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ASYMMETRIC SYNTHESIS OF *O*-METHYLNEFERINE†

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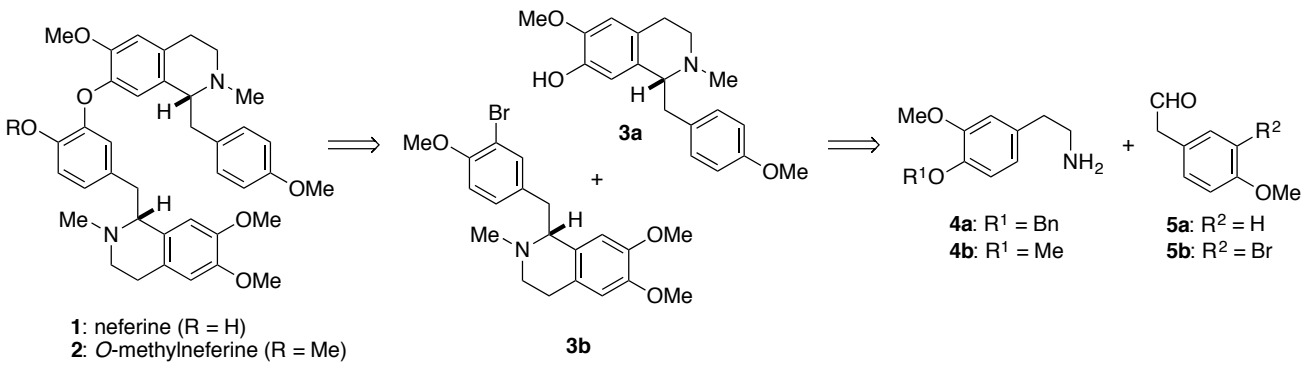
Abstract – Diastereoselective Pictet–Spengler reaction of 2-arylethylamine bearing an *N*-(*R*)-1-(1-naphthyl)ethylcarbamoyl group with arylacetaldehyde gave 1-benzyltetrahydroisoquinoline in good yield with moderate diastereoselectivity. The reaction was applied to asymmetric synthesis of *O*-methyl derivative of neferine, an alkaloid of the lotus embryo, *Nelumbo nucifera* Gaertner.

INTRODUCTION

During the course of our study on the chemical constituents and pharmacological activities of the embryo of lotus seeds, *Nelumbo nucifera* Gaertner,[1] we required an *O*-methyl derivative of neferine (**1**), one of the major alkaloids of lotus embryos.[2,3] For asymmetric synthesis of *O*-methylneferine (**2**), we decided to develop an efficient synthetic route, in which Pictet–Spengler isoquinoline synthesis and Ullmann coupling are used as key reactions. The retrosynthetic strategy is shown in Scheme 1. Biaryl ether linkage of two benzyltetrahydroisoquinoline units in *O*-methylneferine **2** would be formed by Ullmann coupling of the corresponding phenol **3a** (top) and bromide **3b** (bottom). Each isoquinoline (**3a** and **b**) was prepared by Pictet–Spengler reaction of the corresponding amine **4** and aldehyde **5**.



Scheme 1. Structure and Retrosynthetic Strategy of *O*-Methylneferine

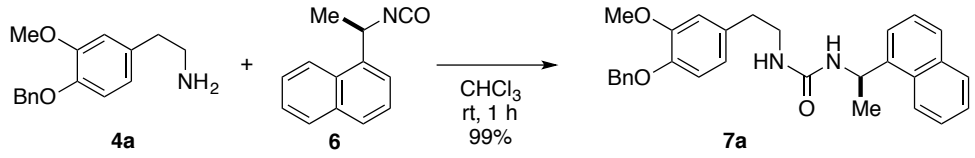
†This paper is dedicated to Prof. Kiyoshi Tomioka on the occasion of his 70th birthday.

The Pictet–Spengler reaction is one of the most efficient procedures to construct the tetrahydroisoquinoline skeleton as in the biosynthetic pathway;[4] however, in the asymmetric synthesis of benzylisoquinoline alkaloids, the Pictet–Spengler reaction is not often employed because of easy enolization of phenylacetaldehyde promoted by 2-arylethylamine.[5] To overcome the problem, carbamate and sulfonamide derivatives are used instead of free amine.[6] In such modifications, chiral auxiliaries are introduced on carbamoyl and sulfonyl groups to achieve diastereoselective cyclization.[7]

In this paper, we describe the development of a new diastereoselective Pictet–Spengler reaction mediated by the chiral auxiliary of the (*R*)-1-(1-naphthyl)ethylcarbamoyl group and asymmetric synthesis of *O*-methylneferine by using Ullmann coupling as the key reaction.

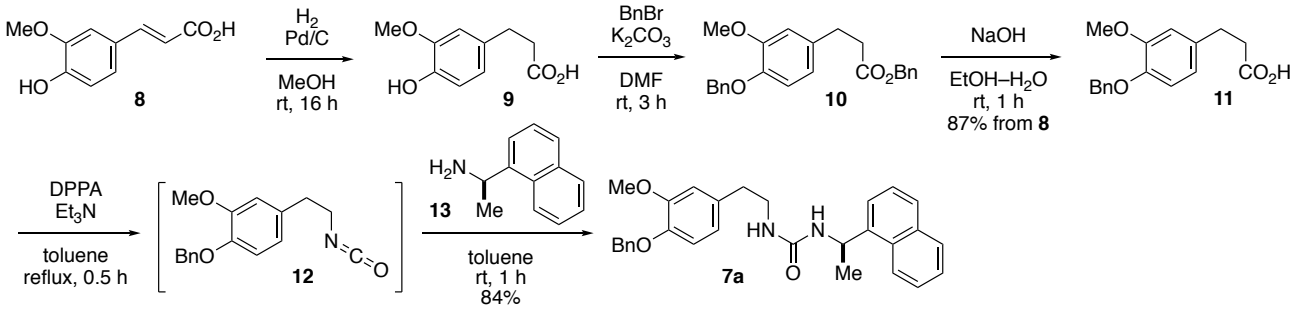
RESULTS AND DISCUSSION

While many diastereoselective Pictet–Spengler reactions of chiral carbamate derivatives have been developed as described above, chiral urea derivatives are rarely used for the Pictet–Spengler reaction.[8] We choose chiral urea **7** as a substrate for diastereoselective Pictet–Spengler reaction (Scheme 2). Urea **7a**, which consists of the top-half of *O*-methylneferine, is easily prepared by the reaction of 2-arylethylamine **4a**[9] and Pirkle reagent (*R*)-1-(1-naphthyl)ethyl isocyanate **6**.[10] This chiral auxiliary, (*R*)-1-(1-naphthyl)ethylcarbamoyl group, has often been used for the resolution of racemates, including tetrahydroisoquinolines, by forming diastereomers that are easily separable by column chromatography or recrystallization.[11]



