Synthesis of 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines *via* Pummerer-type cyclization of *N*-(arylmethyl)-*N*-methyl-2-aryl-2-(phenylsulfinyl) acetamides

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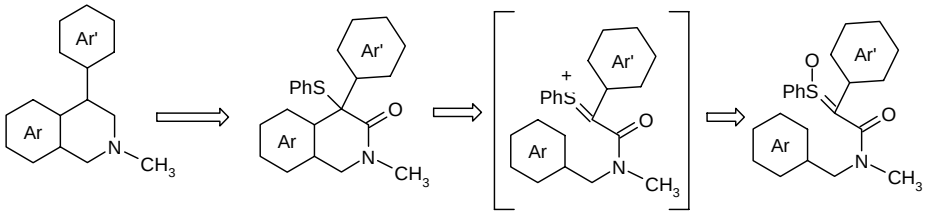
Abstract

The synthesis of 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines (16) was achieved *via* the intramolecular cyclization of *N*-(arylmethyl)-*N*-methyl-2-aryl-2-(phenylsulfinyl)acetamides (10) utilizing the Pummerer reaction as key step. Trifuoroacetic anhydride induced cyclization of the sulfoxides 10 at ambient temperature readily provided 4-aryl-2-methyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-ones (11) in almost quantitative yield. Subsequent reductive removal of the phenylsulfanyl group from 11 with $NaBH_4$-$NiCl_2$ followed by the reduction of the lactam function of the resulting 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-ones (15) furnished the title products 16 in excellent yields. This conversion offers a total synthesis of (±)-cherylline 16g, an amaryllidaceae alkaloid.

Keywords: Tetrahydroisoquinolines, Pummerer reaction

Introduction

It is well known that the *in situ* formed thionium ion generated under acidic conditions from an α-sulfinylacyl precursor (Pummerer reaction) is a particularly powerful electrophilic group reacting efficiently with nucleophilic carbon species such as alkenes, aromatics and enol ethers. This reaction was successfully applied for the synthesis of various carbocycles and heterocycles.[1] Ishibashi *et al.* widely explored the reaction and used it as the key strategy for the synthesis of nitrogen heterocycles such as oxyindoles,[2] 3-oxo-1,2,3,4-tetrahydroisoquinolines,[3] 1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one,[4] and for the synthesis of alkaloids such as erythrinan[5] and cephalotaxine.[6]

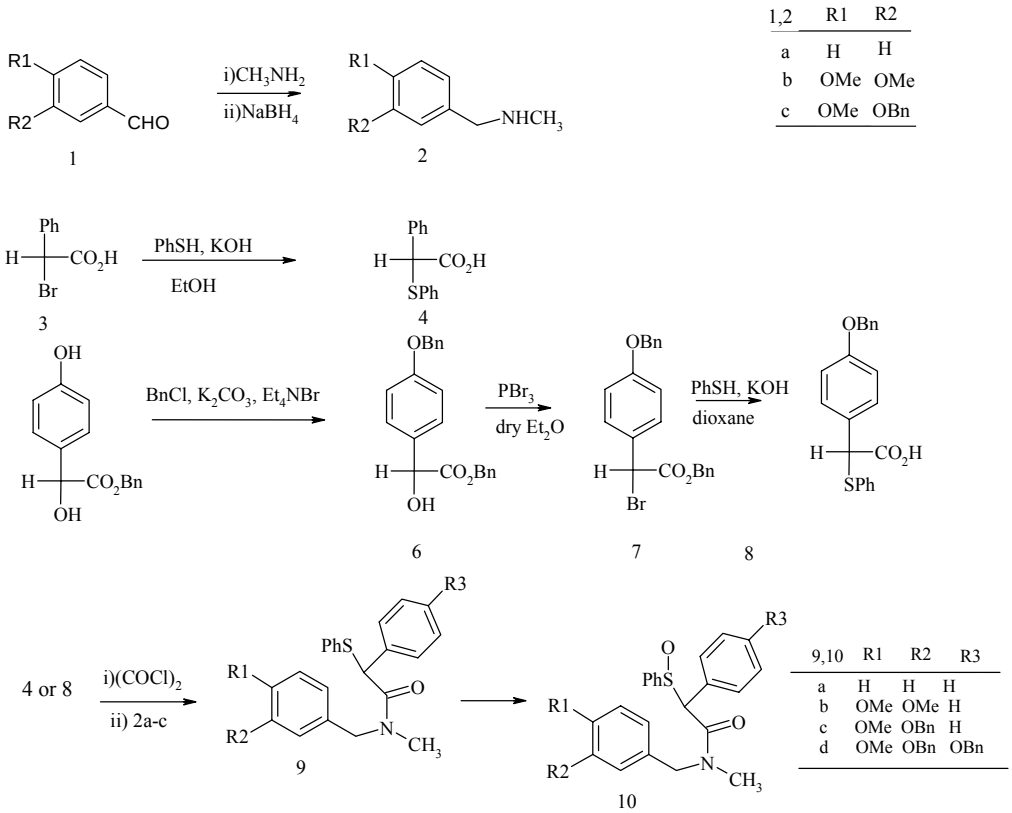


Scheme 1

In this paper we show that the intramolecular cyclization of *N*-benzyl-*N*-methyl-2-aryl-2-(phenylsulfinyl)acetamides provides a convenient method for the construction of the 4-aryl-1,2,3,4-tetrahydroisoquinoline ring system, a physiologically interesting class of compounds[7] including (±)-cherylline, an amaryllidaceae alkaloid[8] (Scheme 1).

Results and Discussion

The *N*-(arylmethyl)-*N*-methyl-2-aryl-2-(phenylsulfinyl)acetamides (10a−d) were prepared as follows (Scheme 2). Treatment of 2-bromophenylacetic acid (3) with potassium benzenethiolate in eyhanol under reflux provided 2-(phenylsulfanyl)acetic acid (4). The acid chloride prepared from 4 was condensed with the amines 2a−c giving rise to the corresponding amides 9a−c.



1,2	R1	R2
a	H	H
b	OMe	OMe
c	OMe	OBn

9,10	R1	R2	R3
a	H	H	H
b	OMe	OMe	H
c	OMe	OBn	H
d	OMe	OBn	OBn

Scheme 2

The preparation of (±)-2-(4-benzyloxyphenyl)-2-(phenylsulfanyl)acetic acid (8) started from (±)-2-(4-hydroxyphenyl)-2-hydroxyacetic acid (5) (Scheme 2). Alkylation of 5 with benzyl chloride in the presence of potassium carbonate and tetraethylammonium bromide (TEAB) in refluxing acetone gave benzyl (±)-2-(4-benzyloxyphenyl)-2-hydroxyacetate (6). Bromination of 6 with phosphorus tribromide in dry diethyl ether yielded benzyl (±)-2-(4-benzyloxyphenyl)-2-bromoacetate (7). Treatment of 7 with potassium benzenethiolate in dioxane under reflux afforded 8; the corresponding acid chloride was condensed with the amine 2c and afforded the amide 9d. The ^{1}H NMR spectra of 9a−d indicated a mixture of *E/Z* isomers with respect to the rotational isomerism of the amide group. Oxidation of the sulfides 9a−d with sodium metaperiodate in aqueous methanol or acetone afforded a diastereomeric mixture of sulfoxides 10a−d, respectively.

