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Anthony J. Kiessling [a] & Cynthia K. McClure [a]
[a] Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716

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THE CONVERSION OF AMIDES TO ESTERS WITH MEERWEIN'S REAGENT. APPLICATION TO THE SYNTHESIS OF A CARFENTANIL PRECURSOR.

Anthony J. Kiessling[1a] and Cynthia K. McClure[1b*]

Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware, 19716

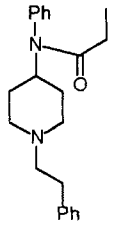
An efficient two step transformation of 1° and 2° amides to methyl and ethyl esters has been developed using trimethyl- and triethyloxonium tetrafluoroborates, and dilute acid. This methodology was applied to 1-benzyl-4-phenylamino-4-piperidinecarboxamide, a precursor in the synthesis of carfentanil, to produce the methyl ester in 60% yield and the ethyl ester in 80% yield.

Introduction

The 4-anilidopiperidine opiods are known to have powerful analgesic properties. Fentanyl, **1**, was the first to be tested and was found to be 50 - 100 times more powerful

*To whom correspondence should be addressed.

than morphine.[2] Of the possible 4 - alkyl analogs of fentanyl, carfentanil, **2**, has been observed to be the most powerful at 1000 times the strength of morphine[3], and (±)-3-methyl-carfentanil, **3**, was found to be the longest acting.[4d,f] These compounds have been used in conjunction with other forms of anesthesia during surgical procedures.



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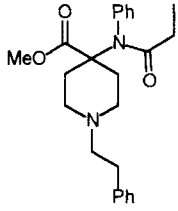

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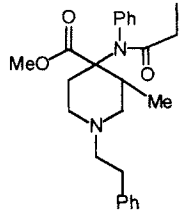
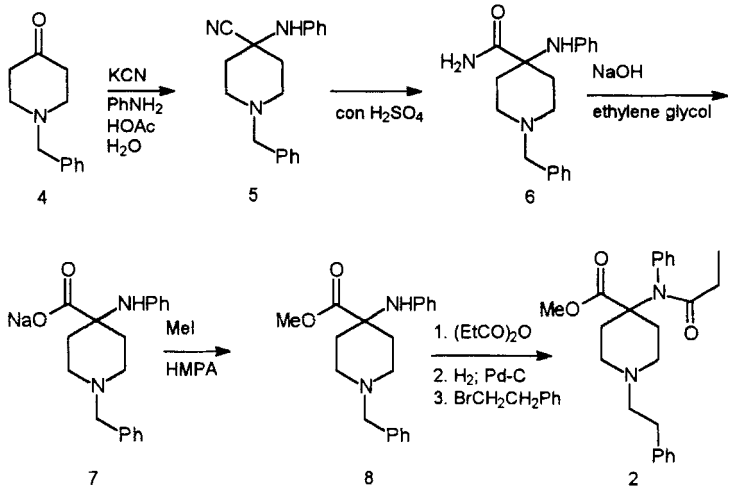


3

While the total syntheses of carfentanil and related compounds have been known for some time, the original synthesis suffered from several low yielding and tedious steps.[4] In particular, the conversion of amide **6** to ester **8** involved the carboxylate salt **7** as an intermediate (Scheme 1). This salt was difficult to handle, and subsequent methylation gave poor results. Our attention focused on applying other methodologies to this difficult transformation.

A method for the transformation of amide to ester which has received little attention involves the use of an imidate ester as an intermediate (see eq. 1). This procedure has been utilized to deprotect acylated amines[5], and to transform lactams to various amino acid esters.[6] However, synthesis of methyl esters using imidates as intermediates has been limited to conversion of nitriles to esters.[7] Imidate esters are easily produced from the amide by treatment with Meerwein's reagent[8], and from the nitrile by the Pinner synthesis (See eq. 2).

