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Asymmetric Synthesis of (−)-Nupharamine and (−)-(5*S*,8*R*,9*S*)-5-(3-Furyl)-8-methyloctahydroindolizidine from *β*-Amino Ketones and the Intramolecular Mannich Reaction

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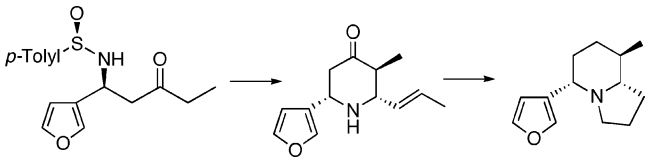
Received February 22, 2006



The asymmetric synthesis of the 2,3,6-trisubstituted piperidine core of the antitumor *Nuphar* alkaloids was readily achieved by using the intramolecular Mannich reaction and a sulfinimine-derived *β*-amino ketone.

Substituted piperidines, a common structural motif in many alkaloid natural products (indolizidine, quinolizidine), continue to be important targets for asymmetric synthesis due to their significant biological properties and scarce availability from natural sources.[1] The primary challenge associated with their preparation is the strategic placement of the multiple ring functionalities having the desired stereochemistry. Efforts in our laboratory have exploited the intramolecular Mannich reaction[2] of enantiopure amines, derived from *N*-sulfinyl *δ*-amino *β*-ketoesters with diverse aldehydes for the highly stereoselective, one-pot assembly of 2,3,6-tetrasubstituted 4-piperidones.[3] These sulfinimine (*N*-sulfinyl imine)-derived chiral building blocks were employed in concise asymmetric syntheses of monosubstituted piperidines such as (*R*)-(+)-2-phenylpiperidine,[4] disubstituted piperidines such as the four isomers of 4-hydroxypipecolic acid[5] and (−)-SS20846A,[4] and trisubstituted piperidines including the frog skin toxin (+)-241D[6] and the quinolizidine alkaloids (−)-lasubine I,[7] (+)-lasubine II,[8] and (−)-epimyrtine.[9] More recent studies with enantiopure *β*-amino ketones **1**[10] and aldehydes (R‴CHO) have revealed that the intramolecular Mannich reaction protocol is an important new source of stereodefined 2,3,6-trisubstituted and 2,3,5,6-tetrasubstituted 4-piperidones **2** and **3** (Scheme 1). These sulfinimine-derived building blocks were employed in efficient asymmetric syntheses of the poison frog alkaloids (−)-indolizidine 209B (**4**)[11] and (−)-indolizidine 223A (**5**).[12]

In an effort to extend and explore the scope and limitations of the intramolecular Mannich reaction/*β*-amino ketone protocol for the synthesis of functionalized piperidines we have turned our attention to the *Nuphar* alkaloids.[1,13] The *Nuphar* alkaloids are a large family of sesquiterpenoid and triterpenoid alkaloids having piperidine, indolizidine, and quinolizidine ring systems and are isolated from aquatic plants of the genus *Nuphar* (Nymphaeaceae).[14] Several members of this family of alkaloids have shown antibiotic, antifungal,[13a,b] and central paralytic effects,[15] as well as potent immunosuppressive[13d] and antitumor

(1) For recent reviews on the asymmetric synthesis of piperidines and indolizine alkaloids see: (a) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675. (b) Felpin, F. X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (d) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (e) Michael, J. P. *Nat. Prod. Rep*. **2005**, *22*, 603.

(2) For a review of the application of the Mannich reaction in alkaloid synthesis see: Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.

(3) For reviews on asymmetric synthesis of heterocycles with sulfinimines, see: (a) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (b) Davis, F. A.; Yang, B.; Deng, J.; Wu, Y.; Zhang, Y.; Rao, A.; Fang, T.; Goswami, R.; Prasad, K. R.; Nolt, M. B.; Anilkumar, G. *Phosphorus, Sulfur, Silicon* **2005**, *180*, 1109.

(4) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041.

(5) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.

(6) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169.

(7) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623.

(8) Davis, F. A.; Rao, A.; Carroll, P. J. *Org. Lett.* **2003**, *5*, 3855.

(9) Davis, F. A.; Zhang, Y.; Anilkumar, G. *J. Org. Chem.* **2003**, *68*, 8061.

(10) Davis, F. A.; Nolt, M. B.; Wu, Y.; Prasad, K. R.; Li, D.; Yang, B.; Bowen, K.; Lee, S. H.; Eardley, J. H. *J. Org. Chem*. **2005**, *70*, 2184.

