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Syntheses of 1,2-Diamino and 1,2-Aminoalcohol Derivatives in the Piperidine and Pyrrolidine Series as Anti-amnesic Agents

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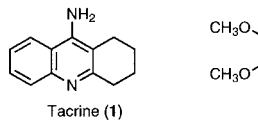
Abstract—Tacrine, one of the drugs available for Alzheimer's disease based on the cholinergic approach, suffers from considerable toxicity. Many analogues of tacrine has been prepared which retain the pharmacologically rich aminopyridine or aminoquinoline motifs. The current research is a continuation of our efforts in the area of 11-aminobenzoquinolizidines (**4**) and 10-aminobenzoindolizidines (**5**) (cf. ref 9). A serendipitous discovery led us to the biologically active open chain analogue **9**, and we proceeded to elaborate on this molecule. Overall, the compounds we prepared were poor inhibitors of acetylcholinesterase as compared to tacrine. The single exception was compound **20** which exhibited an effect comparable to that of tacrine, but only at a dose in the order of 10^{-3} M. However, despite the poor acetylcholinesterase inhibition by **9**, this compound was found to be an effective antiamnesic agent.

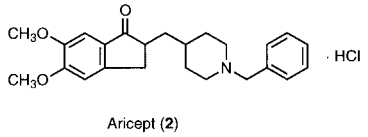
Introduction

The cholinergic approach to Alzheimer's disease received an encouraging signal due to the recent approval of tacrine hydrochloride (Cognex®) as the first drug for the treatment of this disease; it was launched in 1993. Tacrine (**1**) is a complex pharmacological agent[1] which also inhibits the enzyme acetylcholinesterase (AcChE), thus maintaining synaptic residence of acetylcholine (AcCh).[2] Two other AcChE inhibitors have been marketed recently: donezepil (Aricept® (**2**)[3] and rivastigmine (Exelon) (**3**).[4]

The deficiency of tacrine as a drug is related to liver toxicity and peripheral cholinomimetic actions.[5] Tacrine belongs to the well known structural class of aminopyridines[6] which represent an interesting group of potassium channel blockers, but are toxic. It also incorporates the template of 4-aminoquinoline, well known for diverse pharmacological activity.[7] Furthermore, tacrine possesses a relatively flat aromatic structure which may be prone to intercalation.



Tacrine (**1**)



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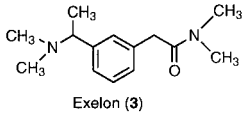
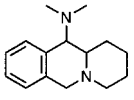


Exelon (**3**)

Many analogues of tacrine have been prepared.[8] Most of these are structurally closely related to the parent compound and retain the aminopyridine or aminoquinoline moiety.

Our approach to the problem of maintaining the AcChE inhibitory activity while diminishing the toxicity is based on the incorporation of the 11-amino benzoquinolizidine (**4**) and 10-aminobenzoindolizidine (**5**) moieties as the templates for AcChE inhibitors. In **4** and **5** we have eliminated the pyridine and quinoline



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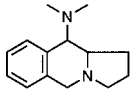

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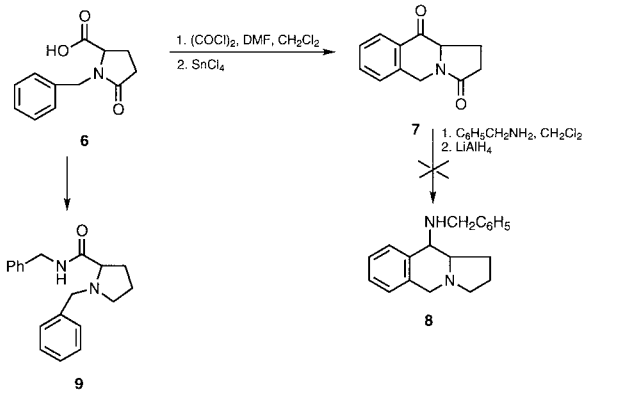
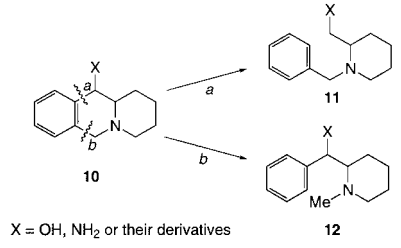
moieties while maintaining the two amino functionalities and rendering the molecule less flat. We have recently reported the preparation of these two classes of compounds.[9]



During an attempt to cyclize compound **6** to the ketoamide **7**, using oxalyl chloride followed by stannic chloride, the erroneous assumption was made that the desired cyclization had taken place. Thus the crude product was treated with benzylamine followed by $LiAlH_4$ at room temperature in order to generate compound **8**. As we discovered, the cyclization **6**→**7** had not occurred and the acid chloride derivative of **6** reacted with the amine to give the benzylamide which was selectively reduced to compound **9**. This compound was subjected to biological evaluation and proved to be an interesting lead.

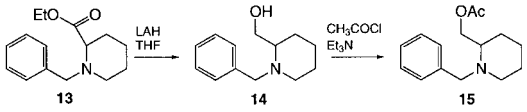
In today's climate of combinatorial libraries, multikilo sample sophisticated screening procedures, computerized rational design, and X-ray crystallographic ligand-receptor determinations, it is instructive to be able to find a lead by a serendipitous process such as described above coupled with the absence of preconceived ideas about structure–activity relationships.

In the present report, we describe the design and syntheses of open chain analogues of benzoquinolizine and benzoindolizidine derivatives. A benzylpiperidine compound (such as **11**), and a methylpiperidine compound (such as **12**), were attractive target molecules obtained by disconnecting bond *a* or *b* in structure **10**.

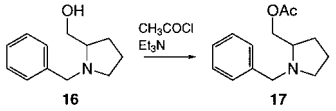


Chemistry

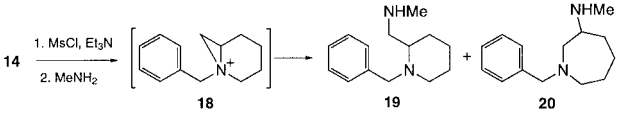
Ethyl *N*-benzylpipecolinate (**13**)[10] was reduced with $LiAlH_4$ (LAH) to give an alcohol **14**. The alcohol was converted to an acetate **15**.



