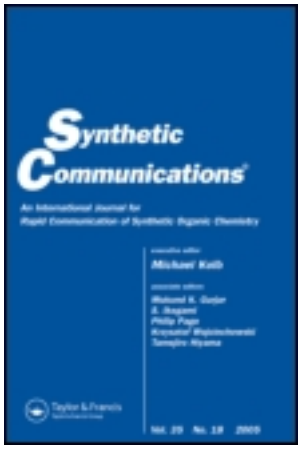


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Total Synthesis of (±)-Armepavines and (±)-Nuciferines From (2-Nitroethenyl)benzene Derivatives

Chia-Fu Chang [a], Chu-Yun Huang [a], Yu-Chao Huang [a], Kuan-Yu Lin [a], Yean-Jang Lee [a] & Chau-Jong Wang [b]

[a] Department of Chemistry, National Changhua University of Education, Changhua, Taiwan

[b] Institute of Biochemistry, Chung Shan Medical University, Taichung, Taiwan

Available online: 05 Nov 2010

To cite this article: Chia-Fu Chang, Chu-Yun Huang, Yu-Chao Huang, Kuan-Yu Lin, Yean-Jang Lee & Chau-Jong Wang (2010): Total Synthesis of (±)-Armepavines and (±)-Nuciferines From (2-Nitroethenyl)benzene Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:23, 3452-3466

To link to this article: http://dx.doi.org/10.1080/00397910903435411

Synthetic Communications®, 40: 3452–3466, 2010

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903435411

Taylor & Francis
Taylor & Francis Group

TOTAL SYNTHESIS OF (±)-ARMEPAVINES AND (±)-NUCIFERINES FROM (2-NITROETHENYL)BENZENE DERIVATIVES

Chia-Fu Chang,[1] Chu-Yun Huang,[1] Yu-Chao Huang,[1] Kuan-Yu Lin,[1] Yean-Jang Lee,[1] and Chau-Jong Wang[2]

[1]*Department of Chemistry, National Changhua University of Education, Changhua, Taiwan*

[2]*Institute of Biochemistry, Chung Shan Medical University, Taichung, Taiwan*

A concise route to armepavine* 1 *and nuciferine* 2 *and* 3*, which can be isolated from the leaves of* Nelumbo nucifera *(Nymphaceae), has been achieved in which the longest linear sequence is only six steps from commercially available benzaldehyde in 28%, 21%, and 20% overall yield, respectively. The key transformations in the synthesis are the radical cyclization of aryl bromide with Bu_3SnH and the Pictet–Spengler reaction of N-substituted amine with aldehyde.

Keywords: Armepavine; Nef; nuciferines; Pictet–Spengler

INTRODUCTION

As part of our research aiming to uncover new natural products with improved biological activities, including antioxidant, anti-human immunodeficiency virus (HIV), and tumor growth inhibition activities, we attended to the flavonoid, coumestan, and maleimide family.[1] Recently, several structurally interesting alkaloids with substituted isoquinoline[2] have been isolated from the leaves of *Nelumbo nucifera* (Nymphaceae) and show significant anti-HIV activity (EC_{50} value of 0.8 μg/mL, TI > 125)[3] and also inhibit platelet aggregation[3] (Fig. 1). Although armepavine (**1**) and nuciferine (**2**) have been synthesized by several groups,[2c,4] they were achieved with very time-consuming and complicated synthetic approaches. To overcome these technical difficulties, we report our studies on the synthesis of nuciferine analogs from the readily available (2-nitroethenyl)benzene derivatives by sequential Pictet–Spengler and radical cyclization.

Retrosynthetic analysis (Scheme 1) suggested that **2** and **3** can be secured by Heck coupling or radical cyclization[4i] of **4**. The latter should be accessible from **5** and **6** with Pictet–Spengler[5] or Bischler–Napieralski[6] reactions. In addition, commercially

Received August 25, 2009.

Address correspondence to Yean-Jang Lee, Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan. E-mail: leeyj@cc.ncue.edu.tw

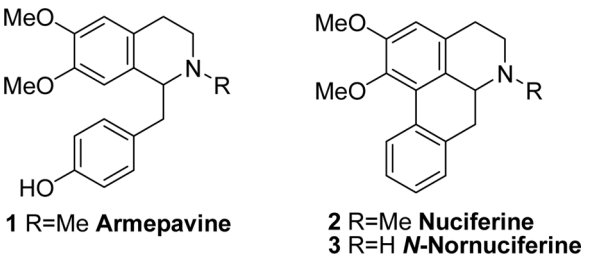
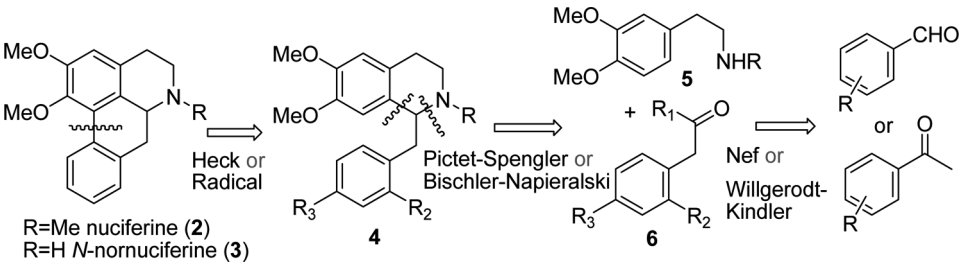


Figure 1. Armepavine and nuciferines from the leaves of *Nelumbo nucifera* (Nymphaceae).

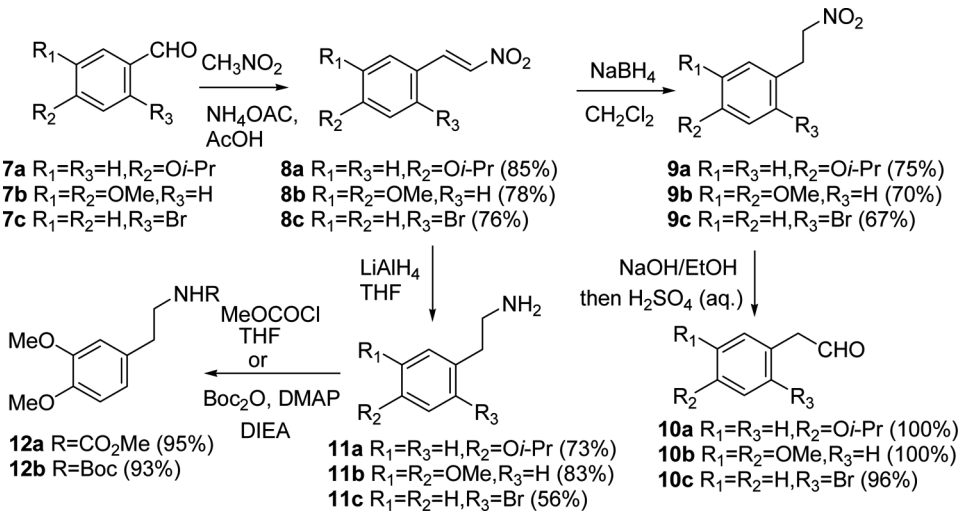


Scheme 1. Retrosynthesis of (±)-nuciferines.

available ketones and aldehydes would allow facile introduction of a wide range of different substituents of **5** and **6** by Nef[7] or Willgerodt–Kindler[8] reactions.

