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A Convenient Route to β-Aryl-substituted Cyclic Enamines as Key Synthetic Intermediates of *Sceletium* and *Amaryllidaceae* Alkaloids

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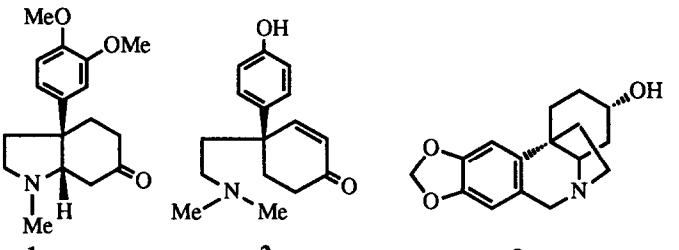
Summary: Aryl groups were introduced into the position β to the nitrogen atom of cyclic amines by carrying out the anodic α-methoxylation of cyclic amine derivatives, the elimination of methanol from the oxidized products, the halomethoxylation of the resulting α,β-unsaturated cyclic amine derivatives, the replacement of the α-methoxy group with an aryl group, and the silver ion-promoted migration of the α-aryl group to the β-position, consecutively. This method was applied to the synthesis of some alkaloids such as (±)-mesembrine.

The *Sceletium* alkaloids represented by mesembrine **1** and joubertiamine **2** have been attractive synthetic targets over this two decades because of their interesting physiological activities and structural features related with the more complex *Amaryllidaceae* alkaloids such as elwesine **3**.[1] Since these alkaloids are characterized by a skeleton of a *cis*-3a-aryloctahydroindole **A**, efforts of synthetic chemists have been directed to devise efficient routes to the construction of **A**. One of the convenient routes so far exploited for the construction of **A** involves β-aryl-substituted α,β-unsaturated pyrrolidines **B**.

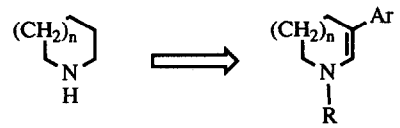


1 **2** **3**

A **B**

There have been known a few methods for the construction of **B**, that is, the acid-catalyzed cyclization of 2-aryl-4-amino aldehyde acetal,[2] the attack of aryllithium to N-methyl-3-pyrrolidone followed by acid-catalyzed dehydration,[3] the thermally induced rearrangement of 1-arylcyclopropylaldimine,[4] or a formal [2+3]cycloaddition between aryl olefins and dimethyl N-methoxycarbonyl-N-methoxymethylaminomalonate.[5] The starting compounds in these methods, however, are not always easily available and these methods are applicable only to the preparation of β-aryl-substituted α,β-unsaturated pyrrolidines such as **B**.

In our continuing studies on the utilization of anodic α-methoxylation of carbamates to the synthesis of nitrogen-containing heterocycles,[6] we exploited a new route for the construction of β-aryl-substituted cyclic enamines **7** (**B** in a case of R=Me), key synthetic intermediates for **1**, **2** and **3**, starting from pyrrolidine **4** (Scheme 1). This new route was also applicable to β-aryl-substituted cyclic enamines **8** and **9**, intermediates for the synthesis of homologues of **1**, starting from easily available cyclic amines **5** and **6** (Scheme 1). This paper describes these results.



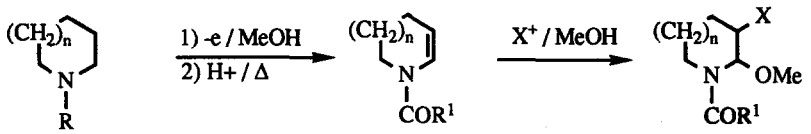
4 ; n=0 **7** ; n=0 (**B**; R=Me)
5 ; n=1 **8** ; n=1
6 ; n=2 **9** ; n=2

Scheme 1

Results and Discussion

Our strategy for the introduction of aryl groups into the β position of **4-6** is shown in Scheme 2, which involves the transformation of **4-6** to α,β-unsaturated cyclic amine derivatives **14-17** by utilizing anodic oxidation, the halomethoxylation of **14-17** affording **18-22**, the replacement of α-methoxy group of **18-22** with an aryl group to give β-halo-α-aryl cyclic amine derivatives **23-27**, the silver ion-promoted migration of the aryl group of **23-27** to α,β-unsaturated β-aryl cyclic amine derivatives **28-31**, and the reduction of **28-31**.