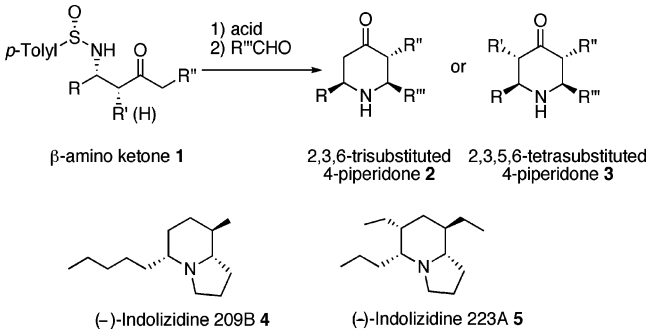
(11) Davis, F. A.; Yang, B. *Org. Lett.* **2003**, *5*, 5011.

(12) Davis, F. A.; Yang, B. *J. Am. Chem. Soc.* **2005**, *127*, 8398.

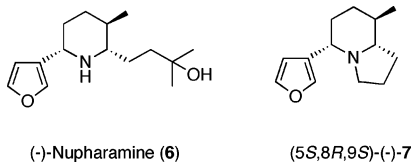
(13) (a) Wróbel, J. T. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, pp 441−465. (b) Cybuski, J.; Wróbel, J. T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1989; Vol. 35, pp 215−257. (c) Matsuda, H.; Shimode, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2001**, *9*, 1031.

10.1021/jo060371j CCC: $33.50
Published on Web 05/02/2006

SCHEME 1



SCHEME 2



acitivities.[16] The core structure of these heterocycles contains a trisubstituted piperidine ring with a 3-furyl substituent at C-6 and a methyl group at C-3, and this structure should be amenable to synthesis by using our Mannich/β-amino ketone protocol.[13] Representative examples of these compounds are (−)-nupharamine (**6**) and (−)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**7**) (Scheme 2). Several multistep asymmetric syntheses of (−)-nupharamine (**6**)[17] have been described employing Diels−Alder reactions,[18] an intramolecular aza-Wittig reaction,[19] and a cross metathesis/reductive amination reaction[20] as key steps. The only reported asymmetric synthesis of (−)-**7** employed an intermolecular Diels−Alder reaction.[18b]

Results and Discussion

The requisite β-amino ketone (R_S,1*S*)-(−)-(*p*-toluenesulfinyl)-1-amino-1-(3-furyl)pentan-3-one (**9**) was readily prepared by adding the preformed potassium enolate of methyl ethyl ketone to (*R*)-(−)-*N*-(3-furylmethylene)-*p*-toluenesulfinamide (**8**) (Scheme 3). The amino ketone (−)-**9** was obtained as a single diastereoisomer in 84% isolated yield. Sulfinimine (−)-**8** was prepared in 92% yield by reaction of commercially available (*R*)-(−)-*p*-toluenesulfinamide (*p*-TolylS(O)NH_2) with 3-furfural in the presence of $Ti(OEt)_4$.[21] Removal of the *N*-sulfinyl auxiliary in **9** was effected by treatment with 6 equiv of TFA in MeOH,

SCHEME 3

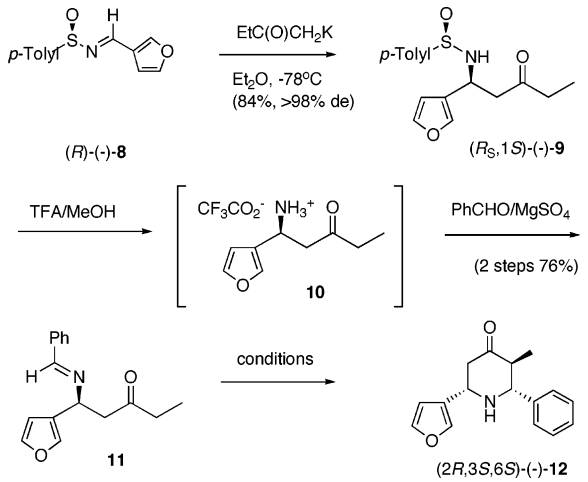


TABLE 1. Intramolecular Mannich Reaction of Imine 11 with Benzaldehyde

entry	acid (equiv)	reaction conditions	isolated **12** (%)
1	PTSA (6)	benzene, rt, 16 h	34
2	PTSA (6)	benzene, 45 °C, 3 h	38
3	PTSA (6)	benzene, 60 °C, 3 h	67
4	CSA (6)	benzene, 60 °C, 3 h	48
5	PPTS (6)	benzene, 60 °C, 3 h	42
6	$Yb(OTf)_3$ (1)	DCM rt, 8 h	24
7	$Yb(OTf)_3$ (1)	DCM, reflux, 8 h	30
8	$Yb(OTf)_3$ (1)	benzene, 60 °C, 3 h	38
9	$Yb(OTf)_3$ (6)	benzene, 60 °C, 3 h	42

which afforded the free amine **10** as the trifluoroacetate salt. The salt was quickly passed through a short pad of silica gel to remove the sulfinyl byproducts and concentrated, and the residue was immediately treated with benzaldehyde in DCM in the presence of anhydrous $MgSO_4$, which afforded the crude imine **11** in 76% yield for the two steps (Scheme 3). Our concern that the furan ring might not survive these conditions, because of its acid sensitivity, was apparently unfounded. However, for the same reasons, the Mannich cyclization was initially explored and optimized with the benzaldehyde imine substrate **11** (Scheme 3).

