Pergamon

Tetrahedron 58 (2002) 7449–7461

TETRAHEDRON

A one-pot synthesis of 3-amino-3-arylpropionic acids

C. Y. K. Tan[a] and D. F. Weaver[a,b,*]

[a]*Department of Chemistry, Queen's University, Kingston, Ont., Canada, K7L 3N6*
[b]*Department of Medicine (Neurology) and Chemistry, Dalhousie University, Halifax, NS, Canada B3H 4J3*

Received 24 September 2001; revised 9 July 2002; accepted 11 July 2002

Abstract—3-Aminopropionic acids (β-amino acids) are biologically active compounds of interest in medicinal and pharmaceutical chemistry. Twenty-one 3-amino-3-arylpropionic acids were synthesized via a facile one-pot synthesis. In addition, a series of mechanistic studies have been performed to optimize the production of these β-amino acids. The reaction mechanism of this one-pot synthesis of β-amino acids, as well as the electronic effect of *para*-substitution and the influence of solvent polarity on the proposed reaction mechanism are discussed.

1. Introduction

The synthesis of 3-aminopropionic acids, also known as β-amino acids, has recently attracted increasing attention due to their significant pharmacological properties.[1] β-Amino acids are not only components of pharmacologically relevant natural products,[2] but are also of great value in the synthesis of complex compounds, such as peptides[3] and β-lactam antibiotics.[4] These properties have resulted in numerous recent studies pertaining to their syntheses.[5] Owing to their importance as potential drugs and drug intermediates in medicinal chemistry, the search for simple scaleable syntheses of β-amino acids is of continuing interest.

Most recent methods for the synthesis of β-amino acids require extensive multi-step preparations.[5] In addition, over the years, many works that utilized the condensation of an aldehyde, malonic acid and an amine to generate other 3-aminopropionic acids have been reported.[6] However, in this paper, we report a facile and efficient one-pot synthesis of aromatic substituted 3-aminopropionic acids, 3-amino-3-arylpropionic acids (Part I). In addition, we also studied the reaction mechanism (Part II) to optimize the yield of these 3-amino-3-arylpropionic acids. This synthesis is a substantive modification of a reaction described by Rodionow and Postovskaja for the preparation of cinnamic acids.[7]

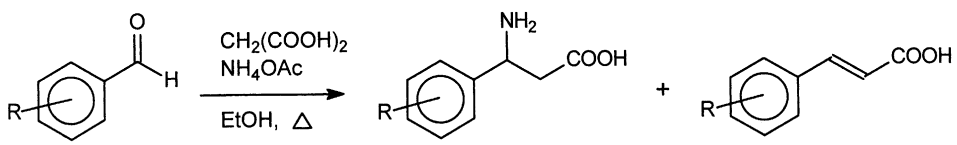
In Part I, the synthesis of twenty-one 3-amino-3-arylpropionic acids will be described; in Part II, a series of mechanistic studies was performed. These studies have three goals: Goal (i) to investigate the reaction mechanism of this one-pot synthesis of β-amino acids, Goal (ii) to evaluate the influence of electronic effects of substituents at the *para*-position upon the reaction mechanism, and Goal (iii) to determine the role that solvent polarity plays in the product distribution.

2. Results and discussion

2.1. Part I

This synthesis involves a single step in which a benzaldehyde derivative was refluxed with 1 equiv. of malonic acid and 2 equiv. of ammonium acetate in ethanol (Scheme 1) to give the 3-amino-3-arylpropionic acid and its corresponding cinnamic acid as side product.

The 3-amino-3-arylpropionic acid was then isolated by

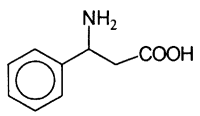
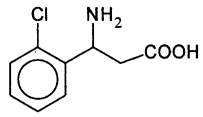
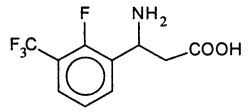
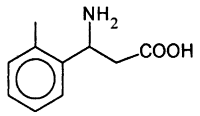
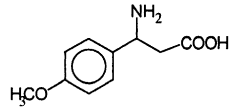
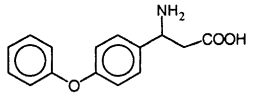
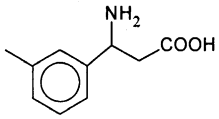
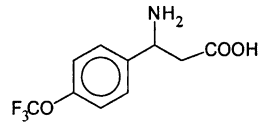
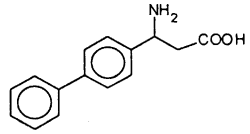
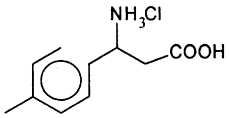
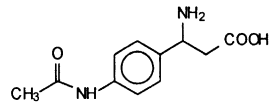
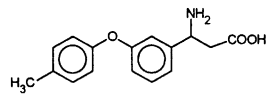
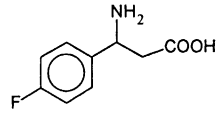
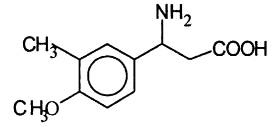
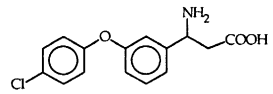
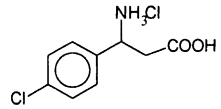
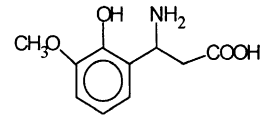
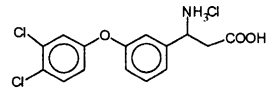
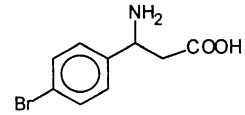
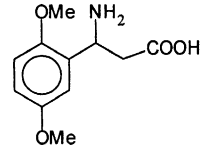
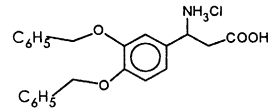


Scheme 1. One-pot synthesis of 3-amino-3-arylpropionic acids.

