REGIO- AND STEREOSELECTIVE ADDITION OF NUCLEOPHILES TO 1-PHENOXYCARBONYL-2,3-DIHYDROPYRIDINIUM SALTS†

Daniel L. Comins*, Geewon Chung and Michael A. Foley

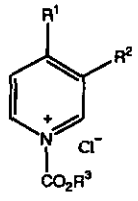
Department of Chemistry, North Carolina State University, Raleigh, North Carolina 27695-8204, U.S.A.

Abstract - Several 2-alkyl-1-phenoxycarbonyl-Δ^3-piperidines were prepared by the addition of alkylzinc iodides to dihydropyridinium salt (**9**). The treatment of 4-hydroxy-2-methyl-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (**12**) with allyltrimethylsilane in the presence of a variety of Lewis acids was studied and found to give *cis*- and *trans*-2-6-dialkyl-Δ^3-piperidines (**14**) and (**15**) in moderate to good yield. Among the Lewis acids studied, stannyl chloride gave the best yield with good stereoselectivity (84:16) favoring the *cis*-isomer (**14**). The analogous reaction of the 4-methoxy derivative (**13**) with organozinc reagents was examined and found to give the *cis*-isomers (**17**) as the major products. Using this methodology, the *cis*-piperidine alkaloid, (±)-dihydropinidine, was prepared in six steps from 4-methoxypyridine.

The reaction of 1-acylpyridinium salts (**1**) with nucleophiles is a valuable method for the preparation of substituted dihydropyridines,[1] dihydropyridones,[2] and various pyridines.[3] We have studied this reaction extensively in our laboratories, using various pyridines as starting materials and organometallics as nucleophiles.[1-4] The regioselectivity of the addition is dependent on the structure of the starting pyridine, the organometallic, the acyl

†*Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.*

halide and the reaction conditions. In the absence of a substituent at the 4-position of the 1-acylpyridinium salt, the reaction can give a mixture of 1,2- and 1,4-dihydropyridines. Many aryl,[3a] vinyl,[5] and alkynyl[5,6] Grignard reagents give mainly C-2 addition, but reaction with most alkyl Grignard[1] or organozinc[7] reagents results in poor C-2 vs C-4 regioselectivity. Examination of the literature indicated that a higher degree of C-2 addition might occur with aliphatic organometallics if a 1-acyl-2,3-dihydropyridinium salt (**2**) is used as the electrophile. To this end a study was initiated on the preparation and reactivity of *N*-acyliminium salts (**2**), and we now report the full details of our work in this area.[8]



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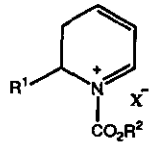

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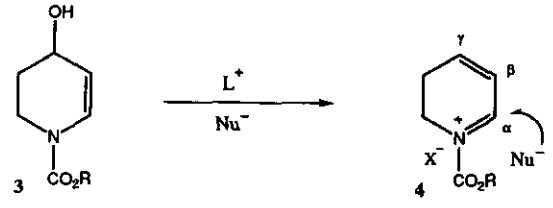
Kozikowski[9] and we[10] have reported that γ-hydroxyenecarbamates, i.e. **3**, can be converted to 1-acyl-2,3-dihydropyridinium salts (**4**) in situ on treatment with Lewis acids. Attack by nucleophiles, i.e. allyltrimethylsilane, silyl enol ethers, and hydride reagents, gives mainly addition at the α-site of the conjugated iminium salt. We wanted to look at this type of reaction using organozinc reagents as nucleophiles. Since the γ-hydroxy group would react with the organometallic, the analogous γ-methoxy compound (**8**) was prepared with the intent to use the methoxy group as a trigger to form the conjugated iminium ion (**9**) *in situ*. Using a modification of Kozikowski's procedure,[9] phenyl chloroformate was added to 4-methoxypyridine (**5**) and potassium triisopropoxyborohydride (KTPBH) in 2-propanol to give a 53% yield of dihydropyridone (**6**) on acidic workup. A similar reaction using $NaBH_4$ as the reducing agent gave **6** in 34% yield. Reduction of **6** with $NaBH_4/CeCl_3$ gave alcohol (**7**) in high yield.



3 **4**

Treatment of **7** with pyridinium *p*-toluenesulfonate (PPTS) in methanol provided the methoxy derivative (**8**) in 79% yield. The *N*-acyliminium ion (**9**) was generated in benzene in the presence of an organozinc reagent[11] by the addition of BF_3•OEt_2 at room temperature. The organozinc reagents added to the α-position of **9** to give the tetrahydropyridines (**10**) in good to excellent yield (Table I). A short reaction time (10 min) is essential, as decomposition of the products occurs on prolonged exposure to the BF_3•OEt_2 present in the reaction mixture.