The crude imine **11** was next treated with 6 equiv of *p*-toluenesulfonic acid monohydrate in dry benzene at room temperature for 16 h. After the reaction was quenched with aqueous $NaHCO_3$, the desired tetrasubstituted piperidine (−)-**12** was isolated as a single diastereoisomer, but only in 34% yield (Scheme 3) (Table 1, entry 1). Increasing the temperature improved the yield of **12** and also reduced the reaction time (Table 1, entry 2). When the reaction was run at 60 °C in benzene for 3 h (−)-**12** was obtained in 67% yield (Table 1, entry 3). Use of acids such as camphorsulfonic acid (CSA) and pyridinium *p*-toluenesulfonate (PPTS) resulted in lower yields (Table 1, entries 4 and 5). Use of the lanthanide triflate salt, $Yb(OTf)_3$, also resulted in no improvement in the yields (Table 1, entries 6−9).

Using amine salt **10**, we next explored the Mannich cyclization with crotonaldehyde and ethyl *E*-4-oxo-2-butenoate imines **13a** and **13b**, respectively. When the crude imines were subjected to the optimized Mannich cyclization conditions (TsOH, PhH, 60 °C), the corresponding tetrasubstituted piperidines (−)-**14a** and (−)-**14b** were isolated as single isomers

(14) (a) LaLonde, R. T.; Wong, C.-F.; Das, K. C. *J. Am. Chem. Soc.* **1972**, *94*, 8522. (b) Maurer, B.; Ohloof, G. *Helv. Chim. Acta* **1976**, *59*, 1169.

(15) (a) Arata, Y.; Ohashi, T. *Yakugaku Zasshi* **1957**, *77*, 236. (b) Kokate, M.; Kawasaki, I.; Matsutani, S.; Kusumoto, S.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 698. (c) Wong, C. F.; Auer, E.; LaLonde, R. T. *J. Org. Chem.* **1970**, *35*, 517.

(16) (a) Matsuda, H.; Morikawa, T.; Oda, M.; Asao, Y.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4445. (b) Matsuda, H.; Yoshida, K.; Miyagawa, K.; Nemoto, Y.; Asao, Y.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1567.

(17) Shimizu, I.; Yamazaki, H. *Chem. Lett.* **1990**, 777.

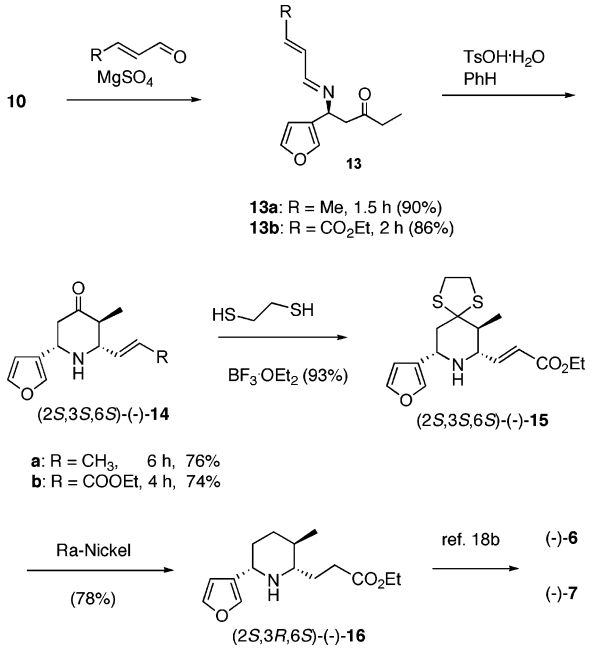
(18) (a) Shishido, Y.; Kibayashi, C. *Tetrahedron Lett.* **1991**, *32*, 4325. (b) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736.

(19) Honda, T.; Ishikawa, F.; Yamane, S. *J. Chem. Soc., Chem. Commun.* **1994**, 499.

(20) Blechert, S.; Gebauer, J. *Synlett* **2005**, 2826.

(21) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **2000**, *77*, 50.