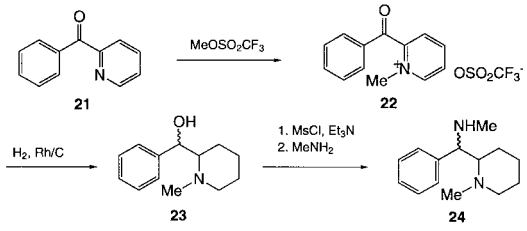
A pyrrolidine acetate analogue **17** was similarly synthesized from commercially available (*S*)-(–)-1-benzyl-2-pyrrolidinemethanol (**16**, Aldrich).



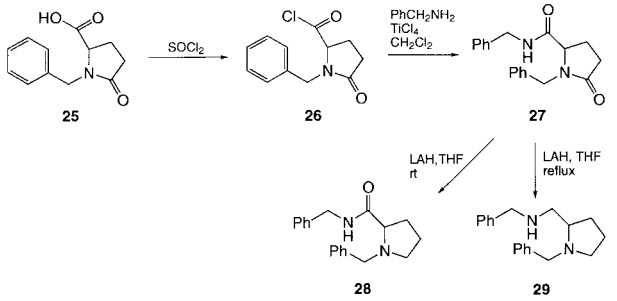
For the synthesis of the amino analogue, alcohol **14** was treated with mesyl chloride and triethylamine followed by reaction of the mesylate with methylamine to give the desired amino derivative of *N*-benzylpiperidine **19** and a rearranged homopiperidine derivative **20** in a ratio of about 1:1.[11] For a detailed discussion of the NMR analysis of **19** and **20**, see Experimental. Both products should be derived from the same aziridinium intermediate **18**.



The preparation of *N*-methylpiperidine **24** followed a known procedure.[12] 2-Benzoylpyridine **21** was methylated with methyl trifluoromethanesulfonate. The resulting pyridinium salt **22** was hydrogenated in the presence of rhodium on carbon. Both the pyridine ring and the carbonyl were reduced to give product **23**. The alcohol was converted to a methylamine derivative **24** (as a mixture of diastereoisomers) by the generation of mesylate followed by the reaction with methylamine.

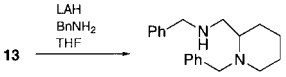


For the synthesis of pyrrolidine analogue **29**, *N*-benzylpyrrolidone-5-carboxylic acid (**25**) was converted to acid chloride **26** and then to benzylamide **27**. Amide **27** was reduced to the pyrrolidine amide **28** with LAH at room temperature.



Compound **27** was completely reduced to pyrrolidine **29** when it was refluxed in the presence of LAH in THF.

Synthesis of the piperidine analogue of compound **28** is straightforward. Amidation of ethyl ester **13** with a lithium aluminum amide reagent[13] from LAH and benzylamine gave benzylamide **30** directly.



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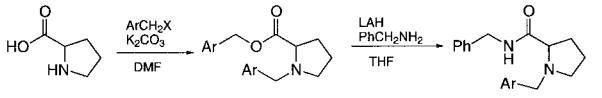
Similarly, this ester amidation reaction was used to synthesize the analogues of prolinamide **28**. Thus, *dl*-proline was converted to the *N*-substituted ester **31** by the reaction of proline with arylmethyl chloride and potassium carbonate in DMF. Ester **31** was converted to the amide **32** directly with the lithium aluminum amide reagent. However, methoxybenzylated compound **31d** failed to give amidation product.



31a, Ar = 4-Nitrophenyl
31b, Ar = 3-Chlorophenyl
31c, Ar = 2-Naphthyl
31d, Ar = 4-Methoxy

32a, Ar = 4-Nitrophenyl
32b, Ar = 3-Chlorophenyl
32c, Ar = 2-Naphthyl

Biological Studies

Overall, these piperidine and pyrrolidine derivatives were poor inhibitors of acetylcholinesterase, as compared to that observed with tacrine (Table 1).

The single exception was **20** which exhibited an effect comparable to that of tacrine, but only at a dose in the order of 10^{-3} M. In general, cholinesterase inhibition was similar to that determined for acetylcholinesterase. However, in one case a stimulatory effect was observed at higher concentrations (see compound **32a**). Inhibition of acetylcholinesterase by these piperidine and pyrrolidine derivatives appeared competitive in nature as kinetic studies with **9** and tacrine revealed an equivalent K_i of 0.03 mM acetylthiocholine iodide substrate (Fig. 1). However, the inhibitory concentration of tacrine (5 μM) was 100 times lower than that observed for **9** (500 μM) (data not shown for tacrine).

Within this series of piperidine and pyrrolidine derivatives, **9** was found to be an effective anti-amnesic agent in vivo despite lacking acetylcholinesterase inhibitory actions (Fig. 2). Thus, this piperidine and pyrrolidine series would appear to include agents with an anti-amnesic action that is independent of an anti-cholinesterase effect. Moreover, **9** was devoid of any overt behavioral toxicity when administered alone.

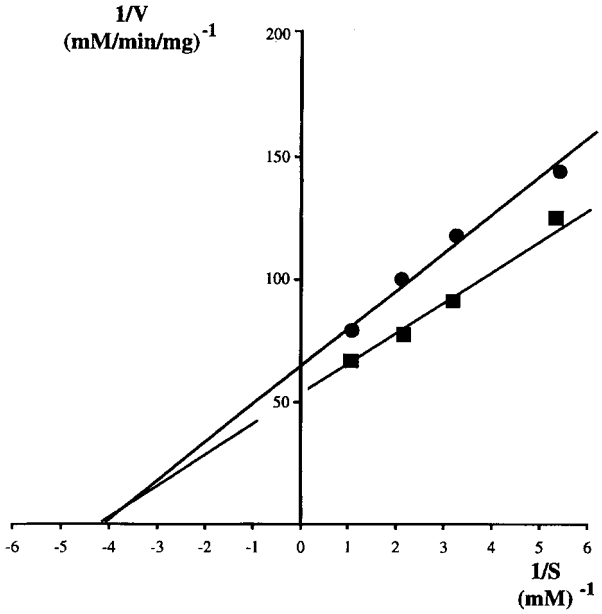


Figure 1. Influence of piperidine and pyrrolidine derivatives on rat brain acetylcholinesterase activity. The data is illustrated as Lineweaver–Burke plots for control (closed squares) and **9** (0.5 mM; closed circles)

