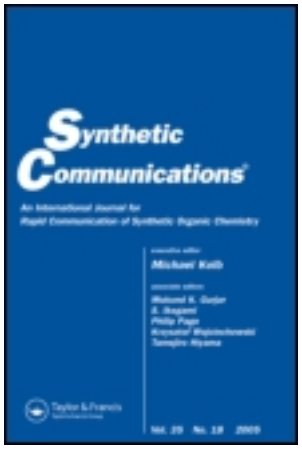

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Efficient Synthesis of a New Series of Piperidine Ring-Modified Analogs of (±)-threo-Methyl Phenyl(piperidin-2-yl)acetate

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EFFICIENT SYNTHESIS OF A NEW SERIES OF PIPERIDINE RING-MODIFIED ANALOGS OF (±)-*THREO*-METHYL PHENYL(PIPERIDIN-2-YL)ACETATE

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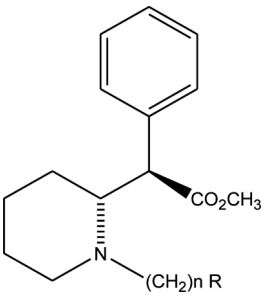
GRAPHICAL ABSTRACT



Abstract *A series of novel piperidine ring modified analogs of (±)-*threo*-methyl phenyl (piperidin-2-yl)acetate was synthesized by direct alkylation and reductive amination procedure, using sodium borohydride over molecular sieves. The chemical structures of these compounds were established based on mass spectra, ^1H NMR spectra, and CHN elemental analysis data. Several significant modifications in the literature methodologies were made to make the reaction more efficient, and good yields were generally obtained.*

Keywords Methyl phenyl(piperidin-2-yl)acetate; piperidine; reductive amination; ring modification

INTRODUCTION

Dopamine is an important neurotransmitter in the central nervous system, and malfunction of dopaminergic systems is implicated, for example, in Parkinson's disease, Huntington's chorea, and schizophrenia. This neurotransmitter is also involved in the reward system believed to underlie drug addition. Its action is primarily mediated by several receptor subtypes with different structural requirements for exogenous ligands. In both animals and humans, cocaine is one of the most reinforcing drugs known; hence it has great abuse potential. The abuse of cocaine (and other

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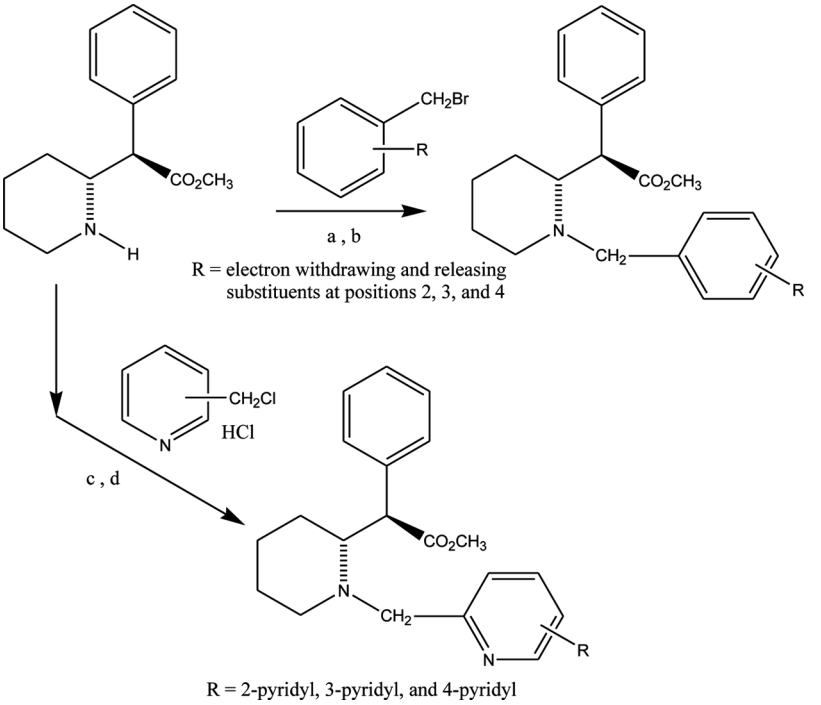
stimulant drugs) is one of the greatest concerns of the society today and has therefore become a focus of medical, social, and political leaders. Methyl phenyl(piperidin-2-yl)acetate was first synthesized in 1944 by Panizzon[1] and was identified as a stimulant in 1954.[2] A review on the synthesis of commercially pure (′R, 2′R)-(+)-*threo*-methyl phenyl(piperidin-2-yl)acetate hydrochloride has been published.[3] The original method of Pannizzon[1] for the synthesis of methyl phenyl(piperidin-2-yl)acetate often gave mixtures of products that may require tedious chromatographic separations, resulting generally in a very poor yield. A diverse group of methylphenidate analogs have been synthesized. Because both the phenyl ring and the piperidine ring of methylphenidate are important for the binding at the DAT (dopamine transporter protein), the design of the analogs of methylphenidate has mainly focused on modifying these two pharmacophores.

Detailed reviews of piperidine analogs of cocaine, tropanes, and GBR 12935 compounds have been reported in the literature.[4,5] Furthermore, the synthesis of piperidine ring-modified analogs of methylphenidate has been reported in the literature.[5,6] These analogs basically involve the replacement of the piperidine ring with other secondary amines with five, seven, and eight-membered rings. Over the past several years, the chemical synthesis of a series of (±)-*threo*-methyl phenyl (piperidin-2-yl)acetate analogs has been reported,[4–14] but not many reports include piperidine ring-modified analogs synthesis with methyl phenyl(piperidine-2-yl) acetate as the starting point for the syntheses.