Keywords: 3-amino-3-arylpropionic acids; β-amino acids; one-pot synthesis; reaction mechanism.
* Corresponding author. Tel.: +1-902-494-7183; fax: +1-902-494-1310; e-mail: weaver@chem3.chem.dal.ca

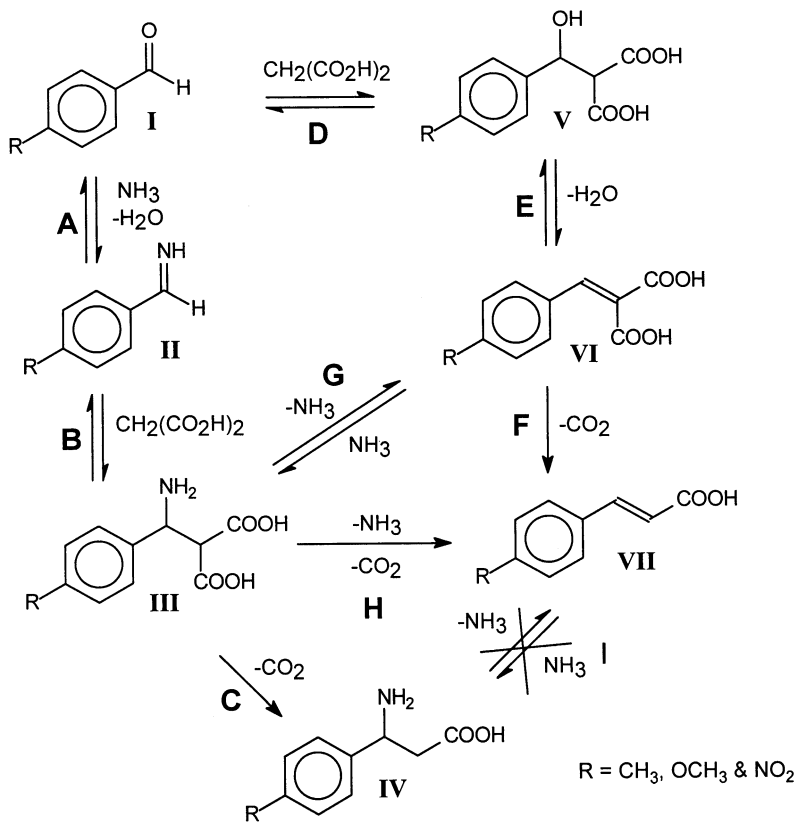
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00824-4

Table 1. Structures and yields of synthesized 3-amino-3-arylpropionic acids

Compounds	Yield (%)	Compounds	Yield (%)	Compounds	Yield (%)
(1) 	67	(8) 	28	(15) 	16
(2) 	19	(9) 	70	(16) 	68
(3) 	46	(10) 	46	(17) 	40
(4) 	54	(11) 	30	(18) 	56
(5) 	62	(12) 	53	(19) 	33
(6) 	65	(13) 	17	(20) 	43
(7) 	69	(14) 	22	(21) 	36

filtration of the reaction mixture and was subjected to further work up as described in Section 3. However, there were preparations in which the 3-amino-3-arylpropionic acid remained dissolved in the reaction mixture. In these cases, the corresponding cinnamic acid, which was the minor side product, precipitated out of solution. The cinnamic acid was removed by filtration and the filtrate was evaporated to give the corresponding 3-amino-3-arylpropionic acid. The crude 3-amino-3-arylpropionic acid was purified as described in Section 3. Using these procedures, twenty-one 3-amino-3-arylpropionic acids were synthesized in yields ranging from 17 to 70% as shown in Table 1. Among these 3-amino-3-arylpropionic acids, nineteen are novel compounds.

This one-step reaction was affected by both the steric and



Scheme 2. The proposed reaction mechanism of the synthesis of 3-amino-3-arylpropionic acids.

electronic effects of the substituents on the phenyl ring. Compounds with a substituent at the *ortho*-position of the phenyl ring give lower yields of the 3-amino-3-arylpropionic acids due to a steric effect. Compounds **2**, **8** and **13**–**15**, have yields of less than 30%. An obvious trend was identified by comparing **2**, **3** and **4**, as the methyl substituent was moved from the *ortho* to the *meta* and then to the *para*-positions, the corresponding yield increased. In terms of electronic effect, substituents with electronic-donating groups in the *para*-position (i.e. **9** and **16**) lead to higher yield than with electron-withdrawing groups including the non-substituted **1**. Further investigation on the electronic effect is discussed in Part II.