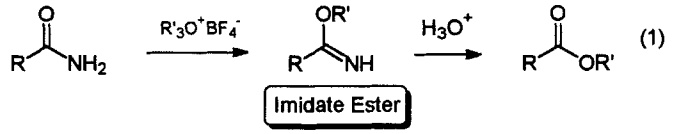
Scheme 1

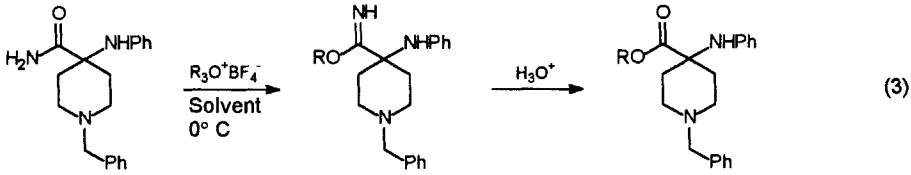


Discussion

At first, both methods (eq 1 & 2) appeared to have application to the synthesis of carfentanil. Nitrile **5** is easily produced from the piperidone **4**, aniline and KCN under acidic conditions, although in low yields.[4g,9] We found that the yield of the nitrile was greatly improved when the reaction was carried out in a sealed flask. However, upon treatment with Meerwein's reagent or any acid except concentrated H_2SO_4, nitrile **5** underwent a retro-Strecker reaction to yield aniline, piperidone and none of the desired ester. Since amide **6** is readily available from nitrile **5** by treatment with concentrated H_2SO_4[4a], it seemed reasonable to propose that this amide could be converted to methyl imidate ester **9a**, and then hydrolyzed to the methyl ester **8** (eq. 3).

To test the method, amides **11 a-f** were prepared[10] or purchased[11], and converted to the corresponding methyl imidate esters **12 a-f**, (see Table 1). These reactions were typically run in CH_3CN at 0 °C for 4-8 hrs using a slight excess of trimethyloxonium tetrafluoroborate. The presence of the imidate esters was confirmed





6

9
a: R=Me
b: R=Et

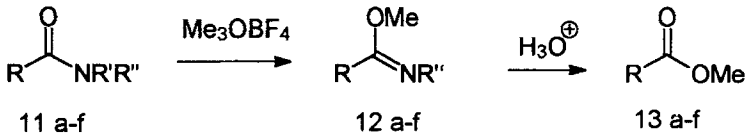
8: R=Me, 60% (Solvent = CH_3CN)
10: R=Et, 75% (Solvent = CH_2Cl_2)

by GC/MS analysis of the crude product. The crude imidate esters were then hydrolyzed with dilute HCl at room temperature over 4 hrs to yield the corresponding methyl esters **13 a-f** in good yields. The product esters were compared with commercially available samples of the esters by spectroscopic methods.

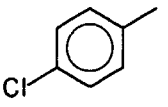
When this method was applied to amide **6**, only a modest yield was obtained of the methyl ester **8** from the amide (eq. 3). Investigation of the side products indicated that methylation was occurring at the piperidine or aniline nitrogen. This methylation was very competitive with O-alkylation. Attempts at improving the ratio of *O*-alkylation to *N*-alkylation included changing the temperature of the reaction (0 °C - 80 °C) and varying the solvents, but were unsuccessful (see Table 2).

For comparison, the triethyloxonium tetrafluoroborate was prepared as a solution (1M in CH_2Cl_2) and applied to the same series of amides. Typically, the amide was taken up in CH_2Cl_2 at 0 °C, an excess of ethyl Meerwein's reagent was added, and the reaction was stirred at room temperature until complete by TLC (1-2 days). Analysis by GC/MS of the crude product mixtures confirmed the presence of the imidate esters. The crude imidates were then hydrolyzed with dilute HCl over 4 hrs to produce the

