: Calcd for $C_{18}H_{21}NO_4$: 315.1469. Found: 315.1453.

2-Bromo-4,5-dimethoxy-*N*-(2,3-dimethoxybenzyl)phenethylamine (**13a**): Yield: 85%. Amorphous. ^{1}H-NMR δ: 7.1—6.7 (3H, m, Ar-H×3), 6.98, 6.78 (each 1H, each s, Ar-H), 3.85, 3.84, 3.83. 3.82 (total 14H, each s, OMe×4, NCH_2Ar), 2.87 (4H, s, NCH_2CH_2Ar). MS *m/z* (%): 411, 409 (M^+, 0.11, 0.12), 330 (65), 181 (100), 151 (100). HR-MS: Calcd for $C_{19}H_{24}BrNO_4$: 409.0887. Found: 409.0856.

2-Bromo-4,5-dimethoxy-*N*-(2,3-methylenedioxybenzyl)phenethylamine (**13b**): Yield: 84%. Amorphous. ^{1}H-NMR δ: 6.99, 6.74 (each 1H, each s, Ar-H), 6.76 (3H, s, Ar-H×3), 5.92 (2H, s, OCH_2O), 3.84, 3.83 (total 8H, each s, OMe×2, NCH_2Ar), 2.89 (4H, s, NCH_2CH_2Ar). MS *m/z* (%): 314 (M^+-Br, 40), 231 (7), 164 (100). Picrate: yellow needles, mp 185—187 °C (EtOH–$CHCl_3$). *Anal*. Calcd for $C_{18}H_{20}BrNO_4\cdot C_6H_3N_3O_7$: C, 46.24; H, 3.72; N, 8.99. Found: C, 46.54; H, 3.78; N, 8.70.

2-Bromo-*N*-(2,3-dimethoxybenzyl)-4,5-methylenedioxyphenethylamine (**13c**): Yield: 88%. Amorphous. ^{1}H-NMR δ: 7.1—6.6 (5H, m, Ar-H×5), 5.92 (2H, s, OCH_2O), 3.86, 3.83, 3.79 (total 8H, each s, OMe×2, NCH_2Ar), 2.84 (4H, s, NCH_2CH_2Ar). MS *m/z* (%): 314 (M^+-Br, 6), 180 (58), 151 (100).

2-Bromo-4,5-methylenedioxy-*N*-(2,3-methylenedioxybenzyl)phenethylamine (**13d**): Yield: 69%. Amorphous. ^{1}H-NMR δ: 6.98, 6.73 (each 1H, each s, Ar-H×2), 6.8—6.5 (3H, m, Ar-H×3), 5.94, 5.93 (each 2H, each s, OCH_2O×2), 3.82 (2H, s, NCH_2Ar), 2.85 (4H, s, NCH_2CH_2Ar). MS *m/z* (%): 298 (M^+-Br, 26), 215 (11), 164 (100), 185 (100).

***N*-(3,4-Dimethoxybenzyl)-*N*-(2,3-dimethoxyphenethyl)-α-(methylthio)acetamide (5)** α-(Methylthio)acetyl chloride (**4**, 250 mg, (2.0 mmol)) was added to a solution of the amine (**2a**, 645.4 mg (1.9 mmol)) in CH_2Cl_2 (10 ml) at 0 °C in the presence of Et_3N (200 mg (2.0 mmol)), and the reaction mixture was stirred for 1.5 h. The mixture was successively washed with dil. HCl, 10% K_2CO_3 aq. and then saturated NaCl aq. and dried. The solvent was evaporated off and the residue was chromatographed on silica gel with C_6H_6 : AcOEt (4 : 1) to give the amide (**5**, 659.5 mg, 81%). Amorphous. IR cm^{-1}: 1630 (NCO). ^{1}H-NMR δ: 7.0—6.7 (6H, m, Ar-H×6), 4.71, 4.49 (each 1H, each s, NCH_2Ar), 3.87 (6H, s, OMe×2), 3.89, 3.79 (each 3H, each s, OMe×2), 3.52 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2Ar$), 3.33, 3.07 (total 2H, each s, SCH_2CO), 2.76 (2H, t, J=6 Hz, $NCH_2C\underline{H}_2Ar$), 2.22 (3H, s, SMe). MS *m/z* (%): 419 (M^+, 5), 268 (3), 180 (8), 164 (100), 151 (59). HR-MS: Calcd for $C_{22}H_{29}NO_5S$: 419.1763. Found: 419.1748.