The goal of our synthetic work is to synthesize β-amino acids to be screened in high throughput assays for biological activity relevant to neurologic disease. Since this is preliminary screening work, the syntheses were developed to rapidly produce inexpensive racemic mixtures. However, we anticipate that the use of a chiral amine (rather than ammonium acetate) would impart asymmetry and would support an asymmetric version of this reaction.

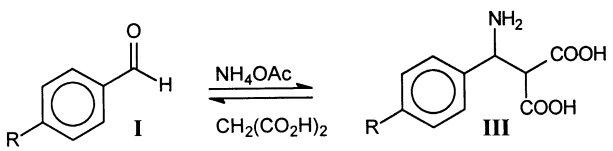
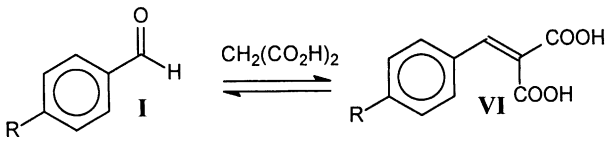
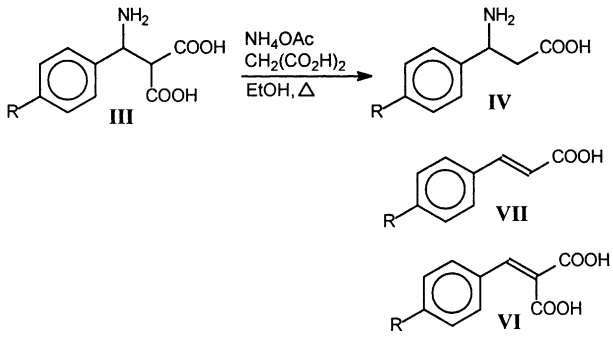
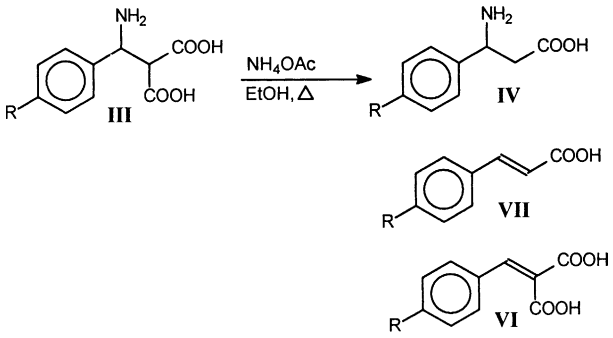
2.2. Part II

2.2.1. Background to mechanistic problem. In investigating the mechanism of Knoevenagel's synthesis of cinnamic acids, Rodionow[7] discovered that in addition to the desired cinnamic acid derivatives, corresponding β-amino acids were also produced when benzaldehyde analogues were allowed to react with malonic acid and ammonia. He proposed that the reaction mechanism proceeded through a single pathway (pathway A–B, C and H, Scheme 2). Addition of ammonia to the corresponding benzaldehyde derivative **I** gave the Schiff base **II**. Subsequent addition of malonic acid to **II** (step B) then afforded the amino dicarboxylic acid intermediate **III**. Hereafter, **III** could either be decarboxylated (step C) to produce the corresponding β-amino acid **IV** or be deaminated and decarboxylated (step H) to give the corresponding cinnamic acid **VII**. He concluded that the formation of the β-amino acid **IV** was through the decarboxylation of the amino dicarboxylic acid **III** and not by an addition reaction of ammonia to the double bond of the corresponding cinnamic acid **VII**. Hence, the formation of **VII** occurred only through the decarboxylation and deamination of **III**.

In this study, we found that the reaction mechanism of this one-pot reaction was more complex, involving more than just one pathway. In turn, we proposed that the reaction has two main pathways, A–B, C, H, G (pathway A–B) and D–E, F, G, H, C (pathway D–E) (Scheme 2), with key intermediates, **III** and **VI**, respectively. In addition, these key intermediates, **III** and **VI**, were interchangeable between these two main pathways via step G. With these intermediates, we were then able to show that they could be further reacted to produce both the corresponding β-amino acid and cinnamic acid. Our study demonstrated that the β-amino acid and cinnamic acid could be produced through both pathways A–B and D–E, rather than only through pathway A–B as claimed by Rodionow.