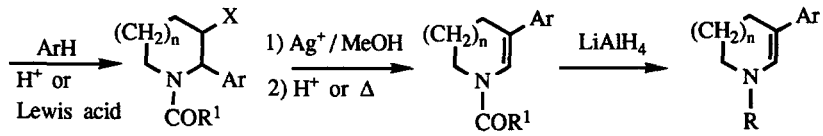
Key intermediates **18-22** were easily prepared from **4-6** through **10-13** and **14-17** by our reported methods.[7,8] The yileds of **14-17** from **10-13** and of **18-22**[9] from **14-17** are shown in Scheme 2. The subsequent α-arylation of **18-22** was achieved by acid-treating of **18-22** with aromatic compounds, though the reaction conditions had to be carefully selected.[10] Namely, titanium tetrachloride in methylene chloride was effective for pyrrolidine derivatives **18-20** but it was not toward a piperidine derivative **21** and a hexahydroazepine derivative **22**, which were α-arylated by using sulfuric acid in acetic acid. Since **21** and **22** were easy to be converted by acid to the corresponding α,β-unsaturated carbamates **C**, α-arylation of **21** and **22** might be effectively achieved by Brönsted acids which protonated **C** to afford α-cation **D** (Scheme 3).



4 ; n=0, R=H
5 ; n=1, R=H
6 ; n=2, R=H
10 ; n=0, R=CO_2Me
11 ; n=0, R=COPh
12 ; n=1, R=CO_2Me
13 ; n=2, R=CO_2Me

14 ; n=0, R^1=OMe (76%)
15 ; n=0, R^1=Ph (54%)
16 ; n=1, R^1=OMe (83%)
17 ; n=2, R^1=OMe (77%)

18 ; n=0, R^1=OMe, X=Br (66%)
19 ; n=0, R^1=OMe, X=I (93%)
20 ; n=0, R^1=Ph, X=I (57%)
21 ; n=1, R^1=OMe, X=Br (94%)
22 ; n=2, R^1=OMe, X=Br (74%)



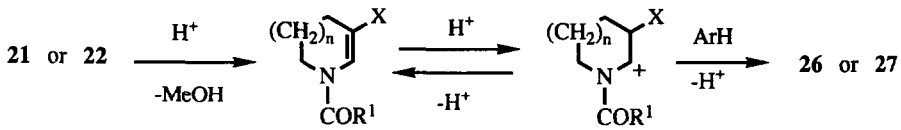
23a ; n=0, R^1=OMe, X=Br
24a,b ; n=0, R^1=OMe, X=I
25c ; n=0, R^1=Ph, X=I
26a,b ; n=1, R^1=OMe, X=Br
27a ; n=2, R^1=OMe, X=Br

28a,b ; n=0, R^1=OMe
29c ; n=0, R^1=Ph
30a,b ; n=1, R^1=OMe
31a ; n=2, R^1=OMe

7a,b ; n=0, R=Me
7c ; n=0, R=CH_2Ph
8a,b ; n=1, R=Me
9a ; n=2, R=Me

a ; 3,4-dimethoxyphenyl
b ; 4-methoxyphenyl
c ; 3,4-(methylenedioxy)phenyl

Scheme 2



Scheme 3

Aromatic compounds possessing electron-donating substituents were usable as α-arylation reagents but benzene was not because of its low nucleophilicity. The results at α-arylation step are shown in Table 1.[9]

Table 1. α-Arylation of β-Halo-α-methoxy Amine Derivatives **18-22**

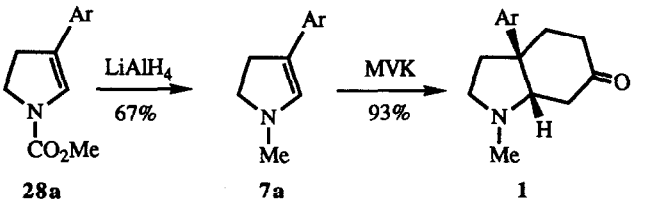
run	substrate	n	X	R^1	Ar	Yield of **23-27** (%)
1	**18**	0	Br	OMe	3,4-dimethoxyphenyl	**23a** (83)
2	**19**	0	I	OMe	3,4-dimethoxyphenyl	**24a** (90)
3	**19**	0	I	OMe	4-methoxyphenyl	**24b** (48)
4	**20**	0	I	Ph	3,4-(methylenedioxy)phenyl	**25c** (39)
5	**21**	1	Br	OMe	3,4-dimethoxyphenyl	**26a** (51)
6	**21**	1	Br	OMe	4-methoxyphenyl	**26b** (48)
7	**22**	2	Br	OMe	3,4-dimethoxyphenyl	**27a** (54)