***N*-(3,4-Dimethoxybenzyl)-*N*-(2,3-dimethoxyphenethyl)-α-(methylsulfinyl)acetamide (6)** *m*-CPBA (80%, 687.5 mg (3.2 mmol)) was added portion-wise to a solution of the amide (**5**, 1.32 g (3.2 mmol)) in CH_2Cl_2 (30 ml). The reaction mixture was stirred under ice-cooling for 1 h, washed with sat. $NaHCO_3$ aq. and then sat. NaCl aq., and dried. The solvent was evaporated off and the residue was chromatographed on alumina with $CHCl_3$ to give the sulfoxide (**6**, 1.25 g, 91%). Amorphous. IR cm^{-1}: 1630 (NCO). ^{1}H-NMR δ: 7.0—6.6 (6H, m, Ar-H×6), 4.71, 4.49 (total 2H, each s, NCH_2Ar), 3.86 (6H, s, OMe×2), 3.9—3.7 (2H, m, SCH_2CO), 3.85, 3.84 (each 3H, each s, OMe×2), 3.6—3.4 (2H, m, $NC\underline{H}_2CH_2Ar$), 2.9—2.6 (2H, m, $NCH_2C\underline{H}_2Ar$), 2.76 (12/7 H), 2.66 (9/7 H) (total 3H, each s, SMe). MS *m/z* (%): 435 (M^+, 1), 372 (1), 164 (100). HR-MS: Calcd for $C_{22}H_{29}NO_6S$: 435.1752. Found: 435.1733.

7,8-Dimethoxy-2-(3,4-dimethoxybenzyl)-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (7a) and 7,8-Dimethoxy-3-(2,3-dimethoxybenzyl)-1-methylthio-1,2,4,5-tetrahydrobenzazepin-2-one (8a) From Sulfoxide (**6**): a) with *p*-TsOH: *p*-TsOH (175 mg (1.0 mmol)) was added to a solution of the sulfoxide (**6**, 219 mg (0.50 mmol)) in CCl_4 (3 ml) and the mixture was refluxed with stirring for 20 min. The mixture was washed with sat. $NaHCO_3$ aq. and sat. NaCl aq., then dried. The solvent was evaporated off and the residue was chromatographed on silica gel with C_6H_6 : AcOEt (10 : 1). The first fraction gave the benzazepinone (**8a**, 70.5 mg, 34%). Colorless plates. mp 112—115 °C (MeOH). IR cm^{-1}: 1630 (NCO). ^{1}H-NMR δ: 7.3—6.7 (3H, m, Ar-H×3), 6.71, 6.48 (each 1H, each s, Ar-H×2), 4.94, 4.59 (each 1H, AB-q, J=15 Hz, NCH_2Ar), 4.72 (1H, s, C_1-H), 4.9—4.5, 3.5—3.1 (each 1H, m, C_4-H), 3.88, 3.87, 3.85, 3.82 (each 3H, each s, OMe×4), 3.0—2.8 (2H, m, C_5-H), 2.53 (3H, s, SMe). MS *m/z* (%): 417 (M^+, 31), 370 (63), 342 (100), 266 (58), 151 (52). *Anal*. Calcd for $C_{22}H_{27}NO_5S$: C, 63.29; H, 6.25; N, 3.35. Found: C, 63.33; H, 6.25; N, 3.15. The second fraction gave the isoquinolinone (**7a**, 50.3 mg, 24%). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.0—6.4 (3H, m, Ar-H×3), 6.83, 6.77 (each 1H, AB-q, J=8 Hz, Ar-H×2), 4.36 (1H, s, C_4-H), 4.51, 4.37 (2H, AB-q, J=17 Hz, C_1-H), 3.86, 3.84 (each 3H, each s, OMe×2), 3.78 (6H, s, OMe×2), 3.16 (2H, t, J=7 Hz, $NC\underline{H}_2CH_2Ar$), 2.89 (2H, t, J=7 Hz, $NCH_2C\underline{H}_2Ar$), 2.19 (3H, s, SMe). MS *m/z* (%): 417 (M^+, 4), 370 (8), 164 (100). HR-MS: Calcd for $C_{22}H_{27}NO_5S$: 417.1608. Found: 417.1595. b) with CH_3SO_3H: **7a** (25%) and **8a** (41%). c) with CF_3CO_2H: **7a** (17%) and **8a** (46%).

From Amine (**3a**) with **9**: According to the general procedure for 4-methylthio-2-phenethylisoquinolin-3-ones, **3a** gave **7a** (29%) and **8a** (43%).