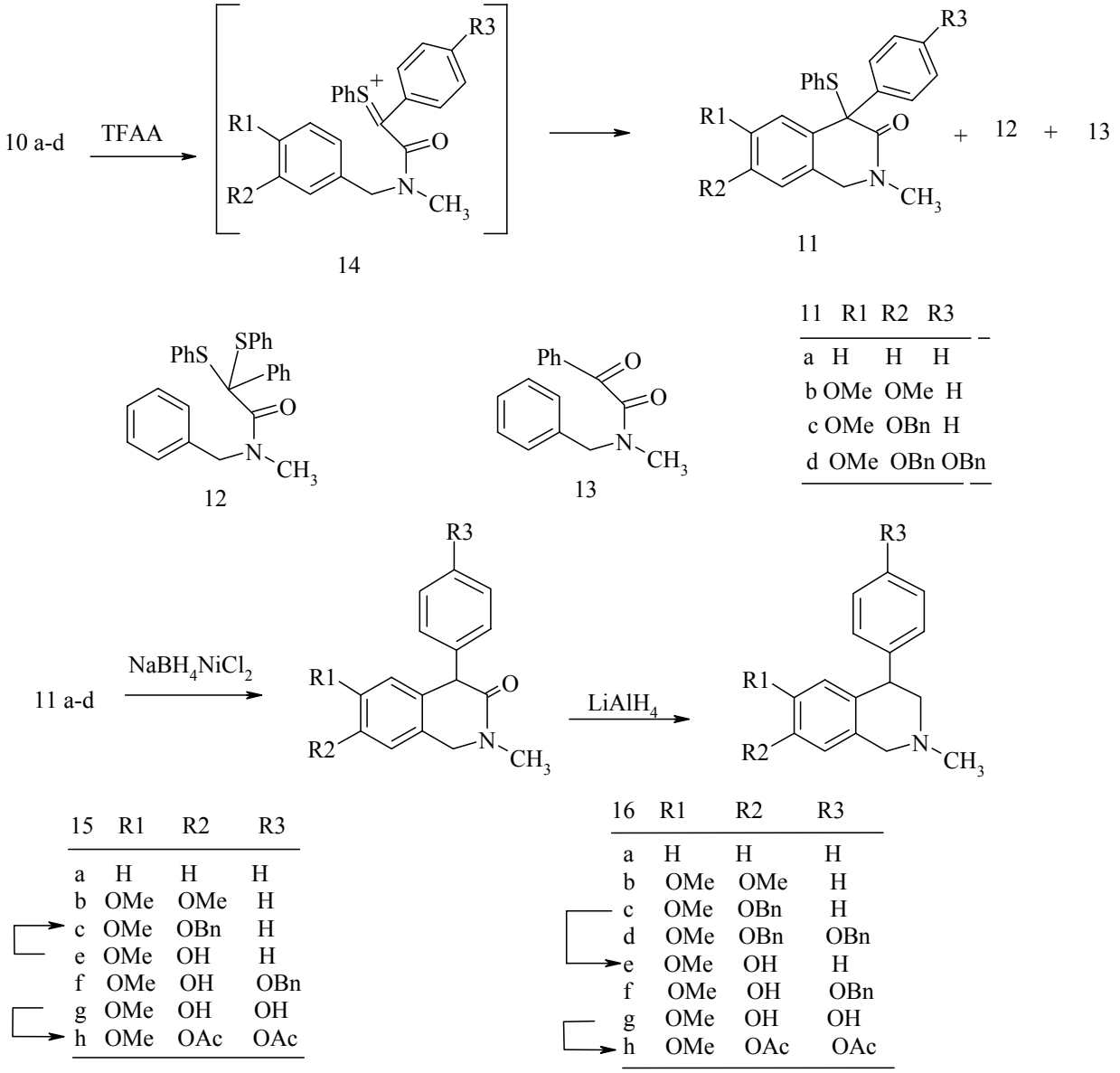
When a solution of the sulfoxide 10b in benzene was treated with TFAA at room temperature for 10 min, the expected cyclization was readily induced, and 6,7-dimethoxy-2-methyl-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydoisoquinolin-3-one (11b) was formed (Scheme 3). Cyclization of 10c also occurred under similar conditions and furnished 11c.

*00*cking the alkoxy groups enhancing the nucleophilicity of the phenyl ring of the *N*-benzylacetamide moiety, and on treatment with TFAA in benzene at room temperature the tetrahydoisoquinolin-3-one 11a was obtained in only 20% yield together with non-cyclized products 12 and 13. Addition of $BF_3{\cdot}Et_2O$[9] to a benzene solution of 10a containing TFAA considerably improved the cyclization reaction and increased the yield of 11a at the expense of the side products 12 and 13. On the contrary, the sulfoxide 10d bearing a benzyloxy group in two benzene rings, when treated with TFAA in benzene at room temperature rapidly decomposed to give a complex mixture, and no products could be isolated from this reaction mixture. Previously, we noticed that this Pummerer-type cyclization in some cases[9a] was strongly dependent on the solvent used. Therefore, we carried out the reaction in several solvents and found that tetrahydrofuran (THF) dramatically improved the cyclization reaction. Thus, reaction of 10d with TFAA in THF induced the expected cyclization at room temperature leading to its completion within 10 min and furnishing 11d. Similarly, the reaction of 10c in THF afforded 11c, although the cyclization in this solvent was slower (300 min) compared with the reaction carried out in benzene as described above. These results demonstrate that the cyclization of 10 readily proceeds under mild conditions. The putative reaction intermediate, the sulfonium ion 14, features the C=S bond in conjugation with the 2-aryl group. This is considered to favor the formation of the electrophilic intermediate 14, and, in turn, facilitates the intramolecular cyclization reaction.

We achieved the conversion of the 4-aryl-2-methyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-ones 11 into 4-aryl-2-methyl-1,2,3,4-tetrahydroisoquinolines 16 by conventional reductive steps (Scheme 3).

Reductive removal of the phenylsulfanyl group of 11a−b occurred on treatment with $NaBH_4$−$NiCl_2$ in methanol−THF to afford 2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-ones 15a−b. Subsequent reduction of 15a−b with lithium aluminum hydride (LAH) furnished the

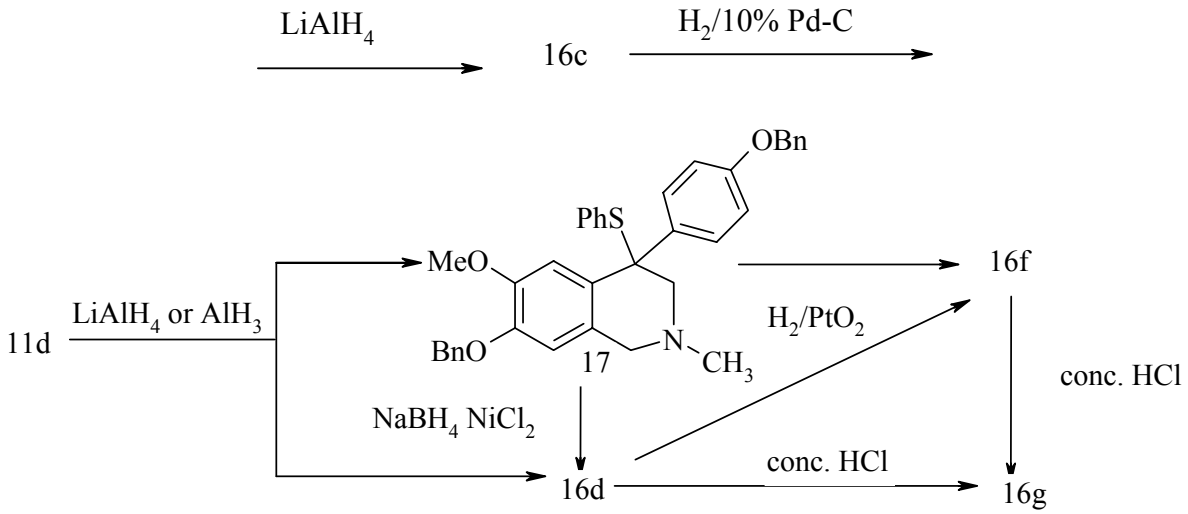
corresponding 2-methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines 16a−b



Scheme 3

Desulfurization of 7-benzyloxy-6-methoxy-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one 11c by treatment with $NaBH_4$−$NiCl_2$ in MeOH-THF also caused concomitant debenzylation and afforded 7-hydroxy-6-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (15e). The 7-benzyloxy derivative 15c was prepared by benzylation of 15e, which, in turn, upon reduction with LAH provided the tetrahydroisoquinoline derivative 16c. Reductive desulfurization of 11d with $NaBH_4$−$NiCl_2$ proceeded with concomitant debenzylation and gave two products, 4-(4-benzyloxyphenyl)-7-hydroxy-6-methoxy-2-methyl-

1,2,3,4-tetrahydroisoquinolin-3-one (15f) and 7-hydroxy-4-(4-hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (15g). Sequential treatment of 11d with $NaBH_4$−$NiCl_2$ and conc. HCl produced 15g as sole product. Reduction of 15g with LAH in diethyl ether followed by acetylation of the product yielded (±)-cherylline diacetate 16h, though in rather low yield (12%). This poor result may be due to the extreme insolubility of 15g in the solvent used. This difficulty was overcome as follows (Scheme 4). We incidentally found that treatment of 11c with LAH in THF caused not only the reduction of the lactam carbonyl group but also the reductive removal of the phenylsulfanyl group to give 16c in one step. Hydrogenation of 16c with 10% Pd−C caused the removal of the benzyl group to afford (±)-4'-dehydroxycherylline 16e.