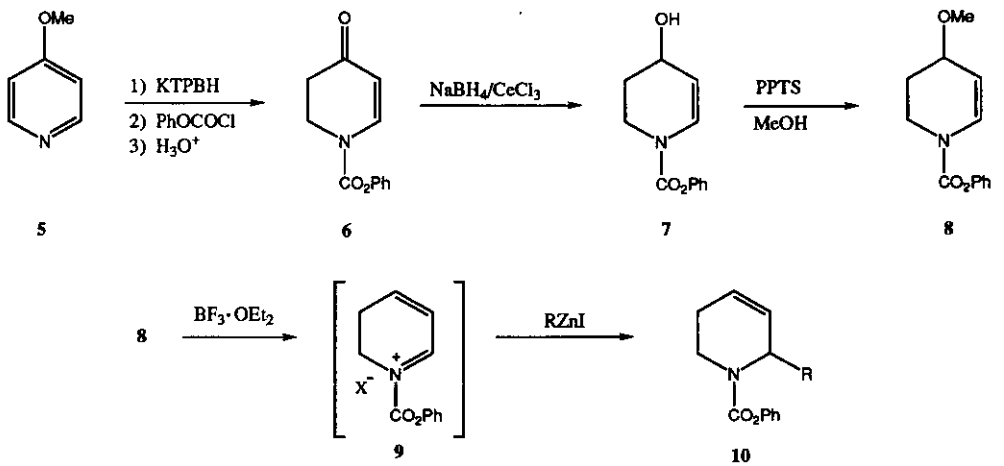


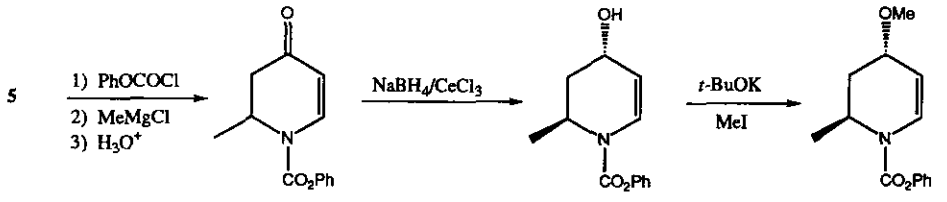
Table I. Synthesis of 2-Alkyl-Δ^3-piperidines (**10**) from **8**.

Entry	RZnI[a]	Product[b] 10a-f R	Yield[c]
a	MeZnI	Me	93
b	*n*-BuZnI	*n*-Bu	71
c	$Cl(CH_2)_4ZnI$	$(CH_2)_4Cl$	77
d	$EtO_2C(CH_2)_2ZnI$	$(CH_2)_2CO_2Et$	97
e	$EtO_2C(CH_2)_3ZnI$	$(CH_2)_3CO_2Et$	82
f	$EEO(CH_2)_3ZnI$[d]	$(CH_2)_3OH$	64

[a]Reactions were performed on a 0.5-3.0 mmol scale. [b]All products gave the expected ir and nmr spectra and elemental analysis. [c]Yields are of purified products obtained from radial plc. [d]EE = 1-ethoxyethyl.

To determine if a modification of this methodology could be used to prepare 2,6-dialkyl-Δ^3-piperidines in a stereoselective manner, the Lewis acid mediated addition of nucleophiles to γ-hydroxy- and γ-methoxy-tetrahydropyridines (**12**) and (**13**) was investigated. The starting materials (**12** and **13**) were prepared in two and three steps from 4-methoxypyridine (**5**). The addition of methylmagnesium chloride to 4-methoxy-1-phenoxycarbonylpyridinium chloride gave the dihydropyridone (**11**) in 91% yield.[2a] Reduction of **11** with $NaBH_4/CeCl_3$ provided alcohol (**12**) in 97% yield, as a 92:8 mixture of *trans*- and *cis*-isomers. Treatment of **12** with potassium *tert*-butoxide and methyl iodide in THF gave the methoxy derivative (**13**) in 87% yield.

The reactions of alcohol (**12**) were investigated first. On treatment of **12** with allyltrimethylsilane in the presence of a variety of Lewis acids, the 2,6-disubstituted tetrahydropyridines (**14**) and (**15**) were formed in good yield (Table II). No 4-substituted products were detected, a result in accord with the known kinetic preference for addition at the α-site of a conjugated iminium ion.[9,10,12] Among the Lewis acids used, stannyl chloride gave the best yield with good stereoselectivity (84:16) favoring the *cis*-isomer.



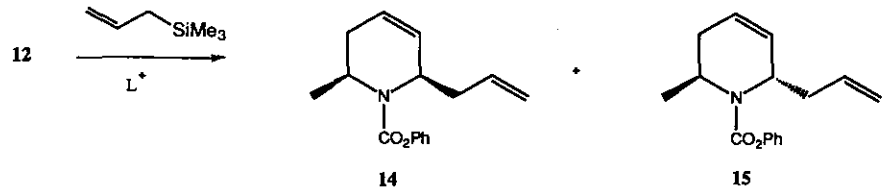


Table II. Synthesis of 2,6-Dialkyl-Δ^3-piperidines (**14**) and (**15**) from **12** and Allyltrimethylsilane.

Entry[a]	Solvent	Lewis Acid (equiv)	Ratio[b] **14**:**15**	Yield[c],% **14**	Recovered[d] **12**, %
a	CH_2Cl_2	$SnCl_4$ (1.2)	84:16	79	3
b	CH_2Cl_2	$SnCl_4$ (1.0)	83:17	52	11
c	CH_3CN	$BF_3{\cdot}Et_2O$ (1.1)	88:12	40	0
d	CH_2Cl_2	$TiCl_4$ (1.3)	83:17	41	9
e	CH_2Cl_2	$TiCl_4$ (1.0)	86:14	28	17
f	CH_2Cl_2	$AlCl_3$ (2.0)	82:18	54	10

[a]Reactions were performed on a 2-3 mmol scale. [b]The ratio of **14** to **15** was determined by gc analysis. [c]Yields are of purified **14** obtained from radial plc. [d]Yields of recovered **12** isolated by radial plc.

The preferential formation of the *cis*-isomer (**14**) can be explained by stereoelectronically preferred[13] axial attack of the nucleophile on the intermediate *N*-acyliminium ion (**16**) (Figure 1). Due to a strong $A^{(1,3)}$ strain between the methyl substituent at C-2 and the *N*-acyl group, the methyl group at C-2 will occupy the axial position in the flat-chair conformation (**16**).[14] It is assumed that the minor *trans*-diastereomer (**15**) arises *via* a boat transition state.