7,8-Dimethoxy-2-(3,4-methylenedioxyphenethyl)-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (7b) and 3-(2,3-Dimethoxybenzyl)-7,8-methylenedioxy-1-methylthio-1,2,4,5-tetrahydrobenzazepin-2-one (8b) According to the general procedure for 4-methylthio-2-phenethylisoquinolin-3-ones, **3b** gave **8b** (41%) and **7b** (30%).

8b: Amorphous. IR cm^{-1}: 1635 (NCO). ^{1}H-NMR δ: 7.0—6.8 (3H, m, Ar-H×3), 6.70, 6.47 (each 1H, each s, Ar-H×2), 5.91 (2H, s, OCH_2O), 4.92, 4.61 (each 1H, AB-q, J=15 Hz, NCH_2Ar), 4.67 (1H, s, C_1-H), 4.8—4.4, 3.5—3.1 (each 1H, m, C_4-H), 3.87, 3.84 (each 3H, each s, OMe×2), 2.9—2.7 (2H, m, C_5-H), 2.33 (3H, s, SMe). MS *m/z* (%): 401 (M^+, 13), 354 (65), 324 (47), 151 (100). HR-MS: Calcd for $C_{21}H_{23}NO_5S$: 401.1295. Found: 401.1295.

7b: Colorless plates. mp 122—123 °C (MeOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.99, 6.86 (2H, AB-q, J=8.5 Hz, Ar-H×2), 6.7—6.5 (3H, m, Ar-H×3), 5.90 (2H, s, C_4-H), 3.86, 3.81 (each 3H, each s, OMe×2), 3.7—3.2 (2H, m, $NC\underline{H}_2CH_2Ar$), 2.84 (2H, t, J=7 Hz, $NCH_2C\underline{H}_2Ar$), 2.21 (3H, s, SMe). MS *m/z* (%): 401 (M^+, 4), 355 (21), 206 (84), 148 (100). *Anal*. Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.68; H, 5.86; N, 3.37.

General Procedure for 4-Methylthio-2-phenethylisoquinolin-3-ones A solution of α-chloro-α-(methylthio)acetyl chloride (**9**, 10 mmol) in CH_2Cl_2 (10 ml) was added dropwise under ice-cooling to a solution of the amine (**3** or **13**, 9 mmol) and Et_3N (10 mmol) in CH_2Cl_2 (30 ml), and the mixture was stirred for 20 min. $SnCl_4$ (11 mmol) was added under ice-cooling to the reaction mixture. The mixture was stirred for 1 h and washed with H_2O, sat. $NaHCO_3$ aq., and sat. NaCl aq., then dried. The solvent was evaporated off and the residue was chromatographed on silica gel with C_6H_6 : AcOEt (10 : 1) to give the product.

2-(2-Bromo-4,5-dimethoxyphenethyl)-7,8-dimethoxy-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**14a**): Yield: 78%. Pale-yellow needles. mp 131—133 °C (MeOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.00, 6.70 (each 1H, each s, Ar-H×2), 6.98, 6.86 (each 1H, AB-q, J=8.5 Hz, Ar-H×2), 4.54, 4.40 (each 1H, AB-q, J=17 Hz, C_1-H), 4.36 (1H, s, C_4-H), 3.86, 3.83, 3.79, 3.68 (each 3H, each s, OMe×4), 3.85—3.75 (2H, m,

NC$\underline{H}_2$CH$_2$Ar), 3.00 (2H, t, J=7 Hz, NCH$_2$C$\underline{H}_2$Ar), 2.21 (3H, s, SMe). MS m/z (%): 497, 495 (M$^+$, 6, 6), 450, 448 (18, 12), 368 (14), 242 (93), 206 (100), 64 (29). *Anal*. Calcd for $C_{22}H_{26}BrNO_5S$: C, 53.22; H, 5.28; N, 2.82. Found: C, 53.04; H, 5.41; N, 2.57.

2-(2-Bromo-4,5-dimethoxyphenethyl)-7,8-methylenedioxy-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**14b**): Yield: 80%. Colorless needles. mp 121—123 °C (MeOH–Et$_2$O). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.02, 6.52 (each 1H, each s, Ar-H×2), 6.73 (2H, s, Ar-H×2), 5.95 (2H, s, OCH$_2$O), 4.48, 3.83 (each 1H, AB-q, J=16 Hz, C$_1$-H), 4.39 (1H, s, C$_4$-H), 3.85, 3.50 (each 3H, each s, OMe×2), 4.0—3.5, 3.1—2.8 (each 2H, m, NCH$_2$CH$_2$Ar), 2.22 (3H, s, SMe). MS m/z (%): 481, 479 (M$^+$, 8, 6), 435, 433 (16, 19), 352 (7), 242 (100), 189 (36), 164 (23). *Anal*. Calcd for $C_{21}H_{22}BrNO_5S$: C, 52.51; H, 4.62; N, 2.92. Found: C, 52.55; H, 4.61; N, 2.65.

