Pergamon

Tetrahedron Letters 42 (2001) 2063–2068

TETRAHEDRON LETTERS

Solid-phase Zincke route to pyridinium, tetrahydropyridine, and piperidine derivatives: vesamicol analogs

Masahiro Eda[a] and Mark J. Kurth[b,*]

[a]*Welfide Corporation, 2-25-1, Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan*
[b]*Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616-5295, USA*

Received 21 November 2000; revised 6 December 2000; accepted 7 December 2000

Abstract—Optically active derivatives of vesamicol are prepared using solid-phase chemistry. Zincke coupling of resin-bound amino ethers (trityl linker) with 2,4-dinitrophenyl pyridinium salts delivers Zincke products which can be (1) liberated from the resin (TFA) or (2) reduced ($NaBH_4$) to tetrahydropyridine derivatives and liberated. Subsequent reduction (H_2/Pd) gives piperidines. © 2001 Elsevier Science Ltd. All rights reserved.

Newly synthesized acetylcholine is transported for storage and subsequent impulse-driven quantal release from the cytosol into synaptic vesicles in cholinergic neurons by vesicular acetylcholine transporter (VAChT). Vesamicol [*trans*-2-(4-phenylpiperidino)cyclohexanol, **1**] is an inhibitor of VAChT (Fig. 1).[1] This inhibition results in respiratory paralysis, spasms, and death in animals.[2] In spite of its potency as an anticholinergic, vesamicol also displays α-adrenoreceptor activity[3] and high affinity for σ-receptors.[4] Previous studies on the structure–activity relationships of vesamicol analogs indicate that **1** acts enantioselectively with (+)-*R*,*R*-**1** (eutomer) being 25-fold more potent than (–)-*S*,*S*-**1**[5] (distomer). Replacing the cyclohexyl moiety with a fused bicyclic fragment such as 1,2,3,4-tetrahydronaphthyl (benzovesamicol, **2a**) shows a 40-fold higher affinity for VAChT than **1**.[6] Introduction of an amino substituent on the naphthyl ring (**2b**) results in improved selectivity against σ-receptors.[4] The tetrahydropyridine derivative (**3**), while 5-fold less potent than **1**, still has significant activity.[6] Interestingly, Efange and co-workers reported that flexible vesamicol analog **4**, which lacks the cyclohexyl moiety of **1**, is equipotent with **1**.[7] With this backdrop in mind, we have launched a solid-phase combinatorial effort to develop more potent and selective ligands for VAChT.[8]

Our synthetic approach to this class of compounds is to prepare flexible benzovesamicol analogs or further simplified analogs as represented by **5** including pyridinium, tetrahydropyridine, or piperidine scaffolds—with the (*R*)-configuration expected to be the eutomer (Fig. 2). We report here the use of solid-phase synthesis techniques to prepare analogs of **5**.

Displacement of chiral alkyl halide by pyridines as a route to these chiral pyridinium salts is not convenient since such chiral alkyl halides are not easily available

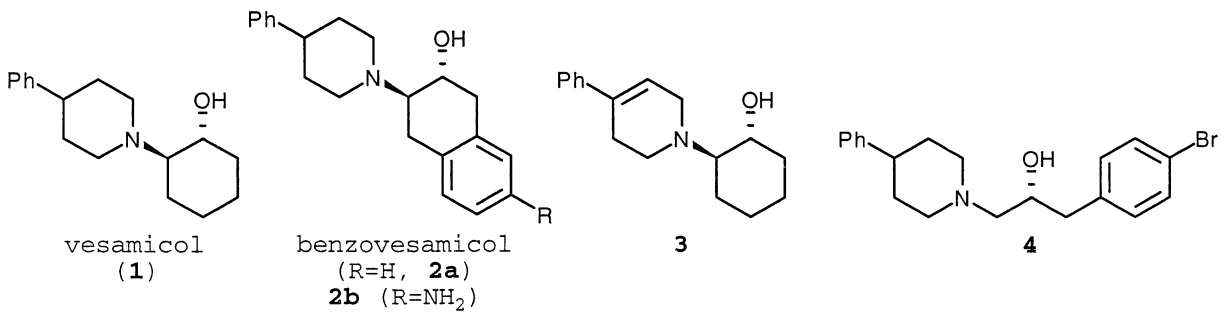


Figure 1. Inhibitors of VAChT.

* Corresponding author.

