# A Novel Asymmetric Route to the 1,3-Disubstituted Tetrahydroisoquinoline, (−)-Argemonine†

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Chiral bicyclic lactam **13** was converted to the natural product (−)-argemonine **9** in six steps. This novel route to argemonine represents a general strategy for the preparation of chiral 1,3-disubstituted tetrahydroisoquinolines.

Previous studies utilizing chiral nonracemic bicyclic lactams as vehicles for elaboration to various alkaloidal systems has led to the development of several efficient routes to the preparation of piperidine, indolizidine, and tetrahydroisoquinoline natural products (Scheme 1).[1] To date this has included the synthesis of (+)-monomorine (**1**), (−)-coniceine (**2**), and (+)-cryptostyline II (**3**). We now present the first report of an asymmetric total synthesis of (−)-argemonine (**6**), a member of the pavine family of natural products.[2]

The approach to be described herein was based on previous successes involving stereoselective reduction of chiral lactams containing a fused aromatic such as **4**. We will demonstrate how we have been able to use this finding to readily access (−)-argemonine (**6**). The basis for the present approach lies in the fact the lactam carbonyl in **4** was observed not to reduce during the process of cleaving the C−O bond. It was anticipated that the carbonyl group in **5** could be utilized in subsequent steps to facilitate stereoselective introduction of substituents at the 3-position of the resulting tetrahydroisoquinoline.

The retrosynthetic approach to (−)-argemonine is shown in Scheme 2. The target may be seen to arise from the intramolecular electrophilic cyclization of the benzyl substituent onto imminium ion **7** followed by reductive cleavage of the *tert*-butyl carbamate to the corresponding *N*-methyl analog. The requisite, transient iminium ion should present itself after reduction of the lactam **8** to the carbinol amine followed by treatment with an appropriate Lewis acid. The 3-isoquinolone **8** would be accessed by reductive cleavage of the lactam **9** (as in **4** → **5**) followed by removal of the auxiliary and Boc acylation of the resulting isoquinolin-3-one.

The key intermediate **9** was prepared by condensation of the known keto acid **10**,[3] with (*S*)-phenylglycinol under reflux with toluene as the solvent (Scheme 3). Azeotropic removal of water left the bicyclic lactam **9** as a single diastereomer in 90% yield. When **9** was treated with Red-Al, under previously used conditions[1c] (−78 °C warming to 0 °C) a significant amount (20−30%) of overreduction occurred producing the isoquinoline **12**. Although this was a useful reduction path (*vide supra*), it was not the required intermediate that would lead to argemonine. Conditions were ultimately found which did not reduce the lactam carbonyl in **11**. By maintaining the temperature of the Red-Al reduction of **9** below −30 °C, the lactam survived and only the aminal linkage suffered reductive cleavage to **11**. The latter was obtained in 90% yield as a >95:5 mixture of diastereomers.

At this juncture in the study the absolute (or relative) stereochemistry of **11** was still unknown. The phenylglycinol moiety was, of course, known to be *S*, but the stereochemistry of the 1-benzyl group was yet to be determined. This was nicely accomplished by taking advantage of the observation which produced the overreduction product **12** when the bicyclic lactam **9** was reduced earlier. It was subsequently found that lithium aluminum hydride reduction of **11** cleanly gave **12** which after debenzylation with $H_2$/Pd−C afforded the isoquinoline **13**. Following formalin−formic acid treatment, the Pictet−Spengler cyclization ensued to give (−)-xylopinine **14** in 90% yield. The latter possessed $[\alpha]^{23}_D$ −283 (*c* 0.32, $CHCl_3$) and compared well with the literature value of $[\alpha]^{23}_D$ −275.[4] The sign of rotation of both compounds being the same, confirmed that we had prepared xylopinine in its natural configuration of *S*. Thus, we may safely conclude that the C-1 position of **11** was also *S* and that reductive cleavage of **9** had occurred with retention at the aminal center.

Having shown that not only did we access the protoberberine alkaloid family (e.g. **14**), but we were also confident regarding the absolute stereochemistry of **11**. With this information in hand, we continued our study en route to argemonine.