2-(2-Bromo-4,5-methylenedioxyphenethyl)-7,8-dimethoxy-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**14c**): Yield: 72%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.99, 6.78 (each 1H, AB-q, J=8.5 Hz, Ar-H×2), 6.99, 6.72 (each 1H, each s, Ar-H×2), 5.91 (2H, s, OCH$_2$O), 4.55, 4.42 (each 1H, AB-q, J=16 Hz, C$_1$-H), 4.36 (1H, s, C$_4$-H), 3.86, 3.82 (each 3H, each s, OMe×2), 3.72 (2H, t, J=7 Hz, NC$\underline{H}_2$CH$_2$Ar), 2.97 (2H, t, J=7 Hz, NCH$_2$C$\underline{H}_2$Ar), 2.24 (3H, s, SMe). MS m/z (%): 434, 432 (M$^+$−47, 4, 3), 400 (8), 352 (14), 206 (100), 151 (51).

2-(2-Bromo-4,5-methylenedioxyphenethyl)-7,8-methylenedioxy-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**14d**): Yield: 88%. Colorless plates. mp 119—121 °C (MeOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.94, 6.66 (each 1H, each s, Ar-H×2), 6.75 (2H, s, Ar-H×2), 5.97, 5.90 (each 2H, each s, OCH$_2$O×2), 4.55, 4.11 (each 1H, AB-q, J=16 Hz, C$_1$-H), 4.38 (1H, s, C$_4$-H), 3.72 (2H, t, J=7 Hz, NC$\underline{H}_2$CH$_2$Ar), 2.97 (2H, t, J=7 Hz, NCH$_2$C$\underline{H}_2$Ar), 2.24 (3H, s, SMe). MS m/z (%): 418, 416 (M$^+$−47, 34, 39), 228 (39), 190 (100), 175 (65), 148 (53). *Anal*. Calcd for $C_{20}H_{18}BrNO_5S$: C, 51.73; H, 3.91; N, 3.02. Found: C, 51.86; H, 3.78; N, 2.80.

General Procedure for Alkylation of Isoquinolin-3-ones A solution of lithium diisopropylamide (LDA) (3.2 ml (0.1 M sol. in THF) (3.2 mmol)) was added to a solution of isoquinolin-3-one (**14**, 2.12 mmol) in THF (20 ml) at −78 °C in a stream of N$_2$ and stirred for 1 h. Methyl iodide or ethyl iodide (3.2 mmol) was added to the reaction mixture at room temperature and stirred for 1 h. Sat. NH$_4$Cl aq. (1 ml) was added to the mixture and extracted with CHCl$_3$. The extract was washed with sat. NaCl aq. and dried. The solvent was evaporated off and the residue was chromatographed on silica gel with hexane : AcOEt (4 : 1) to give the product.

2-(2-Bromo-4,5-dimethoxyphenethyl)-7,8-dimethoxy-4-methyl-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**17a**): Yield: 80%. Colorless needles. mp 131.5—132 °C (MeOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.15, 6.88 (each 1H, AB-q, J=8.5 Hz, Ar-H×2), 7.01, 6.71 (each 1H, each s, Ar-H×2), 4.62, 4.45 (each 1H, AB-q, J=16 Hz, C$_1$-H), 3.87, 3.84, 3.80, 3.70 (each 3H, each s, OMe×4), 3.75—3.65 (2H, br s, NCH$_2$C$\underline{H}_2$Ar), 2.99 (2H, t, J=7 Hz, NCH$_2$C$\underline{H}_2$Ar), 2.03 (3H, s, SMe), 1.95 (3H, s, C$_4$-Me). MS m/z (%): 511, 509 (M$^+$, 1.1, 1.1),464, 462 (71, 69), 219 (100). *Anal*. Calcd for $C_{23}H_{28}BrNO_5S$: C, 54.12; H, 5.53; N, 2.74. Found: C, 53.86; H, 5.75; N, 2.76.