PII: S0040-4039(00)02351-0

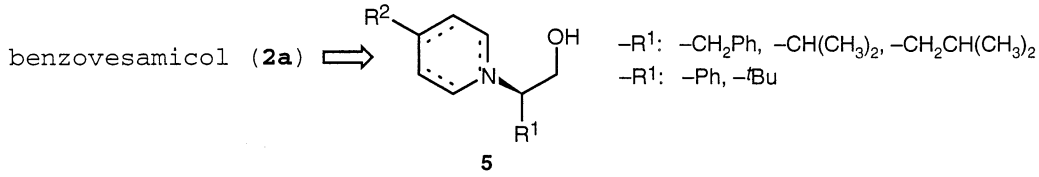
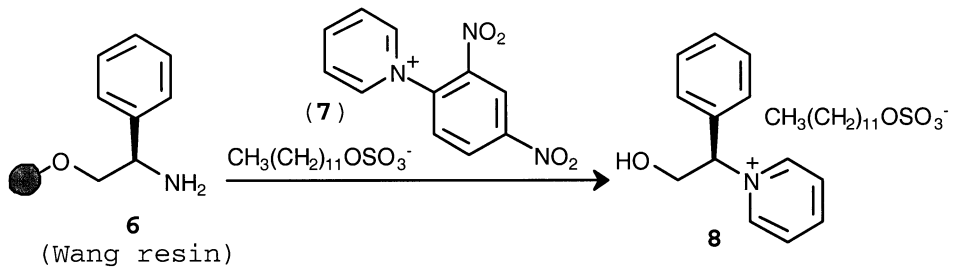


Figure 2. Vesamicol-like targets for solid-phase synthesis.

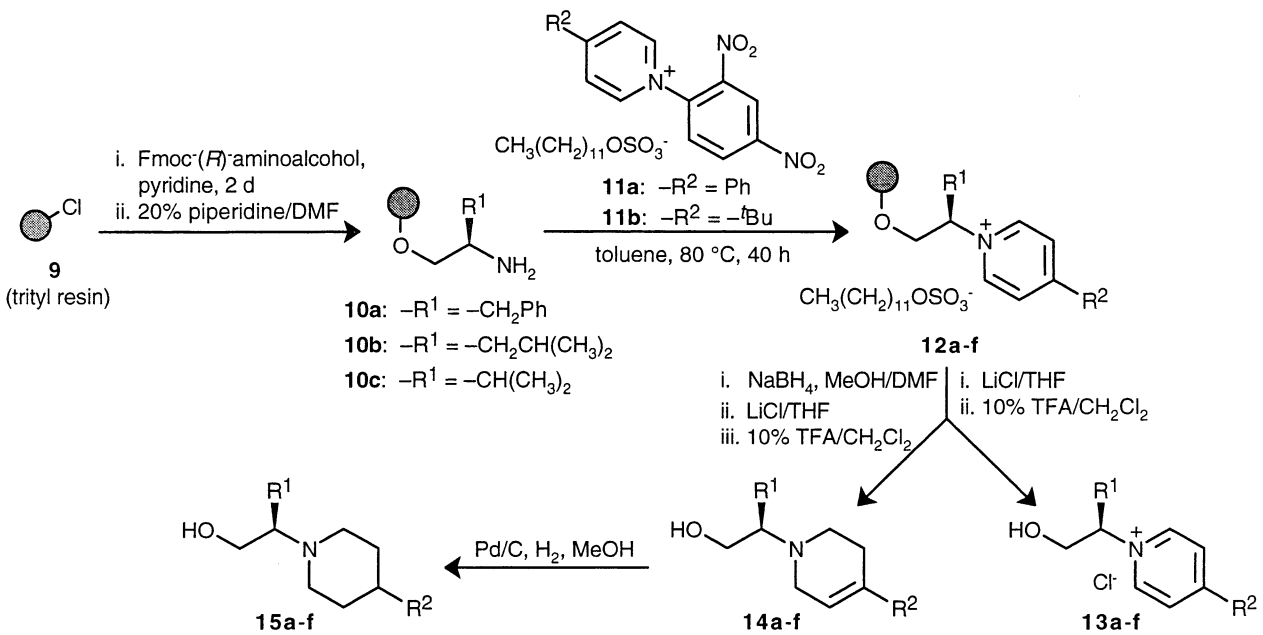
and these reactions often result in significant racemization by a competing S_N1 process. In contrast, Marazano and co-workers have reported applying the Zincke reaction in the synthesis of pyridinium salts with a stereogenic carbon directly linked to the nitrogen of the pyridinium ring.[9] The Zincke reaction is an excellent method for the synthesis of chiral pyridinium salts and this methodology has been extended to the preparation of chiral 2-pyridones,[10] 1,4-dihydropyridines,[11] 1,2,3,6-tetrahydropyridines,[12] and piperidines[13] from chiral pyridinium salts.

Recently, we applied a solid-phase Zincke method to the synthesis of pyridinium salts in a search for cystic fibrosis transmembrane conductance regulator activators.[14] Reaction of (*R*)-phenylglycinol functionalized resin **6** and 1-(2,4-dinitrophenyl)pyridinium dodecyl sulfate (**7**) with triethylamine in toluene followed by resin cleavage gave **8** in good yield and in high purity (Scheme 1). Under these solid-phase Zincke conditions, compound **8** was obtained with $[\alpha]_D^{24} = -50°$ (solution phase Zincke reaction; $[\alpha]_D^{24} = -44°$).[13] This success prompted us to prepare other chiral derivatives of **5** using the solid-phase Zincke reaction.

