Investigation of Samarium Diiodide as a Reagent for the Formation of Carbon-Carbon Bonds

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by
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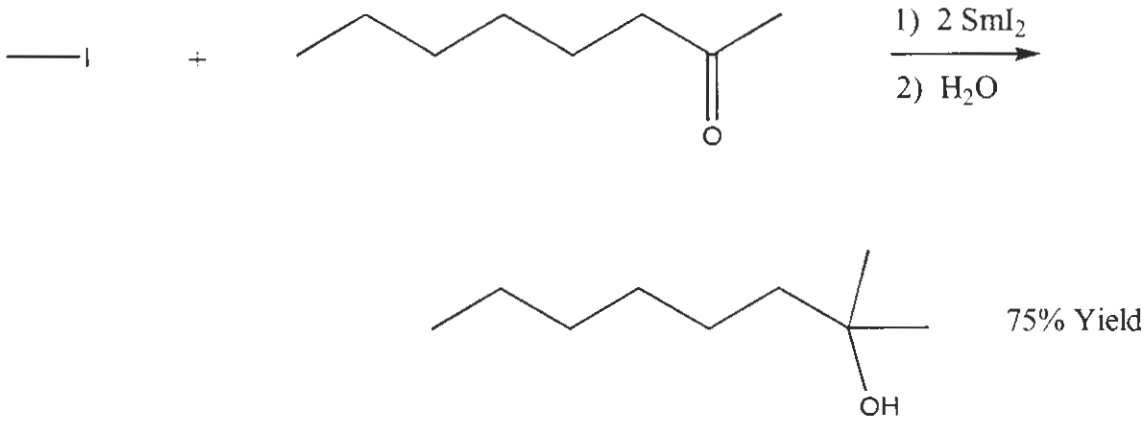
Background and Introduction

Chemical reactions that result in the formation of carbon-carbon bonds are of primary importance to synthetic chemists. The successful synthesis of desirable compounds requires not only the ability to manipulate functionalized sites, but also the means to alter a molecule's carbon framework. Unfortunately, the latter often proves to be a very difficult task.

Consider, as an example, the oxidation of isopropanol to form acetone. A standard undergraduate organic chemistry text[1] describes at least five sets of reaction conditions by which this transformation can be made to occur. Compare this transformation to the addition of a two-carbon chain to isopropanol to give 2-pentanol. The same organic chemistry text does not offer a single set of reaction conditions by which this reaction can be made to occur. Such a simple-looking manipulation of a molecule often adds a multitude of additional steps to synthetic endeavors. When a new synthetic methodology is found which produces one or more carbon-carbon bonds, the study and optimization of this methodology is therefore the subject of many research efforts.

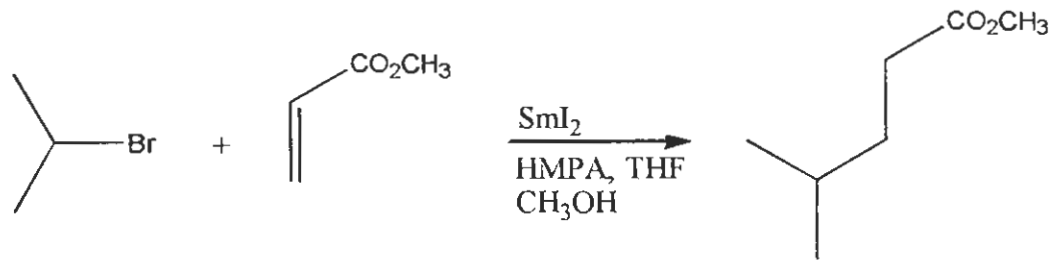
The use of divalent samarium compounds for the formation of carbon-carbon bonds began in the 1970's. In studies of organic reactions using lanthanide reagents, Evans and coworkers found that samarium metal could be reacted with organic iodides to give effective Grignard-type reagents[2,3]. In the late 1970's and early 1980's, the divalent samarium diiodide was the subject of many investigations[4]. Kagan and coworkers reported a convenient synthesis of samarium diiodide, (from samarium metal and 1,2-diiodoethane), and gave many examples of its uses, including the reductive addition of alkyl groups to ketones[5] (figure **1**).

Figure 1. An early samarium diiodide reaction reported by Kagan and coworkers.



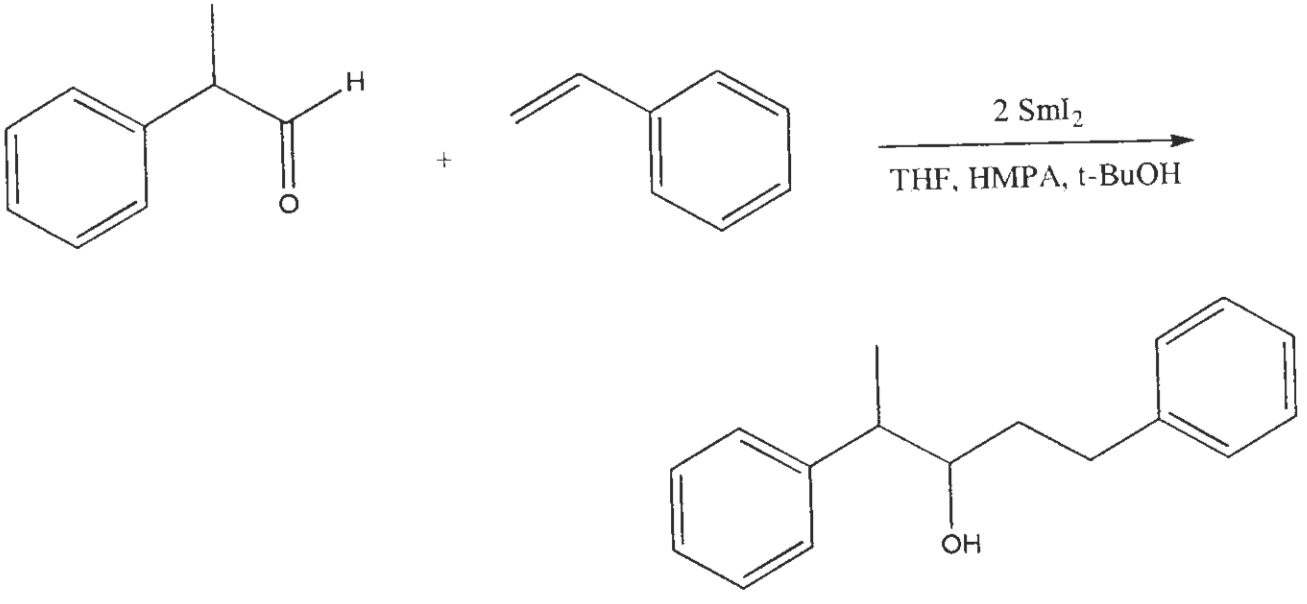
In 1996, Molander and Harris published a comprehensive review in which the samarium diiodide reactions known to date were summarized[4]. Samarium diiodide had been found to be a very effective one-electron reductant and initiator of radical reactions. In a typical example, it was found that samarium diiodide would react with alkyl halides by homolytically cleaving the carbon-halogen bond to give the corresponding alkyl radicals. These radicals would then react with alkenes to give addition products (figure **2**).

Figure 2. Samarium diiodide acting as a radical generator.



Similarly, samarium diiodide will donate one electron to the π-systems of both ketone and aldehyde carbonyls, with the resulting radicals going on to react with alkenes to give new carbon-carbon bonds. See figure 3.

Figure 3. Samarium diiodide facilitating a radical reaction by donating one electron to the π-system of an aldehyde.