RESULTS AND DISCUSSION

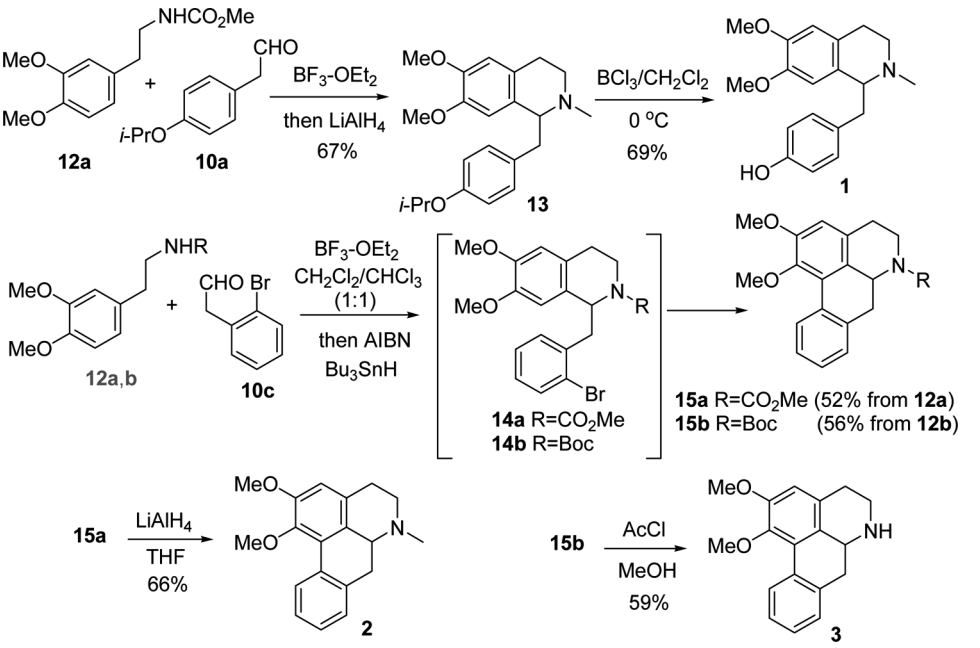
With the aim of developing a concise route to synthesize aryl acetaldehyde and amine with diverse substituents, the commercially available **7a**–**c** were used to prepare the corresponding aldehydes **10a**–**c** and amines **11a**–**c** from this compound (Scheme 2). In the beginning of our synthesis, aldehydes **7a**–**c** were transformed by aldol condensation with CH_3NO_2/NH_4OAc under acetic acid to obtain the corresponding nitro compounds **8a**–**c** in excellent yield. Subsequently, selective 1,4-reduction of conjugated **8a**–**c** proceeded with $NaBH_4$ to provide the saturated nitro product **9a**–**c**. According to the Nef-type reaction, the nitro group of **9a**–**c** was readily changed to the carbonyl group under acidic conditions to give the desired **10a** and **10b** in quantitative yield, respectively, as well as **10c** in 96% yield. At the same time, compounds **11a**–**c** were prepared by direct reduction of **8a**–**c** with $LiAlH_4$ in tetrahydrofuran (THF) at 0 °C. With **10a** and **11b** in hand, we tried to synthesize tetrahydroisoquinoline **13** through the coupling of **10a** and **11b** using the Pictet–Spengler reaction. However, the acid-catalyzed reaction using different Lewis acids, such as trifluoroacetic acid (TFA), HCl, *p*-toluenesulfonic acid (*p*-TSA), and BF_3-OEt_2, to give **13** was unsuccessful. The major product was the recovered starting material or amine hydrochloride salt. This problem could be due to the need for anhydrous conditions, because the iminium salt is readily hydrolyzed under



Scheme 2. Synthesis of aryl amines and aryl aldehydes.

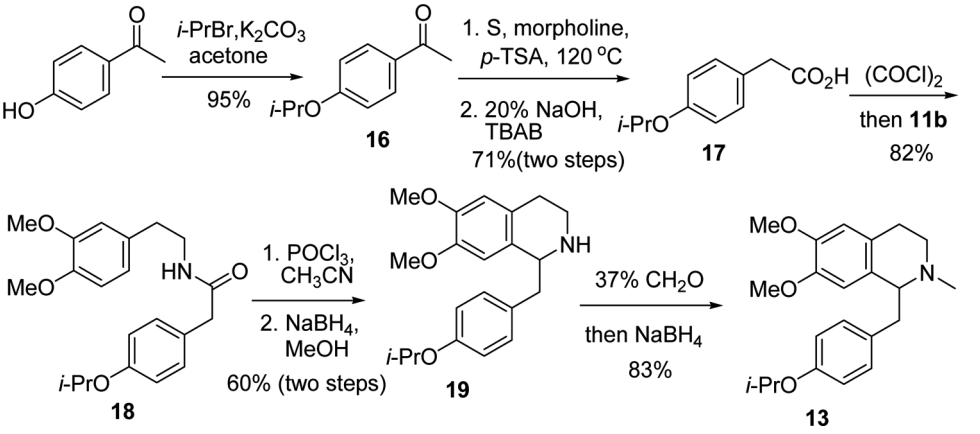
acid-catalyzed reactions. Therefore, we sought to overcome this problem by converting the primary amine into the secondary amine. Amine **11b** was protected with the electron-withdrawing groups CO_2Me and Boc to provide **12a, b**, respectively (Scheme 2). Subsequently, the *N*-methoxycarbonyl hydroisoquinoline obtained under BF_3-OEt_2 catalysis by condensation-cyclization of *N*-methoxycarbonyl amine **12a** with aldehyde **10a** may be used without further purification, and then the process proceeded smoothly using the reductive reaction with $LiAlH_4$ to provide the desired product **13** (67%) in three steps (Scheme 3). Finally, the isopropyl group in **13** was removed with BCl_3 in CH_2Cl_2 at 0 °C to afford armepavine **1** in 69% yield. The structure of **1** was confirmed by x-ray crystallography.[9] With the success of achieving **12a, b**, we employed the same Lewis acid BF_3-OEt_2–catalyzed Pictet–Spengler reaction in nuciferines **2** and **3** syntheses. Coupling of **12a, b** respectively with aldehyde **10c** proceeded readily in mixed solvent (CH_2Cl_2/$CHCl_3$ 1:1) under BF_3-OEt_2 catalysis to give the bromoarmepavine **14a, b**, which can then undergo the radical cyclization with azobisisobutyronitrile (AIBN)/Bu_3SnH to accomplish **15a, b** in 52% and 56% yield, respectively. Trying to obtain **15a, b** via palladium-catalyzed coupling[2c,4g] proved unsuccessful. With precursor **15a, b** in hand, completion of the final steps in the nuciferine syntheses was straightforward, requiring either reduction or deprotection. Previous reduction of the methoxycarbonyl group in compound **15a** with $LiAlH_4$ provided the *N*-methyl nuciferine **2** in 66% yield. Also, direct acid-catalyzed deprotection of the *t*-butoxycarbonyl group in compound **15b** with AcCl/MeOH furnished the expected product **3** in 59% yield. ^1H and ^{13}C NMR spectra of the synthetic products are in agreement with those of reported natural product derivatives.