Scheme 2. Preparation of Chiral Urea from Amine and Pirkle Reagent

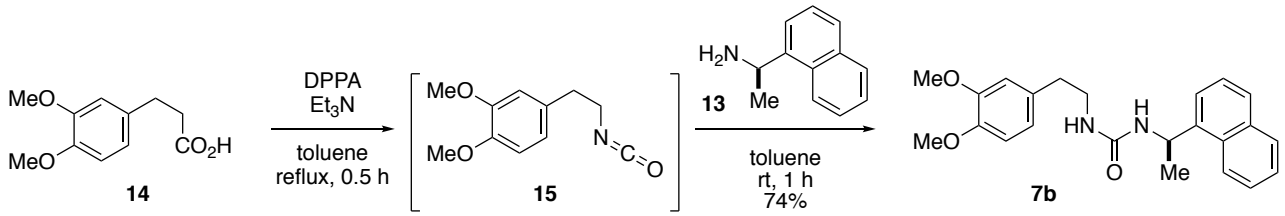
Although Pirkle reagent is commercially available, it is expensive and its stability is not very high; therefore, we have developed an alternate preparation method (Scheme 3).



Scheme 3. Preparation of Chiral Urea (Top-Half) through Curtius Rearrangement with DPPA

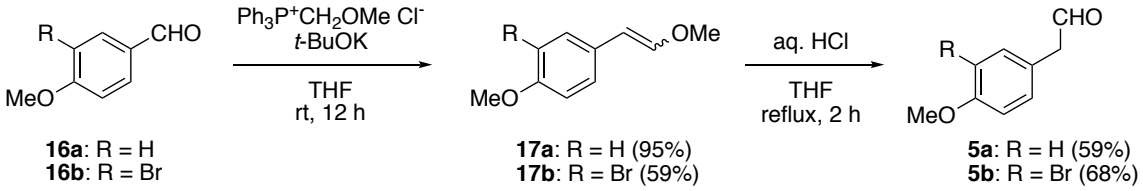
Thus, ferulic acid (**8**) was hydrogenated in the presence of palladium on charcoal to give carboxylic acid **9**.[12] Benzyl protection of the phenol of **9** with benzyl bromide and potassium carbonate in DMF gave the ether **10**. Carboxylic ester of **10** was hydrolyzed by sodium hydroxide to give carboxylic acid **11** in 87% yield in three steps. Curtius rearrangement of **11** with diphenylphosphoryl azide (DPPA) and triethylamine in refluxing toluene gave isocyanate **12**, which was directly treated with (*R*)-1-(1-naphthyl)-ethylamine **13** to give desired urea **7a** in 84% yield.[13]

The other urea **7b**, for synthesis of the bottom-half of *O*-methylneferine, was prepared by the same procedure from carboxylic acid **14** *via* isocyanate **15** as shown in Scheme 4.



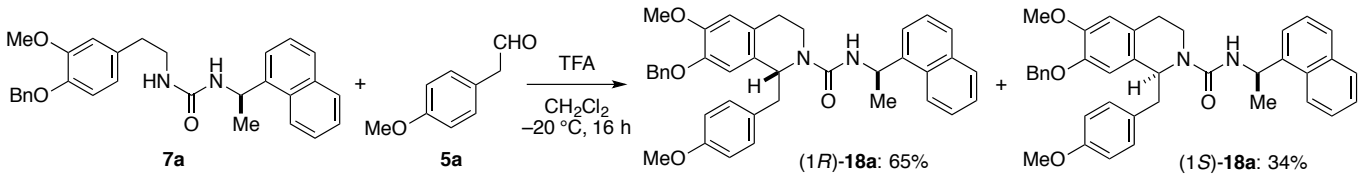
Scheme 4. Preparation of Chiral Urea (Bottom-Half) through Curtius Rearrangement with DPPA

Aldehydes **5a** and **b** were prepared by a two step procedure (Scheme 5). According to the reported method, arylaldehyde **16** was converted by the Wittig reaction to the enol ether **17**.[14] Hydrolysis of **17** with aqueous hydrochloric acid in THF gave arylacetaldehyde **5**.



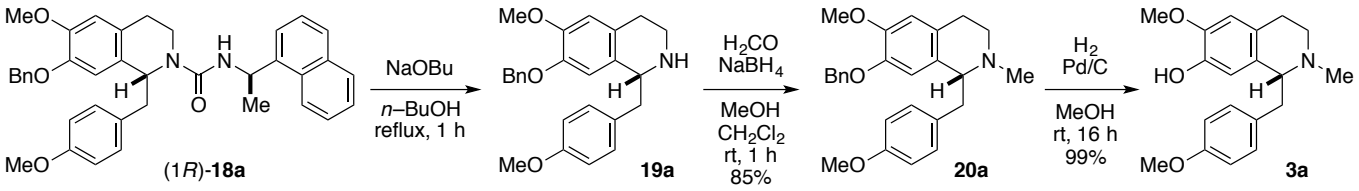
Scheme 5. Preparation of Aldehydes

The Pictet–Spengler reaction of chiral urea **7a** and arylacetaldehyde **5a** was catalyzed by trifluoroacetic acid (TFA) in dichloromethane for 16 h at –20 °C giving, after silica gel column chromatography, tetrahydroisoquinolines (1*R*)-**18a** and (1*S*)-**18a** in 65% and 34% isolated yields, respectively (Scheme 6). Stereochemistry of (*1R*)-**18a** was determined by specific rotation of **3a** (*vide infra*).[2]



