JOC*Article*

Asymmetric Synthesis of the Quinolizidine Alkaloid (−)-Epimyrtine with Intramolecular Mannich Cyclization and *N*-Sulfinyl *δ*-Amino *β*-Ketoesters

Franklin A. Davis,* Yulian Zhang, and Gopinathan Anilkumar

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

fdavis@temple.edu

Received June 24, 2003

A concise, six-step, enantioselective synthesis of (−)-epimyrtine employing the *N*-sulfinyl *δ*-amino *β*-ketoester chiral building block is described.

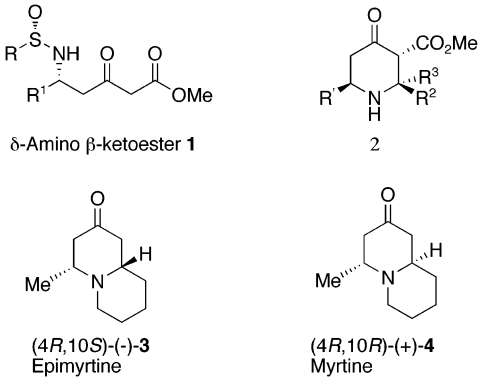
N-Sulfinyl *δ*-amino *β*-ketoesters **1** are new sulfinimine (*N*-sulfinyl imine) derived polyfunctionalized chiral building blocks that provide efficient access to mono- and bicyclic alkaloids with a minimum of chemical manipulation and protecting, deprotecting group chemistry (Scheme 1).[1] These building blocks have been employed in concise asymmetric syntheses of mono-,[2] di-, and trisubstituted piperidines;[2−4] the quinolizidine alkaloid (−)-lasubine II; and cis 5-substituted prolines.[5,6] The amine salt of **1** undergoes an intramolecular Mannich reaction with aldehydes and ketones to produce 2,3,4,6-tetrasubstituted piperidines **2** and was employed in the enantioselective synthesis of the dendrobate alkaloid (+)-241D.[7] As a test of this methodology's ability to rapidly and stereospecifically assemble densely substituted piperidines as well as to define the scope and limitations of the intramolecular Mannich cyclization of **1** we describe here an efficient asymmetric synthesis of (−)-epimyrtine (**3**).

(−)-Epimyrtine (**3**) and (+)-myrtine (**4**) are naturally occurring quinolizidine alkaloids isolated from *Vaccinium myrtillus*.[8] Although several racemic syntheses of these compounds have been reported[9] there is only a single asymmetric synthesis of (−)-**3**[9] and two asymmetric syntheses of (+)-**4**.[8b,10] In the synthesis of (−)-**3**, Gelas-Mialhe and co-workers employed an intramolecular *N*-acyliminium ion cyclization strategy.[9]

In the method presented here the requisite (R_S,*R*)-(−)-methyl 3-oxo-5-methyl-5-(*p*-toluenesulfinylamino)-hexanoate (**7**) was prepared by the addition of the sodium enolate of methyl acetate to (*R*)-(−)-**5** to give *β*-amino ester (−)-**6** in 88% yield and >97% de (Scheme 2). The sodium enolate was again added to (−)-**6** affording (−)-**7** in 90% yield. While *δ*-amino *β*-ketoesters can often be prepared in one pot by addition of excess methyl acetate enolate to the sulfinimine, in this instance yields were poorer and the selectivity suffered. Next, (−)-**7** was treated with TFA/MeOH and the reaction solution passed through a short plug of silica gel to remove the sulfinyl byproducts. The crude trifluoroacetate salt of **8** in MeOH afforded piperidine **10** on reaction with 1 equiv of 5-benzyloxy pentanal (**9**)[11] in a 3:1 mixture of diastereoisomers and in 68% yield for the two steps. Decarboxylation with LiOH/MeOH or refluxing in HCl gave a single diastereomeric piperidine **11** in 25% yield. The cis relationship of the 2,6-substituents is predicted by our transition state model for the intramolecular Mannich cyclization in which $A^{1,3}$ strain favors the cis product.[3] This conformation was confirmed by decoupling studies and NOE experiments that revealed the diaxial orientation of the C(2) and C(6) protons in **11**.