Table 1. Inhibition of rat cholinesterase and acetylcholinesterase activity by piperidine and pyrrolidine derivatives and tacrine[a]

Compd	Acetylcholinesterase[b]			Total cholinesterase[b]		
	10^{-3}M	10^{-5}M	10^{-7}M	10^{-3}M	10^{-5}M	10^{-7}10M
15	34.59 ± 04.76	83.55 ± 07.07	77.09 ± 08.05	47.27 ± 05.89	79.70 ± 11.96	92.95 ± 05.63
17	36.37 ± 02.90	71.34 ± 00.91	67.46 ± 01.65	60.57 ± 06.41	103.73 ± 03.52	102.71 ± 05.69
9	68.41 ± 09.52	83.09 ± 13.71	92.13 ± 01.78	81.87 ± 11.92	100.63 ± 14.41	111.39 ± 03.49
29	28.05 ± 00.81	108.58 ± 03.39	125.12 ± 14.24	29.54 ± 03.68	109.07 ± 05.67	118.58 ± 04.07
24	82.00 ± 07.48	106.05 ± 12.99	106.79 ± 07.02	76.29 ± 07.83	110.04 ± 16.74	102.92 ± 13.73
19	40.16 ± 08.81	94.28 ± 05.75	116.18 ± 17.00	43.43 ± 06.93	84.77 ± 08.35	100.99 ± 16.20
20	09.75 ± 00.89	45.47 ± 21.80	54.94 ± 18.82	26.41 ± 03.29	42.13 ± 17.10	53.13 ± 14.26
27	92.06 ± 05.14	96.78 ± 08.28	89.72 ± 09.89	107.51 ± 03.81	108.45 ± 04.06	96.03 ± 09.68
30	88.19 ± 16.84	82.68 ± 03.46	94.56 ± 09.20	132.75 ± 34.44	95.76 ± 07.59	95.20 ± 07.88
31a	52.03 ± 10.43	93.00 ± 07.54	96.19 ± 11.01	59.41 ± 06.89	95.29 ± 10.40	97.54 ± 17.64
32a	93.67 ± 07.96	89.77 ± 08.46	106.18 ± 09.96	273.85 ± 23.09	106.63 ± 15.22	70.80 ± 32.34
31b	55.13 ± 07.64	87.41 ± 01.88	91.34 ± 00.93	46.99 ± 04.08	88.95 ± 10.52	92.49 ± 03.27
31c	55.15 ± 07.16	92.08 ± 04.26	98.28 ± 11.80	57.87 ± 05.42	101.04 ± 10.15	96.13 ± 05.01
32c	41.11 ± 10.90	60.32 ± 12.59	56.37 ± 13.39	35.58 ± 09.73	63.16 ± 16.76	60.09 ± 16.38
32b	87.78 ± 05.21	93.93 ± 03.20	86.70 ± 06.97	51.54 ± 20.35	128.43 ± 09.84	119.89 ± 20.62
31d	78.94 ± 16.66	94.46 ± 03.90	100.55 ± 18.25	68.86 ± 37.58	62.76 ± 00.63	62.11 ± 04.31
Tacrine	05.42 ± 00.62	07.35 ± 00.05	42.81 ± 02.78	17.82 ± 00.91	14.93 ± 06.12	42.97 ± 04.50

[a] Values represent the mean ± Sem for three independent experiments.
[b] Activity was determined as mmol/min/mg protein and is presented as percent of the control value.

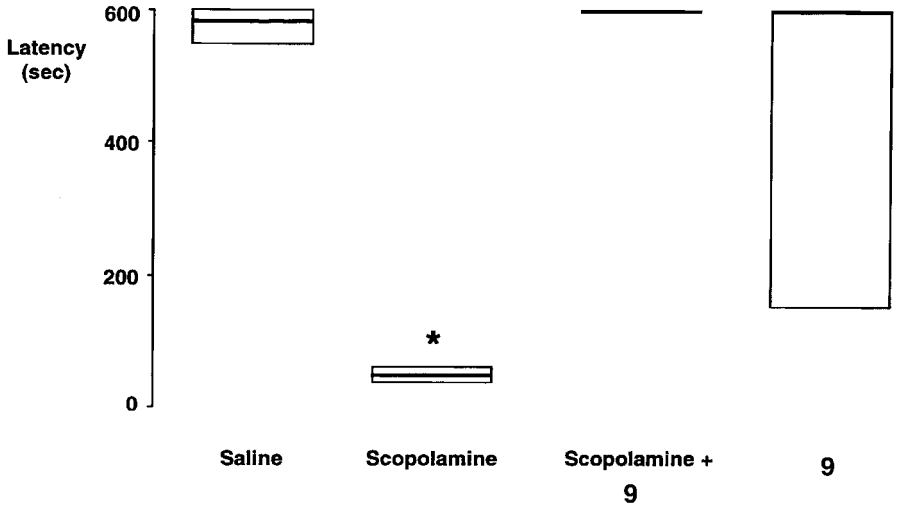


Figure 2. Reversal of scopolamine-induced amnesia of a passive avoidance response by **9**. The data is presented as box plots showing the median and interquartile range ($n=6$). The box plot marked with an asterisk is significantly different ($p < 0.05$) from all other values. The dose of **9** employed was 30 mg/kg.

Structure–Activity Relationship

The structure–activity relationship defining compound **9** as the antiamnesic lead may be summarized as follows: (1) pyrrolidine ring is preferred to piperidine and (2) the unsubstituted benzene ring, with benzyl group on the pyrrolidine nitrogen, is preferred to a benzene ring with electron-withdrawing substituents and to a naphthalene ring.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Varian spectrometer at 300 MHz for proton and 75.4 MHz for carbon in $CDCl_3$ solution. The predicted carbon spectra were obtained from the ACD Labs CNMR program. Peak positions are indicated in ppm downfield from internal TMS in δ units. Mass spectra were obtained on a MAT CH-5-DF (FAB), and Finnigan 8230 B (EI) mass spectrometers. IR spectra were recorded on a Perkin–Elmer 1420 Ratio Recording IR spectrophotometer. Flash column chromatography was done on silica gel (E. M. Merck silica gel 60, 230–400 mesh) in the stated solvents. Melting points were obtained on a Thomas–Hoover apparatus and are uncorrected. Product purities were routinely checked by TLC. THF was tested for peroxides (aqueous KI) prior to use and used without further purification or drying. All reactions were performed under a nitrogen atmosphere in oven- or flame-dried glassware unless otherwise noted. The multiplicities of the ^{13}C signals were determined by DEPT experiments; s = C; d = CH; t = CH_2; q = CH_3. Methylamine was obtained from either a lecture bottle (Aldrich) or aqueous solution (40%, Fluka) by distillation. Ethyl pipecolinate was purchased from Aldrich.