The reaction of pyridine-swollen trityl chloride resin **9** with Fmoc-protected (*R*)-phenylalaninol, (*R*)-leucinol, and (*R*)-valinol, and subsequent Fmoc deprotection gave the amino alcohol attached resin (**10a–c**; Scheme 2). The actual amino alcohol loading of resin **10** was determined by ultraviolet spectrophotometric analysis of the adduct formed between the Fmoc decomposition product and piperidine during the deprotection of the Fmoc group. The Zincke reaction of **10a–c** with 5 equiv. of **11a,b** gave **12a–f**. Conversion to the chloride salt using lithium chloride in THF and cleavage from

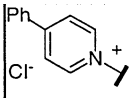
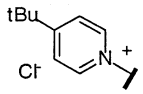
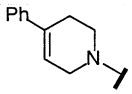
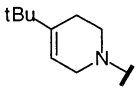
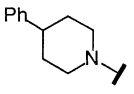
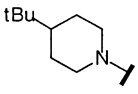
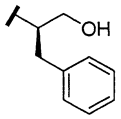
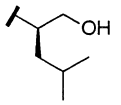
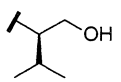


Scheme 1. Solid-phase route to Zincke products.



Scheme 2. Solid-phase route to tetrahydropyridines and piperidines.

Table 1. Vesamicol-like library members[a]

						
	**13a**: +176 (82 %)	**13d**: +113 (80 %)	**14a**: +37 (44 %)	**14d**: +23 (47 %)	**15a**: +30 (33 %)	**15d**: +15 (37 %)
	**13b**: +22 (87 %)	**13e**: +21 (84 %)	**14b**: -3 (61 %)	**14e**: -15 (32 %)	**15b**: -14 (58 %)	**15e**: -16 (28 %)
	**13c**: +32 (89 %)	**13f**: +26 (93 %)	**14c**: -14 (58 %)	**14f**: -[b] (35 %)	**15c**: +7 (52 %)	**15f**: -[b] (35 %)

[a] Yields of isolated product from **10** are given in parenthesis. [b] Within ±3°.

the resin with 10% trifluoroacetic acid in CH_2Cl_2 gave crude **13a–f** in good yield and high purity (92–98% purity by HPLC analysis using UV detection at 254 nm). Simple reversed-phase flash column chromatography gave pure **13a–f** in 80–93% isolated yield based on the loading of **10a–c**. Sodium borohydride reduction of **12a** in the mixed solvent methanol/DMF (1:1), followed by cleavage from the resin gave the crude 1,2,3,6-tetrahydropyridine **14a**. Simple post treatment by partition between ether and 5N NaOH, followed by evaporation of the ether layer gave **14a** in moderate purity (86% HPLC purity by UV detection at 254 nm). Further purification using flash column chromatography gave pure **14a** in 44% isolated yield from **10a**. Compounds **14b–f** were synthesized in a similar manner (32–61% isolated yield from **10a–c**). Hydrogenation of compound **14a–f** gave **15a–f** in 28–58% yield from **10a–c**. The optical rotations of these compounds and chemical yields from **10a–c** are shown in Table 1.

We have established a convenient method for the preparation of chiral pyridinium, tetrahydropyridine, and piperidine derivatives as vesamicol analogs using the solid-phase Zincke reaction. Preparation and biological evaluation of a larger library of these compounds is currently under investigation.

1. Experimental

All chemicals were obtained from commercial supplies and used without further purification. Trityl resin (substitution 0.95 mmol/g) was purchased from Novabiochem. Analytical TLC was carried out on precoated plates (Merck silica gel 60 for normal phase and C_{18} silica gel 60 for reversed phase) and visualized with UV right. Flash column chromatography was performed with silica (Merck, 70–230 mesh) for normal phase and Chromatorex ODS (Fuji Silysia Chemical Ltd, 100–200 mesh) for reversed phase. ^1H and ^{13}C NMR spectra were recorded in CD_3OD (300 or 400 MHz for ^1H NMR and 75 or 100 MHz for ^{13}C NMR), and chemical shifts were reported in parts per million (δ) relative to the solvent peaks (δ 3.30 and 49.0 ppm respectively). The purity of selected final compounds was determined by HPLC analysis (Symmetry® C_{18}, 4.6×150 mm; Waters); linear gradient elution of 20–100% MeOH/phosphoric acid buffer solution (pH 7.0) for 20 min; flow rate 1 mL/min; detection, 254 nm.

