JOC Article

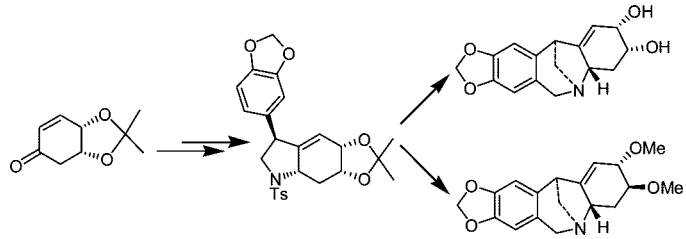
An Expedient Route to Montanine-Type Amaryllidaceae Alkaloids: Total Syntheses of (−)-Brunsvigine and (−)-Manthine

An-Wei Hong, Tsung-Hui Cheng, Vellingiri Raghukumar, and Chin-Kang Sha*

Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan, ROC

cksha@mx.nthu.edu.tw

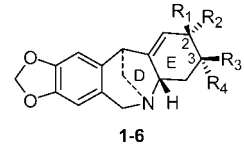
Received June 2, 2008



The first total syntheses of (−)-brunsvigine (**1**) and (−)-manthine (**2**) were accomplished in 10 and 18 steps, respectively. (−)-Quinic acid was converted to enone **12** in five steps. Iodination of enone **12** followed by stereoselective reduction yielded α-iodo allylic alcohol **16**. Conversion of alcohol **16** into Weinreb amide **11** followed by anionic cyclization gave bicyclic enone **10**. Stereoselective reduction of enone **10** and subsequent protection afforded pivaloate **9**. Grignard addition of **8** to **9** and detosylation afforded amine derivative **19**. Pictet−Spengler cyclization of **19** with Eschenmoser's salt and subsequent hydrolysis gave enantiomerically pure (−)-brunsvigine (**1**). For the total synthesis of (−)-manthine (**2**), the key intermediate **7** was hydrolyzed to diol **21**. Conversion of **21** into **22** followed by regioselective cleavage with DIBAL furnished alcohol **25**. Alcohol **25** was converted to the corresponding triflate **26**, which on treatment with CsOAc and 18-crown-6 gave stereoinverted acetate **27**. Hydrolysis of acetate **27** followed by methylation afforded compound **29**. Detosylation of **29** afforded amine derivative **30**. Pictet−Spengler cyclization of **30** followed by debenzylation gave alcohol **33**. Finally, methylation of alcohol **33** afforded (−)-manthine (**2**).

Introduction

(−)-Brunsvigine and (−)-manthine, which are representative members of montanine-type Amaryllidaceae alkaloids **1**−**6**,[1−3] incorporate an intriguing pentacyclic 5,11-methanomorphanthridine as the core skeleton. These alkaloids differ only in the stereochemistry of the C2 and C3 oxygen substituents in the E ring (Figure 1).[4] When Wildman and co-workers initiated the investigation of Amaryllidaceae alkaloids in 1955,[5] they isolated (−)-manthine (**2**) from *Haemathus* species and (−)-brunsvigine (**1**) from *Brunsvigia cooperi* and *Brunsvigia radulosa* Herp.[1,2] These montanine-type alkaloids possess important biological activities including anxiolytic, antidepressant, and anticonvulsant-type effects.[6,7] In conjunction with these activities, the unique pentacyclic structure of these alkaloids has stimulated considerable interest from the synthetic community.



1-6

	R_1	R_2	R_3	R_4	
1	H	OH	H	OH	(−)-brunsvigine
2	H	OMe	OMe	H	(−)-manthine
3	OMe	H	OH	H	(−)-coccinine
4	H	OH	OH	H	(−)-pancracine
5	H	OMe	OH	H	(−)-montanine
6	H	OMe	OAc	H	(−)-*O*-acetylmontanine

FIGURE 1. Structure of montanine-type Amaryllidaceae alkaloids.

(1) Dry, L. J.; Poynton, M. E.; Thompson, M. E.; Warren, F. L. *J. Chem. Soc.* **1958**, 4701.
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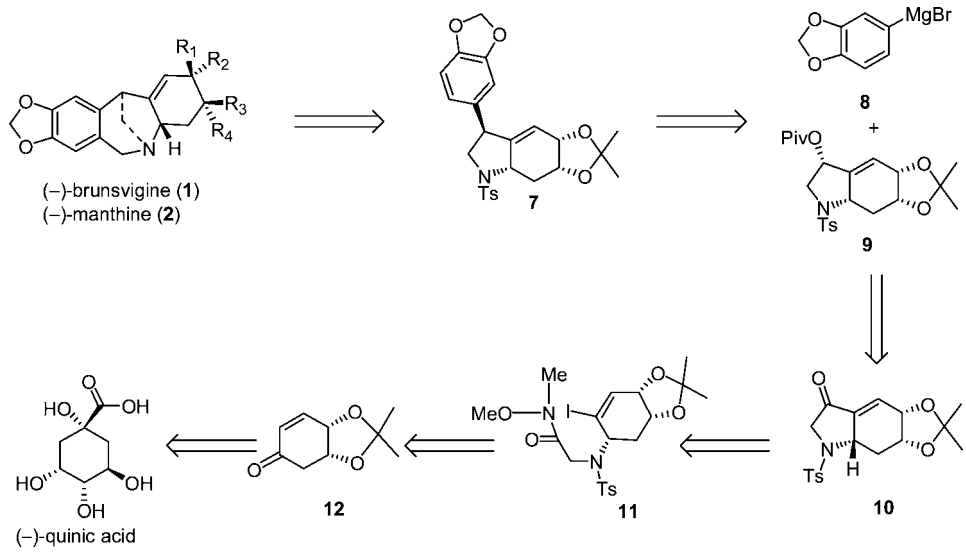
10.1021/jo801089y CCC: $40.75
Published on Web 09/10/2008