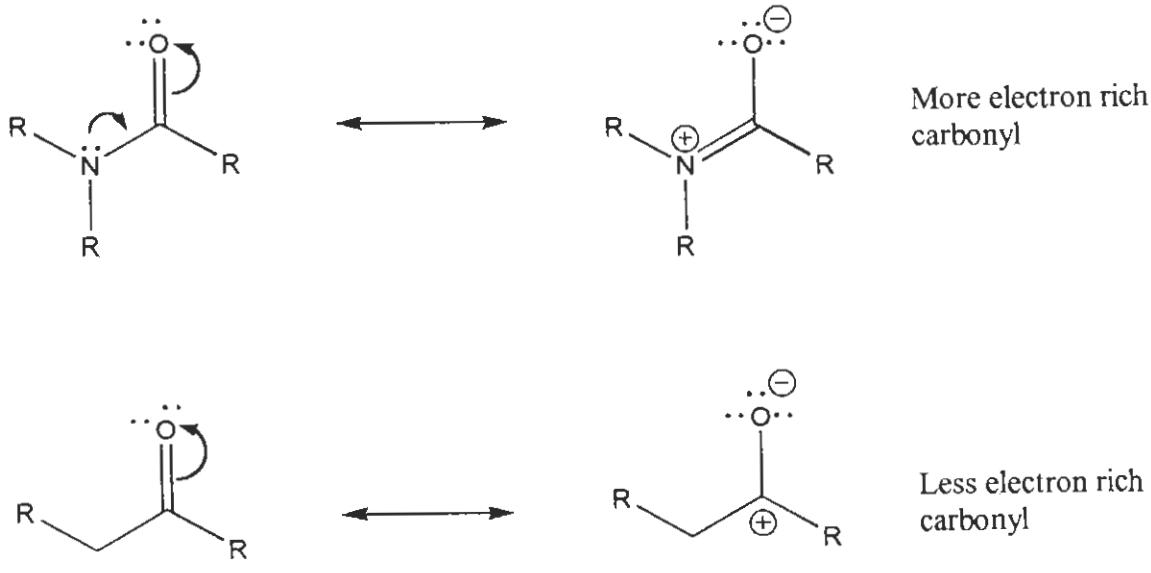


While many ketones and aldehydes have been shown to react in this manner, the use of amides in samarium diiodide reactions has generally been limited to the role of radical acceptor[4]. Notable exceptions are the reported couplings of amides using samarium diiodide and samarium metal to give diaminoalkenes[4].

One thought as to why amides have thus far shown little promise as radical precursors involves the resonance donation of the amide nitrogen's lone pair of electrons. Figure 4 illustrates

how this donation results in a carbonyl π-system which is more electron rich than that found in ketones and aldehydes.

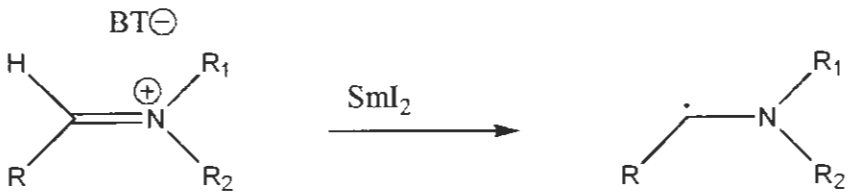
Figure 4. The effects of amide nitrogen lone pair donation on relative carbonyl electron density.



It is expected that this more electron rich π-system is a relatively poorer single electron acceptor.

Recently, Aurrecoechea and coworkers reported that iminium cations would accept a single electron from samarium diiodide to yield the corresponding radicals[6] (figure **5**).

Figure 5. Formation of a radical from an iminium cation using samarium diiodide.

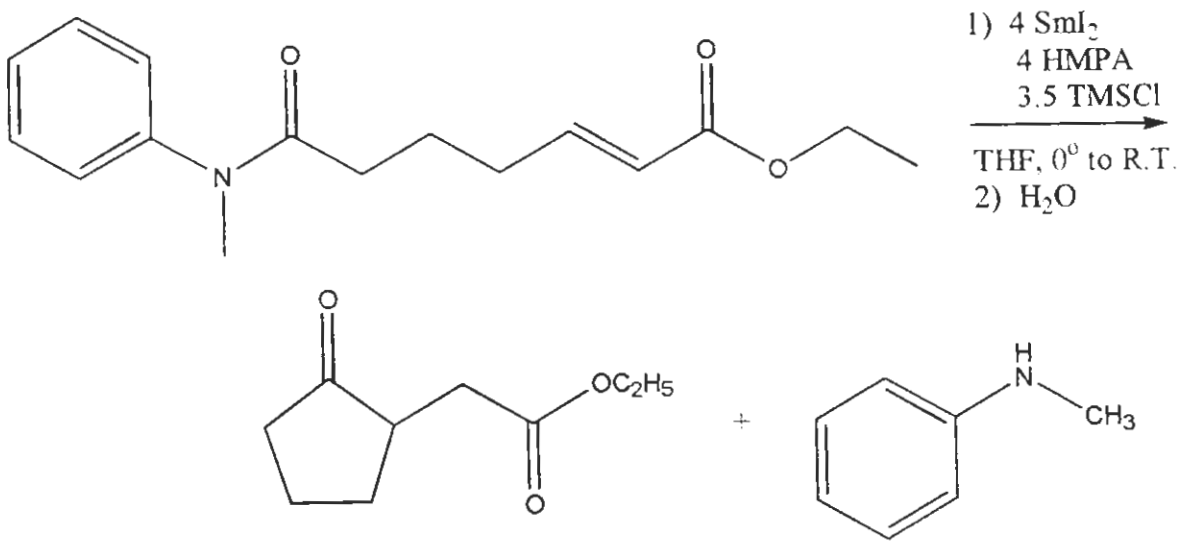


$BT^{\ominus}$ = Benzotriazolyl anion

These radicals would then react with tethered alkenes to give the corresponding ring-closure products.

It was thought that if an amide were first reacted with an electrophile to give a similar iminium-type species, it might be made to undergo a similar reaction. In 1998, McDonald and coworkers accomplished this task using trimethylsilylchloride as the electrophile (figure **6**).

Figure 6. The reaction of an amide in a samarium diiodide initiated radical ring-closure reaction.



This reaction showed two immediate limitations. First, the combination of trimethylsilylchloride and tetrahydrofuran sometimes resulted in products believed to be the result of tetrahydrofuran ring-opening reactions. Additionally, despite many trials involving many different reaction conditions and reactant ratios, yields of the ring-closure product could not be obtained in greater that 40%.

The solution to the first problem was found in a 1997 communication by Charette and coworkers. Charette comments on the use of triflic anhydride as an electrophile for the production of iminium cations from secondary and tertiary amides[7]. It was found that the use of triflic anhydride in the place of trimethylsilylchloride in the samarium diiodide reaction alleviated the problem of solvent ring-opening reactions.

The second problem was thought to be more complicated. It was not entirely clear where, in the hypothetical reaction mechanism, the problem was occurring. If the amide carbonyl π-system was too electron-rich, then the formation of the radical might be hampered. However, if the amide