1.1. (*R*)-1-(1-Hydroxy-3-phenylpropan-2-yl)-4-phenylpyridinium chloride (13a)

To a suspension of resin **10a** (963 mg, 0.27 mmol) and **11a**[14] (764 mg, 1.4 mmol) in toluene (10 mL) was added triethylamine (0.040 mL), and the resulting mixture was stirred at 80°C for 40 h. The resin was collected on the glass filter and washed with DMF, MeOH, DMF, MeOH, CH_2Cl_2, and MeOH (4 mL each) to give **12a**. To this resin **12a** (113 mg, 0.03 mmol) was added 0.17 M lithium chloride in THF (2 mL) and the resulting suspension was stirred for 30 min, filtered, and 0.17 M lithium chloride in THF solution (2 mL) was added again. After the suspension was stirred for an additional 30 min, the resin was collected on the glass filter and washed with THF, MeOH, DMF, MeOH, CH_2Cl_2, MeOH, and CH_2Cl_2 (4 mL each). To this resin was added 10% trifluoroacetic acid in CH_2Cl_2 (2 mL) and the suspension was stirred for 30 min, filtered, and 10% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added again. After being stirred for an additional 30 min, the suspension was filtered and the resin was collected on the glass filter, washed with MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, and CH_2Cl_2 (2 mL each). Filtrate and washings were combined and evaporated in vacuo. The residue was purified by reversed phase column chromatography (MeOH/H_2O/1N HCl = 50/50/1) to give a slightly yellow amorphous product (8 mg, 82%); 98.5% purity based on HPLC (t_R = 12.53 min). $[\alpha]_D^{24}$ = +176° (*c* 0.01, MeOH). ^1H NMR (300 MHz): δ 3.34 (dd, 1 H, *J* = 9.6, 14.1 Hz), 3.50 (dd, 1 H, *J* = 6.0, 14.1 Hz), 4.10 (d, 2 H, *J* = 5.7 Hz), 5.08 (m, 1 H), 7.24 (m, 5 H), 7.60–7.63 (m, 3 H), 7.97 (dd, 2 H, *J* = 1.8, 8.1 Hz), 8.34 (d, 2 H, *J* = 6.9 Hz), 8.99 (d, 2 H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz): δ 37.7, 63.9, 76.3, 125.6, 128.4, 129.0, 129.9, 129.9, 130.8, 133.4, 134.9, 136.5, 145.0, 158.1.

1.2. (*R*)-1-(1-Hydroxy-4-methylpentan-2-yl)-4-phenylpyridinium chloride (13b)

This was prepared as a slightly yellow viscous oil using a method similar to that described for **13a** (87%); 99.2% purity based on HPLC ($t_R = 11.76$ min). $[\alpha]_D^{24} = +22°$ (*c* 0.004, MeOH). ^{1}H NMR (300 MHz): δ 0.98 (d, 3 H, $J = 6.6$ Hz), 1.02 (d, 3 H, $J = 6.6$ Hz), 1.49 (m, 1 H), 1.92 (m, 1 H), 2.08 (m, 1 H), 3.98 (m, 2 H), 7.66 (m, 3 H), 8.03 (d, 2 H, $J = 3.9$ Hz), 8.43 (d, 2 H, $J = 5.1$ Hz), 9.06 (d, 2 H, $J = 5.1$ Hz). ^{13}C NMR (75 MHz): δ 21.2, 22.0, 24.8, 38.9, 63.9, 72.5, 124.9, 128.0, 129.8, 132.3, 134.0, 143.9, 157.2.

1.3. (*R*)-1-(1-Hydroxy-3-methylbutan-2-yl)-4-phenylpyridinium chloride (13c)

This was prepared as a colorless viscous oil using a method similar to that described for **13a** (89%); 99.9% purity based on HPLC ($t_R = 9.88$ min). $[\alpha]_D^{24} = +32°$ (*c* 0.003, MeOH). Spectral data has been reported previously.[14]

1.4. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-phenylpropan-2-yl)pyridinium chloride (13d)

This was prepared as a slightly viscous oil using a method similar to that described for **13a** (87%); 99.9% purity based on HPLC ($t_R = 11.91$ min). $[\alpha]_D^{24} = +113°$ (*c* 0.004, MeOH). ^{1}H NMR (300 MHz): δ 1.40 (s, 9 H), 3.29 (dd, 2 H, $J = 9.9$, 14.4 Hz), 3.46 (dd, 1 H, $J = 5.7$, 14.4 Hz), 4.06 (d, 2 H, $J = 5.4$ Hz), 5.00 (m, 1 H), 7.20 (m, 5 H), 8.05 (d, 2 H, $J = 6.6$ Hz), 8.85 (d, 2 H, $J = 6.6$ Hz). ^{13}C NMR (100 MHz): δ 29.0, 36.3, 36.6. 62.7, 75.1, 125.1, 127.3, 128.8, 128.9, 135.4, 143.3, 172.1.

1.5. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-4-methylpentan-2-yl)pyridinium chloride (13e)

This was prepared as a yellow viscous oil using a method similar to that described for **13a** (84%); 99.2% purity based on HPLC ($t_R = 11.00$ min). $[\alpha]_D^{24} = +21°$ (*c* 0.003, MeOH). ^{1}H NMR (400 MHz): δ 0.93 (d, 3 H, $J = 6.8$ Hz), 0.97 (d, 3 H, $J = 6.8$ Hz), 1.39 (m, 1 H), 1.44 (s, 9 H), 1.83 (m, 1 H), 2.00 (m, 1 H), 3.86 (dd, 1 H, $J = 7.6$, 12.4 Hz), 3.94 (dd, 1 H, $J = 3.6$, 12.4 Hz), 4.77 (m, 1 H), 8.13 (d, 2 H, $J = 6.4$ Hz), 8.92 (d, 2 H, $J = 6.4$ Hz). ^{13}C NMR (100 MHz): δ 22.2, 22.9, 25.8, 30.2, 37.6, 39.9, 64.9, 73.5, 126.6, 144.5, 173.3.

