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A stereoselective multi-component synthesis of alpha-oxy-beta-substituted-beta-amino esters

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A Stereoselective Multi-Component Synthesis of α-Oxy-β-Substituted-β-Amino Esters

By

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ABSTRACT

JOFFE, AVRUM A Stereoselective Multi-Component Synthesis of
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Previous work has shown that chlorotitanium enolates of methylmethoxy acetate add to aryl aldimines in a stereoselective fashion. Aryl aldimines are non-enolizable, which contributes to their ability to add to the enolates. Previous attempts to add the enolates to enolizable alkyl aldimines were unsuccessful. By using a multi-component process in which the aldimine is synthesized in-situ, we have expanded the scope of this chemistry to the enolizable alkyl aldimines. Furthermore, the multi-component process has proven to be stereoselective for the anti-adduct.

Table of Contents

Index of Figures

Index of Tables

Index of Charts

A. Introduction:

β-amino acids and their derivatives are very important compounds because of their biological activity. One such example is the natural anti-cancer compound Taxol (Figure 1), which can be extracted from the bark of the Pacific Yew tree. The β-amino ester side chain is required for biological activity; many derivatives thereof have been synthesized in the laboratory.[1]

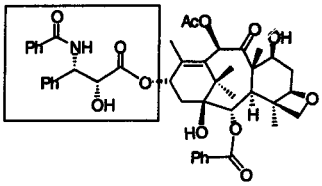

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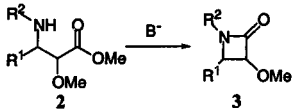
Figure 1. Taxol

β-amino esters are also conceptual synthetic intermediates of β-lactams. The β-lactam group of antibiotics includes Penicillin and Ampicillin. The conversion occurs readily in a strong base as an intramolecular nucleophilic acyl transfer (Figure 2).



2 **3**

Figure 2. Cyclization to the β-Lactam

B. Synthesis of α-oxy-β-substituted-β-amino Esters:

There are two conceptual approaches to the synthesis of α-oxy-β-substituted-β-amino esters. Figure 3 illustrates two retro-synthetic pathways of the esters, which show the two places for carbon-carbon bond formation.

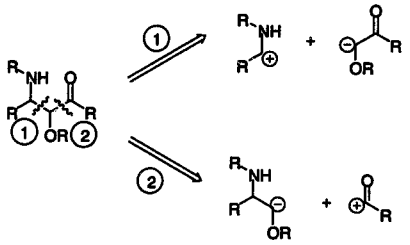


Figure 3: Retro-Synthetic Pathways to β-amino Esters

Pathway 1 is conceivable with the use of imine and enolate synthons in which an enolate can add electrophilically to an imine, forming the desired β-amino ester (Figure 4). Pathway 2 is conceivable with the use of eneamine and acid chloride synthons, for example (Figure 5). The substitution on the carbon-carbon double bond of the eneamine (labeled with an arrow) would have to be non-enolizable to ensure that the proper eneamine could be reacted.

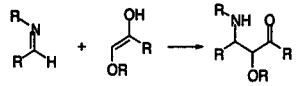


Figure 4: Pathway 1

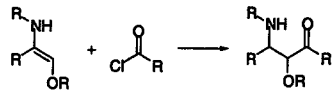


Figure 5: Pathway 2

A synthetic approach utilizing Pathway 1 is by addition of a pre-made aryl imine with a chlorotitanium enolate of methylmethoxy acetate, a method developed by Adrian and co-workers.[2] Figure 4 illustrates the addition of chlorotitanium enolates of methylmethoxy acetate (4) to pre-made aryl imines (5), resulting in the α-oxy-β-substituted-β-amino ester diastereomers (6,7). This addition results in two new stereogenic centers that are circled in Figure 6.

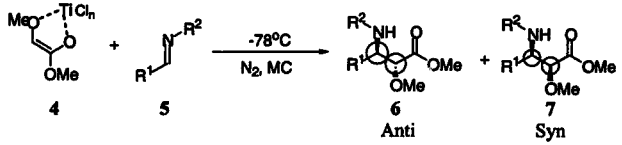


Figure 6: Enolate-Imine Reaction

The first diastereomer (6) has anti relative stereochemistry as the oxy and amino groups bend into different planes relative to the carbon chain backbone. The second diastereomer (7) has syn relative stereochemistry as the oxy and amino groups bend into the same plane relative to the carbon chain backbone.

C. Imine Formation

The formation of an imine can be accomplished by reaction between an aldehyde and an amine. A molecule of water is afforded as a byproduct (Scheme 1).

Scheme 1

8 **9** **5**

Imines undergo hydrolysis rather readily, and therefore the above scheme is an equilibrium. It is therefore necessary to remove the water from solution in order to drive the reaction toward imine formation.

The water molecule can be removed from the solution without having to physically isolate the imine. By using molecular sieves to soak up the water like a sponge, the reactants in the mixture will be freed of water molecules. There is also the possibility of using organometallics, whose use as a dehydrating agent has been explored by Professor Mark Snapper, et. al.[3] Snapper and co-workers were experimenting with enantioselective pathways to aryl amines, by which an imine is reacted with weakly nucleophilic dialkyl zincs in the presence of chiral catalysts. In reacting with water, dialkyl zinc will form methane gas (CH_4) and zinc salts. The methane would be in the form of gas which would bubble out of solution, and the zinc salts could be easily extracted into an aqueous phase during the workup of a reaction.

Adrian's group had a great deal of success isolating imines formed from o-anisidine and various non-enolizable, aryl aldehydes.[2] However, attempts to isolate enolizable, alkyl imines have thus far failed. Adrian's group hypothesized that the imines

themselves were enolizing and possibly polymerizing on removal from the solvent. So the imines may have been forming in solution, but they could not be isolated to use in subsequent reactions.

D. Imine Reactivity:

Previous work by Cozzi et. al. shows that the need for imine activation is dependant on the nature of the enolate being added to it.[4] Cozzi and co-workers successfully applied this in their use of imines of various aldehydes and p-anisidine, and their addition to enolates of 2-pyridyl thioesters to form β-lactams stereoselectively. The p-anisidine was sufficiently adding to the aldehydes to afford the desired imines, and the para-methoxyphenyl (PMP) imine substituent was found to be sufficiently activating for it to add to the enolates. Activation of the imine implies that it is being pushed into a more electrophilic state. Similar to the findings of Cozzi, imines with an ortho-methoxyphenyl (OMP) nitrogen substituent (Figure 7), have been found to be sufficiently activated by Adrian and co-workers.[5]

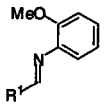


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Figure 7: ortho-methoxyphenyl N-Substituted Imine

Furthermore, Adrian et. al. found that the inductive effect of drawing electrons away from the nitrogen that the OMP substituent was promoting formation of the β-amino ester over the β-lactam. The lack of electron availability from the nitrogen prevents it from performing intramolecular nucleophilic attack.[5]

Another important feature of the OMP N-substitution is the ease at which the group can be removed leaving the free amine. One common method of OMP removal is that of Kronenthal which employs the CAN reagent (cerium ammonium nitrate).[6]

E. Multi-Component Synthesis

There are several advantages of using a multi-component synthesis over a linear synthesis. In linear syntheses there are multiple steps that require the introduction and removal of reagents, as well as the isolation of intermediates. In a multi-component synthesis, three or more reactants come together in one reaction vessel produce a compound that contains a part of each reactant with a core set of atoms.[7] Multi-component syntheses save a great amount of time and effort by eliminating reagent removal and intermediate isolation. In library synthesis using multi-component processes, any one of the types of inputs can be varied, affording a possible library as expansive as the available inputs. Commercial availability of reactants is therefore a limiting factor in developing libraries using multi-component syntheses.