1-(Phenylmethyl)-2-piperidinemethanol (14). A suspension of LAH (410 mg) in THF (50 mL) was refluxed for 30 min. It was cooled to rt, a solution of ester **13** (10 mmol, 2.47 g) in 5 mL of THF was added dropwise, and the mixture was stirred overnight. It was quenched by sequential addition of H_2O (0.4 mL), NaOH (15%, 0.4 mL) and H_2O (1.2 mL). The resulting suspension was filtered and the filtrate was concentrated in vacuo to give **14** as a pale-yellow oil (1.78 g, 87%): ^{1}H NMR (300 MHz) δ 7.30 (m, 5H), 4.06 (d, $J=13.4$ Hz, 1H), 3.84 (dd, $J=10.8$, 4.3 Hz, 1H), 3.52 (dd, $J=10.8$, 3.9 Hz, 1H), 3.31 (d, $J=13.4$ Hz, 1H), 2.86 (m, 1H), 2.77 (br s, OH), 2.44 (m, 1H), 2.13 (m, 1H), 1.30–1.70 (m, 6H); ^{13}C NMR (75.4 MHz) δ 138.98 (s), 128.76 (d), 128.24 (d), 126.90 (d), 62.23 (t), 60.90 (d), 57.66 (t), 50.79 (t), 27.30 (t), 24.05 (t), 23.35 (t); MS (EI), *m/e* 174 (100), 91 (56); HRMS (FAB) calcd. for ($C_{13}H_{19}NO$ + H) 206.1545, found 206.1546.

1-(Phenylmethyl)-2-piperidinemethyl acetate (15). A solution of CH_3COCl (1.27 mmol, 90 μL) in CH_2Cl_2 (2 mL) was added to a solution of alcohol **14** (1.16 mmol, 237 mg) and Et_3N (1.27 mmol, 177 μL) in CH_2Cl_2 (5 mL) at 0°C. The mixture was stirred at rt for 2 h and then diluted with CH_2Cl_2 (50 mL). The solution was washed with Na_2CO_3 (satd., 10 mL) and H_2O (10 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (99/0.8/0.2) to give **15** as a yellow oil (256 mg): ^{1}H NMR (300 MHz) δ 7.30 (m, 5H), 4.27 (dd, $J=11.5$, 4.8 Hz, 1H), 4.20 (dd, $J=11.5$, 5.2 Hz, 1H), 3.99 (d, $J=13.7$ Hz, 1H), 3.34 (d, $J=13.7$ Hz, 1H), 2.75 (dt, $J=11.9$, 4.2 Hz, 1H), 2.58 (m, 1H), 2.13 (m, 1H), 2.06 (s, CH_3), 1.30–1.80 (m, 6H); ^{13}C NMR (75.4 MHz) δ 171.00 (s), 139.42 (s), 128.74 (d), 128.09 (d), 126.72 (d), 65.70 (t), 59.51 (d), 58.70 (t), 51.56 (t), 28.97 (t), 25.19 (t), 23.06 (t), 20.98 (q); MS (FAB), *m/e* 248 (72, M + H), 174 (100); HRMS (FAB) calcd for ($C_{15}H_{21}NO_2$ + H) 248.1651, found 248.1648.

(*S*)-(−)-1-Benzyl-2-pyrrolidinemethyl acetate (17). A solution of CH_3COCl (5.76 mmol, 410 μL) in CH_2Cl_2 (10 mL) was added to a solution of (*S*)-(−)-1-benzyl-2-pyrrolidinemethanol (Aldrich, 5.23 mmol, 1.00 g) and Et_3N (5.76 mmol, 803 μL) in CH_2Cl_2 (40 mL) at 0°C.

The mixture was stirred at rt for 5 h and then diluted with CH_2Cl_2 (100 mL). The solution was washed with Na_2CO_3 (satd., 20 mL) and H_2O (20 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (99/0.8/0.2) to give **17** as a yellow oil (717 mg, 65%): ^{1}H NMR (300 MHz) δ 7.31 (m, 5H), 4.06 (m, 3H), 3.41 (d, J = 13.2 Hz, 1H), 2.92 (m, 1H), 2.81 (m, 1H), 2.25 (m, 1H), 2.05 (s, CH_3), 1.95 (m, 1H), 1.70 (m, 3H); ^{13}C NMR (75.4 MHz) δ 171.04 (s), 139.48 (s), 128.78 (d), 128.15 (d), 126.83 (d), 67.12 (t), 61.79 (d), 59.43 (t), 54.40 (t), 28.40 (t), 22.89 (t), 20.94 (q); MS (FAB), *m*/*e* 234 (84, M + H), 160 (100); HRMS (FAB) calcd for ($C_{14}H_{19}NO_2$ + H) 234.1494, found 234.1506.

1-Benzyl-2-(*N*-methylaminomethyl)piperidine (19) and 1-benzyl-3-(*N*-methylamino)hexahydroazepine (20). Triethylamine (3.61 mmol, 503 μL) was added to a solution of alcohol **14** (3.28 mmol, 673 mg) followed by the addition of $MeSO_2Cl$ (3.61 mmol, 279 μL). The mixture was stirred for 3 h and concentrated in vacuo. The residue was transferred to a bomb and $MeNH_2$ (20 mL) was added. It was heated at 110°C for 14 h. NaOH (1 N, 10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated in vacuo to give a red oil. It was chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH = 150/8/1) to give **19** as a yellow oil (115 mg), **20** as a yellow oil (84 mg) and also a mixture of both isomers as a yellow oil (350 mg).