1.6. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-methylbutan-2-yl)pyridinium chloride (13f)

This was prepared as a colorless viscous oil using a method similar to that described for **13a** (93%); 99.9% purity based on HPLC ($t_R = 8.83$ min). $[\alpha]_D^{24} = +26°$ (*c* 0.004, MeOH). ^{1}H NMR (300 MHz): δ 0.76 (d, 3 H, $J = 6.6$ Hz), 1.18 (d, 3 H, $J = 6.6$ Hz), 1.45 (s, 9 H), 2.45 (m, 1 H), 4.06 (d, 2 H, $J = 5.7$ Hz), 4.37 (m, 1 H), 8.16 (d, 2 H, $J = 6.3$ Hz), 8.89 (d, 2 H, $J = 6.3$ Hz). ^{13}C NMR (100 MHz): δ 19.4, 19.6, 30.2, 30.7, 37.6, 62.5, 81.1, 126.5, 144.7, 173.4.

1.7. (*R*)-1-(1-Hydroxy-3-phenylpropan-2-yl)-4-phenyl-1,2,5,6-tetrahydropyridine (14a)

To a suspension of resin **12a** (405 mg, 0.11 mol) in the mixed solvent of DMF (2 mL) and MeOH (2 mL) was added sodium borohydride ($NaBH_4$) (45 mg, 1.19 mmol), and the resulting mixture was stirred for 4 h, filtered, and DMF (2 mL), MeOH (2 mL), and $NaBH_4$ (45 mg, 1.19 mmol) were added again. After the suspension was stirred for an additional 4 h, the resin was collected on a glass filter, washed with DMF, a mixed solvent of DMF and water, THF, MeOH, THF, and MeOH (4 mL each). To this resin was added 0.17 M lithium chloride in THF (2 mL) and the suspension was stirred for 30 min, filtered, and 0.17 M lithium chloride in THF (2 mL) was added again. After the suspension was stirred for an additional 30 min, the resin was collected on a glass filter and washed with THF, MeOH, DMF, MeOH, CH_2Cl_2, and MeOH (4 mL each). To this resin was added 10% trifluoroacetic acid in CH_2Cl_2 (2 mL) and stirred for 30 min, filtered, and 10% trifluoroacetic acid in CH_2Cl_2 (2 mL) was added again. After stirring for an additional 30 min, the suspension was filtered and the resin was washed with CH_2Cl_2, MeOH, CH_2Cl_2, MeOH, CH_2Cl_2, and MeOH (2 mL each). The filtrate and washings were combined and evaporated in vacuo. To this residue was added MeOH (1 mL) and the resulting solution was poured into 5N NaOH (10 mL) and extracted with Et_2O (10 mL×2). The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane = 1/1) to give **12a** as white needles (44% from **10a**); mp 106–108°C. $[\alpha]_D^{24} = +37°$ (*c* 0.005, MeOH). ^{1}H NMR (300 MHz): δ 2.53–2.69 (m, 3 H), 2.84–3.09 (m, 4 H), 3.43–3.65 (m, 4 H), 6.13 (m, 1 H), 7.16–7.42 (m, 10 H). ^{13}C NMR (75 MHz): δ 29.5, 33.6, 47.0, 50.2, 61.1, 68.4, 122.9, 125.7, 127.0, 127.9, 129.2, 129.3, 130.1, 136.2, 141.3, 141.9.

1.8. (*R*)-1-(1-Hydroxy-4-methylpentan-2-yl)-4-phenyl-1,2,5,6-tetrahydropyridine (14b)

This was prepared as a yellow amorphous solid using a method similar to that described for **14a** (61% from **10b**); $[\alpha]_D^{24} = -3°$ (*c* 0.009, MeOH). ^{1}H NMR (300 MHz): δ 0.95 (d, 6 H, $J = 6.6$ Hz), 1.25–1.45 (m, 2 H), 1.68 (m, 1 H), 2.54 (m, 2 H), 2.73 (m, 1 H), 2.79 (q, 1 H, $J = 5.7$ Hz), 2.90 (q, 1 H, $J = 5.7$ Hz), 3.36 (d, 1 H, $J = 2.7$ Hz), 3.37 (d, 1 H, $J = 2.7$ Hz), 3.58 (dd, 1 H, $J = 4.5$, 11.4 Hz), 3.65 (dd, 1 H, $J = 6.9$, 11.4 Hz), 6.12 (m, 1 H), 7.18–7.44 (m, 5 H). ^{13}C NMR (75 MHz): δ 22.8, 23.8, 26.8, 29.6, 37.1, 46.8, 50.0, 62.3, 64.0, 123.0, 125.7, 127.8, 129.2, 136.1, 142.0.