2-(2-Bromo-4,5-methylenedioxyphenethyl)-7,8-dimethoxy-4-methyl-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**17b**): Yield: 78%. Colorless needles. mp 134—135 °C (EtOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.16, 6.89 (each 1H, AB-q, J=8.8 Hz, Ar-H×2), 6.99, 6.73 (each 1H, each s, Ar-H×2), 5.93, 5.91 (each 1H, AB-q, J=1.5 Hz, OCH$_2$O), 4.62, 4.47 (each 1H, AB-q, J=16 Hz, C$_1$-H), 3.87, 3.83 (each 3H, each s, OMe×2), 3.86—2.84 (4H, m, NCH$_2$CH$_2$Ar), 2.06 (3H, s, SMe), 1.95 (3H, s, C$_4$-Me). MS m/z (%): 496, 494 (M$^+$+1, 0.4, 0.7), 41 (100). *Anal*. Calcd for $C_{22}H_{24}BrNO_5S$: C, 53.45; H, 4.89; N, 2.83. Found: C, 53.50; H, 5.04; N, 2.82.

2-(2-Bromo-4,5-methylenedioxyphenethyl)-7,8-methylenedioxy-4-methyl-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**17c**): Yield: 81%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.98, 6.65 (each 1H, each s, Ar-H×2), 6.93, 6.77 (each 1H, AB-q, J=8.3 Hz, Ar-H×2), 5.98—5.88 (4H, m, OCH$_2$O×2), 4.63, 4.14 (each 1H, AB-q, J=15.6 Hz, C$_1$-H), 3.77—2.83 (4H, m, NCH$_2$CH$_2$Ar), 2.07 (3H, s, SMe), 1.95 (3H, s, C$_4$-Me). MS m/z (%): 480, 478 (M$^+$+1, 0.2, 0.2), 41 (100). *Anal*. Calcd for $C_{21}H_{20}BrNO_5S$: C, 52.73; H, 4.21; N, 2.93. Found: C, 52.49; H, 4.37; N, 2.79.

2-(2-Bromo-4,5-dimethoxyphenethyl)-4-ethyl-7,8-dimethoxy-4-methylthio-1,2,3,4-tetrahydroisoquinolin-3-one (**18a**): Yield: 74%. Colorless needles. mp 133—134 °C (MeOH). IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 7.14, 6.92 (each 1H AB-q, J=8.8 Hz, Ar-H×2), 7.01, 6.71 (each 1H, each s, Ar-H×2), 4.51, 4.44 (each 1H, AB-q, J=16.6 Hz, C$_1$-H), 3.88, 3.83, 3.82, 3.69 (each 3H, each s, OMe×4), 3.82—3.01 (4H, m, NCH$_2$CH$_2$Ar), 2.17—2.03 (2H, m, C$\underline{H}_2$Me), 2.00 (3H, s, SMe), 0.76 (3H, t, J=7.3 Hz, CH$_2$$\underline{Me}$). MS m/z (%): 525, 523 (M$^+$, 1.2, 1.4), 234 (91), 233 (100). *Anal*. Calcd for $C_{24}H_{30}BrNO_5S$: C, 54.95; H, 5.76; N, 2.67. Found: C, 54.94; H, 5.69; N, 2.53.

General Procedure for Desulfurization of Methylthioisoquinolin-3-ones Raney Ni (W-4, 4 g) was added to a solution of methylthioisoquinolin-3-one (**14** , **17**, or **18**, 1.8 mmol) in ethanol (20 ml), and the reaction mixture was refluxed for 2 h. The Raney Ni was filtered off and washed with hot ethanol. The filtrate and washings were combined and concentrated. The residue was chromatographed on alumina with CHCl$_3$ to give the product.

7,8-Dimethoxy-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-3-one (**15a**):Yield: 88% (from **14a**); 90% (from **7a**). Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.83 (2H, s, Ar-H×2), 6.79, 6.78, 6.73 (each 1H, each s, Ar-H×3), 4.38 (2H, s, C$_1$-H), 3.85, 3.84, 3.78, 3.77 (each 3H, each s, OMe×4), 3.74 (each 1H, t, J=8 Hz, NC$\underline{H}_2$CH$_2$Ar), 3.54 (2H, s, C$_4$-H), 2.88 (each 1H, t, J=8 Hz, NCH$_2$C$\underline{H}_2$Ar). MS m/z (%): 371 (M$^+$, 13), 192 (26), 164 (100). HR-MS: Calcd for $C_{21}H_{25}NO_5$: 371.1730. Found: 371.1725.

2-(3,4-Dimethoxyphenethyl)-7,8-methylenedioxy-1,2,3,4-tetrahydroisoquinolin-3-one (**15b**):Yield: 80%. Amorphous. IR cm^{-1}: 1630 (NCO). ^{1}H-NMR δ: 6.77 (2H, s, Ar-H×2), 6.72, 6.61 (each 1H, AB-q, J=8 Hz, Ar-H×2), 6.63 (1H, s, Ar-H), 5.94 (2H, s, OCH$_2$O), 4.14 (2H, s, C$_1$-H), 3.85, 3.67 (each 3H, each s, OMe×2), 3.72 (2H, t, J=7 Hz, NC$\underline{H}_2$CH$_2$Ar), 3.53 (2H, s, C$_4$-H), 2.85 (2H, t, J=7 Hz, NCH$_2$C$\underline{H}_2$Ar). MS m/z (%): 355 (M$^+$, 6), 220 (3), 176 (13), 164 (100), 151 (6). HR-MS: Calcd for $C_{20}H_{21}NO_5$: 355.1418. Found: 355.1436.