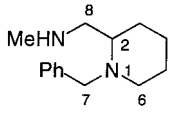
19. ^{1}H NMR (300 MHz) δ 7.32 (m, 5H), 3.97 (d, J = 13.7 Hz, 1H), 3.28 (d, J = 13.7 Hz, 1H), 2.80 (dt, J = 12.2, 4.2 Hz, 1H), 2.74 (d, J = 4.4 Hz, 1H), 2.42 (m, 1H), 2.36 (s, CH_3), 2.08 (ddd, J = 12.7, 9.2, 3.3 Hz, 1H), 1.25–1.76 (m, 6H, including NH); ^{13}C NMR (75.4 MHz) δ 139.90 (s), 128.62 (d), 128.16 (d), 126.65 (d), 60.70 (d), 57.70 (t), 54.02 (t), 51.86 (t), 36.93 (q), 29.09 (t), 24.61 (t), 23.79 (t); MS (FAB), *m*/*e* 219 (100, M + H), 188 (9), 174 (16), 129 (3), 84 (3); HRMS (FAB) calcd for ($C_{14}H_{22}N_2$ + H) 219.1861, found 219.1866.

20. 1H NMR (300 MHz) δ 7.23 (m, 5H), 3.64 (s, 2H), 2.52–2.71 (m, 5H), 2.18 (s, 3H), 1.25–1.87 (m, 6H); ^{13}C NMR (75.4 MHz) δ 140.07 (s), 128.82 (d), 128.10 (d), 126.77 (d), 63.75 (t), 59.37 (d), 58.31 (t), 56.60 (t), 34.33 (t), 33.83 (q), 29.28 (t), 22.63 (t); HRMS (EI) calcd for ($C_{14}H_{22}N_2$ + H) 218.1783, found 218.1778.

NMR Analysis of 19 and 20. The ^{13}C and DEPT spectra showed one CH_3, one CH and 6 CH_2 groups for a total of 8 aliphatic signals in both **19** and **20**. The ^{1}H NMR and ^{13}C NMR were correlated by means of a HSQC (heteronuclear single-quantum correlation) spectrum. In the ^{1}H spectrum of **19** the methylene (C-7) is an AB (δ 3.9 and 3.3) suggesting crowding; in **20** the methylene protons are equivalent (δ 3.65). The ^{13}C spectra of **19** and **20** show the C-7 methylene signal (δ 6.02) further upfield in **19** also suggesting steric crowding (γ effect) C-8 methylene. The HMBC (heteronuclear multiple bond correlation) spectrum of **19** showed a three bond correlation of the NCH_3 proton to the C-8 methylene carbon, a three bond correlation of both the C-7 methylene protons to the C-7 methine carbon; also cross peaks can be seen from both C-8 methylene protons to the *N*-CH_3 carbon. The HMBC spectrum of **20** showed a three bond correlation of the *N*-CH_3 protons to the C-3 methine carbon, a three bond correlation of the C-8 protons to the C-2 methylene carbon, and both C-2 methylene protons to the C-8 carbon. That the *N*-CH_3 protons are correlated to a CH2 group in **19** and a CH group in **20** clearly defines the two structures. Calculated shifts obtained from the ChemIntosh C-13 NMR module helped assign the signals for C-4, C-5 and C-6 where the lack of resolution did not permit the exact assignment of the large number of cross peaks (see Tables 2 and 3).

Synthesis of 24. Compound **24** was prepared according to the literature[8] starting from **21**. The crude product was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (150/8/1) to give pure **24** as an oily mixture of diastereoisomers. ^{1}H NMR (300 MHz) δ 7.15 (m, 5H), 5.15 (d, J = 3.0 Hz), 3.49 (d, J = 9.3 Hz),

Table 2. ^{13}C Found and calculated values for compound **19**

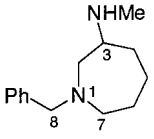


19

Assignments	Found	Calcd[a]	Δ
4	23.33	25.7	+2.4
5	24.09	27.9	+3.8
3	28.31	29.7	+1.4
NCH_3	36.28	37.1	+0.8
6	51.40	51.7	+0.3
8	53.21	61.3	+8.1
7	57.59	59.9	+2.3
2	59.64	53.7	−5.9

[a] From ChemIntosh C-13 NMR module calculation.

Table 3. ^{13}C Found and calculated values for compound **20**



20

Assignment	Found	Calcd	Δ
5	22.54	22.6	+0.1
6	29.12	29.4	+0.3
4	33.04	30.7	−2.3
NCH_3	33.48	34.6	+1.2
7	57.71[a]	53.2	−4.5
2	56.48[a]	56.5	0
8	63.63	59.7	−3.9
3	59.25	56.2	−3.1

[a] May be interchanged.

2.60–3.03 (m), 2.46 (s, CH_3), 2.24 (s, CH_3), 2.19 (td, $J=11.4$, 3.6 Hz), 2.06 (dt, $J=11.4$, 6.3 Hz), 0.90–1.70 (m); ^{13}C NMR (75.4 MHz) δ 142.05, 141.28, 128.30, 128.08, 127.84, 126.98, 126.56, 125.67, 70.44, 68.28, 66.00, 65.15, 57.23, 52.59, 43.03, 37.66, 34.70, 25.69, 23.78, 23.26, 23.22, 20.12, 19.29; MS (FAB), *m/e* 219 (100, M + H), 206 (33), 168 (32); HRMS (FAB) calcd for ($C_{14}H_{22}N_2$ + H) 219.1861, found 219.1854.

Synthesis of 27. Oxalyl chloride (12 mmol, 6 mL of 2 M solution in CH_2Cl_2) and DMF (0.3 mL) was added to a solution of *N*-benzyl-2-oxopyrrolidine-5-carboxylic acid (**25**, 10.7 mmol, 2.34 g). The mixture was stirred at rt for 1.5 h, and then benzylamine (42.7 mmol, 4.67 mL) was added. The mixture was washed with ice-cold HCl (1 N, 10 mL), $NaHCO_3$ (10%, 10 mL) and H_2O (20 mL). The organic phase was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (400/10/1) to give **27** as a solid (2.11 g): ^1H NMR (300 MHz) δ 7.12–7.40 (m, 10H), 5.88 (br s, NH), 5.01 (d, $J=14.7$ Hz, 1H, 4.46 (dd, $J=14.6$, 6.1 Hz, 1H), 4.30 (dd, $J=14.6$, 5.5 Hz, 1H), 3.90 (d, $J=14.3$ Hz, 1H), 3.85 (dd, $J=8.8$, 4.0 Hz, 1H), 2.02–2.66 (m, 4H); ^{13}C NMR (75.4 MHz) δ 175.79, 170.92, 137.61, 135.68, 128.83, 128.81, 128.40, 127.92, 127.82, 127.79, 60.73, 45.82, 43.58, 29.68, 23.54; MS (FAB), *m/e* 309 (100, M + H), 174 (20), 91 (95); Anal. calcd for $C_{19}H_{20}N_2O_2 \cdot 0.1H_2O$: C, 73.57; H, 6.56; N, 9.03. Found: C, 73.37; H, 6.51; N, 9.22.