Table 1. Conversion of Amides to Methyl Esters



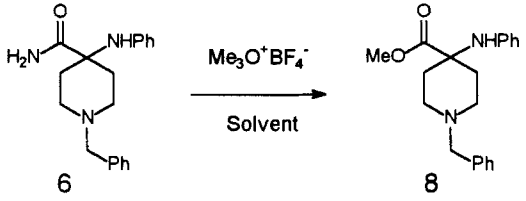
11 a-f 12 a-f 13 a-f

Amide	R	R'	R"	Yield of Ester (%)
11 a		H	H	75
b	"	H	Me	73
c	"	H	*i*-Pr	68
d	$CH_3(CH_2)_{10}$	H	H	75
e	"	H	Me	64
f	"	H	*i*-Pr	76

corresponding ethyl esters in good yields. Samples of the chlorobenzimidates **14a-c** and the carfentanil precursor imidate **9b** were purified by preparative TLC to obtain NMR and MS data (see Experimental Section). As before, the product esters were compared with commercially available samples of the esters. The results are summarized in Table 3.

When applied to the carfentanil synthesis (eq 3), amide **6** was converted to the ethyl ester **10** in a comparatively good yield, up to 80% for the two step process requiring less than 24 hrs. The ethyl Meerwein's reagent does not appear to alkylate the available nitrogens as did the methyl Meerwein's reagent and can be used in up to 6 equivalents with good results. The ethyl ester had previously been synthesized by refluxing the parent acid in ethanol/H_2SO_4 for 16 hrs (40% yield) and treating the sodium carboxylate with ethyl bromide (80%).[49] Producing the ethyl ester from the amide via the ethyl imidate avoids the difficult to handle carboxylate salt. This method also affords a higher

Table 2. Summary of Reaction Conditions



6 8

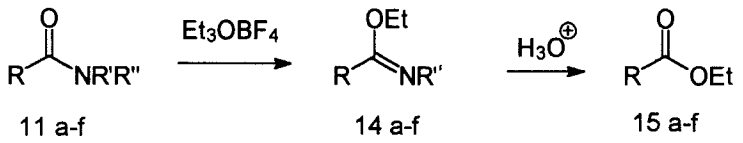
Solvent	Conditions[a]	Yield of Ester (%)
CH_2Cl_2	RT (≤ 3d)	0
CH_2Cl_2	Reflux (≤ 3d)	0
CH_2Cl_2	Reflux with Na_2PO_4 (≤ 3d)	0
$ClCH_2CH_2Cl$	Reflux with Na_2PO_4 (≤ 3d)	10
CH_3NO_2	RT Na_2PO_4 (≤ 3d)	15 - 20
CH_3NO_2	Reflux with Na_2PO_4 (≤ 3d)	Trace with loss of starting material
CH_3NO_2	0°C, 4 h	45
CH_3CN	0°C, 1 d	60

[a] Amide was taken up in solvent, then 1.1 equivalent of methyl Meerwein's reagent added at 0°C. Reaction mixture was then warmed to room temperature or reflux and stirred for the indicated time under argon.

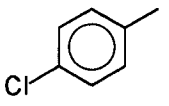
yield and is milder than the ethanolysis of either the amide or the acid. The ethyl esters prepared by these two methods were identical by NMR and GC/MS.

In conclusion, both the trimethyl- and triethyloxonium tetrafluoroborates have proved useful in the conversion of primary and secondary amides to the corresponding methyl and ethyl esters under mild conditions. The trimethyloxonium tetrafluoroborate has been shown to competitively alkylate nitrogen and oxygen in **6**, while the triethyloxonium tetrafluoroborate primarily alkylated at oxygen. Both reagents are easily produced[8] and have recently become commercially available.