SCHEME 4



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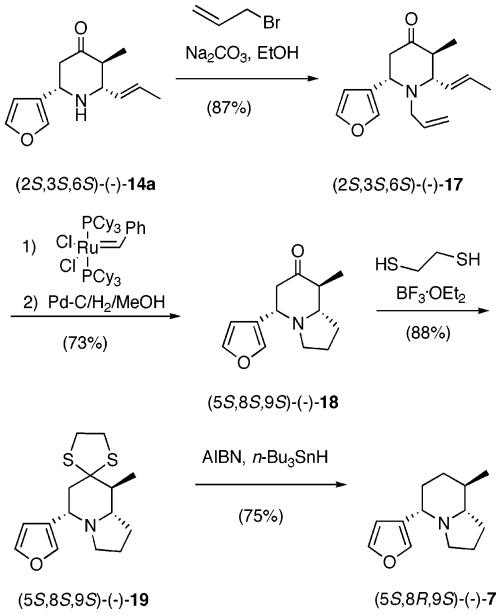

in good yield (Scheme 4). To prepare *Nuphar* alkaloids (−)-**6** and (−)-**7** requires removal of the 4-oxo group in (−)-**14b**, which was easily accomplished by formation of the thioketal with ethanedithiol/BF_3·OEt_2 to give (−)-**15**. When treated with Raney-Ni (−)-**15** gave (2*S*,3*R*,6*S*)-(−)-**16** in 78% yield (Scheme 4). Barluenga and co-workers[18b] prepared (−)-**16** in a series of nine steps from a chiral aminodiene and the resulting compound was used as a common intermediate in the synthesis of (−)-nupharamine (**6**) and (−)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**7**). Our synthesis of this key intermediate required only 6 steps (4 operations) from the readily prepared sulfinimine (*R*)-(−)-**8**. As (−)-**16** is the key intermediate, our procedure represents a formal asymmetric synthesis of *Nuphar* alkaloids (−)-**6** and (−)-**7**.

A more concise synthesis of indolizidine alkaloid (−)-(5*S*,8*R*,9*S*)-**7** employs piperidone (−)-**14a** and ring-closing metathesis (Scheme 5). Heating piperidine (−)-**14a** with allyl bromide gave the diene (−)-**17**, which was subjected to ring closing metathesis with Grubbs' first-generation catalyst. The crude reaction product was hydrogenated (5% Pd−C/H_2) to give indolizidine (−)-**18** in 73% isolated yield for the two-step sequence. The 7-oxo group was removed as before by conversion into the thioketal (−)-**19** followed by radical desulfurization with *n*-Bu_3SnH/AIBN to give the target (−)-(5*S*,8*R*,9*S*)-5-(3-furyl)-8-methyloctahydroindolizidine (**7**) in 75% yield (Scheme 5).

In summary an efficient protocol for the highly stereoselective synthesis of the 2,3,6-trisubstituted piperidine core structure of the *Nuphar* alkaloids was devised with use of the Mannich cyclization and sulfinimine (*N*-sulfinyl imine)-derived β-amino ketones. The requisite β-amino ketone was prepared by the highly diastereoselective addition of the potassium enolate of methyl ethyl ketone to a 3-furyl sulfinimine.

Experimental Section

(*R*)-(−)-*N*-(3-Furylmethylene)-*p*-toluenesulfinamide (8). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon were placed 0.59 g (3.83 mmol) of *R*-(−)-*p*-toluenesulfinamide in dichloromethane (50 mL). To this solution was added 0.82 mL (3.83 mmol) of 3-furaldehyde and 4.01 mL (19.1 mmol) of $Ti(OEt)_4$ at room temperature. The reaction mixture was stirred at room temperature for 5 h and poured into a 250-mL beaker containing a 50 mL ice−water mixture, then the solution was vigorously stirred for 10 min. At this time, DCM (25 mL) was added, the solution was extracted with DCM (2 × 25 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (hexanes/EtOAc, 9:1) gave 1.10 g (92%) of a white solid, mp 75−77 °C; $[\alpha]^{20}_D$ −308.5 (*c* 1.01, $CHCl_3$); IR (neat) 3054, 2921, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 7.92 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.39 (s, 1H), 7.28 (d, J = 7.6 Hz, 2H), 6.78 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) 152.6, 148.1, 144.9, 141.9, 130.0, 125.0, 124.3, 108.2, 21.7; HRMS calcd for $C_{12}H_{11}NO_2S$ (M + H) 234.0588, found 234.0587.