It is worth noting that an alternative construction[4g] of armepavine **1** was created by Willgerodt–Kindler and Bischler–Napieralski reactions (Scheme 4). Using the Willgerodt–Kindler and hydrolysis procedures, the phenylacetic acid **17** can be readily prepared from the commercially available hydroxyacetophenone in excellent



Scheme 3. Synthesis of (+/−)-armepavines and (+/−)-nuciferines.

yield (three steps, 67%). First, the protection of hydroxyacetophenone was employed with *i*-PrBr and K_2CO_3 to obtain **16** in 95% yield, and then the acetophenone **16** was readily transformed by sulfur and morpholine with catalyst *p*-TSA under refluxing conditions to afford the expected thioacetomorpholide, which could directly be used by hydrolysis with 20% NaOH and catalyst tetrabutylammonium bromide (TBAB) to provide the desired acid **17**. The acetic acid **17** was treated with oxalyl chloride, followed by reaction with the readily available phenylethamine **11b** to obtain the



Scheme 4. Synthesis of isoquinoline **13**.

desired amide **18** in 82% yield. With the required amide **18** in hand, the Bischler–Napieralski cyclization with $POCl_3$ in acetonitrile gave the isoquinimium ion, which can undergo the reduction with $NaBH_4$ to afford isoquinoline **19** in 60% yield (two steps). Sequential condensation and reduction of **19** with formaldehyde and $NaBH_4$, respectively, provided the isopropyl armepavine **13** in 83% yield.

CONCLUSION

In summary, a concise route to armepavine **1** and nuciferine **2** and **3** has been achieved in which the longest linear sequence is only six steps from commercially available benzaldehyde in 28%, 21%, and 20% overall yield, respectively. Alternatively, **1** was also accomplished in 19% overall yield from commercially available 4-hydroxyacetophenone by a route in which the longest linear sequence is only eight steps. Thus, it is demonstrated that using the Lewis acid BF_3-OEt_2-catalyzed Pictet–Spengler reaction gives a good yield and is easily modified to give access to a variety of different armepavine and nuciferine analogs. The preparation of these compounds is currently under way, and their biological activities will be investigated to evaluate the efficacy of these compounds as antitumor agents.

EXPERIMENTAL

Melting points were determined on a Mel Temp II melting-point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker 300 spectrometer. Chemical shifts are reported in parts per million (δ, ppm) using $CHCl_3$ (δ_H 7.26) as an internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a Jeol JMS-HX 110 mass spectrometer from National Chung-Tsing University, Taichung. Elemental analyses were performed on a Heracus CHN-OS Rapid spectrometer in the Taichung Instrumentation Center, National Science Council, Taiwan. Solvents were freshly distilled prior to use from phosphorus pentoxide or CaH_2. THF was distilled from sodium diphenyl ketyl. All reactions were carried out under a nitrogen atmosphere unless otherwise stated. Silica gel (silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous $MgSO_4$.

1-Isopropoxy-4-(2-nitrovinyl)benzene (8a)[10]

A solution of 4-isopropoxy benzaldehyde (**7a**) (1.51 g, 9.2 mmol) in NH_4OAC (1.40 g) / AcOH (20.0 mL) was stirred for 10 min at 25 °C, followed by slow addition of CH_3NO_2 (2.0 mL, 36.9 mmol) with stirring for 5 min. The resulting mixture was heated to reflux at 120 °C for 4 h, then quenched by addition of ice water (10.0 mL) and extracted with CH_2Cl_2 (3 × 30.0 mL). The combined organic layers was concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane-CH_2Cl_2 2:1) to obtain the desired **8a** (1.62 g, 85%) as an orange solid: mp 50–51 °C, ^{1}H NMR δ: 1.21 (d, $J = 6.0$ Hz, 6H), 4.48 (hept, $J = 6.0$ Hz, 1H), 6.77 (d, $J = 8.7$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 2H), 7.36 (d, $J = 13.5$ Hz, 1H), 7.80 (d, $J = 13.5$ Hz, 1H); ^{13}C NMR :δ 21.7, 70.1, 116.1, 121.9, 131.1, 134.6, 139.0, 161.4.

1,2-Dimethoxy-4-(2-nitrovinyl)benzene (8b)

According to previous procedures, 3,4-dimethoxy benzaldehyde (**7b**) (1.73 g, 10.4 mmol) in NH_4OAC (1.58 g) / AcOH (20.0 mL) was stirred for 10 min at 25 °C, followed by slow addition of CH_3NO_2 (2.3 mL, 41.7 mmol) with stirring for 5 min. The resulting mixture was heated to reflux at 120 °C for 4 h, then quenched by addition of ice water (10.0 mL) and extracted with CH_2Cl_2 (3×30.0 mL). The combined organic layers was concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane-CH_2Cl_2 2:1) to provide the expected **8b** (1.70 g, 78%) as an orange solid: mp 131–132 °C (lit.[11] mp 140–142 °C), ^{1}H NMR δ :3.84 (s, 3H), 3.85 (s, 3H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.94 (d, $J = 1.8$ Hz, 1H), 7.09 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.46 (d, $J = 13.5$ Hz, 1H), 7.87 (d, $J = 13.5$ Hz, 1H); ^{13}C NMR :δ 55.8, 55.9, 110.2, 111.2, 122.7, 124.5, 135.0, 139.2, 149.4, 152.7.

1-Bromo-2-(2-nitrovinyl)benzene (8c)

Compound **8c** was prepared, using the previous procedure, from 2-bromo benzaldehyde (**7c**) (1.00 g, 5.4 mmol) in NH_4OAC (0.73 g)/AcOH (15.0 mL), followed by slow addition of CH_3NO_2 (1.0 mL, 19.2 mmol) with stirring for 5 min. The resulting mixture was heated to reflux at 120 °C for 4 h, then quenched by addition of ice water (10.0 mL) and extracted with CH_2Cl_2 (3×20.0 mL). The combined organic layers was concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane-CH_2Cl_2 2:1) to provide the expected **8c** (0.94 g, 76%) as a light yellow solid: mp 87–88 °C (lit.[11] mp 86–87 °C); ^{1}H NMR δ 7.21–7.32 (m, 2H), 7.44 (d, $J = 13.8$ Hz, 1H), 7.48 (dd, $J = 7.5$, 1.8 Hz, 1H), 7.58 (dd, $J = 7.5$, 1.8 Hz, 1H), 8.26 (d, $J = 13.8$ Hz, 1H); ^{13}C NMR :δ 126.2, 128.0, 128.4, 130.1, 132.9, 133.8, 137.4, 138.7.

1-Isopropoxy-4-(2-nitroethyl)benzene (9a)

To a solution of **8a** (0.71 g, 3.4 mmol) in MeOH/CH_2Cl_2 (15.0/15.0 mL) was cooled for 10 min at 0 °C. One portion of $NaBH_4$ (0.19 g, 5.1 mmol) the solution was added to and stirred for 20 min, followed by the other portion of $NaBH_4$ (0.19 g, 5.1 mmol) at 0 °C. The mixture was allowed to stir for 30 min and then quenched with distilled H_2O, which was extracted with CH_2Cl_2 (3×20.0 mL). After removal of solvent, the residue was subjected to column chromatography (SiO_2, hexane–ethyl acetate 8:1) to provide **9a** (0.54 g, 75%) as an oil. ^{1}H NMR δ :1.24 (d, $J = 6.0$ Hz, 6H), 3.14 (t, $J = 7.2$ Hz, 2H), 4.42 (hept, $J = 6.0$ Hz, 1H), 4.46 (t, $J = 7.2$ Hz, 2H), 6.74 (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR :δ 21.9, 32.6, 69.8, 76.5, 116.1, 127.3, 129.5, 157.1; HRMS (EI) calcd. for $C_{11}H_{15}NO_3$ (M^+) 209.1052; found 209.1048.