Table 3. Conversion of Amides to Ethyl Esters



11 a-f 14 a-f 15 a-f

Amide	R	R'	R"	Yield of Ester (%)
11 a		H	H	81
b	"	H	Me	80
c	"	H	*i*-Pr	81
d	$CH_3(CH_2)_{10}$	H	H	66
e	"	H	Me	94
f	"	H	*i*-Pr	63

Experimental

^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer as solutions in $CDCl_3$ unless noted otherwise. Chemical shifts are reported in ppm downfield from internal standard TMS. Compounds were purified as specified and gave spectroscopic data consistent with being >95% the assigned structure. Mass spectra were obtained on a Hewlett Packard HO 5970 set at 70 eV. Gas chromatography was performed on a Hewlett Packard model 5890A using an Alltech Econo-Cap column (phase SE-54, length 30 meters, ID 0.25 mm, film thickness 0.25 μ), He flowrate 1 ml /min, temperature Program A (start 150 °C hold 5 min, ramp 10 °C/min. to 250 °C, hold until complete), temperature Program B (start 50 °C hold 5 min, ramp 10 °C/min. to 250 °C, hold until complete). Column chromatography was performed using Aldrich 28,850-0 silica gel. The solvent mixtures used for column chromatography are reported in

volume/volume mixtures. R_f values indicated refer to thin layer chromatography on Analtech 2.5 x 10 cm, 250M analytical plates coated with silica gel GF. Preparative TLC was performed using Analtech Uniplates with silica GF, 2.0 mm thickness. Melting points were taken on a Lab Device Mel-Temp and are uncorrected. CH_3CN, CH_3NO_2, $ClCH_2CH_2Cl$ and CH_2Cl_2 were distilled from CaH_2 before use.

Preparation of 1-benzyl-4-phenylamino-4-piperidinecarbonitrile (5). Into a 250 ml round-bottomed flask were placed 1-benzyl-4-piperidone (18 ml, 97.2 mmol), aniline (10 ml, 107 mmol), and glacial acetic acid (21.6 ml). While the mixture was stirring at 0 °C, an aqueous solution of KCN was prepared by dissolving KCN (7.3 g, 112 mmol) in water (25.0 ml). The KCN solution was placed in an addition funnel, and slowly added to the reaction mixture over 30 min. The addition funnel was replaced with a ground glass stopper, and the reaction mixture was stirred at rt for 18 h. During this time a copious precipitate formed. The reaction mixture was poured onto a mixture of ice (100 g) and concentrated aqueous NH_4OH (100 ml). The mixture was extracted with CH_2Cl_2 (3 x 30 ml). The combined organic extracts were washed with water (20 ml), dried over $MgSO_4$ and solvent removed in vacuo. The resulting oily solid was triturated with Et_2O. A white crystalline solid was collected by vacuum filtration (21.6 g, 74.3 mmol, 76% yield, mp 143-144°C); R_f=0.59 (5% MeOH/CH_2Cl_2); ^1H and ^{13}C NMR were consistent with those previously published[4b]; GC/MS R_t = 14.5 min Program A; *m/z* (rel intensity) 264 (72), 263 (M^+ - CN, 100), 187 (5), 172 (34), 144 (31), 91 (78), 77 (21).

Preparation of 1-benzyl-4-phenylamino-4-piperidinecarboxamide (6). The preparation followed the previously published procedure; the ^1H and ^{13}C NMR data were consistent with those published.[4a]

Typical preparation of methyl 4-chlorobenzoate (13a). 4-Chlorobenzamide **11a** (77.8 mg, 0.500 mmol), Na_2HPO_4 (100 mg, 0.685 mmol), and trimethyloxonium

tetrafluoroborate (82.0 mg, 0.550 mmol) were placed in a 5 ml reaction vial that was then flushed with argon. While at 0 °C, CH_3CN (1 ml) was added. The mixture was stirred at rt until the reaction appeared complete by TLC (6 h). The reaction mixture was then added to 10% aqueous $NaHCO_3$ (1 ml) and the layers were separated. The aqueous layer was extracted with ether (3 x 2 ml). The organic layers were combined and washed with brine (1 ml), dried with $MgSO_4$ and concentrated in vacuo to yield a yellowish oil.