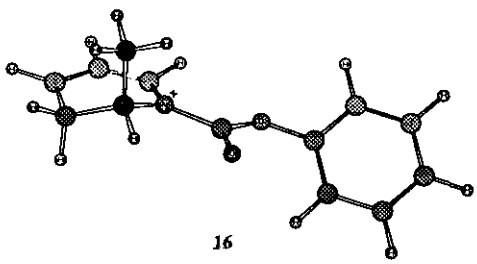


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Figure 1. Computer generated structure (MMX).

The Lewis acid mediated reaction of the 4-methoxytetrahydropyridine (**13**) with organozinc reagents was examined. The reactive *N*-acyliminium ion was generated in situ by adding $BF_3{\cdot}OEt_2$ to **13** in the presence of an organozinc reagent. The organozinc reagents were conveniently made by the addition of a THF solution of the Grignard reagent to anhydrous $ZnBr_2$ in toluene at room temperature.[16] The results of this study are summarized in Table III. The major diastereomers (**17a-c**) were isolated by chromatography, and their relative stereochemistry was assigned as cis based on ^1H nmr analysis.

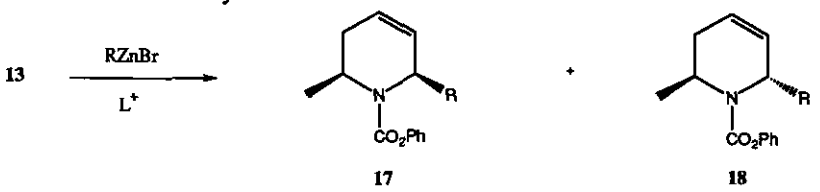


Table III. Synthesis of 2,6-Dialkyl-Δ^3-piperidines (**17**) and (**18**) from **13**.

Entry[a]	Solvent	RZnBr	Ratio[b] **17**:**18**	Yield[c], % **17** and **18**
a	toluene/THF	*n*-PrZnBr	80:20	91
b	toluene/THF	PhZnBr	79:21	75
c	toluene/THF	*i*-PrZnBr	58:42	64

[a]Reactions were performed on a 2-3 mmol scale. [b]The ratio of **17** and **18** was determined by gc analysis. [c]Yields are of a mixture of **17** and **18** isolated from radial plc.

To confirm the stereochemical assignments, and to expand the scope of this methodology to the preparation of 2,6-dialkylpiperidines, the catalytic hydrogenation of tetrahydropyridines (**14**) and (**15**) was investigated using various catalysts (Table IV). The *cis*-tetrahydropyridine (**14**) was reduced cleanly with a palladium or platinum catalyst to give the *cis*-piperidine (**19**) (entries a and b). The *trans*-tetrahydropyridine (**15**), however, showed considerable

isomerization during catalytic reduction with 5% Pd/C (Entry c). Presumably, the palladium catalyst effects some double bond migration[17] to give enecarbamate (**21**), which is reduced stereoselectively to the *cis*-piperidine (**19**). This isomerization can be effectively controlled by using platinum or rhodium on carbon as the hydrogenation catalyst (Entries d and e). In this manner the reduction of **15** provides the *trans*-product (**20**) in high yield.

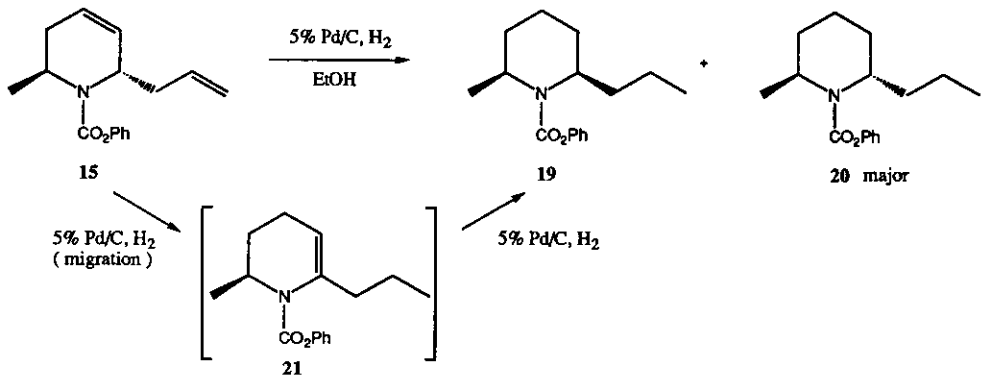
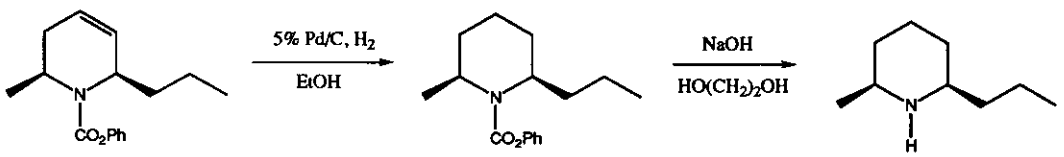


Table IV. Catalytic Hydrogenation of Tetrahydropyridines (**14**) and (**15**).

Entry[a]	Compound	Catalyst[b]	Ratio[c] **19**:**20**	Yield[d], % **19** and **20**
a	14	5% Pd/C	99:1	99
b	14	5% Pt/C	99:1	98
c	15	5% Pd/C	25:75	98
d	15	5% Pt/C	5:95	98
e	15	5% Rh/C	6:94	97

[a]Reactions were performed on a 1 mmol scale in absolute ethanol. [b]The hydrogenation was carried out at atmospheric pressure and at room temperature. [c]The ratio of **19** and **20** was determined by gc analysis. [d]Yields are of a mixture of **19** and **20** isolated from radial plc.