SCHEME 1. Retrosynthesis of (−)-Brunsvigine (1) and (−)-Manthine (2)



Since Overman reported the first total synthesis of (±)-pancracine,[8] several total syntheses of natural products in this family have been published. In a series of accounts,[9] Hoshino and co-workers reported two elegant schemes to construct the 5,11-methanomorphanthridine ring system, resulting in preparation of (±)-montanine, (±)-coccinine, (±)-pancracine, (±)-brunsvigine, and (±)-*O*-acetylmontanine. In 1993, Overman and Shim reported the first asymmetric total synthesis of (−)-pancracine[10] employing an aza-Cope−Mannich reaction as the key step. Weinreb et al. reported an enantioselective total syntheses of (−)-coccinine and (−)-pancracine with a formal total synthesis of (−)-brunsvigine.[11] Ishibashi and co-workers reported a clever total synthesis of (±)-pancracine[12] employing radical cyclization as the key step. Pandey's group utilized a 1,3-dipolar cycloaddition of a nonstabilized azomethine ylide to construct the 5,11-methanomorphanthridine ring system.[13] Several formal total syntheses of various members of alkaloids of the montanine type are reported, and the syntheses of antipodes of the natural products, (+)-coccinine[14] and (+)-brunsvigine,[15] have also been described.

Although a massive synthetic effort has been directed toward almost all members of the montanine-type alkaloids, there has been no report other than our own[16] of the total syntheses of (−)-brunsvigine (**1**) and (−)-manthine (**2**). Herein, we report our total syntheses of enantiomerically pure (−)-brunsvigine (**1**) and (−)-manthine (**2**).

We envisaged that the unique 5,11-methanomorphanthridine ring system of (−)-brunsvigine (**1**) and (−)-manthine (**2**) might be established by a Pictet−Spengler reaction (Scheme 1). The necessary variation at C2 and C3 stereocenters would be accessible by taking advantage of synthetic transformations. Key intermediate **7** would be generated from a coupling of Grignard **8** and compound **9**. Compound **9** would be obtained from reduction and esterification of enone **10**. Enone **10** might be prepared from Weinreb amide **11** via an anionic cyclization. Weinreb amide **11** could be obtained from commercially available (−)-quinic acid through a sequence of transformations of functional groups.

Results and Discussion

Our synthetic efforts began with commercially available (−)-quinic acid. The requisite chiral enone **12** was prepared from (−)-quinic acid by adapting a literature procedure.[17] Iodination of enone **12** was accomplished with Johnson's procedure[18] to provide iodoenone **13**. Compound **13** upon treatment with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$[19] afforded a mixture of epimers **14** and **16**, which were separated by column chromatography. As β-isomer **16** was used in the synthesis, the unwanted α-isomer **14** was consequently converted into the required β-isomer via a Mitsunobu reaction. Treatment of **14** with *p*-nitrobenzoic acid in the presence of triphenylphosphine and diethyl azodicarboxylate gave **15**. Compound **15** was hydrolyzed with NaOH in MeOH to give compound **16**. Introduction of the Weinreb amide side chain to compound **16** afforded compound **11**. Anionic cyclization of Weinreb amide **11** in the presence of *n*-BuLi thus furnished the desired bicyclic enone **10** (Scheme 2).

Total Synthesis of (−)-Brunsvigine (1). Stereoselective reduction of enone **10** with $NaBH_4/CeCl_3 \cdot 7H_2O$ gave the corresponding alcohol **18**, which was then converted to pivaloate