The crude imidate was taken up in 10% aqueous HCl (5 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (5 ml) and separated. The aqueous layer was extracted with ether (2 x 5ml). The combined organic extracts were washed with brine (2 ml), dried with $MgSO_4$ and concentrated in vacuo to yield an oil. The oil was purified with a silica gel plug using 2% EtOAc/Hex to yield methyl 4-chlorobenzoate **13a** (63.9 mg, 0.375 mmol, 75% yield, mp = 41-43 °C, lit. 42-44 °C[12]). The spectra were consistent with commercially available sample.[13]

Typical preparation of methyl dodecanoate (13d). Lauramide **11d** (99.7 mg, 0.500 mmol), Na_2HPO_4 (100 mg, 0.685 mmol), and trimethyloxonium tetrafluoroborate (82.0 mg, 0.550 mmol) were placed in a 5 ml reaction vial and flushed with argon. While at 0 °C, CH_3CN (1 ml) was added. The mixture was stirred at rt until the reaction appeared complete by TLC, typically within 6 h. The reaction mixture was then added to 10% aqueous $NaHCO_3$ (1 ml) and the layers were separated. The aqueous layer was extracted with ether (3 x 2 ml). The organic layers were combined and washed with brine (1 ml), dried with $MgSO_4$ and concentrated in vacuo to yield the crude imidate as a yellowish oil.

The crude imidate **12d** was taken up in 10% HCl (5 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (5 ml) and separated. The aqueous layer was extracted with ether (2 x 5ml). The combined organic extracts were washed with brine (2

ml), dried with $MgSO_4$ and concentrated in vacuo to yield an oil. The oil was purified with a silica gel plug using 2% EtOAc/Hex to yield methyl laurate **13d** (80.4 mg, 0.375 mmol, 75% yield, bp 260 °C, lit. 262 °C[12]). The spectra were consistant with commercially available sample.[14]

Typical preparation of ethyl 4-chlorobenzoate (15a). Into a 25 ml round-bottomed flask was placed 4-chlorobenzamide **11a** (77.8 mg,0.500 mmol), Na_2HPO_4 (500 mg, 3.42 mmol) and CH_2Cl_2 (6 ml). The flask was flushed with argon then cooled to 0 °C, and triethyloxonium tetrafluoroborate (3 ml, 1M CH_2Cl_2, 3 mmol) was added dropwise. The reaction was stirred at rt until complete. TLC showed that the amide was consumed after 18 h. The reaction mixture was poured into Na_2CO_3 (5 ml, 10% aq) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were washed with brine (3 ml) and dried with $MgSO_4$. Removal of the solvent in vacuo yielded a yellowish, semicrystalline material. For analytical purposes, a sample was purified by preparative TLC to yield O-ethyl 4-chlorobenzimidate **14a**. Prep. plate R_f = 0.44 (40% EtOAc/Pet. Ether); ^{1}H NMR 7.69 - 7.66 (m, 2H); 7.37 - 7.34 (m, 2H); 6.20 (bd, 1H); 4.27 (q, 2H, J = 7.1 Hz); 1.39 (t, 3H, J = 7.1 Hz); ^{13}C NMR 165.5, 136.0, 130.4, 127.6, 127.2, 60.8, 13.1; GC/MS R_t = 16.2 min, Program A; *m/z* (rel intensity) 184 (9), 183 (M^+ 7), 182 (23), 157 (19), 155 (58), 141 (63), 140 (55), 139 (59), 138 (100), 113 (11), 111 (36), 102 (14), 75 (32); HRMS mass calculated for $C_9H_{10}ClNO$ 183.0351, found 183.0360.