Recent work by List et. al. examines multi-component formation of β-amino carbonyl compounds from ketones, aldehydes, and amines in Mannich type reactions using a proline catalyst (Figure 8).[8] The wide array of aldehydes used by List suggests that it is possible to synthesize imines of both enolizable and non-enolizable nature, and highly stereoselective β-amino carbonyls.

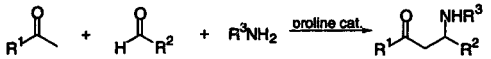


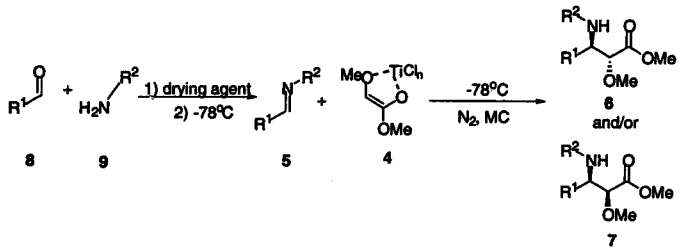
Figure 8: Multi-component Synthesis of β-substituted-β-amino carbonyl

Successes such as List's in using multi-component syntheses is highly suggestive of possible success in forming α-oxy-β-substituted-β-amino esters using various aldehydes and ortho-anisidine to form imines which can then add to chlorotitanium enolates of methylmethoxy acetate.

F. Thesis Proposal:

We were interested in determining a method to extend our stereoselective preparation of α-oxy-β-substituted-β-amino esters to both enolizable and non-enolizable imines. The inability to isolate enolizable imines from solution leads to the possibility of a multi-component synthesis in which the imine is formed in-situ to which the chlorotitanium enolates of methylmethoxy acetate (4) is added to afford the desired α-oxy-β-substituted-β-amino ester.

Scheme 2



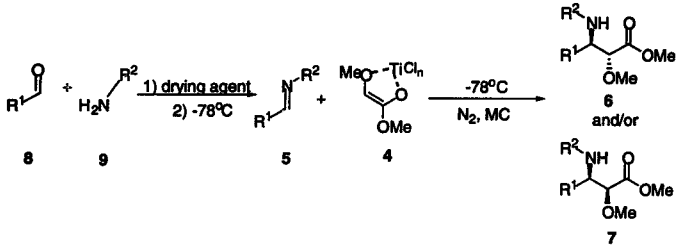
8 9 5 4 6 7

There are several questions that must be answered: What conditions are necessary to enable these multi-component syntheses? Will the use of a multi-component process have effects on diastereoselectivity and yields? Success will not only make syntheses of α-oxy-β-substituted-β-amino esters easier and more efficient with the multi-component process, but open the doors to a much more expansive synthetic library of α-oxy-β-substituted-β-amino incorporating all types of β-substitutions.

Results & Discussion:

We have developed an efficient multi-component method of preparation for α-oxy-β-substituted-β-amino esters that is both stereoselective and affords good to excellent yields (Scheme 2). This method does not require isolation of imine, nor does it require imine activation by Lewis acid. Most importantly, the imines are no longer limited to pre-made aryl imines.

Scheme 2



In initial studies, both enolizable and non-enolizable aldehydes were mixed with o-Anisidine. Since the imine formation affords one equivalent of water per equivalent of imine, a dehydrating agent was required to remove the water. 4 Å molecular sieves were our first choice. The chlorotitanium enolates of methylmethoxy acetate, formed according to the method of Adrian et. al.,[2] were then added to the imines in the next step of the multi-component process. It was found that the imines formed with enolizable aldehydes were not reacting with the enolates to afford the desired β-amino esters. One possibility we considered was that the presence of water was still having an effect on enolizable imines. The water was still present in solution, but just absorbed by the molecular sieves like a sponge. With that hypothesis in mind, the molecular sieves were

replaced with dimethyl zinc as the drying agent for syntheses with enolizable aldehydes. The use of dimethyl zinc did indeed afford us the desired adducts. Hereafter, imines prepared using molecular sieves as the dehydrating agent will be referred to as having been prepared using Method A. Likewise, imines prepared using dimethyl zinc as the dehydrating agent will be referred to as having been prepared by Method B. Further detail of these methods can be found in the experimental.

Scheme 2

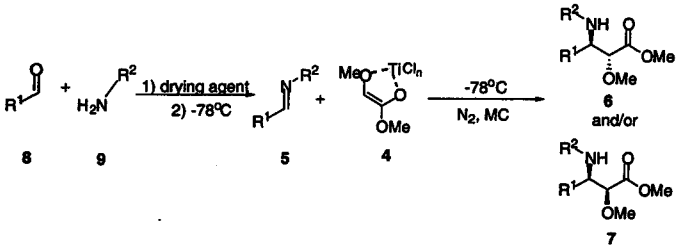


Table 1: Results with Non-Enolizable Imines

entry	R^1	R^2	% conver.[a]	yield (%)[b]	d.r. (A:S)[c]	Prev. yield (%)[d]	prev. d.r. (A:S)[e]
1	p-ClPh	OMP	> 99%	80%	92:8	95%	95:5
2	p-MePh	OMP	92%	72%	95:5	95%	92:8
3	b-naphthyl	OMP	> 99%	80%	96:4	87%	92:8
4	Ph	PMP	81%	71%	79:21	77%	79:21
5	t-Cinnamyl	OMP	> 99%	57%	99:1	-	-
6	Cyclohexenyl	OMP	94%	75%	96:4	-	-
7	tert-Bu	OMP	—	NR[f]	NR	NR	NR

[a]percent conversion determined using ^{1}H NMR of the crude reaction mixture. [b]Isolated Yield. [c]Determined using HPLC of the isolated material. [d]Data from reference #2. [e]Data from reference #2. [f]No Reaction.

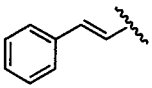
The stereoselection of all of the entries for the anti adduct is good to excellent, ranging from 79:21 (anti:syn) to 99:1. In using our synthesis with some of the aryl, non-enolizable imines used by Adrian et. al.[2] (entries 1-4,7) we found that the results were very similar. The ^{1}H-NMR spectra of the repeated entries confirms their identity in

relation to those produced by the previous group. Entry 4 was synthesized using an imine with a para-methoxyphenyl (PMP) N-substituent as opposed to the OMP. This was to demonstrate that the mechanism by which stereoselection was achieved was indeed similar to that observed in previous work by Adrian's group, as the use of PMP had been observed to decrease stereoselectivity.

Entry 7, with its tert-butyl group in the R^1 position was found to be unreactive just as had been found by the previous group. We believe this reaction to have failed due to the steric bulkiness of the tert-butyl group, not because it is an alkyl substituent as previously proposed. The steric hindrance must come into play during the enolate-imine reaction, as the imine has been synthesized previously by Adrian et. al.[5]

The two new β-amino esters with the t-cinnamyl (entry 5) and cyclohexenyl (entry 6) β-substitutions demonstrated very high diastereoselectivity for the anti adduct. Both substituents used non-enolizable aldehydes (Chart 1), and the conversions were excellent. Results suggest that using the multi-component process results in greater stereoselection overall, as all entries except #1 were more stereoselective.

Chart 1



t-cinnamyl

cyclohexenyl

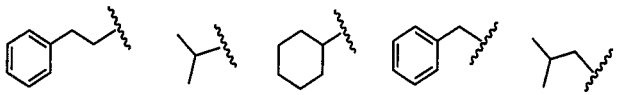
Table 2: Results with Enolizable Imines

entry	R^1	R^2	% conver.[a]	yield (%)[b]	d.r. (A:S)[c]
8	Hydrocinnamyl	OMP	> 99%	74%	92:8
9	Isobutyryl	OMP	> 99%	43%	83:17
10	Isovaleryl	OMP	> 99%	63%	83:17
11	Phenylacetyl	OMP	> 99%	38%	94:6
12	Cyclohexanyl	OMP	92%	75%	84:16

[a]percent conversion determined using ^{1}H NMR of the crude reaction mixture. [b]Isolated Yield.
[c]Determined using HPLC of the isolated material.