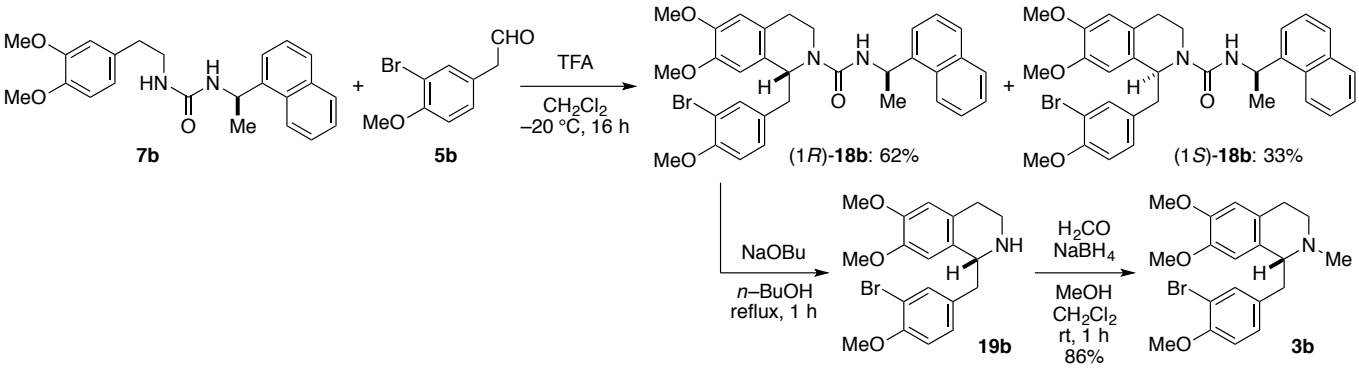
Scheme 6. Diastereoselective Pictet–Spengelr Reaction

The chiral auxiliary of the major diastereomer (1*R*)-**18a** was removed by treating with sodium butoxide in refluxing butanol, giving amine **19a** (Scheme 7).[11] Reductive *N*-methylation with formalin and sodium borohydride, followed by hydrogenolysis of the benzyl group of **20a** in the presence of palladium on charcoal gave phenol **3a**, the top-half of *O*-methyneferine.[3,15]



Scheme 7. Synthesis of Top-Half

The other isoquinoline **3b**, the bottom-half, was also synthesized from chiral urea **7b** and aldehyde **5b** by the same procedure as shown in Scheme 8. Thus, the Pictet–Spengler reaction of chiral urea **7b** with aldehyde **5b** gave tetrahydroisoquinolines (1*R*)-**18b** and (1*S*)-**18b** in 62% and 33% isolated yields, respectively. (1*R*)-**18b** was converted to bromide **3b**, the bottom-half of *O*-methylneferine, by the same reaction sequence as described above.

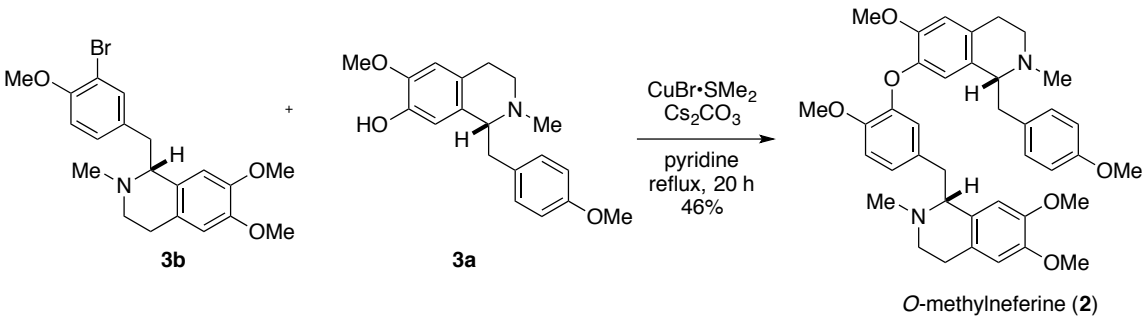


Scheme 8. Synthesis of Bottom-Half

Ullmann coupling of phenol **3a** (top-half) and bromide **3b** (bottom-half) was mediated by copper(I) bromide–dimethyl sulfide complex and cesium carbonate in refluxing pyridine for 20 h, giving *O*-methylneferine (**2**) in 46% yield (Scheme 9). Spectroscopic and analytical data of **2** agreed well with *O*-methylneferine, which was synthesized by methylation of natural neferine.[16]

In conclusion, we have developed a novel diastereoselective Pictet–Spengler reaction controlled by (*R*)-1-(1-naphthyl)ethylcarbamoyl group. Although the diastereoselectivity of this Pictet–Spengler reaction is not so high, the chemical yield is quantitative, and the products, benzyltetrahydroisoquinolines bearing the (*R*)-1-(1-naphthyl)ethylcarbamoyl group, are quite easily separable by silica gel column

chromatography, indicating that this reaction is of practical use for asymmetric synthesis of tetrahydroisoquinoline alkaloids. We have also synthesized *O*-methylneferine by using this Pictet–Spengler reaction. The present synthetic route is more efficient than our previous one.[2]



Scheme 9. Ullmann Coupling Giving *O*-Methylneferine

EXPERIMENTAL

All melting points were recorded on Yanagimoto hot plate melting points apparatus and are uncorrected. IR spectra were taken by Jasco FT/IR-4200 spectrophotometer. NMR spectra were taken by Varian Mercury 300 (300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR) or Varian VXR-500 (500 MHz for ^{1}H- and 125 MHz for ^{13}C-NMR) spectrophotometers. MS and HRMS spectra were taken by Hitachi M-4000 spectrometer. Optical rotations were taken by Jasco DIP-370 polarimeter.