The above methodology was used in a synthesis of the *cis*-piperidine alkaloid, (±)-dihydropinidine.[18] The tetrahydropyridine **(17a)** was hydrogenated using 5% Pd/C as catalyst to give piperidine **(19)**. Hydrolysis of **19** gave (±)-dihydropinidine **(22)** in 60% yield. This strategy should be amenable to the synthesis of numerous *cis*-2,6-dialkyl-Δ^3-piperidines and *cis*-2,6-dialkylpiperidine alkaloids.[19]



17a **19** **22**

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian XL-300 or a General Electric GN-300 spectrometer. Infrared spectra were recorded on a Perkin-Elmer model 7500 spectrophotometer. Radial preparative layer chromatography (radial plc) was carried out on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1-, 2-, or 4-mm thickness of Kieselgel 60 PF_{254} containing gypsum.

4-Oxo-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (6). To a 50-ml, round-bottomed flask equipped with a stir bar and purged with nitrogen was added 4-methoxypyridine (1.0 ml, 10 mmol) in dry 2-propanol (20 ml). This solution was cooled to -23 °C and potassium triisopropoxyborohydride (20 ml, 20 mmol, 1 M solution in THF) was added. To this stirred solution, phenyl chloroformate (1.14 ml, 11 mmol) in dry ether (3 ml) was added dropwise over a 10 min period. The reaction mixture became heterogeneous and turned a pale yellow color. Stirring was continued for 1 h and the reaction mixture was poured into 10% HCl (30 ml). Stirring was continued for 10 min and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 ml). The combined organic extracts were washed with brine (25 ml) and dried over $MgSO_4$. The solution was filtered and concentrated

to give the crude product. Purification by radial plc (SiO_2, 30% EtOAc/hexanes) and recrystallization (CH_2Cl_2/hexanes) gave 1.15 g (53%) of **6** as white needles: mp 103 - 104 °C; ^1H nmr ($CDCl_3$) δ 7.9 (d, 1 H, J = 8 Hz), 7.5 - 7.1 (m, 5 H), 5.6 - 5.4 (br s, 1 H), 4.3 - 4.1 (br s, 2 H), 2.7 (t, 2 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 193, 151, 143, 130, 126, 125, 121, 108, 32, 36; ir ($CDCl_3$) 3083, 2902, 1742, 1669, 1605, 1495, 1464, 1422, 1374, 1354, 1331, 1305, 1251, 1216, 1201, 1183, 1165, 1117, 1083, 1046, 1025, 985, 970, 909, 810, 730 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.09; H, 5.34; N, 6.23.

4-Hydroxy-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (7). To a 25-ml, round-bottomed flask equipped with a stir bar and purged with nitrogen was added **6** (605 mg, 2.78 mmol) in MeOH (12 ml). The solution was cooled to 0 °C and $CeCl_3 \cdot 7H_2O$ (1.04 g, 2.78 mmol) was added. After stirring for 10 min, $NaBH_4$ (151 mg, 4 mmol) was added slowly in 25-mg portions. Stirring at 0 °C was continued for 0.5 h. The mixture was allowed to warm up to room temperature and then poured into water (25 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were washed with brine (25 ml) and dried over K_2CO_3. The solution was filtered and concentrated to afford 467 mg (76%) of crude product as a clear oil, which was used directly in the next step: ^1H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 6 H), 5.3 - 5.1 (m, 1 H), 4.2 - 4.0 (m, 1 H), 3.7 - 3.5 (m, 1 H), 2.1 - 1.9 (br s, 2 H); ir ($CDCl_3$) 3333, 2254, 1722, 1646, 1495, 1417, 1377, 1304, 1237, 1204, 1165, 1051, 996 cm^{-1}.

4-Methoxy-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (8). To a 50-ml, round-bottomed flask equipped with a stir bar and purged with nitrogen was added crude **7** (863 mg, 3.94 mmol) in MeOH (20 ml). To this solution was added pyridinium p-toluenesulfonate (530 mg, 2.1 mmol). After stirring for 1 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 ml). Stirring was continued for 10 min, then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were washed with brine (25 ml) and dried over K_2CO_3. The solution was filtered and concentrated to

afford the crude product. Purification by radial plc (SiO_2, 30-50% EtOAc/hexanes) gave 727 mg (79%) of **8** as a clear oil: ^{1}H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 6 H), 5.3 - 5.1 (m, 1 H), 4.1 - 3.9 (m, 1 H), 3.8 (m, 1 H), 3.7 - 3.4 (m, 1 H), 3.38 (s, 3 H), 2.1 (m, 1 H), 1.8 (m, 1 H); ^{13}C nmr ($CDCl_3$) δ 158, 151, 130, 128, 126, 122, 118, 108, 48, 38, 24; ir ($CDCl_3$) 3403, 3044, 2933, 2888, 2821, 1726, 1651, 1594, 1496, 1472, 1415, 1365, 1327, 1304, 1236, 1205, 1165, 1141, 1103, 1074, 1025, 1000, 915, 863, 752 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.13; H, 6.16; N, 5.96.

2-Methyl-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10a). General Procedure for the Preparation of Tetrahydropyridines 10. To a 10-ml, round-bottomed flask equipped with a stir bar and purged with nitrogen was added Zn(Cu) couple (0.34 g, 5.14 mmol) and benzene (4 ml). To this suspension was added methyl iodide (0.16 ml, 2.57 mmol) and DMA (0.25 ml). The suspension was refluxed for 3 h. To a separate 25-ml, round-bottomed flask equipped with stir bar and purged with nitrogen was added **8** (0.2 g, 0.86 mmol) in benzene (5 ml). The preformed methylzinc iodide was transferred *via* cannula to the flask containing **8**. Boron trifluoride etherate (0.16 ml, 1.29 mmol) was added *via* syringe. The suspension was stirred for 10 min and then poured into 10% HCl (25 ml). After stirring for 10 min, the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 ml). The combined organic extracts were washed with brine (25 ml) and dried over $MgSO_4$. The solution was filtered and concentrated to afford the crude product as a light yellow oil. Purification by radial plc (SiO_2, 20% EtOAc/hexanes) gave 174 mg (93%) of **10a** as a clear oil: ^{1}H Nmr ($CDCl_3$) δ 7.5 - 7.1 (m, 5 H), 5.9 - 5.8 (br s, 1 H), 5.8 - 5.7 (br s, 1 H), 4.7 - 4.5 (m, 1 H), 4.3 (m, 1 H), 3.2 - 2.9 (m, 1 H), 2.4 - 2.2 (m, 1 H), 2.1 - 2.0 (m, 1 H), 1.4 - 1.2 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 157, 151, 129, 125, 122, 120, 49, 38, 37, 25, 20; ir ($CDCl_3$) 3368, 3038, 2976, 2932, 2360, 2252, 1712, 1657, 1595, 1497, 1456, 1420, 1363, 1331, 1298, 1282, 1264, 1232, 1207, 1164, 1150, 1110, 1087, 1067, 1056, 1025, 1008, 909, 805, 734 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.78; H, 6.87; N, 6.37.