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(9) (a) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079. (b) Ishizaki, M.; Hoshino, O. *J. Org. Chem.* **1992**, *57*, 7285. (c) Ishizaki, M.; Kurihara, K.-I.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101.
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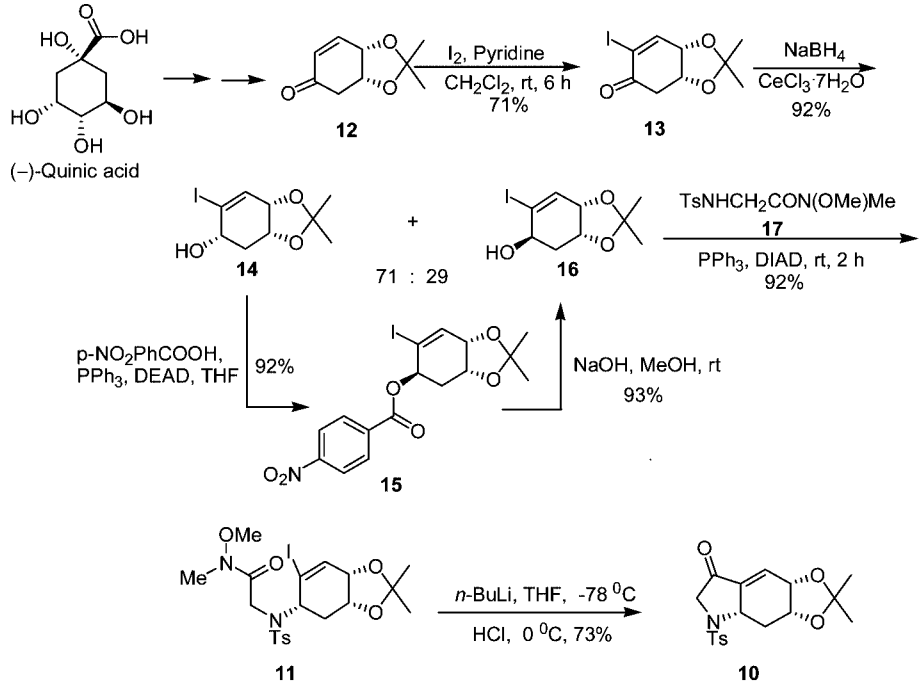
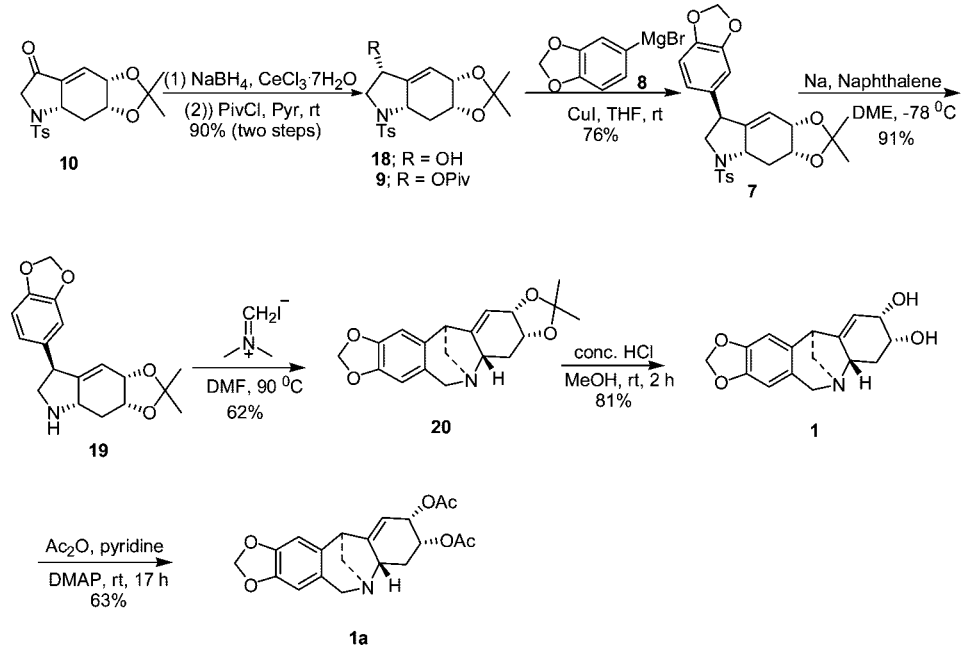
SCHEME 2. Synthesis of Chiral Azabicyclic Enone 10