The difficulty in removing the piperidine 3-carbomethoxy group indicated the need for a more efficient decarboxylation process. The use of *tert*-butyl esters was considered a possible alternative because such esters are

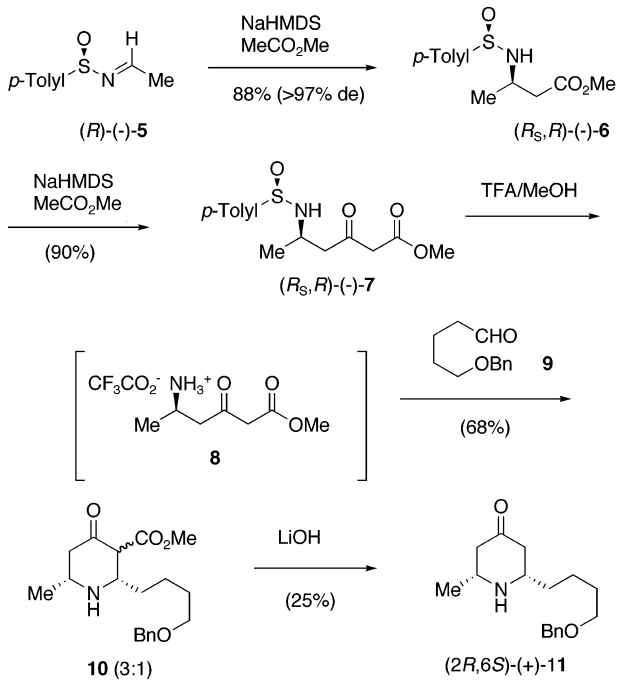
SCHEME 1



(1) For a review see: Davis, F. A.; Chao, B.; Andemichael, Y. W.; Mohanty, P. K.; Fang, T.; Burns, D. M.; Rao, A.; Szewczyk, J. M. *Heteroatom Chem*. **2002**, *13*, 486.
(2) Davis, F. A.; Chao, B.; Fang, T.; Szewczyk, J. M. *Org. Lett.* **2000**, *2*, 1041.
(3) Davis, F. A.; Chao, B. *Org. Lett.* **2000**, *2*, 2623.
(4) Davis, F. A.; Fang, T.; Chao, B.; Burns, D. M. *Synthesis* **2000**, 2106.
(5) Davis, F. A.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, *4*, 1599.
(6) Davis, F. A.; Yang, B.; Deng, J. *J. Org. Chem*. **2003**, *68*, 5147.
(7) Davis, F. A.; Chao, B.; Rao, A. *Org. Lett.* **2001**, *3*, 3169.
(8) (a) Slosse, P.; Hootele, C. *Tetrahedron Lett*. **1978**, 397. (b) Slosse, P.; Hootele, C. *Tetrahedron* **1981**, *37*, 4287.
(9) For leading references see: Gardette, D.; Gelas-Mialhe, Y.; Gramain, J.-C.; Perrin, B.; Remuson, R. *Tetrahedron*: *Asymmetry* **1998**, *9*, 1823.
(10) Comins, D. L.; LaMunyon, D. H. *J. Org. Chem*. **1992**, *57*, 5807.
(11) Zhang, R.; Wang, Z.; Wei, F.; Huang, Y. *Synth. Commun*. **2002**, *32*, 2187.

10.1021/jo030208d CCC: $25.00 © 2003 American Chemical Society
Published on Web 09/18/2003

SCHEME 2



generally easily decarboxylated under mild acidic conditions.[12] Furthermore, the fact that it was necessary to redesign our substrate presented the opportunity to evaluate the effect on the cyclization of transposing sulfinimine and aldehyde groups. This redesign also necessitates a change in the absolute configuration of the sulfinimine.

Treatment of the sulfinimine (*S*)-(+)-**12** with the sodium enolate of methyl acetate gave the β-amino ester (S_SS)-(+)-**13** in excellent yield and >97% de (Scheme 3). Reaction of the ester with the sodium enolate of *tert*-butyl acetate afforded (+)-**14** in 90% isolated yield. Removal of the sulfinyl group with TFA/MeOH, as before, and reaction of the crude trifluoroacetate amine salt with acetaldehyde gave tetrasubstituted piperidine (+)-**15** in 78% isolated yield for the two steps. Importantly, under the acidic conditions necessary for the Mannich cyclization, decarboxylation did not take place. However, refluxing (+)-**15** with 10 equiv of TFA in $CHCl_3$ for 2 h gave an 83% yield of trisubstituted piperidine (−)-**16**. Notable is the fact that epimerization of the piperidine stereocenters was not detected. The cis structure of the 2,6-substituents was determined by NOE experiments and conversion into the natural product (see below).