1,2-Dimethoxy-4-(2-nitroethyl)benzene (9b)

Compound **9b** was prepared, using the previous procedure, from **8b** (0.59 g, 2.9 mmol) in MeOH/CH_2Cl_2 (10.0/10.0 mL), cooled for 10 min at 0 °C. One portion of $NaBH_4$ (0.16 g, 4.3 mmol) was added, followed by the other portion of $NaBH_4$

(0.16 g, 4.3 mmol) with stirring for 30 min at 0 °C. The resulting mixture was then quenched by addition of distilled H_2O (5.0 mL) and extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic layers were concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 8:1) to give the expected **9b** (0.42 g, 70%) as a yellow oil (lit.[12] mp 53–54 °C);^{1}H NMR δ :3.19 (t, $J = 7.2$ Hz, 2H), 3.80 (s, 3H), 3.82 (s, 3H), 4.51 (t, $J = 7.2$ Hz, 2H), 6.63 (d, $J = 1.8$ Hz, 1H), 6.67 (dd, $J = 8.1$,1.8 Hz, 1H), 6.74 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR :δ 33.1, 55.9, 55.9, 76.5, 111.5, 111.7, 120.6, 128.0, 148.3, 149.2.

1-Bromo-2-(2-nitroethyl)benzene (9c)

According to previous procedures, **8c** (0.45 g, 2.0 mmol) in $MeOH/CH_2Cl_2$ (10.0/10.0 mL) was cooled down to 0 °C, and one portion of $NaBH_4$ (0.19 g, 5.1 mmol) was added with stirring for 10 min, followed by the other portion of $NaBH_4$ (0.19 g, 5.1 mmol) at 0 °C. The mixture was allowed to stir for 20 min and then quenched with distilled H_2O, which was extracted with CH_2Cl_2 (3 × 15.0 mL). After removal of solvent, the residue was subjected to column chromatography (SiO_2, hexane–ethyl acetate 8:1) to obtain **9c** (0.30 g, 67%) as an oil.^{1}H NMR δ 3.34 (t, $J = 7.5$ Hz, 2H), 4.54 (t, $J = 7.5$ Hz, 2H), 7.04–7.20 (m, 3H), 7.46 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR δ 33.7, 74.2, 124.2, 127.9, 129.2, 131.0, 133.1, 134.9.

4-Isopropoxyphenylacetaldehyde (10a)

A mixture of **9a** (0.51 g, 2.4 mmol) and NaOH (0.39 g, 9.8 mmol) in ethanol (5.0 mL) was stirred for 10 min at 25 °C, and then the solvent was evaporated in vacuo to give the desired sodium nitronate, which was dissolved in distilled H_2O (5.0 mL). The solution was added into the two-layer mixture of concentrated H_2SO_4/H_2O (2.5/5.0 mL) and pentane (20.0 mL) for 1 h at 0 °C and then warmed to 25 °C. After stirring for 4 h, the resulting suspension was extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic layers was concentrated in vacou, and the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 5:1) to provide the expected **10a** (0.43 g, 100%) as an oil. ^{1}H NMR δ :1.31 (d, $J = 6.3$ Hz, 6H), 3.57 (d, $J = 2.4$ Hz, 2H), 4.51 (hept, $J = 6.3$ Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.4$ Hz, 2H), 9.67 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR :δ 22.0, 49.7, 69.9, 116.3, 123.4, 130.6, 157.2, 199.8, HRMS (EI) calcd. for $C_{11}H_{14}O_2$ (M^+) 178.0994; found 178.0988.

3,4-Dimethoxyphenylacetaldehyde (10b)[13]

A solution of **9b** (0.49 g, 2.3 mmol) and NaOH (0.37 g, 9.2 mmol) in ethanol (5.0 mL) was stirred for 10 min at 25 °C, and then the removal of solvent in vacuo gave the intermediate sodium nitronate, which was dissolved in distilled H_2O (5.0 mL). The solution was introduced into the two-layer mixture of concentrated H_2SO_4/H_2O (2.5/5.0 mL) and pentane (20.0 mL) for 1 h at 0 °C and then warmed to 25 °C. After stirring for 5 h, the resulting suspension was extracted with CH_2Cl_2 (3 × 20.0 mL). The combined organic layers was concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane-CH_2Cl_2 1:1) to provide

the expected **10b** (0.42 g, 100%) as an oil.[1]H NMR δ 3.56 (d, $J = 2.4$ Hz, 2H), 3.81 (s, 6H), 6.64 (d, $J = 1.8$ Hz, 1H), 6.70 (dd, $J = 8.1, 1.8$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 9.66 (t, $J = 2.4$ Hz, 1H); ^{13}C NMR δ 50.1, 55.8, 55.9, 111.6, 112.6, 121.8, 124.1, 148.4, 149.3, 199.5.

2-Bromophenylacetaldehyde (10c)[14]

Compound **10c** was prepared, using the previous procedure, from **9c** (0.30 g, 1.3 mmol) and NaOH (0.21 g, 5.2 mmol) in ethanol (5.0 mL) and stirred for 10 min at 25 °C, and then the solvent was evaporated in vacuo to give the desired sodium nitronate, which was dissolved in distilled H_2O (3.0 mL). The solution was added into the two-layer mixture of concentrated H_2SO_4/H_2O (2.0/4.0 mL) and pentane (15.0 mL) for 1 h at 0 °C and then warmed to 25 °C. After stirring for 3 h, the resulting suspension was extracted with CH_2Cl_2 (3×15.0 mL). The combined organic layers were concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 10:1) to obtain the aldehyde **10c** (0.25 g, 96%) as an oil.[1]H NMR [$(CD_3)_2CO$] δ :3.92 (d, $J = 1.2$ Hz, 2H), 7.19–7.37 (m, 3H), 7.62 (d, $J = 8.1$ Hz, 1H), 9.74 (t, $J = 1.2$ Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$] δ 50.0, 124.6, 127.8, 129.1, 132.2, 132.6, 133.6, 197.6.

2-(4-Isopropoxyphenyl)ethylamine (11a)[15]

$LiAlH_4$ (0.22 g, 5.8 mmol) was added to a solution of **8a** (0.40 g, 1.9 mmol) in dried THF (10.0 mL) at 0 °C and then stirred under N_2 overnight at room temperature. The reaction was quenched with distilled H_2O (5.0 mL), which was extracted with CH_2Cl_2 (3×10.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl–acetate–MeOH 8:2:1) to provide the desired **11a** (0.25 g, 73%) as an oil.[1]H NMR δ :1.25 (d, $J = 6.0$ Hz, 6H), 1.66 (brs, 2H), 2.61 (t, $J = 6.9$ Hz, 2H), 2.85 (t, $J = 6.9$ Hz, 2H), 4.43 (hept, $J = 6.0$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 2H), 7.02 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR :δ 22.0, 38.9, 43.5, 69.9, 115.9, 129.7, 131.5, 156.3.

2-(3,4-Dimethoxyphenyl)ethylamine (11b)[16]

A mixture of **8b** (0.30 g, 1.4 mmol) and $LiAlH_4$ (0.16 g, 4.3 mmol) in dried THF (10.0 mL) was stirred at 25 °C and then heated to reflux under N_2 for 3 h. The reaction was quenched with distilled H_2O (5.0 mL), which was extracted with CH_2Cl_2 (3×10.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, ethyl acetate-MeOH 19:1) to provide the desired **11b** (0.21 g, 83%) as an oil (lit.[17] mp 155–156 °C);[1]H NMR δ :1.30 (brs, 2H), 2.58 (t, $J = 6.9$ Hz, 2H), 2.81 (t, $J = 6.9$ Hz, 2H), 3.80 (s, 3H), 3.87 (s, 3H), 6.60–6.66 (m, 3H); ^{13}C NMR δ 39.2, 43.2, 55.4, 55.5, 111.0, 111.7, 120.3, 132.0, 147.1, 148.5.

