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An Enantioselective Access to 1-Alkyl-1,2,3,4-tetrahydroisoquinolines. Application to a New Synthesis of (−)-Argemonine†

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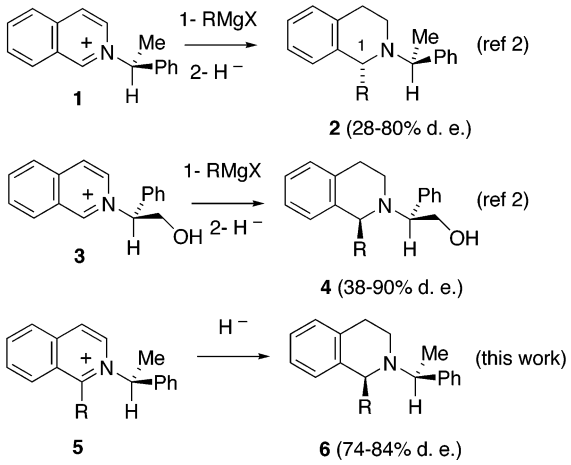
Potassium ferricyanide oxidation of salt **1** gave isoquinolinone **7** whose treatment with Grignard reagents resulted in a high-yield formation of substituted isoquinolinium salts **5**. The selectivity of the reduction of these salts to give derivatives **6** has been studied. Particularly good selectivities (82−84%) were observed when R is a benzylic group. On the basis of these results, a practical and enantioselective synthesis of the natural alkaloid (−)-argemonine is presented.

We recently reported[1] that isoquinolinium salts **1**, now readily available using the Zincke procedure,[2] can be alkylated by Grignard reagents to give, after reduction, chiral 1-alkyl-1,2,3,4-tetrahydroisoquinolines **2**. This process offers the advantage of starting from readily available 1-phenylethylamine as a chiral auxiliary, but is limited in some cases by the relatively poor diastereoselectivity of the Grignard attack, ranging from 28% to 80%. Use of a phenylethanol chiral auxiliary (salt **3**) resulted in increased selectivities (38−90%) in favor of derivatives **4**. In both cases the lowest selectivities, 32% or less, were observed using benzylic Grignard reagents. To improve the efficiency of this approach, we anticipated that reduction of isoquinolinium salts of general structure **5** would give a more selective access to tetrahydroisoquinolines **6**. Indeed, this reaction would take advantage of 1,3-allylic strain effects in salts **5**. These effects are likely to block the rotation of the chiral auxiliary, fixing the R group and the C−H bond in a syn relationship for steric reasons, and thus differentiating the two diastereotopic faces of the isoquinolinium ring. Due to these effects (attack of the hydride from the less hindered side) formation of isoquinolines **6** as major isomers was expected.[3]

In this paper we report a convenient access to salts **5** and their stereoselective reduction to tetrahydroisoquinolines **6** with diastereoisomeric excesses ranging from 74% to 84%.[4] The selectivities now obtained with benzylic Grignard reagents have allowed a new and practical enantioselective synthesis of the natural pavine alkaloid (−)-argemonine.[5]



Our approach was based on the facile oxidation of isoquinolinium salts to isocarbostyril derivatives using potassium ferricyanide oxidation[6,7] (Scheme 1).

Thus, treatment of salt **1** with potassium ferricyanide in alkaline medium afforded isoquinolinone **7** in 77% yield. We observed that heating of salt **1** in the presence

† This article is dedicated to the memory of François Frappier, Directeur de recherche au CNRS, Muséum National d'Histoire Naturelle, Paris, who passed away on February 23, 2003.

‡ Institut de Chimie des Substances Naturelles.

§ Centro de Quimica.

(1) Barbier, D.; Marazano, C.; Riche, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1998**, *63*, 1767−1772.

(2) Barbier, D.; Marazano, C.; Das, B. C.; Potier, P. *J. Org. Chem.* **1996**, *61*, 9596−9598.

(3) For a review of 1,3-allylic strain effects see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

(4) For a related approach see: Kaufmann, C. R.; Polniaszek, R. P. *J. Am. Chem. Soc.* **1989**, *111*, 4859−4863.

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(7) For previous use of this oxidation process in the pyridinium series see: Gnecco, D.; Marazano, C.; Enríquez, R.; Terán, J.; Sánchez, S. M.; Galindo, A. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2027−2029.