The α-aryl group of thus obtained **23-27** was migrated to the β-position by treating with silver nitrate in methanol.[11] The desired α,β-unsaturated β-aryl cyclic amine derivatives **28-31** were obtained by treatment of the β-aryl-α-methoxy products without the isolation with *p*-toluenesulfonic acid. The results of α,β-aryl migration are summarized in Table 2.

Table 2. α,β-Migration of α-Aryl Group of β-Halo-α-aryl Cyclic Amines **23-27**

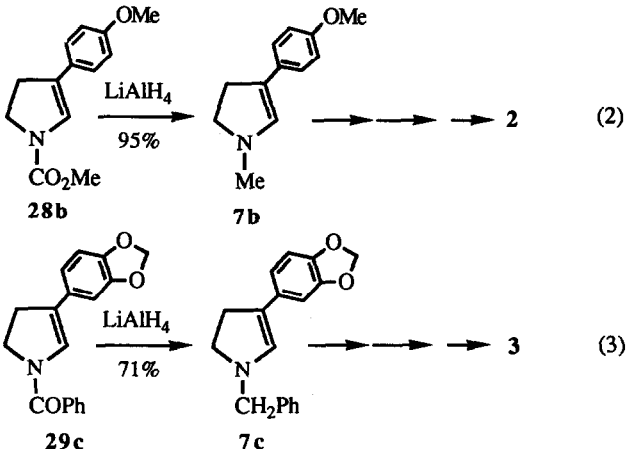
run	substrate	n	X	R^1	Ar	Yield of **28-31**(%)
1	**23a**	0	Br	OMe	3,4-dimethoxyphenyl	**28a** (66)
2	**24a**	0	I	OMe	3,4-dimethoxyphenyl	**28a** (72)
3	**24b**	0	I	OMe	4-methoxyphenyl	**28b** (66)
4	**25c**	0	I	Ph	3,4-(methylenedioxy)phenyl	**29c** (64)
5	**26a**	1	Br	OMe	3,4-dimethoxyphenyl	**30a** (77)
6	**26b**	1	Br	OMe	4-methoxyphenyl	**30b** (93)
7	**27a**	2	Br	OMe	3,4-dimethoxyphenyl	**31a** (58)

Some of α,β-unsaturated β-aryl cyclic amine derivatives were converted to naturally occurring alkaloids. Namely, β-(3,4-dimethoxyphenyl)pyrrolidine derivative **28a** was reduced by $LiAlH_4$ to give an enamine **7a**, of which reaction with methyl vinyl ketone has been known to give (±)-mesembrine **1** (eq 1).[12]

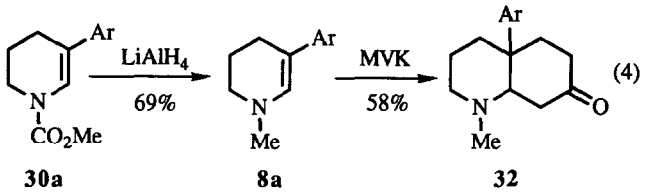


Ar= 3,4-dimethoxyphenyl

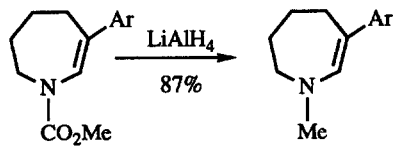
The reduction of **28b** and **29c** with $LiAlH_4$ gave enamines **7b** and **7c** which were key synthetic intermediates of joubertiamine **2** and elwesine **3**, respectively (eqs 2 [13] and 3 [14]).



Six-membered cyclic enamines **8a, b** were obtained from **30a, b** (**a**; 69%, **b**; 100%), and **8a** was utilized as a building block for the synthesis of a bicyclic ketone **32**,[9] a homologue of mesembrine **1** (eq 4). A seven-membered enamine **9a** was also prepared by $LiAlH_4$ reduction of **31a** in 87% yield (eq 5).