Spectral data. 2-*n*-Butyl-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10b). ^{1}H Nmr ($CDCl_3$) δ 7.4 - 7.1 (m, 5 H), 5.9 -5.8 (br s, 1 H), 5.8 - 5.7 (br s, 1 H), 4.6 - 4.5 (br s, 1 H), 4.3 - 4.2 (m, 1 H), 3.2 -2.9 (m, 1 H), 2.4 - 2.2 (m, 1 H), 2.0 (m, 1 H), 1.8 (br s, 2 H), 1.4 (m, 4 H), 1.0 -0.9 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 154, 152, 129, 128, 125, 121, 53, 38, 37, 34, 28, 26, 23, 14; ir ($CDCl_3$) 3038, 2959, 2933, 2861, 2360, 2253, 1712, 1654, 1595, 1496, 1458, 1424, 1364, 1338, 1276, 1207, 1164, 1150, 1073, 1050, 1025, 998, 909, 735 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.19; H, 8.14; N, 5.40.

2-(4-Chlorobutyl)-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10c). ^{1}H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 5 H), 6.0 - 5.8 (br s, 1 H), 5.8 - 5.7 (br s, 1 H), 4.7 - 4.5 (d, 1 H, J = 16 Hz), 4.3 - 4.2 (dd, 1 H, J = 14 and 4 Hz), 3.6 (t, 2 H, J = 4 Hz), 3.2 - 2.9 (m, 1 H), 2.4 - 2.2 (m, 1 H), 2.1 (m, 1 H), 1.8 (m, 2 H), 1.7 - 1.4 (m, 4 H); ^{13}C nmr ($CDCl_3$) δ 154, 151, 129, 128, 125, 121, 52, 45, 38, 33, 32, 25, 23; ir ($CDCl_3$) 3037, 2939, 2252, 1711, 1654, 1595, 1496, 1461, 1423, 1364, 1338, 1254, 1207, 1164, 1152, 1070, 999, 909, 732 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClNO_2$: C, 65.41; H, 6.86; N, 4.77. Found: C, 65.40; H, 6.84; N, 4.73.

2-(2-Ethoxycarbonylethyl)-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10d). ^{1}H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 5 H), 6.0 - 5.8 (br s, 1 H), 5.8 - 5.6 (br s, 1 H), 4.6 (d, 1 H, J = 16 Hz), 4.3 - 4.2 (m, 1 H), 4.2 - 4.0 (m, 2 H), 3.2 -2.9 (m, 1 H), 2.6 - 2.2 (m, 3 H), 2.1 - 1.9 (m, 3 H), 1.3 - 1.1 (m, 3 H); ^{13}C nmr ($CDCl_3$) δ 173, 154, 151, 130, 128, 127, 125, 121, 61, 52, 39, 37, 31, 29, 14; ir ($CDCl_3$) 2935, 2254, 1714, 1595, 1496, 1424, 1374, 1338, 1241, 1207, 1164, 1057, 1026 cm^{-1}. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.30; H, 7.01; N, 4.75.

2-(3-Ethoxycarbonylpropyl)-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10e). ^{1}H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 5 H), 6.0 - 5.8 (br s, 1 H), 5.8 - 5.6 (br s, 1 H), 4.7 - 4.5 (m, 1 H), 4.4 - 4.2 (m, 1 H), 4.2 - 4.0 (m, 2 H), 3.2 - 2.9 (m, 1 H), 2.4 - 2.2 (m, 3 H), 2.1 - 2.0 (m, 1 H), 1.9 - 1.6 (m, 4 H), 1.3 (t, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$)

δ 173, 154, 151, 130, 129, 128, 125, 122, 61, 52, 38, 37, 34, 25, 21, 14; ir ($CDCl_3$) 3083, 2938, 2254, 1713, 1595, 1496, 1483, 1423, 1370, 1339, 1276, 1206, 1163, 1059, 1026, 909 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.18; H, 7.08; N, 4.44.

2-(3-Hydroxypropyl)-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridine (10f). ^1H Nmr ($CDCl_3$) δ 7.4 - 7.0 (m, 5 H), 5.9 - 5.8 (br s, 1 H), 5.8 - 5.6 (br s, 1 H), 4.6 - 4.4 (br s, 1 H), 4.3 - 4.1 (m, 1 H), 3.8 (br s, 2 H), 3.2 - 2.9 (m, 1 H), 2.4 - 2.2 (m, 1 H), 2.2 - 1.9 (m, 2 H), 1.8 - 1.6 (m, 4 H); ir ($CDCl_3$) 3625, 3448, 3039, 2938, 2253, 1708, 1654, 1595, 1496, 1463, 1424, 1365, 1339, 1259, 1207, 1164, 1149, 1072, 908, 731 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.71; H, 7.20; N, 5.42.