To complete the synthesis of (−)-epimyrtine (**3**) all that was required was deprotection of the benzyl group and cyclization to form the quinolizidine ring (Scheme 3). However, initial attempts to remove the benzyl group with use of Pd/C and H_2 at atmospheric pressure were unsuccessful, but when the pressure was increased to 50 psi (+)-**17** was obtained in 80% yield. Interestingly, with $Pd(OH)_2$, 2 drops of TFA, and atmospheric hydrogen pressure (+)-**17** was isolated in 95% yield. In the absence of TFA no reaction occurred, which suggests the nitrogen may be deactivating the catalysts and can be eliminated if the salt is employed. Next, attempts to effect cyclization as before, using TsCl and pyridine, resulted in extensive decomposition.[3] Alternatively, treatment of the alcohol with triphenyl phosphine, CCl_4, and triethylamine resulted in (4*R*,10*S*)-(−)-epimyrtine (**3**) in 77% isolated yield for the two steps. Compound (−)-**3** exhibited properties consistent with those reported for the natural product.[9]

In summary, a concise enantioselective synthesis of the quinolizidine alkaloid (−)-epimyrtine (**3**) was accomplished in six steps with an overall yield of 41% from the sulfinimine. The decarboxylation step was improved by employing the *tert*-butyl ester.

Experimental Section

Sulfinimines were prepared as described earlier from (*R*)-(−)- and (*S*)-(+)-*p*-toluenesulfinamide; acetaldehyde or 5-benzyloxy pentanal (**9**);[11] and $Ti(OEt)_4$.[13]

(*R*)-(−)-*N*-(Acetylidene)-*p*-toluenesulfinamide (5). Flash chromatography (CH_2Cl_2) afforded 0.13 g (93%) as a yellow oil; $[\alpha]^{20}_D$ −418.2 (*c* 1.20, $CHCl_3$); IR (neat) 1640, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.23 (q, 1 H, J = 5 Hz), 7.55 (d, 2 H, J = 8 Hz), 7.29 (d, 2 H, J = 8 Hz), 2.38 (s, 3H), 2.19 (d, 3 H, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 163.6, 141.7, 129.7, 125.3, 124.4, 22.3, 21.3. Anal. Calcd for $C_9H_{11}NOS$: C, 59.61; H, 6.12; N, 7.73. Found: C, 59.33; H, 6.38; N, 7.60.

(*S*)-(+)-*N*-(5-Benzyloxy-1-pentylidene)-*p*-toluenesulfinamide (12). Flash chromatography (EtOAc/hexane, 2:8) gave 8.3 g (97%) of a yellow oil; $[\alpha]^{20}_D$ 235.5 (*c* 0.94, $CHCl_3$); IR (neat) 3228, 2937, 2862, 1096 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (t, 1 H, J = 4.62 Hz), 7.38 (dd, 2 H, J = 1.7 Hz, 6.66 Hz), 7.14 (m, 7 H), 4.29 (s, 2 H), 3.28 (t, 2 H, J = 7.1 Hz), 2.33 (m, 2 H), 2.22 (s, 3H), 1.52 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 167.4, 14.2, 142.1, 138.9, 130.2, 128.8, 128.0, 127.9, 125.0, 73.3, 70.1, 36.1, 29.5, 22.6, 21.8, 14.6. HRMS calcd for $C_{19}H_{23}NO_2S$ (M + Na) 352.1347, found 352.1348. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.43; H, 7.09; N, 4.24.