In pathway D–E, addition of malonic acid to the

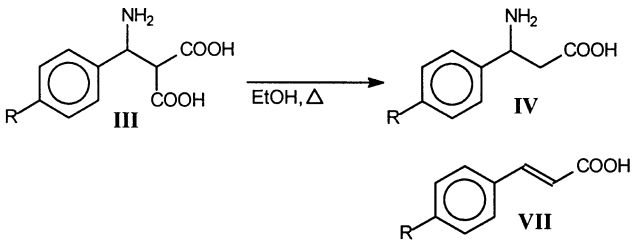
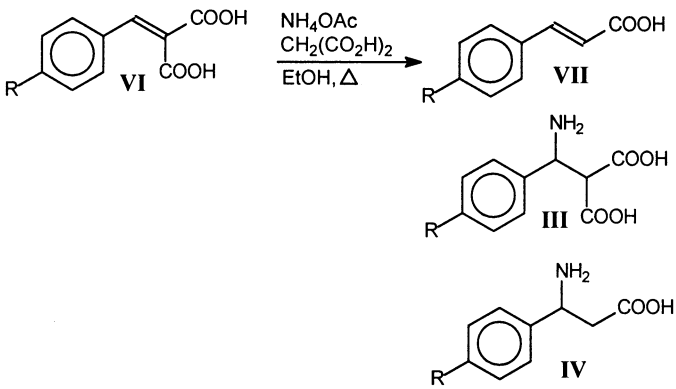
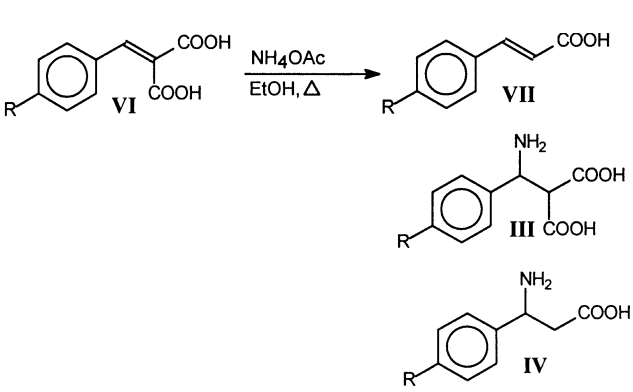
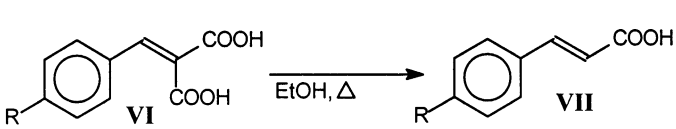
Table 2. Percentage yields of intermediates **III**–**VII** in various reactions

No.	Reactions	(Equation, yield %)		
		R=CH_3	R=OCH_3	R=NO_2
1.		Eq. (1) 74	Eq. (8) 85	Eq. (15) 54
2.		Eq. (2) 77	Eq. (9) 67	Eq. (16) 87
3.		Eq. (3) 67 (66) 25 (25) 5 (5)	Eq. (10) 73 19 5	Eq. (17) 40 53 5
4.		Eq. (4) 63 (65) 29 (27) 7 (6)	N.A. – – –	N.A. – – –

benzaldehyde derivative **I** afforded the hydroxy dicarboxylic acid intermediate **V** as proposed by Hann and Lapworth.[8] Subsequent dehydration (step E) then produced the cinnamic dicarboxylic acid intermediate **VI**. Intermediate **VI**, could either be decarboxylated (step F) to afford the corresponding cinnamic acid **VII**, or converted to the amino dicarboxylic acid intermediate **III** (via step G) in the presence of ammonia. Part of the pathway D–E, condensation of the benzaldehyde and malonic acid to produce the corresponding cinnamic acid, is an example of a Knoevenagel condensation.[9,13]

2.2.2. Overall approach to mechanistic studies. To study the reaction mechanism of this one-pot synthesis of β-amino acids (Goal (i)), we divided the proposed reaction mechanism into logical parts. First, we synthesized the reaction intermediates **III** and **VI**. Intermediate **III** was synthesized in the presence of 1 equiv. of the corresponding benzaldehye derivative, 2 equiv. of ammonium acetate and 1 equiv. of malonic acid in ethanol. The reaction was allowed to stir at room temperature to give the corresponding intermediate **III**. Intermediate **VI** was obtained by stirring the corresponding benzaldehye derivative with 2 equiv. of malonic acid and 0.01 equiv. of ammonium acetate in ethanol at room temperature. Second, we subjected these intermediates to various experiments to study further steps C and F–H. These experiments involved reaction of intermediates **III** and **VI** in ethanol with: (1) 2 equiv. of ammonium acetate and 1 equiv. of malonic acid, (2) 2 equiv. of ammonium acetate, (3) refluxing conditions only (without the presence of ammonium acetate or malonic acid). A control experiment with the presence of water to mimic the actual one-pot reaction conditions was also performed. The results of these experiments are summarized in Table 2. The mechanism was studied using three different benzaldehyde derivatives: *p*-tolualdehyde (a series), *p*-anisaldehyde (b series) and *p*-nitrobenzaldehyde (c series). In addition, each reaction was carried out in

Table 2 (*continued*)

No.	Reactions	(Equation, yield %)		
		$R=CH_3$	$R=OCH_3$	$R=NO_2$
5.		Eq. (5) 62 (62) 32 (32)	Eq. (11) 76 19	Eq. (18) 47 47
6.		N.A. – – –	Eq. (12) 85 – 13	Eq. (19) 88 7 3
7.		Eq. (6) 72 (73) – 27 (25)	Eq. (13) 88 – 11	Eq. (20) 86 8 4
8.		Eq. (7) 93 (94)	Eq. (14) 94	Eq. (21) 93

N.A.: not applicable; values in paranthesis: control experiment with the present of 1 equiv. of H_2O.

three different solvents: methanol, ethanol and 2-propanol. These permitted us to study whether *para*-substitutions (electronic effect) on the phenyl ring (Goal (ii)) and the polarity of the solvents (Goal (iii)) could affect the reaction mechanism and its yield.