Scheme 4

Reduction of 11d with LAH yielded two products, dibenzyl cherylline 16d and dibenzyl 4-phenylthiocherylline 17. On the other hand, treatment of 11d with aluminum hydride selectively reduced the lactam carbonyl group and produced 17. Reductive desulfurization of 17 with $NaBH_4$−$NiCl_2$ afforded 16d, together with the partially debenzylated product 16f. Dibenzyl cherylline 16d was resistant to debenzylation under hydrogenolytic conditions. For example, hydrogenation of 16d over 10% Pd−C in MeOH failed, while hydrogenation over PtO_2 in acetic acid selectively caused debenzylation of the 7-benzyloxy group to afford 4'-*O*-benzyl cherylline 16f. Hydrolysis of either 16d or 16f with conc. HCl furnished (±)-cherylline 16g in good yields. In summary, the synthesis of (±)-cherylline 16g starting from the amine 2c was achieved in five steps with a total yield of about 35%.

In conclusion, we present a convenient synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinolines using the Pummerer reaction as a key step. The acid-induced intramolecular cyclization under C−C-bond formation between the α-C of 2-aryl-2-(phenylsulfinyl)acetamides and the *ortho*-C of the attached *N*-arylmethyl group effectively proceeded under extremely mild conditions. This

method is applicable for the construction of 4-aryl-1,2,3,4-tetrahydroisoquinoline ring systems[10] bearing an acid labile group such as the benzyloxy substituent, and it offers a useful alternative synthesis of (±)-cherylline 16g in addition to the many previously reported ones.[11]

Experimental Section

General Procedures. Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus. Thin layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F_{254} plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). Medium pressure liquid chromatography (MPLC) was performed on Kusano CIG prepacked column. Spectral data were obtained with the following instruments: JASCO FT/IR-5000 spectrometer (IR), Hitachi U-3200 spectrophotometer (UV), JEOL JNM-EX90 (^{1}H NMR 90 MHz, ^{13}C NMR 22.5 MHz) or JEOL JMS-AL 300 (^{1}H NMR 300 MHz, ^{13}C NMR 75.0 MHz), JEOL JMS-AX 505H (Low resolution LRMS and high resolution HRMS at 70 eV (EI-MS) or at 270 eV (CI-MS, reactant gas *iso*butane) using direct or GC-MS inlet systems.
The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4 or $MgSO_4$ before concentration *in vacuo*. *N*-Arylmethyl-*N*-methylamines 2a−c were prepared according to the known method by condensation of arylaldehydes 1a−c with methylamine followed by reduction with $NaBH_4$.[12]

2-Phenyl-2-(phenylsulfanyl)acetic acid (4). A solution of 2-bromo-2-phenylacetic acid (3) (9.7 g, 45.1 mmol) and KOH (3.3 g, 58.9 mmol) in EtOH (75 mL) was slowly added to a solution of KOH (3.3 g, 58.9 mmol) and benzenethiol (5.0 g, 45.0 mmol) in EtOH (75 mL) at rt under argon atmosphere. The mixture was refluxed under stirring for 4 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was acidified with 5% HCl and extracted with $CHCl_3$. Recrystallization of the residual solid from $CHCl_3$-Et_2O gave 4 (9.1 g, 83%) as pale yellow plates, mp 100−103 °C (lit.[13] mp 102−103 °C); IR (KBr): 1694, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 4.89 (s, 1H), 6.02 (br s, 1H), 7.0−7.8 (m, 10H); LRMS *m/z* 244 (M^+), 199 (base peak). Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.43; H, 5.10.
Benzyl 2-(4-benzyloxyphenyl)-2-hydroxyacetate (6). A solution of (±)-4-hydroxymandelic acid (5) (10.0 g, 53.8 mmol), benzyl chloride (20 g, 157 mmol), K_2CO_3 (22 g, 159 mmol), and TEAB (2.3 g, 11.0 mmol) in acetone (150 mL) was refluxed under stirring for 24 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residual oil was chromatographed, eluting with ethyl acetate/hexane (1:3) to give 6 (12.9 g, 68%) as colorless needles from ethyl acetate, mp 100−102 °C. Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.62; H, 5.92.
Benzyl 2-(4-benzyloxyphenyl)-2-bromoacetate (7). Phosphorous tribromide (1.5 mL, 5.4 g, 20.3 mmol) was added to a solution of 6 (14.0 g, 40.2 mmol) in Et_2O (50 mL) under ice-cooling

and the mixture was stirred at rt for 2 h. Flash chromatography of the reaction mixture over SiO_2 with Et_2O gave an oily material. This was further chromatographed, eluting with ethyl acetate/hexane (1:20) to give 7 (16.0 g, 97%) as colorless prisms from $CHCl_3$-Et_2O, mp 51−54 °C; IR (KBr): 1744, 1607, 1512 cm^{-1}; ^1H NMR (90 MHz, CDC_3): δ 5.37 (1H, s), 5.06 (2H, s), 5.20 (2H, s), 6.9−7.5 (14H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 46.4, 67.7, 69.8, 114.9, 127.2, 127.7, 127.9, 128.2, 128.4, 130.0, 134.9, 136.4, 159.3, 168.0; LRMS *m/z* 410 (M^+), 91 (base peak); HRMS Calcd. for $C_{22}H_{19}O_3Br(M^+)$: 410.0517. Found 410.0477.

2-(4-Benzyloxyphenyl]-2-(phenylsulfanyl)acetic acid (8). A solution of 7 (13.0 g, 31.6 mmol) and KOH (2.7 g, 48.2 mmol) in dioxane (100 mL) was added to a solution of KOH and benzenethiol (3.25 mL, 3.5 g, 31.6 mmol) in dioxane (200 mL) at rt under argon atmosphere, and the mixture was refluxed for 3 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*, and the residue was diluted with 5% HCl and extracted with $CHCl_3$. The residual oil was chromatographed, eluting with ethyl acetate to give 8 (11.1 g, 99%) as colorless needles from Et_2O-hexane, mp 133−136 °C; IR (KBr): 1707, 1690, 1607, 1510 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 4.44 (1H, br s), 4.86 (1H, s), 5.05 (2H, s), 6.8−7.4 (14H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 55.6, 70.1, 115.1, 127.2, 127.4, 128.0, 128.1, 128.6, 129.1, 129.8, 132.6, 133.5, 136.7, 159.0, 176.3; LRMS *m/z* 350 (M^+), 91 (base peak). Anal. Calcd. for $C_{21}H_{18}O_3S$: C, 71.98; H, 5.18. Found: C, 71.92; H, 5.29.