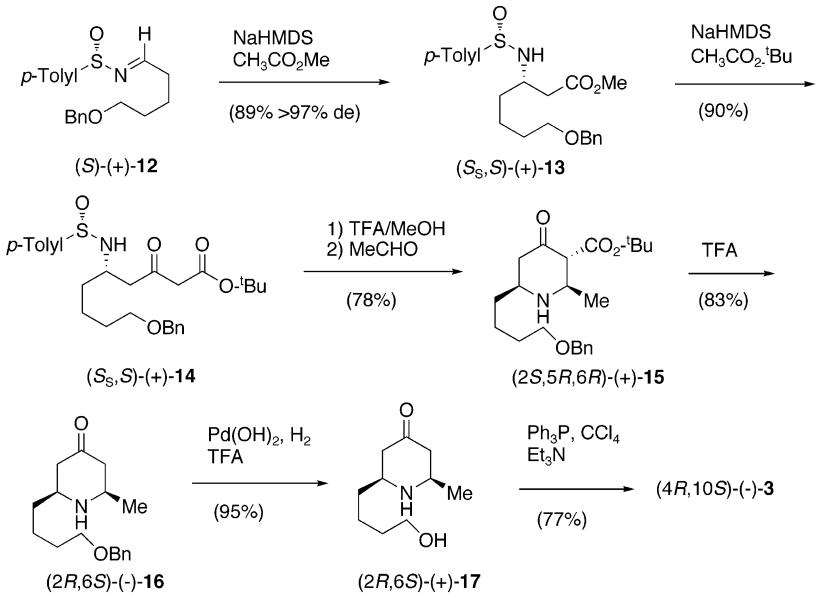
Typical Procedure for the Preparation of (R_S,*R*)-(−)-Methyl *N*-(*p*-Toluenesulfinyl)-3-amino-3-methylpropanoate (6). In a 200-mL, oven-dried, one-necked, round-bottomed flask equipped with a magnetic stirring bar and an argon balloon were placed ether (40 mL) and NaHMDS (5.81 mL, 5.81 mmol, 1.0 M solution in THF). At this time the reaction mixture was cooled to −78 °C and methyl acetate (0.46 mL, 5.81 mmol) was added. After the mixture was stirred for 50 min, a solution of sulfinimine (−)-**5** (0.8 g, 4.47 mmol) in THF (6 mL) was added dropwise and stirring was continued for 2 h. The reaction mixture was quenched by addition of sat. NH_4Cl (50 mL) at −78 °C; the solution was warmed to room temperature and extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (25 mL), dried (Na_2SO_4), and concentrated to give the crude product, which was purified by flash chromatography (50% EtOAc/hexane) to give 1.0 g (88%) as a yellow oil in >97% de; $[\alpha]^{20}_D$ −128 (*c* 1.5, $CHCl_3$); IR (neat) 3209, 1739, 1088, 1055, 811 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.57 (d, 2 H, J = 8 Hz), 7.28 (d, 2 H, J = 8 Hz), 4.63 (d, 1 H, J = 8 Hz), 3.78 (m, 1 H), 3.65 (s, 3H), 2.49 (m, 2 H), 2.40 (s, 3 H), 1.33 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.4, 142.4, 141.9, 130.2, 126.4, 52.3, 47.8, 42.7, 23.0, 22.0. HRMS calcd for $C_{13}H_{17}NO_3S$ (M + Na) 278.0827, found 278.0824. Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.12; H, 7.01; N, 5.35.

(S_S,*S*)-(+)-Methyl *N*-(*p*-Toluenesulfinyl)-3-amino-7-benzyloxyheptanoate (13). Flash chromatography (EtOAc/hexane, 1:9) gave 3.53 g (89%) of a yellow oil; >99% de; $[\alpha]^{20}_D$ +65.3 (*c* 0.11, $CHCl_3$); IR (neat) 3206, 2862, 1737, 1437, 1096

(12) Baty, J. D.; Jones, G.; Moore, C. *J. Chem. Soc. C* **1967**, 2645.

(13) (a) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1043. (b) Fanelli, D. L.; Szewczyk, J. M.; Zhang, Y.; Reddy, G. V.; Burns, D. M.; Davis, F. A. *Org. Synth.* **1999**, *77*, 50.

SCHEME 3



cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.59 (d, 2 H, J = 8.3 Hz), 7.36 (m, 7 H), 4.52 (m, 3 H), 3.67 (m, 4 H), 3.51 (t, 2 H, J = 6.2 Hz), 2.61 (m, 2 H), 2.42 (s, 3 H), 1.65 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 172.4, 142.7, 141.7, 139.0, 129.9, 128.8, 128.0, 127.9, 125.9, 73.3, 70.4, 53.0, 52.1, 40.8, 36.0, 29.7, 23.2, 21.7. HRMS calcd for $C_{22}H_{29}NO_2S$ (M + Na) 426.1712, found 426.1710. Anal. Calcd for $C_{22}H_{29}NO_2S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.00; H, 7.17; N, 3.50.