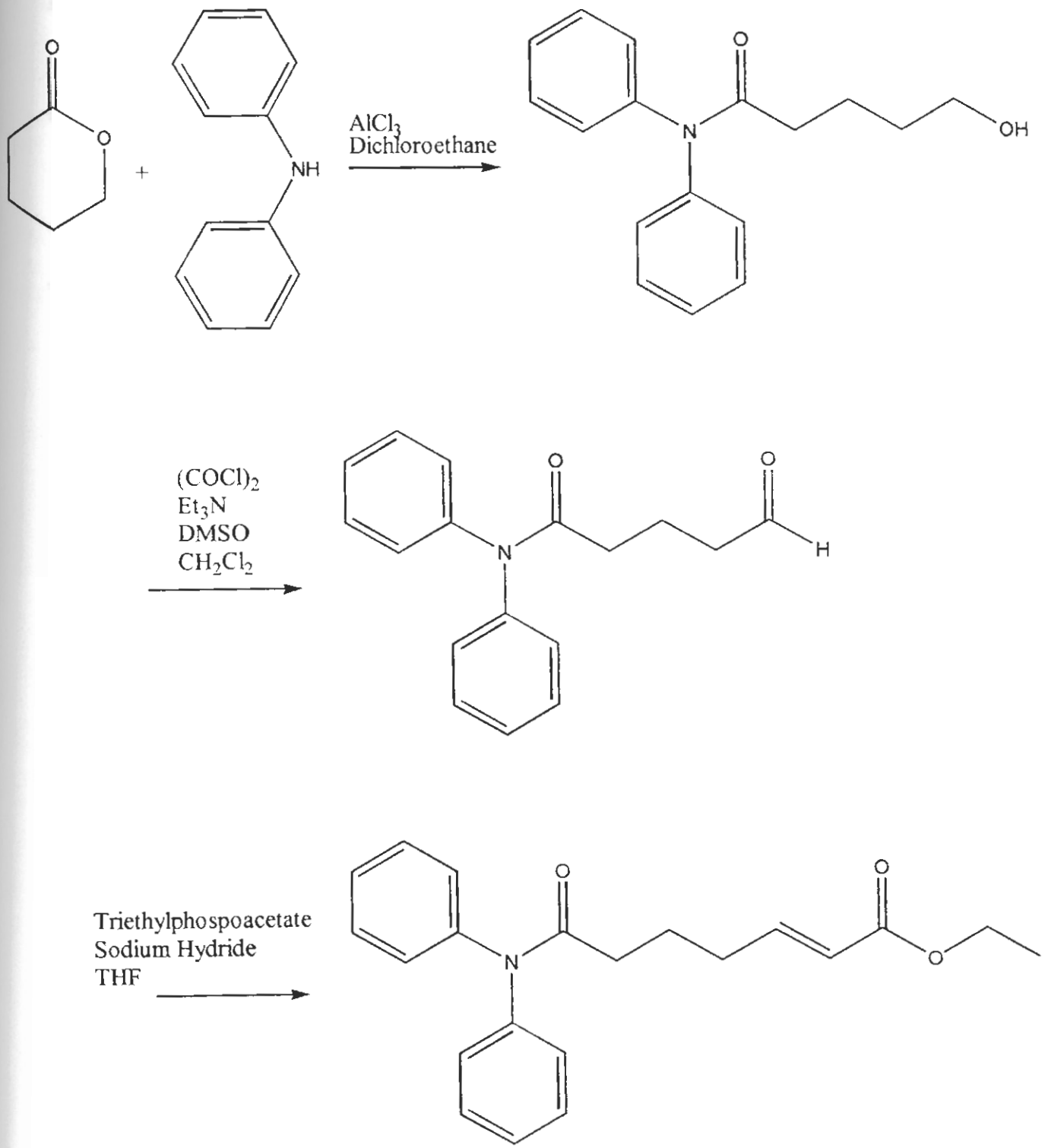
carbonyl π-system was too electron-poor, then the resulting radical might be stabilized to the point that it would tend not to react further as desired. Fortunately, through the variation of the nitrogen R-groups, the electronic nature of the π-system could be tuned in a somewhat predictable manner. With this strategy in mind, McDonald and coworkers synthesized the di-*n*-butyl analogue of their initial amide. It was hoped that this amide, having a more electron-rich carbonyl π-system, would produce a greater yield of the desired product in the samarium diiodide reaction. Unfortunately, it was found that this molecule did not participate at all in the desired reaction.

The next logical step was to try an amide having a more electron-poor carbonyl π-system than the original amide. The diphenyl analogue was chosen. Reported herein is the synthesis of *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate and its use in a samarium diiodide ring-closure reaction.

Results and Discussion

Our original reaction scheme for the synthesis of *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate is illustrated in figure 7.

Figure 7. The first proposed reaction scheme for the synthesis of *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate.

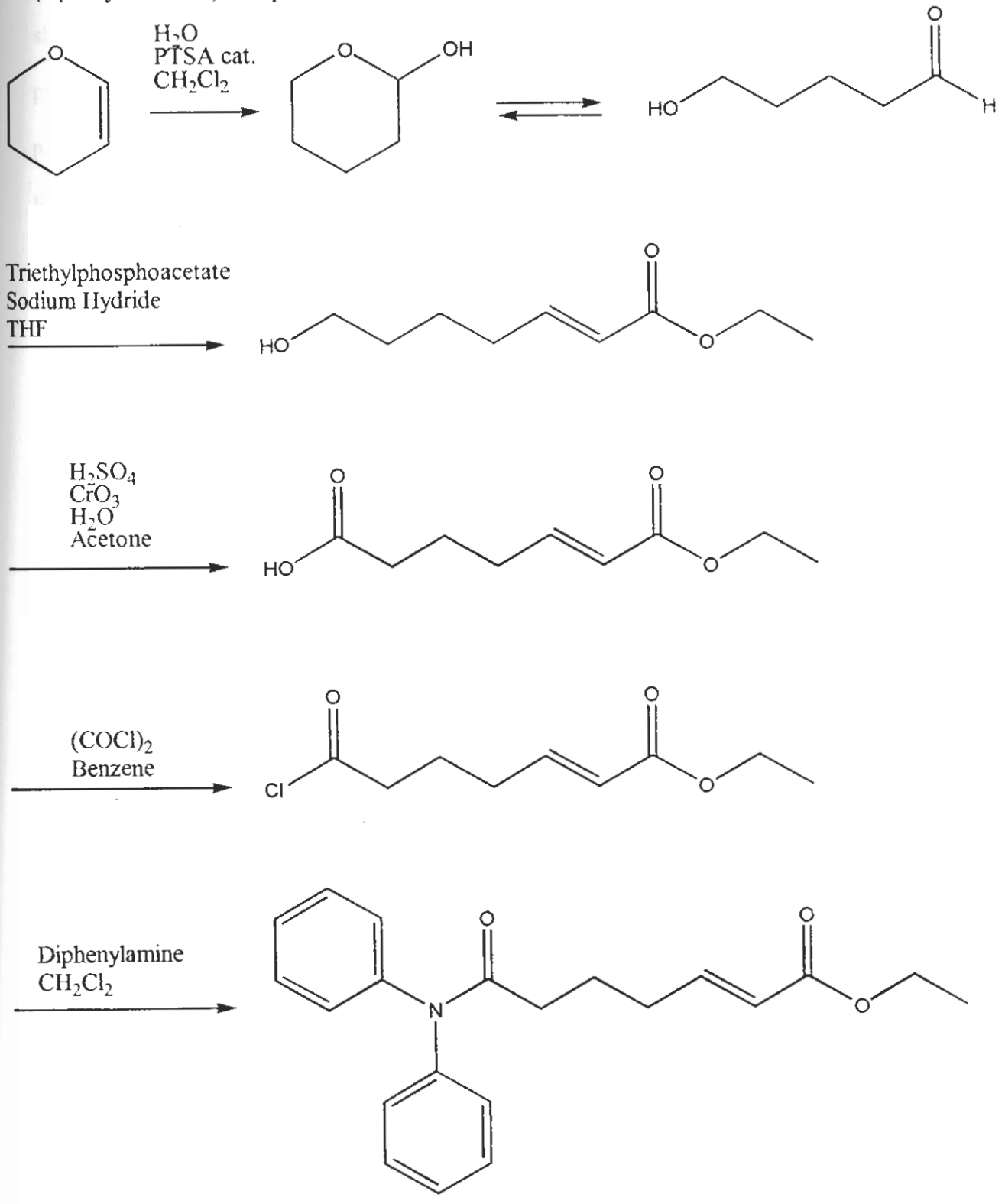


The first reaction is a ring-opening nucleophilic acyl substitution. Bigg and coworkers reported the use of aluminum trichloride in similar reactions for the generation of ω-hydroxyalkylamides[8]. The second reaction involves the oxidation of a primary alcohol to an aldehyde, for which Swern oxidation conditions were initially employed. The third reaction is a Wittig-type addition which used triethylphosphoacetate and sodium hydride to generate the necessary reagent.

When these reactions were performed, the best accessible NMR instrument was a 60 MHz continuous wave model which gave, at best, very poor peak resolution. As a result, product characterization was often very difficult and uncertain. When the product of the third reaction in the sequence failed to give any ^{1}H NMR signals in the alkene region, it became clear that the reaction scheme was not successful. We suspected that the failure of the third reaction to give the expected Wittig adduct might possibly have been the result of the second reaction failing to give the expected oxidation product. We therefore tried running the second reaction under an alternative set of oxidation conditions. Rather than the initial Swern conditions, we tried the TEMPO/sodium hypochlorite system[9]. When this reaction failed in several attempts to produce anything resembling the desired product, the first reaction became suspect, and we decided it was best to try an alternative synthetic scheme. It might be worth noting, in retrospect, that while Bigg and coworkers did report the use of the lactone-opening reaction for the generation of both primary and secondary amides, they did not report the synthesis of any secondary amides in which the second R group was larger than an ethyl group[8].