Cleavage of the phenylglycinol moiety in **11** was the next step to be addressed, and we found that this could be accomplished using dissolving metal reduction conditions. Treatment of **11** with sodium and liquid ammonia resulted in clean formation of isoquinolin-3-one **15**.[5] It was observed that the reaction mixture must be quenched with solid ammonium chloride as soon as an excess of sodium was added in order to prevent decomposition of the product (Scheme 4). Following N-Boc protection of **15**, it was necessary to reduce the lactam to the corresponding carbinolamine **16**. Attempted reduction of **8** following Speckamp's procedure[6] with sodium borohydride in acidic ethanol at −20 °C led only to starting material. This prompted an examination of the proce-

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(2) For previous synthesis of argemonine see: (a) Nomoto, T.; Takayama, H. *J. Chem. Soc., Chem. Commun.* **1982**, *19*, 1113. (b) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601.

(3) Palmquist, U.; Nilsson, A.; Pettersson, T.; Rolán, A. *J. Org. Chem.* **1979**, *44*, 196.

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(5) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656.

(6) Hubert, J. C.; Wijnberg, J. B.; Speckamp, N. C. *Tetrahedron* **1975**, *31*, 1437.

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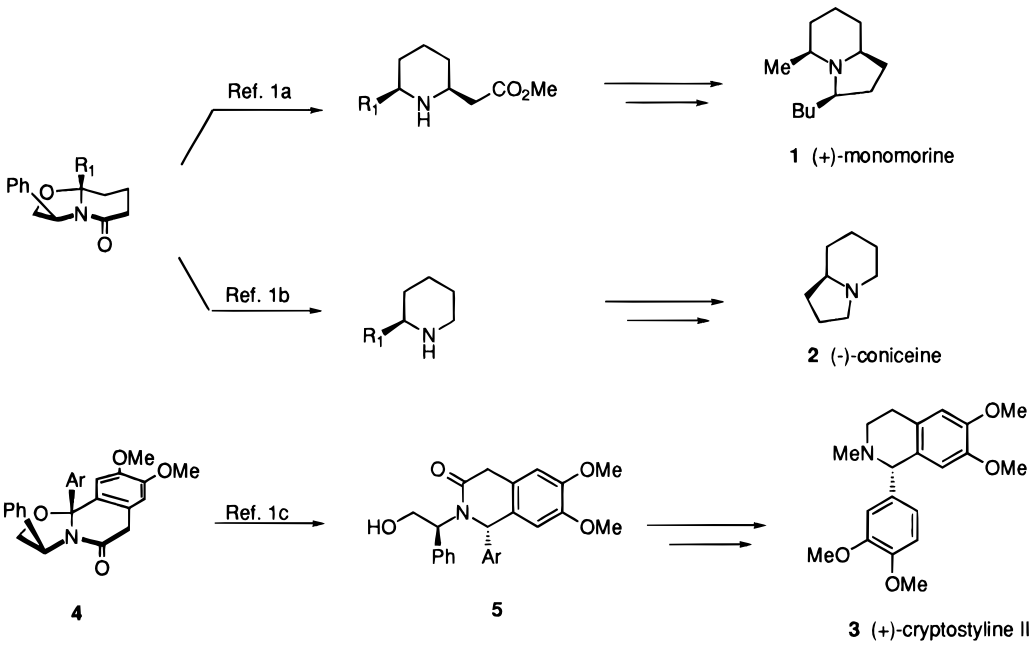
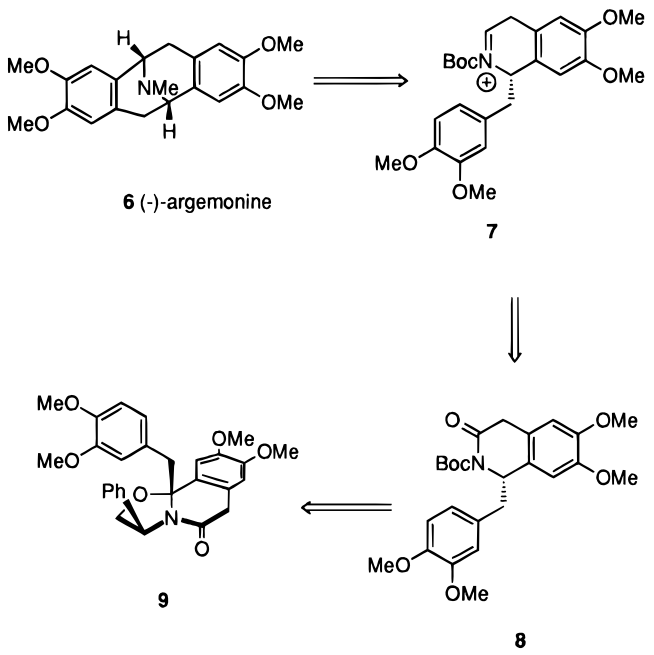
**Scheme 1**