The rationale for this study is to synthesize a new series of piperidine ring-modified analogs of (±)-*threo*-methyl phenyl(piperidin-2-yl)acetate derivatives by making several significant modifications to existing literature methodologies to make the reaction more efficient and hence produce compounds with improved yields. The compounds should be useful in the synthesis of novel ligands for testing as pharmaceutical agents. We now report the efficient synthesis of several new piperidine ring-modified analogs of methyl phenyl(piperidin-2-yl)acetate.

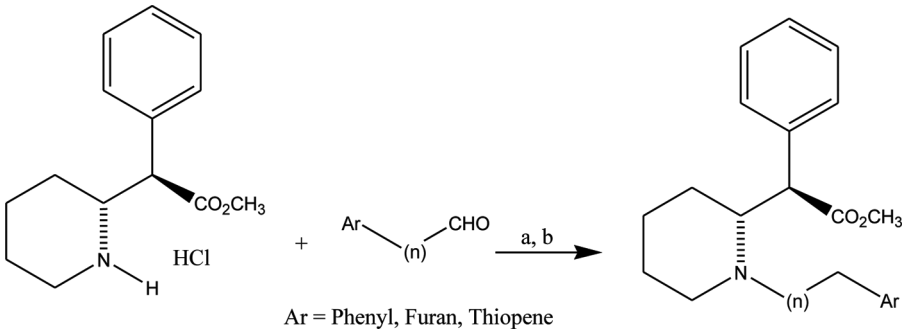
CHEMISTRY

The synthesis of methyl phenyl(piperidin-2-yl)acetate has previously been described in the literature, based on the alkylation of 2-bromopyridine with various phenylacetonitrile anions. The original method developed by Panizzon[1] was modified in a previous report.[14] This study further expands the scope of these modifications to synthesize a new series of benzyl, substituted-benzyl, and other aromatic ring derivatives. The alkylation reagent was carefully selected so that it could serve two purposes: (1) protection of the amine function and (2) easy modification into the required pharmacophore. The N-alkylation was accomplished by using three methods depending upon the final product: (a) using a substituted alkyl halide in the presence of a base,[7,8] (b) using a substituted acid chloride,[8,9] and (c) using a substituted aldehyde followed by reduction with sodium cyanoborohydride (reductive amination).[8] A summary of these methods is described in Schemes 1 and 2, respectively. Several synthetic strategies employed for the direct alkylation of methyl phenyl(piperidin-2-yl)acetate to produce analogs with extended methylene linkage between the piperidine nitrogen and the benzyl ring synthesis, as well as other aromatic rings, was unsuccessful because of formation of polyalkylated compounds.



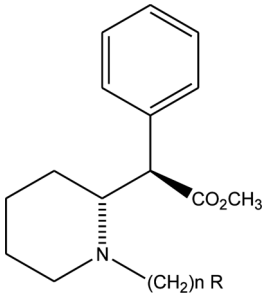
Scheme 1. General scheme for synthesis of N-benzl methyl phenyl(piperidin-2-yl)acetate analogs. Reagents and conditions: (a) Powdered potassium carbonate (K_2CO_3), acetone; (b) potassium iodide (KI), room temperature, overnight; (c) potassium iodide (KI), acetone; and (d) potassium carbonate (K_2CO_3), room temperature, 24 h.

Thus, the synthesis of these new piperidine ring-modified analogs was successfully achieved by a standard reductive amination procedure, using sodium borohydride over molecular sieves (Scheme 2). The synthesis was extended to other aromatic systems and their substituted analogs.



Scheme 2. General scheme for synthesis of extended alkyl chain and other aromatic rings methyl phenyl (piperidin-2-yl)acetate analogs. Reagents and conditions: (a) triethylyamine (Et_3N), methanol (MeOH), molecular sieves (4A); and (b) sodium cyanoborohydride ($NaBH_3CN$), room temperature, overnight.

Table 1. Physical and analytical data of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate derivatives