Synthesis of 28. Amide **27** (1.28 mmol, 397 mg) was added to a suspension of LAH (140 mg) in THF (10 mL). The mixture was stirred at rt overnight, and quenched by the successive addition of H_2O (140 μL), NaOH (aqueous, 15%, 140 μL) and H_2O (420 μL). The suspension was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (400/10/1) to give **28** as an oil (319 mg, 85%): ^1H NMR (300 MHz) δ 7.71 (br s, NH), 7.13–7.36 (m, 10H), 4.40 (d, $J=6.0$ Hz, 2H), 3.85 (d, $J=12.6$ Hz, 1H), 3.48 (d, $J=13.2$ Hz, 1H), 3.28 (dd, $J=10.2$, 4.8 Hz, 1H), 2.99 (ddd, $J=8.9$, 6.8, 2.1 Hz, 1H), 1.60–2.41 (m, 5H); ^{13}C NMR (75.4 MHz) δ 174.47, 138.50, 138.47, 128.71, 128.67, 128.42, 127.60, 127.35, 127.24, 67.39 (d), 59.96 (t), 53.95 (t), 42.96 (t), 30.71 (t), 24.16 (t); MS (FAB), *m/e* 295 (85, M + H), 160 (100); The amine was converted to the hydrochloride and crystallized from 2-PrOH/MeOH/ether to give a solid: mp 157–159°C; Anal. calcd for $C_{19}H_{22}N_2O \cdot HCl \cdot 0.1H_2O$: C, 68.60; H, 7.03; Cl, 10.66; N, 8.42. Found: C, 68.45; H, 7.00; Cl, 10.52; N, 8.29.

Synthesis of 29. A solution of amide **27** (1.62 mmol, 0.50 g) in THF (5 mL) was added dropwise to a suspension of LAH (710 mg) in THF (30 mL). The mixture was refluxed for 12 h and then quenched by the successive addition of H_2O (0.7 mL), aqueous NaOH (15%, 0.7 mL) and H_2O (2.1 mL). The suspension was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (150/8/1) to give **29** as a yellow oil (327 mg): ^1H NMR (300 MHz) δ 7.30 (m, 9H), 3.93 (d, $J=12.9$ Hz, 1H), 3.78 (d, $J=4.8$ Hz, 2H), 3.27 (d, $J=13.2$ Hz, 1H), 2.92 (m, 1H), 2.60–2.75 (m, 3H), 2.18 (q, $J=8.6$ Hz, 1H), 1.60–2.00 (m, 4H), NH is not discernible; ^{13}C NMR (75.4 MHz) δ 140.71, 139.94, 128.68, 128.28, 128.16, 128.02, 126.74, one aromatic signal is not discernible, 63.74, 59.23, 54.59, 54.22, 52.05, 29.01, 22.95; MS (FAB), *m/e* 281 (65, M + H), 160 (100); The amine was converted to the hydrochloride. The resulting solid softens gradually on melting: Anal. calcd for $C_{19}H_{24}N_2 \cdot 2HCl \cdot 1.5H_2O$: C, 60.00; H, 7.69; Cl, 18.64; N, 7.36. Found: C, 60.17; H, 7.45; Cl, 18.25; N, 7.51.

Synthesis of 30. A mixture of LAH (10 mmol) in THF (20 mL) was refluxed for 90 min. It was cooled to 25°C and benzylamine (50 mmol, 5.46 mL) was added dropwise with stirring. Stirring was continued at 25°C until precipitation was complete. Ethyl ester **13** (10 mmol, 2.47 g) was added to the suspension dropwise and the mixture was stirred at 25°C overnight. The reaction was then carefully quenched by successive addition of H_2O (0.4 mL), NaOH (15%, 0.4 mL) and H_2O (1.2 mL). Stirring was continued until the new precipitate became white and powdered. After filtration, the precipitate was carefully rinsed with CH_2Cl_2 (2×10 mL) and the combined organic phase were dried over Na_2SO_4 and concentrated in vacuo to give an oil. It was chromatographed on silica gel eluting with CH_2Cl_2/MeOH/NH_4OH (400/10/1) to give a colorless solid (2.18 g, 70%): mp 68–71°C; ^1H NMR (300 MHz) δ 7.10–7.30 (m, 10H), CH_2NH is an AB of an ABX pattern, 4.48 (dd, $J_B=13$ Hz, $J_{NH}=5.7$ Hz, 1H), 4.45 (dd, $J_A=13$ Hz, $J_{NH}=5.7$ Hz, 1H), 3.85 (d, $J=13.8$ Hz, 1H), 3.15 (d, $J=13.8$ Hz, 1H), 2.88 (m, 2H), 1.20–2.10 (m, 8H, including NH); ^{13}C NMR (75.4 MHz) δ 174.88, 138.34, 137.90, 128.70, 128.51, 128.31, 127.80, 127.45, 127.09, 67.78, 60.84, 51.66, 43.12, 30.42, 24.75, 23.48; MS (FAB), *m/e* 309 (75, M + H), 174 (100), 91 (52); Anal. calcd for $C_{20}H_{24}N_2O$: C, 77.89; H, 7.84; N, 9.08. Found: C, 78.11; H, 7.80; N, 9.08. The free base was converted to the hydrochloride and crystallized from 2-PrOH/MeOH/ether to give a colorless solid: mp 170–172°C; Anal. calcd for $C_{20}H_{24}N_2O \cdot HCl$: C, 69.65; H, 7.31; Cl, 10.28; N, 8.12. Found: C, 69.70; H, 7.15; Cl, 10.10; N, 8.15.