**Scheme 2**




dure reported by Chamberlin[7] in which the analogous reduction was carried out in methanol at 0 °C without the addition of acid. Under these conditions the lactam **8** was cleanly reduced to the carbinolamine **16**. The latter was treated directly with *tert*-butyldimethylsilyl triflate to generate the intermediate imminium ion which was rapidly captured by the electron rich aromatic ring. In the course of this cyclization, the Boc group was also cleaved to yield amine **17**. The synthesis was completed by treating the secondary amine with formalin followed by sodium borohydride which afforded (−)-argemonine (**6**) in 60% yield ($[\alpha]^{25}_D$ −229 (*c* = 0.38, EtOH), lit.[8] $[\alpha]^{25}_D$ −214). Once again, the sign of rotation and the absolute configuration of the synthetic material matched that of the natural product.[8] Furthermore, the spectroscopic data for our synthetic sample was identical to the literature values.[2b]

In summary, the previously reported route[1c] to 1-substituted tetrahydroisoquinolines has now been extended to include 1,3-disubstituted tetrahydroisoquinolines. This has led to the first asymmetric synthesis of (−)-argemonine.

## Experimental Section

**General.** All reactions were carried out under argon in septum-stoppered flasks. Unless otherwise noted, reagents were added by syringe, and organic extracts were dried over anhydrous $Na_2SO_4$, filtered through a fritted glass funnel, and concentrated with a rotary evaporator at aspirator pressure (30−40 mm). Flash chromatography was performed with Amicon (200−400 mesh) silica gel. Thin layer chromatography (TLC) was performed with Merck F-254 silica gel plates. Preparative thin layer chromatography was carried out on Merck PSC-Fertirplatten Kieselgel 60 $F_{254}$ plates.

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and ether were distilled under $N_2$ from sodium/benzophenone immediately prior to use. Dichloromethane ($CH_2Cl_2$), benzene, toluene, and triethylamine were distilled from $CaH_2$ immediately prior to use.

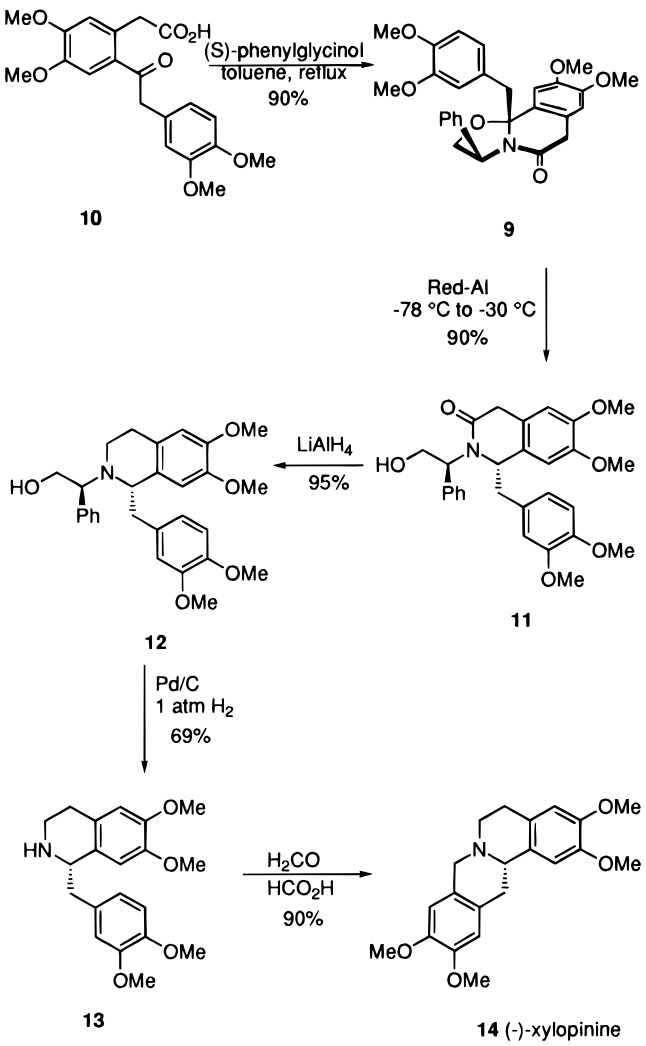
Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA.