2.2.3. Goal (i), investigation of the reaction mechanism. In the first series (a series) of reactions, in which *p*-tolualdehyde was used, intermediate **IIIa** was produced in a reasonable yield of 74% (Eq. (1) of Table 2) along with a trace of **VIa**. This result suggested that pathway A–B was the dominant pathway of the reaction. The reaction of **VIa** to give product also verified the hypothesis that **VIa** was an intermediate in the reaction pathway. To obtain a sufficient amount of **VIa** for subsequent investigations, a different reaction condition was used. In this reaction, ammonium acetate was added as the catalyst to activate the malonic acid to produce intermediate **Va**. Subsequent dehydration then afforded the more stable intermediate **VIa** in 77% yield (Eq. (2) of Table 2). Furthermore, we also employed a different method in obtaining **VIa**.[10] In this method, we subjected *p*-tolualdehyde and malonic acid, in a bed of alumina, to microwave radiation. After the work up, **VIa** was obtained in 61% yield.

In a study by Corey, he proposed that in general, water elimination (step E) and decarboxylation (step F) should occur simultaneously in a Knoevenagel condensation.[11]

Moreover, he also proposed that α,β-unsaturated malonic acids decarboxylate readily only where the α-carbon atom was not linked by a double bond. In our investigation, however, we were able to isolate intermediate **VI**, which provided evidence that water elimination and decarboxylation steps do not necessary occur simultaneously. In our case, water elimination clearly occurred prior to the decarboxylation, which was in agreement with a study by Patai.[12] In addition, we were able to decarboxylate **VI**, in which the α-carbon atom of **VI** was linked by a double bond to the corresponding cinnamic acid **VII**.

Next, we subjected **IIIa** to three different reaction conditions. The purpose was to examine whether different reactant(s) would dictate the pathway that intermediate **IIIa** was following and thus which product(s) would be formed. The products that resulted from these three reactions (Eqs. (3)–(5) of Table 2) were quite similar; in all three different reactions, the β-amino acid was the predominant product (60–70%) and the corresponding cinnamic acid was the side product (25–30%). These results suggested that **IIIa** underwent decarboxylation via step C to yield the β-amino acid more readily than other steps (G–F, and H). In the presence of ammonium acetate (Eqs. (3) and (4) of Table 2), intermediate **VIa** was produced as a minor side product (5–10%), while there was no evidence of **VIa** in the absence of ammonium acetate (Eq. (5) of Table 2). Hence, in the presence of ammonium acetate, **IIIa** might have taken either a two step reaction through step G (deamination) then step F (decarboxylation) and/or a one step reaction via step H (deamination and decarboxylation) in producing **VIIa** in addition to the decarboxylation of **IIIa** to give **IVa**. However, in the absence of ammonium acetate, **IIIa** underwent step H and step C instead. A plausible explanation of this observation was, in the presence of excess ammonia, ammonia abstracted the acidic proton (α carbon) to give intermediate **VIa** followed by decarboxylation to give the cinnamic acid **VII**.

As with **IIIa**, intermediate **VIa** was also subjected to two different experiments. These results suggested that in the presence of ammonium acetate, intermediate **IIIa** was produced via Michael addition of NH_3 (step G) followed by decarboxylation of **IIIa** (step C) to afford the corresponding β-amino acid **IVa**. Concurrently, decarboxylation of **VIa** via step F then yielded the cinnamic acid **VIIa**. In the absence of ammonium acetate, decarboxylation of **VIa** then afforded the corresponding cinnamic acid. In summary, results from this series of reactions with *p*-tolualdehyde, supported the proposed mechanism. Furthermore, the results also suggested that the synthesis of β-amino acid was the main pathway of the reaction.

In the control experiments, both **IIIa** and **VIa** were subjected to the same varying reaction conditions as mentioned above except an equal amount of water was added in each reaction to mimic the actual one-pot reaction condition. The results of these control experiments (Eqs. (3)–(7) of Table 2) were very close to the corresponding reactions without added water. (These results suggest that the presence of a small quantity of water does not affect the reaction mechanism or the product distribution.)?

In the second series (b series) of reactions, *p*-anisaldehyde was employed. As with *p*-tolualdehyde series, this series of reactions was also divided into two parts. In the first part, we investigated steps A, B, D and E via the synthesis of intermediate **IIIb** and **VIb**. Intermediate **IIIb** was produced in a higher yield (85%, Eq. (8) of Table 2) for *p*-anisaldehyde than for *p*-tolualdehyde. However, intermediate **VIb** from *p*-anisaldehyde was produced in a much lower yield (67%, Eq. (9) of Table 2) than for *p*-tolualdehyde and at a much slower rate. Both the yield and the rate of reaction of **VIb** could be improved by subjecting the reaction to heat. Once again these results suggested that **IIIb** and **VIb** were true intermediates for the one-pot reaction and that **IIIb** underwent pathway A–B, whereas **VIb** underwent pathway D–E, similar to *p*-tolualdehyde series. The possible explanation for the differences in yields of intermediate **IIIb** and **VIb** will be discussed later.

In the second part, intermediates **IIIb** and **VIb** were then subjected to various experimental conditions to study the subsequent steps of the reaction mechanism. Results from both reactions (Eqs. (10) and (11) of Table 2) carried out on **IIIb** were similar. Both sets of reactions produced the corresponding β-amino acid (via step C) and cinnamic acid (via steps G–F and/or step H). In the presence of ammonium acetate, there was a trace of **VIb** as well, the same observation as with the *p*-tolualdehyde series. These suggested that **IIIb** underwent both steps G and H.