Comp. no.	n	R	Mp (°C)	Yield (%)	Molecular formula (M)	Elemental analysis (%) (Calc./found) C	H	N
1A	1	Phenyl	69–70	81	$C_{21}H_{25}NO_2$ (323.20)	78.03 78.01	7.80 7.81	4.32 4.31
1B	1	2-Chlorobenzyl	151–152	78	$C_{21}H_{24}NO_2Cl$ (357.16)	70.60 70.62	6.78 6.77	3.90 3.91
1C	1	3-Chlorobenzyl	179–180	74	$C_{21}H_{24}NO_2Cl$ (357.16)	70.60 70.61	6.78 6.77	3.90 3.91
1D	1	4-Chlorobenzyl	169–170	71	$C_{21}H_{24}NO_2Cl$ (357.16)	70.60 70.63	6.78 6.77	3.90 3.91
1E	1	4-Nitrobenzyl	170–172	65	$C_{21}H_{24}N_2O_4$ (368.18)	68.50 68.51	6.57 6.56	7.60 7.60
1F	1	4-Methoxybenzyl	164–165	61	$C_{22}H_{27}NO_3$ (353.47)	74.76 74.75	7.72 7.71	3.95 3.94
2A	2	Phenyl	154–155	62	$C_{22}H_{27}NO_2$ (337.22)	78.34 78.33	8.08 8.08	4.14 4.13
2B	3	Phenyl	160–161	55	$C_{23}H_{29}NO_2$ (351.22)	78.64 78.65	8.33 8.32	3.98 3.98
2C	4	Phenyl	140–141	82	$C_{24}H_{31}NO_2$ (365.25)	78.90 78.91	8.56 8.55	3.83 3.82
2D	5	Phenyl	136–137	87	$C_{25}H_{33}NO_2$ (379.29)	79.15 79.17	8.78 8.77	3.68 3.68
2E	6	Phenyl	156–157	89	$C_{26}H_{35}NO_2$ (393.27)	79.39 79.38	8.98 8.97	3.55 3.54
3A	1	2-Thiopene	180–181	85	$C_{19}H_{23}NO_2S$ (329.20)	69.31 69.32	7.05 7.05	4.25 4.23
3B	1	3-Thiopene	175–176	80	$C_{19}H_{23}NO_2S$ (329.20)	69.31 69.32	7.05 7.05	4.25 4.26
3C	1	5-Chlorothiopene	172–173	68	$C_{19}H_{22}NO_2SCl$ (363.91)	62.71 62.72	6.11 6.10	3.85 3.85
3D	1	2-Furan	170–171	88	$C_{19}H_{23}NO_3$ (313.20)	72.84 72.84	7.41 7.40	4.46 4.46
3E	1	3-Furan	181–182	86	$C_{19}H_{23}NO_3$ (313.20)	72.84 72.84	7.41 7.40	4.46 4.45
3F	1	2-Pyridyl	153–154	87	$C_{20}H_{24}N_20_2$ (324.20)	74.08 74.07	7.47 7.46	8.63 8.63
3G	1	3-Pyridyl	159–160	78	$C_{20}H_{24}N_20_2$ (324.20)	74.08 74.07	7.47 7.46	8.63 8.62

(*Continued*)

Table 1. Continued

Comp. no.	n	R	Mp (°C)	Yield (%)	Molecular formula (M)	Elemental analysis (%) (Calc./found) C	H	N
3H	1	4-Pyridyl	140–141	82	$C_{20}H_{24}N_20_2$ (324.20)	74.08 74.07	7.47 7.46	8.63 8.62
4	1	H	Liquid	80	$C_{15}H_{25}NO_2$ (247.165)	72.87 72.85	8.56 8.55	5.67 5.68

Several synthetic strategies were employed for the direct alkylation of methyl phenyl(piperidine-2-yl)acetate to produce analogs with extended methylene linkage between the piperidine nitrogen and the benzyl ring synthesis. These methods were unsuccessful because of formation of polyalkylated compounds. Thus, the synthesis of these new N-alkylated derivatives was successfully achieved by a standard reductive amination procedure, using sodium cyanoborohydride over molecular sieves (Scheme 2).

RESULTS AND DISCUSSION

The results of the alkylation of methyl phenyl(piperidin-2-yl)acetate with appropriate aryl halide, substituted aryl halide, and aldehyde in suitable solvents to give the desired methyl phenyl(piperidin-2-yl)acetate derivatives are summarized in Table 1. From the results, these compounds were synthesized in good yields (80% and above), and pure crystals of each compound were obtained. Several solvents were attempted for the alkylation process. In general, acetone, methanol, and methylene chloride were found to be the best solvents of choice because the products were obtained in relatively pure form (single spot on thin-layer chromatography, TLC). Several solvent systems were attempted for the recrystallization process, but a mixture of ethyl acetate and hexane was found to give the purest form of these compounds, supported by spectral data. The chemical structure of these compounds was established based on the mass (MS) and ^{1}H NMR spectral data. All compounds synthesized in this study gave satisfactory elemental analysis data and were within 0.4% of calculated values.

CONCLUSION

In conclusion, a mixture of methyl phenyl(piperidin-2-yl)acetate, powdered potassium carbonate, and appropriate aryl halide and substituted aryl halide was reacted in an appropriate solvent at room temperature overnight by standard alkylation procedure. Also, a mixture of methyl phenyl(piperidin-2-yl)acetate, the appropriate aldehyde in methanol, followed by the addition of triethylamine (Et_3N) and sodium cyanoborohydride ($NaBH_3CN$), was reacted by a standard reductive amination procedure. An aqueous workup procedure gave the desired target compounds in good yield. This route may serve as an excellent synthetic methodology for synthesis of new piperidine ring-modified analogs of (±)-*threo*-methyl phenyl(piperidin-2-yl)acetate in good yields.

EXPERIMENTAL

Compounds were synthesized utilizing reagents commercially available from Aldrich Chemical Co. and Fisher Scientific without further purification. Melting points were determined in open capillary tubes on a Meltemp melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Bruker Avance (AV) 400 spectrometer at 400 MHz. Chemical shifts are quoted in parts per million (ppm) from internal standard tetramethylsilane (TMS). All solvents and chemicals were of research grade and were obtained from Merck and Lancaster. The progress of the reaction was monitored by TLC. Mass spectra were obtained using a Micromass LCT mass spectrometer operating at 20 eV. Elemental analyses were performed on a Perkin-Elmer 2400 CHN analyzer instrument and were within 0.4% of calculated values.