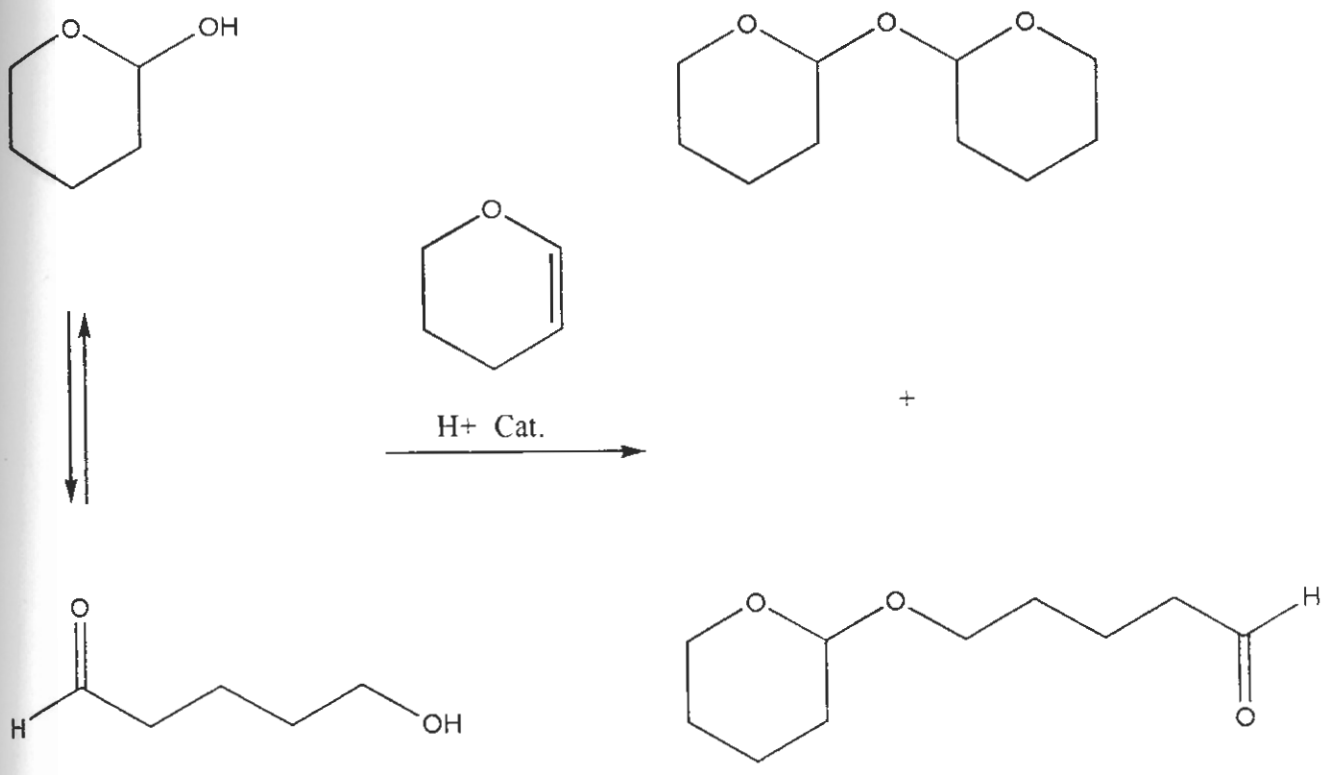
The second reaction scheme is shown in figure **8**.

Figure 8. The second proposed reaction scheme for the synthesis of *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate.



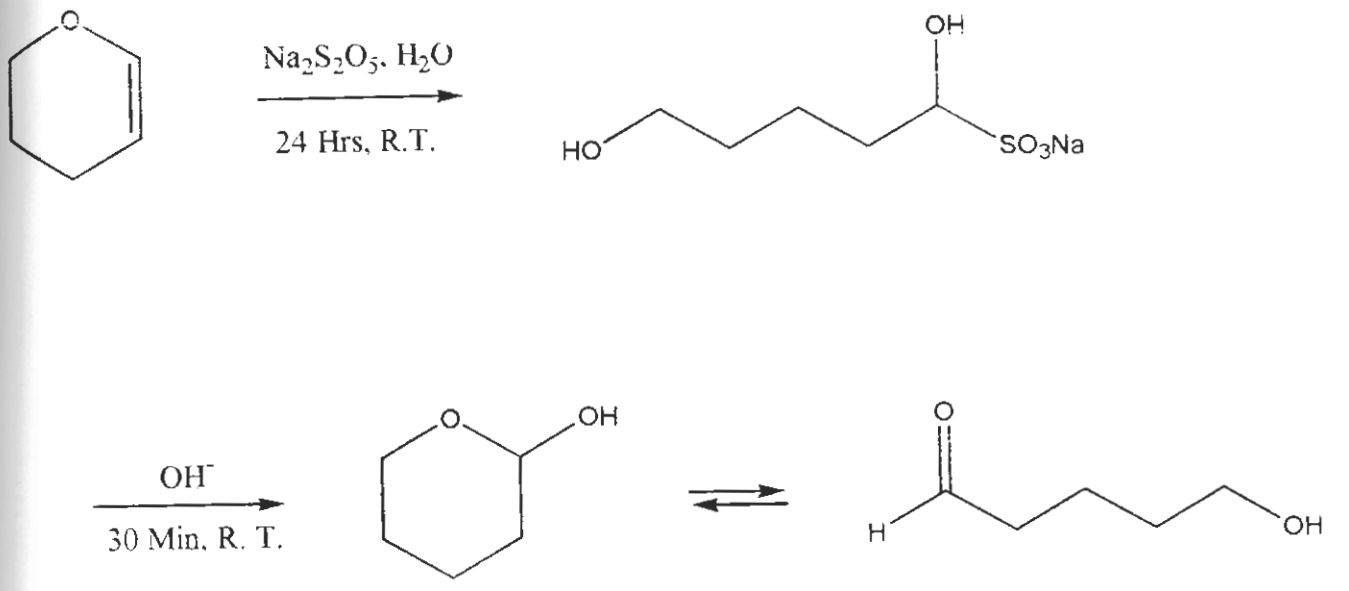
This scheme begins with the acid-catalyzed addition of water across the double bond of 3,4-dihydro-2H-pyran. While the gas chromatograph traces of the product from the initial trials of this reaction showed significant byproduct peaks, the volatility of the desired product prevented effective purification. The crude reaction product was used in the next reaction, but like the product of the previous Wittig reaction, this one failed show any signals in the alkene region of the ^{1}H NMR. Following a paper by Pattenden and coworkers, an alternative Wittig reagent, (ethoxycarbomethylene)triphenylphosphorane, was tried, and this produced trace amounts of the desired product[10]. The low yield was presumed to be due to the small amount of the desired starting material actually present in the starting reaction mixture, and the merits of the first reaction in the sequence were again brought into question. In a communication by Vinczer and coworkers, the problem of byproducts in the first reaction is addressed. Vinczer states that under the acidic conditions present in the reaction mixture, the reaction product can add to the starting material to produce two different byproducts[11]. These side reactions are shown in figure **9**.

Figure 9. Side reactions in the acid-catalyzed hydration of 3,4-dihydro-2H-pyran.



To alleviate this problem, Vinczer proposes an alternative set of reaction conditions in which a stoichiometric amount of sodium metabisulfite is used in the place of a catalytic amount of a protic acid. He claims that the sodium metabisulfite, (which produces sodium bisulfite in aqueous solution), both makes the solution sufficiently acidic to catalyze the hydration and reacts with the product to give a sodium salt which does not react further. The addition of hydroxide liberates the desired organic. This proposed reaction is shown in figure **10**.

Figure 10. Vinczer's synthesis of 5-hydroxypentanal.