2-Methyl-4-oxo-1-phenoxycarbonyl-1-2,3,4-tetrahydropyridine (11).[2a] To a stirred solution (-23 °C) of 4-methoxypyridine (1.0 ml, 10 mmol) in THF (50 ml) was added phenyl chloroformate (1.25 ml, 10 mmol). After 20 min, MeMgCl (4.0 ml, 12 mmol, 3 M solution in THF) was added. The reaction mixture was stirred for 30 min and then warmed to room temperature. A solution of 10% HCl (20 ml) was added and the mixture was stirred for 20 min. The aqueous layer was extracted with three 20-ml portions of ether, and the combined organic extracts were dried over anhydrous $MgSO_4$. Filtration and concentration gave the crude product which was purified by radial plc (silica gel, 30% EtOAc/hexanes) to give 2.104 g (91%) of **11** as a light yellow solid: mp 89-91 °C. ^1H Nmr ($CDCl_3$) δ 7.9 (m, 1 H), 7.1 - 7.4 (m, 5 H), 5.4 (d, 1 H, J = 6 Hz), 4.9 (t, 1 H, J = 6 Hz), 3.0 (dd, 1 H, J = 15 and 6 Hz), 2.4 (d, 1 H, J = 18 Hz), 1.4 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 193.7, 152.0, 141.5, 130.3, 130.2, 128.0, 122.3, 109.2, 50.8, 42.0, 17.5; ir (nujol) 3070, 2975, 2930, 2820, 1725, 1645, 1590, 1492, 1452, 1415, 1350, 1270, 1203, 1165, 1105, 1070, 1045, 1023, 946, 905, 812, 745, 718, 688 cm^{-1}.

4-Hydroxy-2-methyl-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (12). To a stirred solution (0 °C) of **11** (1.332 g, 5.76 mmol) in MeOH (50 ml) was added $CeCl_3 \cdot 7\ H_2O$ (2.15 g, 5.76 mmol). After stirring 30 min at 0

°C, $NaBH_4$ (0.324 g, 8.64 mmol) was added slowly. The reaction mixture was stirred for 30 min, and the solution was allowed to warm to room temperature. Water (30 ml) was added and the solution was stirred for 30 min. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic extracts were washed with brine (20 ml) and dried over K_2CO_3. Filtration and concentration gave the crude product. Purification by radial plc (silica gel, 30% EtOAc/hexanes) gave 1.303 g (97%) of **12** as a white solid: mp 88-90 °C. ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 6.9 (d, 1 H, J = 9 Hz), 5.0 (d, 1 H, J = 6 Hz), 4.6 (m, 2 H), 2.2 (m, 1 H), 1.9 (dt, 1 H, J = 12 and 6 Hz), 1.6 (d, 1 H, J = 6 Hz), 1.3 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 152, 131, 127, 125, 123, 112, 62, 49, 37, 18; ir (nujol) 3485, 2930, 2866, 1684, 1643, 1459, 1376, 1259, 1205, 1080, 750, 723 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.86; H, 6.51; N, 6.04.

2-Allyl-6-methyl-1-phenoxycarbonyl-1,2,5,6-tetrahydropyridines: 2,6-*cis*- (14) and 2,6-*trans*- (15). To a stirred solution (-78 °C) of **12** (0.604 g, 2.6 mmol) in CH_2Cl_2 (25 ml) was added allyltrimethylsilane (0.83 ml, 5.2 mmol). After 30 min, stannyl chloride (2.6 ml, 2.6 mmol, 1 M solution in hexane) was added. After stirring 1 h at -78 °C, the solution was quenched with saturated aqueous $NaHCO_3$ (30 ml). The aqueous phase was extracted with three 20-ml portions of CH_2Cl_2. The combined organic phases were washed with brine (20 ml). After drying over K_2CO_3, the solvent was removed *in vacuo* to give the crude product, which was purified by radial plc (silica gel, 5% EtOAc/hexanes) to yield 0.542 g (81%) of **14** and 0.067 g (10%) of **15** as clear oils.

Spectral data. 14: ^{1}H Nmr ($CDCl_3$) δ 7.1 - 7.4 (m, 5 H), 5.8 - 5.9 (m, 3 H), 5.1 - 5.2 (m, 2 H), 4.75 (t, 1 H, J = 7 Hz), 4.5 (br s, 1 H), 2.7 (m, 1 H), 2.4 - 2.5 (m, 2 H), 2.0 (dd, 1 H, J = 18 and 6 Hz), 1.3 (d, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 152, 137, 135, 129, 127, 126, 122, 118, 54, 53, 52, 31, 22; ir (nujol) 3037, 3040, 2978, 2930, 2840, 1715, 1648, 1591, 1408, 1340, 1309, 1240, 1206, 1162, 1150, 1105, 1095, 1030, 998, 960, 912, 880, 862, 830, 784, 750, 710, 686 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.45; N, 5.42.

15: ^{1}H Nmr ($CDCl_3$) δ 7.1 - 7.4 (m, 5 H), 5.8 - 5.9 (m, 3 H), 5.1 - 5.2 (m, 2 H), 4.3 - 4.4 (br s, 2 H), 2.7 (t, 2 H, J = 7 Hz), 2.5 (d, 1 H, J = 18 Hz), 2.1 (dd, 1 H, J = 18 and 6 Hz), 1.3 (d, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 157, 152, 137, 135, 130, 129, 126, 122, 118, 117, 53, 52, 48, 31; ir (nujol) 3072, 3038, 2976, 2928, 1708, 1595, 1489, 1438, 1392, 1380, 1350, 1305, 1287, 1237, 1204, 1160, 1140, 1105, 1053, 1039, 994, 910, 826, 741, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.62; H, 7.48; N, 5.44.