(R_S,1*S*)-(−)-*N*-(*p*-Toluenesulfinyl)-1-amino-1-furyl-pentan-3-one (9). In a 100-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed diethyl ether (50 mL) and the solution was cooled to −78 °C. At this time, 8.55 mL (4.29 mmol) of KHMDS (0.5 M solution in toluene) was added via syringe, followed by dropwise addition of 0.28 mL (3.2 mmol) of methyl ethyl ketone. The reaction mixture was stirred at this temperature for 1 h at which time 0.5 g (2.14 mmol) of (*R*)-(−)-**8** in diethyl ether (10 mL) was added via cannula. After 30 min, the reaction mixture was quenched by addition of saturated NH_4Cl (10 mL) solution at −78 °C and the reaction mixture was warmed to room temperature. Water (10 mL) was added, the solution was extracted with ether (2 × 20 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (20% EtOAc/hexane) gave 0.54 g (84%) of a colorless oil: $[\alpha]^{20}_D$ −109.4 (*c* 1.00, $CHCl_3$); IR (neat) 3197, 2362, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 2H), 7.41 (s, 1H), 7.36 (s, 1H), 7.24 (d, J = 7.6 Hz, 2H), 6.40 (s, 1H), 5.02 (d, J = 5.5 Hz, 1H), 4.82 (dd, J = 6.4, 5.5 Hz, 1H), 2.90 (d, J = 6.4 Hz, 2H), 2.38 (s, 3H), 2.33 (q, J = 7.5 Hz, 2H), 0.96 (t, J = 12.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) 209.6, 143.9, 143.6, 141.8, 140.5, 130.5, 128.3, 127.9, 110.2, 49.0, 48.9, 37.2, 21.7, 7.7; HRMS calcd for $C_{16}H_{19}NO_3SLi$ (M + Li) 312.1246, found 312.1242.

(2*R*,3*S*,6*S*)-(−)-6-(3-Furyl)-3-methyl-2-phenyl-4-piperidone (12). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.02 g (0.065 mmol) of (−)-**9** in anhydrous methanol (10 mL). The solution was cooled to 0 °C, and after 0.03 mL (0.39 mmol)

of TFA was added via syringe the mixture was warmed to room temperature. After the reaction mixture was stirred for 2 h the solvent was concentrated, EtOAc/hexane (1:1, 2 mL) was added, and the solution was passed through a short silica gel pad, eluting with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl products. Elution with methanol gave the crude ammonium triflate salt, which was concentrated and placed in a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. Dichloromethane (5 mL) was added followed by 0.007 g (0.065 mmol) of benzaldehyde via syringe, then 0.2 g of anhydrous $MgSO_4$ was added. The reaction mixture was stirred at room temperature for 3 h, concentrated, and washed with saturated $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated to give 0.018 g (76%) of brown oil of the crude imine **11**: ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 7.80 (s, 1H), 7.52 (m, 4H), 7.38 (m, 2H), 6.38 (s, 1H), 4.80 (m, 1H), 3.14 (m, 1H), 2.80 (dd, J = 7.2, 6.0 Hz, 1H), 2.42 (q, J = 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H). In a 25-mL one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.017 g (0.065 mmol) of the crude imine **11** in anhydrous benzene (5 mL). To the solution was added 0.09 g (0.39 mmol) of *p*-toluenesulfonic acid monohydrate and the reaction mixture was heated in an oil bath at 60 °C for 3 h. At this time the solvent was concentrated, and the residue was washed with saturated $NaHCO_3$ (2 × 5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (20% EtOAc/hexane, 1% Et_3N) afforded 0.012 g (67%) of a colorless oil: $[\alpha]^{23}_D$ −87.3 (*c* 0.1, $CHCl_3$); IR (neat) 2324, 1690, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 7H), 6.39 (s, 1H), 4.03 (dd, J = 7.0, 5.2 Hz, 1H), 3.52 (d, J = 7.2 Hz, 1H), 2.55 (m, 2H), 2.60 (m, 1H), 1.70 (br s, 1H), 0.98 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 210.3, 144.9, 142.7, 139.8, 129.4, 128.3, 128.1, 127.4, 109.0, 69.3, 52.5, 51.8, 50.0, 11.1; HRMS calcd for $C_{16}H_{17}NO_2Li$ (M + Li) 262.1420, found 262.1425.

(2*S*,3*S*,6*S*)-(−)-2-((*E*)-Ethyl-4-oxo-butenoxy)-3-methyl-6-(3-furyl)-4-piperidone (14b). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.05 g (0.163 mmol) of (−)-**9** in anhydrous methanol (10 mL). The solution was cooled to 0 °C, and 0.07 mL of TFA (0.978 mmol) was added via syringe. After the reaction mixture was stirred for 2 h the solvent was concentrated, EtOAc/hexane (1:1, 2 mL) was added, and the solution was passed through a short silica gel pad eluting with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl products. Elution with methanol gave the crude ammonium triflate salt, which was concentrated and placed in a 25-mL one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. Dichloromethane (5 mL) was added at room temperature followed by addition via syringe of 0.02 g (0.163 mmol) of (*E*)-ethyl-4-oxo-2-butenoate followed by 0.2 g of anhydrous $MgSO_4$. The reaction mixture was stirred at room temperature for 2 h, concentrated, and washed with saturated $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated to give 0.031 g (86%) of brown oil of crude **13b**; ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 2.8 Hz, 1H), 7.31 (s, 1H), 6.36 (m, 1H), 6.29 (s, 1H), 4.84 (dd, J = 7.2, 6.0 Hz, 1H), 4.22 (q, J = 7.4 Hz, 2H), 3.39 (m, 1H), 3.15 (dd, J = 8.2, 6.4 Hz, 1H), 2.90 (dd, J = 8.2, 4.6 Hz, 1H), 2.38 (dq, J = 7.6, 4.2 Hz, 2H), 1.30 (t, J = 7.8 Hz, 3H), 1.01 (t, J = 7.6 Hz, 3H).