2-(2-Bromophenyl)ethylamine (11c)[18]

$LiAlH_4$ (0.22 g, 5.8 mmol) was added to a solution of **8c** (0.44 g, 1.9 mmol) in dried THF (10.0 mL) at 0 °C, and then stirred under N_2 overnight at room

temperature. The reaction was quenched with distilled H_2O (5.0 mL), which was extracted with CH_2Cl_2 (3 × 10.0 mL). The combined organic layers was concentrated in vacuo, and the residue was subjected to flash chromatography (SiO_2, hexane–ethyl–acetate–MeOH 8:2:1) to provide the expected **11c** (0.20 g, 56%) as a oil. ^{1}H NMR δ :1.55 (brs, 2H), 2.80–2.93 (m, 4H), 6.99–7.03 (m, 1H), 7.16–7.20 (m, 2H), 7.47 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR δ 40.1, 42.0, 124.6, 127.4, 128.0, 130.9, 132.9, 139.0.

Methyl *N*-[2-(3,4-Dimethoxyphenyl)ethyl]carbamate (12a)[19]

A solution of **11b** (1.00 g, 5.5 mmol) in dried THF (30.0 mL) was dissolved, followed by dropwise addition of methyl chloroformate (0.5 mL, 6.6 mmol) under N_2 at 0 °C. The resulting solution was stirred at room temperature, and the reaction was monitored by thin-layer chromatography (TLC). The reaction was quenched with distilled H_2O (20.0 mL), which was extracted with CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl-acetate 1:1) to provide the desired **12a** (1.25 g, 95%) as an oil. ^{1}H NMR δ 2.69 (t, $J = 6.9$ Hz, 2H), 3.35 (q, $J = 6.9$ Hz, 2H), 3.60 (s, 3H), 3.80 (s, 3H), 3.87 (s, 3H), 4.80 (brs, 1H), 6.65–6.68 (m, 2H), 6.75 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR δ 35.6, 42.3, 52.0, 55.7, 55.8, 111.3, 111.9, 120.6, 131.2, 147.6, 148.9, 157.0.

tert-Butyl *N*-[2-(3,4-Dimethoxyphenyl)ethyl]carbamate (12b)

According to the procedure of Toste and Still,[20] a mixture of **11b** (1.40 g, 7.7 mmol), dimethylaminopyradine (DMAP; 0.05 g, 0.4 mmol), and N,N-diisopropylethylamine (DIEA; 2.00 g, 15.5 mmol) in dried CH_2Cl_2 (30.0 mL) was added to Boc_2O (2.00 g, 9.2 mmol) with dropwise at 0 °C. Stirring continued at 0 °C for 30 min and at room temperature for 2 h. The reaction was quenched with saturated aqueous solution of NH_4Cl (10.0 mL), which was extracted with CH_2Cl_2 (3 × 30.0 mL). Evaporation and chromatography (SiO_2, hexane–ethyl–acetate–CH_2Cl_2 1:1:1) gave **12b** (2.02 g, 93%) as a white solid: mp 61–62 °C. ^{1}H NMR δ 1.21 (s, 9H), 2.50 (t, $J = 6.9$ Hz, 2H), 3.10 (t, $J = 6.9$ Hz, 2H), 3.61 (s, 3H), 3.63 (s, 3H), 4.60 (brs, 1H), 6.49–6.60 (m, 3H); ^{13}C NMR δ 28.3, 35.7, 42.0, 55.6, 55.7, 78.9, 111.3, 111.9, 120.6, 131.5, 147.5, 148.8, 155.8.

1-(4-Isopropoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (13)

A mixture of **12a** (0.51 g, 2.1 mmol) and **10a** (0.75 g, 4.2 mmol) in mixed solvents of CH_2Cl_2 and $CHCl_3$ (20.0/20.0 mL) was introduced by dropwise addition of BF_3-OEt_2 (0.5 mL, 3.9 mmol) at −78 °C for 1 h. The resulting solution was stirred at room temperature, and the reaction was monitored by TLC. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10.0 mL), which was extracted with CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the crude product was directly used with no further purification. To a solution of the crude product in dried THF (40.0 mL), $LiAlH_4$ (0.24 g, 6.3 mmol) was added at 0 °C under N_2. The reaction was quenched with distilled H_2O (10.0 mL), which was extracted with

CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, CH_2Cl_2-ethyl acetate–MeOH 10:2:1) to provide the desired **13** (0.50 g, 67%) as an oil. ^1H NMR [$(CD_3)_2CO$] δ :1.45 (d, $J = 6.0$ Hz, 6H), 2.42 (s, 3H), 2.44–2.81 (m, 4H), 2.99–3.15 (m, 2H), 3.56 (s, 3H), 3.63 (t, $J = 6.0$ Hz, 1H), 3.82 (s, 3H), 4.52 (hept, $J = 6.0$ Hz, 1H), 6.32 (s, 1H), 6.57 (s, 1H), 6.74 (d, $J = 8.4$ Hz, 2H), 7.01 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR [$(CD_3)_2CO$] :δ 21.4, 25.3, 39.9, 42.1, 47.0, 54.9, 55.0, 64.7, 69.1, 111.5, 111.7, 115.1, 126.4, 129.6, 130.7, 132.0, 147.0, 147.6, 156.1; HRMS (EI) calcd. for $C_{22}H_{29}NO_3$ (M^+) 355.2147; found 355.2142.

1,2-Dimethoxy-4,5,6a,7-tetrahydrodibenzo[*de,g*] quinoline-6-carboxylic Acid Methyl Ester (15a)[2c]

Compound **15a** was prepared, using the previous procedure, from **12a** (0.30 g, 1.3 mmol) and **10c** (0.50 g, 2.5 mmol) in mixed solvents of CH_2Cl_2 and $CHCl_3$ (20.0/20.0 mL), followed by dropwise addition of BF_3-OEt_2 (0.3 mL, 2.5 mmol) at − 78 °C for 1 h by TLC monitoring. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10.0 mL), which was extracted with CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the crude **14a** was directly used no further purification. A mixture of **14a** (0.53 g, 1.3 mmol), AIBN (0.01 g, 63.2 μmol), and Bu_3SnH (0.37 g, 1.3 mmol) in dried toluene (35.0 mL) was heated to reflux under N_2. The reaction was monitored by TLC and quenched with addition of cyclohexane (10.0 mL), which was extracted with CH_2Cl_2 (3 × 35.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 5:1) to obtain the desired **15a** (0.22 g, 52%) as an oil.^1H NMR δ 2.51 (d, $J = 15.0$ Hz, 1H), 2.66–2.89 (m, 4H), 3.52 (s, 3H), 3.62 (s, 3H), 3.74 (s, 3H), 4.31 (d, $J = 10.5$ Hz, 1H), 4.61 (d, $J = 12.9$ Hz, 1H), 6.53 (s, 1H), 7.10–7.20 (m, 3H), 8.31 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR δ 30.2, 35.2, 38.9, 51.6, 52.6, 55.9, 59.9, 111.5, 126.0, 127.0, 127.5, 127.6, 128.3, 128.4, 129.6, 131.7, 136.7, 145.6, 152.0, 155.9.