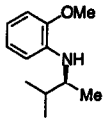
The stereoselectivities of the β-amino esters synthesized with alkyl, enolizable imines were also good to excellent, ranging from 83:17 (anti:syn) to 94:6. The yields were generally fair to good. A portion of entry 9 was lost in a spill during the workup. Entry 11 was very difficult to isolate as many other compounds appeared in the crude reaction mixture after the workup. It required repeated purification by column chromatography. The substituents of the enolizable alkyl imines can be seen in Chart 2.

Chart 2



A potential drawback of using dimethyl zinc as the dehydrating agent is its ability to act as a nucleophile. The organometallic could potentially add to the aldehyde interfering with imine formation, or it could add to the imine preventing β-amino ester formation. Dimethyl zinc is not a particularly good nucleophile, and so we were confident that it would perform as a dehydrating agent and not interfere with the

synthesis in any other way. However, trace amounts of the methyl adduct (11) were found in all of the reaction mixtures.



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In performing thin layer chromatography, we found that the methyl adduct has a much high R_f than the β-amino ester, and so it was quite easy to isolate using flash chromatography. The methyl adduct was present in reaction mixtures in quantities less than 5% relative to the β-amino ester, as determined using peak integration values in the HPLC of the crude reaction mixture (Figure 9). In most reaction mixtures, the methyl adduct was present in quantities less than 1%.

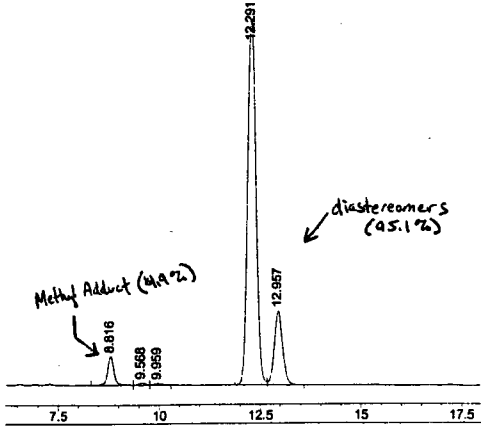
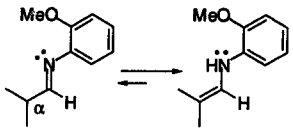


Figure 9: HPLC of Crude Reaction Mixture with Methyl Adduct

In using dimethyl zinc as a dehydrating agent for enolizable imine synthesis, we proposed an explanation for the previous inability to synthesize β-amino esters with enolizable imines. Work done by De Savignac examines the dynamics of enolizable, alkyl imines in solution in which there exists an equilibrium between the imine and the eneamine (Figure 10). The eneamine forms when the α-carbon is deprotonated and a double bond is formed.



Imine

Eneamine
very stable π-n-π
conjugated system*

Figure 10: Imine/Eneamine Equilibrium

De Savignac explains that the eneamine is stabilized by the presence of a π-n-π conjugated system. The first bonded pair of π-electrons come from the double bond formed when the imine enolizes. The non-bonded electron pair (n) is located on the nitrogen. And the second group of π-electrons comes from the phenyl ring of the o-methoxyphenyl substituent. Together an extended, stable conjugated system is formed. So in solutions of enolizable imines, the eneamine may be present in significant proportions. De Savignac also demonstrated the direct relationship between the pK_a of the amine and the imine/eneamine equilibrium. As the pK_a decreases, or the amine becomes more acidic, the lesser the amount of imine in the equilibrium.[9] The pK_a of o-Anisidine is approximately 4.49.

A subsequent experiment showed that the imine was in greater quantity after reaction with dimethyl zinc. A solution of isobutyraldehyde and o-anisidine (two components of entry 9) was examined with ^{1}H NMR both before and after the addition of dimethyl zinc. The characteristic imine peak at approximately 7.[illegible] ppm was barely visible out of the baseline of the spectrum taken before the addition of dimethyl zinc. The spectrum taken after the addition of dimethyl zinc shows an increase in imine concentration by nearly 4-fold (Figures A12).

There may be a mechanism involving dimethyl zinc that pushes the imine/eneamine in greater favor of the imine so that it may add to the enolate affording the desired adducts. As previously mentioned, dimethyl zinc will react with the water in the solution forming methane gas (CH_4) and zinc hydroxide ($Zn(OH)_2$). The zinc hydroxide must therefore be the key factor in pushing the imine/eneamine equilibrium to the imine, as it is the component that remains in solution.

A mechanism of chelation is most fitting for the proposed situation. The zinc hydroxide could potentially chelate with the non-bonded pair of electrons on the nitrogen, as well as the non-bonded pair of electrons on the oxygen of the methoxy group (Figure 11). Such a chelation could essentially lock the imine into form allowing to react with the enolate. It implies that the imine prefers to chelate with the zinc hydroxide rather than deprotonate and form the eneamine.

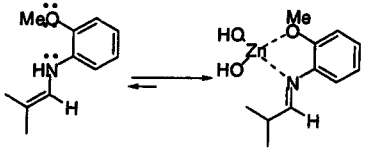


Figure 11: Imine Chelation with Zinc Hydroxide

The diastereomeric ratios were determined using HPLC. In all cases, the anti adduct was the first eluted, typically 0.5 minutes before the syn adduct (Figure 12). Figure 12 shows two spectra, in which different ratios of diastereomers were observed. The results could be confirmed by ^{1}H NMR spectra for only a few products in which the diastereomer peaks were sufficiently separated and easily distinguishable. But in most cases, the diastereomeric ratios were determined exclusively with HPLC.

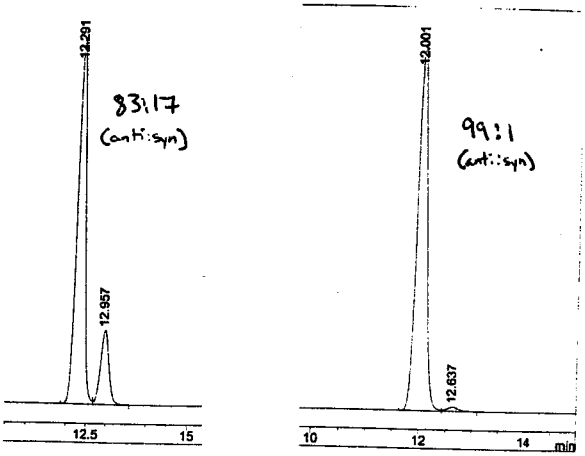
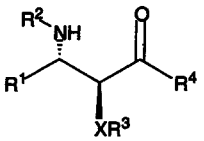


Figure 12: HPLC examples.

Overall, formation of α-oxy-β-substituted-β-amino esters by a multi-component process involving imine formation in-situ results in very good yields with very good stereoselectivity for the anti-adduct. As found by Adrian et. al., the degree to which the anti-adduct is selected varies by imine substituent whether it be aryl, enolizable, non-enolizable, alkyl, or a combination thereof. This leads to the possibility of a potentially extensive library of β-amino esters formed with chlorotitanium enolates, with four possible sites of diversity, of which the only foreseeable limitation is the number of available aldehydes.



X = O or S

Figure 13: Scaffold of Possible Library

Experimental

General.