Ar=3,4-dimethoxyphenyl



(5)

9a **31a** Ar=3,4-dimethoxyphenyl

As exemplified by these examples, our method can provide a variety of β-aryl-substituted cyclic enamines which are versatile intermediates in the synthesis of nitrogen-heterocycles.

EXPERIMENTAL

General. IR spectra were recorded on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were measured on a Varian Gemini 200 spectrometer with TMS as an internal standard. Mass spectra were obtained on a JEOL IMSDX 300 instrument. Elemental analyses were determined by the Center for Instrumental Analysis of Kyoto University. Electrochemical oxidation was carried out by using DC Power Supply (GP 050-2) of Takasago Seisakusho, Ltd.

Anodic Oxidation of N-Acylated Cyclic Amines 10-13.

Anodic oxidation of **10-13** was carried out in methanol using tetraethylammonium *p*-toluenesulfonate as a supporting electrolyte according to our previously reported method.[15]

Preparation of α,β-Unsaturated Cyclic Amine Derivatives 14-17.

Preparation of **14** (anodic α-methoxylation;83%,[15] elimination of methanol;91%[7]), **16** (anodic α-methoxylation;86%,[15] elimination of methanol;96%[7]), and **17** (anodic α-methoxylation 89%,[16] elimination of methanol 86%[8]) has been reported. Compound **15** was prepared according to the method for the preparation of **14** from **10**.

15 (overall yield from **11**; 54%): mp 99-100°C; IR (KBr) 3075, 2950, 2880, 1640, 1620, 1585, 1457, 1423, 1380, 840, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.63-2.80 (m, 2H), 4.05 (t, 2H, *J* =8Hz), 5.15-5.25 (m, 1H), 6.40-6.52 (m, 1H), 7.35-7.65 (m, 5H) ; exact mass calcd for $C_{11}H_{11}NO$: 173.0841, found: 173.0858.

Halomethoxylation-General Procedure.

Compounds **18, 19, 21,** and **22** were known compounds.[8] Compound **20** was prepared as follows. Iodine (40.2 mmol) was added into a solution of **15** (28.1 mmol) and sodium methoxide (42.2 mmol) in methanol (20 mL) at room temperature and the mixture was stirred for 1 h. Then the solution was poured into a mixture of aqueous $Na_2S_2O_3$ and aqueous $NaHCO_3$, and the organic portion was extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by recrystallization from methylene chloride.

20 (57%): mp 99-100°C; IR (KBr) 3040, 2970, 1637, 1410, 1180, 1163, 1073, 850, 796, 730, 705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.15-2.35 (m, 1H), 2.50-2.80 (m, 1H), 3.12 (s, 2H), 3.56 (b s, 1H), 3.65-3.80 (m, 1H), 3.85-4.05 (m, 1H), 4.28-4.40 (m, 1H), 4.93 (s, 0.7H), 5.87 (s, 0.3H), 7.35-7.80 (m, 5H); Anal. Calcd for $C_{12}H_{14}NO_2I$: C, 43.52; H, 4.26; N, 4.23; I, 38.32. Found: C, 43.22; H, 4.19; N, 4.10; I, 38.52.

Replacement of α-Methoxy Group with Aryl Group-General Procedure.

β-Halo-α-aryl cyclic amine derivatives **23-27** were prepared by acid-catalyzed reaction of **18-22** with aromatic compounds. The reaction of **18-20** with aromatic compounds yielding **23-25** was achieved by using a Lewis acid catalyst. On the other hand, sulfuric acid in acetic acid was used to prepare **26** from **21** or hexahydroazepine derivative **27** from **22**. General procedures for each case were as follows.

Titanium tetrachloride (5.12 mmol) was added into a solution of **18** (4.27 mmol) in dry methylene chloride (8 mL) under a nitrogen atmosphere at -78°C, and the solution was stirred for 5 min. Then, after a solution of veratrole (12.8 mmol) in methylene chloride (4 mL) was added, the resulting solution was allowed to stand until the temperature raised to room temperature (3 hrs). The usual work up and isolation by column chromatography (silica gel, hexane/AcOEt) gave **23a** (1.22 g, 3.55 mmol) in 83% yield. Compound **24a** from **19** was prepared by a similar method. In cases of the reactions of **19** with anisole and of **20** with 1,3-benzodioxole, slight modifications of the method described above were necessary because the products **24b** and **25c** were further transformed to unidentified materials by standing the reaction mixtures at room temperature. The reaction of **19** with anisole was carried out at -78°C for 1hr. In the reaction of **20** with 1,3-benzodioxole which was carried out at -78°C, the solution was warmed to -10°C, stirred at the temperature for 4.5 hrs, and then worked up.