In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.031 g (0.011 mmol) of the crude imine **13b** in anhydrous benzene (5 mL) followed by the addition of 0.015 g (0.066 mmol) of *p*-toluenesulfonic acid monohydrate. After heating the mixture at 60 °C in an oil bath for 4 h, the solvent was concentrated and the residue was washed with saturated $NaHCO_3$ (2 × 5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (20% EtOAc/hexane, 1% Et_3N) afforded 0.023 g (74%) of a colorless oil: $[\alpha]^{23}_D$ −76.5 (*c* 0.1, $CHCl_3$); IR (neat) 3127, 3054, 2921, 1610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 1H), 7.14 (s, 1H), 6.78 (dd, J = 8.4, 6.6 Hz, 1H), 6.28 (s, 1H), 5.80 (d, J = 10.4 Hz, 1H), 4.13 (q, J = 7.8 Hz, 2H), 3.78 (td, J = 7.4, 2.3 Hz, 1H), 3.12 (td, J = 7.4, 2.3 Hz, 1H), 2.38 (d, J = 7.8 Hz, 2H), 2.18 (m, 1H), 1.44 (br s, 1H), 1.09 (t, J = 7.6 Hz, 3H), 0.80 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 209.1, 166.3, 147.6, 145.3, 142.5, 140.4, 124.5, 109.7, 64.6, 61.0, 52.2, 50.3, 31.2, 14.5, 10.5; HRMS calcd for $C_{15}H_{19}NO_4$ (M + H) 277.1314, found 277.1314.

(2*S*,3*S*,6*S*)-(−)-1-Aza-2-((*E*)-ethyl-4-oxo-butenoxy)-3-methyl-6-(3-furyl)-1′,3′-dithiospiro[5,4]decane (15). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.02 g (0.72 mmol) of (−)-**14b** in CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. To the solution was added 0.037 mL (4 mmol) of ethanedithiol and 0.056 mL (4 mmol) of boron trifluoride via syringe. The reaction was warmed to room temperature, stirred for 2 h, and quenched by addition of 2 N NaOH (10 mL). The solution was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography gave 0.024 g (93%) of a yellow oil: $[\alpha]^{23}_D$ −76.5 (*c* 0.1, $CHCl_3$); IR (neat) 2921, 2729, 1345 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 7.4 Hz, 1H), 7.21 (s, 1H), 6.82 (dd, J = 8.4, 6.6 Hz, 1H), 6.40 (s, 1H), 5.86 (d, J = 10.2 Hz, 1H), 4.18 (q, J = 7.8 Hz, 2H), 3.98 (dd, J = 6.6, 2.1 Hz, 1H), 3.23 (m, 6H), 2.38 (d, J = 8.4, 2.2 Hz, 1H), 2.21 (m, 1H), 1.58 (br s, 1H), 1.21 (t, J = 7.6 Hz, 3H), 1.08 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 167.5, 146.7, 142.3, 139.3, 124.8, 122.7, 109.5, 68.4, 63.5, 60.9, 51.6, 43.7, 40.2, 39.7, 30.5, 12.4, 12.2; HRMS calcd for $C_{17}H_{23}NO_3S_2$ (M + H) 353.1119, found 353.1121.

(2*S*,3*R*,6*S*)-(−)-2-(2-Ethoxycarbonylethyl)-6-(3-furyl)-3-methylpiperidine (16). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.3 g of Raney 2800 Nickel (Aldrich). The Raney nickel was washed with absolute EtOH (2 × 10 mL) and 0.05 g (0.14 mmol) of (−)-**15** in absolute EtOH (10 mL) was added. The reaction mixture was refluxed for 2 h and cooled to room temperature, then the catalyst was removed by filtration. The filtrate was washed with EtOH and the combined washings were concentrated and purified by preparative TLC (CH_2Cl_2/EtOAc, 1:1) to afford 0.029 g (78%) of a colorless oil: $[\alpha]^{23}_D$ −38.7 (*c* 1.6, CH_2Cl_2) [lit.[18b] $[\alpha]^{23}_D$ −39.3 (*c* 1.8, CH_2Cl_2)]; IR (neat) 2921, 2729, 1345 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 1H), 7.20 (s, 1H), 6.39 (s, 1H), 4.13 (q, J = 7.4 Hz, 2H), 3.58 (dd, J = 11.2, 2.2 Hz, 1H), 2.43 (dd, J = 8.8, 6.7 Hz, 1H), 2.42 (t, J = 7.7 Hz, 1H), 2.26 (td, J = 8.4, 3.0 Hz, 1H), 1.97 (m, 1H), 1.77 (m, 2H), 1.62 (m, 4H), 1.44 (br s, 1H), 1.25 (t, J = 7.3 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H). Spectral properties were identical with those of (−)-**16** previously reported.[18b]