Analytical high performance liquid chromatography (HPLC) was used to determine the quantitative Anti-Syn ratios using a Zorbax SB-C18 4.6mm x 25mm column. Acetonitrile was used as the eluting solvent in an acetonitrile-water solvent system. Several different gradients were used to separate the diastereomers (Table 3). All HPLC flow rates were 1mL per minute.

Table #3: HPLC Elution Gradients

Gradient #	% ACN at Start[a]	% ACN at Finish	Gradient Time[b]
1	55%	60%	12
2	55%	65%	12
3	55%	65%	13
4	55%	70%	12
5	55%	70%	13
6	55%	70%	15

[a]% Acetonitrile in H_2O, [b]Time over which acetonitrile concentration changes.

A Varian-200 spectrometer was used to record both ^1H (200 MHz) and ^{13}C (50 MHz) NMR spectra. Chemical shifts are reported in units of ppm from TMS which is used as the internal standard. Thin layer chromatography used Whatman K6F Silica Gel 60 Å (0.25mm) analytical glass plates. Flash chromatography was performed using Fischer silica gel 60 Å (200-425 mesh). Infrared (IR) spectra were recorded using a Mattson Genesis FTIR instrument.

All reactions were run under N_2 in dichloromethane (CH_2Cl_2) solvent. The CH_2Cl_2 was distilled from CaH_2 under N_2 immediately before use. All enolate formations were performed in 1 hour. Imine-enolate reaction times vary as indicated.

Typical Procedures.

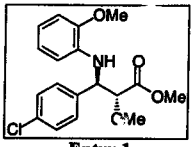
Preparation of Non-Enolizable Imines, Method A: To a stirred mixture of crushed 4 Å molecular sieves in 6mL of CH_2Cl_2 was added 1 molar equivalent of aldehyde, followed by approximately 1.05 molar equivalents of ortho-methoxyaniline. After 30 minutes at room temperature, the mixture is cooled to –80°C.

Preparation of Enolizable Imines, Method B: To a stirred solution of 1 molar equivalent of aldehyde in 6mL of CH_2Cl_2 was added approximately 1.05 molar equivalents of ortho-methoxyaniline. After 15 minutes at room temperature, 1.06 molar equivalents of dimethyl zinc $(CH_3)_2Zn$ (2M in toluene) was added. Bubbling commenced immediately indicating the formation of methane gas and zinc salts. The solution was allowed to stir for an additional 15 minutes at room temperature before being cooled to –80°C.

Quench: For reactions performed using method A, the cold reaction mixture was suction-filtered directly into a stirring solution of 1M HCl and allowed to warm to room temperature. For reactions performed using method B, the 1M HCl was added to the cold reaction mixture which was then removed from the cold bath and allowed to warm to room temperature with stirring.

Workup: In all cases the quenched reaction mixtures were transferred into a separatory funnel, shaken, and separated. The aqueous phase was extracted twice with CH_2Cl_2. The combined organics were washed with a solution of saturated $NaHCO_3$, followed by a solution of saturated NaCl. The organic phase was then dried with $MgSO_4$, filtered, and concentrated in vacuo.

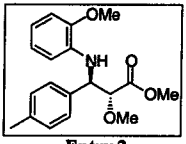
Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-(4-chloro)phenylpropanoate



Entry 1

Reaction time was 3 hours. The crude is a brown oil, and isolated as a yellow oil that slowly crystallizes. The isolated yield was 80% with a diastereomeric ratio of 92:8 (anti:syn). R_f=0.23 (SiO_2, 40% hexane/CH_2Cl_2); 200 MHz ^{1}H NMR δ 7.25 (s, 4H), 6.71 (m, 3H), 6.40 (dd, 1H, J = 2.0Hz, J = 2.0Hz), 4.81 (d, 1H, J = 5.0Hz), 4.19 (d, 1H, J = 5.0Hz), 3.89 (s, 3H), 3.68 (s, 3H), 3.45 (s, 3H); The ^{1}H NMR peaks confirm the identity of the compound based on previous characterization by Adrian et. al.[2]

Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-(4-methyl)phenylpropanoate

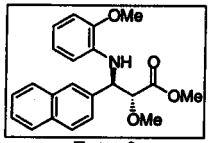


Entry 2

Reaction time was 20 hours. The crude is a brown oil that slowly crystallizes. The isolated is a pale yellow oil that crystallized more quickly. The isolated yield was 72%, with a diastereomeric ratio of 95:5. The isolated was re-crystallized yielding small, white crystals with a melting point of 83°C-85°C. R_f=0.10 (SiO_2, 30% hexane/CH_2Cl_2); 200 MHz ^{1}H NMR δ 7.19 (d, 2H, J = 8.0Hz), 7.07 (d, 2H, J = 8.0Hz), 6.67 (m, 3H), 6.46 (dd, 1H, J = 7.0Hz, J = 2.0Hz), 4.81 (d, 1H, J = 5.0Hz), 4.20 (d, 1H, J = 5.0Hz), 3.88 (s, 3H),

3.67 (s, 3H), 3.44 (s, 3H), 2.28 (s, 3H); The ^{1}H NMR peaks confirm the identity of the compound based on previous characterization by Adrian et. al.[2]

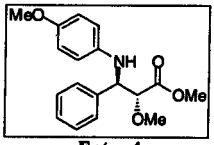
Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-naphthylpropanoate



Entry 3

Reaction time was 19 hours. The crude is a brown oil that crystallized quickly. The isolated was a pale yellow that crystallized quickly. The isolated yield is 80%, with a diastereomeric ratio of 96:4 (anti:syn). The isolated was re-crystallized in 95% ethanol, yielding white needles with a melting point of 119°C-120°C. R_f=0.17 (SiO_2, 25% hexane/CH_2Cl_2); 200 MHz ^{1}H NMR δ 7.78 (m, 4H), 7.44 (m, 3H), 6.68 (m, 3H), 6.47 (dd, 1H, J = 7.0Hz, J = 2.0Hz), 5.48 (bs, 1H), 4.99 (d, 1H, J = 5.0Hz), 4.28 (d, 1H, J = 5.0Hz), 3.91 (s, 3H), 3.63 (s, 3H), 3.45 (s, 3H); The ^{1}H NMR peaks confirm the identity of the compound based on previous characterization by Adrian et. al.[2]

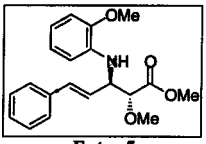
Methyl 3-(4-methoxyphenyl)amino-2-methoxy-3-phenylpropanoate



Entry 4

Reaction time was 23 hours. The crude is a brown oil and isolated as a yellow oil. The isolated yield is 71%. The diastereomeric ratio is 79:21 (anti:syn). R_f=0.26 (SiO_2, 2.5/37.5/60% ether/hexane/CH_2Cl_2). ^{1}H NMR; δ 7.28 (m, 5H), 6.70 (d, 2H, J = 9.0Hz), 6.56 (d, 2H, J = 9.0Hz), 4.75 (d, 1H, J = 5.0Hz), 4.18 (d, 1H, J = 5.0Hz), 3.69 (s, 3H), 3.62 (s, 3H), 3.43 (s, 3H); The ^{1}H NMR peaks confirm the identity of the compound based on previous characterization by Adrian et. al.[2]

Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-t-cinnamylpropanoate

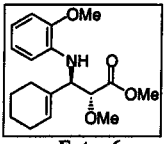


Entry 5

Reaction time was 23 hours. The crude product was a yellow-orange oil that crystallized quickly. The diastereomeric ratio of the crude adduct was 99:1 (anti:syn). The ^{1}H-NMR of the crude showed very little contaminant, if any. The crude yield was 98%. The solid was then recrystalized in 95% ethanol, resulting in 57% yield of the anti diastereomer only. R_f = 0.25 (SiO_2, 1% Et_2O/CH_2Cl_2). IR (Thin Film); 3403, 2946, 2835, 1744, 1675, 1597, 747 cm^{-1}; 200 MHz ^{1}H NMR; δ 7.28 (m, 5H), 6.77 (m, 4H), 6.60 (d, 1H, J = 16.0

Hz), 6.17 (dd, 1H, J = 16.0, J = 7.0 Hz), 4.85 (d, 1H, J = 5.0 Hz), 4.50 (m, 1H), 4.12 (d, 1H, J = 4.0 Hz), 3.88 (s, 3H), 3.76 (s, 3H), 3.48 (s, 3H). Elemental Analysis calculated for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; found: C, 70.32; H, 6.79; N, 4.06; HPLC (gradient #3): t_R = 12.0 min (major diastereomer), t_R = 12.6 min (minor diastereomer).