23a (83%): mp 116-118°C; IR (KBr) 2950, 2920, 2850, 1695, 1445, 1385, 1255, 1015, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10-2.60 (m, 2H), 3.55-4.05 (m, 5H), 3.86 (s, 3H), 3.89 (s,3H), 4.32 (d, 1H, J =5Hz), 5.18-5.35 (m, 1H), 6.67-6.90 (m, 3H); Anal. Calcd for $C_{14}H_{18}NO_4Br$: C, 48.85; H, 5.27; N, 4.07; Br, 23.21. Found: C, 48.66; H, 5.15; N, 4.17; Br, 23.20

24a (90%): IR (neat) 2970, 1718, 1600, 1522, 1460, 1390, 1264, 1145, 1038, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10-2.45 (m, 2H), 3.55-4.05 (m, 5H), 3.67 (s,3H), 3.89 (s, 3H), 4.25-4.35 (m, 1H), 5.22-5.40 (m, 1H), 6.65-6.88 (m, 3H); exact mass calcd for $C_{14}H_{18}NO4I$: 391.0282, found: 391.0263.

24b (48%): mp 73-75°C; IR (KBr) 2950, 1690, 1610, 1517, 1457, 1385, 1250, 905, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00-2.42 (m, 2H), 3.52-4.10 (m, 5H), 3.78 (s,3H), 4.22-4.32 (m, 1H), 5.23-5.40 (m, 1H), 6.88 (d, 2H, J =8Hz), 7.12 (d, 2H, J =8Hz); exact mass calcd for $C_{13}H_{16}NO_3$: 234.1130, found: 234.1107.

25c (39%): mp 138-140°C; IR (KBr) 1630, 1500, 1450, 1402, 1265, 1255, 1160, 1041, 935, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.12-2.50 (m, 2H), 3.67-4.40 (m, 3H), 5.05 (s, 0.6H), 5.60 (b s, 0.4H), 5.98 (s, 2H), 6.55-6.90 (m, 3H), 7.20-7.68 (m, 5H); exact mass calcd for $C_{18}H_{16}NO_3$: 294.1130, found: 294.1094.

Titanium tetrachloride was not effective toward the reaction of piperidine derivative **21** and hexahydroazepine derivative **22** with aromatic compounds. Into a solution of **21** (20.0 mmol) in acetic acid (15 mL) containing sulfuric acid (0.3 mL) was added veratrole (47.8 mmol) at room temperature, and the solution was stirred overnight at the temperature. Aqueous $NaHCO_3$ solution was gradually added until the solution was neutralized, the organic portion was extracted with methylene chloride, and the products were purified by column chromatography (silica gel, hexane/AcOEt).

26a (51%): IR (neat) 2950, 2845, 1695, 1593, 1510, 1445, 1410, 1257, 1142, 1119, 1028, 765, 747 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40-1.54 (m, 1H), 1.89-2.31 (m, 3H), 2.95 (dt, 1H, J =13, 4Hz), 3.78 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.17-4.30 (m, 1H), 5.02-5.09 (m, 1H), 5.67 (b s, 1H), 6.68-6.89 (m, 3H); exact mass calcd for $C_{15}H_{20}NO_4Br$:357.0576, found: 357.0587

26b (48%): IR (neat) 2970, 1705, 1618, 1520, 1450, 1415, 1257, 1183, 1120, 1040, 790, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38-2.30 (m, 4H), 2.89 (dt, 1H, J =13, 4Hz), 3.77 (s, 3H), 3.80 (s, 3H), 4.15-4.30 (m,

1H), 5.00-5.10 (m, 1H), 5.66 (b s, 1H), 6.90 (d, 2H, J =8Hz), 7.11 (d, 2H, J =8Hz); Anal. Calcd for $C_{14}H_{18}NO_3Br$: C, 51.23; H, 5.53; N, 4.27; Br, 24.35. Found: C, 51.17; H, 5.35; N, 4.13; Br, 24.46.