As with intermediate **VIb**, three different experiments were carried out. Reactions 6 and 7 (Eqs. (12) and (13) of Table 2) produced both β-amino acid (10–15%) and cinnamic acid (85–90%). However, in absence of ammonium acetate (Eq. (14) of Table 2), only cinnamic acid was produced. These results implied that **VIb** underwent steps G and F, and it also helped to explain the higher yield of cinnamic acid over β-amino acid, similar to the *p*-tolualdehyde series. A plausible explanation was that there were two paths that could produced the cinnamic acid compared to a single two-step process (steps G–C) in attaining the β-amino acid. In summary, the results from the *p*-anisaldehyde series complemented the *p*-tolualdehyde series, supporting the proposed reaction mechanism.

In the third series (c series) of reactions, *p*-nitrobenzaldehyde was used. Again, the investigation was divided into two parts. In the first part, intermediates **IIIc** and **VIc** were synthesized. Intermediate **IIIb** was produced in 54% (Eq. (15) of Table 2) yield, the lowest among the three series of reactions. Intermediate **VIc** was however produced (via step D) in a much higher yield (87%, Eq. (16) of Table 2). As with the previous two series of reactions, once **IIIc** and **VIc** were obtained, different experiments were then carried out to investigate the subsequent steps of the reaction mechanism (steps C, F, G and H). First, intermediate **IIIc** was subjected to two different sets of reactions (Eqs. (17) and (18) of Table 2). The percentage yield of the β-amino acid and the cinnamic acid in both reactions were similar, about a one to one ratio. This result suggested that decarboxylation in step C for this series was slower than the previous two series. This outcome also provided one of the reasons why the yield of β-amino acid for this series was much lower than the previous two. Once

Table 3. Percentage yield and the ratio of the β-amino acid **IV** over the cinnamic acid **VII** in three different solvent systems

		Methanol		Ethanol		2-propanol	
		Yield (%)	Ratio[a]	Yield (%)	Ratio[a]	Yield (%)	Ratio[a]
p-Anisaldehyde	**IV**	76	3.2	70	2.4	51	1.1
	VII	24		30		48	
p-tolualdehyde	**IV**	64	1.8	54	1.2	51	1.1
	VII	36		45		48	
p-Nitrobenzaldehyde	**IV**	15	0.12	27	0.4	33	0.5
	VII	84		73		66	

[a] Yield ratio of intermediate **IV** over intermediate **VII**.

again, as with previous two series of experiments, in the presence of ammonium acetate, there was a trace of **VIc** detected. Intermediate **VIc** was again subjected to three different reactions (Eqs. (19)–(21) of Table 2). As with the previous series of reactions, the results from these three reactions suggested that **VIc**, in the presence of ammonium acetate, underwent Michael addition of ammonia via step G to give the corresponding β-amino acid along with the decarboxylation of **VIc** to yield the corresponding cinnamic acid. In the absence of ammonium acetate, **VIc** underwent decarboxylation (via path F) to afford the corresponding cinnamic acid only. In summary, the results from this series of reaction as with two previous series (a and b) supported the proposed reaction mechanism of this one-pot synthesis of β-amino acids.

2.2.4. Goal (ii), evaluate the electronic effect of the *para*-substituents upon the reaction mechanism. In Goal (ii), we determined whether electronic effects play a role in this reaction. Examining the ratio of the yield of the β-amino acid to its corresponding cinnamic acid, (Table 3) revealed that *p*-anisaldehyde (electron-donating group) has the largest ratio, followed by *p*-tolualdehyde (as the control), then *p*-nitrobenzaldehyde (electron-withdrawing group). The same trend was consistent in all three solvent systems. This observation suggested that this one-pot synthesis of β-amino acid was more effective with phenyl groups having an electron-donating group substituted at the *para*-position. A plausible reason was that specific stabilization of canonical forms of the resonance structures facilitated the addition of the ammonia to the aldehyde functional group. Thus when R is an electron-donating group, it stabilized the canonical forms of benzaldehyde derivative. This explanation was also supported by the result from Reactions 1 and 2 of Table 2, where the yield of intermediate **3** increased with $R{=}OCH_3{>}CH_3{>}NO_2$.

2.2.5. Goal (iii), investigate the solvent effects upon the product distribution. The final objective of this study was to determine whether polarity of the solvent system affects the reaction. To accomplish this, we subjected each benzaldehyde derivative to three different solvent systems: methanol, ethanol and 2-propanol. For each benzaldehyde derivative, all reactions were refluxed in the same oil bath with the external temperature set to 83°C to eliminate any differences in the reaction conditions. The outcome of this study (Table 3), showed that the yield of β-amino acid increased with increasing polarity of the solvent, whereas the yield of cinnamic acid increased with decreasing polarity for methyl and methoxy substituents. However, these observations were inverted with the more hydrophobic functional group (nitro substituent). A plausible explanation for these observations was that as the polarity of the solvent decreased, the solubility of intermediate **VI** (for both methyl and methoxy functional groups) decreased. Hence, not only intermediate **III** precipitated out; intermediate **VI** also started to precipitate which ultimately led to larger yields of cinnamic acid. On the other hand, the solubility of intermediate **VI** (nitro functional group) increased with decreasing polarity of the solvent, due to its less polar functional group. This caused the equilibrium to shift more to pathway A–B, whereas intermediate **III** precipitated out as the reaction was refluxed.