The crude imidate **14a** was taken up in 10% aqueous HCl (5 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (5 ml) and the layers were separated. The aqueous layer was extracted with ether (2 x 5ml). The combined organic extracts were washed with brine (2 ml), dried with $MgSO_4$ and concentrated in vacuo to yield an oil. The oil was purified through a silica gel plug using 2% EtOAc/Hexane to yield ethyl 4-chlorobenzoate **15a** as a colorless oil (75.8 mg, 0.405 mmol, 81%, bp 271 °C, lit. 273 °C[12]). The spectra were consistent with a comercially available sample.[15]

Typical preparation of ethyl laurate (15d). Into a 25 ml round-bottomed flask was placed methyl dodecamide **11d** (106.7 mg,0.500 mmol), Na_2HPO_4 (500 mg, 3.42 mmol) and CH_2Cl_2 (6 ml). The flask was flushed with argon then cooled to 0 °C, and triethyloxonium tetrafluoroborate (3 ml, 1M CH_2Cl_2, 3 mmol) was added dropwise. The reaction was stirred at rt until complete. TLC showed the amide was consumed after 12 h. The reaction mixture was poured into Na_2CO_3 (5 ml, 10% aq) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were washed with brine (3 ml) and dried with $MgSO_4$. Removal of the solvent in vacuo yielded a yellowish, semicrystalline material.

The crude imidate was taken up in 10% aqueous HCl (5 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (5 ml) and separated. The aqueous layer was extracted with ether (2 x 5ml). The combined organic extracts were washed with brine (2 ml), dried with $MgSO_4$ and concentrated in vacuo to yield an oil. The oil was purified through a silica gel plug using 2% EtOAc/Hex to yield ethyl laurate **15d** as a colorless oil (107.3 mg, 0.470 mmol, 94%, bp 236 °C, lit. 237 °C[12]). The spectra were consistent with a commercially available sample.[16]

Preparation of methyl 1-benzyl-4-phenylamino-4-piperidinecarboxylate (8). Into a 5 ml reaction vial were placed 1-benzyl-4-phenylamino-4-piperidinecarboxamide **6** (502.5 mg, 1.624 mmol), Na_2HPO_4 (325 mg, 2.22 mmol), and trimethyloxonium tetrafluoroborate (266.2 mg, 1.786 mmol) then flushed with argon. While at 0 °C, CH_3CN (3.4 ml) was added. The mixture was stirred at rt until the reaction appeared complete by TLC. The reaction mixture was then added to 10% aqueous $NaHCO_3$ (1 ml) and the layers were separated. The aqueous layer was extracted with ether (3 x 2 ml). The organic layers were combined and washed with brine (1 ml), dried with $MgSO_4$ and concentrated in vacuo to yield **9a** as a yellowish oil. A sample of the oil was purified by preparative TLC R_f = 0.55 (10% MeOH/CH_2Cl_2). ^1H NMR 7.30-7.25 (m, 7H); 7.16 (t, 1H, J = 7.9 Hz); 6.76 (t, 1H, J = 7.3 Hz); 6.56 (dd, 2H, J = 8.4, 0.7 Hz); 3.82 (s, 1H); 3.48 (s,

1H); 2.71 (bd, 2H, J = 11.5 Hz); 2.22 (td, 2H, J = 12.7, 3.2 Hz); 2.12 (t, 2H, J = 12.3 Hz); 1.91 (bd, 2H, J = 12.0 Hz); ^{13}C NMR 175.5, 143.9, 138.1, 129.1, 128.2, 127.1, 118.8, 116.6, 63.2, 58.1, 53.9, 48.9, 31.7, GC/MS R_t = 17.2 min; *m/z* (rel intensity) 323 (M^+, <1), 308 (1), 263 (2), 230 (18), 215 (20), 177 (7), 146 (19), 118 (20), 91 (100), 56 (22); HRMS mass calculated for $C_{20}H_{25}N_3O$ 323.1998, found 323.1998.