27a (54%): IR (neat) 2950, 2854, 2840, 1690, 1592, 1513, 1455, 1440, 1399, 1337, 1258, 1190, 1142, 1080, 1023, 980, 879, 766, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40-1.80 (m, 3H), 1.82-2.00 (m, 1H), 2.10-2.32 (m, 1H), 2.41-2.58 (m, 1H), 2.73-2.90 (m, 1H), 3.50-3.80 (m, 1H), 3.72 and 3.76 (s and s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.36 (t, 1H, J =10Hz), 5.30 (d 0.4H, J =10Hz), 5.50 (d, 0.6H, J =10Hz), 6.80-7.05 (m, 3H); exact mass calcd for $C_{16}H_{22}NO_4Br$: 371.0733, found: 371.0694.

Preparation of α,β-Unsaturated β-Aryl Cyclic Amines. General procedure is exemplified by the transformation of **23a** and **24a** to **28a**. Into a solution of **23a** (0.58 mmol) in methanol (10 mL) was added silver nitrate (1.15 mmol) at room temperature and the solution was heated at the reflux temperature for 30 min. After the solution was cooled and the precipitate was filtered off, the filtrate was poured into aqueous $NaHCO_3$. The organic layer was extracted with methylene chloride, dried over $MgSO_4$ and evaporated to give a residue. Into a solution of the residue in methylene chloride (5 mL) was added a catalytic amount of *p*-toluenesulfonic acid at room temperature and the mixture was stirred for 30 min. Then, the solution was poured into aqueous $NaHCO_3$ and the organic layer was extracted with methylene chloride. The organic layer was dried over $MgSO_4$, evaporated, and subjected to column chromatography (silica gel, hexane/AcOEt) to give **28a**. This product was also obtained from **24a** by a similar procedure except the condition of the reaction of **24a** with silver nitrate, in which refluxing was not necessary (at room temperature, 30 min).

28a (66% from **23a**, 72% from **24a**): mp 116-118°C; IR (KBr) 3095, 2940, 1692, 1622, 1461, 1403, 1314, 1257, 1148, 1025, 988, 845, 809, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.98 (q, 2H, J =10Hz), 3.80 (s, 3H), 3.88 (s, 3H), 3.90 (s,3H), 3.82-4.00 (m, 2H), 6.79-7.09 (m, 4H); exact mass calcd for $C_{14}H_{17}NO_4$: 263.1157, found: 263.1145.

Transformation of 24b to 28b, and 25c to 29c. This transformation was achieved by a similar procedure to the formation of **24a** to **28a**.

28b (66%): mp 106-108°C; IR (KBr) 3100, 2950, 1680, 1630, 1606, 1445, 1404, 1343, 1318, 1250, 1178, 1120, 1038, 984, 860, 824, 790, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (q, 2H, J =10Hz), 3.78 (s, 3H), 3.81 (s, 3H), 3.83-4.20 (m, 2H), 6.80-7.50 (m, 5H); exact mass calcd for $C_{13}H_{15}NO_3$: 233.1052, found: 233.1060.

29c (64%): mp 120-122°C; IR (KBr) 2900, 2850, 1615, 1505, 1455, 1410, 1260, 1220, 1035, 935, 857, 805, 715, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.01 (t, 2H, J =10Hz), 4.18 (t, 2H, J =10Hz), 5.94 (s, 2H), 6.65-7.00 (m, 4H), 7.32-7.67 (m, 5H); exact mass calcd for $C_{18}H_{15}NO_3$: 293.1052, found: 293.1058.

Transformation of 26a,b to 30a,b. β-Bromopiperidine derivatives **26a,b** were transformed into **30a,b** in one pot by heating a solution of **26a,b** (0.65 mmol) in methanol (7 mL) containing silver nitrate (0.98 mmol) at the reflux temperature. The work up procedure was similar to those described above.

30a (77%): IR (neat) 2960, 1700, 1650, 1520, 1450, 1395, 1330, 1260, 1200, 1150, 1120, 1070, 1030, 980, 810, 770, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89-2.07 (m, 2H), 2.45 (t, 2H, J =6Hz), 3.58-3.72 (m, 2H), 3.81 (s, 3H), 3.88 (s, 3H), 3.92 (s, 3H), 6.78-7.00 (m, 3H), 7.15 (b s, 0.53H), 7.5 (b s, 0.47H); exact mass calcd for $C_{15}H_{19}NO_4$: 277.1314, found: 277.1307.