SCHEME 3. Total Synthesis of (−)-Brunsvigine



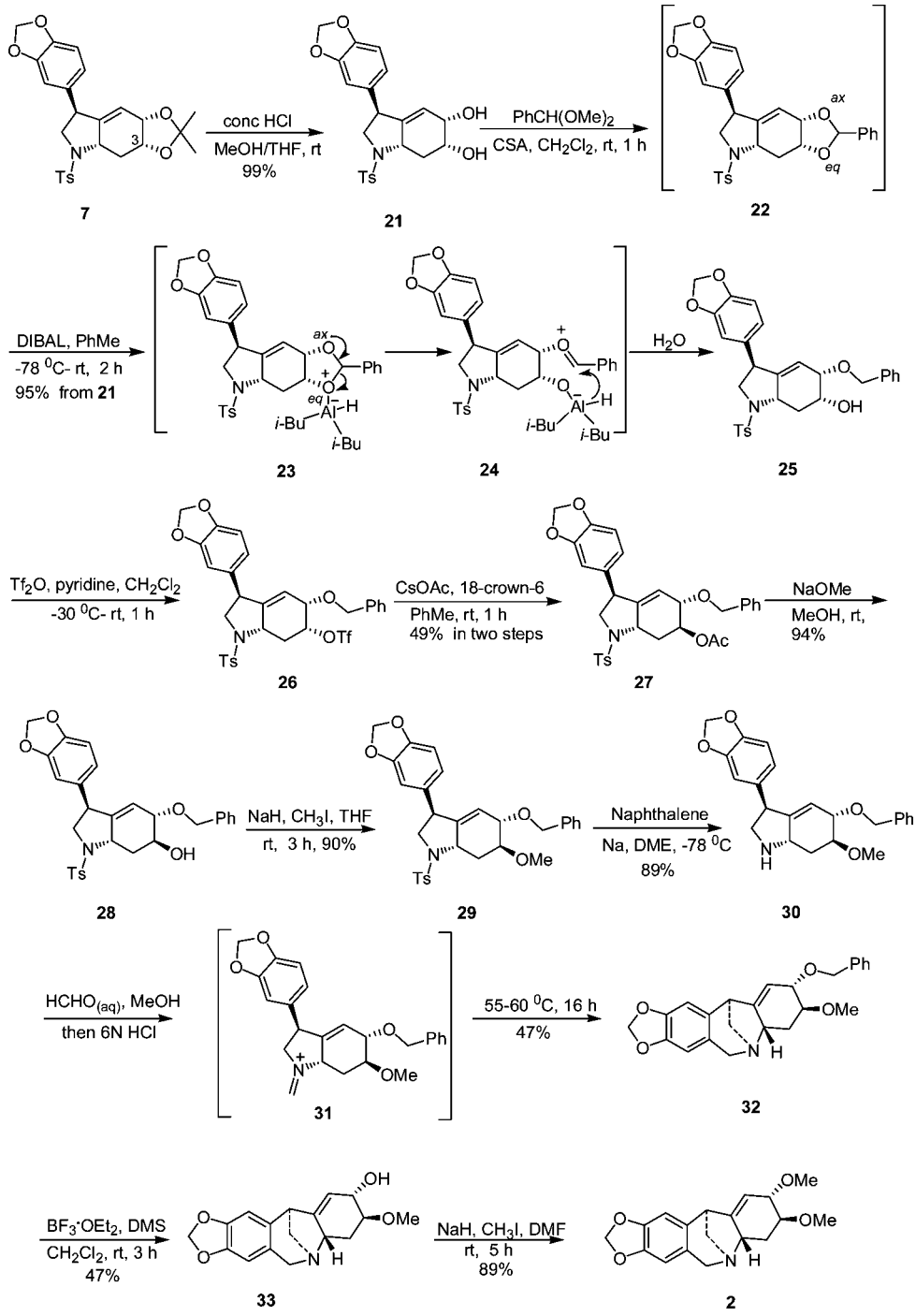
9. The stereochemistry of **9** was unambiguously assigned through a single-crystal X-ray analysis.[20] A CuI-mediated S_N2 reaction of **9** with 3,4-(methylenedioxy)phenylmagnesium bromide (**8**) afforded key intermediate **7**[21] in 76% yield. Detosylation of **7** was executed on titration with sodium naphthalide at −78 °C to produce amine **19**.

To complete the synthesis, we treated amine **19** with dimethylmethyleneimmonium iodide[22] and subsequently hydrolyzed the ketal group to yield (−)-brunsvigine (**1**) (Scheme 3) with an overall yield of 12% from chiral enone **12**. The specific rotation $[\alpha]^{23}_D$= −76.3 (*c* 1.02, EtOH; lit. $[\alpha]^{20}_D$= −76.6 (*c* 1.0, EtOH)), melting point, and spectral data of **1** agree with literature data.[1,2] To confirm the structure, we converted the synthetic (−)-brunsvigine (**1**) to the stable crystalline diacetate **1a**. Structure of **1a** was determined by single-crystal X-ray analysis.[20]

Total Synthesis of (−)-Manthine (2). After having success with the total synthesis of (−)-brunsvigine (**1**), we turned our attention to the synthesis of (−)-manthine (**2**). We began the synthesis with key intermediate **7** (Scheme 4). However, in this

(20) X-ray data of compounds **16** and **1a** are presented in the Supporting Information.
(21) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892.
(22) Clark, R. C.; Warren, R. L.; Pachler, K. G. R. *Tetrahedron* **1975**, *31*, 1855.

SCHEME 4. Total Synthesis of (−)-Manthine



synthetic route, we had to find a suitable method to invert the C−O bond in the C3 stereocenter.