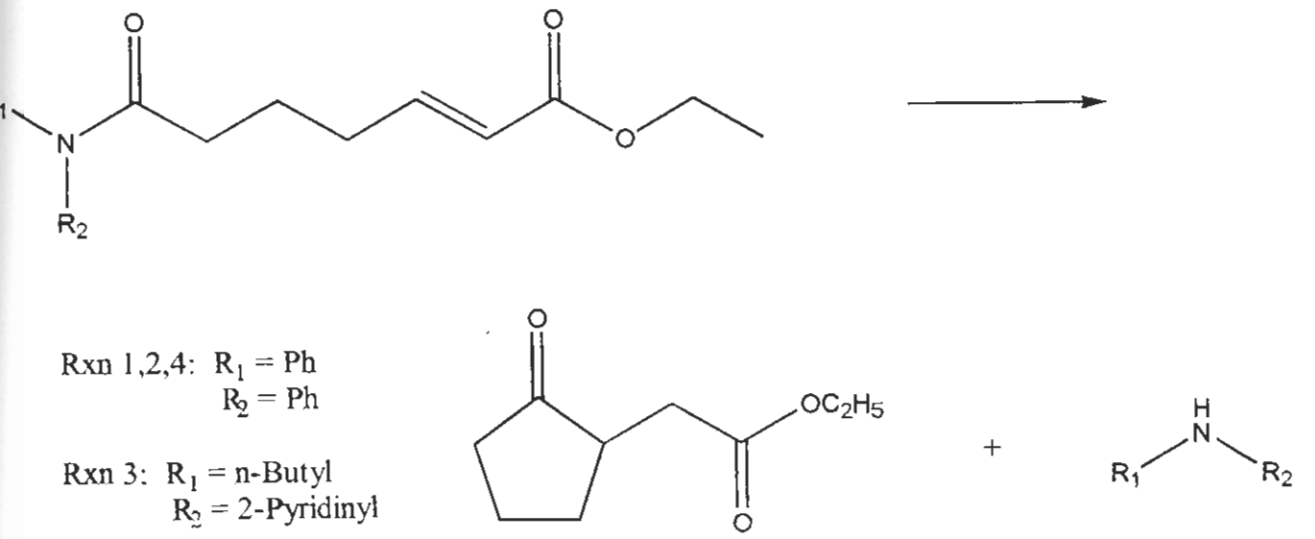
In our experience, Vinczer's second claim held true; the addition of sodium metabisulfite kept the desired reaction product from participating in further additions. However, we found that the sodium salt was not acidic enough to catalyze the hydration, so we used it in addition to catalytic amounts of *para*-toluenesulfonic acid. With the improved reaction conditions, a reasonable amount of 5-hydroxypentanal was produced with minimal amounts of byproduct. The crude mixture was reacted with (ethoxycarbomethylene)triphenylphosphorane in the Wittig reaction, and for the first time, a significant amount of *trans*-ethyl-7-hydroxy-2-heptenoate was produced.

Fortunately, the remainder of the synthesis was fairly straightforward. A standard Jones workup yielded ethyl-6-carboxy-*trans*-hex-2-enoate. Following an experimental from Tufariello's synthesis of Histrionicotoxin, oxalyl chloride was used to convert the acid to an acid chloride[12]. The

resulting acid chloride was reacted *in situ* with diphenylamine to give *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate, the amide of interest.

Four samarium diiodide reactions were performed. As the oxidation of samarium diiodide from the +2 to the +3 oxidation state is normally accompanied by a dramatic color change from deep blue to pale yellow, the reactions were run until the this color change was complete, (from 4 to 20 hours). The reactions were then quenched and extracted, and the products were studied by gas chromatography. The first, second, and fourth reactions were performed with *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate. The third reaction was performed with *trans*-ethyl-7-*N,N*-(phenyl-2-pyridyloxamido)-2-heptenoate which was synthesized using a different amine in the same reaction scheme. The intended samarium diiodide reaction is shown in figure **11**.

Figure 11. The intended samarium diiodide reaction.



The specific reactions are summarized in table 1.

Table 1. The samarium diiodide reactions.

SmI_2 Rxn	Amide	Reaction conditions	Product
1	trans-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate	1) 1.8 eq Tf_2O at -40°C CH_2Cl_2 .2M 2) Remove CH_2Cl_2 under vacuum 3) 0.5 mL THF, -40°C 4) 4 eq SmI_2 4 eq HMPA Added simlutaneously from separate syringes.	No ester, Some amine
2	trans-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate	1.3 eq Tf_2O at -40°C .5 mL THF, -40° C added to 4 eq SmI_2 4 eq HMPA	No ester, Some amine
3	trans-ethyl-7-*N,N*-(phenyl-2-pyridyloxamido)-2-heptenoate	1.3 eq Tf_2O at -40°C .5 mL THF, -40° C added to 4 eq SmI_2 4 eq HMPA	Trace ester, Some amine
4	trans-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate	1.3 eq fresh Tf_2O at -40°C .5 mL THF, -40° C added to 4 eq SmI_2 4 eq HMPA	Some ester, Some amine

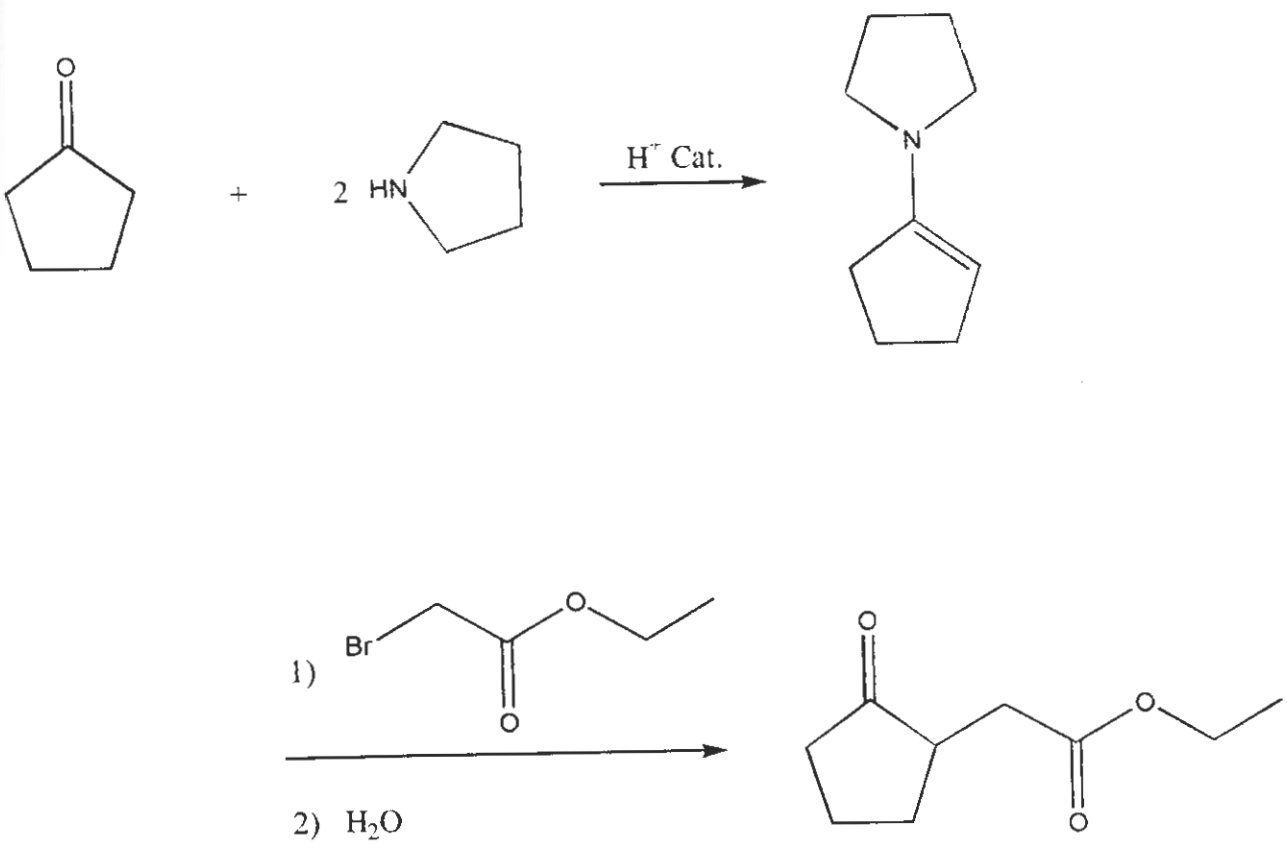
The first reaction was performed under conditions which most closely resembled those which had been successful in past reactions. When that reaction showed no evidence of ester product, alternate conditions were tried. It was thought that by adding the iminium ion to the samarium