General procedures for *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-2-phenyl-2-(phenylsulfanyl) acetamide (9b)

A solution of 8 (6.5 g, 26.6 mmol) and oxalyl chloride (16.9 g, 132.3 mmol) was stirred at rt for 2 h. Removal of excess oxalyl chloride by repeated evaporation under reduced pressure gave an oily material. To a solution of this chloride in $CHCl_3$ (50 mL) a solution of the amine 2b[14] (2.7 g, 26.7 mmol) and triethylamine (4.0 g, 22.1 mmol) in $CHCl_3$ (50 mL) was slowly added under ice-cooling, and the mixture was stirred at rt for 3 h. The residual oil was chromatographed eluting with $CHCl_3$/benzene (1:2) to give 9b (5.5 g, 57%) as a yellow gum: IR (neat): 1647, 1516 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.83, 2.94 (total 3H, each s), 3.70, 3.75, 3.85 (total 6H, each s), 4.41, 4.68 (total 2H, d, J = 15 Hz), 5.11, 5.14 (total 1H, each s), 6.4−6.8 (3H, m), 7.2−7.3 (10H, m); LRMS *m/z* 407 (M^+), 298 (base peak); HRMS Calcd. for $C_{24}H_{25}NO_3$ (M^+): 407.1555, found 407.1592.

***N*-Benzyl-*N*-methyl-2-phenyl-2-(phenylsulfanyl)acetamide (9a).** From 2a (7 g, 57.8 mmol) and 8 (14.2 g, 40.5 mmol); column chromatography (ethyl acetate/hexane 1:9) gave 9a (15.8 g, 79%) as a yellowish gum: IR (neat): 1646 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.82, 2.96 (total 3H, each s), 4.49, 4.55 (total 1H, each d, J = 15 Hz), 5.04, 5.16 (total 1H, each s), 6.9−7.6 (15H, m); LRCIMS *m/z* 348 ($M + H^+$); HRMS Calcd. for $C_{22}H_{21}NOS$ (M^+) 347.1344, found 347.1354.

***N*-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-2-phenyl-2-(phenylsulfanyl)acetamide (9c).** From 2c (4.0 g, 15.5 mmol) and 4 (5.7 g, 23.4 mmol); column chromatography (ethyl acetate/hexane 3:4) gave 9c (6.5 g, 87%) as colorless prisms from ethyl acetate-hexane, mp 116−119 °C; IR (KBr): 1628, 1514 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.75, 2.84 (total 3H,

each s), 3.84, 3.86 (total 3H, each s), 4.40, 4.34, 4.60 (total 2H, each d, *J* = 15 Hz), 4.95, 5.00 (total 2H, each s), 5.06, 5.12 (total 1H, each s), 6.4−6.9 (3H, m), 7.1−7.4 (15H, m); LRMS *m/z* 483 (M^+), 374 (base peak).

***N*-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-2-(4-benzyloxyphenyl)-2-(phenylsulfanyl) acetamide (9d).** From 2c (7.0 g, 27.2 mmol) and 8 (11.3 g, 32.3 mmol); column chromatography (ethyl acetate/hexane 7:10) gave 9d (14.7 g, 92%) as pale yellow gum: IR (neat): 1642, 1607, 1512 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.75, 2.84 (total 3H, each s, 3.84, 3.86 (total 3H, each s), 4.33, 4.40, 4.59 (total 2H, d, *J* = 15 Hz), 4.9−5.1 (5H, m), 6.4−7.4 (22H, m); LRMS m/z 590 (M^+), 480 (base peak).

General procedures for *N*-(3,4-Dimethoxybenzyl)-*N*-methyl-2-phenyl-2-(phenylsulfinyl) acetamide (10b)

A solution of 9b (4.0 g, 9.83 mmol) and $NaIO_4$ (3.2 g, 15.0 mmol) in MeOH (50 mL) and H_2O (30 mL) was heated under reflux for 1.5 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$ and washed with brine. The product was chromatographed, eluting with $CHCl_3$/benzene (1:2) to give 10b (3.0 g, 72%) as colorless needles from $CHCl_3$-Et_2O, mp 161−164 °C; IR (KBr): 1631, 1516, 1026 cm^{-1}; UV (EtOH, nm, ε): 233 (11400), 276 (4200); ^1H NMR (90 MHz, $CDCl_3$): δ 2.80, 2.98 (total 3H, each s), 3.77, 3.78, 3.84, 3.87 (total 6H, each s), 3.6−4.8 (3H, m), 6.5−7.5 (13H, m); LRMS *m/z* 298 (M^+ - SOPh), 151 (base peak).

***N*-Benzyl-*N*-methyl-2-phenyl-2-(phenylsulfinyl)acetamide (10a).** From 9a (15 g, 43.1 mmol); column chromatography (ethyl acetate/hexane 1:2) gave 10a (15.4 g, 98%) as a yellow gum: IR (neat): 1637 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$): δ 2.59, 2.80, 3.00 (total 3H, each s), 3.8−5.0 (3H, m), 6.4−8.0 (15H, m); LRFABMS *m/z* 364 (M + H^+); HRFABMS Calcd. for $C_{22}H_{22}NO_2S$ (M + H^+) 364.1372, found 364.1355.

N-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-2-phenyl-2-(phenylsulfinyl)acetamide (10c). From 9c (4.0 g, 8.2 mmol); column chromatography (ethyl acetate/hexane 1: 2) gave 10c (3.0 g, 72%) as colorless plates from ethyl acetate-hexane, mp 130−132 °C; IR (KBr): 1638, 1516, 1046 cm^{-1}; UV (EtOH, nm, ε): 275 nm (6600); ^1H NMR (90 MHz, $CDCl_3$): δ 2.71, 2.87 (total 3H, each s), 3.84, 3.87 (total 3H, each s), 4.4−5.1 (5H, m), 6.6−7.5 (8H, m); LRMS *m/z* 374 (M^+-SOPh), 91 (base peak).

***N*-(3-Benzyloxy-4-methoxybenzyl)-*N*-methyl-2-(4-benzyloxyphenyl)-2-(phenylsulfinyl) acetamide (10d).** From 9d (10 g, 18.8 mmol); column chromatography (ethyl acetate/hexane 1:2) gave 10d (9.0 g, 87%) as colorless needles from ethyl acetate-hexane, mp 78−81 °C; IR (KBr): 1638, 1607, 1512, 1048 cm^{-1}; UV (EtOH, nm, ε): 237 (23200), 275 (8500); ^1H NMR (90 MHz, $CDCl_3$): δ 2.71, 2.87 (total 3H, each s), 3.84, 3.86 (total 3H, each s), 4.4−5.2 (7H, m), 6.6−7.5 (22H, m). Anal. Calcd. for $C_{31}H_{30}NO_5S$: C, 70.43; H, 5.72; N, 2.65. Found: C, 70.21; H, 5.56, N, 2.70.

Pummerer reaction of 10a. i) A solution of TFAA (1.45 g, 6.9 mmol) in benzene (5 mL) was added to a solution of 10a (500 mg, 1.38 mmol) in benzene (45 mL) at rt, and the mixture was

stirred for 20 h under argon atmosphere. After removal of the solvent *in vacuo*, the product was chromatographed eluting with ethyl acetate/hexane (1:9) to give 12 (192 mg, 15%) and 13 (83 mg, 24%). Further elution with ethyl acetate/hexane (2:5) gave 11a (96 mg, 20%).

2-Methyl-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one (11a). Pale yellow prisms from ether, mp 136−138 °C; IR (KBr): 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.95 (3H, s), 3.36, 4.09 (total 1H, each d, *J* = 16 Hz), 6.8−7.7 (14H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.1, 51.8, 63.4, 123.8, 127.0, 127.3, 127.4, 128.0, 128.1, 129.0, 129.2, 130.6, 131.2, 131.3, 136.5, 137.6, 141.1, 168.2; LRCIMS *m/z* 346 ($M^+ + H$). Anal. Calcd. for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05. Found: C, 76.39; H, 5.65; N, 4.01.

***N*-Benzyl-*N*-methyl-2-phenyl-2,2-bis(phenylsulfanyl)acetamide (12).** Colorless prisms from ether, mp 148.5−150.5 °C; IR (KBr): 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.67 (3H, s), 4.45 (2H, s), 6.7−7.7 (20H, m); LRCIMS *m/z* 456 ($M^+ + H^+$), 346 (base peak).