Our next phase of synthesis accordingly began with hydrolysis of the acetonide moiety in **7** to furnish diol **21**. Treatment of diol **21** with dimethoxymethylbenzene and camphorsulfonic acid gave intermediate **22**. Compound **22** was not isolated and immediately subjected to regioselective cleavage with diisobutylaluminum hydride (DIBAL)[9b] to give alcohol **25**. This reaction presumably proceeded through complexation of DIBAL with an oxygen atom of the acetal unit in **22**. Since the *axial* oxygen of **22** is more hindered, the DIBAL may prefer to coordinate with the less hindered *equatorial* oxygen to form the complex **23**. Reductive cleavage of **23**→**24** led to formation of 3-hydroxy product **25** exclusively.

Exposure of **25** to trifluoromethanesulfonic anhydride and pyridine in dichloromethane afforded the corresponding triflate **26**. Compound **26** was efficiently transformed to the corresponding stereoinverted acetate **27** using cesium acetate and 18-crown-6 in toluene.[23] Hydrolysis of **27** with sodium methoxide in methanol gave compound **28**. Methylation of compound **28** afforded compound **29**. Detosylation of **29** with sodium and

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naphthalene in DME at –78 °C gave amine derivative **30**.[24] Treatment of **30** at rt with aqueous formaldehyde and methanolic HCl generated iminium intermediate **31**, which readily underwent Pictet−Spengler cyclization[11b,12,25] to give **32**. Deprotection of the benzyl group in **32** followed by methylation finally afforded (−)-manthine (**2**). The specific rotation $[\alpha]^{25.9}_D$ = −78.4 (*c* 0.50, $CHCl_3$; lit. $[\alpha]^{25.9}_D$ = −80.0 (*c* 0.51, $CHCl_3$)), melting point, and spectral data of the synthetic (−)-manthine (**2**) agree satisfactorily with the literature data.[3,9]

In summary, we have developed a concise and expedient route toward the total syntheses of (−)-brunsvigine (**1**) and (−)-manthine (**2**). Our syntheses feature an efficient and stereocontrolled construction of bicyclic enone **10** employing anionic cyclization. A sequence of synthetic transformations on bicyclic enone **10** established the pivotal framework **7**. Pictet−Spengler cyclization was strategically applied to construct the 5,11-methanomorphanthridine ring system that led to the first total syntheses of (−)-brunsvigine (**1**) and (−)-manthine (**2**). An extension and further application of this method to the total synthesis of other alkaloids are under active investigation in our laboratory.

Experimental Section

(1*S*,13*S*,15*R*,19*S*)-17,17-Dimethyl-5,7,16,18-tetraoxa-12-azahexacyclo[10.9.1.0^{2,10}.0^{4,8}.0^{13,21}.0^{15,19}]docosa-2,4(8),9,20-tetraene (20). To a solution of **19** (75.2 mg, 0.239 mmol) in dry DMF (6 mL) was added dimethylmethyleneimmonium iodide (812 mg, 4.39 mmol). The reaction mixture was stirred at 90−100 °C for 6 h. Upon cooling to 0 °C, the reaction mixture was quenched with water (2 mL) and basified on addition of aqueous NH_3 (3 mL). The aqueous phase was extracted with chloroform (10 mL × 3). The combined extract was washed with brine (5 mL) and dried over Na_2SO_4. Concentration and chromatography on a silica gel column (methanol/$CHCl_3$ 1:30) gave **20** (48 mg, 62%). Data for **20**: IR (neat) ν_{max} 2983, 2936, 2882, 1503, 1482, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.45 (s, 1H), 5.88 and 5.85 (AB quartet, 2H, *J* = 1.4 Hz), 5.69 (dd, 1H, *J* = 2.2, 2.2 Hz), 4.48−4.43 (m, 1H), 4.33 and 3.77 (AB quartet, 2H, *J* = 17.0 Hz), 4.26 (ddd, 1H, *J* = 11.6, 5.6, 5.6 Hz), 3.33−3.00 (m, 1H), 3.11 (dd, 1H, *J* = 10.8, 2.0 Hz), 3.08−3.03 (br s, 1H), 3.04 (d, 1H, *J* = 10.8 Hz), 2.28 (ddd, 1H, *J* = 11.6, 5.6, 5.6 Hz), 1.46 (s, 3H), 1.34 (s, 3H), 1.32 (ddd, 1H, *J* = 11.6, 11.6, 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (C), 146.7 (C), 146.0 (C), 132.1 (C), 124.4 (C), 112.2 (CH), 109.4 (C), 107.1 (CH), 106.7 (CH), 100.7 (CH_2), 73.6 (CH), 71.6 (CH), 62.0 (CH), 60.7 (CH_2), 55.0 (CH_2), 45.2 (CH), 33.0 (CH_2), 27.7 (CH_3), 25.1 (CH_3); MS (EI) *m*/*z* 327 (M$^+$, 100), 312 (32), 252 (65), 223 (21), 212 (19); HRMS (EI) *m*/*z* calcd for $C_{19}H_{21}NO_4$ 327.1470, found 327.1472; $[\alpha]^{18.8}_D$ = −83.5 (*c* 1.33, $CHCl_3$).