In conclusion, results from these investigations support our proposed reaction mechanism for this one-pot synthesis of 3-amino-3-arylpropionic acid, as shown in Scheme 2. The synthesis of 3-amino-3-arylpropionic acid is via the main pathway. The substituent on the benzene ring does play an important role in the reaction with the synthesis of 3-amino-3-arylpropionic acid being favored by substituent(s) with electron-donating property. Finally, polarity of the solvent also affects the product distribution. One can influence the synthesis of 3-amino-3-arylpropionic acid by selecting the proper solvent for the particular benzaldehyde derivative.

3. Experimental

Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ACF-200 (200 MHz) spectrometer with D_2O, D_2O/K_2CO_3, CD_3OD or $CDCl_3$ as solvents. Infrared (IR) spectra were recorded on a Bomem MB-120 spectrophotometer using KBr disks. Melting points (mp) were determined using a Mel-Temp II capillary apparatus and are uncorrected. Elemental analyses were performed by G–C–L Laboratories (Guelph, Canada). Solvents were purified using standard methods.

3.1. Part I

*General Procedure for **4**, **6**, **20** and **21***. 4-Methylbenzaldehyde (2.4 g, 20.0 mmol), ammonium acetate (3.1 g, 40.2 mmol), and malonic acid (2.1 g, 20.2 mmol) were refluxed in EtOH (50 mL) for 7 h. The reaction mixture was cooled to room temperature and a white solid was collected. The white solid was then dissolved in 20 mL of 1.0N HCl followed by evaporation to dryness. Subsequent recrystallization with EtOH then yielded **4** as white crystals (2.2 g, 54%).

*General Procedure for **2**, **13**, and **15***. 2-Methylbenzaldehyde (6.94 mL, 60.0 mmol), ammonium acetate (6.4 g, 80.0 mmol), and malonic acid (6.24 g, 60.0 mmol) were refluxed in EtOH (80 mL) for 16 h. The reaction mixture was allowed to cool to room temperature and the cinnamic acid was removed by filtration. The filtrate was evaporated to give a white solid, which was collected by filtration and dissolved in a warm (70°C) solution of Na_2CO_3 (4 g) in 50 mL of H_2O. The aqueous layer was then acidified to pH 7 with 1.0N HCl added dropwise to give a white solid.

Subsequent recrystallization of the solid from hot MeOH afforded **2** as white crystals (2.04 g, 19%).

*General Procedure for **1**, **3**, **5**, **7–12**, **14**, **16–19***. 2,5-Dimethoxybenzaldehyde (4.98 g, 30.0 mmol), ammonium acetate (3.1 g, 40.2 mmol), and malonic acid (3.1 g, 30.2 mmol) were refluxed in EtOH (50 mL) for 6 h. The reaction mixture was allowed to cool to room temperature before the white solid was collected by filtration. This white solid was then recrystallized twice from hot MeOH to afford **14** as white crystals (1.49 g, 22%).

3.1.1. 3-Amino-3-phenylpropionic acid (1). **1** was obtained as white crystals, mp 220–221°C (lit. 220–227°C,[6a] 216°C,[6d] 216–218°C,[6j] 21–219°C[6k]); IR (KBr) 3035, 1625 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.26–7.33 (m, 5H), 4.50 (t, J=7.30 Hz, 1H), 2.59–2.82 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.9, 136.5, 129.5, 129.3, 127.5, 52.2, 38.1. Anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.26; H, 6.55; N, 8.42.

3.1.2. 3-Amino-3-(2-methyl)phenylpropionic acid (2). Compound **2** as white crystals was obtained, mp: 219°C; IR (KBr) 3160, 1607 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.05–7.30 (m, 4H), 4.39 (t, J=7.35 Hz, 1H), 2.42 (dd, J=6.56, 1.93 Hz, 2H), 2.25 (d, J=5.35 Hz, 3H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.9, 136.8, 134.9, 131.3, 129.3, 127.2, 125.9, 47.8, 38.1, 18.6. Anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.90; H, 7.76; N, 7.78.

3.1.3. 3-Amino-3-(3-methyl)phenylpropionic acid (3). Compound **3** was obtained as white crystals, mp 226–227°C; IR (KBr) 2937, 1625 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.91–7.20 (m, 4H), 4.38 (t, J=7.37 Hz, 1H), 2.31–2.42 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (D_2O/K_2CO_3) δ 170.3, 137.4, 134.5, 128.3, 127.4, 126.3, 122.7, 50.4, 36.4, 18.8. Anal. calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.88; H, 7.60; N, 7.83.

3.1.4. Hydrochloride of 3-amino-3-(4-methyl)phenylpropionic acid (4). White crystals of **4** was obtained, mp 208–210°C; IR (KBr) 3018, 1601 cm^{-1}; ^1H NMR (D_2O) δ 7.11–7.20 (m, 4H), 4.13 (t, J=7.35 Hz, 1H), 2.40–2.47 (m, 2H), 2.19 (s, 3H); ^{13}C NMR (D_2O) δ 172.1, 138.4, 135.1, 131.1, 127.5, 52.1, 37.1, 18.7. Anal. calcd for $C_{10}H_{14}NO_2Cl$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.35; H, 6.04; N, 6.45.