**Bicyclic Lactam 9.** Keto-acid **10**[3] (2.0 g, 5.32 mmol) was dissolved in 44 mL of toluene, and 0.73 g (5.32 mmol) of (*S*)-phenylglycinol was added. The flask was equipped with a Dean−Stark apparatus, and the solution was heated to reflux. After 14 h the reaction mixture was cooled and concentrated to afford 2.4 g of crude product. Chromatography on 50 g of silica gel with ethyl acetate afforded 2.27 g (90%) of bicyclic lactam **10**: mp 148−150 °C, $[\alpha]^{23}_D$ +90.7 (*c* 1.5, $CHCl_3$); IR (neat) 2955, 1664, 1515 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 2.43 (d, *J* = 18.4, 1), 3.04 (m, 3), 3.49 (s, 3), 3.78 (s, 3), 3.83 (s, 6), 4.37 (t, *J* = 7.26, 1), 4.52 (dd, *J* = 5.20, 8.8, 1), 5.53 (m, 1), 5.91 (s, 1), 6.21 (d, *J* = 7.90, 1), 6.44 (s, 1), 6.57 (d, *J* = 8.0, 1), 6.83 (s, 1), 7.42 (m, 7); $^{13}C$ NMR (75 MHz) $\delta$ 37.2, 47.0, 55.4, 55.9, 56.0, 59.1, 69.1, 96.9, 107.4, 109.0, 110.3, 113.5, 122.8, 123.6, 126.7, 127.0, 127.7, 128.2, 128.6, 139.0, 147.9, 149.1, 168.7. Anal. Calcd for $C_{28}H_{29}NO_6 \cdot {}^1/_2\ H_2O$ : C: 69.42; H: 6.20; Found: C: 69.51; H: 6.10.

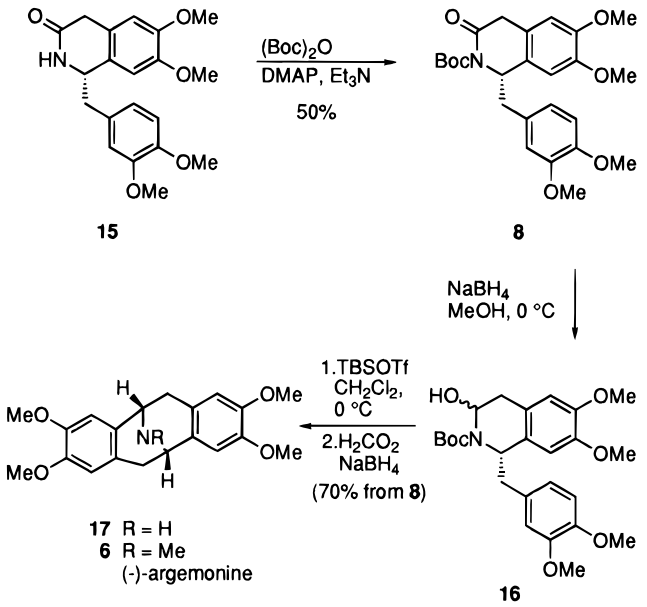
(7) Chamberlin, R. A.; Nguyen, H. D., Chung, J. Y. *J. Org. Chem.* **1984**, *49*, 1682.

(8) Chan, R. P.; Graig, J. C.; Manske, R. H.; Soine, T. O. *Tetrahedron* **1967**, *23*, 4209, reports $[\alpha]_D$ −214 (*c* = 3.3, EtOH).