(*R*)-1-(4-Benzyloxy-3-methoxyphenethyl)-3-[1-(1-naphthyl)ethyl]urea (7a).

Method A: To a solution of amine **4a**[9] (2.57 g, 10 mmol) in $CHCl_3$ (50 mL) was added Pirkle reagent **6** (1.92 mL, 11 mmol) at 0 °C. After being stirred for 1 h at room temperature (rt), the solvent was evaporated and the residue was purified by silica gel column chromatography ($CHCl_3$/EtOAc = 9/1) to give **7a** (4.54 g, 99%) as a white powder.

Method B: To a solution of carboxylic acid **11** (11.4 g, 40 mmol; *vide infra*) in toluene (120 mL) were added triethylamine (6.08 mL, 44 mmol) and DPPA (8.64 mL, 40 mmol) at 0 °C, and then the whole was refluxed for 0.5 h. The reaction mixture was cooled with ice bath, a solution of (*R*)-1-(1-naphthyl)-ethylamine **13** (6.84 g, 40 mmol) in toluene (40 mL) was added. After being stirred for 1 h at rt, water was added, and the mixture was extracted with $CHCl_3$. Combined organic layers were washed with 10% hydrochloric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate, filtered, and evaporated. The residue was purified by silica gel column chromatography ($CHCl_3$/EtOAc = 9/1) to give **7a** (15.3 g, 84%) as a white powder of mp 158–161 °C. $[\alpha]^{20}_D$ –33.6 (*c* 1.00, $CHCl_3$). IR (Nujol) cm^{-1}: 3320, 1617, 1512. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58 (3H, d, *J* = 6.6 Hz), 2.61 (2H, m), 3.33 (2H, dd, *J* = 9.7, 6.6 Hz), 3.75 (3H, s), 4.18 (1H, t, *J* = 5.8 Hz), 4.59 (1H, d, *J* = 6.0 Hz), 5.06 (2H, s), 5.54 (1H, m), 6.40 (1H, dd, *J* = 8.3, 1.9 Hz), 6.60 (1H, d, *J* = 1.9 Hz), 6.60 (1H, d, *J* = 8.3 Hz), 7.27–7.56 (9H, m), 7.76 (1H, d, *J*

= 7.9 Hz), 7.86 (1H, dd, *J* = 7.4, 1.9 Hz), 8.08 (1H, dd, *J* = 7.7, 1.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.4, 36.0, 41.7, 46.2, 56.0, 71.2, 112.6, 114.2, 120.7, 122.5, 123.4, 125.5, 125.9, 126.6, 127.4, 128.0, 128.2, 128.7, 129.0, 131.0, 132.5, 134.1, 137.5, 139.5, 146.8, 149.8, 157.7. MS (EI) *m/z*: 454 (M^+), 91. HRMS (EI) *m/z*: 454.2262 (Calcd for $C_{29}H_{30}N_2O_3$: 454.2256).

(*R*)-1-(3,4-Dimethoxyphenethyl)-3-[1-(1-naphthyl)ethyl]urea (7b). By the same procedure for preparation of **7a**, 3-(3,4-dimethoxyphenyl)propanoic acid **14** (8.40 g, 40 mmol) was treated with triethylamine (6.08 mL, 44 mmol) and DPPA (8.64 mL, 40 mmol) in toluene (120 mL), then with (*R*)-1-(1-naphthyl)ethylamine **13** (6.84 g, 40 mmol) in toluene (40 mL) to give, after silica gel column chromatography ($CHCl_3$/EtOAc = 9/1), **7b** (11.2 g, 74%) as a white powder of mp 161–164 °C. $[\alpha]^{22}_D$ –35.2 (*c* 1.00, $CHCl_3$). IR (Nujol) cm^{-1}: 3318, 1615, 1518. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.52 (3H, d, *J* = 6.9 Hz), 2.59 (2H, m), 3.27 (2H, dd, *J* = 9.9, 6.3 Hz), 3.71 (3H, s), 3.76 (3H, s), 4.52 (1H, t, *J* = 5.2 Hz), 4.94 (1H, d, *J* = 7.1 Hz), 5.53 (1H, m), 6.46 (1H, dd, *J* = 8.0, 1.7 Hz), 6.55 (1H, d, *J* = 1.7 Hz), 6.56 (1H, d, *J* = 8.0 Hz), 7.36–7.54 (4H, m), 7.74 (1H, d, *J* = 7.8 Hz), 7.84 (1H, dd, *J* = 7.4, 2.2 Hz), 8.07 (1H, dd, *J* = 7.4, 1.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.4, 36.0, 41.8, 46.3, 55.9, 56.0, 111.3, 111.9, 120.7, 122.5, 123.4, 125.5, 125.9, 126.5, 128.2, 129.0, 131.0, 131.7, 134.1, 139.4, 147.6, 149.0, 157.7. MS (EI) *m/z*: 378 (M^+), 164. HRMS (EI) *m/z*: 378.1945 (Calcd for $C_{23}H_{26}N_2O_3$: 378.1943).

3-(4-Benzyloxy-3-methoxyphenyl)propanoic acid (11).[12] A mixture of ferulic acid **8** (19.4 g, 100 mmol) and 10% palladium on charcoal (1.0 g) in MeOH was stirred under hydrogen atmosphere for 16 h at rt. Filtration of the reaction mixture, followed by concentration gave carboxylic acid **9**. To a solution of crude **9** in DMF (100 mL) were added potassium carbonate (34.5 g, 250 mmol) and benzyl bromide (26.4 mL, 220 mmol), and the mixture was stirred for 3 h at rt. After being cooled, water was added, and the whole was extracted with a mixture of toluene and hexane (4/1). Combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give benzyl ester **10**. To a solution of crude **10** in EtOH (50 mL) was added a solution of sodium hydroxide (8.0 g, 200 mmol) in water (50 mL), and the mixture was stirred for 1 h at rt. Reaction mixture was washed with Et_2O, acidified with 10% hydrochloric acid, and then extracted with Et_2O. Combined organic layers were washed with brine, dried over sodium sulfate, filtered, and evaporated. The residue was recrystallized from EtOAc to give **11** (24.8 g, 87%) as colorless needles of mp 95–97 °C. IR (Nujol) cm^{-1}: 3500–3100, 1691. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.65 (2H, t, *J* = 7.7 Hz), 2.89 (2H, t, *J* = 7.7 Hz), 3.87 (3H, s), 5.12 (2H, s), 6.67 (1H, dd, *J* = 8.2, 1.9 Hz), 6.75 (1H, d, *J* = 1.9 Hz), 6.81 (1H, d, *J* = 8.2 Hz), 7.26–7.45 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 30.4, 36.1, 56.2, 71.3, 112.4, 114.4, 120.3, 127.5, 128.0, 128.7, 133.6, 137.5, 146.9, 149.8, 179.5.