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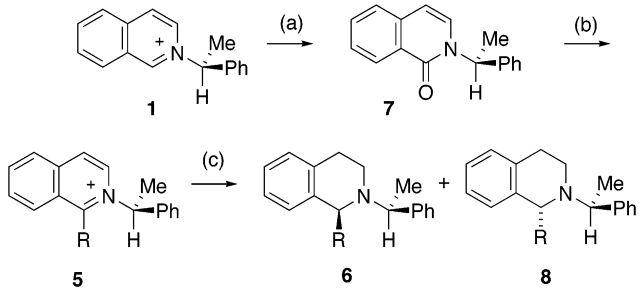
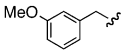
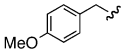
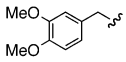
SCHEME 1. Preparation and Stereoselective Reduction of Isoquinolinium Salts 5[a]



[a] Reagents and conditions: (a) $K_3Fe(CN)_6$, MeOH, KOH, 1 h, 0 °C, then H_2O−toluene, 45 °C. (b) (i) $CeCl_3$, toluene; (ii) RMgX, THF; (iii) HBr, H_2O. (c) $NaBH_4$, MeOH.

TABLE 1. Synthesis and Stereoselective Reduction of Salts 5

R	salts 5 (% yield from **7**)	products (% yield)[a]	d.e.[b]
Me	**5a** (93)	**6a**-**8a** (77)	74
Ph	**5b** (25)	**6b**-**8b** (97)	74
	**5c** (91)	**6c**-**8c** (95)	84
	**5d** (90)	**6d**-**8d** (95)	82
	**5e** (92)	**6e**-**8e** (92)	84

[a] % yield of diastereoisomeric mixtures of **6**−**8** after filtration over alumina. [b] Calculated from ^{1}H NMR and GC analysis of the crude reaction mixture.

of potassium hydroxide resulted in rapid racemization. Fortunately, prior treatment with potassium ferricyanide allowed recovery of product **7** with excellent enantiomeric purity (>98% ee) as shown by HPLC on a chiral column (Chiracel OD).

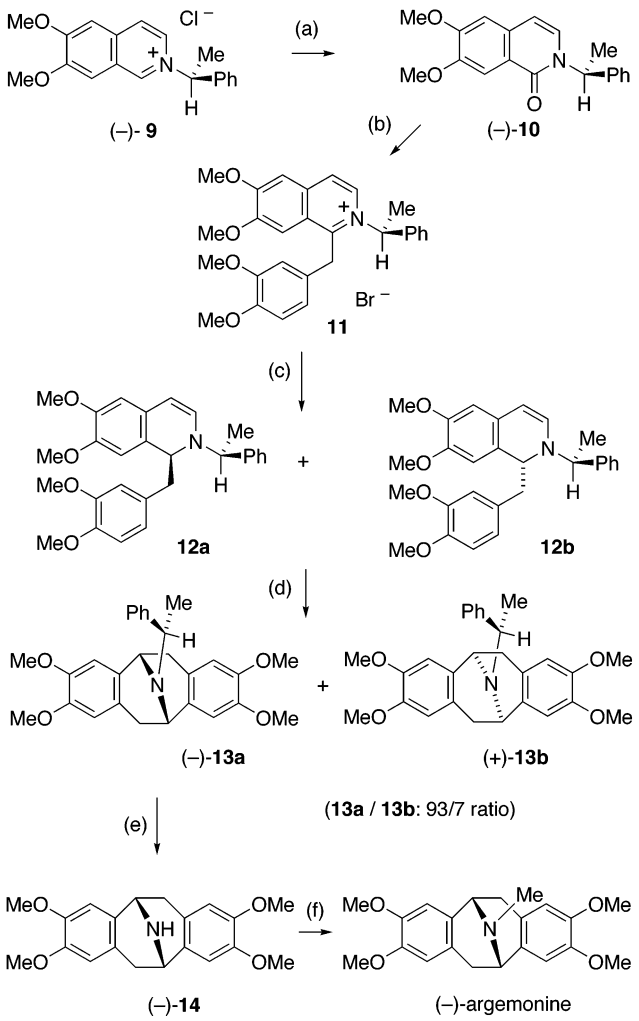
The results of Grignard reactions of derivative **7** in the presence of $CeCl_3$ followed by treatment with HBr to give salts **6** are presented in Table 1.[8]