**Scheme 3**




**Scheme 4**




**Isoquinolin-3-one 11.** Lactam **9** (2 g, 4.21 mmol) was dissolved in 10.5 mL of THF and cooled to −78 °C. To the stirring solution was added 2.80 mL (8.41 mmol, 3 M) of Red-Al in toluene down the side of the flask. The flask was placed in a −30 °C cooling bath and stirred 6 h. The reaction mixture was quenched by addition of 3.5 mL of $H_2O$ and then allowed to warm to rt. The resulting solution was diluted with $CHCl_3$ and stirred 30 min, after which time the solution was further diluted with $H_2O$, and the two phases were separated. The aqueous phase was extracted with $CHCl_3$ (5 × 50 mL), and the combined organic extracts were dried and concentrated to afford 1.83 g (90%) of **11**: $[\alpha]^{23}_D$ −6.18 (*c* 1.4, $CHCl_3$); IR (neat) 3400, 2936, 1629, 1515, 1261 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 2.70 (m, 3), 3.31 (d, $J$ = 19.3, 1), 3.60 (s, 3), 3.67 (s, 3), 3.82 (s, 3), 3.85 (s, 3), 4.13 (dd, $J$ = 6.1, 1), 4.33 (m, 2), 5.20 (m, 1), 5.97 (s, 1), 6.18 (s, 1), 6.26 (d, $J$ = 7.67, 1), 6.53 (s, 1), 6.66 (d, $J$ = 8.1, 1), 7.30 (m, 5); $^{13}C$ NMR (75 MHz) $\delta$ 37.4, 41.3, 55.6, 55.8, 55.9, 63.2, 64.0, 64.6, 109.1, 109.6, 110.7, 113.0, 122.3, 124.6, 126.2, 128.1, 128.8, 136.9, 147.2, 148.0, 148.3, 171.6. Anal. Calcd for $C_{28}H_{31}NO_6$: C: 70.44; H: 6.50; Found: C: 70.20; H: 6.64.

**Isoquinoline 12.** Isoquinolin-3-one **11** (600 mg, 1.25 mmol) was dissolved in 6.3 mL of THF and cooled to 0 °C. To the solution 95 mg (2.50 mmol) of lithium aluminum hydride was added, and the cooling bath was removed. After 3 h the reaction mixture was cooled to 0 °C, and 95 $\mu$L of $H_2O$ was added followed by 95 $\mu$L of 10% NaOH then 0.29 mL of $H_2O$. Chloroform was added, and the solution was stirred 30 min, filtered, and concentrated. Chromatography on 18 g of silica gel with 1:1 hexane:ethyl acetate afforded 486 mg (84%) of **12**: mp 60−62 °C, $[\alpha]^{23}_D$ +44.7 (*c* 2.0, $CHCl_3$); IR (neat) 2934, 1514, 1262 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 2.32 (m, 1), 2.56 (m, 1), 2.69 (m, 1), 2.89 (dd, $J$ = 6.4, 13.6, 1), 3.13 (m, 2), 3.65 (s, 3), 3.75 (m, 2), 3.80 (s, 3), 3.82 (s, 3), 3.95 (t, $J$ = 5.1, 1), 4.10 (t, $J$ = 6.1, 1), 6.20 (s, 1), 6.36 (d, $J$ = 1.8, 1), 6.48 (s, 1), 6.56 (d, $J$ = 8.1, 1), 6.73 (d, $J$ = 8.2, 1), 7.28 (m, 5). $^{13}C$ NMR (75 MHz) $\delta$ 26.4, 39.9, 41.4, 55.7, 55.7, 55.8, 60.3, 62.2, 65.1, 110.8, 111.0, 112.7, 121.2, 127.3, 127.7, 128.2, 128.7, 129.3, 131.6, 138.5, 146.6, 147.3, 147.4, 148.2. Anal. Calcd for $C_{28}H_{33}NO_5$: C: 72.57; H: 7.13. Found: C: 72.33; H: 7.28.

**1-Benzylisoquinoline 13.** Isoquinoline **12** (230 mg, 0.49 mmol) was dissolved in 10 mL of EtOH and 1.7 mL of 1 N HCl. A 500 mg amount of 10% Pd/C was added, and the solution was placed under a balloon of hydrogen. After 12 h the reaction mixture was filtered and concentrated. The resulting solid was taken up in 1 N HCl and extracted with $Et_2O$ (2 × 10 mL). The aqueous solution was made basic with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3 × 20 mL). The combined organic portions were dried and concentrated to give 141 mg (82%) of **13**. $[\alpha]^{23}_D$ −27.6 (*c* 2.5, $CHCl_3$); IR (neat) 2913, 1513, 1261 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta$ 1.95 (s, 1), 2.63−2.94 (m, 4), 3.18 (m, 2), 3.82 (s, 3), 3.85 (s, 6), 3.86 (s, 3), 4.12 (dd, $J$ = 4.40, 9.30, 1), 6.58 (s, 1), 6.66 (s, 1), 6.81 (m, 3). $^{13}C$ NMR (75 MHz) $\delta$ 29.4, 40.8, 42.1, 55.7 (2), 55.8, 55.8, 56.7, 109.2, 111.1, 111.7, 112.2, 121.3, 127.3, 130.3, 131.3, 146.8, 147.3, 147.5, 148.8. Anal. Calcd for $C_{20}H_{25}NO_4 \cdot H_2O$: C: 66.48; H: 7.48. Found: C: 66.26; H: 7.01.