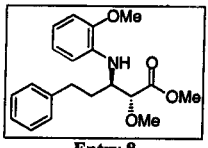
Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-cyclohex(1-ene)propanoate



Entry 6

Reaction time was 19 hours. The crude product is a brown oil and isolated as a yellow oil. The diastereomeric ratio is 96:4 (Anti:Syn). R_f = 0.17 (SiO_2, 25% hexane/CH_2Cl_2). The isolated yield is 75%. IR (Thin Film): 3415, 2929, 2835, 1749, 1684, 1596, 1454, 1116, 1028, 733cm^{-1}; 200 MHz ^{1}H NMR; δ 6.73(m, 4H), 6.57 (d, 1H, J = 8.0Hz), 5.68 (m, 1H), 4.96 (m, 1H), 4.08 (d, 1H, J = 5.0Hz), 3.86 (s, 3H), 3.73 (s, 3H), 3.43 (s, 3H), 2.04 (m, 4H), 1.52 (m, 4H); HRMS calculated for $C_{18}H_{25}NO_4$, 319.1784, found 319.1783; HPLC (gradient #5): t_R = 11.9 min (major diastereomer), t_R = 12.3 min (minor diastereomer).

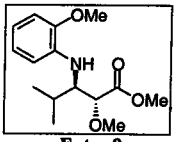
Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-hydrocinnamylpropanoate



Entry 8

Reaction time was 3 hours. The diastereomeric ratio was determined to be 92:8 (anti:syn). The isolated yield was 74%. R_f = 0.11 (SiO_2, 35% hexane/CH_2Cl_2). IR (Thin Film): 3399, 2946, 2831, 1749, 1596, 1514, 1454, 1121, 1023, 739 cm^{-1}; 200 MHz ^1H NMR; δ 7.22 (m, 5H), 6.80 (m, 4H), 6.64 (d, 1H, J = 8.0 Hz), 4.48 (m, 1H), 3.87 (s, 3H), 3.76 (m, 1H), 3.66 (s, 3H), 3.35 (s, 3H), 2.73 (m, 2H), 1.90 (m, 2H); HRMS calculated for $C_2H_{25}NO_4$, 343.1784, found 343.1780; HPLC (gradient #6): t_R = 14.7 min (major diastereomer), t_R = 15.2 min (minor diastereomer).

Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-isobutyrylpropanoate

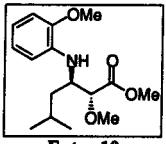


Entry 9

Reaction time was 24 hours. The diastereomeric ratio was determined to be 83:17 (anti:syn). The isolated yield was 43%. R_f = 0.10 (SiO_2, 10% hexane/CH_2Cl_2). IR (Thin Film): 3426, 2957, 1749, 1602, 1509, 1454, 1028, 733 cm^{-1}; 200 MHz ^1H NMR; δ 6.72 (m, 4H), 4.38 (d, 1H, J = 8.0 Hz), 4.01 (m, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 3.38 (s, 3H), 2.07 (m, 2H), 1.25 (s, 1H), 0.96 (dd, 6H, J = 6.0Hz, J = 7.0Hz); HRMS calculated

for $C_{15}H_{23}NO_4$, 281.1627, found 281.1633; HPLC (gradient #1): t_R = 11.7 min (major diastereomer), t_R = 12.3 min (minor diastereomer).

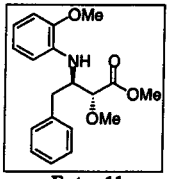
Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-isovalerylpropanoate



Entry 10

Reaction time was 23 hours. The crude is a brown oil and isolated as a brown oil. The diastereomeric ratio is 83:17 (Anti:Syn). The isolated yield is 63%. R_f = 0.17 (SiO_2, 10% hexane/CH_2Cl_2); IR (Thin Film): 3410, 2951, 1749, 1602, 1509, 1454 cm^{-1}; 200 MHz ^1H NMR; δ 6.78 (m, 4H), 4.38 (m, 1H), 3.96 (d, 1H, J = 3.0Hz), 3.85 (s, 3H), 3.77 (s, 3H), 3.36 (s, 3H), 1.63 (m, 2H), 1.19 (m, 1H), 0.87 (dd, 6H, J = 7.0Hz, J = 6.0Hz); HRMS calculated for $C_{16}H_{25}NO_4$, 295.1770, found 295.1776; HPLC (gradient #2): t_R = 11.2 min (major diastereomer), t_R = 11.8 min (minor diastereomer).

Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-(phenyl)acetylpropanoate



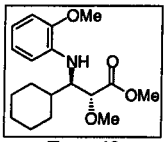
Entry 11

Reaction time was 24 hours. The diastereomeric ratio is 94:6 (Anti:Syn).

The crude is a brown oil and isolated as a yellow oil. The isolated yield is 30%.

R_f = 0.14 (SiO_2, 20% hexanes/CH_2Cl_2). IR (Thin Film): 3405, 2924, 1749, 1602, 1509, 1454, 1219, 1121, 1028, 733cm^{-1}; 200 MHz ^1H NMR; δ 7.25 (m, 5H), 6.76 (m, 4H), 4.55 (m, 1H), 4.12 (m, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.42 (s, 3H), 2.91 (d, 2H, J = 6.0Hz); HRMS calculated for $C_{19}H_{23}NO_4$, 329.1627, found 329.1627; HPLC (gradient #4): t_R = 10.1 min (major diastereomer), t_R = 11.3 min (minor diastereomer).

Methyl 3-(2-methoxyphenyl)amino-2-methoxy-3-cyclohexanylpropanoate



Entry 12

Reaction time was 24 hours. The crude is a brown oil and isolated as a yellow oil. The diastereomeric ratio is 84:16 (Anti:Syn). The isolated yield was 75%. R_f = 0.10 (SiO_2, 40% hexane/CH_2Cl_2). IR (Thin Film): 3421, 2924, 2848, 1744, 1520, 1247, 1023, 744

cm^{-1}; 200 MHz ^1H NMR; δ 6.73(m, 4H), 4.45 (m, 1H), 4.29 (m, 1H), 4.02 (d, 1H, J = 2.0Hz), 3.85 (s, 3H), 3.65 (s, 3H), 3.38 (s, 3H), 1.39 (m, 10H); HRMS calculated for $C_{18}H_{27}NO_4$, 321.1940, found 321.1937; HPLC (gradient #6): t_R = 15.7 min (major diastereomer), t_R = 16.9 min (minor diastereomer).

References

1 Borman, S. *Chem. Eng. News.* **1991,** 69(35), 11-18.

2 Adrian, J.C., Jr., Barkin, J.L., Fox, R.J., Chick, J.E., Hunter, A.D., Nicklow, R.A. *J. Org. Chem.* **2000,** 65, 6264-6267.