Typical Procedure for the Preparation of (R_S,*R*)-(−)-3-Oxo-5-*N*-(*p*-toluenesulfinylamino)-5-methylhexanoate 7. In a 25-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed NaHMDS (3.46 mL, 1.0 M solution in THF) in THF (6 mL). The solution was cooled to −78 °C and anhydrous methyl acetate (0.28 mL, 3.46 mmol) was added via syringe. After the mixture was stirred for 1 h at this temperature a solution of (R_S,*R*)-(−)-**6** (0.22 g, 0.87 mmol) in THF (4 mL) was added and the reaction mixture was quenched after 4 h with sat. NH_4Cl (1 mL). Water (5 mL), was added and the solution was extracted with EtOAc (2 × 25 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography gave 0.23 g (90%) of a yellow oil; $[\alpha]^{20}_D$ −111.0 (*c* 0.84, $CHCl_3$); IR (neat) 3219, 1652, 1558, 1457, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 2 H, J = 8.5 Hz), 7.22 (d, 2 H, J = 8.5 Hz), 4.65 (d, 1 H, J = 8 Hz), 3.69 (m, 1 H), 3.66 (s, 3 H), 3.34 (s, 2 H), 2.78 (m, 2H), 2.34 (s, 3 H), 1.29 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 201.8, 167.8, 142.5, 141.9, 130.1, 126.3, 53.0, 51.0, 50.1, 47.3, 23.0, 21.9. HRMS calcd for $C_{14}H_{19}NO_4S$ (M + Na) 320.0933, found: 320.0937. Anal. Calcd for $C_{14}H_{19}NO_4S$: C, 56.55; H, 6.44; N, 4.71. Found: C, 56.11; H, 6.40; N, 4.83.

(S_S,*S*)-(+)-*tert*-Butyl 3-Oxo-5-*N*-(*p*-toluenesulfinylamino)-9-benzyloxynonanoate (14). The procedure, as described above, was applied to the synthesis of (+)-**14** except that the sodium enolate of *tert*-butyl acetate was added to (+)-**13**. Flash chromatography gave 2.0 g (90%) of a yellow oil; $[\alpha]^{20}_D$ 46.0 (*c* 0.5, $CHCl_3$); IR (neat) 3211, 2932, 2861, 1733, 1715, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.55 (d, 2H, J = 8.2 Hz), 7.33 (m, 7 H), 4.50 (s, 2 H), 4.42 (d, 1 H, J = 9.3 Hz), 3.68 (m, 1 H), 3.48 (t, 2 H, J = 6.2 Hz), 3.30 (s, 2 H), 2.87 (t, 2 H, J = 4.7 Hz), 2.40 (s, 3 H), 1.70 (m, 6 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 202.2, 166.1, 142.3, 141.3, 138.6, 129.5, 128.4, 127.6, 127.5, 125.5, 82.2, 72.9, 70.1, 52.4, 51.2, 48.6, 35.4, 29.3, 28.0, 23.0, 21.4. HRMS calcd for $C_{27}H_{37}NO_5S$ (M + H) 488.2473, found 488.2473. Anal. Calcd for $C_{27}H_{37}NO_5S$: C, 66.50; H, 7.65; N, 2.87. Found: C, 66.51; H, 7.56; N, 2.87.

Methyl 2-(4-Benzyloxybutyl)-6-methyl-4-oxo-piperidine-3-carboxylate (10). In a 10-mL, oven-dried, one-necked, round-bottom flask, equipped with a magnetic stirring bar and N_2 balloon, was placed (−)-**7** (0.1 g, 0.337 mmol) in MeOH (2.5 mL). Trifluoroacetic acid (0.16 mL, 2.02 mmol) was added to the reaction mixture at room temperature and the solution was stirred for 45 min. The solvent was concentrated and the residue was passed through a small plug of silica gel and eluted with 30% EtOAc in hexane (30 mL). The amine salt was eluted with MeOH (50 mL), the solvent was concentrated, and the residue was dissolved in CH_2Cl_2 (1.5 mL). To this solution was added aldehyde **9** (0.065 g, 0.337 mmol) in CH_2Cl_2 (3.0 mL) and the reaction mixture was stirred at room temperature for 8 h. At this time the reaction mixture was quenched with saturated $NaHCO_3$ (1 mL), extracted with EtOAc (4 × 10 mL), dried (Na_2SO_4), and concentrated. Preparative TLC (EtOAc:hexane 1:1) gave 0.077 g (68%) of an oil as a 3:1 mixture of inseparable diastereomers as determined by integration of the methoxy groups in the ^{1}H NMR spectra.