**(−)-Xylopinine 14.** Amine **13** (56 mg, 0.16 mmol) was dissolved in 0.40 mL of 37% formalin and 0.62 mL of 88% formic acid. The flask was equipped with a cold finger condenser and heated to 90 °C. After 2 h the reaction mixture was cooled and concentrated *in vacuo*. The resulting yellow oil was taken up in $CHCl_3$ and made basic with saturated $NaHCO_3$. The solution was extracted with $CHCl_3$ (3 × 10 mL), dried, and concentrated to afford 52 mg (90%) of xylopinine (**14**): mp 179−180 °C, $[\alpha]^{23}_D$ −283.1(*c* 0.32, $CHCl_3$); $^1H$ NMR (300 MHz) $\delta$ 2.65 (m, 2), 2.84 (dd, $J$ = 11.2, 15.3, 1), 3.14 (m, 2), 3.24 (dd, $J$ = 3.72, 16.0, 1), 3.59 (dd, $J$ = 3.60, 11.2, 1), 3.67 (d, $J$ = 14.7, 1), 3.85 (s, 3), 3.86 (s, 3), 3.87 (s, 3), 3.89 (s, 3), 3.94 (d, $J$ = 14.6, 1), 6.58 (s, 1), 6.62 (s, 1), 6.67 (s, 1), 6.74 (s, 1); $^{13}C$ NMR (75 MHz) $\delta$ 29.4, 36.7, 51.7, 56.1, 56.2, 56.3, 56.3, 58.6, 59.9, 108.8, 109.3, 111.6 (2), 126.6, 126.7, 127.0, 130.1, 147.7 (2), 147.9 (2).

**Isoquinolin-3-one 15.** Isoquinolin-3-one **11** (560 mg, 1.17 mmol) was dissolved in 20 mL of THF and cooled to −78 °C. The flask was equipped with a cold finger condenser, approximately 40 mL of ammonia was condensed into the flask, and the cooling bath was removed. After the solution reached reflux sodium was added in several small portions until the blue color persisted. Once the blue color persisted for 30 s the reaction mixture was quenched by addition of solid ammonium chloride. The cold finger was removed, and the

ammonia was allowed to evaporate under a stream of argon. The resulting slurry was diluted with $H_2O$ and $CHCl_3$, the two phases were separated, and the aqueous layer was extracted with $CHCl_3$ (5 × 40 mL). The combined organic portions were dried and concentrated. Chromatography on 20 g of silica gel with 5% MeOH:$CH_2Cl_2$ afforded 355 mg (85%) of lactam **15**: mp 137−138 °C, $[\alpha]^{23}_D$ −36.2 (*c* 0.32, $CHCl_3$); IR (neat) 3221, 2936, 1665, 1516, 1261 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 2.76 (d, $J$ = 20.2, 1), 2.88 (dd, $J$ = 5.8, 13.4, 1), 3.02 (dd, $J$ = 4.6, 13.2, 1), 3.18 (d, $J$ = 20.2, 1), 3.66 (s, 3), 3.82 (s, 3), 3.84 (s, s, 6), 4.69 (m, 1), 6.29 (s, 1), 6.46 (s, 1), 6.58 (m, 2), 6.72 (d, $J$ = 8.2, 1), 6.85 (m, 1); $^{13}C$ NMR (75 MHz) $\delta$ 34.9, 45.0, 55.7, 55.8, 55.9, 56.1, 57.2, 108.9, 110.1, 111.0, 112.9, 122.4, 124.1, 125.2, 128.0, 147.7, 148.0, 148.5, 171.6. Anal. Calcd for $C_{20}H_{23}NO_5$: C: 67.23; H: 6.44. Found: C: 67.15; H: 6.46.