Major isoquinoline derivatives **6a**−**c**,**e** and minor isoquinolines **8a**−**c**,**e** were characterized by comparison with the enantiomeric authentic samples previously obtained from the addition of the same Grignard reagents on salt **1**.[1]

From these results it can be concluded that, in the case of methyl or phenyl Grignard reagents, the observed selectivities are in a similar range compared to those obtained from salts **1** or **3**, using the same reagents (74% selectivity for **6a** and **6b** compared to 28% (R = Me) and 74% (R = Ph) for the corresponding derivatives **2** and 76% (R = Me) and 90% (R = Ph) for the corresponding derivatives **4**). By contrast these selectivities are significantly higher in the case of benzylic Grignard reagents. For example, preparation of isomer **6c** proceeded with an excess of 84% while the selectivities observed for the corresponding derivatives **2** (R = (3-OMe)-Ph-CH_2−) and **4** (R = (3-OMe)-Ph-CH_2−) were as low as 24% and 38%, respectively.

(8) Experimental details for the preparation of isomer **6d** are presented as a typical procedure.

SCHEME 2. Synthesis of (−)-Argemonine[a]



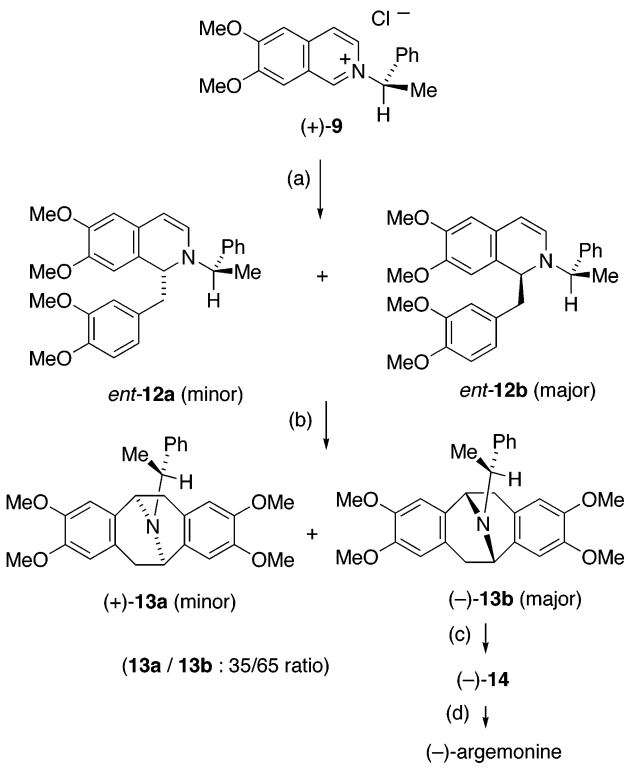
[a] Reagents and conditions: (a) $K_3Fe(CN)_6$, MeOH, KOH, 1 h, 0 °C, then H_2O−toluene, 45 °C (62% yield). (b) (i) $CeCl_3$, toluene; (ii) $(MeO)_2PhCH_2MgCl$, THF; (iii) HBr, H_2O (92% yield). (c) $LiAlH_4$, THF, −78 °C (77% yield for (−)-**13a**). (d) HCO_2H, H_3PO_4 (77% yield). (e) H_2, Pd/C, H^+ (77% yield). (f) HCHO, $NaBH_4$ (95% yield).

This new enantioselective and efficient approach to 1-benzyl isoquinoline derivatives was used for a synthesis of the natural pavine alkaloid (−)-argemonine according to Scheme 2.