(2*R*,6*S*)-(+)-2-(4-Benzyloxybutyl)-6-methylpiperidin-4-one (11). In a 10-mL, one-necked, round-bottom flask fitted with a magnetic stirring bar and reflux condenser was placed ester **10** (0.070 g, 0.21 mmol) in THF (2 mL). Lithium hydroxide (0.026 g, 0.63 mmol) was added to the solution followed by H_2O (1 mL). The reaction mixture was refluxed for 12 h and cooled to room temperature, and H_2O (2 mL) was added. The solution was extracted with EtOAc (4 × 5 mL), and the organic phase was dried ($MgSO_4$) and concentrated. Preparative TLC (EtOAc:hexane 1:1) gave 0.014 g (25%) of an oil; $[\alpha]^{20}_D$ 8.3 (*c*, 0.56, $CHCl_3$); IR (neat) 1706, 1652, 1551 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35−7.25 (m, 5 H), 4.49 (s, 2 H), 3.47 (t, 2 H, J = 6.0 Hz), 3.42 (m, 1 H), 3.31 (m, 1H), 2.52−2.44 (m, 2 H), 2.18−2.11 (m, 2 H), 1.64−1.60 (m, 2 H), 1.42−1.39 (m, 4 H), 1.15 (d, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 208.7, 137.6, 127.5, 126.8, 126.7, 72.1, 69.7, 51.7, 48.5, 46.8, 46.6, 33.4, 28.6, 21.9, 20.6. HRMS calcd for $C_{17}H_{25}NO_2$ (M + Na) 298.1798, found 298.1777.

Typical Procedure for the Preparation of *tert*-Butyl (2*S*,5*R*,6*R*)-(+)-2-methyl-6-(4-benzyloxybutyl)-4-oxo-piperidine-3-carboxylate (15). In a 200-mL, one-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, and argon balloon was placed (+)-**14** (1.00 g, 2.05 mmol) in methanol (100 mL). TFA (2 mL) was added dropwise to the solution and the reaction mixture was stirred at room temperature for 30 min. The solution was concentrated and loaded on a short pad of silica and eluted with 30% EtOAc/

hexane to remove the side products and then with methanol to give the amine salt. The methanol solution was concentrated and CH_2Cl_2 (60 mL) was added, followed by acetaldehyde (1.13 mL, 20.5 mmol). The reaction mixture was stirred for 1 h at room temperature and diluted with ethyl acetate (50 mL), and the solution was treated with K_2CO_3 (1.00 g) and sat. $NaHCO_3$ (20 mL). The organic phase was separated, dried (Na_2SO_4), and concentrated. Flash chromatography (50% EtOAc/hexane) gave 0.60 g (78%) of a yellow oil; $[\alpha]^{20}_D$ +37.0 (*c* 1.0, $CHCl_3$); IR (neat) 3302, 1733, 1710, 1367, 1150, 1115 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 4.42 (s, 2 H), 3.40 (t, 2 H, J = 6.3 Hz), 3.16 (m, 1 H), 2.80 (m, 2 H), 2.38 (dd, 1 H, J = 2.9 Hz, 13 Hz), 1.95 (m, 1 H), 1.55 (m, 2 H), 1.41 (m, 13H), 1.15 (d, 3 H, J = 6.1 Hz); ^{13}C NMR ($CDCl_3$) δ 202.0, 167.2, 137.4, 127.4, 126.6, 80.6, 71.9, 69.0, 65.2, 55.2, 53.5, 46.8, 35.6, 28.7, 27.0, 21.4, 20.2. HRMS calcd for $C_{22}H_{33}NO_4$ (M + Na) 398.2294, found 398.2296. Anal. Calcd for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.03; H, 8.90; N, 3.56.