7,8-Dimethoxy-2-(3,4-methylenedioxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-3-one (**15c**):Yield: 77%. Amorphous. IR cm^{-1}: 1635 (NCO). ^{1}H-NMR δ: 6.83 (2H, s, Ar-H×2), 6.70 (1H, s, Ar-H), 6.75—6.65 (2H, m, Ar-H×2), 5.91 (2H, s, OCH$_2$O), 4.24, 3.54 (each 1H, AB-q, J=16 Hz, C$_1$-H), 3.85 (6H, s, OMe×2), 3.6—2.5 (6H, m, NCH$_2$CH$_2$Ar, C$_4$-H). MS m/z (%): 355 (M$^+$, 8), 207 (39), 192 (31), 148 (100). HR-MS: Calcd for $C_{20}H_{21}NO_5$: 355.1418. Found: 355.1436.

7,8-Methylenedioxy-2-(3,4-methylenedioxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-3-one (**15d**): Yield: 78%. Amorphous. IR cm^{-1}: 1635 (NCO). ^{1}H-NMR δ: 6.9—6.5 (5H, m, Ar-H×5), 5.95, 5.93 (each 2H, each s, OCH$_2$O×2), 4.24 (2H, s, C$_1$-H), 3.69 (2H, t, J=8 Hz, NC$\underline{H}_2$CH$_2$Ar), 3.56, 3.51 (each 1H, AB-q, J=17 Hz, C$_4$-H), 2.83 (2H, t, J=8 Hz, NCH$_2$C$\underline{H}_2$Ar). MS m/z (%): 339 (M$^+$, 6), 191 (8), 176 (19), 148 (100). HR-MS: Calcd for $C_{19}H_{17}NO_5$: 339.1105. Found: 339.1100.

7,8-Dimethoxy-2-(3,4-dimethoxyphenethyl)-4-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**19a**): Yield: 88%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.9—6.7 (5H, m, Ar-H×5), 4.36 (2H, s, C$_1$-H), 3.85, 3.83, 3.79, 3.78 (each 3H, each s, OMe×4), 3.8—3.65 (2H, m, NC$\underline{H}_2$CH$_2$Ar), 3.48 (1H, q, J=7.3 Hz, C$_4$-H), 2.87 (2H, t, J=7.5 Hz, NCH$_2$C$\underline{H}_2$Ar), 1.41 (3H, d, J=7.3 Hz, C$_4$-Me). MS m/z (%): 385 (M$^+$, 6), 219 (7), 206 (9), 164 (100). HR-MS: Calcd for $C_{22}H_{27}NO_5$: 385.1887. Found: 385.1911.

7,8-Dimethoxy-2-(3,4-methylenedioxyphenethyl)-4-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**19b**): Yield: 91%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.87, 6.85 (each 1H, AB-q, J=8.8 Hz, Ar-H×2), 6.73—6.67 (3H, m, Ar-H×3), 5.92, 5.91 (each 1H, AB-q, J=2 Hz, OCH$_2$O), 4.38, 4.35 (each 1H, AB-q, J=16.6 Hz, C$_1$-H), 3.86, 3.81 (each 3H, each s, OMe×2), 3.8—3.6 (4H, m, NCH$_2$CH$_2$Ar), 3.47 (1H, q, J=7.3 Hz, C$_4$-H), 1.42 (3H, d, J=7.3 Hz, C$_4$-Me). MS m/z (%): 369 (M$^+$, 13), 221 (63), 206 (46), 148 (100). HR-MS: Calcd for $C_{21}H_{23}NO_5$: 369.1574. Found: 369.1614.

7,8-Methylenedioxy-2-(3,4-methylenedioxyphenethyl)-4-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (**19c**): Yield: 95%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.8—6.6 (5H, m, Ar-H×5), 5.95, 5.90 (each 2H, each s, OCH$_2$O×2), 4.25, 4.18 (each 1H, AB-q, J=16 Hz, C$_1$-H), 3.8—3.53 (2H, m, NC$\underline{H}_2$CH$_2$Ar), 3.09 (1H, q, J=7.3 Hz, C$_4$-H), 2.9—2.7 (2H, m, NCH$_2$C$\underline{H}_2$Ar), 1.41 (3H, d, J=7.3 Hz, C$_4$-Me). MS m/z (%): 353 (M$^+$, 9), 205 (27), 190 (33), 148 (100). HR-MS: Calcd for $C_{20}H_{19}NO_5$: 353.1262. Found: 353.1304.