4-Methoxy-2-methyl-1-phenoxycarbonyl-1,2,3,4-tetrahydropyridine (13). To a stirred solution (-78 °C) of **12** (2.628 g, 11.3 mmol) in THF (50 ml) was added methyl iodide (4.22 ml, 67.8 mmol). After 10 min, a potassium *tert*-butoxide solution (1.53 g, 13.6 mmol) in THF (10 ml) was transferred *via* a double-tipped needle into the stirred reaction mixture. The mixture was stirred for 20 min at -78 °C, warmed to room temperature for 30 min, and quenched with saturated aqueous $NaHCO_3$ (30 ml). The aqueous layer was separated from the THF solution and extracted with ether (3 x 20 ml). The organic layers were combined, dried over K_2CO_3, and concentrated to give the crude product. Purification by radial plc (silica gel, 20% EtOAc/hexanes) gave 2.432 g (87%) of **13** as a light yellow solid: mp 64-66 °C. ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 6.9 (d, 1 H, J = 9 Hz), 5.1 (br s, 1 H), 4.6 (br s, 1 H), 4.1 (m, 1 H), 3.4 (s, 3 H), 2.2 (d, 1 H, J = 12 Hz), 1.8 (dt, 1 H, J = 9 and 6 Hz), 1.3 (br s, 3 H); ^{13}C nmr ($CDCl_3$) δ 152, 130, 126, 125, 122, 108, 70, 56, 48, 33, 19, 18; ir (nujol) 2950, 2920, 2852, 1730, 1708, 1659, 1648, 1590, 1483, 1460, 1450, 1414, 1375, 1338, 1266, 1203, 1103, 1069, 815, 770, 741, 727, 690 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.11; H, 6.94; N, 5.70.

6-Methyl-1-phenoxycarbonyl-2-propyl-1,2,5,6-tetrahydropyridines (17a and 18a): General procedure for the preparation of 2,6-*cis*- (17) and 2,6-*trans*-tetrahydropyridines (18). To a 25-ml, round-bottomed flask equipped with a stir bar and purged with nitrogen was added $ZnBr_2$ (2.975 g, 12 mmol, dried overnight at 140 °C *in vacuo*) in toluene (15 ml). After stirring 10 min, *n*-PrMgCl (6 ml, 12 mmol, 2 M solution in THF) was added dropwise, and stirring was continued for 1 h. To a separate 100-ml, round-bottomed flask equipped with a stir bar and purged

with nitrogen was added **13** (0.75 g, 3 mmol) in toluene (20 ml). The preformed alkylzinc bromide was transferred *via* a double-tipped needle to the solution containing **13** at room temperature, and the mixture was cooled to 0 °C. To this mixture was added BF_3•Et_2O (0.55 ml, 4.5 mmol), then the solution was warmed to room temperature and stirred for 10 min. The suspension was poured into 10% HCl (30 ml) and, after 10 min, the organic layer was separated. The aqueous layer was extracted with ether (3 x 30 ml). The combined organic extracts were washed with brine (25 ml) and dried over K_2CO_3. Filtration and concentration afforded the crude product. The crude product was purified by radial plc (silica gel, 20% EtOAc/hexanes) to give 0.708 g (91%) of the 2,6-disubstituted products (**17a** and **18a**). Further purification by radial plc (silica gel, 1-10% EtOAc/hexanes) provided analytical samples.

Spectral data. 17a: ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 5.8 (m, 2 H), 4.75 (t, 1 H, J = 7 Hz), 4.4 (br s, 1 H), 2.5 (d, 1 H, J = 18 Hz), 1.95 (dd, 1 H, J = 18 and 6 Hz), 1.8 (m, 1 H), 1.5 (m, 2 H), 1.3 (d, 3 H, J = 7 Hz), 1.0 (t, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 153, 131, 127, 126, 123, 53, 52, 45, 40, 39, 30, 22, 20, 15; ir (neat) 3035, 2956, 2924, 2864, 1710, 1592, 1491, 1450, 1408, 1345, 1333, 1309, 1239, 1205, 1150, 1123, 1094, 1038, 996, 935, 903, 880, 829, 782, 750, 705, 687 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.30; H, 8.36; N, 5.25.

18a: ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 5.9 (m, 2 H), 4.3 (br s, 2 H), 2.5 (d, 1 H, J = 18 Hz), 2.1 (d, 1 H, J = 18 Hz), 1.8 (m, 2 H), 1.3 - 1.4 (m, 5 H), 0.95 (t, 3 H, J = 7 Hz); ^{13}C nmr ($CDCl_3$) δ 152, 131, 127, 124, 122, 53, 52, 48, 38, 32, 31, 21, 19, 15; ir (neat) 3040, 2954, 2925, 2866, 1710, 1593, 1490, 1450, 1394, 1380, 1344, 1308, 1289, 1239, 1202, 1160, 1140, 1106, 1040, 935, 900, 873, 820, 781, 736, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C. 74.19; H, 8.20; N, 5.38.

17b: ^{1}H Nmr ($CDCl_3$) δ 7.0 - 7.5 (m, 10 H), 6.0 (m, 2 H), 5.75 (s, 1 H), 4.8 (m, 1 H), 2.6 (d. 1 H, J = 18 Hz), 2.05 (dd, 1 H, J = 18 and 6 Hz), 1.2 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 155.8, 152.0, 143.1, 130.3, 129.0, 127.8, 127.0, 125.8, 123.3, 122.0, 55.6, 47.0, 31.5, 21.9; ir (neat) 3030, 2948, 2920, 2846, 1720, 1591, 1490, 1450, 1405, 1375, 1344, 1299, 1205, 1160, 1149, 1035, 884, 744, 696, 685 cm^{-1}; Hrms Calcd for 293.1416, found 293.1417.