(2*R*,6*S*)-(−)-2-(4-Benzyloxybutyl)-6-methyl-4-oxopiperidine (16). In a 100-mL, one-necked, round-bottomed flask fitted with magnetic stirring bar, condenser, and argon balloon was placed (+)-**15** (0.40 g, 1.07 mmol) in $CHCl_3$ (50 mL) and TFA (5 mL). The reaction mixture was refluxed for 2 h and concentrated. The residue was treated with sat. $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (2 × 30 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash chromatography (MeOH/CH_2Cl_2, 5:95) to give 0.24 g (83%) of a yellow oil; $[\alpha]^{20}_D$ −3.6 (*c* 1.0, C_6H_6); IR (neat) 3311, 2934, 2860, 1715, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 4.42 (s, 2 H), 3.41 (t, 2 H, J = 6.3 Hz), 2.89 (m, 1H), 2.88 (m, 1 H), 2.27 (m, 2H), 2.00 (m, 2 H), 1.56 (m, 3 H), 1.42 (m, 4 H), 1.13 (d, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 210.1, 139.2, 129.1, 128.3, 128.2, 73.6, 70.7, 57.1, 52.8, 50.8, 48.7, 37.5, 30.4, 23.3, 23.1. HRMS calcd for $C_{17}H_{25}NO_2$ (M + Na) 298.1783, found 298.1787. Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.04; H, 9.18; N, 4.71.

(2*S*,6*R*)-(+)-2-(4-Hydroxybutyl)-6-methyl-4-oxopiperidine (17). In a 25-mL, one-necked, round-bottomed flask fitted with magnetic stirring bar, rubber septum, and hydrogen balloon was placed (−)-**16** (0.20 g, mmol) in THF (5 mL). To the solution was added $Pd(OH)_2$ (0.02 g, 20% on carbon) and 2 drops of TFA. The reaction mixture was stirred at room temperature for 3 h under an atmosphere of H_2, after which time the solution was filtered and concentrated. Flash chromatography (MeOH/CH_2Cl_2, 5:95) gave 0.128 g (95%) of a colorless oil; $[\alpha]^{20}_D$ 3.57 (*c* 1.4, MeOH); IR (neat) 3421, 1649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.61 (t, 2 H, J = 6.3 Hz), 2.92 (m, 1 H), 2.89 (m, 1 H), 2.29 (m, 2 H), 1.99 (m, 2 H), 1.52 (m, 6 H), 1.15 (d, 3 H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 209.6, 62.9, 56.9, 53.8, 52.5, 50.5, 48.4, 37.0, 32.9, 22.9, 22.3. HRMS calcd for $C_{10}H_{19}NO_2$ (M + H) 186.1480; found 186.1487. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.79; H, 10.25; N, 7.52.

(4*R*,10*S*)-(−)-Epimyrtine (3). In a 25-mL, one-necked, round-bottomed flask fitted with magnetic stirring bar, rubber septum, and argon balloon were placed (+)-**17** (0.036 g, 0.19 mmol) in MeCN (3 mL). A solution of Et_3N (0.028 mL, 0.20 mmol) in CCl_4 (0.028 mL, 0.29 mmol) was added and the solution was cooled to 0 °C. At this time triphenylphosphine (0.047 g, 0.18 mmol) was added and the reaction mixture was stirred for 45 min, warmed to room temperature, and stirred for 20 h. To the reaction mixture was added sat. $NaHCO_3$ (5 mL) and the solution was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated. Flash chromatography (MeOH/CH_2Cl_2, 2:98) gave 0.025 g (77%) of an oil; $[\alpha]^{20}_D$ −17.4 (*c* 0.7, $CHCl_3$) [lit.[9] $[\alpha]^{28}_D$ −18 (*c* 5.4, $CHCl_3$); lit.[8b] $[\alpha]^{25}_D$ −19 (*c* 0.4, $CHCl_3$)]. HRMS calcd for $C_{10}H_{17}NO$ (M + H) 168.1388, found 168.1387. ^1H NMR ($CDCl_3$) δ 3.34 (br d, 1 H, J = 11.0 Hz), 2.50−2.25 (m, 4 H), 2.24−2.12 (m, 1 H), 1.90−1.55 (m, 6 H), 1.50−1.25 (m, 2 H), 1.20 (d, 3 H, J = 5.7 Hz). Spectral properties were in agreement with literature values.[9]

Acknowledgment. We thank Dr. Charles Debrossie, Director of Temple NMR facilities, for helpful discussion and Dr. Bing Wang (GlaxoSmithKline) for aid in the NOE studies. This work was supported by a grant from the National Institute of General Medical Sciences (GM 51982).

Supporting Information Available: Spectral data for compounds where only HRMS is available. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030208D