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylacetamide (13).**[15] A pale yellow gum; IR (neat): 1679, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.85, 3.00 (total 3H, each s), 4.40, 4.74 (total 2H, each s), 7.1−8.3 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.3, 34.4, 49.8, 53.4, 127.7, 127.8, 128.1, 128.2, 128.7, 128.8, 128.9, 129.0, 129.5, 129.7, 134.68, 134.70, 133.0, 133.1, 134.8, 135.7, 167.1, 167.3, 191.4; LRCIMS *m/z* 254 ($M^+ + H$); HRMS Calcd. for $C_{16}H_{15}NO_2$ (M^+) 253.1101, found 253.1096.

ii) A solution of 10a (500 mg, 1.38 mmol) and TFAA (1.45 g, 6.9 mmol) in benzene (45 mL) was stirred at rt under argon atmosphere for 10 min. To this solution $BF_3{\cdot}Et_2O$ (0.59 g, 4.15 mmol) was added and the mixture was stirred at rt for 1 h. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The residual oil was chromatographed eluting with ethyl acetate/hexane (1:6) to give 12 (<1 mg) and 13 (65 mg, 19%). Further elution with ethyl acetate/hexane (1:2) gave 11a (248 mg, 52%).

6,7-Dimethoxy-2-methyl-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one (11b).

i) In benzene: TFAA (0.17 ml, 1.18 mmol) was added to a solution of 10b (100 mg, 1.38 mmol) in benzene (7 mL) at rt under argon atmosphere, and the mixture was stirred for 10 min at the same temperature. The residual oil was chromatographed eluting with $CHCl_3$, and the eluate was further purified by MPLC with ethyl acetate to give 11b (94 mg, 98%) as pale yellow plates from ethyl acetate-hexane, mp 149−152 °C; IR (KBr): 3458, 1643, 1520 cm^{-1}; UV (EtOH, nm, ε): 288 (4700); ^1H NMR (90 MHz, $CDCl_3$): δ 2.93 (3H), 3.29, 4.05 (each 1H, d, *J* = 16 Hz), 3.69, 3.85 (each 3H, s), 6.30, 6.55 (each 1H, s), 7.1−7.6 (10H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 35.1, 51.6, 55.9, 63.5, 105.7, 112.7, 123.9, 127.4, 128.0, 128.1, 129.0, 129.2, 131.4, 136.6, 141.2, 148.4, 148.6, 168.1; LRCIMS *m/z* 407 ($M^+ + H$), 57 (base peak); HRMS Calcd. for $C_{24}H_{23}NO_3S$ (M^+) 405.1396, found 405.1051.

ii) In THF: TFAA (0.17 mL, 240 mg, 1.18 mmol) was added to a solution of 10b. (100 mg, 1.38 mmol) in THF (7 mL) at rt under argon atmosphere, and the mixture was stirred for 5 h at the same temperature. The residual oil was chromatographed, eluting with $CHCl_3$. The eluate was further purified by MPLC with ethyl acetate/hexane (1/3) to give 11b (88 mg, 92%).

7-Benzyloxy-6-methoxy-2-methyl-4-phenyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one (11c). TFAA (2.8 mL, 4.1 g, 20.0 mmol) was added to a solution of 10c (2.0 g, 4.01 mmol) in benzene (70 mL) at rt under argon atmosphere, and the mixture was stirred for 1 h. The residual oil was chromatographed, eluting with 1/3 ethyl acetate/hexane to give 1.89 g (99%) of 11c as pale yellow plates from ethyl acetate-hexane: mp 137−139 ^{o}C; IR (KBr): 1651, 1516 cm^{-1}; UV (EtOH, nm, ε): 289 (4400); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.89 (3H, s), 3.17, 3.96 (each 1H, d, *J* = 16 Hz), 3.69 (3H, s), 5.11 (2H, s), 6.30, 6.66 (each 1H), 7.0−7.6 (15H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 35.0, 51.4, 55.9, 63.5, 70.9, 108.4, 113.2, 123.8, 127.2, 127.4, 127.9, 128.0, 129.0, 129.2, 129.7, 131.3, 136.6, 141.1, 147.5, 149.1, 168.0; LRCIMS *m/z* 482 (M + H^{+}), 218 (base peak). Anal. Calcd. for $C_{30}H_{27}NO_2S$: C, 74.82; H, 5.65; N, 2.91. Found: C, 74.57; H, 5.75; N, 3.08.

Pummerer reaction of 10d. i) In benzene: TFAA (0.12 ml, 169 mg, 0.83 mmol) was added to a solution of 10d (100 mg, 0.17 mmol) in benzene (7 mL) at rt under argon atmosphere, and the mixture was stirred for 15 min at the same temperature. After removal of the solvent *in vacuo*, the residual oil was chromatographed, eluting with ethyl acetate/hexane (1:2) but gave no characterizable product.

7-Benzyloxy-4-(4-benzyloxyphenyl)-6-methoxy-2-methyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinolin-3-one (11d). ii) In THF: TFAA (0.12 mL, 169 mg, 0.83 mmol) was added to a solution of 10d (100 mg, 0.17 mmol) in THF (7 mL) at rt under argon atmosphere, and the mixture was stirred at the same temperature for 10 min. The residual oil was chromatographed eluting with ethyl acetate/hexane (1:2) to give 11d (91 mg, 94%) as pale yellow gum; IR (neat): 1651, 1607, 1510 cm^{-1}; UV (EtOH, nm, ε): 284 (4700); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.88 (3H, s), 3.18, 3.95 (each 1H, d, *J* = 16 Hz), 3.72 (3H, s), 5.06, 5.11 (each 2H, s), 6.30, 6.72 (each 1H, s), 6.8−7.5 (19H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 35.1, 51.5, 56.0, 63.0, 70.1, 71. 0, 108.5, 111.3, 114.3, 123.9, 127.2, 127.5, 127.9, 128.0, 128.0, 128.5, 129.1, 129.7, 130.3, 131.6, 133.4, 136.5, 136.7, 137.0, 147.5, 149.1, 158.1, 168.1; LRMS *m/z* 478 (M^{+} -SPh), 110 (base peak).

Reductive Desulfurization of 11a-c. General Procedure. To a stirred solution of 11 (a, b or c) (1 mol eq) in MeOH-THF (3:1) (100 mL) with $NiCl_2 \cdot 6H_2O$ (7 mol eq) was added under ice-cooling and in small portions $NaBH_4$ (21 mol eq). After the addition was complete stirring was continued at rt for 20 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The products were purified by recrystalization or column chromatography.

2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-one (15a). From 11a (1 g, 2.46 mmol); recrystalization from ether gave 15a (611 mg, 89%) as pale yellow needles, mp 119−121 ^{o}C; IR (KBr): 1625 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.09 (3H, s), 4.31, 4.64 (each 1H, d, *J* = 16 Hz), 4.87 (1H, s), 7.1−7.4 (9H, m,); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.9, 52.4, 52.6, 125.2, 127.0, 127.1, 127.8, 127.9, 128.5, 128.6, 131.5, 135.6, 138.9, 169.9; LRMS *m/z* 237 (M^{+}), 179 (base peak). Anal. Calcd. for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.11; H, 6.53; N, 5.85.

6,7-Dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (15b). From 11b (620 mg, 1.53 mmol); column chromatography ($CHCl_3$) gave 15b (332 mg, 73%) as a yellow

gum: IR (KBr): 3449, 1643, 1518 cm^{-1}; UV (EtOH, nm, ε): 286 (2200); ^1H NMR (90 MHz, $CDCl_3$): δ 3.07 (3H, s), 3.80, 3.90 (each 3H, s), 4.23, 4.64 (each 1H, d, *J* = 16 Hz), 4.77 (1H, s), 6.57, 6.71 (each 1H, s), 7.1−7.3 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 34.7, 52.1, 52.3, 55.9, 56.0, 108.1, 111.0, 123.3, 127.0, 127.5, 127.9, 128.5, 139.4, 148.2, 148.9, 169.7; LRMS *m/z* 297 (M^+), 297 (base peak).