The crude imidate **9a** was then taken up in 10% HCl (15 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (10 ml) and separated. The aqueous layer was extracted with ether (2 x 10ml). The combined organic extracts were washed with brine (2 ml), dried with $MgSO_4$ and concentrated in vacuo to yield an oil. The oil was purified with a silica gel plug using 2% EtOAc/Hex to yield ester **8** as a pale yellow oil which solidified upon standing (316.1 mg, 0.974 mmol, 60% yield, mp 78-79 °C, lit. 80.5 °C[4f]). ^{1}H and ^{13}C NMR were identical with those previously reported.[4a,b]

Preparation of ethyl 1-benzyl-4-phenylamino-4-piperidinecarboxylate (10). Into a 25 ml round-bottomed flask was placed 1-benzyl-4-phenylamino-4-piperidinecarboxamide **6** (514.3 mg, 1.662 mmol), Na_2HPO_4 (1.66 g, 11.35 mmol) and CH_2Cl_2 (20 ml). The flask was flushed with argon then cooled to 0 °C, and triethyloxonium tetrafluoroborate (1M CH_2Cl_2, 10 ml, 10 mmol) was added dropwise. The reaction was stirred at rt until complete. TLC showed that the amide was consumed after 18 h. The reaction mixture was poured into Na_2CO_3 (5 ml, 10% aq) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were washed with brine (3 ml) and dried with $MgSO_4$. Removing solvent in vacuo yielded **9b** as a yellowish, semicrystalline material. A portion of the oil was purified by preparative TLC R_f = 0.60 (10% MeOH/CH_2Cl_2); ^{1}H NMR 7.31 - 7.12 (m, 8H); 6.79 - 6.73 (m, 1H); 6.58 - 6.54 (m, 2H); 4.23 (q, 2H, J = 7.1 Hz); 3.80 (bs, 1H); 3.48 (s, 2H); 2.74 - 2.68 (m, 2H); 2.31 - 2.25 (m, 2H); 2.13 - 2.04 (m, 2H); 1.92 - 1.87 (m, 2H); 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR 174.8, 144.0, 138.1, 129.1,

129.0, 128.2, 127.1, 118.8, 116.6, 114.0, 63.3, 62.2, 58.1, 31.8, 14.2; GC/MS R_t = 17.7 min, Program B; *m/z* (rel intensity) 337 (M^+ 4), 308 (7), 265 (8), 215 (50), 191 (11), 146 (44), 118 (13), 91 (100); HRMS mass calculated for $C_{21}H_{27}N_3O$ 337.2154, found 337.2150.

The crude imidate **9b** was taken up in 10% aqueous HCl (15 ml) and stirred at rt for 4-5 h. The reaction mixture was added to ether (10 ml) and the layers were separated. The aqueous layer was extracted with ether (2 x 10 ml). The combined organic extracts were washed with brine (2 ml), dried with $MgSO_4$ and concentrated in vacuo to yield **13** as an oil. Flash chromatography (2% MeOH/CH_2Cl_2) yielded ethyl ester **10** as a colorless oil (R_f = 0.55, 5% MeOH/CH_2Cl_2; 411.2 mg, 1.215 mmol, 75% yield); ^{1}H NMR 7.32-7.28 (m, 5H); 7.13 (t, 2H, *J* = 8.0 Hz); 6.73 (t, 1H, *J* = 7.3 Hz); 6.58 (d, 2H, *J* = 8.5 Hz); *J* = 7.2 Hz); 3.51 (bs, 1H); 2.59 (bd, 2H, *J* = 4.0 Hz); 2.41 (bt, 2H, *J* = 10.7 Hz); 2.24 (td, 2H, *J* = 11.8, 3.8 Hz); 2.01 (bd, 2H, *J* = 13.7 Hz); 1.14 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR 175.2, 145.3, 138.5, 129.1, 128.3, 127.1, 118.8, 115.8, 63.0, 61.0, 58.6,49.1, 33.3, 14.1; GC/MS R_t = 14.2 min, Program A; *m/z* (rel intensity) 338 (M^+ 4), 265 (14), 245 (42), 216 (67), 172 (100), 146 (26), 91 (72); mp (dihydrochloride) 210.2 °C, lit. 211.0 °C.[4g]

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(1) (a) Current address: Department of Chemistry, Salisbury State University, Salisbury, MD, 21801. (b) Current address: Department of Chemistry and Biochemistry, Montana State University, Bozeman, Montana, 59717

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