1.9. (*R*)-1-(1-Hydroxy-3-methylbutan-2-yl)-4-phenyl-1,2,5,6-tetrahydropyridine (14c)

This was prepared as a yellow oil using a method similar to that described for **14a** (58% from **10c**); $[\alpha]_D^{24} = -14°$ (*c* 0.007, MeOH). ^{1}H NMR (300 MHz): δ 0.95 (d, 3 H, $J = 6.9$ Hz), 1.03 (d, 3 H, $J = 6.9$ Hz), 1.98 (dq, 1 H, $J = 6.9$, 13.5 Hz), 2.33 (dt, 1 H, $J = 4.2$, 7.5 Hz), 2.51 (br, 2 H), 2.91 (dt, 1 H, $J = 5.4$, 11.7 Hz), 3.00 (dt, 1 H,

$J=5.4$, 11.4 Hz), 3.41 (m, 2 H), 3.64 (dd, 1 H, $J=7.5$, 11.4 Hz), 3.74 (dd, 1 H, $J=4.2$, 11.4 Hz), 6.11 (m, 1 H), 7.18–7.41 (m, 5 H). ^{13}C NMR (75 MHz): δ 19.0, 20.9, 27.7, 28.9, 46.7, 49.6, 59.1, 70.9, 122.3, 124.6, 126.7, 128.1, 135.0, 141.1.

1.10. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-phenylpropan-2-yl)-1,2,5,6-tetrahydropyridine (14d)

This was prepared as slightly yellow needles using a method similar to that described for **14a** (47% from **10a**); mp 97–99°C. $[\alpha]_D^{24}=+23°$ (c 0.005, MeOH). ^{1}H NMR (400 MHz): δ 1.03 (s, 9 H), 2.20 (m, 2 H), 2.59 (dd, 1 H, $J=9.2$, 13.2 Hz), 2.69 (m, 1 H), 2.83 (m, 1 H), 2.87 (m, 1 H), 2.91 (dd, 1 H, $J=4.4$, 13.2 Hz), 3.21 (m, 1 H), 3.29 (m, 1 H), 3.48 (dd, 1 H, $J=4.4$, 11.2 Hz), 3.54 (dd, 1 H, $J=7.2$, 11.2 Hz), 5.46 (m, 1 H), 7.12–7.27 (m, 5 H). ^{13}C NMR (100 MHz): δ 26.8, 29.2, 33.4, 35.7, 47.4, 50.1, 61.0, 68.5, 117.3, 127.1, 129.4, 130.2, 141.5, 145.5.

1.11. (*R*)-4-(1,1-Dimethylethyl)-1-(hydroxy-4-methylpentan-2-yl)-1,2,5,6-tetrahydropyridine (14e)

This was prepared as a yellow oil using a method similar to that described for **14a** (32% from **10b**); $[\alpha]_D^{24}=-15°$ (c 0.004, MeOH). ^{1}H NMR (400 MHz): δ 0.90 (d, 3 H, $J=2.8$ Hz), 0.92 (d, 3 H, $J=2.8$ Hz), 1.02 (s, 9 H), 1.22–1.37 (m, 2 H), 1.62 (m, 1 H), 2.16 (br, 2 H), 2.58–2.66 (m, 2 H), 2.74 (dt, 1 H, $J=5.6$, 11.2 Hz), 3.16 (m, 2 H), 3.53 (dd, 1 H, $J=4.8$, 11.6 Hz), 3.59 (dd, 1 H, $J=6.8$, 11.6 Hz), 5.44 (m, 1 H). ^{13}C NMR (100 MHz): δ 22.6. 23.9, 26.8, 26.8, 29.2, 35.7, 36.9, 47.0, 49.8, 62.2, 64.0, 117.3, 145.4.

1.12. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-methylbutan-2-yl)-1,2,5,6-tetrahydropyridine (14f)

This was prepared as a yellow oil using a method similar to that described for **14a** (31% from **10c**); ^{1}H NMR (400 MHz): δ 0.89 (d, 3 H, $J=6.8$ Hz), 0.98 (d, 3 H, $J=6.8$ Hz), 1.00 (s, 9 H), 1.94 (dq, 1 H, $J=6.8$, 14.8 Hz), 2.13 (m, 2 H), 2.25 (dt, 1 H, $J=4.4$, 7.2 Hz), 2.72 (dt, 1 H, $J=5.6$, 11.2 Hz), 2.81 (dt, 1 H, $J=5.6$, 11.2 Hz), 3.21 (m, 2 H), 3.55 (dd, 1 H, $J=7.2$, 11.2 Hz), 3.66 (dd, 1 H, $J=4.4$, 11.2 Hz), 5.42 (m, 1 H). ^{13}C NMR (75 MHz): δ 19.8, 22.0, 27.2, 28.6, 29.2, 35.7, 48.0, 50.5, 60.0, 71.9, 117.6, 145.3.