(±)-*threo*-N-Benzyl Methyl Phenyl(piperidin-2-yl)acetate (1A)

A mixture of (±)-*threo*-methyl phenyl(piperidin-2-yl)acetate (100 mg, 0.40 mmol), powdered potassium carbonate (250 mg), and benzyl bromide (70 mg, 0.46 mmol) in acetone (20 mL) was stirred overnight at room temperature. The mixture was filtered, and the filtrate and the washings were evaporated in vacuo. The residue was chromatographed on 5 g of silica gel using 5% MeOH in chloroform to give pure (TLC, one spot $R_F = 0.42$) compound. The hydrochloride salt was obtained by addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 112 mg (81%) of **1A** as white solid: mp 69–70 °C (lit.[15]; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m,1H), 3.66–3.49 (m,1H), 3.71 (s, 3H, OCH_3), 3.97–3.93 (d, 1H, $J = 13.4$), 3.84–3.97 (d, 1H, $J = 13.2$), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H) ppm; MS-CI m/z 324.20 calcd. for $C_{21}H_{26}NO_2$ (MH+). Anal. calcd. for $C_{21}H_{26}NO_2$: C, 78.03; H, 7.80; N, 4.32. Found: C, 78.01; H, 7.81; N, 4.31.

(±)-*threo*-N-(2-Chlorobenzyl) Methyl Phenyl(piperidin-2-yl)-acetate (1B)

A mixture of (±)-*threo*-methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 2-chlorobenzyl (82 mg, 0.40 mmol) in acetone (20 mL) was alkylated by a method virtually identical to that employed to synthesize **1A**. The compound was converted to its hydrochloride salt, and recrystallization from EtOAc–hexane provided 100 mg (78%) of **1B** as a off-white solid: mp 151–152 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.3$), 3.78–3.74 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.2$), 7.4–7.2 (m, 9H, aromatic-H) ppm; MS-CI m/z 358.160 calcd. for $C_{21}H_{25}NO_2$ Cl (MH+). Anal. calcd. for $C_{21}H_{25}NO_2$ Cl: C, 70.60; H, 6.78; N 3.90. Found: C, 70.62; H, 6.77; N, 3.91.

(±)-*threo*-N-(3-Chlorobenzyl) Methyl Phenyl(piperidin-2-yl)-acetate (1C)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 3-chlorobenzyl (82 mg, 0.40 mmol) in acetone (20 mL) was alkylated by a method

virtually identical to that employed to synthesize **1A**. The compound was converted to its hydrochloride salt, and recrystallization from EtOAc–hexane provided 70 mg (74%) of **1C** as a off-white solid: mp 179–180 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.3$), 3.78–3.74 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.2$), 7.4–7.2 (m, 9H, aromatic-H) ppm; MS-CI m/z 358.160 calcd. for $C_{21}H_{25}NO_2$ Cl (MH+). Anal. calcd.. for $C_{21}H_{25}NO_2$ Cl: C, 70.60; H, 6.78; N, 3.90. Found: C, 70.60; H, 6.78; N, 3.90.

(±)-*threo*-N-(4-Chlorobenzyl) Methyl Phenyl(piperidin-2-yl)-acetate (1D)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 4-chlorobenzyl (64 mg, 0.40 mmol) in acetone (20 mL) was alkylated by a method virtually identical to that employed to synthesize **1A**, except that KI (0.25 g) was added to the reaction mixture to enhance the reactivity of the 4-chlorobenzyl chloride. In addition, the reaction time was increased to 48 h, and the crude product was filtered through a silica-gel column to give the pure compound. The compound was converted to its hydrochloride salt, and recrystallization from EtOAc–hexane provided 70 mg (71%) of **1D** as a off-white solid: mp 169–170 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.3$), 3.78–3.74 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.2$), 7.4–7.2 (m, 9H, aromatic-H) ppm; MS-CI m/z 358.160 calcd. for $C_{21}H_{25}NO_2$ Cl (MH+). Anal. calcd. for $C_{21}H_{25}NO_2$ Cl: C, 70.60; H, 6.78; N, 3.90. Found: C, 70.63; H, 6.77; N, 3.91.

(±)-*threo*-N-(4-Nitrobenzyl) Methyl Phenyl(piperidin-2-yl)-acetate (1E)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 4-nitrobenzyl bromide (86 mg, 0.40 mmol) in acetone (20 mL) was alkylated by a method virtually identical to that employed to synthesize **1A**. The resulting compound was converted to its hydrochloride salt, and recrystallization from EtOAc–hexane provided 70 mg (65%) of **1E** as a yellow solid: mp 170–172 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.3$), 3.78–3.74 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.2$), 7.4–7.2 (m, 9H, aromatic-H) ppm; MS-CI m/z 369.18 calcd. for $C_{21}H_{24}N_2O_4$ (MH+). Anal. calcd. for $C_{21}H_{24}N_2O_4$: C, 68.50; H, 6.57; N, 7.60. Found: C, 68.51; H, 6.56; N, 7.60.

(±)-*threo*-N-(4-Methoxylbenzyl) Methyl Phenyl(piperidin-2-yl)-acetate (1F)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 4-methoxylbenzyl chloride (63 mg, 0.40 mmol) in acetone (20 mL) was alkylated by a method virtually identical to that employed to synthesize **1D**. The resulting compound was converted to its hydrochloride salt, and recrystallization from

EtOAc–hexane provided 80 mg (61%) of **1F** as a white solid: mp 164–165 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.58–2.53 (m, 1H), 3.66–3.49 (m, 1H), 3.70 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.3$), 3.78–3.74 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.2$), 7.4–7.2 (m, 5H, aromatic-H), 7.6–7.5 (m, 2H, aromatic-H), 8.1–8.0 (m, 2H, aromatic-H) ppm; MS-CI m/z 354.20 calcd. for $C_{22}H_{28}NO_3$ (MH+). Anal. calcd. for $C_{22}H_{28}NO_3$: C, 74.76; H, 7.72; N, 3.95. Found: C, 74.75; H, 7.71; N, 3.94.