Potassium ferricyanide oxidation of salt (−)-**9**[2] afforded isoquinolinone (−)-**10**, which was recovered in 62% yield. Treatment of the latter with 3,4-dimethoxybenzylmagnesium chloride under the conditions used for preparation of salts **5a**−**e** then gave salt **11** in excellent yield. The reduction of salt **11** to give the dihydro derivatives **12a** and **12b** was accomplished at −78 °C, using $LiAlH_4$ in THF. The ratio of isomers **12a**/**12b** was estimated to be 93/7 by ^{1}H NMR spectroscopy but the instability of these compounds precluded further studies. For this reason these derivatives were cyclized directly in acidic medium[9] to give stable pavine derivatives (−)-**13a** and (+)-**13b**. The ratio of these isomers was confirmed to be 93/7 by ^{1}H NMR spectroscopy and comparison with authentic samples (vide infra). The structure of the major

(9) Battersby, A. R.; Binks, R. *J. Chem. Soc.* **1955**, 2888−2896.

SCHEME 3[a]



[a] Reagents and conditions: (a) $(MeO)_2PhCH_2MgX$, THF. (b) HCO_2H, H_3PO_4. (c) H_2, Pd/C, H^+. (d) HCHO, $NaBH_4$.

isomer **13a** was unambiguously established after hydrogenolysis of the chiral auxiliary to give secondary amine (−)-**14**, which was methylated to finally afford natural (−)-argemonine.

To unambiguously characterize isomers **12b** and **13b** we also treated salt (+)-**9** (Scheme 3) with 3,4-dimethoxybenzylmagnesium chloride under the conditions used in our previous paper.[1] The reaction afforded the enantiomer of **12b**, *ent*-**12b**, as the major isomer but, as expected, with poor selectivity (30% de).

Isomers (+)-**13a** and (−)-**13b** are difficult to separate with classical chromatographic methods, but could be separated with reverse-phase HPLC (eluent MeOH/H_2O/NEt_3:60/40/0.3). Isomer (−)-**13b** gave as expected secondary amine (−)-**14** and once again natural (−)-argemonine.

These last results illustrate the superiority of the approach depicted in Scheme 2. While this approach required two more steps compared to that depicted in Scheme 3, this is largely compensated by the better selectivities obtained.

The reported results completed our reported approach, in particular good stereoselectivities are now available for the enantioselective synthesis of 1-benzyl tetrahydroisoquinolines. This allowed a nonracemic synthesis of natural pavine alkaloids.

Experimental Section

Synthesis of (−)-Argemonine: 2-(1*S*)-(−)-2-(1-Phenylethyl)-6,7-dimethoxyisoquinolinone 10. Isoquinolinium salt **9** (0.55 g, 1.67 mmol), in MeOH (20 mL), was treated with potassium ferricyanide (6 g, 18.4 mmol) and KOH (1.4 g, 26 mmol) followed by toluene (20 mL) and H_2O (20 mL), following the procedure used for the preparation of isoquinolinone **7**. Pure isoquinolinone **10** was obtained as a pale yellow oil (0.31 g, 1 mmol, 62% yield): $[\alpha]_D$ −313 (*c* 2.3, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1649, 1596; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.76 (d, J = 7 Hz, 3H), 3.98 (s, 3H), 4.02 (s, 3H), 6.39 (d, J = 7.5 Hz, 1H), 6.58 (q, J = 7 Hz, 1H), 6.84 (s, 1H), 6.88 (d, J = 7.5 Hz, 1H), 7.12 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.8, 52.2, 56.1, 56.2, 105.9, 106.0 (2C), 108.1, 120.0, 126.7, 127.4 (2C), 127.7, 128.7, 132.0, 140.8, 149.2, 153.4 (2C), 161.4; MS (CI, isobutane) *m*/*z* 310 (MH^+), 308, 206; HRMS (CI, isobutane) calcd for $C_{19}H_{20}NO_3$ (MH^+) 310.1459, found 310.1444.

Isoquinolinium Salt 11. A solution of isoquinolinone **10** (400 mg, 1.3 mmol) in dry toluene (5 mL) was treated with cerium chloride (1.6 g, 4.2 mmol) and 3,4-dimethoxybenzylmagnesium chloride (0.11 M in THF, 47 mL) followed by HBr (16% in H_2O, 5 mL) in the conditions used for the preparation of salt **5d**. Salt **11** was obtained as a yellow powder (624 mg, 1.2 mmol, 92% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.02 (d, J = 6.9 Hz, 3H), 3.84 (s, 6H), 4.09 (s, 3H), 4.18 (s, 3H), 5.37 (d, J = 17 Hz,1H), 5.44 (d, J = 17 Hz, 1H), 6.37 (dd, J = 1.7 Hz, 8 Hz, 1H), 6.48 (q, J = 6.9 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 7.07 (m, 2H), 7.14 (d, J = 1.7 Hz, 1H), 7.32 (m, 3H), 7.69 (s, 1H), 7.85 (s, 1H), 8.17 (d, J = 7 Hz, 1H), 8.54 (d, J = 7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 34.4, 55.8, 56.2, 56.8, 57.4, 64.2, 105.7, 106.9, 111.4, 111.9, 119.5, 124.1, 124.6, 127.0, 129.3 (5C), 131.1, 136.0 (2C), 136.7, 148.5, 153.5, 154.1, 157.7; MS (electrospray) *m*/*z* 444 (M^+).