**Isoquinolin-3-one 8.** Lactam **15** (50 mg, 0.14 mmol) was dissolved in 0.50 mL of $CH_2Cl_2$ and 0.039 mL (0.28 mmol) of $Et_3N$, and 0.13 mL (0.56 mmol) of $(Boc)_2O$ and 34 mg (0.28 mmol) of 4-(dimethylamino)pyridine were added. The flask was equipped with a cold finger condenser, and the solution was heated to reflux. After 4 h the solution was concentrated *in vacuo* and chromatographed on 3 g of silica gel with 80% ethyl acetate:hexane to afford 32 mg (50%) of lactam **8**: $[\alpha]^{23}_D$ +45.7 (*c* 4.0, $CHCl_3$); IR (neat) 2935, 2835, 1768, 1717, 1515, 1233 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 1.55 (s, 9), 2.90 (d, $J$ = 19.8, 1), 3.01 (m, 2), 3.31 (d, $J$ = 19.8, 1), 3.64 (s, 3), 3.70 (s, 3), 3.81 (s, 3), 3.81 (s, 3), 5.32 (t, $J$ = 4.9, 1), 6.22 (s, 1), 6.32 (s, 1), 6.42 (d, $J$ = 7.1, 1), 6.47 (s, 1), 6.68 (d, $J$ = 8.1, 1); $^{13}C$ NMR (75 MHz) $\delta$ 28.0, 38.6, 42.2, 55.6, 55.8, 55.9 (2), 61.2, 83.2, 109.5, 109.6, 110.9, 113.0, 122.4, 123.4, 125.8, 128.4, 147.4, 148.0, 148.4, 148.6, 152.1, 169.6.

**Tetracyclic Isoquinoline 17.** Isoquinolin-3-one **8** (78 mg, 0.17 mmol) was dissolved in 0.85 mL of MeOH and cooled to 0 °C. To the solution was added 64 mg (1.7 mmol) of $NaBH_4$. After 80 min the reaction mixture was poured onto 2 mL of saturated $NaHCO_3$ and 2 mL of $CHCl_3$ that had been cooled to 0 °C. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic portions were dried and concentrated to afford 58 mg of the aminal. The crude material was dissolved in 1.26 mL of $CH_2Cl_2$ and cooled to 0 °C. To the solution was added 66 $\mu$L (0.38 mmol) of TMSOTf, and the solution was warmed to rt. After 20 min the flask was equipped with a cold finger condenser and heated to reflux. After 2 h the reaction mixture was cooled to rt and quenched by addition of saturated $NaHCO_3$. The aqueous layer was extracted with $CHCl_3$ (3 × 10 mL), the combined organic portion was dried and concentrated to give 52 mg (70%) of **17**: mp 212 °C, $[\alpha]^{23}_D$ −118.3 (*c* 2.7, $CH_2Cl_2$); IR (neat) 2916, 2832, 1515, 1262, 1120 $cm^{-1}$; $^1H$ NMR (300 MHz) $\delta$ 2.76 (d, $J$ = 16.1, 2), 3.32 (dd, $J$ = 5.6, 16.1, 2), 3.77 (s, 6), 3.84 (s, 6), 4.41 (d, $J$ = 6.9, 2), 6.44 (s, 2), 6.61 (s, 2). $^{13}C$ NMR (75 MHz) $\delta$ 37.4, 50.2, 56.0, 56.3, 109.8, 112.0, 124.6, 130.7, 147.8, 148.3.

**Argemonine (6).** Isoquinoline **17** (13 mg, 0.038 mmol) was dissolved in 1 mL of MeOH, and 62 $\mu$L of formalin was added. After stirring 30 min 31 mg (0.82 mmol) of sodium borohydride was added, and the solution was stirred an additional 3 h and concentrated *in vacuo*. The resulting white solid was partitioned between 5% NaOH and $CHCl_3$. The two phases were separated, and the aqueous phase was extracted with $CHCl_3$ (3 × 5 mL). The combined organic portions were dried and concentrated to afford analytically pure 13 mg (96%) argemonine (**6**): mp 138−140 °C, $[\alpha]^{23}_D$ −229.5 (*c* 0.38, EtOH); $^1H$ NMR (300 MHz) $\delta$ 2.53 (s, 3), 2.59 (d, $J$ = 16.2, 2), 3.40 (dd, $J$ = 5.58, 2), 6.45 (s, 2), 6.61 (s, 2); $^{13}C$ NMR (75 MHz) $\delta$ 33.6, 40.9, 55.7, 55.9, 56.4, 110.0, 111.4, 123.9, 129.9, 147.4, 147.8.

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**Supporting Information Available:** NMR spectra for **6**, **8**, **15**, and **17** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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