3 Porter, J.R., Traverse, J.F., Hoveyda, A.H., Snapper, M.L. *J. Am. Chem. Soc.* **2001,** 123, 984-985.

4 Annunziata, R., Cinquini, M., Cozzi, R., Borgia, A. L., *J. Org. Chem.* **1992,** 57, 6339-6342.

5 Adrian, J.C., Jr., Barkin, J.L., Hassib, L. *Tetrahedron Letters.* 1999, 40, 2457-2460.

6 Kronenthal, D.R., Han, C.Y., Taylor, M.K. *J. Org. Chem.* **1982,** 47, 2765-2768.

7 Armstrong, R.W., Combs, A.P., Tempest, P.A., Brown, S.D., Keating, T.A. *Acc. Chem. Res.* **1996,** 29, 123-131.

8 List, B., Pojarliev, P., Biller, W.T., Martin, H.J. *J. Am. Chem. Soc.* **2002,** 124, 827-833.

9 De Savignac, A., Bon, M., Lattes, A. *Bull. Chim. Soc.* **1972,** 8, 3167-3173.

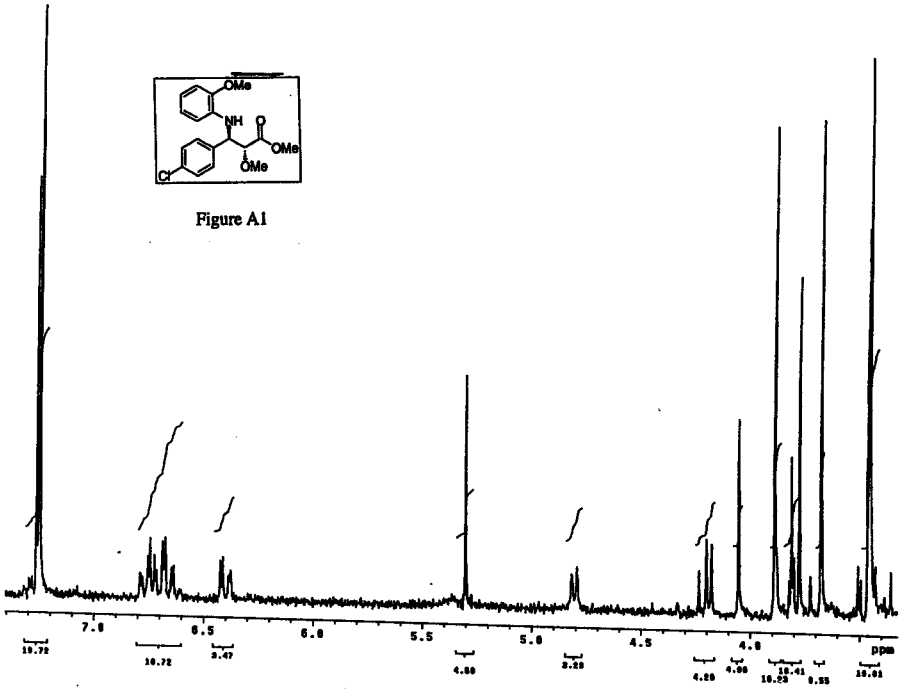

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Figure A1

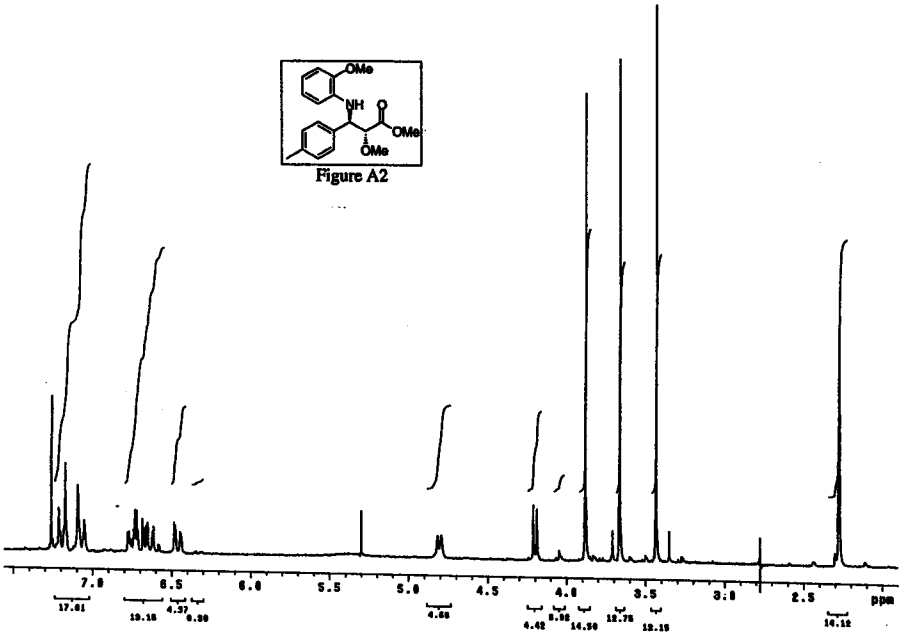
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Figure A2

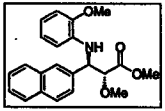
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Figure A3

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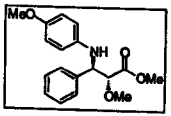