1-Methoxy-4-(2-methoxyvinyl)benzene (17a).[14] To a suspension of (methoxymethyl)triphenylphosphonium chloride (18.9 g, 55 mmol) in THF (50 mL) was added potassium *tert*-butoxide (6.33 g, 55

mmol) at 0 °C, and the mixture was stirred for 0.5 h at rt. A solution of *p*-anisaldehyde **16a** (6.80 g, 50 mmol) in THF (50 mL) was added, and the whole was stirred for 12 h at rt. Saturated ammonium chloride solution was added, and the mixture was extracted with Et_2O. Combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated. Hexane was added to the residue, and insoluble material was filtered off. Concentration of the filtrate, followed by silica gel column chromatography (hexane/EtOAc = 19/1) gave **17a** (7.75 g, 95%) as a colorless oil. ^{1}H-NMR indicated *trans* : *cis* = 5 : 4. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.66 (3H, s, *trans*), 3.75 (3H, s, *cis*), 3.79 (3H, s, *trans*), 3.79 (3H, s, *cis*), 5.17 (1H, d, *J* = 7.0 Hz, *cis*), 5.78 (1H, d, *J* = 13.2 Hz, *trans*), 6.05 (1H, d, *J* = 7.0 Hz, *cis*), 6.82 (2H, d, *J* = 8.8 Hz, *trans*), 6.83 (2H, d, *J* = 8.8 Hz, *cis*), 6.93 (1H, d, *J* = 13.2 Hz, *trans*), 7.15 (2H, d, *J* = 8.8 Hz, *trans*), 7.51 (2H, d, *J* = 8.8 Hz, *cis*).

2-Bromo-1-methoxy-4-(2-methoxyvinyl)benzene (17b). By the same procedure for preparation of **17a**, 3-bromo-4-methoxybenzaldehyde **16b** (10.8 g, 50 mmol) was treated with (methoxymethyl)triphenylphosphonium chloride (18.9 g, 55 mmol) and potassium *tert*-butoxide (6.33 g, 55 mmol) in THF (100 mL) to give, after silica gel column chromatography (hexane/EtOAc = 19/1), **17b** (7.20 g, 59%) as a colorless oil. ^{1}H-NMR indicated *trans* : *cis* = 5 : 4. IR (neat) cm^{-1}: 1642, 1600, 1497. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.66 (3H, s, *trans*), 3.77 (3H, s, *cis*), 3.87 (3H, s, *trans*), 3.88 (3H, s, *cis*), 5.11 (1H, d, *J* = 6.8 Hz, *cis*), 5.70 (1H, d, *J* = 13.0 Hz, *trans*), 6.08 (1H, d, *J* = 6.8 Hz, *cis*), 6.80 (1H, d, *J* = 8.5 Hz, *trans*), 6.82 (1H, d, *J* = 8.5 Hz, *cis*), 6.92 (1H, d, *J* = 13.0 Hz, *trans*), 7.10 (1H, dd, *J* = 8.5, 2.2 Hz, *trans*), 7.42 (1H, d, *J* = 2.2 Hz, *trans*), 7.43 (1H, dd, *J* = 8.5, 2.2 Hz, *cis*), 7.82 (1H, d, *J* = 2.2 Hz, *cis*). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 56.0, 56.1, 56.4, 60.5, 103.3, 103.7, 111.1, 111.4, 111.7, 112.0, 125.0, 128.1, 129.5, 130.1, 130.4, 132.6, 147.2, 148.3, 153.5, 153.7. MS (EI) *m*/*z*: 242 (M^+), 148. HRMS (EI) *m*/*z*: 241.9943 (Calcd for $C_{10}H_{11}BrO_2$: 241.9942).

4-Methoxyphenylacetaldehyde (5a).[14] To a solution of **17a** (2.46 g, 15 mmol) in THF (15 mL) was added 5% hydrochloric acid (7.5 mL), and the whole was refluxed for 2 h. After being cooled, water was added, and the mixture was extracted with Et_2O. Combined organic layers were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4/1) to give **5a** (1.35 g, 59%) as a colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.62 (2H, d, *J* = 2.5 Hz), 3.81 (3H, s), 6.91 (2H, d, *J* = 8.8 Hz), 7.13 (2H, d, *J* = 8.8 Hz), 9.72 (1H, t, *J* = 2.5 Hz).

3-Bromo-4-methoxyphenylacetaldehyde (5b). By the same procedure for preparation of **5a**, enol ether **17b** (2.86 g, 20 mmol) was treated with 5% hydrochloric acid (10 mL) in THF (20 mL) to give, after silica gel column chromatography (hexane/EtOAc = 4/1), **5b** (3.10 g, 68%) as a colorless oil. IR (neat) cm^{-1}: 1723, 1603, 1497. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.62 (2H, s), 3.89 (3H, s), 6.89 (1H, d, *J* = 8.2 Hz), 7.12 (1H, d, *J* = 8.2 Hz), 7.41 (1H, s), 9.72 (1H, s). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 49.4, 56.5, 112.1,

112.5, 125.6, 130.0, 134.5, 155.4, 199.1. MS (EI) *m/z*: 228 (M^+), 199. HRMS (EI) *m/z*: 227.9786 (Calcd for $C_9H_9BrO_2$: 227.9786).