Synthesis of 4-Phenylbutyraldehyde

In a 100-mL round-bottom flask fitted with a reflux condenser, PCC (2.15 g, 0.009985 mol) was suspended in dry methylene chloride (30 mL). A solution of 4-phenylbutanol (1 g, 0.006656 mol) in methylene chloride (10 mL) was then added in one portion to the magnetically stirred suspension to give a dark reaction mixture. The reaction mixture was allowed to proceed at room temperature overnight. Dry ether (60 mL) was added, and the supernatant liquid was decanted from a black gum. The insoluble residue was washed with dry ether (3×20 mL) and becomes a black granular solid. The combined organic solution was passed through a short pad of florisil and the solvent removed in vacuo provided 75 mg (76%) of titled compound as a yellow liquid. ^{1}H NMR ($CDCl_3$): consistent with the structure of the compound with characteristic aldehyde proton.

Synthesis of 5-Phenylpentyraldehyde

In a 100-mL round-bottom flask fitted with a reflux condenser, PCC (1.968 g, 0.00913 moles) was suspended in dry methylene chloride (30 mL). A solution of 5-phenylpentanol (1 g, 0.006656 mol) in methylene chloride (10 mL) was oxidized by a method similar to that described for 4-phenylbutyraldehyde. Removal of solvent in vacuo provided 65 mg (71%) of the titled compound as a yellow liquid. ^{1}H NMR ($CDCl_3$): consistent with the structure of the compound with characteristic aldehyde proton.

Synthesis of 6-Phenylhexyraldehyde

In a 100-mL round-bottom flask fitted with a reflux condenser, PCC (1.81 g, 0.008413 mol) was suspended in dry methylene chloride (30 mL). A solution of 6-phenylhexanol (1 g, 0.006656 mol) in methylene chloride (10 mL) was oxidized by a method similar to that described for 4-phenylbutyraldehyde. Removal of solvent in vacuo provided 65 mg (71%) of the titled compound as a yellow liquid. ^{1}H NMR ($CDCl_3$): consistent with the structure of the compound with characteristic aldehyde proton.

(±)-*threo*-N-(Phenylethyl) Methyl Phenyl(piperidin-2-yl)acetate (2A)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.172 g) and 2-phenylacetaldehyde (0.2 mL) was dissolved in methanol (25 mL), followed by the addition of Et_3N (0.4 g), and reductively alkylated. Into the solution were added 4-A molecular sieves (4 g), and the reaction mixture was stirred at room

temperature for 1.5 h. $NaBH_3CN$ (0.15 g, 2.38 mmol) was added into the solution, and the reaction was continued for an additional 18 h. The mixture was filtered, and the filtrate and the washings were evaporated in vacuo. The residue was chromatographed on 10 g of silica gel using $CHCl_3$–MeOH (25:1) to give pure (TLC, one spot $R_F = 0.38$) titled compound. The hydrochloride salt was obtained by addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 87 mg (62%) of **2A** as a white solid: mp 154–155 °C; ^{1}H NMR ($CDCl_3$): d 1.6–0.9 (m, 6H), 2.4 (m, 1H), 2.8–2.6 (t, 2H), 2.9–3.0 (t, 2H), 3.4 (m, 1H), 3.65 (s, 3H, OCH_3), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H) ppm; MS-CI m/z 338.22, calcd. for $C_{22}H_{28}NO_2$ (MH+). Anal. calcd. for $C_{22}H_{27}NO_2$: C, 78.34; H, 8.08; N, 4.14. Found: C, 78.33; H, 8.08; N, 4.13.

(±)-*threo*-N-(Phenylpropyl) Methyl Phenyl(piperidin-2-yl)-acetate (2B)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.16 g), 3-phenylpropionaldehyde (0.2 mL), and triethylamine (0.3 mL) in methanol (30 mL) was reductively alkylated by employing a method virtually identical to that used for **2A**, with the exception that an aqueous workup procedure was employed in the isolation process. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 49 mg (55%) of **2B** as white solid: 160–161 °C; ^{1}H NMR ($CDCl_3$): d 1.6–0.9 (m, 6H), 1.8–1.6 (t, 2H), 2.4 (m, 1H), 2.8–2.6 (m, 4H), 3.1–3.2 (m, 1H), 3.4 (m, 1H), 3.61 (s, 3H, OCH_3), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H) ppm; MS-CI m/z 352.22, calcd. for $C_{23}H_{30}NO_2$ (MH+). Anal. calcd. for $C_{23}H_{29}NO_2$: C, 78.64; H, 8.33; N, 3.98. Found: C, 78.65; H, 8.32; N, 3.98.