30b (93%): IR (neat) 2950, 1700, 1690, 1640, 1510, 1440, 1385, 1258, 1190, 1180, 1115, 1032, 910, 823, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88-2.06 (m, 2H), 2.43 (t, 2H, J =6Hz), 3.58-3.72 (m, 2H), 3.79 (s, 3H),

3.80 (s, 3H), 6.85 (d, 2H, *J* =9Hz), 7.11-7.40 (m, 3H); exact mass calcd for $C_{14}H_{17}NO_3$: 247.1208, found: 247.1190.

Transformation of 27a to 31a. β-Bromohexahydroazepine derivative **27a** was transformed into **31a** by a procedure similar to that in the transformation of **23a** to **28a.**

31a (58%): mp 71-73°C; IR (neat) 2950, 1695, 1640, 1520, 1453, 1395, 1250, 1035, 910, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70-1.95 (m, 4H), 2.58-2.70 (m, 2H), 3.66-3.83 (m, 2H), 3.78 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.60-6.95 (m, 4H); exact mass calcd for $C_{16}H_{21}NO_4$: 291.1470, found: 291.1485.

Synthesis of α,β-Unsaturated β-Aryl Cyclic Enamines 7a, 7b, 7c, 8a, 8b and 9a.

$LiAlH_4$ (0.754mmol) was added into a solution of **28a** (0.377 mmol) in dry ether (7 mL) and the solution was refluxed under a nitrogen atmosphere for 1hr. After the solution was cooled, it was diluted by ether (10mL) and the precipitate was filtered off. The solid was washed with ether, and the combined organic solution was evaporated *in vacuo* to give a crystallized enamine **7a** in 67% yield.

Cyclic enamines **7b**,[14] **7c**,[13] **8a**, **8b** and **9a** were prepared by a similar procedure for synthesis of **7a** from **28a**. Enamines **7a**,[12] **7b**[14] and **7c**[13] are known compounds and identified by comparison of their physical data (IR and NMR spectra, and mp) with those described in references.

7a (67%): mp 68-69°C; IR(KBr) 2920, 2840, 1615, 1580, 1518, 1255, 1145, 1020, 815, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.65 (s, 3H), 2.79 (t, 2H, J=9Hz), 3.15 (t, 2H, J=9Hz), 3.86 (s, 3H), 3.89 (s, 3H), 6.32 (s. 1H), 6.70-6.85 (m, 3H).

7b (95%): mp 94-96°C; IR (KBr) 2950, 2920, 2800, 1625, 1610, 1520, 1265, 1190, 1170, 1060, 1040, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.63 (s, 3H), 2.77 (t, 2H, *J* =9Hz), 3.13 (t, 2H, *J* =9Hz), 3.79 (s, 3H), 6.29 (s, 1H), 6.81 (d, 2H, *J* =7Hz), 7.16 (d, 2H, *J* =7Hz).

7c (71%): mp 62-63°C; IR (KBr) 2900, 2825, 1615, 1505, 1490, 1450, 1230, 1150, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.75 (t, 2H, *J* =9Hz), 3.16 (t 2H, *J* =9Hz), 3.99 (s, 2H), 5.90 (s, 2H), 6.35-7.05 (m, 4H), 7.20-7.50 (m, 5H).

8a (69%): mp 76-77°C; IR (KBr) 2925, 2825, 1630, 1510, 1320, 1240, 1140, 1090, 1020, 900, 850, 800, 760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95-2.10 (m, 2H), 2.38 (t, 2H, *J* =6Hz), 2.72 (s, 3H), 2.92 (t, 2H, *J* =5Hz), 3.86 (s, 3H), 3.90 (s, 3H), 6.34 (s, 1H), 6.75-6.90 (m, 3H); exact mass calcd for $C_{14}H_{19}NO_2$: 233.1416, found: 233.1388.