(1*R*)- and (1*S*)-7-Benzyloxy-6-methoxy-1-(4-methoxybenzyl)-2-[*N*-((*R*)-1-(1-naphthyl)ethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline ((1*R*)- and (1*S*)-18a). *General Procedure for the Pictet–Spengler Reaction*. To a solution of urea **7a** (227 mg, 0.5 mmol) and aldehyde **5a** (83 mg, 0.55 mmol) in CH_2Cl_2 (2.5 mL) was added trifluoroacetic acid (0.26 mL, 3.5 mmol) at –20 °C. After 16 h at the same temperature, water was added, and the whole was extracted with EtOAc. Combined organic layers were washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give (1*R*)-**18a** (190 mg, 65%) and (1*S*)-**18a** (99 mg, 34%), respectively. **(1*R*)-18a**: white foam of mp 98–100 °C. $[\alpha]^{24}_D$ –70.2 (*c* 1.00, benzene). IR (Nujol) cm^{-1}: 3343, 1612, 1511. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, d, *J* = 6.6 Hz), 2.52 (1H, ddd, *J* = 15.9, 5.2, 4.5 Hz), 2.74–2.85 (2H, m), 2.84 (1H, dd, *J* = 13.3, 5.0 Hz), 2.96 (1H, dd, *J* = 13.3, 7.5 Hz), 3.18 (1H, ddd, *J* = 12.6, 9.4, 4.5 Hz), 3.81 (3H, s), 3.85 (3H, s), 4.01 (1H, d, *J* = 7.4 Hz), 4.77 (1H, dd, *J* = 7.5, 5.0 Hz), 5.00 (2H, s), 5.63 (1H, m), 6.45 (1H, s), 6.59 (1H, s), 6.84 (2H, d, *J* = 8.5 Hz), 7.00 (2H, d, *J* = 8.5 Hz), 7.27–7.51 (9H, m), 7.75 (1H, d, *J* = 8.2 Hz), 7.83 (1H, dd, *J* = 7.1, 2.2 Hz), 8.05 (1H, dd, *J* = 7.4, 2.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.7, 28.2, 42.2, 43.4, 45.9, 55.6, 56.2, 57.9, 71.7, 111.9, 113.8, 114.3, 122.4, 123.8, 125.4, 125.8, 126.5, 127.5, 127.8, 128.0, 128.1, 128.6, 128.7, 128.8, 130.8, 131.0, 131.2, 134.1, 137.3, 139.9, 146.4, 148.7, 157.0, 158.8. MS (EI) *m/z*: 388, 341, 268, 250, 198, 182. *Anal*. Calcd for $C_{38}H_{38}N_2O_4 \cdot 0.25H_2O$: C, 77.20; H, 6.56; N, 4.74. Found: C, 77.27; H, 6.59; N, 4.79. **(1*S*)-18a**: white foams of mp 105–108 °C. $[\alpha]^{23}_D$ +54.4 (*c* 1.00, benzene). IR (Nujol) cm^{-1}: 3343, 1612, 1511. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 (3H, d, *J* = 6.9 Hz), 2.57 (1H, ddd, *J* = 15.9, 5.2, 4.7 Hz,), 2.76–2.82 (2H, m), 2.82 (1H, dd, *J* = 13.3, 6.0 Hz), 2.96 (1H, dd, *J* = 13.3, 7.0 Hz), 3.23 (1H, ddd, *J* = 12.9, 9.6, 4.7 Hz), 3.64 (3H, s), 3.86 (3H, s), 4.35 (1H, d, *J* = 6.6 Hz), 4.91 (1H, dd, *J* = 7.0, 6.0 Hz), 4.98 (2H, s), 5.66 (1H, m), 6.41 (1H, s), 6.60 (2H, d, *J* = 8.8 Hz), 6.61 (1H, s), 6.87 (2H, d, *J* = 8.8 Hz), 7.16 (1H, d, *J* = 7.1 Hz), 7.36–7.54 (8H, m), 7.75 (1H, d, *J* = 8.2 Hz), 7.84 (1H, dd, *J* = 7.1, 2.2 Hz), 8.07 (1H, dd, *J* = 7.4, 2.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.5, 28.1, 42.3, 46.6, 45.9, 55.3, 56.3, 57.9, 71.5, 111.9, 113.8, 114.3, 122.4, 123.8, 125.4, 125.8, 126.4, 127.5, 127.7, 128.0, 128.1, 128.2, 128.7, 128.9, 130.6, 130.7, 131.2, 134.1, 137.3, 139.9, 146.4, 148.7, 157.0, 158.8. MS (EI) *m/z*: 388, 268, 198, 182. *Anal*. Calcd for $C_{38}H_{38}N_2O_4$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.52; H, 6.62; N, 4.77.

(1*R*)- and (1*S*)-7-Benzyloxy-6-methoxy-1-(3-bromo-4-methoxybenzyl)-2-[*N*-((*R*)-1-(1-naphthyl)-ethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline ((1*R*)- and (1*S*)-18b). According to the General Procedure for the Pictet–Spengler Reaction, urea **7b** (4.50 g, 12 mmol) reacted with aldehyde **5b** (3.00 g, 13.2 mmol) in the presence of TFA (6.24 mL, 84 mmol) in CH_2Cl_2 (60 mL) for 16 h at –20 °C to give, after silica gel column chromatography (hexane/EtOAc = 9/1), (1*R*)-**18b** (4.41 g, 62%) and (1*S*)-**18b**