(±)-*threo*-N-(Phenylbutyl) Methyl Phenyl(pieridin-2-yl)acetate (2C)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.172 g), 4-phenylbutyraldehyde (0.19 g, 0.001275 mol), and triethylamine (0.3 mL) in methanol (30 mL) was reductively alkylated by employing a method virtually identical to that used for **2B**, with the exception that an aqueous workup procedure was employed in the isolation process. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) gave 91 mg (82%) of **2C** as a white solid: mp 140–141 °C; ^{1}H NMR ($CDCl_3$): d 1.6–0.9 (m, 6H), 1.8–1.6 (t, 4H), 2.4 (m, 1H), 2.6–2.58 (m, 4H), 3.1–3.2 (m, 1H), 3.4 (m, 1H), 3.61 (s, 3H, OCH_3), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H), ppm; MS-CI m/z 366.3, calcd. for $C_{24}H_{32}NO_2$ (MH+). Anal. calcd. for $C_{24}H_{31}NO_2$: C, 78.90; H, 8.56; N, 3.83. Found: C, 78.91; H, 8.55; N, 3.82.

(±)-*threo*-N-(Phenylpentyl) Methyl Phenyl(piperidin-2-yl)-acetate (2D)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.16 g), 5-phenylpentyraldehyde (0.2 g, 0.001275 mol), and triethylamine (0.3 mL) in methanol (30 mL) was reductively alkylated by employing a method virtually

identical to that used for **2B**, with the exception that an aqueous workup procedure was employed in the isolation process. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo and recrystallization (EtOAc-hexane) provided 81 mg (87%) of **2D** as a white solid: mp 136–137 °C; ^{1}H NMR ($CDCl_3$): d 1.6–0.9 (m, 6H), 1.8–1.7 (t, 4H), 2.4 (m, 1H), 2.5–2.2 (m, 4H), 2.6 (t, 2H), 3.1–3.2 (m, 1H), 3.4 (m, 1H), 3.61 (s, 3H, OCH_3), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H) ppm; MS-CI m/z 380.25, calcd. for $C_{25}H_{34}NO_2$ (MH+). Anal. calcd. for $C_{25}H_{33}NO_2$: C, 79.15; H, 8.78; N, 3.68. Found: C, 79.17; H, 8.77; N, 3.68.

(±)-*threo*-N-(Phenylhexyl) Methyl Phenyl(piperdin-2-yl)acetate(2E)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.17 g), 6-phenylhexyraldehyde (0.23 g, 0.001275 mol), and triethylamine (0.3 mL) in methanol (30 mL) was reductively alkylated by employing a method virtually identical to that used for **2B**, with the exception that an aqueous workup procedure was employed in the isolation process. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo and recrystallization (EtOAc–hexane) provided 95 mg (89%) of **2E** as a white solid: mp 156–157 °C; ^{1}H NMR ($CDCl_3$): d 1.6–0.9 (m, 6H), 1.8–1.7 (t, 4H), 2.4 (m, 1H), 2.5–2.2 (m, 6H), 2.6 (t, 2H), 3.1–3.2 (m, 1H), 3.4 (m, 1H), 3.61 (s, 3H, OCH_3), 4.2–4.1 (d, 1H, $J = 10.4$), 7.4–7.2 (m, 10H, aromatic-H) ppm; MS-CI m/z 394.30, calcd. for $C_{26}H_{36}NO_2$ (MH+). Anal. calcd. for $C_{26}H_{35}NO_2$: C, 79.39; H, 8.98; N, 3.55. Found: C, 79.38; H, 8.97; N, 3.54.

Synthesis of 2-Chloromethyl Pyridine

Pyridine-2-methanol (2 g, 0.018 mol) was added to $SOCl_2$ (10 mL, cooled in an ice bath) with stirring over a period of 15 min via a graduated glass funnel. After the initial exothermic reaction has subsided, the reaction mixture was heated under reflux for an additional 20 min. The solution obtained was cooled in an ice bath and overlayed with an equal volume of petroleum ether (40–60 °C boiling range) (instead of ligroin). After vigorous scratching and stirring with a glass rod, the lower layer was separated by filtration to give a light brown solid. The solid from the first filtration was washed several times (with petroleum ether and diethyl ether) to remove residual thionyl chloride. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOH–EtOAc, 1:1) provided 2.1 g (70%) of the titled compound as a light brown solid: mp 119–121 °C. ^{1}H NMR ($CDCl_3$): consistent with the structure assigned to the product.

Synthesis of 3-Chloromethyl Pyridine

3-Chloromethyl pyridine was prepared from pyridine-3-methanol (2 g, 0.018 mol) and $SOCl_2$ (10 mL, cooled in an ice bath) employing a method virtually identical to that used for 2-chloromethyl pyridine. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOH–EtOAc, 1:1) provided 2.3 g (72.5%) of the titled compound

as a light brown solid: mp 140–143 °C. ^{1}H NMR ($CDCl_3$): consistent with the structure assigned to the product.

Synthesis of 4-Chloromethyl Pyridine

4-Chloromethyl pyridine was prepared from pyridine-4-methanol (2 g, 0.018 mol) and $SOCl_2$ (10 mL, cooled in an ice bath) by a method virtually identical to that employed to synthesize 2-chloromethyl pyridine. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOH–EtOAc, 1:1) provided 2.08 g (69.2%) of the titled compound as a light brown solid: mp 160–162 °C. ^{1}H NMR ($CDCl_3$): consistent with the structure assigned to the product.