1.13. (*R*)-1-(1-Hydroxy-3-phenylpropan-2-yl)-4-phenylpiperidine (15a)

A suspension of **14a** (10 mg) and palladium (10 wt% on activated carbon, 5 mg) in MeOH (5 mL) was stirred for 4 h under a hydrogen atmosphere. The reaction solution was filtered through Celite, and the filtrate was evaporated in vacuo to furnish the product as a yellow solid (76%); mp 84–86°C. $[\alpha]_D^{24}=+30°$ (c 0.004, MeOH). ^{1}H NMR (400 MHz): δ 1.72 (m, 1 H), 1.81 (m, 3 H), 2.49 (m, 2 H), 2.55 (dd, 1 H, $J=9.6$, 13.2 Hz), 2.69 (m, 1 H), 2.85 (m, 1 H), 2.94 (m, 1 H), 2.95 (dd, 1 H, $J=4.8$, 13.2 Hz), 3.06 (brd, 1 H, $J=12$ Hz), 3.45 (dd, 1 H, $J=4.4$, 11.2 Hz), 3.54 (dd, 1 H, $J=8.0$, 11.2 Hz), 7.10–7.30 (m, 10 H). ^{13}C NMR (100 MHz): δ 33.6, 35.0, 35.2, 44.3, 49.1, 52.8, 61.1, 69.3, 127.0, 127.1, 127.8, 129.4, 129.4, 130.2, 141.6, 147.7.

1.14. (*R*)-1-(1-Hydroxy-4-methylpentan-2-yl)-4-phenylpiperidine (15b)

This was prepared as a colorless oil using a method similar to that described for **15a** (95%); $[\alpha]_D^{24}=-14°$ (c 0.007, MeOH). ^{1}H NMR (400 MHz): δ 0.93 (d, 6 H, $J=6.4$ Hz), 1.21 (ddd, 1 H, $J=6.0$, 8.4, 13.6 Hz), 1.39 (ddd, 1 H, $J=5.2$, 8.4, 14.0 Hz), 1.62–1.75 (m, 3 H), 1.78 (br, 2 H), 2.51 (m, 2 H), 2.59 (dt, 1 H, $J=3.2$, 11.2 Hz), 2.67 (m, 1 H), 2.92 (brt, 2 H, $J=14.0$ Hz), 3.51 (dd, 1 H, $J=4.8$, 11.2 Hz), 3.57 (dd, 1 H, $J=7.6$, 11.2 Hz), 7.10–7.26 (m, 5 H). ^{13}C NMR (100 MHz): δ 22.8, 23.7, 26.7, 35.0, 35.1, 37.1, 44.3, 50.0, 51.6, 62.1, 64.8, 127.1, 127.8, 129.4, 147.7.

1.15. (*R*)-1-(1-Hydroxy-3-methylbutan-2-yl)-4-phenylpiperidine (15c)

This was prepared as a yellow oil using a method similar to that described for **15a** (89%); $[\alpha]_D^{24}=+7°$ (c 0.005, MeOH). ^{1}H NMR (400 MHz): δ 0.90 (d, 3 H, $J=6.8$ Hz), 1.02 (d, 3 H, $J=6.8$ Hz), 1.67 (dq, 2 H, $J=4.0$, 11.6 Hz), 1.76 (m, 2 H), 1.89 (m, 1 H), 2.24 (ddd, 1 H, $J=4.0$, 7.6, 8.0 Hz), 2.48 (tt, 1 H, $J=4.0$, 12.0 Hz), 2.69 (ddt, $J=2.8$, 4.8, 11.6 Hz), 2.90 (m, 2 H), 3.53 (dd, 1 H, $J=7.6$, 11.2 Hz), 3.65 (dd, 1 H, $J=4.0$, 11.2 Hz), 7.10–7.30 (m, 5 H). ^{13}C NMR (100 MHz): δ 20.3, 22.2, 28.8, 35.6, 35.7, 44.5, 51.3, 51.9, 60.1, 72.9, 127.0, 127.8, 129.4, 148.0.

1.16. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-phenylpropan-2-yl)piperidine (15d)

This was prepared as a white solid using a method similar to that described for **15a** (79%); mp 83–85°C. $[\alpha]_D^{24}=+15°$ (c 0.004, MeOH). ^{1}H NMR (400 MHz): δ 0.86 (s, 9 H), 0.99 (m, 1 H), 1.27 (m, 1 H), 1.34 (m, 1 H), 1.69 (brd, 2 H), 2.32 (dt, 1 H, $J=2.0$, 11.6 Hz), 2.50 (m, 2 H), 2.77 (m, 1 H), 2.90 (dd, 2 H, $J=4.4$, 13.2 Hz), 3.01 (brd, 1 H), 3.41 (dd, 1 H, $J=4.4$, 11.2 Hz), 3.49 (dd, 1 H, $J=8.0$, 11.2 Hz), 7.10–7.25 (m, 5 H). ^{13}C NMR (100 MHz): δ 27.9, 28.2, 28.4, 32.9, 33.5, 48.2, 49.3, 53.1, 60.9, 69.1, 127.0, 129.4, 130.2, 141.6.