(2.36 g, 33%), respectively. **(1*R*)-18b**: white foams of mp 91–94 °C. $[\alpha]^{16}_{D}$ –52.0 (*c* 1.00, benzene). IR (Nujol) cm^{-1}: 3340, 1633. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.40 (3H, d, *J* = 6.6 Hz), 2.57 (1H, ddd, *J* = 16.0, 5.3, 4.7 Hz), 2.75–2.85 (2H, m), 2.92 (1H, dd, *J* = 13.4, 6.0 Hz), 3.05 (1H, dd, *J* = 13.4, 7.7 Hz), 3.27 (1H, ddd, *J* = 12.1, 8.8, 4.7 Hz), 3.73 (3H, s), 3.85 (3H, s), 3.89 (3H, s), 4.19 (1H, d, *J* = 6.6 Hz), 4.91 (1H, dd, *J* = 7.7, 6.0 Hz), 5.70 (1H, m), 6.35 (1H, s), 6.59 (1H, s), 6.81 (1H, d, *J* = 8.3 Hz), 6.99 (1H, dd, *J* = 8.3, 1.9 Hz), 7.34–7.52 (5H, m), 7.76 (1H, d, *J* = 7.4 Hz), 7.84 (1H, dd, *J* = 7.1, 2.2 Hz), 8.07 (1H, dd, *J* = 7.4, 1.7 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 21.6, 28.0, 42.0, 43.4, 45.9, 56.1, 56.2, 56.5, 57.6, 110.6, 111.4, 111.8, 112.2, 122.5, 123.8, 125.5, 125.9, 126.5, 126.9, 128.1, 128.5, 128.8, 130.1, 131.3, 132.5, 134.1, 134.3, 139.7, 147.3, 148.0, 155.0, 156.8. MS (EI) *m/z*: 390, 198, 192, 182. **(1*S*)-18b**: white foams of mp 101–103 °C. $[\alpha]^{21}_{D}$ +44.4 (*c* 1.00, benzene). IR (Nujol) cm^{-1}: 3340, 1633. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.59 (3H, d, *J* = 6.0 Hz), 2.62 (1H, ddd, *J* = 15.9, 5.5, 4.9 Hz), 2.75–2.83 (2H, m), 2.88 (1H, dd, *J* = 13.2, 6.6 Hz), 3.06 (1H, dd, *J* = 13.2, 6.9 Hz), 3.35 (1H, ddd, *J* = 12.6, 8.3, 4.9 Hz), 3.71 (3H, s), 3.73 (3H, s), 3.85 (3H, s), 4.51 (1H, d, *J* = 7.1 Hz), 5.07 (1H, dd, *J* = 6.9, 6.6 Hz), 5.75 (1H, m), 6.29 (1H, s), 6.60 (1H, s), 6.62 (1H, d, *J* = 8.2 Hz), 6.89 (1H, dd, *J* = 8.2, 2.2 Hz), 7.23 (1H, d, *J* = 2.2 Hz), 7.39–7.52 (4H, m), 7.77 (1H, d, *J* = 8.2 Hz), 7.84 (1H, dd, *J* = 7.5, 2.1 Hz), 8.12 (1H, dd, *J* = 7.7, 2.0 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 22.3, 28.0, 42.1, 43.4, 46.4, 56.1, 56.1, 56.4, 57.4, 110.8, 111.4, 111.5, 111.9, 122.3, 123.7, 125.5, 125.9, 126.5, 126.8, 128.1, 128.7, 128.9, 129.2, 131.1, 132.4, 134.1, 134.4, 139.9, 147.3, 148.0, 154.7, 156.8. MS (EI) *m/z*: 390, 198, 192, 182. *Anal*. Calcd for $C_{32}H_{33}BrN_2O_4 \cdot 0.5H_2O$: C, 64.21; H, 5.73; N, 4.68. Found: C, 64.15; H, 5.69; N, 4.61.

(*R*)-7-Benzyloxy-6-methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (20a). A mixture of (1*R*)-**18a** (887 mg, 1.5 mmol) and sodium butoxide (2 M in *n*-butanol, 7.5 mL, 15 mmol) was refluxed for 1 h. After being cooled, water was added, and the mixture was extracted with CH_2Cl_2. Combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated to give amine **19a**. To a solution of crude **19a** in MeOH (20 mL) were added formalin (37%, 1.1 mL, 15 mmol) and sodium borohydride (370 mg, 10 mmol), and the mixture was stirred for 1 h at rt. 10% Acetic acid (24 mL) and 10% ammonia solution (16 mL) were successively added, and the whole was extracted with Et_2O. Combined organic layers were washed with brine, dried over potassium carbonate, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/EtOH = 4/1) to give **20a** (512 mg, 85%) as a colorless oil. $[\alpha]^{20}_{D}$ +15.4 (*c* 1.00, benzene). IR (neat) cm^{-1}: 1610, 1511. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.50 (3H, s), 2.57 (1H, m), 2.69–2.85 (2H, m), 2.71 (1H, dd, *J* = 13.7, 7.4 Hz), 3.06 (1H, dd, *J* = 13.7, 5.2 Hz), 3.16 (1H, m), 3.60 (1H, dd, *J* = 7.4, 5.2 Hz), 3.77 (3H, s), 3.84 (3H, s), 4.77 (1H, d, *J* = 12.4 Hz), 4.84 (1H, d, *J* = 12.4 Hz), 6.01 (1H, s), 6.57 (1H, s), 6.79 (2H, d, *J* = 8.8 Hz), 6.95 (2H, d, *J* = 8.8 Hz), 7.27–7.34 (5H, m). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.6, 39.9, 42.6, 46.9, 55.0,

55.7, 64.7, 70.6, 111.5, 113.4, 113.7, 126.5, 127.0, 127.5, 128.2, 129.2, 130.6, 131.9, 137.2, 145.3, 147.7, 157.7. MS (EI) *m/z*: 404 (MH^+), 282. HRMS (EI) *m/z*: 404.2201 (Calcd for $C_{26}H_{30}NO_3$ (MH^+): 404.2226).