4-Ethyl-7,8-dimethoxy-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroisoquinolin-3-one (**20a**):Yield: 83%. Amorphous. IR cm^{-1}: 1640 (NCO). ^{1}H-NMR δ: 6.86—6.7 (5H, m, Ar-H×5), 4.36 (2H, s, C$_1$-H), 3.86, 3.84, 3.79, 3.78 (each 3H, each s, OMe×4), 3.75—3.6 (2H, m, NC$\underline{H}_2$CH$_2$Ar), 3.40 (1H, t, J=7 Hz, C$_4$-H), 2.89 (2H, t, J=7.3 Hz, NCH$_2$C$\underline{H}_2$Ar), 1.8—1.67 (2H, m, C$\underline{H}_2$Me), 0.83 (3H, t, J=7.3 Hz, CH$_2$$\underline{Me}$). MS m/z (%): 399 (M$^+$, 5), 164 (100). HR-MS: Calcd for $C_{23}H_{29}NO_5$: 399.2044. Found: 399.2106.

General Procedure for Protoberberines A mixture of isoquinolin-3-one (**15**, **19**, or **20**, 0.82 mmol), anhyd. K$_2$CO$_3$ (2.2 mmol) and POCl$_3$ (4.2 mmol) in CH$_3$CN (17 ml) was heated with stirring at 60 °C in a stream

of N_2 for 40 min (2 h for **19** and **20**) and concentrated. MeOH (15 ml) was added to the residue and $NaBH_4$ (13 mmol) was added to the mixture. The reaction mixture was refluxed (or stirred at room temperature for **19** and **20**) for 1 h. The solvent was evaporated off and K_2CO_3 aq. was added to the residue. The mixture was extracted with $CHCl_3$ and the extract was washed with NaCl aq. and dried. The solvent was evaporated off and the residue was chromatographed on silica gel with $CHCl_3$ to give the product. The synthetic alkaloids were identical with the corresponding authentic samples in ^{1}H-NMR spectra and thin-layer chromatographic behavior.

(±)-Tetrahydropalmatine (**16a**): Yield: 76%. Pale-yellow plates. mp 150—152 °C (MeOH) (mp 147 °C[13]). ^{1}H-NMR δ: 6.89, 6.80 (each 1H, AB-q, J=8.5 Hz, Ar-H×2), 6.73, 6.62 (each 1H, each s, Ar-H×2), 4.24, 3.52 (each 1H, AB-q, J=15 Hz, C_8-H), 3.89, 3.87 (each 3H, each s, OMe×2), 3.85 (6H, s, OMe×2), 3.8—2.7 (7H, m, C_5, C_6, C_{13}, C_{13a}-H). MS m/z (%): 355 (M^+, 100), 324 (15), 190 (30), 164 (97). *Anal*. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.97; H, 7.09; N, 3.94.

(±)-Sinactine (**16b**): Yield: 78%. Colorless needles. mp 169—171 °C (MeOH) (mp 167—168 °C[5g]). ^{1}H-NMR δ: 6.73, 6.62 (each 1H, each s, Ar-H×2), 6.67 (2H, s, Ar-H×2), 5.96, 5.93 (each 1H, AB-q, J=1.5 Hz, OCH_2O), 4.10, 3.55 (each 1H, AB-q, J=15 Hz, C_8-H), 3.89, 3.87 (each 3H, each s, OMe×2), 3.7—2.4 (7H, m, C_5, C_6, C_{13}, C_{13a}-H). MS m/z (%): 339 (M^+, 59), 190 (28), 148 (100). *Anal*. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.62; H, 6.24; N, 4.26.

(±)-Canadine (**16c**): Yield: 68%. Pale-yellow plates. mp 172—174 °C (MeOH) (mp 167—168 °C[5g]). ^{1}H-NMR δ: 6.86, 6.79 (each 1H, AB-q, J=8 Hz, Ar-H×2), 6.72, 6.59 (each 1H, each s, Ar-H×2), 5.91 (2H, s, OCH_2O), 4.24, 3.54 (each 1H, AB-q, J=16 Hz, C_8-H), 3.85 (6H, s, OMe×2), 3.6—2.5 (7H, m, C_5, C_6, C_{13}, C_{13a}-H). MS m/z (%): 339 (M^+, 60), 174 (18), 164 (100), 149 (67). *Anal*. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.74; H, 6.36; N, 4.18.