7-Hydroxy-6-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (15e). From 11c (1.5 g, 3.12 mmol); recrystallization from ethyl acetate-hexane gave 15e (620 mg, 73%) as pale yellow needles, mp 255−258 °C; IR (KBr): 1611 cm^{-1}; UV (EtOH, nm, ε): 287 (2900); ^1H NMR (90 MHz, $CDCl_3$): δ 3.06 (3H, s), 3.81 (3H, s), 4.18, 4.59 (each 1H, d, *J* = 16 Hz), 4.76 (1H, s), 5.69 (1H, s), 6.55, 6.79 (each 1H, s), 7.0−7.3 (5H, m); LRMS *m/z* 283 (M^+), 283 (base peak).

7-Benzyloxy-6-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinolin-3-one (15c). A solution of 15e (0.5 g, 1.77 mmol), benzyl chloride (247 mg, 1.94 mmol), and K_2CO_3 (244 mg, 1.77 mmol) in acetone (100 mL) was refluxed for 26 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The residue was extracted with $CHCl_3$, and the extract was washed with 10% NaOH and brine. Recrystallization of the residual solid from ethyl acetate-hexane gave 15c (350 mg, 53%) as colorless needles, mp 123−126 °C; IR (KBr): 1651, 1516 cm^{-1}; UV (EtOH, nm, ε): 285 (4100); ^1H NMR (90 MHz, $CDCl_3$): δ 3.02 (3H, s), 3.77 (3H, s), 4.14, 4.56 (each 1H, d, *J* = 16 Hz), 4.75 (1H, s), 5.14 (2H, s), 6.58, 6.73 (each 1H, s), 7.0−7.5 (10H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 34.7, 52.1, 52.1, 56.0, 71.3, 111.0, 111.5, 123.3, 127.0, 127.2, 127.8, 128.2, 128.5, 136.9, 139.4, 147.3, 149.6, 169.6; LRMS *m/z* 373 (M^+), 91 (base peak). Anal. Calcd. for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 76.30; H, 6.28; N, 3.68.

Reductive Desulfurization of 11d. i) To a stirred solution of 11d (0.7 g, 1.19 mmol) and $NiCl_2 \cdot 6H_2O$ (2.0 g, 8.40 mmol) in MeOH-THF (3:1) (20 mL) was added in small portions and under ice-cooling $NaBH_4$ (1.0 g, 26.4 mmol). After the addition was complete stirring was continued at rt for 1 h. After removal of inorganic precipitates by filtration, the filtrate was concentrated *in vacuo*. The product was chromatographed eluting with $CHCl_3$, and the eluate was further purified by preparative TLC developed with $CHCl_3$ /MeOH (9.5:10) to give 15f (120 mg, 26%) and 15g (108 mg, 30%).

4-(4-Benzyloxyphenyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquino-lin-3-one (15f). Colorless needles from $CHCl_3$-Et_2O, mp 245−247 °C; IR (KBr): 1615, 1510 cm^{-1}; UV (EtOH, nm, ε): 229 (10000), 284 (3000); ^1H NMR (90 MHz, $CDCl_3$): δ 3.05 (3H, s), 3.82 (3H, s), 4.17, 4.57 (each 1H, d), 4.70 (1H, s), 5.01 (2H, s), 5.64 (1H, s), 6.54, 6.78 (each 1H, s), 6.86, 7.06 (each 2H, d, *J* = 9 Hz), 7.2−7.5 (5H, m); LRMS *m/z* 389 (M^+), 91 (base peak); HRMS Calcd. for $C_{24}H_{23}NO_4$ (M^+): 389.1624, found 389.1612.

7-Hydroxy-4-(4-hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (15g). Colorless needles from $CHCl_3$ -MeOH, mp 275−277 °C; IR (KBr): 3322, 1601, 1512 cm^{-1}; ^1H NMR (pyridine-d_5): δ 3.00 (3H, s), 3.67 (3H, s), 4.15, 4.60 (each 1H, d, *J* = 16 Hz), 5.01 (1H, s), 6.85, 7.13 (each 1H, s), 7.13, 7.40 (each 2H, d, *J* = 9 Hz); LRMS *m/z* 299 (M^+, base peak).

Anal. Calcd. for $C_{17}H_{17}NO_4 \cdot 0.5\ H_2O$: C, 66.19; H, 5.56; N, 4.55. Found: C, 66.80; H, 5.86; N, 4.54.

ii) 11d (0.5 g, 0.87 mmol) was reduced with $NaBH_4$ (0.7 g, 18.4 mmol) and $NiCl_2 \cdot 6H_2O$ (1.4 g, 5.88 mmol) as described under I). A solution of the crude product in EtOH-$CHCl_3$ (2:1) (15 mL) and conc. HCl (15 mL) was refluxed for 4 h. After concentration of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The residual oil was chromatographed, eluting with $CHCl_3$/MeOH (9:10) to give 15g (152 mg, 60%).

7-Acetoxy-4-(4-acetoxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (15h).A solution of 15g (80 mg, 0.27 mmol) in Ac_2O (2 mL, 2.2 g, 21.2 mmol) and pyridine (4 mL, 3.9 g, 49.5 mmol) was allowed to stand at rt for 17 h. The reaction mixture was diluted with $CHCl_3$, and the organic layer was washed, in turn, with 10% HCl, 10% NaOH, and brine. The residual oil was chromatographed, eluting with ethyl acetate/hexane (3:4) to give 15h (102 mg, 99%) as a colorless gum; IR (KBr): 1765, 1651, 1506 nm^{-1}; UV(EtOH, nm, ε): 278 (3000); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.27, 2.33 (each 3H, s), 3.05 (3H, s), 3.76 (3H, s), 4.19, 4.58 (each 1H, d, *J* = 16 Hz), 4.81 (1H, s), 6.66, 6.94 (each 1H, s), 6.98, 7.17 (each 2H, d, *J* = 9 Hz); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 20.5, 21.0, 34.8, 51.6, 51.9, 56.0, 112.1, 119.8, 121.6, 123.7, 128.9, 133.6, 136.0, 138.8, 149.8, 150.9, 168.9, 169.0, 169.3; LRMS *m/z* 383 (M^+), 83 (base peak).

Reduction of 15 with $LiAlH_4$.

General experimental procedure

To a solution of 15 (1 molar eq) in dry THF (30−100 mL) was added under ice-cooling $LiAlH_4$(1 molar eq), and the mixture was refluxed for 1−2 h. Et_2O saturated with water was added to the reaction mixture, and insoluble material was filtered off. The product was chromatographed to give 16. In the case of 15g the starting material (52%) was recovered, and the product 16g was characterized as the diacetate 16h (12%).

2-Methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (16a). From 15a (200 mg, 0.84 mmol); column chromatography (ethyl acetate/hexane 2:3) gave 16a (119 mg, 63%) as pale yellow prisms from Et_2O, mp 29−31 °C (lit.[10] HCl salt, mp 169−174 °C); IR (KBr): 1598 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (3H, s), 2.57 (1H, dd, *J* = 8, 11 Hz), 3.03 (1H, ddd, *J* = 1, 6, 11 Hz), 3.61, 3.76 (each 1H, d, *J* = 15 Hz), 4.28 (1H, br dd, *J* = 6, 8 Hz), 6.8−7.7 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.95, 46.00, 58.5, 61.9, 125.9, 126.2, 126.3, 126.4, 128.3, 129.1, 129.4, 135.2, 137.1, 144.7; LRMS *m/z*: 223 (M^+), 179 (base peak); HRMS Calcd. for $C_{16}H_{17}N$ (M^+): 223.1362, found 223.1389.

6,7-Dimethoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (16b). From 15b (530 mg, 1.78 mmol); column chromatography ($CHCl_3$) gave 16b (400 mg, 79%) of as a yellow oil; IR (KBr): 1514 cm^{-1}; UV (EtOH, nm, ε): 288 (3300); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.41 (3H, s), 2.52 (1H, dd, *J* = 8, 11 Hz), 3.00 (1H, ddd, *J* = 1, 5, 11 Hz), 3.61 (2H, br s), 3.64, 3.86 (each 3H, s), 4.20 (1H, br dd, *J* = 5, 8 Hz), 6.34, 6.57 (each 1H, s), 7.1−7.4 (5H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 45.3, 45.6, 55.5, 57.9, 61.7, 108.7, 111.9, 126.1, 127.3, 128.0, 128.7, 128.7, 144.6, 147.3, 147.4.