1,2-Dimethoxy-4,5,6a,7-tetrahydrodibenzo[*de,g*] quinoline-6-carboxylic Acid *tert*-Butyl Ester (15b)[2c]

A mixture of **12b** (0.28 g, 1.0 mmol) and **10c** (0.39 g, 2.0 mmol) in mixed solvents of CH_2Cl_2 and $CHCl_3$ (20.0/20.0 mL) was stirred and followed by dropwise addition of BF_3-OEt_2 (0.3 mL, 2.5 mmol) at − 78 °C for 1 h by TLC monitoring. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (10.0 mL), which was extracted with CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the crude **14b** was directly used no further purification. A mixture of **14b** (0.46 g, 1.0 mmol), AIBN (0.01 g, 63.2 μmol), and Bu_3SnH (0.29 g, 1.0 mmol) in dried toluene (30.0 mL) was heated to reflux under N_2. The reaction was monitored by TLC and quenched with addition of cyclohexane (10.0 mL), which was extracted with CH_2Cl_2 (3 × 30.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 4:1) to obtain the desired **15b** (0.21 g, 56%) as a white solid: mp 184–185 °C, ^1H NMR δ 1.41 (s, 9H), :2.56 (d, $J = 14.4$ Hz, 1H), 2.70–2.90 (m, 4H), 3.64 (s, 3H), 3.81 (s, 3H), 4.34 (d, $J = 9.9$ Hz, 1H), 4.58 (d, $J = 12.9$ Hz, 1H), 6.59 (s, 1H), 7.12–7.25 (m, 3H), 8.35 (d, $J = 7.8$ Hz,

1H); ^{13}C NMR δ 28.5, 30.4, 35.4, 38.4, 51.6, 55.9, 60.0, 79.8, 111.4, 126.5, 126.9, 127.5, 127.6, 128.1, 128.4, 129.8, 131.7, 137.0, 145.5, 151.9, 154.6; HRMS (EI) calcd. for $C_{23}H_{27}NO_4$ (M^+) 381.1940; found 381.1943.

4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)phenol (1)

BCl_3 (1.6 mL, 1 M) was added dropwise to a solution of **13** (0.58 g, 1.6 mmol) in CH_2Cl_2 (50.0 mL) at 0 °C. The reaction was stirred at room temperature and monitored by TLC. The resulting reaction was quenched by treatment with saturated aqueous solution of $NaHCO_3$ (5.0 mL), which was extracted with CH_2Cl_2 (3 × 50.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 7:1) to afford **1** (0.35 g, 69%) as a white solid: mp 155–156 °C (lit.[4b] mp 166 °C); ^{1}H NMR δ :2.54 (s, 3H), 2.59–2.96 (m, 4H), 3.13–3.28 (m, 2H), 3.53 (s, 3H), 3.71 (s, 1H), 3.74 (t, $J = 7.5$ Hz, 1H), 3.83 (s, 3H), 5.97 (s, 1H), 6.56 (s, 1H), 6.63 (d, $J = 8.1$ Hz, 2H), 6.90 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR δ 24.3, 40.3, 41.9, 45.8, 55.4, 55.7, 64.8, 111.1, 111.2, 115.5, 124.9, 128.3, 130.4, 130.7, 146.2, 147.3, 155.0; HRMS (FAB+H) calcd. for $C_{19}H_{24}NO_3$ [$(M+H)^+$] 314.1756; found 314.1766.

1,2-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline (2)

A solution of **15a** (0.14 g, 0.4 mmol) in THF (10.0 mL) was treated by dropwise addition of $LiAlH_4$ (1.6 mL of 1 M in THF, 1.6 mmol) at 0 °C for 1 h. The resulting reaction was quenched with distilled H_2O (5.0 mL) and allowed to warm to room temperature. When a gelatinous mixture formed, it was diluted with CH_2Cl_2 (20.0 mL). The mixture was filtered, washing with CH_2Cl_2 and MeOH. The solvent was evaporated, and the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 1:6) to afford **2** (80 mg, 66%) as a colorless oil (lit.[21] mp 165 °C).^{1}H NMR δ :2.38–2.62 (m, 3H), 2.47 (s, 3H), 2.93–3.15 (m, 4H), 3.76 (s, 3H), 3.85 (s, 3H), 6.55 (s, 1H), 7.12–7.25 (m, 3H), 8.29 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR δ 29.1, 35.0, 43.9, 53.2, 55.8, 60.2, 62.3, 111.2, 126.8, 127.0, 127.3, 127.7, 127.8, 128.3, 128.6, 132.1, 136.4, 145.1, 152.0; HRMS (EI) calcd. for $C_{19}H_{21}NO_2$ (M^+) 295.1572; found 295.1568.

1,2-Dimethoxy-5,6,6a,7-tetrahydro-4*H*-dibenzo[*de,g*]quinoline (3)

Compound **15b** (0.10 g, 0.3 mmol) was dissolved in MeOH (5.0 mL) and followed by dropwise addition of AcCl (30.0 μL, 0.4 mmol) at room temperature. The reaction was stirred at room temperature and monitored by TLC for 3 h. The resulting reaction was quenched by treatment with saturated aqueous solution of $NaHCO_3$ (3.0 mL), which was extracted with CH_2Cl_2 (3 × 10.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, CH_2Cl_2–ethyl acetate–MeOH 8:4:1) to provide the desired **3** (44 mg, 59%) as a yellow solid: mp 208–209 °C (lit.[4a] mp 136–137 °C);^{1}H NMR δ :2.56–2.79 (m, 3H), 2.89–2.96 (m, 2H), 3.28–3.30 (m, 1H), 3.54 (s, 3H), 3.72–3.78 (m, 1H), 3.76 (s, 3H),

6.52 (s, 1H), 7.09–7.19 (m, 3H), 7.13 (s, 1H), 8.26 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR δ 28.6, 37.0, 42.9, 53.4, 55.9, 60.2, 111.7, 126.6, 127.1, 127.4, 127.7, 127.8, 128.3, 128.4, 132.0, 135.7, 145.3, 152.3; HRMS (EI) calcd. for $C_{18}H_{19}NO_2$ (M^+) 281.1416; found 281.1410.

(4-Isopropoxyphenyl)acetic Acid (17)

i-PrBr (3.3 mL, 35.1 mmol) was added to a mixture of 4-hydroxyacetophenone (3.31 g, 24.3 mmol) and K_2CO_3 (4.15 g, 30.1 mmol) in acetone (50.0 mL) at 50 °C and then refluxed at 70 °C for 8 h by TLC monitoring. After cooling, the solution was evaporated in vacuo, and the brown residue was subjected to flash chromatography (SiO_2, hexane–CH_2Cl_2 10:1) to give **16** (4.12 g, 95%) as a colorless oil.^{1}H NMR δ : 1.30 (d, $J = 6.0$ Hz, 6H), 2.48 (s, 3H), 4.58 (hept, $J = 6.0$ Hz, 1H), 6.84 (d, $J = 8.7$ Hz, Hz, 2H), 7.86 (d, $J = 8.7$ Hz, 2H); ^{13}C NMR :δ 21.8, 26.2, 70.0, 115.0, 129.7, 130.6, 162.0, 198.0. A mixture of **16** (3.01 g, 16.9 mmol), sulfur (1.08 g, 33.8 mmol), morpholine (4.4 mL, 50.3 mmol), and *p*-toluenesulfonic acid (97 mg, 0.5 mmol) was refluxed at 120 °C for 4 h. After completion of the reaction, the mixture was allowed to cool, and 20% NaOH (20.0 mL) and tetrabutylammonium bromide (27 mg, 85.0 μmol) were added. Hydrolysis continued for further 8 h at 100 °C. The cooled reaction mixture was filtered and the filtrate was acidified with HCl to pH 2, which was extracted with ethyl acetate (3 × 50.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–ethyl acetate 10:1) to afford **17** (2.33 g, 71%) as a white solid: mp 56–57 °C (lit.[22] mp 57–61 °C),^{1}H NMR δ :1.32 (d, $J = 6.0$ Hz, 6H), 3.56 (s, 2H), 4.51 (hept, $J = 6.0$ Hz, 1H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.17 (d, $J = 8.7$ Hz, 2H), 11.98 (brs, 1H); ^{13}C NMR δ 22.0, 40.1, 69.9, 115.9, 125.1, 130.4, 157.1, 178.3.