Figure A4

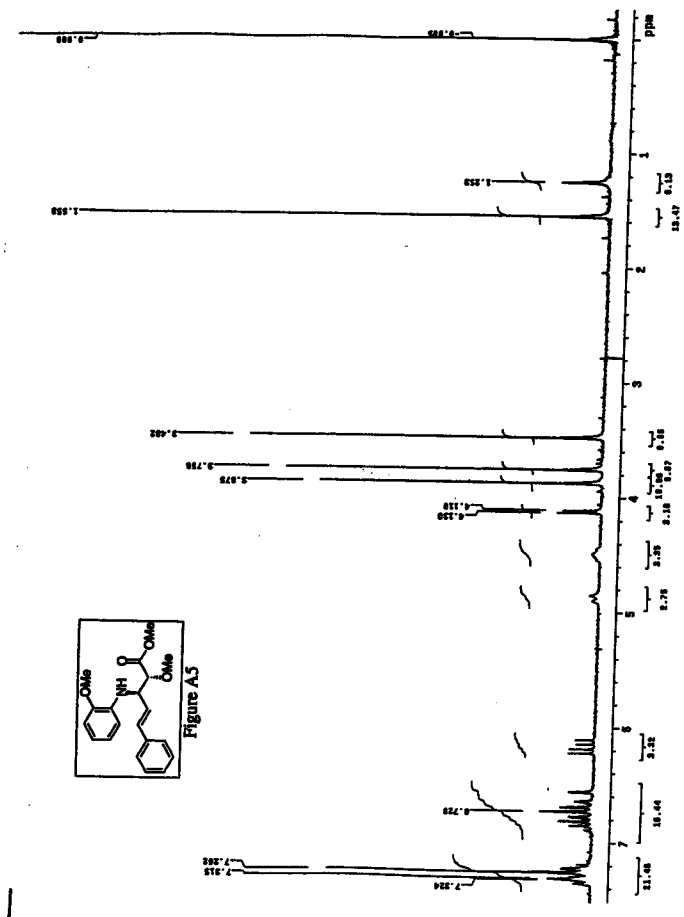


Figure A5

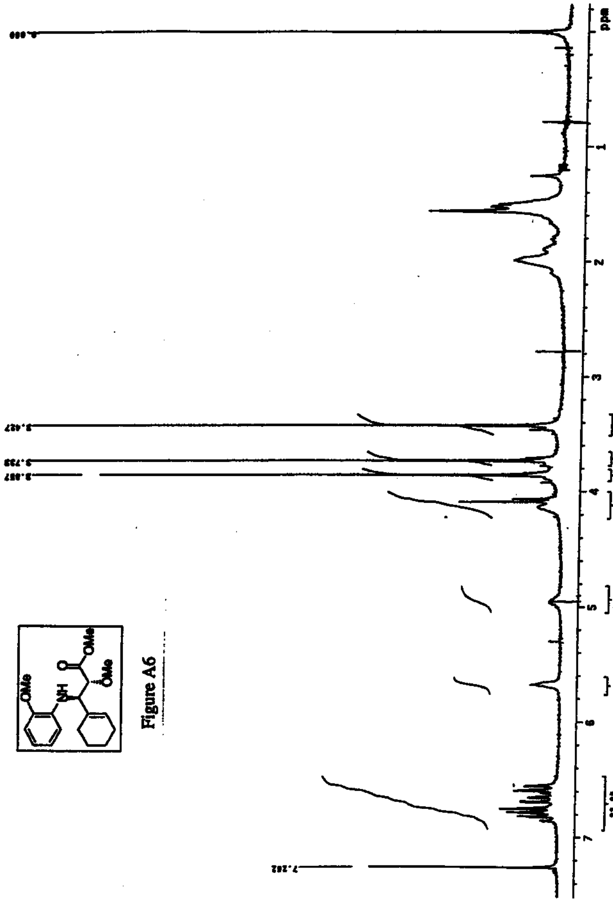
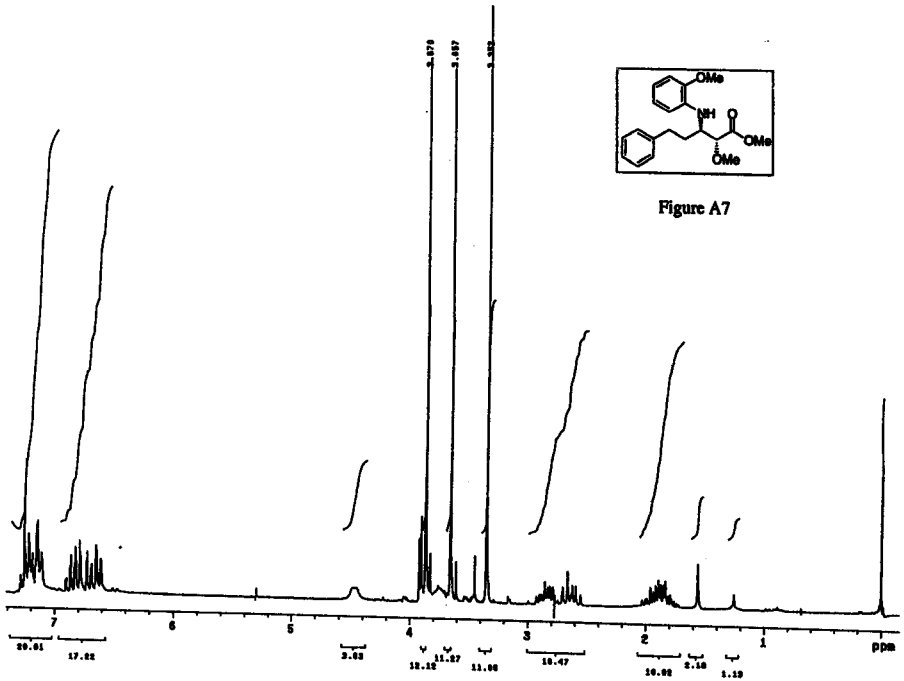


Figure A6



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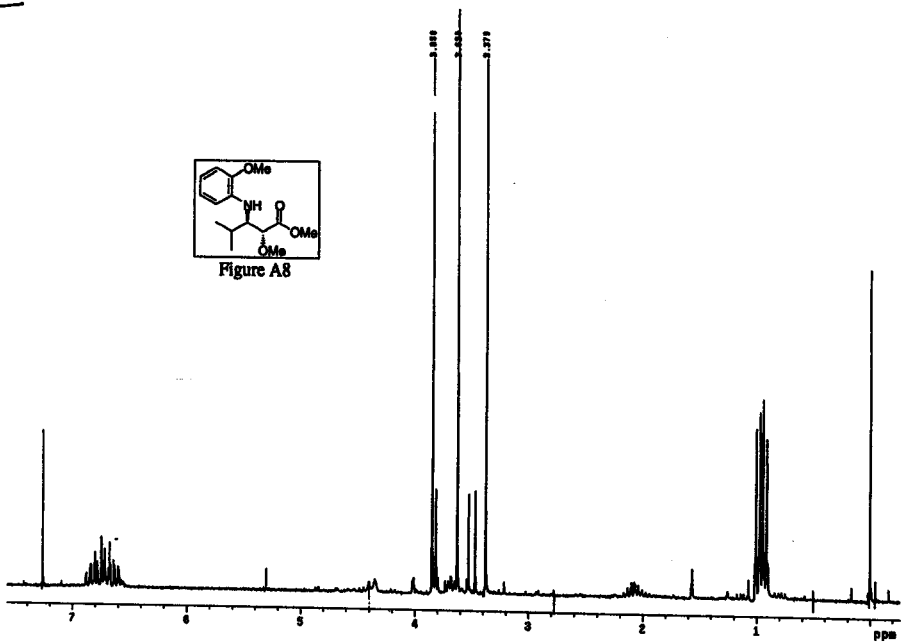


Figure A8

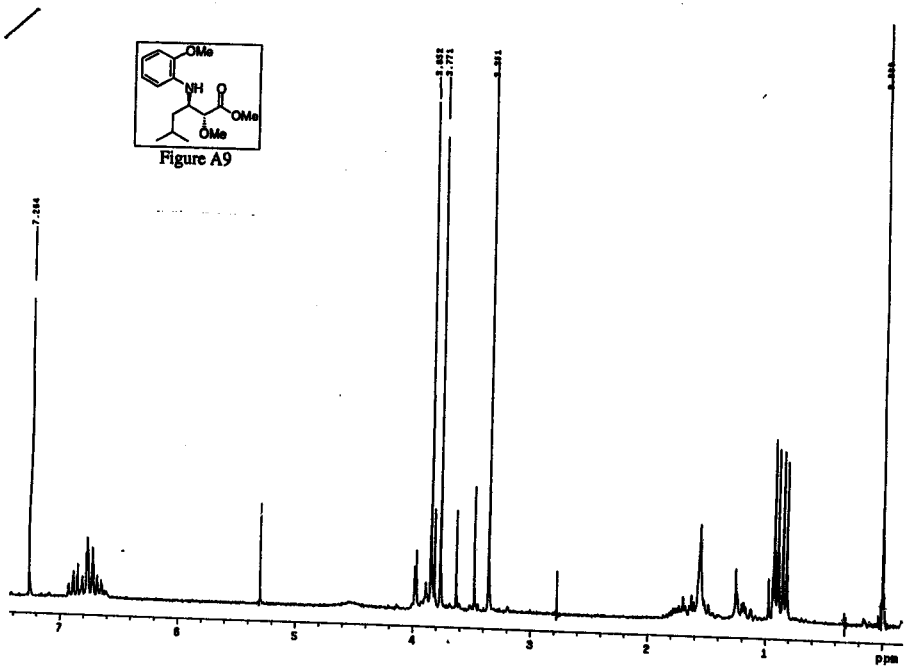
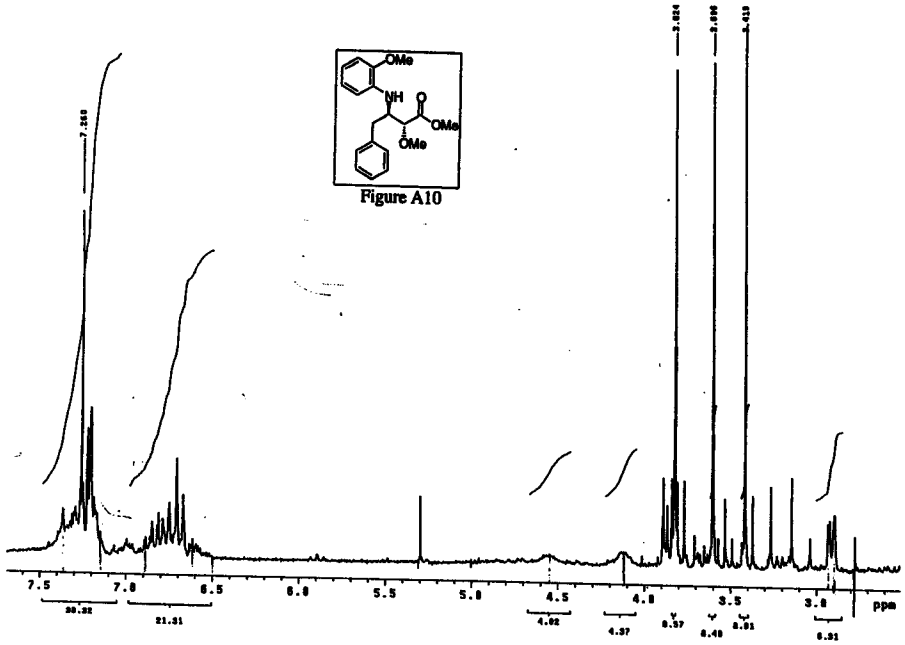