(2*S*,3*S*,6*S*)-(−)-6-(3-Furyl)-3-methyl-2-[(*E*)-1-propenyl]-4-piperidone (14a). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.04 g (0.137 mmol) of (−)-**9** in anhydrous methanol (10 mL). The solution was cooled to 0 °C, and TFA (0.06 mL, 0.824 mmol) was added via syringe. After the reaction mixture was stirred for 2 h the solvent was concentrated, EtOAc/hexane (1:1, 2 mL) was added, and the solution was passed through a short silica gel pad eluting with 30% EtOAc/hexane to remove the *p*-toluenesulfinyl products. Elution with methanol gave the crude ammonium triflate salt, which was concentrated and placed in a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon. Dichloromethane (5 mL) was added at room temperature followed by addition via syringe of 0.013 g (0.136 mmol) of 4-methyl-3-penten-1-al and 0.2 g of anhydrous $MgSO_4$. The reaction mixture was stirred at room temperature for 1.5 h, concentrated, and washed with saturated $NaHCO_3$ (5 mL). The solution was extracted with EtOAc (3 × 5 mL), dried (Na_2SO_4), and concentrated to give 0.026 g (90%) of a brown oil; ^{1}H NMR ($CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 1H), 7.32 (s, 1H), 7.25 (d,

J = 7.2 Hz, 1H), 6.26 (s, 1H), 6.15 (m, 2H), 4.60 (m, 2H), 3.02 (t, J = 7.2 Hz, 1H), 2.38 (q, J = 7.6 Hz, 2H), 1.80 (d, J = 6.4 Hz, 3H), 0.96 (t, J = 7.6 Hz, 3H).

In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar and argon balloon was placed 0.026 g (0.012 mmol) of the crude imine **13a** in anhydrous benzene (5 mL), followed by 0.017 g (0.073 mmol) of *p*-toluenesulfonic acid monohydrate. After the reaction mixture was stirred at 60 °C for 6 h, the solvent was concentrated and the residue was washed with saturated $NaHCO_3$ (2 × 5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Column chromatography (20% EtOAc/hexane, 1% Et_3N) afforded 0.018 g (76%) of a colorless oil: $[\alpha]^{23}_D$ −76.5 (*c* 0.1, $CHCl_3$); IR (neat) 3054, 2921, 1712, 1551 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (m, 2H), 6.40 (s, 1H), 5.62 (m, 1H), 5.40 (dd, J = 10.2, 6.5 Hz, 1H), 3.90 (dd, J = 6.2, 5.2 Hz, 1H), 2.98 (dd, J = 10.2, 6.8 Hz, 1H), 2.48 (m, 2H), 2.24 (m, 1H), 1.72 (br s, 1H), 1.65 (d, J = 7.8 Hz, 3H), 0.92 (d, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) 210.3, 143.5, 139.0, 132.3, 129.8, 113.0, 109.8, 66.7, 62.8, 53.4, 50.9, 18.1, 10.7; HRMS calcd for $C_{13}H_{17}NO_2$ (M + H) 219.1259, found 219.1260.

(2*S*,3*S*,6*S*)-(−)-6-(3-Furyl)-3-methyl-2-[(*E*)-1-propenyl]-1-(2-propenyl)-4-piperidone (17). In a 50-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar and condenser was placed 0.1 g (0.456 mmol) of (−)-**14a** in anhydrous EtOH (10 mL). To the reaction mixture were added allyl bromide (0.275 g, 0.19 mL, 2.28 mmol) and anhydrous solid Na_2CO_3 (0.5 g). The reaction mixture was refluxed for 2 h, cooled to room temperature, filtered, and concentrated. Water (10 mL) was added to the residue, and the solution was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Chromatography (10% EtOAc/hexane) afforded 0.102 g (87%) of a colorless oil: $[\alpha]^{23}_D$ −68.5 (*c* 0.1, $CHCl_3$); IR (neat) 3227, 3057, 2821, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.54 (m, 2H), 6.52 (s, 1H), 5.86 (m, 1H), 5.63 (m, 1H), 5.42 (m, 1H), 5.12 (dd, J = 6.4, 5.2 Hz, 1H), 4.98 (dd, J = 6.4, 5.2 Hz, 1H), 3.80 (dd, J = 12.3, 6.8 Hz, 1H), 3.45 (m, 2H), 3.18 (dd, J = 10.4, 7.2 Hz, 1H), 2.88 (t, J = 7.1 Hz, 1H), 2.40 (m, 1H), 1.75 (dd, J = 10.4, 6.8 Hz, 1H), 1.63 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$) 201.3, 144.5, 143.9, 140.3, 132.3, 126.2, 123.4, 109.8, 107.7, 70.5, 58.3, 49.7, 48.3, 34.8, 18.7, 8.9; HRMS calcd for $C_{16}H_{21}NO_2$ (M + H) 259.1572, found 259.1580.