N-[2-(3,4-Dimethoxyphenyl)-ethyl]-2-(4-isopropoxyphenyl)-acetamide (18)

Oxalyl chloride (0.2 mL, 2.4 mmol) was added to a solution of **17** (0.39 g, 2.0 mmol) in dried CH_2Cl_2 (15.0 mL) dropwise at room temperature with stirring for 30 min, followed by evaporation to give the residue, which was directly used with no further purification. A solution of the crude product in dried CH_2Cl_2 (20.0 mL) was cooled to 0 °C, followed by dropwise addition of **11b** (0.36 g, 2.0 mmol) in CH_2Cl_2 (10.0 mL) for 1 h. The resulting reaction was quenched by treatment with saturated aqueous solution of $NaHCO_3$ (5.0 mL), which was extracted with CH_2Cl_2 (3 × 30.0 mL). After the removal of solvent, the residue was subjected to flash chromatography (SiO_2, hexane–CH_2Cl_2–ethyl acetate 5:1:1) to provide the desired **18** (0.59 g, 82%) as a white solid: mp 80–81 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.26 (d, $J = 6.0$ Hz, 6H), 2.66 (t, $J = 7.2$ Hz, 2H), 3.35 (s, 2H), 3.36 (q, $J = 7.2$ Hz, 2H), 3.73 (s, 3H), 3.80 (s, 3H), 4.55 (hept, $J = 6.0$ Hz, 1H), 6.62–6.65 (m, 1H), 6.76–6.81 (m, 4H), 7.01 (brs, 1H), 7.13 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR [$(CD_3)_2CO$] :δ 21.4, 35.0, 40.7, 42.1, 55.0, 55.2, 69.2, 111.9, 112.6, 115.5, 120.6, 128.1, 130.1, 132.1, 147.9, 149.3, 156.7, 170.3; HRMS (EI) calcd. for $C_{21}H_{27}NO_4$ (M^+) 357.1940; found 357.1939.

1-(4-Isopropoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (19)

$POCl_3$ (0.1 mL, 1.1 mmol) was added to a solution of **18** (0.26 g, 0.7 mmol) in dried acetonitrile (10.0 mL) at room temperature, and the resulting solution was refluxed for 2 h. The reaction was quenched with saturated aqueous solution of $NaHCO_3$ (3.0 mL), which was extracted with CH_2Cl_2 (3×10.0 mL). After the removal of solvent, the crude product was directly used no further purification. The crude reaction mixture was dissolved in MeOH (10.0 mL) at room temperature for 5 min. $NaBH_4$ (0.11 g, 2.9 mmol) was added at room temperature, and the solution was stirred and monitored by TLC for 1 h. The solvent was evaporated and the residue was subjected to flash chromatography (SiO_2, CH_2Cl_2–ethyl acetate 1:15) to obtain **19** (0.15 g, 60%) as a colorless oil.^{1}H NMR δ :1.33 (d, $J = 6.0$ Hz, 6H), 2.18 (brs, 1H), 2.70–2.95 (m, 4H), 3.11–3.25 (m, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 4.08–4.12 (m, 1H), 4.52 (hept, $J = 6.0$ Hz, 1H), 6.59 (s, 1H), 6.62 (s, 1H), 6.85 (d, $J = 8.4$ Hz, 2H), 7.14 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR δ 22.1, 29.4, 40.6, 41.7, 55.8, 55.9, 56.8, 69.8, 109.4, 111.7, 116.0, 127.2, 130.3, 130.4, 130.7, 146.9, 147.3, 156.5.

Compound 13 from 19

To a solution of **19** (0.14 g, 0.4 mmol) in MeOH (5.0 mL), 37% aqueous solution of formaldehyde (0.06 mL, 0.8 mmol) was added at room temperature with stirring for 1 h. $NaBH_4$ (23 mg, 0.6 mmol) was added at room temperature, and the solution was stirred and monitored by TLC for 1 h. The solvent was evaporated and the residue was subjected to flash chromatography (SiO_2, CH_2Cl_2–ethyl acetate 1:7) to obtain **13** (0.12 g, 83%) as a yellow oil.

ACKNOWLEDGMENTS

We thank the National Science Council (NSC) of the Republic of China for financial support (Research Grant NSC 96–2113-M-018–001-MY2). We also acknowledge with appreciation the NSC-supported HRMS spectrometry facility for providing HRMS.

REFERENCES

1. (a) Tseng, T. H.; Lee, Y. J. Evaluation of natural and synthetic compounds from east Asiatic folk medicinal plants on the mediation of cancer. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 347–365, and references therein; (b) Chang, C. F.; Yang, L. Y.; Chang, S. W.; Fang, Y. T.; Lee, Y. J. Total synthesis of demethylwedelolactone and wedelolactone by Cu-mediated/Pd(0) catalysis and oxidation–cyclization. *Tetrahedron* **2008**, *64*, 3661–3666;(c) Cheng, C. F.; Lai, Z. C.; Lee, Y. J. Total synthesis of (±)-camphorataimides and (±)-himanimides by $NaBH_4/Ni(OAc)_2$ or Zn/AcOH stereoselective reduction. *Tetrahedron* **2008**, *64*, 4347–4353.
2. (a) Zhang, A.; Neumeyer, J. L.; Baldessarini, R. J. Recent progress in development of dopamine receptor subtype-selective agents: Potential therapeutics for neurological and psychiatric disorders. *Chem. Rev.* **2007**, *107*, 274–302, and references therein;

(b) Wright, C. W.; Marshall, S. J.; Russell, P. F.; Anderson, M. M.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Schiff Jr, P. L. In vitro antiplasmodial, antiamoebic, and cytotoxic activities of some monomeric isoquinoline alkaloids. *J. Nat. Prod.* **2000**, *63*, 1638–1640; (c) Lafrance, M.; Blaquiere, N.; Fagnou, K. Aporphine alkaloid synthesis and diversification via direct arylation. *Eur. J. Org. Chem.* **2007**, 811–825, and references therein; (d) Woo, S. H.; Sun, N. J.; Cassady, J. M.; Snapka, R. M. Topoisomerase II inhibition by aporphine alkaloids. *Biochem. Pharmacol.* **1999**, *57*, 1141–1145.