(±)-*threo*-N-(Methyl-2-thiopene) Methyl Phenyl(piperidin-2-yl)-acetate (3A)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.260 g, 0.96 mmol) and thiopene-2-aldehyde (0.146 g, 0.11 mL, 1.3 mmol) was in methanol (25 mL) was reductively alkylated employing a method virtually identical to that used for **2A**. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 150 mg (85%) of **3A** as a yellow solid: mp 180–181 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.71 (s, 3H, OCH_3), 3.97–3.93 (d, 1H, $J = 13.4$), 3.84–3.97 (d, 1H, $J = 13.2$), 4.2–4.1 (d, 1H, $J = 10.4$), 6.9 (d, 1H, thiopene-H), 7.3 (dd, 2H, thiopene-H), 7.4–7.2 (m, 5H, aromatic-H), ppm; MS-FB+ m/z 330.20, calcd. for $C_{19}H_{24}NO_2S$ (MH+). Anal. calcd. for $C_{19}H_{23}NO_2S$: C, 69.31; H, 7.05; N, 4.25. Found: C, 69.32; H, 7.05; N, 4.25.

(±)-*threo*-N-(Methyl-3-thiopene) Methyl Phenyl(piperidin-2-yl)-acetate (3B)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.260 g, 0.96 mmol) and thiopene-3-aldehyde (0.146 g, 0.11 mL, 1.3 mmol) in methanol (25 mL) was reductively alkylated by a method virtually identical to that used to synthesize **3A**. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 142 mg (80%) of **3B** as a yellow solid: mp 175–176 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.71 (s, 3H, OCH_3), 3.97–3.93 (d, 1H, $J = 13.4$), 3.84–3.97 (d, 1H, $J = 13.2$), 4.2–4.1 (d, 1H, $J = 10.4$), 7.1 (s, 1H, thiopene-H), 7.4–7.2 (m, 5H, aromatic-H), 7.50 (d, 1H, thiopene-H), 7.60 (d, 1H, thiopene-H) ppm; MS-FB+ m/z 330.20, calcd. for $C_{19}H_{24}NO_2S$ (MH+). Anal. calcd. for $C_{19}H_{23}NO_2S$: C, 69.31; H, 7.05; N, 4.25. Found: C, 69.32; H, 7.05; N, 4.26.

(±)-*threo*-N-Methyl-(5-chlorothiopene) Methyl Phenyl-(piperidin-2-yl)acetate (3C)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 2-chloro-5-(chloromethyl) thiopene (67 mg, 0.40 mmol) in acetone (20 mL) was

alkylated by a method virtually identical to that employed to synthesize **1D**. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo and recrystallization (EtOAc–Hexane) provided 71 mg (68%) of **3C** as a brown solid: mp 171–173 °C; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 3.03–2.95 (m, 1H), 2.77–2.60 (m, 1H), 3.59–3.42 (m, 1H), 3.70 (s, 3H, OCH_3), 3.92–3.89 (d, 1H, $J = 13.2$), 4.10–4.02 (d, 1H, $J = 10.2$), 6.75–6.05 (dd,21H, thiopene), 7.4–7.2 (m, 5H, aromatic-H) ppm; MS-CI m/z 364.120 calcd. for $C_{19}H_{23}NO_2S$ Cl (MH+). Anal. calcd. for $C_{19}H_{22}NO_2SCl$: C, 62.71; H, 6.11; N, 3.85. Found: C, 62.72; H, 6.10; N, 3.85.

(±)-*threo*-N-(Methyl-2-furan) Methyl Phenyl(piperidin-2-yl)-acetate (3D)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.260 g, 0.96 mmol) and 2-furaldehyde (0.125 g, 0.11 mL, 1.3 mmol) was in methanol (25 mL) was reductively alkylated employing a method virtually identical to that used for **2A**. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 110 mg (88%) of **3D** as a white solid: mp 170–171 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m,1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.71 (s, 3H, OCH_3), 3.97–3.93 (d, 1H, $J = 13.4$), 3.84–3.97 (d, 1H, $J = 13.2$), 4.2–4.1 (d, 1H, $J = 10.4$), 6.4 (d, 1H, furan-H), 6.6 (d, 1H, furan-H), 7.4–7.2 (m, 5H, aromatic-H), 7.58 (d, 1H, furan-H) ppm; MS-FB+ m/z 314.20, calcd. for $C_{19}H_{24}NO_3$ (MH+). Anal. calcd. for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.41; 4.46. Found: C, 72.84; H, 7.40; N, 4.46.

(±)-*threo*-N-(Methyl-3-furan) Methyl Phenyl(piperidin-2-yl)-acetate (3E)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate hydrochloride (0.260 g, 0.96 mmol) and 3-furaldehyde (0.125 g, 0.11 mL, 1.3 mmol) in methanol (25 mL) was reductively alkylated by a method virtually identical to that used to synthesize **3D**. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc–hexane) provided 102 mg (86%) of **3E** as a white solid: mp 181–182 °C; The hydrochloride salt was recrystallized from EtOAc–hexane: mp 181–182 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.71 (s, 3H, OCH_3), 3.97–3.93 (d, 1H, $J = 13.4$), 3.84–3.97 (d, 1H, $J = 13.2$), 4.2–4.1 (d, 1H, $J = 10.4$), 6.4 (s, 1H, furan-H), 6.6 (d, 1H, furan-H), 7.4–7.2 (m, 5H, aromatic-H), 7.50 (dd, 2H, furan-H) ppm; MS-FB+ m/z 314.20, calcd. for $C_{19}H_{24}NO_3$ (MH+). Anal. calcd. for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.41; N, 4.46. Found: C, 72.84; H, 7.40; N, 4.45.