Synthesis of 31a. A mixture of 4-nitrobenzyl bromide (22 mmol, 4.75 g), potassium carbonate (11 mmol, 1.52 g) and dl-proline (10 mmol, 1.15 g) in DMF (50 mL) was heated at 60°C for 2 days. It was cooled to room temperature, diluted with ether (50 mL) and filtered. The filtrate was acidified (pH = 4) by the addition of aqueous HCl (15%) and extracted with ether (2×50 mL). The aqueous layer was basified (pH = 9) by the addition of NaOH, extracted with ether (3×100 mL), dried over Na_2SO_4 and concentrated in vacuo to give a yellow solid. The solid was washed with EtOAc to give **31a** as a pale-yellow solid (2.53 g, 68%): mp 88–90°C (EtOAc); ^1H NMR (300 MHz) δ 8.21 (br d, $J=8.7$ Hz, 2H), 8.14 (br d, $J=8.4$ Hz, 2H), 7.51 (br d, $J=8.1$ Hz, 2H), 7.50 (br d, $J=8.4$ Hz, 2H), 5.22 (d, $J=13.5$ Hz, 1H), 5.19 (d, $J=13.2$ Hz, 1H), 4.05 (d, $J=13.8$ Hz, 1H), 3.66 (d, $J=13.8$ Hz, 1H), 3.43 (dd, $J=9.0$, 5.7 Hz, 1H), 3.03 (m, 1H), 2.44 (q, $J=8.7$ Hz, 1H), 2.20 (m, 1H),

1.80–2.10 (m, 3H); ^{13}C NMR (75.4 MHz) δ 173.32, 147.75, 147.15, 146.61, 142.95, 129.28, 128.40, 123.79, 123.47, 65.22, 64.81, 57.91, 53.29, 29.36, 23.30; MS (FAB), *m/e* 386 (100, M + H), 251 (4), 249 (5), 205 (97); Anal. calcd for $C_{19}H_{19}N_3O_6$: C, 59.22; H, 4.97; N, 10.90. Found: C, 59.29; H, 5.02; N, 10.84.

Synthesis of 31b. A mixture of 3-chlorobenzyl chloride (14.9 mmol, 1.89 mL), potassium carbonate (7.43 mmol, 1.03 g) and dl-proline (6.76 mmol, 778 mg) in DMF (10 mL) was heated at 60°C for 2 days. It was cooled to room temperature, diluted with ether (50 mL) and filtered. The filtrate was acidified (pH = 4) by the addition of aqueous HCl (15%) and extracted with ether (2×50 mL). The aqueous layer was basified (pH = 9) by the addition of NaOH, extracted with ether (3×100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F (1/1) to give **31b** as a yellow oil (989 mg, 50%): ^{1}H NMR (300 MHz) δ 7.10–7.30 (m, 8H), 5.07 (m, 2H), 3.89 (d, *J* = 13.2 Hz, 1H), 3.52 (d, *J* = 12.9 Hz, 1H), 3.32 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.03 (m, 1H), 2.40 (q, *J* = 8.7 Hz, 1H), 1.50–2.40 (m, 4H); ^{13}C NMR (75.4 MHz) δ 173.60, 140.77, 137.85, 134.45, 134.05, 129.83, 129.43, 128.89, 128.35, 128.17, 127.22, 127.00, 126.16, 65.33, 65.09, 58.02, 53.21, 29.29, 23.14; MS (FAB), *m/e* 364 (88, M + H), 194 (100), 125 (56); HRMS (FAB) *m/e* calcd for ($C_{19}H_{19}Cl_2NO_2$ + H) 364.0871, found 364.0847.

Synthesis of 31c. A mixture of 2-(bromomethyl)naphthalene (15.5 mmol, 3.43 g), potassium carbonate (7.73 mmol, 1.07 g) and dl-proline (7.03 mmol, 809 mg) in DMF (10 mL) was heated at 60°C for 2 days. It was cooled to room temperature, diluted with ether (50 mL) and filtered. The filtrate was acidified (pH = 4) by the addition of aqueous HCl (15%) and extracted with ether (2 × 50 mL). The aqueous layer was basified (pH = 9) by the addition of NaOH, extracted with ether (3×100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F (1/1) to give **31c** as a yellow oil (1.91 g, 70%): ^{1}H NMR (300 MHz) δ 7.70–7.90 (m, 8H), 7.35–7.50 (m, 6H), 5.24 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 12.3 Hz, 1H), 4.08 (d, *J* = 12.6 Hz, 1H), 3.70 (d, *J* = 12.6 Hz, 1H), 3.37 (dd, *J* = 8.7, 6.0 Hz, 1H), 3.07 (m, 1H), 2.44 (q, *J* = 8.3 Hz, 1H), 1.70–2.20 (m, 4H); ^{13}C NMR (75.4 MHz) δ 173.98, 136.22, 133.32, 133.27, 133.13, 133.06, 132.71, 128.29, 127.95, 127.75, 127.71, 127.64, 127.56, 127.48, 127.42, 127.36, 126.19, 125.88, 125.79, 125.49, one aromatic signal is not discernible, 66.35, 65.26, 58.78, 53.33, 29.36, 23.12; The hydrochloride was prepared with ethereal HCl and was crystallized from MeOH/2-PrOH/ether: mp > 123°C (softens); MS (FAB), *m/e* 396 (100, M + H), 141 (78); Anal. calcd for $C_{27}H_{25}NO_2 \cdot HCl \cdot H_2O$: C, 72.07; H, 6.27; Cl, 7.88; N, 3.11. Found: C, 72.02; H, 6.58; Cl, 7.99; N, 3.07.

Synthesis of 31d. A mixture of 4-methoxybenzyl chloride (22 mmol, 2.98 mL), potassium carbonate (11 mmol, 1.52 g) and dl-proline (10 mmol, 1.15 g) in DMF (50 mL) was heated at 60°C for 2 days. It was cooled to room temperature, diluted with ether (50 mL) and filtered. The filtrate was acidified (pH = 4) by the addition of aqueous HCl (15%) and extracted with ether (2×50 mL). The aqueous layer was basified (pH = 9) by the addition of NaOH, extracted with ether (3×100 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F (1/1) to give **31d** as a yellow oil (1.98 g, 61%): ^{1}H NMR (300 MHz) δ 7.28 (d, *J* = 8.7 Hz, 2H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 5.06 (d, *J* = 12.0 Hz, 1H), 5.02 (d, *J* = 12.0 Hz, 1H), 3.82 (d, *J* = 12.7 Hz, 1H), 3.78 (s, OCH_3), 3.76 (s, OCH_3), 3.48 (d, *J* = 12.7 Hz, 1H), 3.23 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.00 (m, 1H), 2.36 (q, *J* = 8.7 Hz, 1H), 1.67–2.15 (m, 4H); ^{13}C NMR (75.4 MHz) δ 173.85, 159.49, 158.57, 130.15, 129.93, 128.38, 128.10, 113.77, 113.40, 65.85, 64.85, 57.59, 55.09, 55.05, 52.87, 29.14, 22.87; MS (FAB), *m/e* 356 (52, M + H), 190 (50), 121 (100); HRMS (FAB) *m/e* calcd for ($C_{21}H_{25}NO_4$ + H) 356.1862, found 356.1868.