Figure A9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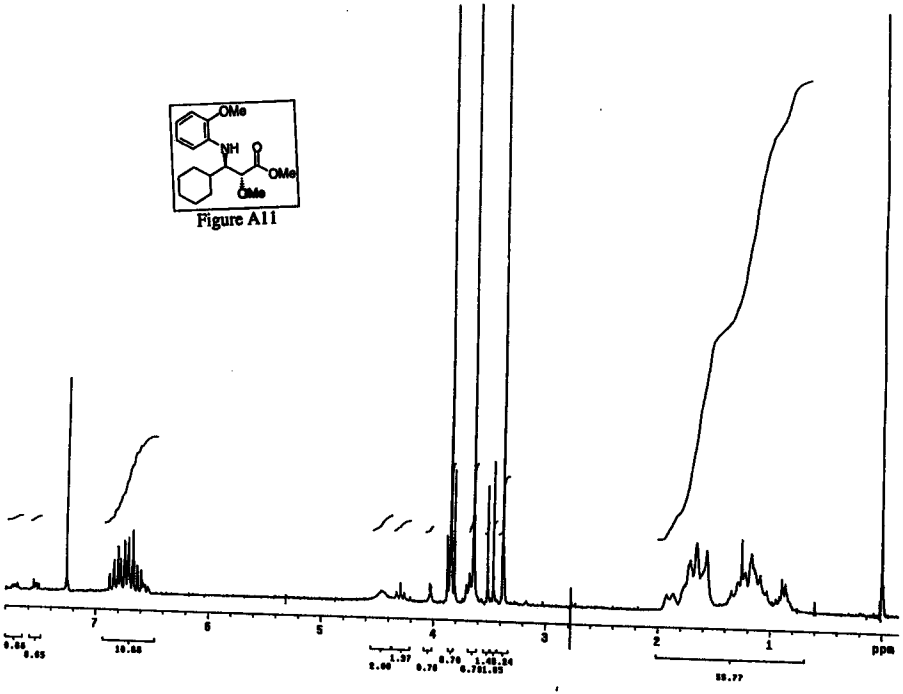

Figure A11

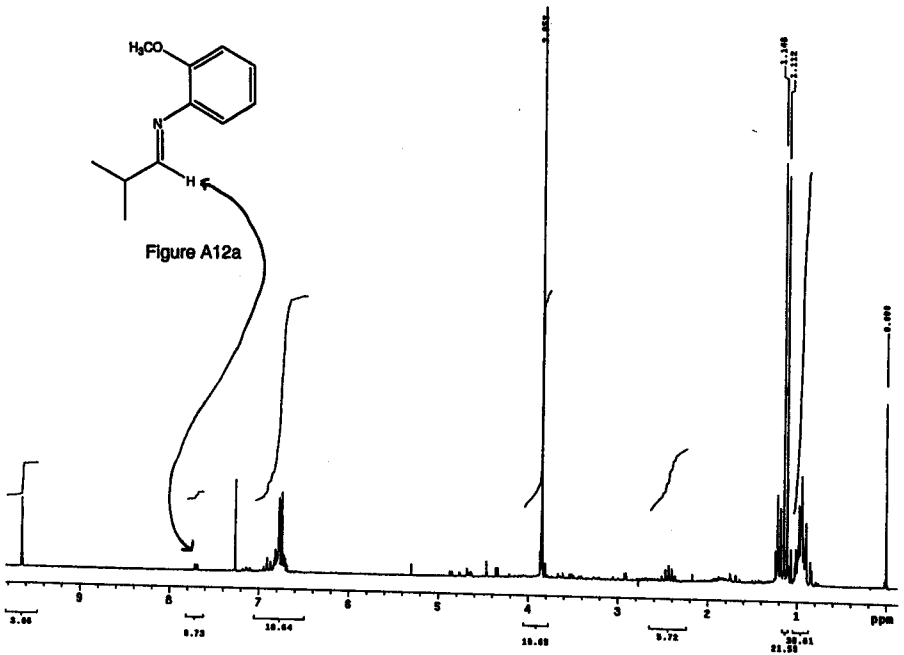

Figure A12a

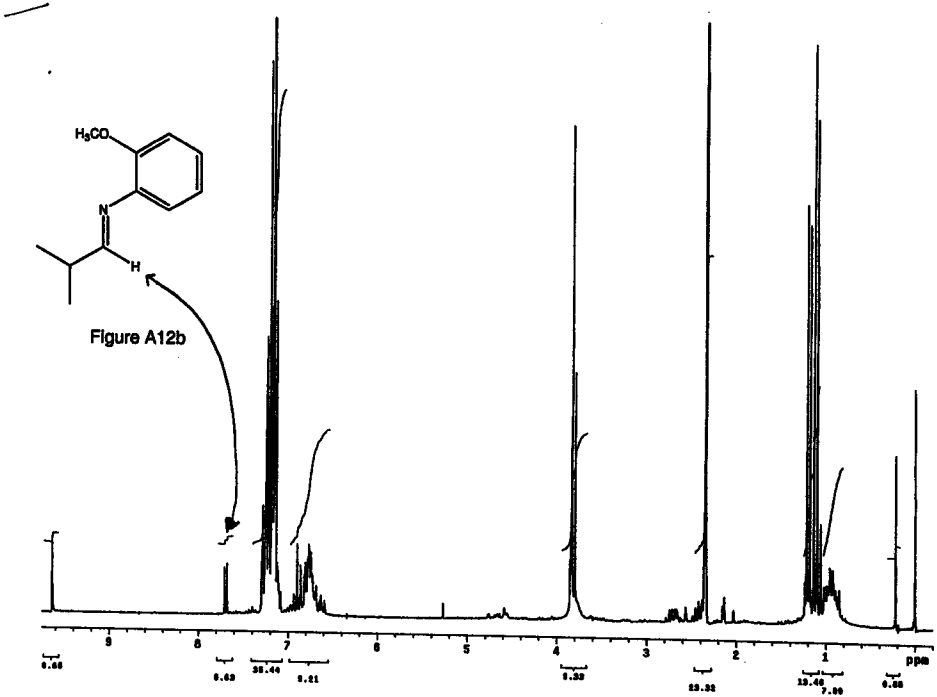

Figure A12b