(±)-*threo*-N-(2-Methylpyridyl) Methyl Phenyl(piperidin-2-yl)-acetate (3F)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 2-chloro methyl pyridine (66 mg, 0.4 mmol) in acetone (20 mL) was alkylated by a

method virtually identical to that used to synthesize **1D**. Recrystallization of the dihydrochloride salt (EtOAc–hexane) provided 71.5 mg (87%) of **3F** as a light brown solid: mp 153–154 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.4$), 3.79–3.75 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.4$), 7.1 (t, 1H, pyridyl-H), 7.3–7.2 (m, 9H, aromatic-H), 7.4 (d, 1H, pyridyl-H), 7.8 (t, 1H, pyridyl-H), 8.45 (d, 1H, pyridyl-H) ppm; MS-FB+ m/z 325.20 calcd. for $C_{20}H_{25}N_2O_2$ (MH+). Anal. calcd. for $C_{20}H_{24}N_2O_2$: C, 74.08; H, 7.47; N, 8.63. Found: C, 74.07; H, 7.46; N, 8.63.

(±)-*threo*-N-(3-Methylpyridyl) Methyl Phenyl(piperidin-2-yl)-acetate (3G)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.39 mmol) and 3-chloromethyl pyridine (66 mg, 0.4 mmol) in acetone (20 mL) was alkylated by employing a method virtually identical to that used for **3F**. Recrystallization of the dihydrochloride salt (EtOAc–hexane) provided 63 mg (78%) of **3G** as a brown solid: mp 159–160 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.4$), 3.79–3.75 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.4$), 7.3–7.2 (m, 9H, aromatic-H), 7.4 (s, 1H, pyridyl-H), 7.6 (d, 1H, pyridyl-H), 8.5 (d, 2H, pyridyl-H) ppm; MS-FB+ m/z 325.20 calcd. for $C_{20}H_{25}N_2O_2$ (MH+). Anal. calcd. for $C_{20}H_{24}N_2O_2$: C, 74.08; H, 7.47; N, 8.63. Found: C, 74.07; H, 7.46; N, 8.62.

(±)-*threo*-N-(4-Methylpyridyl) Methyl Phenyl(piperidin-2-yl)-acetate (3H)

A mixture of (±)-*threo* methyl phenyl(piperidin-2-yl)acetate (89 mg, 0.38 mmol) and 4-chloro-methylpyridine (66 mg, 0.4 mmol) in acetone (20 mL) was alkylated by a method virtually identical to that used to synthesize **3F**. Recrystallization of the dihydrochloride salt (EtOAc–hexane) provided 78 mg (82%) of **3G** as a brown solid: mp 140–141 °C; ^{1}H NMR ($CDCl_3$): d 1.6–1.1 (m, 6H), 2.58–2.53 (m, 1H), 3.03–2.95 (m, 1H), 3.66–3.49 (m, 1H), 3.69 (s, 3H, OCH_3), 3.96–3.91 (d, 1H, $J = 13.4$), 3.79–3.75 (d, 1H, $J = 13.2$), 4.18–4.14 (d, 1H, $J = 10.4$), 7.3–7.2 (m, 9H, aromatic-H), 7.4 (d, 2H, pyridyl-H), 8.5 (d, 2H, pyridyl-H) ppm; Ms-FB+ m/z 325.20 calcd. for $C_{20}H_{25}N_2O_2$ (MH+). Anal. calcd. for $C_{20}H_{24}N_2O_2$: C, 74.08; H, 7.47; N, 8.63. Found: C, 74.08; H, 7.46; 8.62.

(±)-*threo*-N-Methylmethyl Phenyl(piperidin-2-yl)acetate (4)

A solution of 230 mg (0.99 mmol) of (±)-*threo* methyl phenyl(piperidin-2-yl) acetate in 20 mL of methanol was treated with 0.095 mL (1.28 mmol) 37% HCHO (formaldehyde) solution and allowed to stand at room temperature for 20 min. Methanol (5 mL), acetic acid (0.03 mL), and 5% Pd/C (45 mg) were then added. The resulting mixture was treated with hydrogen gas at 35 psi for 1.5 h at room temperature. The mixture was filtered, and the filtrate and the washings were evaporated in vacuo. The residue was mixed with 5 mL of water, made basic with 15% NaOH solution, and extracted with EtOAc (3×100 mL). The extracts were combined,

washed with water, dried with magnesium sulfate, and evaporated in vacuo. The residue was chromatographed on 5 g of silica gel using 5% MeOH in chloroform to give a yellow residue. Addition of 1 M HCl in ether to a methanol solution of the residue, evaporation of solvents to dryness in vacuo, and recrystallization (EtOAc-hexane) provided 190 mg (80%) of **4** as a yellow viscous liquid; ^{1}H NMR ($CDCl_3$): δ 1.6–1.1 (m, 6H), 2.40 (s, 3H, CH_3), 2.98–2.90 (m, 1H), 2.59–2.42 (m, 1H), 3.1–3.08 (m, 1H), 3.62 (s, 3H, OCH_3), 3.88–3.73 (d, 1H), 7.4–7.2 (m, 5H, aromatic) ppm; MS-CI m/z 248.160 calcd. for $C_{15}H_{22}NO_2$ (MH+) 248.165. Anal. calcd. for $C_{15}H_{21}NO_2$: C, 72.87; H, 8.56; N, 5.67. Found: C, 72.85; H, 8.55; N, 5.68.

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