Dihydroisoquinoline 12a. To a solution of salt **11** (200 mg, 0.38 mmol), suspended in THF (5 mL), was added dropwise, at −78 °C, an excess of $LiAlH_4$ (1 M solution in THF, 1.5 mL). After being stirred for 2 h at −78 °C, the resulting mixture was quenched carefully with cold acetone (2 mL) followed by NaOH (2 N H_2O solution, 5 mL). The reaction products were extracted with Et_2O. Usual workup yielded a mixture of derivatives **12a** and **12b** in a 93/7 ratio as determined by integration of methyl signals in the ^1H NMR spectrum of the crude mixture. These unstable dihydroisoquinolines were used without further purification: MS (CI, isobutane) *m*/*z* 446 (MH^+), 340, 294, 151. Major isomer **12a**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (d, J = 6.9 Hz, 3H), 2.57 (dd, J = 5.1, 12.6 Hz, 1H), 2.76 (dd, J = 9.1, 12.6 Hz, 1H), 3.44 (s, 3H), 3.61 (s, 3H), 3.76 (s, 6H), 4.36 (m, 2H), 5.38 (d, J = 7.2 Hz, 1H), 5.73 (s, 1H), 6.03 (dd, J = 1.1, 7.1 Hz, 1H), 6.15 (d, J = 1.7 Hz, 1H), 6.34 (dd, J = 1.7, 8.1 Hz, 1H), 6.45 (s, 1H), 6.63 (d, J = 8.1 Hz, 1H), 7.15 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 38.9, 55.8, 55.8 (4 C), 61.4, 61.7, 98.5, 105.8, 110.8, 113.5, 120.6, 122.0, 125.3, 127.2, 128.5 (6C), 131.7, 131.1, 139.1, 143.3, 147.3, 147.4 (8C); MS (CI, isobutane) *m*/*z* 446 (MH^+), 340, 294, 151.

Derivative (−)-13a. Crude dihydroisoquinoline **12a** (prepared from 200 mg of salt **11** and accompanied by 7% of isomer **13c**), was dissolved in formic acid (85% in H_2O, 5.3 mL) and orthophosphoric acid (99%, 2 mL). This solution was heated at 100 °C for 2 h. The resulting mixture was diluted with H_2O (10 mL) and washed twice with diethyl ether. The aqueous phase was alkalinized with 2 N NaOH and extracted with $CHCl_3$. Removal of solvent under reduced pressure afforded a mixture of (−)-**13a** accompanied by (+)-**13b** in a 92/8 ratio as determined by GC analysis. Chromatography over silica gel with a mixture of AcOEt/heptane (20/80) allowed recovery of pure (−)-**13a** (130 mg, 0.29 mmol, 77% yield): $[\alpha]_D$ −145 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46 (d, J = 6.5 Hz, 3H), 2.54 (d, J = 16.1 Hz, 2H), 3.30 (dd, J = 5.2, 16.1 Hz, 2H), 3.68 (q, J = 6.5 Hz, 1H), 3.78 (s, 6H), 3.81 (s, 6H), 4.20 (d, J = 5.2 Hz, 2H), 6.46 (s, 2H), 6.55 (s, 2H), 7.27 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5, 33.9 (2C), 52.4 (2C), 55.8 (2C), 56.1 (2C), 59.1, 110.4 (2C), 111.7 (2C), 127.0, 127.4, 128.5 (5C), 125.1 (2C), 130.5 (2C), 146.5, 147.6 (2C), 147.9 (2C); HRMS (IE) calcd for $C_{28}H_{31}NO_4$ 445.2253, found 445.2238.