(5*S*,8*S*,9*S*)-(-)-5-(3-Furyl)-8-methyloctahydroindolizine-7-one (18). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.1 g (0.385 mmol) of (−)-**17** in dichloromethane (10 mL). To the solution was added 0.016 g (5 mol %) of bezylidene-bis-(tricyclohexylphosphine) dichlororuthenium, and the solution was refluxed for 2 h. At this time, the solution was concentrated, then anhydrous methanol (10 mL) was added followed by 0.025 g of 5% Pd/C. The argon balloon was replaced by a hydrogen-filled balloon and the reaction mixture was stirred at room temperature for 2 h. At this time the solution was filtered through a Celite pad, the pad was washed with methanol (3 × 10 mL), and the combined organic phases were concentrated. Column chromatography (20% EtOAc/hexane) of the residue afforded 0.061 g (75%) of a colorless oil: $[\alpha]^{23}_D$ −87.5 (*c* 0.64, $CHCl_3$); IR (neat) 3127, 2921, 1610, 1551 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (d, J = 7.2 Hz, 1H), 7.22 (s, 1H), 6.42 (s, 1H), 3.81 (m, 1H), 3.68 (m, 1H), 3.26 (m, 1H), 2.42 (q, J = 8.2 Hz, 1H), 2.38 (m, 3H), 1.91 (m, 2H), 1.70 (m, 1H), 1.48 (m, 1H), 1.04 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) 211.3, 143.0, 140.7, 121.5, 110.3, 59.4, 52.4, 50.6, 49.7, 45.4, 30.6, 21.9, 10.5; HRMS calcd for $C_{13}H_{17}NO_2$ (M + H) 219.1259, found 219.1262.

(5*S*,8*S*,9*S*)-(−)-5-(3-Furyl)-8-methyloctahydroindolizine-7-spiro-2′-(1′,3′-dithiolane (19). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.02 g (0.8 mmol) of (−)-**18** in CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. To the solution was added 0.037 mL (4 mmol) of ethanedithiol and 0.056 mL (4 mmol) of boron trifluoride via syringe. The reaction mixture was warmed to room temperature, stirred for 2 h, and quenched by addition of 2 N NaOH (10 mL). The solution was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic phases were dried (Na_2SO_4), and concentrated. Chromatography (20% EtOAc/hexane) gave 0.024 g (88%) of a yellow oil: $[\alpha]^{23}_D$ −45.5 (*c* 1.1, $CHCl_3$); IR (neat) 2921, 2729, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 2H), 6.40 (s, 1H), 3.24 (m, 4H), 2.80 (m, 2H), 2.42 (q, J = 8.2 Hz, 1H), 2.33 (m, 2H), 1.70 (m, 3H), 1.62 (m, 2H), 1.45 (m, 1H), 1.06 (d, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) 144.2, 140.7, 127.2, 110.8, 74.8, 70.7, 58.2, 54.9, 53.8, 46.6, 40.3, 39.8, 30.1, 21.7, 13.9; HRMS calcd for $C_{15}H_{21}NOS_2$ (M + H) 295.1065, found 295.1064.

(5*S*,8*R*,9*S*)-(−)-5-(3-Furyl)-8-methyloctahydroindolizidine (7). In a 25-mL, single-necked, round-bottom flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed 0.08 g (2.7 mmol) of thioketal (−)-**19** in benzene (5 mL). To the reaction mixture were added 0.045 g (2.3 mmol) of tributyltinhydride and 0.005 g of AIBN, then the reaction mixture was refluxed for 2 h. At this time the solution was concentrated and partitioned between CH_2Cl_2 and water. The organic phase was dried (Na_2SO_4) and concentrated. Chromatography (Al_2O_3, hexanes/EtOAc, 10:1) gave 0.04 g (75%) of a colorless oil: $[\alpha]^{20}_D$ −98.4 (*c* 1.1, CH_2Cl_2) [lit.[18b] $[\alpha]^{20}_D$ −99.0 (*c* 1.3, CH_2Cl_2)]; IR (neat) 2921, 2729, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38 (m, 2H), 6.42 (s, 1H), 2.90 (dd, J = 8.4, 5.7 Hz, 1H), 2.88 (td, J = 8.8, 2.2 Hz, 1H), 1.98 (m, 2H), 1.39 (m, 8H), 1.13 (m, 1H), 0.9 (d, J = 6.6 Hz, 3H). Spectral properties were identical with those of (−)-**7** previously reported.[18b]

Acknowledgment. This work was supported by a grant from the National Institutes of General Medicinal Sciences (NIGMS 51982).

Supporting Information Available: ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060371J