(−)-Brunsvigine (1). To a solution of **20** (56.0 mg, 0.171 mmol) in anhydrous MeOH (2 mL) was added concd HCl (0.20 mL, 2.40 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then warmed to rt. After stirring for an additional 2 h, the mixture was cooled to 0 °C, then quenched with water (2 mL) and extracted with chloroform (30 mL × 2). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. Concentration gave crude product **1**. Recrystallization from ethyl acetate/*n*-hexane (2:1) gave compound **1** as a colorless crystal (40 mg, 81%): mp 239−241 °C (lit.[1,2] 243 °C); IR (neat) ν_{max} 3328, 2964, 2876, 1485, 1337, 1236 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.47 (s, 1H), 5.89 (d, 1H, *J* = 1.4 Hz), 5.87 (d, 1H, *J* = 1.4 Hz), 5.76−5.75 (m, 1H), 4.36 (d, 1H, *J* = 16.6 Hz), 4.13−4.12 (m, 1H), 3.87 (d, 1H, *J* = 16.5 Hz), 3.68−3.64 (m, 1H), 3.34 (br s, 1H), 3.26−3.24 (m, 1H), 3.18−3.16 (m, 1H), 3.07 (d, 1H, *J* = 11.1 Hz), 2.25−2.22 (m, 1H), 1.58−1.53 (m, 1H); ^{13}C NMR (150 MHz, MeOD/$CDCl_3$) δ 153.2, 148.5, 147.8, 132.8, 124.4, 118.1, 108.4, 107.8, 102.2, 69.6, 67.0, 64.7, 61.0, 56.3, 46.4, 32.7; MS (EI) *m*/*z* 287 (M$^+$, 100), 269 (41), 243 (18), 223 (23), 199 (57), 185 (44), 128 (30), 115 (33); HRMS (EI) *m*/*z* calcd for $C_{16}H_{17}NO_4$ 287.1158, found 287.1151; $[\alpha]^{20}_D$ = −76.3 (*c* 1.02, EtOH).

(1*S*,13*S*,15*R*,16*S*)-15-(Methylcarbonyloxy)-5,7-dioxa-12-azapentacyclo[10.6.1.0^{2,10}.0^{4,8}.0^{13,18}]nonadeca-2(10),3,8,17-tetraen-16-yl acetate (1a). To a solution of (−)-brunsvigine (**1**) (9.9 mg, 0.0347 mmol) and 4-(dimethylamino)pyridine (DMAP) (2.0 mg, 0.0164 mmol) in dry pyridine (2 mL) was added acetic anhydride (25.0 mg, 0.208 mmol) at rt with stirring for 17 h. Concentration and chromatography on a silica gel column (methanol/chloroform) gave compound **1a** (10 mg, 78%). Data for **1a**: mp 184−185 °C (lit. 184 °C); IR (neat) ν_{max} 2938, 2880,1741, 1504, 1480, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.51 (s, 1H), 6.45 (s, 1H), 5.88 and 5.85 (AB quartet, 2H, *J* = 1.2 Hz), 5.54−5.52 (m, 1H), 5.45 (dd, 1H, *J* = 4.0, 4.0 Hz), 4.93 (ddd, 1H, *J* = 12.0, 4.0, 4.0 Hz), 4.30 and 3.80 (AB quartet, 2H, *J* = 16.8 Hz), 3.32−3.25 (br s, 1H), 3.27 (br s, 1H), 3.08 and 3.04 (AB quartet, 2H, *J* = 17.0 Hz), 2.16−2.10 (m, 1H), 2.07 (s, 3H), 1.99 (s, 3H), 1.71 (ddd, 1H, *J* = 12.0, 12.0, 12.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.0, 156.5, 147.0, 146.1, 131.4, 124.5, 112.1, 107.5, 106.9, 100.8, 68.8, 66.1, 63.0, 61.2, 56.0, 45.4, 30.2, 21.0, 20.9; MS (EI) *m*/*z* 371 (M$^+$, 32), 312 (67), 252 (100), 223 (32); HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}NO_6$ 371.1369, found 371.1372.