diiodide and hexamethylphosphoramide, solvent removal could be avoided and the entire system could be kept at -40° C from the time the ion was formed until it was combined with the samarium diiodide. The second reaction likewise produced no visible ester product signal by GC. It was hoped that in the third reaction, with the use of an amide having a more electron-withdrawing R-group (2-pyridyl), the electronic environment of the carbonyl would be more favorable for the desired reaction. Unfortunately, the third reaction showed what was believed to be only a very small gas chromatograph peak resulting from the ester product. Attempts were made to isolate this material through column chromatography purification, but these attempts were not successful. The fourth reaction was run under the same conditions as the second and third, but fresh triflic anhydride was used. Three and one half hours into reaction, an aliquot was taken, and following a water and ether workup, the aliquot was shot on the gas chromatograph. The resulting trace showed a significant peak for the ester product relative to the other species present, (hexamethylphosphoramide and diphenyl amine). Forty-five minutes later, the reaction appeared pale yellow, and like the previous reactions, it was quenched with water and extracted with hexane. When the organic layer from this reaction was gas chromatographed, the ester product peak appeared, (relative to the other peaks present), smaller than it had in the aliquot sample. We wondered if this discrepancy might have been due to the difference in the extraction solvents used. The remaining aqueous layer from reaction four was extracted once again, this time with ether. The gas chromatograph trace of this extraction once again showed a very prominent peak for the ester product relative to the other species present. This sequence of events suggested that it may be worthwhile to investigate not only the samarium diiodide reaction, but also the involved workup. Issues in the workup are one possible way to explain observed discrepancies in the ratio of ester

product to amine product. Mechanistic arguments suggest that this ratio should equal approximately one.

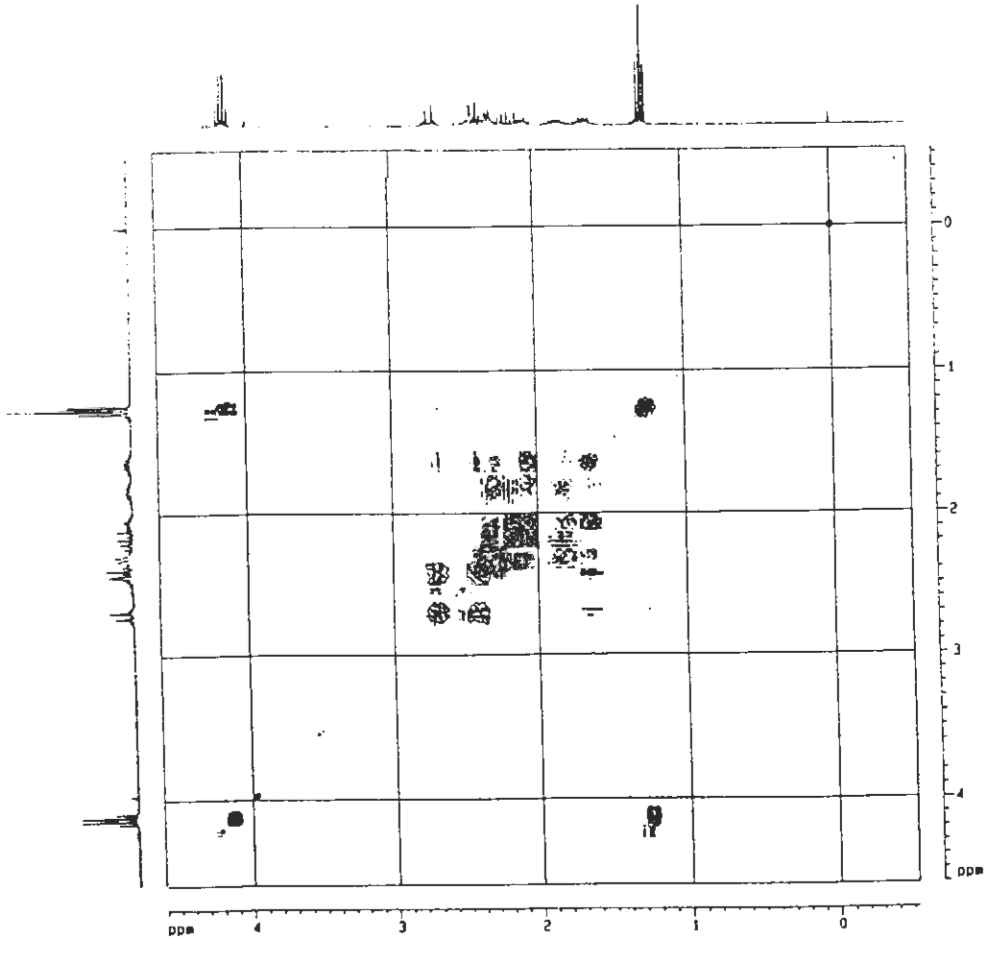
It was thought that the study of the samarium diiodide reactions outlined here could be better pursued if thorough characterization data of the desired ester product could be obtained. For this reason, ethyl-2-(2-oxocyclopentyl)ethanoate was synthesized according to the method reported by Blomquist and coworkers[13]. The two-reaction scheme is shown in figure **12**.

Figure 12. Synthesis of ethyl-2-(2-oxocyclopentyl)ethanoate by known methodology.



The first reaction was a standard enamine preparation performed using a Dean Stark setup[1]. The second reaction employed a nucleophilic attack followed by the elimination of an amine to yield the desired ester[1]. The ester was purified by both column chromatography and a short-path low-pressure distillation. Gas chromatograph, mass spectrometry, and infrared spectrometry data was obtained for this compound. A 300 MHz ^{1}H NMR spectra was obtained, and a COSY experiment was performed. The COSY printout is shown in figure **13**.

Figure 13. The COSY spectra of ethyl-2-(2-oxocyclopentyl)ethanoate.



Summary and Conclusions

A synthetic pathway to *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate was developed. There is reason to think that this pathway is applicable to many similar amides. A samarium diiodide promoted reductive cyclization reaction was attempted on both *trans*-ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate and *trans*-ethyl-7-*N,N*-(phenyl-2-pyridyloxamido)-2-heptenoate. Neither gave outstanding results. Variations in gas chromatograph traces correlated to changes in workup solvent suggested that investigations regarding the workup of the samarium diiodide reaction may be worthwhile. The desired samarium diiodide reaction product was synthesized by known synthetic methodology, and extensive characterization data of this compound was obtained.

Experimental

5-Hydroxypentanal. Following a modified version of Vinczer's procedure[11], sodium metabisulfite (10.5872 g, 0.05569 mol) and *p*-toluenesulfonic acid (0.1041 g, 0.000645 mol) was dissolved in water (30.0 ml, 1.67 mol) to give a clear solution. This solution was transferred to a 250 mL round bottom flask with a stir bar and heated to 50° C in a water bath. To this mixture was added 3,4-dihydro-2H-pyran (10.0 mL, 0.110 mol), which formed an upper layer. A condenser was placed on the flask, and the contents were stirred for 60 minutes at 50-60° C. The solution was then stirred for 30 minutes at 70° C. Additional *p*-toluenesulfonic acid (0.1013 g, 0.000588 mol) was added, and after another hour of stirring at 70° C, the mixture was homogeneous. The water was removed by rotary evaporation to give a white solid. In a 125 mL Erlenmeyer flask, Sodium hydroxide (5.046 g, 0.1262 mol) was dissolved in water (60.0 mL, 3.33 mol). The 250 mL round

bottom flask with the white solid was cooled to 0° C in an ice water bath. The hydroxide solution was added to the flask, with stirring, in 3 portions. The resulting mixture was stirred for 40 minutes, during which time the white solid dissolved and 2 layers became evident. The layers were extracted with ether (3x 30 mL). The combined organic layers were left in a refrigerator over sodium sulfate overnight. The sodium sulfate was removed by filtration, and the ether was removed by distillation. Crude 5-hydroxypentanal was a clear oil (9.2958 g, about 80%). GC (initial temp. 50° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 225° C) 5.770 min.