16b·HCl: Colorless prisms from MeOH, mp 247−248 °C (lit.[10] mp 185−187 °C); LRMS *m/z* 283 (M^+− HCl), 209 (base peak). Anal. Calcd. for $C_{18}H_{23}NO_2Cl$: C, 67.59; H, 6.93; N, 4.34. Found: C, 67.20; H, 6.92; N, 4.06.

7-Benzyloxy-6-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (16c). From 15c (1.5 g, 4.02 mmol); recrystallization from ethyl acetate gave 16c (816 mg, 71%) as colorless plates, mp 136−139 °C; IR (KBr): 1520 cm^{-1}; UV(EtOH, nm, ε): 286 (4200); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.38 (3H, s), 2.50 (1H, dd, *J* = 8, 11 Hz), 2.98 (1H, dd, *J* = 5, 11 Hz), 3.54 (2H, br s), 3.64 (3H, s), 4.20 (1H, br dd, *J* = 5, 8 Hz), 5.11 (2H, s), 6.37, 6.60 (each 1H, s), 7.1−7.5 (10H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 45.6, 45.9, 56.0, 58.1, 62.0, 71.2, 111.8, 112.8, 126.4, 127.3, 127.5, 127.7, 128.3, 128.5, 129.0, 129.6, 137.3, 144.8, 146.8, 148.4; LRMS *m/z* 359 (M^+):, 91 (base peak). Anal. Calcd. for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.30; H, 7.00; N, 4.02.

Reduction of 11c with $LiAlH_4$. To a solution of 11c (500 mg, 1.04 mmol) in dry THF (50 mL) was added under ice-cooling $LiAlH_4$ (79 mg, 2.08 mmol), and the mixture was refluxed for 2.5 h. Et_2O saturated with water was added to the reaction mixture, and insoluble material was filtered off. The product was chromatographed eluting with ethyl acetate/hexane (1:2) to give 16c (170 mg, 46%).

7-Hydroxy-6-methoxy-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (16e). A solution of 16c (0.5 g, 1.40 mmol) in MeOH (50 mL) was hydrogenated over 10% Pd−C under atmospheric pressure at rt for 2.5 h. After removal of the catalyst by filtration, the residual oil was chromatographed eluting with ethyl acetate to give 16e (375 mg, 99%) as colorless needles from benzene, mp 165−166 °C (lit.[11k] mp 161−162 °C); IR (KBr): 1600, 1537 cm^{-1} ; UV (EtOH, nm, ε): 288 (3700); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.39 (3H, s), 2.49 (1H, dd, *J* = 8, 11 Hz), 2.99 (1H, ddd, *J* = 1, 5, 11 Hz), 3.49, 3.66 (each 1H, d, *J* = 15 Hz), 3.64 (3H, s), 4.20 (1H, dd, *J* = 5, 8 Hz), 6.30, 6.60 (each 1H, s), 7.0−7.4 (5H, m,); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 45.5, 45.8, 55.8, 57.9, 62.0, 111.4, 112.0, 126.4, 128.0, 128.2, 128.3, 129.0, 144.3, 144.8, 145.6; LRMS *m/z* 269 (M^+), 165 (base peak); HRMS Calcd. for $C_{17}H_{19}NO_2$(M^+): 269.1413, found 269.1367.

16e·HCl: Colorless prisms from MeOH, mp 247−250 °C. Anal. Calcd. for $C_{17}H_{20}NO_2$ Cl: C, 66.77; H, 6.59; N, 4.58. Found: C, 66.61; H, 6.56; N, 4.44.

Reduction of 11d with $LiAlH_4$. A solution of 11d (0.5 g, 0.85 mmol) and $LiAlH_4$ (65 mg, 1.71 mmol) in THF (20 mL) was refluxed for 24 h. After decomposition of excess hydride with 10% NaOH, the precipitated inorganic material was removed by filtration. The filtrate was extracted with $CHCl_3$. The residual oil was chromatographed eluting with ethyl acetate/hexane (1:2) to give 16d (237 mg, 60%) and 17 (103 mg, 25%).

7-Benzyloxy-4-(4-benzyloxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (16d). Colorless needles from CH_2Cl_2-Et_2O, mp 136−138 °C (lit.[11h] mp 144−145 °C); IR (KBr): 1609, 1510 cm^{-1}; UV (EtOH, nm, ε): 278 (3600), 283 (3800); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.34 (3H, s), 2.46 (1H, dd, *J* = 8, 11 Hz), 2.96 (1H, dd, *J* = 6, 11 Hz), 3.53 (2H, s), 3.65 (3H, s), 4.14 (1H, br dd, *J* = 6, 8 Hz), 5.04, 5.11 (each 2H, s), 6.38, 6.58 (each 1H, s), 6.90, 7.11 (each 2H, d, *J* = 9 Hz), 7.2−7.5 (10H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 44.7, 45.8, 55.9, 58.0, 62.0, 69.9,

71.0, 111.7, 112.7, 114.6, 127.2, 127.4, 127.4, 127.6, 127.8, 128.4, 129.8, 129.9, 137.1, 137.2, 137.2, 146.6, 148.2, 157.4; LRMS *m/z* 466 (M^+), 91 (base peak). Anal. Calcd. for $C_{31}H_{31}NO_3$: C, 79.97; H, 6.71; N, 3.01. Found: C, 79.11; H, 6.73; N, 2.98.

7-Benzyloxy-4-(4-benzyloxyphenyl)-6-methoxy-2-methyl-4-(phenylsulfanyl)-1,2,3,4-tetrahydroisoquinoline (17). A yellow gum; IR (neat): 1607, 1510 cm^{-1}; UV (EtOH, nm, ε): 278 (4000), 285 (4100); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.25 (3H, s), 2.84, 3.07 (each 1H, d, *J* = 12 Hz), 3.22 , 3.50 (each 1H, d, *J* = 15 Hz), 3.64 (3H, s), 5.05, 5.12 (each 2H, s), 6.52 (1H, s, 5-H), 6.8−7.5 (20H, m); ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 45.6, 55.8, 58.0, 59.5, 66.9, 69.9, 70.9, 113.3, 114.0, 114.2, 127.3, 127.4, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 129.4, 129.7, 133.5, 135.7, 137.0, 137.6, 147.1, 147.6, 157.6; LRMS *m/z* 465 (M^+−SPh), 91 (base peak).

Reduction of 11d with AlH_3. A solution of 11d (280 mg, 0.48 mmol) in dry Et_2O (10 mL) was added to a solution of AlH_3 in dry Et_2O (20 mL) prepared *in situ* from $LiAlH_4$ (130 mg) and $AlCl_3$ (152 mg) at 0 °C under argon atmosphere. The mixture was stirred at rt for 2 h. The reaction mixture was diluted with 5% NH_4OH and extracted with $CHCl_3$. The residual solid was chromatographed eluting with ethyl acetate/hexane (1:2) to give 17 (240 mg, 88%).

Desulfurization of 17 with $NiCl_2$−$NaBH_4$. To a solution of 17 (130 mg, 0.23 mmol) and $NiCl_2·6H_2O$ (378 mg, 1.59 mmol) in MeOH-THF (3:1) (10 mL) at 0 °C was added $NaBH_4$ (180 mg, 4.74 mmol), and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The residual oil was chromatographed eluting with ethyl acetate to give 16d (32 mg, 30%). Further elution with $CHCl_3$ gave 16f (21 mg, 25%).