(*R*)-6-Methoxy-1-(4-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (3a). A mixture of **22a** (667 mg, 1.6 mmol), 10% palladium on charcoal (192 mg) and acetic acid (0.38 mL) in MeOH (70 mL) was stirred under hydrogen atmosphere for 16 h at rt. The reaction mixture was filtered, and concentrated. The residue was dissolved in CH_2Cl_2, and was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. Silica gel column chromatography ($CHCl_3$/MeOH = 9/1) gave **3a** (499 mg, 99%) as a colorless oil. $[\alpha]^{27}_D$ +40.0 (*c* 1.00, benzene). IR (neat) cm^{-1}: 1611, 1509. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.54 (3H, s), 2.55 (1H, m), 2.68–2.78 (2H, m), 2.84 (1H, dd, *J* = 14.1, 6.0 Hz), 3.06 (1H, dd, *J* = 14.1, 6.0 Hz), 3.17 (1H, m), 3.67 (1H, t, *J* = 6.0 Hz), 3.78 (3H, s), 3.84 (3H, s), 6.39 (1H, s), 6.53 (1H, s), 6.79 (2H, d, *J* = 8.5 Hz), 7.04 (2H, d, *J* = 8.5 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 24.9, 40.4, 42.3, 46.8, 55.0, 55.6, 64.5, 110.5, 113.3, 113.8, 124.9, 129.6, 130.3, 131.6, 143.4, 145.3, 157.7. MS (EI) *m/z*: 314 (MH^+), 192. HRMS (EI) *m/z*: 314.1751 (Calcd for $C_{19}H_{24}NO_3$ (MH^+): 314.1756).

(*R*)-1-(3-Bromo-4-methoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b). By the same procedure for preparation of **3a**, (1*R*)-**18b** (1.20 g, 2.0 mmol) was treated with sodium butoxide (2 M in *n*-butanol, 10 mL, 20 mmol), followed by formalin (37%, 1.48 mL, 20 mmol) and sodium borohydride (493 mg, 13.3 mmol) in MeOH (13 mL) to give, after silica gel column chromatography (EtOAc/EtOH = 9/1), **3b** (700 mg, 86%) as a colorless oil. $[\alpha]^{18}_D$ +20.2 (*c* 1.00, benzene). IR (neat) cm^{-1}: 1607, 1514. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.51 (3H, s), 2.57 (1H, m), 2.71–2.86 (3H, m), 3.07 (1H, dd, *J* = 13.7, 5.5 Hz), 3.17 (1H, m), 3.63 (3H, s), 3.61 (1H, m), 3.84 (3H, s), 3.85 (3H, s), 6.12 (1H, s), 6.56 (1H, s), 6.77 (1H, d, *J* = 8.3 Hz), 6.95 (1H, dd, *J* = 8.3, 1.9 Hz), 7.33 (1H, d, *J* = 1.9 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 25.6, 40.2, 42.9, 47.1, 55.8, 56.0, 56.4, 64.9, 111.0, 111.3, 111.5, 111.7, 126.4, 129.2, 129.9, 133.9, 134.5, 146.7, 147.5, 154.3. MS (EI) *m/z*: 405 (M^+), 206. HRMS (EI) *m/z*: 405.0932 (Calcd for $C_{20}H_{24}BrNO_3$: 405.0940).

***O*-Methylneferine (2).** To a solution of the phenol **3a** (499 mg, 1.59 mmol) and the bromide **3b** (646 mg, 1.59 mmol) in pyridine (5 mL) were added copper(I) bromide–dimethyl sulfide complex (654 mg, 3.18 mmol) and cesium carbonate (3.11 g, 9.54 mmol), and the mixture was refluxed for 20 h under argon atmosphere. Filtration and concentration of the reaction mixture, followed by silica gel column chromatography ($CHCl_3$/MeOH = 9/1) gave *O*-methylneferine **2** (321 mg, 32%; calculated yield of 46%) as an yellow oil, along with unchanged **3b** (202 mg, 32%). $[\alpha]^{19}_D$ –65.8 (*c* 1.00, MeOH). UV λ_{max} (MeOH) nm (log ε): 231 (4.67), 282 (4.18). IR (KBr) cm^{-1}: 1611, 1510. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.45 (3H, s), 2.48 (3H, s), 2.53 (1H, ddd, *J* = 16.0, 5.0, 4.5 Hz), 2.58 (1H, ddd, *J* = 16.5, 5.0, 5.0 Hz), 2.71 (1H, dd, *J* = 13.5, 7.5 Hz), 2.65–2.73 (2H, m), 2.75–2.81 (2H, m), 2.78 (1H, dd, *J* = 14.0, 6.0 Hz), 2.94

(1H, dd, *J* = 14.0, 5.5 Hz), 3.06 (1H, dd, *J* = 13.5, 5.5 Hz), 3.09–3.16 (2H, m), 3.58 (3H, s), 3.59–3.63 (2H, m), 3.71 (3H, s), 3.78 (3H, s), 3.80 (3H, s), 3.81 (3H, s), 6.04 (1H, s), 6.35 (1H, s), 6.50 (1H, s), 6.59 (1H, d, *J* = 2.0 Hz), 6.61 (1H, s), 6.67 (2H, d, *J* = 8.5 Hz), 6.69 (1H, dd, *J* = 8.0, 2.0 Hz), 6.81 (1H, d, *J* = 8.0 Hz), 6.90 (2H, d, *J* = 8.5 Hz). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 25.2, 26.2, 39.9, 40.6, 42.5, 42.8, 46.7, 47.5, 55.1, 55.6, 55.7, 55.8, 56.1, 64.4, 64.7, 110.9, 111.1, 112.1, 112.2, 113.4, 118.6, 119.3, 124.6, 125.8, 128.3, 129.1, 130.0, 130.4, 131.6, 132.6, 143.2, 146.1, 146.4, 147.3, 148.5, 148.9, 157.7. MS (EI) *m/z*: 639 (MH^+), 517, 206. HRMS (EI) *m/z*: 639.3435 (Calcd for $C_{39}H_{47}N_2O_6$ (MH^+): 639.3434).

***O*-Methylneferine hydrochloride**: mp 163–165 °C. *Anal*. Calcd for $C_{39}H_{48}Cl_2N_2O_6 \cdot 0.5H_2O$: C, 64.99; H, 6.85; N, 3.89. Found: C, 64.72; H, 6.88; N, 3.92.

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