A sample of isomer (−)-**13b** was prepared, according to the procedure presented in Scheme 3, for authentication with the above minor isomer (+)-**13b**. Isomer (−)-**13b**: $[\alpha]_D$ −111 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.37 (d, J = 6.3 Hz, 3H),

2.54 (d, J = 16.2 Hz, 2H), 3.37 (dd, J = 5.7, 16.3 Hz, 2H), 3.70 (q, J = 6.3 Hz, 1H), 3.78 (s, 6H), 3.81 (s, 6H), 4.21 (d, J = 5.6 Hz, 2H), 6.47 (s, 2H), 6.54 (s, 2H), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.0, 34.2 (2C), 51.8 (2C), 55.8 (2C), 56.0 (2C), 58.5, 110.1 (2C), 111.6 (2C), 127.0, 127.5, 127.6 (5C), 124.8 (2C), 130.5 (2C), 145.7, 147.48 (2C), 147.9 (2C); HRMS (IE) calcd for $C_{28}H_{31}NO_4$ 445.2253, found 445.2252.

Derivative (−)-14. Isomer (−)-**13a** (116 mg, 0.26 mmol) was dissolved in AcOEt (5 mL), EtOH (5 mL), and an aqueous solution of HCl (2.4 N). The resulting solution was hydrogenated for 15 h, using 10% Pd/C (10%) as a calatyst. After filtration over Celite and removal of solvent under reduced pressure, H_2O was added. The resulting solution was washed with diethyl ether. The aqueous phase was then alkalinized with 2 N NaOH and extracted with $CHCl_3$. Removal of solvent under reduced pressure afforded pure secondary amine (−)-**14** (60 mg, 0.18 mmol, 67% yield): $[\alpha]_D$ −161 (*c* 0.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 1H), 2.67 (d, J = 16.1 Hz, 2H), 3.27 (dd, J = 5.6, 16.1 Hz, 2H), 3.75 (s, 6H), 3.85 (s, 6H), 4.39 (d, J = 5.6 Hz, 2H), 6.46 (s, 2H), 6.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 37.4 (2C), 50.1 (2C), 55.8 (2C), 56.0 (2C), 109.6 (2C), 111.9 (2C), 124.7 (2C), 130.9 (2C), 147.5 (2C), 148.0 (2C); HRMS (CI, methane) calcd for $C_{20}H_{24}NO_4$ (MH^+) 342.1705, found 342.1735.

(−)-Argemonine. Primary amine (−)-**14** (60 mg, 0.18 mmol) was dissolved in a solution of formic acid (85% in H_2O, 2 mL) and aqueous formaldehyde (37%, 1 mL). The resulting mixture was heated at 90−95 °C for 2.5 h. The crude reaction mixture was alkalinized with NaOH (2 N) and the product extracted with $CHCl_3$. Usual workup furnished pure (−)-argemonine (colorless foam, 47 mg, 0.12 mmol, 75% yield): $[\alpha]_D$ −205 (*c* 0.5, $CHCl_3$) [lit.[10] $[\alpha]_D$ −209 (*c* 0.5, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.53 (s, 3H), 2.58 (d, J = 16.3 Hz, 2H), 3.40 (dd, J = 5.7, 16.3 Hz, 2H), 3.76 (s, 6H), 3.85 (s, 6H), 4.00 (d, J = 5.7 Hz, 2H), 6.45 (s, 2H), 6.61 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.7 (2C), 41.0, 55.8 (2C), 56.1 (2C), 56.5 (2C), 110.2 (2C), 111.6 (2C), 124.0 (2C), 130.11 (2C), 147.6 (2C), 148.0 (2C); HRMS (CI, isobutane) calcd for $C_{20}H_{24}NO_4$ (MH^+) 356.1865, found 356.1839.

Supporting Information Available: Experimental procedure for the preparation of derivatives **7**, **5a**−**e**, and **6a**−**e** and copies of ^{1}H NMR and ^{13}C NMR spectra of derivatives **7**, **5a**−**e**, **6d**, **10**−**14**, and (−)-argemonine. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0357869

(10) Sternitz, F. R.; Seiber, S. N. *J. Org. Chem.* **1966**, *31*, 2925−2933.