8b (100%): mp 82-84°C; IR (KBr) 2940, 2800, 1640, 1510, 1280, 1250, 1190, 1160, 1030, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95-2.10 (m, 2H), 2.36 (t, 2H, *J* =7Hz), 2.70 (s, 3H), 2.91 (t, 2H, *J* =6Hz), 3.79 (s, 3H), 6.33 (s, 1H), 6.82 (d, 2H, *J* =9Hz), 7.19 (d, 2H, *J* =9Hz); exact mass calcd for $C_{13}H_{17}NO$: 203.1310, found: 203.1337.

9a (87%): mp 47-49°C; IR (KBr) 2950, 2860, 1640, 1520, 1255, 1150, 1040, 870, 820, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50-1.85 (m, 4H), 2.58 (t, 2H, *J* =6Hz), 2.79 (s, 3H), 2.91 (t, 2H, *J* =5Hz), 3.86 (s, 3H), 3.89 (s, 3H), 6.09 (s, 1H), 6.78 (s, 3H); exact mass calcd for $C_{15}H_{21}NO_2$: 247.1512, found: 247.1565.

Synthesis of (±)-Mesembrine 1, (±)-Joubertiamine 2 and (±)-Elwesine 3.

The formations of (±)-mesembrine **1** from **7a**,[12] (±)-joubertiamine **2** from **7b**[13] and (±)-elwesine **3** from **7c**[14] have been already reported.

Synthesis of Bicyclic Ketone 32.

A bicyclic ketone **32** was prepared by a procedure similar to the reaction of **7a** with methyl vinyl ketone.[12]

32 (58%): IR (neat) 2955, 2800, 1718, 1528, 1475, 1460, 1265, 1160, 1140, 1033, 918, 738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30-2.54 (m, 10H), 2.23 (s, 3H), 2.72-2.90 (m, 3H), 3.81 (s, 3H), 3.35 (s, 3H), 6.81 (d, 1H, *J* =8Hz), 6.98 (d, 1H, *J* =4Hz), 7.00 (dd, 1H, *J* =8, 4Hz); ^{13}C NMR ($CDCl_3$) 22.10, 29.42, 38.20, 39.32, 41.00, 42.08, 43.51, 56.14, 56.35, 57.34, 69.35, 109.71, 111.72, 118.48, 139.48, 148.00, 149.67, 211.61; exact mass calcd for $C_{18}H_{25}NO_3$: 303.1834, found: 303.1807.

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REFERENCES AND NOTES

1) Jeffs, P.W. In *The alkaloids*, Manske, R.H.F. Ed.; Academic Press: New York, **1981**; vol. XIX, p1.
2) Sanchez, I.H.; Larraza, M.I.; Flores, H.J.; Rojas, I. Alcala, A. *Synth. Commun.*, **1983**, *13*, 35.
3) Curphey, T.J.; Kim, H.L. *Tetrahedron Lett.*, **1968**, *9*, 1441.
4) a)Keely, Jr., S.J.; Tahk, F.C. *J. Am. Chem. Soc.*,**1968**, *90*, 5584.
b)Stevens, R.V. *Acc. Chem. Res.* , **1977**, *10*, 193
5) Shono, T.; Terauchi, J.; Matsumura, Y. *Chem. Lett.*, **1989**, 1963.
6) a) Shono, T.; Matusmura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.*, **1984**, *49*, 300. b) Shono, T.; Matusmura, Y.; Tsubata, K; Uchida, K. *J. Org. Chem.*, **1986**, *51* 2590. c) Matsumura, Y. *J.Synth.Org.Chem.Jpn.*, **1990**, *48*, 814.
7) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T.; Aoki, T. *J. Am. Chem. Soc.*, **1982**, *104*, 6697.
8) Shono, T.; Matusmura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.*, **1987**, *52*, 536.
9) The stereochemistry was not determined.
10) Zaugg, H.E. *Synthesis*, **1970**, 49.
11) Pelter, A.; Ward, R.S.; Balasubramanian, M. *J. Chem. Soc. Chem. Commun.*, **1976**, 151.
12) Stevens, R.V.; Wentland, M.P. *J. Am. Chem. Soc.* , **1968**, *90*, 5580.
13) Stevens, R.V.; Lai, J.T. *J. Org. Chem.*, **1972**, *37*, 2138.
14) Stevens, R.V.; DuPree, L.E.; Loewenstein, P.L. *J. Org. Chem.*, **1972**, *37*, 977.
15) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.*, **1984**, *63*, 206.
16) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.*, **1984**, *49*, 1056.