18b: ^{1}H Nmr ($CDCl_3$) δ 7.1 - 7.5 (m, 10 H), 6.3 - 5.7 (m, 3 H), 4.9 (m, 1 H), 2.75 (dd, 1 H, J = 18 and 6 Hz), 2.2 (d, 1 H, J = 18 Hz), 1.1 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 156.1, 152.0, 129.9, 129.2, 127.7, 126.9, 126.0, 124.2, 122.5, 57.8, 55.2, 45.7, 30.9, 21.8; ir (neat) 3038, 2950, 2920, 2855, 1718, 1596, 1490, 1460, 1450, 1404, 1375, 1362, 1298, 1205, 1163, 1148, 1093, 1032, 880, 744, 692, 685 cm^{-1}; Hrms Calcd for 293.1416, found 293.1417.

17c: ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 5.95 (m, 1 H), 5.8 (m, 1 H), 4.3 (br s, 1 H), 4.2 (s, 1 H), 2.55 (br s, 1 H), 2.4 (m, 1 H), 2.05 (m, 1 H), 1.3 (d, 3 H, J = 6 Hz), 0.95 (d, 3 H, J = 6 Hz), 0.85 (d, 3 H, J = 6 Hz); ^{13}C nmr ($CDCl_3$) δ 155.7, 152.2, 129.9, 125.8, 122.5, 59.2, 48.7, 32.1, 31.2, 21.0, 20.9, 17.1; ir (neat) 3035, 2955, 2920, 2860, 1710, 1656, 1645, 1585, 1487, 1457, 1448, 1395, 1376, 1335, 1285, 1232, 1200, 1158, 1135, 1103, 1088, 1066, 1040, 916. 869, 810, 788, 734, 680, 616 cm^{-1}; Hrms Calcd for 259.1572, found 259.1572.

18c: ^{1}H Nmr ($CDCl_3$) δ 7.2 - 7.4 (m, 5 H), 5.95 (m, 1 H), 5.8 (m, 1 H), 4.8 (m, 1 H), 4.25 (m, 1 H), 2.5 (m, 1 H), 2.0 (m, 2 H), 1.3 (d, 3 H, J = 6 Hz), 1.1 - 0.8 (m, 6 H); ^{13}C nmr ($CDCl_3$) δ 155.3, 152.3, 129.9, 125.8, 122.4, 66.5, 58.7, 45.4, 34.7, 30.8, 21.4, 20.9, 16.0; ir (neat) 3033, 2958, 2920, 2860, 1704, 1589, 1488, 1461, 1447, 1410, 1380, 1336, 1320, 1293, 1232, 1200, 1151, 1123, 1090, 1064, 1030, 994, 967, 910, 871, 849, 829, 792, 780, 745, 735, 698, 682, 651 cm^{-1}; Hrms Calcd for 259.1572, found 259.1574.

General procedure for catalytic hydrogenation of tetrahydropyridines 14, 15, and 17a: To a stirred solution of the 2,6-disubstituted tetrahydropyridine (1.0 mmol) in EtOH (5 ml) was added 5% Pd/C (0.05 wt %). The reaction flask was flushed with H_2 and stirred overnight under a balloon pressure of H_2. The reaction mixture was filtered through silica gel and concentrated to give the crude product, which was purified by radial plc (silica gel, EtOAc/hexanes) to give the piperidines (**19** and **20**) in near quantitative yield.

Spectral data. 19: ^{1}H Nmr ($CDCl_3$) δ 7.2-7.4 (m, 5 H), 4.5 (m, 1 H), 4.3 (m, 1 H), 1.3 - 1.8 (m, 13 H), 0.95 (t, 3 H, J = 9 Hz); ^{13}C nmr ($CDCl_3$) δ 155.1, 152.4, 129.9, 125.7, 122.5, 51.7, 47.4, 38.0 31.0, 28.3, 21.3, 14.8, 14.7; ir (neat) 3070, 3048, 2955, 2933, 2868, 1707, 1590, 1490, 1461, 1451, 1405, 1374, 1360, 1342, 1310, 1270, 1240, 1209, 1155, 1124, 1098, 1067, 1052, 1025, 996, 972, 960, 920, 898, 881, 840, 821, 773, 750, 730, 700, 684 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.64; H, 8.92; N, 5.37.

20: ^{1}H Nmr ($CDCl_3$) δ 7.2-7.4 (m, 5 H), 4.4 (br s, 2 H), 1.3 - 1.9 (m, 13 H), 1.0 (t, 3 H, J = 9 Hz); ^{13}C nmr ($CDCl_3$) δ 155.2, 152.3, 129.9, 125.6, 122.5, 53.0, 48.6, 36.9, 27.9, 24.3, 21.5, 20.8, 14.7; ir (neat) 3070, 3045, 2960, 2930, 2868, 1710, 1593, 1492, 1462, 1450, 1396, 1362, 1351, 1313, 1263, 1208, 1158, 1122, 1098, 1072, 1040, 1028, 995, 902, 835, 752, 733, 687 cm^{-1}. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.37; H, 8.91; N, 5.28.

(±)-Dihydropinidine (22). To a solution of 310 mg (1.19 mmol) of carbamate (**19**) in 2 ml of ethylene glycol was added an aqueous solution of 50% NaOH (2 ml). The mixture was refluxed for 48 h, cooled to room temperature, and extracted with ether (6 x 5 ml). The combined organic extracts were dried over K_2CO_3, filtered and concentrated on a rotary evaporator (water bath at 0 °C) to give the crude product. Kugelrohr distillation (50-90 °C, 18 mmHg) provided 101 mg (60%) of **22** as a colorless oil, which exhibited spectral data identical to literature values[18]; (±)-dihydropinidine•HCl mp 211-213 °C (lit.,[20] mp 210-213 °C).

ACKNOWLEDGEMENT

We express appreciation to the National Institutes of Health (Grants GM 30255 and 34442) for financial support of this research.

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Received, 7th October, 1993