***trans*-Ethyl-7-hydroxy-2-heptenoate.** Following the report of Pattenden[10], to an oven-dried 500 mL round bottom flask was added 5-hydroxypentanal (0.9712 g, 0.08672 mol), dry acetonitrile (100 mL), (ethoxycarbomethylene)triphenylphosphorane (18.7080 g, 0.053700 mol), and a stir bar. An oven-dried condenser was placed on the flask, and the cloudy mixture was refluxed and stirred under nitrogen for 2 hours, during which time it became a transparent yellow solution. The reaction was monitored by GC, which indicated no starting material remaining after 2 hours. The reaction was left stirring at room temperature for an additional 7 hours, after which time water (100 mL), ether (75 mL), and brine (25 mL) were added. The organic layer was removed, and the aqueous layer was extracted with ether (2x 50 mL). The organic extracts were combined, and the solvent was removed by rotary evaporation followed by vacuum pumping. The crude product, a thick mixture of clear liquid and white precipitate, was purified by column chromatography on a 29/42 column of silica gel. The eluent was a gradient of 500 mL 15% EtOAc:Hex, 500 mL 25% EtOAc:Hex, 500 mL 50% EtOAc:Hex, and 750 mL 60% EtOAc:Hex. Fractions of 35-40 mL were collected, and the desired product was present in fractions 25-40. These fractions were combined, and the solvent was removed by rotary evaporation followed by vacuum pumping. Purified *trans*-ethyl-7-hydroxy-2-

heptenoate was a colorless oil (3.311 g, 41.0%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (dt, 1 H, *J*=15.65 Hz, *J*=6.98 Hz), 5.82 (d, 1 H, *J*=14.88 Hz), 4.14 (q, 2 H, *J*=5.49 Hz), 3.92 (bs, 1 H), 3.59 (bs, 2 H), 2.23 (q, 2 H, *J*=6.67 Hz), 1.56 (m, 4 H), 1.28 (t, 3 H, *J*=7.11 Hz).

Ethyl-6-carboxy-*trans*-hex-2-enoate. A 50 mL graduated cylinder was charged with a stir bar and cooled to 0° C in an ice water bath. To this was added chromium trioxide (3.3732 g, 0.03374 mol), water (15.0 ml, 0.833 mol), and concentrated sulfuric acid (3.0 mL, 0.056 mol). The resulting solution was diluted to 20 mL with water. A 250 mL round bottom flask was charged with *trans*-ethyl-7-hydroxy-2-heptenoate (3.1604 g, 0.0184 mol), HPLC grade acetone (30 mL), and a stir bar. It was then fitted with a pressure-equalizing dropping funnel, and cooled to 0° C in an ice water bath. The bright orange chromic acid solution was transferred to the dropping funnel using a water (5 mL) rinse. It was added dropwise to the vigorously stirred ester solution over 2 hours. Within the first few drops, the reaction mixture went from colorless to pea green. After the addition was complete, the reaction mixture was a green solution with chunks of a dark green precipitate present. Water (30 mL) was added, and the mixture was extracted with ether (3x 30 mL). The solvent was removed from the combined organic layers by rotary evaporation and vacuum pumping. The crude product, a viscous green liquid, was purified on a 24/40 column of silica gel. The eluent was a gradient of 200 mL 10% EtOAc:Hex, 200 mL 20% EtOAc:Hex, 200 mL 40% EtOAc:Hex, 200 mL 50% EtOAc:Hex, and 200 mL 75% EtOAc:Hex. Fractions of 35-40 mL were collected, and the desired product was present in fractions 10-17. These fractions were combined, and the solvent was removed by rotary evaporation followed by vacuum pumping. Purified ethyl-6-carboxy-*trans*-hex-2-enoate was a pale yellow oil (2.9405 g, 86.1%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.61 (bs, 1 H), 6.95

(dt, 1 H, *J*=15.66 Hz, *J*=6.92 Hz), 5.86 (d, 1 H, *J*=14.93 Hz), 4.19 (q, 2 H, *J*=7.13 Hz), 2.40 (t, 2 H, *J*=7.36 Hz), 2.28 (q, 2 H, *J*=7.73 Hz), 1.82 (quintet, 2 H, *J*=7.37 Hz), 1.29 (t, 3 H, *J*=6.77 Hz).

***trans*-Ethyl-7-*N,N*-(diphenyloxamido)-2-heptenoate.** As per the procedure reported by Tufariello[12], to an oven-dried 50 mL round bottom flask with a stir bar was added ethyl-6-carboxy-*trans*-hex-2-enoate (0.9895 g, 0.00532 mol) and dry benzene (10 mL) to give a clear solution. The reaction vessel was opened to a nitrogen outlet, and oxalyl chloride (0.80 mL, 0.00931) was added via syringe. The resulting mixture was stirred for 20 hours, during the first 2 of which the evolution of vapor was observed. The benzene was removed by vacuum pumping. To dry methylene chloride (16 mL) was added diphenyl amine (2.7188 g, 0.0161 mol) to give a clear solution. The reaction flask was cooled to 0°C in an ice water bath, and the diphenyl amine solution was added dropwise via syringe. A fine grey precipitate formed, and the reaction mixture was allowed to warm to room temperature. After 26 hours of stirring, to the mixture was added water (20 mL), and it was extracted with ether (3x 20 mL). The solvent was removed from the orange combined organic extracts by rotary evaporation and vacuum pumping. The crude product, a light green liquid, was purified on a 24/40 column of silica gel. The eluent was a gradient of 400 mL 20% EtOAc:Hex and 500 mL 25% EtOAc:Hex. Fractions of 40 mL were collected, and the desired product was present in fractions 10-17. These fractions were combined, and the solvent was removed by rotary evaporation followed by vacuum pumping. Purified *trans*-ethyl-7-(diphenyloxamido)-2-heptenoate was a light orange oil (1.7815 g, 99.4%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5 H), 7.24 (d, 5 H, *J*=7.29 Hz), 6.87 (dt, 1 H, *J*=15.64, *J*=6.94), 5.78 (d, 1 H, *J*=15.64 Hz), 4.15 (q, 2 H, *J*=7.14 Hz), 2.26 (t, 2 H, *J*=7.18 Hz), 2.20 (q, 2 H, *J*=6.98 Hz), 1.83 (quintet, 2 H, *J*=7.20 Hz), 1.26 (t, 3 H, *J*=6.44 Hz).

First samarium diiodide reaction. To an oven-dried 50 mL round bottom Schlenk flask was added *trans*-ethyl-7-(diphenyloxamido)-2-heptenoate (0.0891 g, 0.264 mmol) and a stir bar. Solvent traces were removed from this substance by vacuum pumping. The flask was backfilled with argon, and dry methylene chloride (1.3 mL) was added via syringe. The flask was cooled to -40°C in a chloroform/liquid nitrogen bath. To the flask was added triflic anhydride (0.10 mL, 0.48 mmol), and the resulting transparent solution was stirred for 15 minutes. The flask was removed from the cold bath, and the methylene chloride was removed by vacuum pumping to yield a yellow residue. To liberate the bound stir bar, dry tetrahydrofuran (1 mL) was added. The flask was once again cooled to -40°C in a chloroform/liquid nitrogen bath. Via separate syringes, samarium diiodide (12.0 mL, 0.1 M in THF, 1.2 mmol) and dry hexamethylphosphoramide (0.20 mL, 1.1 mmol) were added simultaneously. The deep-blue mixture was allowed to stir and heat to room temperature over 4 hours, during which time it became a greyish-yellow tone. Water (5 mL) and hexane (10 mL) were added, after which the organic layer was removed. The aqueous layer was extracted with ether (2x 10 mL). Water (5 mL) and brine (5 mL) were added to the aqueous layer, and it was extracted with ether (10 mL). The organic extracts were combined to give a pale yellow solution, and t-butylbenzene (0.0215 g, 0.160 mmol) was added. The remaining aqueous layer was a gooey yellow jelly-like mass. GC (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 5.816 min. (0.1306%), 10.796 min. (0.0533%), 15.483 min (0.1957%).

Second samarium diiodide reaction. To an oven dried 5 mL pointy bottom flask was added *trans*-ethyl-7-(diphenyloxamido)-2-heptenoate (0.0598 g, 0.177 mmol) and a stir bar. Solvent traces were removed from this substance by vacuum pumping. The flask was backfilled with argon,

and dry tetrahydrofuran (1.0 mL) was added via syringe. The flask was cooled to -40°C in a chloroform/liquid nitrogen bath. To the flask was added triflic anhydride (0.04 mL, 0.2 mmol). An oven dried 50 mL round bottom Schlenk flask was charged with samarium diiodide (7.5 mL, 0.1 M in THF, 0.70 mmol), hexamethylphosphoramide (0.13 mL, 0.75 mmol), and a stir bar and cooled to -40°C in a chloroform/liquid nitrogen bath. To this flask, via syringe, was transferred the clear amide/anhydride solution. A deep purple solution resulted. It was allowed to warm to room temperature and stir for 20 hours, during which time the deep purple color persisted. Water (5 mL) and hexane (10 mL) were added, after which the organic layer was removed. The aqueous layer was extracted with ether (2x 5 mL). The organic extracts were combined to give a pale yellow solution. The remaining aqueous layer was a gooey yellow jelly-like mass. GC (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 10.836 min. (0.01647%), 15.492 min. (0.02832%).