1.17. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-4-methylpentan-2-yl)piperidine (15e)

This was prepared as a white solid using a method similar to that described for **15a** (86%); mp 52–54°C. $[\alpha]_D^{24}=-16°$ (c 0.003, MeOH). ^{1}H NMR (400 MHz): δ 0.85 (s, 9 H), 0.89 (d, 3 H, $J=2.4$ Hz), 0.91 (d, 3 H, $J=2.4$ Hz), 1.00 (m, 1 H), 1.16–1.37 (m, 4 H), 1.57–1.69 (m, 3 H), 2.29 (dt, 1 H, $J=2.4$, 12.0 Hz), 2.39 (dt, 1 H, $J=2.4$, 12.0 HZ), 2.59 (m, 1 H), 2.86 (brt, 2 H, $J=12.4$ Hz), 3.48 (dd, 1 H, $J=5.2$, 11.6 Hz), 3.52 (dd, 1 H, $J=7.2$, 11.6 Hz). ^{13}C NMR (100 MHz): δ 22.7, 23.7, 26.7, 27.8, 28.2, 28.4, 32.9, 37.0, 48.2, 50.1, 52.0, 62.0, 64.7.

1.18. (*R*)-4-(1,1-Dimethylethyl)-1-(1-hydroxy-3-methylbutan-2-yl)piperidine (15f)

This was prepared as a colorless oil using a method similar to that described for **15a** (99%); ^{1}H NMR (400 MHz): δ 0.84 (s, 9 H), 0.86 (d, 3 H, J=6.8 Hz), 0.98 (d, 3 H, J=6.8 Hz), 0.98 (m, 1 H), 1.22 (m, 2 H), 1.65 (m, 2 H), 1.86 (dq, 1 H, J=6.8, 11.6 Hz), 2.17 (ddd, 1 H, J=4.4, 8.0, 11.6 Hz), 2.47 (dq, 2 H, J=2.4, 11.6 Hz), 2.87 (m, 1 H), 3.46 (dd, 1 H, J=8.0, 11.2 Hz), 3.59 (dd, 1 H, J=4.4, 11.2 Hz). ^{13}C NMR (100 MHz): δ 20.2, 22.3, 27.8, 28.8, 28.8, 29.0, 32.9, 48.4, 51.0, 52.6, 59.9, 72.7.

Acknowledgements

We are grateful to the National Science Foundation and the Cystic Fibrosis Foundation for financial support of this research. The 400 MHz and 300 MHz NMR spectrometers used in this study were funded in part by a grant from NSF (CHE-9808183).

References

1. Marshall, I. G.; Parsons, S. M. *Trends Neurosci.* **1987**, *10*, 174.
2. Brittain, R. T.; Levy, G. P.; Tyers, M. B. *Eur. J. Pharmacol.* **1969**, *8*, 93.
3. Wannan, G.; Prior, C.; Marshall, I. G. *Eur. J. Pharmacol.* **1991**, *201*, 29.
4. Efange, S. M. N.; Mach, R. H.; Smith, C. R.; Khare, A. B.; Foulon, C.; Akella, S. K.; Childers, S. R.; Parsons, S. M. *Biochem. Pharmacol.* **1995**, *49*, 791.
5. Rogers, G. A.; Parsons, S. M.; Anderson, D. C.; Nilsson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. *J. Med. Chem.* **1989**, *32*, 1217.
6. Rogers, G. A.; Kornreich, W. D.; Hand, K.; Parsons, S. M. *Mol. Pharmacol.* **1993**, *44*, 633.
7. Efange, S. M. N.; Michelson, R. H.; Dutta, A. K.; Parsons, S. M. *J. Med. Chem.* **1991**, *34*, 2638.
8. (a) Efange, S. M. N.; Khare, A. B.; Mach, R. H.; Parsons, S. M. *J. Med. Chem.* **1999**, *42*, 2862; (b) Efange, S. M. N.; Kamath, A. P.; Khare, A. B.; Kung, M.-P.; Mach, R. H.; Parsons, S. M. *J. Med. Chem.* **1997**, *40*, 3905; (c) Efange, S. M. N.; Khare, A. B.; Foulon, C.; Akella, S. K.; Parsons, S. M. *J. Med. Chem.* **1994**, *37*, 2574.
9. Genisson, Y.; Marazano, C.; Mehmandoust, M.; Gnecco, D.; Das, B. C. *Synlett* **1992**, 431.
10. Gnecco, D.; Marazano, C.; Enríquez, R. G.; Terán, J. L.; Sanchez, M. R.; Galindo, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2027.
11. Wong, Y.-S.; Marazano, C.; Gnecco, D.; Das, B. C. *Tetrahedron Lett.* **1994**, *35*, 707.
12. Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185.
13. Diez, A.; Vilaseca, L.; López, I.; Rubiralta, M.; Marazano, C.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1991**, *32*, 2139.
14. Eda, M.; Kurth, M. J.; Nantz, M. H. *J. Org. Chem.* **2000**, *65*, 5131.