(±)-Stylopine (**16d**): Yield: 63%. Pale-yellow needles. mp 198—200 °C ($MeOH–CHCl_3$) (mp 194—195 °C[5g]). ^{1}H-NMR δ: 6.72, 6.58 (each 1H, each s, Ar-H×2), 6.66 (2H, s, Ar-H×2), 5.96, 5.92 (each 1H, AB-q, J=1 Hz, OCH_2O), 5.91 (2H, s, OCH_2O), 4.09, 3.46 (2H, AB-q, J=15 Hz, C_8-H), 3.6—2.4 (7H, m, C_5, C_6, C_{13}, C_{13a}-H). MS m/z (%): 323 (M^+, 27), 174 (12), 148 (100). *Anal*. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.70; H, 5.23; N, 4.52.

(±)-Corydaline (**21a**): Yield: 61%. Colorless needles. mp 136—136.5 °C (EtOH) (mp 135—136 °C[12,14]). ^{1}H-NMR δ: 6.91, 6.83 (each 1H, AB-q, J=8.5 Hz, Ar-H×2), 6.69, 6.61 (each 1H, each s, Ar-H×2), 4.20, 3.51 (each 1H, AB-q, J=16 Hz, C_8-H), 3.88, 3.86 (each 6H, each s, OMe×4), 3.75—2.45 (6H, m, C_5, C_6, C_{13}, C_{13a}-H), 0.95 (3H, d, J=6.8 Hz, C_{13}-Me). MS m/z (%): 369 (M^+, 29), 179 (14), 178 (100). *Anal*. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.55; H, 7.69; N, 3.80.

(±)-Thalictricavine (**21b**): Yield: 68%. Colorless needles. mp 208—209 °C (MeOH) (mp 211.5—212.5 °C[15], 209—210 °C[12]). ^{1}H-NMR δ: 6.89, 6.82 (each 1H, AB-q, J=8.7 Hz, Ar-H×2), 6.68, 6.58 (each 1H, each s, Ar-H×2), 5.93, 5.91 (each 1H, AB-q, J=1.8 Hz, OCH_2O), 4.19, 3.49 (each 1H, AB-q, J=15.6 Hz, C_8-H), 3.86 (6H, s, OMe×2), 3.65—3.0 (6H, m, C_5, C_6, C_{13}, C_{13a}-H), 0.96 (3H, d, J=6.9 Hz, C_{13}-Me). MS m/z (%): 353 (M^+, 30), 178 (100). *Anal*. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.61; H, 6.60; N, 3.95.

(±)-Tetrahydrocorysamine (**21c**): Yield: 55%. Colorless needles. mp 203—204 °C (MeOH) (mp 210—211 °C[16], 207—209 °C[12]). ^{1}H-NMR δ: 6.71, 6.66 (each 1H, AB-q, J=8 Hz, Ar-H×2), 6.68, 6.58 (each 1H, each s, Ar-H×2), 5.95, 5.91 (each 1H, AB-q, J=1.3 Hz, OCH_2O), 5.93, 5.92 (each 1H, AB-q, J=1.0 Hz, OCH_2O), 4.06, 3.48 (each 1H, AB-q, J=15 Hz, C_8-H), 3.7—2.53 (6H, m, C_5, C_6, C_{13}, C_{13a}-H), 0.95 (3H, d, J=7 Hz, C_{13}-Me). MS m/z (%): 337 (M^+, 21), 162 (100). *Anal*. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.31; H, 5.72; N, 4.13.

(±)-13-Ethyltetrahydropalmatine (**22a**): Yield: 63%. Colorless needles. mp 127—128 °C (MeOH). ^{1}H-NMR δ: 6.90, 6.80 (each 1H, AB-q, J=8.8 Hz, Ar-H×2), 6.70, 6.62 (each 1H, each s, Ar-H×2), 4.23, 3.52 (each 1H, AB-q, J=16 Hz, C_8-H), 3.88, 3.87 (each 3H, each s, OMe×2), 3.86 (6H, s, OMe×2), 3.2—2.9 (6H, m, C_5, C_6, C_{13}, C_{13a}-H), 1.53—1.32 (2H, m, $C\underline{H}_2Me$), 0.79 (3H, t, J=7.3 Hz, $CH_2\underline{Me}$). MS m/z (%): 383 (M^+, 42), 193 (19), 192 (100). *Anal*. Calcd for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62; N, 3.65. Found: C, 72.21; H, 7.69; N, 3.66.

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References and Notes

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