Third samarium diiodide reaction. To an oven dried 5 mL pointy bottom flask was added *trans*-ethyl-7-(phenyl-2-pyradyloxamido)-2-heptenoate (0.1508 g, 0.493 mmol) and a stir bar. Solvent traces were removed from this substance by vacuum pumping. The flask was backfilled with argon, and dry tetrahydrofuran (2.0 mL) was added via syringe. The flask was cooled to -40°C in a chloroform/liquid nitrogen bath. To the flask was added triflic anhydride (0.11 mL, 0.65 mmol). An oven dried 50 mL round bottom Schlenk flask was charged with samarium diiodide (20.0 mL, 0.1 M in THF, 2.00 mmol), hexamethylphosphoramide (0.35 mL, 2.0 mmol), and a stir bar and cooled to -40°C in a chloroform/liquid nitrogen bath. To this flask, via syringe, was transferred the cloudy amide/anhydride solution. A deep sea blue solution resulted. It was allowed to warm to room temperature and stir for 20 hours, during which time it changed to a greenish yellow color.

Water (5 mL) was added and the mixture turned first green then yellow. Hexane (10 mL) was added, after which the organic layer was removed. The aqueous layer was extracted with ether (2x 10 mL). The organic extracts were combined to give a pale yellow solution, and t-butyl benzene (0.0255g, 0.190 mmol) was added. The remaining aqueous layer was a gooey yellow jelly-like mass. A crude GC was obtained, and the solvent was removed by rotary evaporation. The crude product, a light yellow liquid, was purified on a 14/20 column of silica gel. The eluent was a gradient of 100 mL 5% EtOAc:Hex, 100 mL 10% EtOAc:Hex, 100 mL 20% EtOAc:Hex, 100 mL 40% EtOAc:Hex, 100 mL 60% EtOAc:Hex, 100 mL 75% EtOAc:Hex, and 100 mL 100% EtOAc. Fractions of 20-25 mL were collected, and thin layer chromatography did not show evidence of the desired product in any fraction. GC (crude) (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 5.840 min. (0.15389%), 10.806 min. (0.18488%), 11.010 min. (0.02845%), 11.450 min. (0.19769%).

Fourth samarium diiodide reaction. To an oven dried 5 mL pointy bottom flask was added *trans*-ethyl-7-(diphenyloxamido)-2-heptenoate (0.1653 g, 0.491 mmol) and a stir bar. Solvent traces were removed from this substance by vacuum pumping. The flask was backfilled with argon, and dry tetrahydrofuran (2.5 mL) was added via syringe. The flask was cooled to -40°C in a chloroform/liquid nitrogen bath. To the flask was added triflic anhydride (0.11 mL, 0.65 mmol). An oven dried 50 mL round bottom Schlenk flask was charged with samarium diiodide (19.5 mL, 0.1 M in THF, 1.95 mmol), hexamethylphosphoramide (0.35 mL, 1.9 mmol), and a stir bar and cooled to -40°C in a chloroform/liquid nitrogen bath. To this flask, via syringe, was transferred the clear amide/anhydride solution. A deep blue solution resulted. It was allowed to warm to room temperature and stir for 3.5 hours, during which time it changed to a light brown color. An aliquot

(1 mL) was taken via syringe. To the aliquot was added water (2 mL), and it was extracted with ether (3x 2 mL). To the combined aliquot organic layers was added t-butylbenzene (0.0070 g, 0.052 mmol), and a GC was taken of the aliquot organic layers. After a total of 4.5 hours, the reaction mixture was a bright orange tone. Water (10 mL) was added and the mixture was extracted with hexane (3x 10 mL). To the combined organic extracts was added t-butylbenzene (0.0187 g, 0.139 mmol), and a GC was taken of the resulting solution. The remaining aqueous mixture was added brine (20 mL), and the resulting mixture was extracted with ether (20 mL). A GC was taken of the ether extract. GC, aliquot (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 5.835 min. (0.42500%), 10.705 min. (0.00376%), 10.870 min. (0.01176%), 15.522 min. (0.02318%). GC, hexane extract (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 5.820 min. (0.05274%), 10.656 min. (0.01955%), 10.851 min. (0.01129%), 15.445 min. (unknown%). GC, ether extract (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 10.665 min. (0.00462%), 10.840 min. (0.01674%), 15.466 min. (0.04956%).

Ethyl-2-(2-oxocyclopentyl)ethanoate. To a 100 mL round bottom flask was added cyclopentanone (3.9995 g, 0.0476 mol) and *para*-toluenesulfonic acid (0.0340 g, 0.000179 mol). To the resulting solution was added tetrahydropyrrole (8.0 mL, 0.096 mol). The resulting mixture became warm, turned from clear to a brownish color, and evolved a mist of vapor. To the mixture was added benzene (48 mL), and the round bottom flask was fitted with a Dean Stark apparatus containing benzene (15 mL). To the Dean Stark apparatus was connected a condenser open to a nitrogen outlet. Cotton was wrapped around the Dean Stark apparatus, and the reaction mixture was heated to reflux with a heating mantle. After 1 hour, approximately 1 mL of water had collected in

the Dean Stark apparatus. After an additional hour, no additional water had collected. The reaction setup was disassembled, and the benzene was removed from the reaction flask by rotary evaporation. The flask was fitted with a condenser having a nitrogen outlet and placed in a water bath. To the flask was added dry acetonitrile (60 mL) via graduated cylinder and ethylbromoacetate (8.0 mL, 0.072 mol) dropwise via syringe. The bath was heated to 50°C, and the reaction was left stirring for 18 hours, during which time it went from an orange tone to a dark red/brown color. The flask was removed from the warm bath, and to it was added water (20 mL), brine (10 mL), hexane (25 mL), and ether (40 mL). The top 2 layers of the resulting 3 layer mixture were drawn off. The remaining aqueous layer was extracted with ether (2x 20 mL), and the solvent was removed from the combined organic layers by rotary evaporation and vacuum pumping. The crude product, a dark orange liquid, was purified on a 24/40 column of silica gel. The eluent was a gradient of 600 mL 25% EtOAc:Hex, 500 mL 50% EtOAc:Hex, 500 mL 75% EtOAc:Hex, and 500 mL 100% EtOAc:Hex. Fractions of 50 mL were collected, and the desired product, with other compounds, was present in fractions 5-8. These fractions were combined, and the solvent was removed by rotary evaporation followed by vacuum pumping. The product was further purified by reduced pressure short path distillation using a cow apparatus. The clear product (8 drops) was the first distillate portion and distilled at 101°C at vacuum line pressure. Purified ethyl-2-(2-oxocyclopentyl)ethanoate was a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, 1 H, *J*=7.14 Hz), 4.12 (q, 1 H, *J*=7.15 Hz), 2.70 (m, 1 H), 2.43 (m, 2 H), 2.31 (m, 2 H), 2.18 (m, 1 H), 2.07 (m, 1 H), 1.82 (m, 1 H), 1.64 (m, 1 H), 1.26 (t, 3 H, *J*=7.14 Hz). IR ($CDCl_3$, cm^{-1}) 3457 (w), 2978 (s), 2880 (m), 2256 (m), 1738 (s). GC, (initial temp. 70° C, initial time 2 min., rate 10° C/min., final time 20 min., final temp. 200° C) 10.998 min. MS (EI) m/z 170 (M^+, 12), 141 (8, $M^+ - CH_2CH_3$), 125 ($M^+ - OCH_2CH_3$, 87), 124 (100), 113 (13), 97 ($M^+ - COOCH_2CH_3$, 47), 96 (49), 83 ($M^+ - CH_2COOCH_2CH_3$, 71), 73 ($M^+ - COCH_2CH_2CH_2CHCH_2$, 33).

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