4-(4-Benzyloxyphenyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (16f). Colorless prisms from $CHCl_3$-Et_2O, mp 179−182 °C; IR (KBr): 1611, 1512 cm^{-1}; UV (EtOH, nm, ε): 278 (5400), 283 (5500); ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.39 (3H, s), 2.47 (1H, dd, *J* = 8, 11 Hz), 2.96 (1H, dd, *J* = 6, 11 Hz), 3.47 (1H, d, *J* = 14 Hz), 3.65 (1H, d, *J* = 14 Hz), 3.66 (3H, s), 4.15 (1H, dd, *J* = 6, 8 Hz), 5.04 (2H, s), 6.32, 6.61 (each 1H, s), 6.90, 7.11 (each 2H, d, *J* = 9 Hz), 7.2−7.4 (5H, m); LRMS *m/z* 375 (M^+), 91 (base peak); HRMS Calcd. for $C_{24}H_{25}NO_3$(M^+): 375.1831, found 375.1829.

Catalytic Debenzylation of 16d. A solution of 16d (160 mg, 0.34 mmol) in AcOH (20 mL) was hydrogenated over PtO_2 (16 mg) at rt under atmospheric pressure for 2.5 h. After removal of the catalyst by filtration, the filtrate was concentrated *in vacuo* to dryness. The residual solid was chromatographed eluting with 1/2 ethyl acetate/hexane to give 60 mg (47%) of 16f and unchanged starting material (27mg, 17%).

4-(4-Hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol[(±)-cherylline] (16g).[11h] A solution of 16d (100 mg, 0.22 mmol) in EtOH (10 mL) and conc. HCl (5 mL) was refluxed for 4 h. After evaporation of the solvent *in vacuo*, the residue was treated with 5% NH_4OH and extracted with $CHCl_3$. The residual solid was chromatographed, eluting with $CHCl_3$/MeOH (9:10) to give 16g (47 mg, 77%) as colorless needles from CH_3Cl−MeOH, mp 214−217 °C (lit.[11a,b] mp 215−216 °C); IR (KBr): 3424, 1516 cm^{-1}; UV(EtOH, nm, ε): 281 (4300), 285 (4300); ^{1}H NMR (90 MHz, acetone-d_6): δ 2.33 (3H, s), 2.45 (1H, dd, *J* = 7, 11 Hz), 2.86 (1H, dd, *J* = 5, 11 Hz), 3.49 (2H, s), 3.60 (3H, s), 4.04 (1H, br dd, *J* = 5, 7 Hz), 6.37, 6.55 (each 1H, s), 6.73, 7.03 (each 2H, d, *J* = 9

Hz), 7.95 (2H, s); ^{13} C NMR (22.5 MHz, acetone-d_6): δ 45.9, 46.6, 56.7, 59.0, 63.2, 113.3, 116.2, 129.3, 129.8, 131.0, 137.6, 146.1, 147.3, 157.0; LRMS *m/z* 285 (M^+), 83 (base peak); HRMS Calcd. for $C_{17}H_{19}NO_3$ (M^+): 285.1365, found 285.1368.

Hydrolytic Debenzylation of 16f. A solution of 16f (30 mg, 0.08 mmol) in EtOH (10 mL) and conc. HCl (5 mL) was refluxed for 4 h. After evaporation of the solvent *in vacuo*, the residue was treated with 5% NH_4OH and extracted with $CHCl_3$. The residual solid was chromatographed, eluting with $CHCl_3$/MeOH (9:10) to give 16g (20 mg, 80%).

7-Acetoxy-4-(4-acetoxy)phenyl-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (16h). Acetylation of 16g with Ac_2O in pyridine gave 16h as a colorless gum; IR (neat): 1767, 1512 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.29 (6H, s), 2.41 (3H, s), 2.54 (1H, dd, *J* = 8, 11 Hz), 2.99 (1H, dd, *J* = 6, 11 Hz), 3.46 (1H, d, *J*= 13 Hz), 3.60 (3H, s), 3.74 (1H, d, *J* = 13 Hz), 4.24 (1H, br dd, *J* = 6, 8 Hz), 6.44, 6.76 (each 1H, s), 7.01, 7.22 (each 2H, d, *J* = 9 Hz); LRMS *m/z* 285 (M^+-COCH_3), 242 (base peak).

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References and Notes

1. Padwa, A.; Gunn, D.E., Jr.; Osterhout, H.*Synthesis* **1997**, 1353.
2. Tamura, Y.; Uenishi, J. I.; Maeda, H.; Choi, H. D.; Ishibashi, H. *Synthesis* **1981**, 534.
3. Tamura, Y.; Uenishi, J. I.; Choi, H. D.; Haruta, J. I.; Ishibashi, H. *Chem. Pharm. Bull.* **1984**, *32*, 1995.
4. Ishibashi, H.; Harada, S.; Okada, M.; Somekawa, M.; Kido, M.; Ikeda, M. *Chem. Pharm. Bull.* **1989**, *37*, 939.
5. (a) Ishibashi, H.; Harada, S.; Sato, K.; Ikeda, M.; Akai, S.; Tamura, Y. *Chem. Pharm. Bull.* **1985**, *33*, 5278. (b) Ishibashi, H.; Sato, K.; Ikeda, M. *J. Chem. Soc., Perkin Trans. I* **1985**, 605.
6. Ishibashi, H.; Kawanami, H.; Iriyama, H.; Ikeda, M. *Tetrahedron Lett.* **1982**, *23*, 2209.
7. Examples of physiologically active compounds having the 4-aryl-1,2,3,4-tetrahydroisoquinoline ring system are (a) Nomifensine. Hunt, P.; Kannengiesser, M. H.; Raynand, J. P. *J. Pharm. Pharmacol.* **1974**, *26*, 370; (b) 4-phenyl-1,2,3,4-tetrahydroisoquinoline. Satoh, M.; Ohta, S.; Nagao, T.; Hirobe, M.; Fukuda, H.; Ono, H. *Jpn. J. Pharmacol.* **1992**, *60*, 121.
8. Brossi, A.; Grethe, G.; Teitel, S.; Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1970**, *35*, 1100.

9. (a) Shinohara, T.; Toda, J.; Sano,T.*Chem. Pharm. Bull.* **1997**, *45*, 813. (b) Shinohara, T.; Takeda, A.; Toda, J.; Ueda, Y.; Kohno, M.; Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 918. (c) Shinohara, T.; Takeda, A.; Toda, J.; Terasawa, N.; Sano, T. *Heterocycles* **1997**, *46*, 555. (d) Shinohara, T.; Takeda, A.; Toda, J.; Sano, T..*Heterocycles* **1998**, *48*, 981. (e) Shinohara, T.; Takeda, A.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **1998**, *46*, 430.
10. Venkov, A.; Vodenicharov, D. *Synthesis* **1990**, 253.
11. (a) Brossi, A.; Grethe, G.; Teitel, S.; Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* **1970**, *35*, 1100. (b) Brossi, A.; Teitel, S. *Tetrahedron Lett*. **1970**, 417. (c) Brossi, A.; Teitel, S. *J. Org. Chem*. **1970**, 35, 3559. (d) Schwartz, M. A.; Scott, S. W. *J. Org. Chem*. **1971**, *36*, 1827. (e) Kametani, T.; Takahashi, K. *Tetrahedron,* **1975**, *31*, 235. (f) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548. (g) Irie, H.; Shiina, A.; Fushimi, T.; Katakawa, J.; Fujii, N.; Yajima, H. *Chem. Lett*. **1980**, 875. (h) Kametani, T.; Higashiyama, K.; Honda, T.; Otomatsu, H.; *J. Chem. Soc., Perkin Trans. 1* **1982**, 2935. (i) Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Heterocycles* **1983**, *20*, 1945. (j) Nomoto, T.; Nasui, N.; Takayama, H.; *J. Chem. Soc., Chem. Commun.* **1984**, 1646. (k) Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull*., **1985**, *33*, 3107. (l) Katakawa, J.; Yoshimatsu, H.; Yoshida, M.; Zhang, Y.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* **1988**, *36*, 3928. (m) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P.; Carpentier, J. F. *Tetrahedron Lett.* **1996**, *37*, 3697. (n) Couture, A.; Deniau, E.; Lebrun, S.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 789.
12. Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T., Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128.
13. Bonner, W. A. *J. Org. Chem.* **1967**, *32*, 2496.
14. Hayes, J. F. *Synlett* **1999**, 865.
15. Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc*. **1985**, *107*, 3235.