Synthesis of 32a. A suspension of LAH (3.19 mmol, 121 mg) in THF (20 mL) was refluxed for 1 h and then cooled to room temperature. Benzylamine (16.0 mmol, 1.7 mL) was added and the mixture was stirred for 1 h. A solution of **31a** (3.19 mmol, 1.23 g) in THF (10 mL) was added and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of H_2O (0.12 mL), NaOH (0.12 mL, 15%) and additional H_2O (0.36 mL). The precipitate was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F to give **32a** as a solid: mp 80–82°C; ^{1}H NMR (300 MHz) δ 8.07 (br d, *J* = 8.7 Hz, 2H), 7.49 (br s, NH), 7.20–7.36 (m, 7H), 4.49 (dd, *J* = 14.4, 6.6 Hz, 1H), 4.33 (dd, *J* = 14.7, 5.1 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 1H), 3.59 (d, *J* = 13.8 Hz, 1H), 3.30 (dd, *J* = 10.2, 5.4 Hz, 1H), 3.01 (ddd, *J* = 9.2, 6.7, 2.4 Hz, 1H), 2.20–2.40 (m, 2H), 1.65–2.00 (m, 3H); ^{13}C NMR (75.4 MHz) δ 173.76, 147.07, 145.83, 138.26, 129.19, 128.66, 127.56, 127.51, 123.58, 67.69, 59.21, 54.10, 42.94, 30.59, 24.11; MS (FAB), *m/e* 340 (100, M + H), 205 (68); Anal. calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.18; H, 6.28; N, 12.37.

Synthesis of 32b. A suspension of LAH (1.26 mmol, 48 mg) in THF (20 mL) was refluxed for 1.5 h and then cooled to room temperature. Benzylamine (6.3 mmol, 0.69 mL) was added and the mixture was stirred for 1 h. A solution of **31b** (1.26 mmol, 460 mg) in THF (10 mL) was added and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of H_2O (50 μL), NaOH (50 μL, 15%) and additional H_2O (150 μL). The precipitate was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F to give **32b** as a yellow oil (323 mg, 71%): ^{1}H NMR (300 MHz) δ 7.63 (br s, NH), 7.14–7.36 (m, 8H), 7.01 (dt, *J* = 7.2, 1.7 Hz, 1H), 4.44 (dd, *J* = 14.7, 6.3 Hz, 1H), 4.38 (dd, *J* = 14.7, 5.7 Hz, 1H), 3.80 (d, *J* = 12.9 Hz, 1H), 3.43 (d, *J* = 12.9 Hz, 1H), 3.25 (dd, *J* = 10.2, 4.8 Hz, 1H), 2.98 (ddd, *J* = 9.2, 6.9, 2.4 Hz, 1H), 2.18–2.37 (m, 2H), 1.94 (m, 1H), 1.64–1.83 (m, 2H); ^{13}C NMR (75.4 MHz) δ 174.07, 140.41, 138.27, 134.13, 129.59, 128.63, 128.58, 127.46, 127.33, 126.68, one

aromatic signal is not discernible, 67.35, 59.27, 53.82, 42.90, 30.54, 24.01; MS (FAB), *m/e* 329 (100, M + H), 194 (28), 125 (13); The hydrochloride was prepared with ethereal HCl and was crystallized from MeOH/2-PrOH/ether: mp 175–177°C; Anal. calcd for $C_{19}H_{21}ClN_2O\cdot HCl$: C, 62.47; H, 6.07; Cl, 19.41; N, 7.67. Found: C, 62.37; H, 6.04; Cl, 19.29; N, 7.63.

Synthesis of 32c. A suspension of LAH (3.82 mmol, 145 mg) in THF (30 mL) was refluxed for 1.5 h and then cooled to room temperature. Benzylamine (19.1 mmol, 2.09 mL) was added and the mixture was stirred for 1 h. A solution of **31c** (3.82 mmol, 1.51 g) in THF (10 mL) was added and the mixture was stirred overnight at room temperature. The reaction was quenched by the addition of H_2O (0.15 mL), NaOH (0.15 mL, 15%) and additional H_2O (0.45 mL). The precipitate was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc/Skelly F (1/1) to give **32c** as a yellow oil (308 mg, 24%): ^{1}H NMR (300 MHz) δ 7.20–7.80 (m, 13 H), 4.41 (dd, J = 15.0, 6.0 Hz, 1H), 4.36 (dd, J = 14.7, 5.7 Hz, 1H), 3.99 (d, J = 12.9 Hz, 1H), 3.62 (d, J = 12.6 Hz, 1H), 3.34 (dd, J = 10.5, 4.8 Hz, 1H), 3.00 (ddd, J = 9.0, 6.6, 2.4 Hz, 1H), 2.40 (td, J = 10.2, 6.6 Hz, 1H), 2.27 (m, 1H), 1.60–2.00 (m, 3H); ^{13}C NMR (75.4 MHz) δ 174.42, 138.39, 135.94, 133.25, 132.62, 128.63, 128.06, 127.65, 127.57, 127.55, 127.34, 127.25, 126.78, 126.05, 125.74, 67.42, 60.10, 53.99, 42.96, 30.65, 24.13; The hydrochloride was prepared with ethereal HCl and was crystallized from MeOH/2-PrOH/ether: mp 191–193°C; MS (FAB), *m/e* 345 (100, M + H), 210 (9), 141 (33); Anal. calcd for $C_{23}H_{24}N_2O\cdot HCl$: C, 72.52; H, 6.62; Cl, 9.31; N, 7.35. Found: C, 72.12; H, 6.66; Cl, 9.33; N, 7.23.

Determination of cholinesterase and acetylcholinesterase activities. The methods are described in ref 9.

Passive avoidance training. The methods are described in ref 9.

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