(3*S*,5*S*,6*R*,7a*S*)-3-(1,3-Benzodioxol-5-yl)-1-[(4-methylphenyl)-sulfonyl]-2,3,5,6,7,7a-hexahydro-1*H*-6-indolediol (21). To a solution of **7** (302 mg, 0.644 mmol) in MeOH/ THF (5 mL/5 mL) was added concd HCl (0.53 mL) at 0 °C with stirring for 10 min. The mixture was warmed to rt and stirred for an additional 2 h. The reaction was then quenched with K_2CO_3 (3 N, 5 mL) and extracted with dichloromethane (30 mL × 3). The combined organic extract was washed with brine (15 mL) and dried over Na_2SO_4. Concentration and chromatography on a silica gel column (ethyl acetate/*n*-hexane 2:1) gave **21** as a white solid (275 mg, 99%). Data for **21**: mp 166.5−166.7 °C; IR (neat) ν_{max} 3411, 2891, 1504, 1491, 1342 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 6.51 (d, 1H, *J* = 8.0 Hz), 6.29 (dd, 1H, *J* = 8.0, 1.6 Hz), 6.19 (d, 1H, *J* = 1.6 Hz), 5.86 (s, 2H), 5.77 (br s, 1H), 4.12 (br s, 1H), 3.89 (dd, 1H, *J* = 10.4, 7.2 Hz), 3.83−3.78 (m, 1H), 3.76−3.68 (br s, 1H), 3.64−3.55 (br s, 1H), 3.26 (dd, 1H, *J* = 10.4, 4.4 Hz), 3.13 (br s, 1H), 2.90 (br s, 1H), 2.64−2.57 (m, 1H), 2.38 (s, 3H), 1.79 (ddd, 1H, *J* = 11.6, 11.6, 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (C), 146.4 (C), 145.2 (C), 143.9 (C), 134.9 (C), 132.9 (C), 129.6 (CH), 127.6 (CH), 123.3 (CH), 120.0 (CH), 108.2 (CH), 107.1 (CH), 101.0 (CH_2), 67.6 (CH), 65.0 (CH), 59.0 (CH), 55.9 (CH_2), 46.0 (CH), 33.3 (CH_2), 21.4 (CH_3); MS (EI) *m*/*z* 429 (M$^+$, 34), 411 (12), 385 (67), 230 (32), 201 (41), 135 (52), 91 (100); HRMS (EI) *m*/*z* calcd for $C_{20}H_{21}NO_6S$ 371.1369, found 371.1372; $[\alpha]^{21.6}_D$ = +90.4 (*c* 1.04, $CHCl_3$).

(3*S*,5*S*,6*R*,7a*S*)-3-(1,3-Benzodioxol-5-yl)-5-(benzyloxy)-1-[(4-methylphenyl)sulfonyl)]-2,3,5,6,7,7a-hexahydro-1*H*-6-indolol (25). To a solution of diol **21** (275 mg, 0.641 mmol) in anhydrous dichloromethane (15 mL) were added camphorsulfonic acid (15.0 mg, 0.065 mmol) and dimethoxymethylbenzene (0.19 mL, 1.28 mmol) at rt with stirring for 1 h. The mixture was then cooled to −78 °C. DIBAL (1.0 M solution in toluene, 6.40 mL, 6.40 mmol) was added dropwise via a syringe. The reaction mixture was stirred for an additional 40 min and then warmed to rt. The reaction mixture was quenched with water (5 mL). Subsequent addition of dichloromethane (13 mL) produced a white gel suspension. The resulting mixture was filtered through Celite; the filtrate was dried over Na_2SO_4. Concentration and chromatography on a silica gel column (ethyl acetate/*n*-hexane 1:1) gave **25** as a colorless oil (316 mg, 95%). Data for **25**: IR (neat) ν_{max} 3542, 2890, 1504, 1490, 1346, 1160 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, *J* = 8.0

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Hz), 7.35−7.25 (m, 5H), 7.22 (d, 2H, J = 8.0 Hz), 6.55 (d, 1H, J = 8.0 Hz), 6.32 (dd, 1H, J = 8.0, 2.0 Hz), 6.22 (d, 1H, J = 2.0 Hz), 5.88 (s, 2H), 5.76−5.73 (m, 1H), 4.70 and 4.59 (AB quartet, 2H, J = 11.4 Hz), 3.91−3.88 (m, 1H), 3.90 (dd, 1H, J = 10.6, 7.2 Hz), 3.79−3.65 (m, 2H), 3.57−3.50 (m, 1H), 3.25 (dd, 1H, J = 10.6, 4.8 Hz), 2.66 (d, 1H, J = 11.2 Hz), 2.66−2.60 (m, 1H), 2.40 (s, 3H), 1.79 (ddd, 1H, J = 11.6, 11.6, 11.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (C), 146.4 (C), 145.6 (C), 143.7 (C), 137.9 (C), 134.9 (C), 133.0 (C), 129.5 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 121.1 (CH), 120.0 (CH), 108.2 (CH), 107.1 (CH), 101.0 (CH_2), 72.3 (CH_2), 72.2 (CH), 67.4 (CH), 59.0 (CH), 55.8 (CH_2), 46.1 (CH), 34.5 (CH_2), 21.4 (CH_3); MS (EI) m/z 519 (M^+, 2), 475 (47), 384 (100), 320 (16), 229 (37); HRMS (EI) m/z calcd for $C_{29}H_{29}NO_6S$ 519.1715, found 519.1716; $[\alpha]^{22.3}_D$ = +90.0 (c 1.02, $CHCl_3$).