3. (a) Kashiwada, Y.; Aoshima, A.; Ikeshiro, Y.; Chen, Y. P.; Furukawa, H.; Itoigawa, M.; Fujioka, T.; Mihashi, K.; Cosentino, L. M.; Morris-Natschke, S. L.; Lee, K. H. Anti-HIV benzylisoquinoline alkaloids and flavonoids from the leaves of *Nelumbo nucifera*, and structure–activity correlations with related alkaloids. *Bioorg. Med. Chem.* **2005**, *13*, 443–448;(b) Chia, Y. C.; Chen, K. S.; Chang, Y. L.; Teng, C. M.; Wu, Y. C. Antiplatelet actions of aporphinoids from Formosan plants. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3295–3300.
4. (a) Gulland, J. M.; Haworth, R. D. Synthetical experiments on the aporphine alkaloids, I: Synthesis of 5,6-dimethoxyaporphine. *J. Chem. Soc.* **1928**, 581–591;(b) Marion, L.; Lemay, L.; Portelance, V. The synthesis of dl-armepavine. *J. Org. Chem.* **1950**, *15*, 216–220;(c) Weisbach, J. A.; Douglas, B. An improved synthesis of noraporphines. *J. Org. Chem.* **1962**, *27*, 3738–3740;(d) Cava, M. P.; Dalton, D. R. An improved synthesis of dl-anonaine. *J. Org. Chem.* **1966**, *31*, 1281–1283;(e) Cava, M. P.; Mitchell, M. J.; Havlicek, S. C.; Lindert, A.; Spangler, R. J. Photochemical routes to aporphines: New syntheses of nuciferine and glaucine. *J. Org. Chem.* **1970**, *35*, 175–179;(f) Costanza, C.; Lenz, G. R.; Lessor, R. A. The synthesis of oxoaporphines and phenanthrenediones from 7-hydroxydehydronoraporphines. *Heterocycles* **1992**, *34*, 465–478;(g) Cuny, G. D. Intramolecular *ortho*-arylation of phenols utilized in the synthesis of the aporphine alkaloids (±)-lirinidine and (±)-nuciferine. *Tetrahedron Lett.* **2003**, *44*, 8149–8152;(h) Zhang, Y. N.; Zhong, X. G.; Zheng, Z. P.; Hu, X. D.; Zuo, J. P.; Hu, L. H. Discovery and synthesis of new immunosuppressive alkaloids from the stem of *Fissistigma oldhamii* (Hemsl) Merr. *Bioorg. Med. Chem.* **2007**, *15*, 988–996;(i) Nimgirawath, S.; Lorpitthaya, R.; Wanbanjob, A.; Taechowisan, T.; Shen, Y. M. Total synthesis and the biological activities of (±)-norannuradhapurine. *Molecules* **2009**, *14*, 89–101.
5. Cox, E. D.; Cook, J. M. The Pictet–Spengler condensation: A new direction for an old reaction. *Chem. Rev.* **1995**, *95*, 1797–1842, and references therein.
6. (a) Buu-Hoï, N. P.; Long, C. T.; Xuong, N. D. α,α-Dimethyl-β-arylethylamines and their behavior in the Bischler-Napieralski reaction. *J. Org. Chem.* **1958**, *23*, 42–45; (b) Jude, Z. M.A.; Ching, C. B.; Bu, J.; McCluskey, A. The first Bischler-Napieralski cyclization in a room temperature ionic liquid. *Tetrahedron Lett.* **2002**, *43*, 5089–5091.
7. (a) Noland, W. E. The Nef reaction. *Chem. Rev.* **1955**, *55*, 137–155, and references therein;(b) Ballini, R.; Petrini, M. Recent synthetic developments in the nitro to carbonyl conversion (Nef reaction). *Tetrahedron* **2004**, *60*, 1017–1047, and references therein.
8. (a) Ott, A. C.; Mattano, L. A.; Coleman, G. H. Preparation of hydroxyphenylalkanoic acids by the Willgerodt reaction. *J. Am. Chem. Soc.* **1946**, *68*, 2633–2634;(b) Alam, M. M.; Adapa, S. R. $Bi(OTf)_3$-catalyzed Baeyer–Villiger oxidation of carbonyl compounds with *m*-CPBA. *Synth. Commun.* **2003**, *33*, 59–63.
9. The x-ray data for **1** is deposited at Cambridge Chrystallographic Data Centre as number CCDC708759.
10. Gusakova, L. A.; Smirnov, B. P.; Chistyakov, I. G. Synthesis of certain liquid crystal substances. *Khim.* **1968**, 22B744.
11. Cochran, T. G.; Huitric, A. C. Nuclear magnetic resonance as a monitor in optical resolution, II: Synthesis and resolution of *cis*- and *trans*-2-(*o*-bromophenyl)cyclohexylamines. *J. Org. Chem.* **1971**, *36*, 3046–3048.

12. Bhattacharjya, A.; Mukhopadhyay, R.; Pakrashi, S. C. Sodium borohydride reduction of nitrostyrenes by reverse addition: A simple and efficient method for the large-scale preparation of phenylnitroethanes. *Synthesis* **1985**, 886–887.
13. Barash, M.; Osbond, J. M. Chemical constitution and amebicidal action, III: Synthesis of an analog of emetine and two stereoisomers of de-ethylemetine. *J. Chem. Soc.* **1959**, 2157–2168.
14. Hartman, G. D.; Philips, B. T.; Halczenko, W. Iminium ion–mediated cyclizations of 4-aryl-1,4-dihydropyridines: Bridging with acetals, carbonyls, and thiocarbonyls. *J. Org. Chem.* **1985**, *50*, 2423–2427.
15. Mndzhoyan, A. L.; Aroyan, A. A.; Ovsepyan, T. R. Amines and derivatives, XI: The preparation of some chloroacetamides and urethans. *Khim. Nauki* **1961**, *14*, 157–163.
16. Kubo, A.; Saito, N.; Kawakami, N.; Matsuyama, Y.; Miwa, T. A facile synthesis of 1,2,3,4-tetrahydroisoquinolines through cyclization of *O,N*-acetals. *Synthesis* **1987**, 824–827.
17. Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Balk, M. A.; Laikos, G. D.; Vishwanath, V. M. Friedel-Crafts acylation with N-(trifluoroacetyl)-α-amino acid chlorides: Application to the preparation of β-arylalkylamines and 3-substituted 1,2,3,4-tetrahydroisoquinolines. *J. Org. Chem.* **1984**, *49*, 4107–4111.
18. Mori, M.; Chiba, K.; Ban, Y. Reactions and syntheses with organometallic compounds, 7: Synthesis of benzolactams by palladium-catalyzed amidation. *J. Org. Chem.* **1978**, *43*, 1684–1687.
19. (a) Kaim, L. E.; Grimaud, L.; Lee, A.; Perroux, Y.; Tirla, C. First carbamates conversion to amides by simple alkyl group transfer from trialkylalanes. *Org. Lett.* **2004**, *6*, 381–383;(b) Ito, Y.; Ushitora, H. Trapping of carbamic acid species with (trimethylsilyl)diazomethane. *Tetrahedron* **2006**, *62*, 226–235.
20. Toste, F. D.; Still, I. W. J. A new route to the synthesis of the naturally occurring benzopentathiepin varacin. *J. Am. Chem. Soc.* **1995**, *117*, 7261–7262.
21. Lu, S. T.; Wu, Y. C. Studies on the alkaloids of *Formosan lauraceous* plants, XXIX: Transformation from aporphine *N*-oxides to 1-(*N*-methyl-*N*-hydroxylaminoethyl)phenanthrene derivatives. *Heterocycles* **1985**, *23*, 3085–3094.
22. Solladie, G.; Pasturel-Jacopé, Y.; Maignan, J. A re-investigation of resveratrol synthesis by the Perkins reaction: Application to the synthesis of aryl cinnamic acids. *Tetrahedron* **2003**, *59*, 3315–3321.