(−)-3-*O*-Methylpancracine (33). To a solution of **32** (8 mg, 0.021 mmol) in anhydrous dichloromethane (0.3 mL) were added dimethylsulfide (0.023 mL, 0.306 mmol) and $BF_3 \cdot OEt_2$ (0.039 mL, 0.306 mmol) at rt. The mixture was stirred for 3 h and quenched with K_2CO_3 (3 N, 2 mL). The resulting mixture was extracted with dichloromethane (5 mL × 3). The combined extract was washed with brine (15 mL) and dried over K_2CO_3. Concentration and chromatography on a silica gel column (chloroform/methanol 8:1) gave **33** as a colorless liquid (2.9 mg, 47%). Data for **33**: IR (neat) ν_{max} 2849, 1650, 1487, 1222, 937, 731 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.56 (s, 1H), 6.47 (s, 1H), 5.89 and 5.87 (AB quartet, 2H, J = 1.4 Hz), 5.60 (br s, 1H), 4.45 and 3.92 (AB quartet, 2H, J = 16.3 Hz), 4.06−4.05 (m, 1H), 3.57−3.56 (m, 1H), 3.51−3.49 (m, 1H), 3.36 (s, 3H), 3.34−3.31 (m, 1H), 3.13 (dd, 1H, J = 10.9, 1.3 Hz), 2.43 (ddd, 1H, J = 12.7, 4.9, 3.7 Hz), 2.13 (br s, 1H), 1.71 (dt, 1H, J = 12.8, 2.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.2 (C), 146.6 (C), 131.0 (C), 129.7 (C), 122.3 (C), 116.5 (CH), 107.6 (CH), 106.9 (CH), 101.0 (CH_2), 80.6 (CH), 66.7 (CH), 59.9 (CH_2), 59.6 (CH), 57.1 (CH_3), 55.3 (CH_2), 45.1 (CH), 27.5 (CH_2); MS (EI) m/z 301 (M^+, 100), 284 (10), 270 (20), 243 (75), 220 (72), 214 (44), 199 (34), 185 (40), 149 (10), 141 (12), 115 (17), 91 (58), 78 (13), 63 (13); HRMS (EI) m/z calcd for $C_{17}H_{19}NO_4$ 301.1314, found 301.1305; $[\alpha]^{26.0}_D$ = −59.8 (c 0.20, $CHCl_3$).

(−)-Manthine (2). To a suspension of NaH (4.9 mg, 0.122 mmol) in anhydrous DMF (0.2 mL) was added a solution of **33** (3.8 mg, 0.012 mmol) in anhydrous DMF (0.2 mL) at 0 °C. The reaction mixture was stirred at rt for 10 min. Iodomethane (0.015 mL, 0.244 mmol) was added. The resulting mixture was stirred for an additional 5 h. Upon cooling to 0 °C, the reaction mixture was quenched with water (0.5 mL) and extracted with dichloromethane (2 mL × 3). The combined extract was washed with brine (5 mL) and dried over Na_2SO_4. Concentration and chromatography on a silica gel column (chloroform/methanol 40:1) gave **2** as a light yellow solid (3.3 mg, 89%), and recrystallization of **2** in *n*-hexane gave colorless crystals. Data for **2**: mp 113.7−115.5 °C (lit.[1,4] 114−116 °C); IR (neat) ν_{max} 2851, 1639, 1483, 1235, 1088, 938 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.43 (s, 1H), 5.87 and 5.84 (AB quartet, 2H, J = 1.5 Hz), 5.54 (br s, 1H), 4.37 and 3.81 (AB quartet, 2H, J = 16.5 Hz), 3.58 (br s, 1H), 3.52−3.51 (m, 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.32−3.27 (m, 2H), 3.09−3.01 (m, 2H), 2.31 (ddd, 1H, J = 13.0, 5.0, 3.5 Hz), 1.42 (dt, 1H, J = 12.0, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (C), 146.8 (C), 146.0 (C), 132.1 (C), 124.2 (C), 113.2 (CH), 107.4 (CH), 106.8 (CH), 100.7 (CH_2), 77.7 (CH), 76.4 (CH), 60.7 (CH_2), 56.8 (CH), 57.4 (CH_3), 56.7 (CH_3), 55.3 (CH_2), 45.6 (CH), 29.1 (CH_2); MS (EI) m/z 315 (M^+, 44), 300 (9), 284 (26), 257 (52), 229 (36), 197 (21), 155 (34), 141 (70), 128 (100), 115 (62), 91 (24), 77 (19); HRMS (EI) m/z calcd for $C_{18}H_{21}NO_4$ 315.1471, found 315.1474; $[\alpha]^{25.9}_D$ = −78.4 (c 0.50, $CHCl_3$; lit.[4] $[\alpha]^{25.9}_D$ = −80.0 (c 0.51, $CHCl_3$).

Acknowledgment. National Science Council of the Republic of China (Taiwan) provided financial support.

Supporting Information Available: Experimental procedures, detailed spectral characterization data; ^{1}H and ^{13}C NMR spectra of compounds **1**, **1a**, **2**, **7**, **9**−**11**, **13**−**16**, **18**−**21**, **25**, **27**−**30**, **32**, and **33**; X-ray data (CIF) for **1a** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801089Y