3.1.5. 3-Amino-3-(4-fluoro)phenylpropionic acid (5). White crystals of **5** were obtained, mp 216–217°C; IR (KBr) 3160, 1606 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.19–7.28 (m, 2H), 6.91–7.03 (m, 2H), 4.11 (t, J=7.39 Hz, 1H), 2.34–2.54 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.9, 165.2, 132.6, 130.0, 116.3, 51.6, 38.1. Anal. calcd for $C_9H_{10}NO_2F$: C, 59.01; H, 5.50; N, 7.65. Found: C, 58.81; H, 5.41; N, 7.53.

3.1.6. Hydrochloride of 3-amino-3-(4-chloro)phenylpropionic acid (6). Compound **6** as white crystals was obtained, mp 188–189°C; IR (KBr) 3006, 1597 cm^{-1}; ^1H NMR (D_2O) δ 7.20–7.31 (m, 4H), 4.13 (t, J=7.2 Hz, 1H), 2.41–2.54 (m, 2H); ^{13}C NMR (D_2O) δ 171.8, 143.9, 135.5, 131.4, 124.7, 51.4, 37.9. Anal. calcd for $C_9H_{11}NO_2Cl_2$: C, 45.79; H, 4.70; N, 5.93. Found: C, 45.53; H, 4.54; N, 5.91.

3.1.7. 3-Amino-3-(4-bromo)phenylpropionic acid (7). Compound **7** as white crystals was obtained, mp 234°C; IR (KBr) 3061, 1594 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.38–7.42 (m, 2H), 7.14–7.17 (m, 2H), 4.09 (t, J=7.25 Hz, 1H), 2.36–2.48 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.7, 135.7, 132.5, 129.6, 123.5, 51.6, 37.9. Anal. calcd for $C_9H_{10}NO_2Br$: C, 44.29; H, 4.13; N, 5.74. Found: C, 44.35; H, 3.93; N, 5.70.

3.1.8. 3-Amino-3-(2-chloro)phenylpropionic acid (8). White crystals of **8** were obtained, mp 219°C; IR (KBr) 3060, 596 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.12–7.38 (m, 4H), 5.05 (t, J=6.4 Hz, 1H), 2.27–2.62 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.6, 133.9, 133.5, 131.0, 130.5, 128.2, 128.1, 48.5, 37.1. Anal. calcd for $C_9H_{10}NO_2Cl$: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.34; H, 4.95; N, 7.04.

3.1.9. 3-Amino-3-(4-methoxy)phenylpropionic acid (9). Compound **9** was obtained as white crystals, mp 239°C (lit.[6d] 232°C); IR (KBr) 3046, 1607 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.11 (d, J=8.71 Hz, 2H), 6.77 (d, J=8.71 Hz, 2H,), 3.96 (t, J=7.85 Hz, 1H), 3.61 (s, 3H), 2.31–2.36 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 182.4, 160.1, 139.4, 129.8, 116.5, 57.9, 55.4, 48.2. Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.46; H, 6.74; N, 7.20.

3.1.10. 3-Amino-3-(4-trifluoromethoxy)phenylpropionic acid (10). Compound **10** as white crystals was obtained, mp 222–223°C; IR (KBr) 3071, 1616 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.32 (d, J=8.71 Hz, 2H), 7.18 (d, J=8.71 Hz, 2H), 4.15 (t, J=7.23 Hz, 1H), 2.44 (dd, J=7.43, 2.91 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.7, 150.0, 135.6, 129.7, 122.5, 121.7, 51.4, 37.9. Anal. calcd for $C_{10}H_{10}NO_3F_3$: C, 48.20; H, 4.04; N, 5.62. Found: C, 48.42; H, 4.20; N, 5.48.

3.1.11. Hydrochloride of 3-amino-3-(4-acetamido)phenylpropionic acid (11). Compound **11** was obtained as white crystals, mp 221–222°C; IR (KBr) 3038, 1604 cm^{-1}; ^1H NMR (D_2O) δ 7.25–7.23 (s, 4H), 4.12 (t, J=7.4 Hz, 1H), 2.44 (dd, J=4.9, 2.5 Hz, 2H), 2.02 (s, 3H); ^{13}C NMR (D_2O) δ 172.0, 171.0, 140.0, 131.7, 128.1, 120.5, 51.8, 38.0, 23.0. Anal. calcd for $C_{11}H_{14}N_2O_3 \cdot 1/2H_2O$: C, 57.13; H, 6.54; N, 12.11. Found: C, 57.33; H, 6.80; N, 12.07.

3.1.12. 3-Amino-3-(3-methyl-4-methoxy)phenylpropionic acid (12). Compound **12** as white crystals was obtained, mp 238–240°C; IR (KBr) 3081, 1610 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.07–7.10 (m, 2H), 6.82–6.88 (m, 1H), 4.09 (t, J=7.29 Hz, 1H), 3.71 (s, 1H), 2.39–2.46 (m, 2H), 2.06 (s, 3H); ^{13}C NMR (D_2O/K_2CO_3) δ 170.5, 157.3, 127.9, 126.1, 125.9, 124.7, 108.8, 53.3, 50.2, 36.5, 13.7. Anal. calcd for $C_{11}H_{15}NO_3 \cdot 1/2H_2O$: C, 60.54; H, 7.39; N, 6.42. Found: C, 60.86; H, 7.17; N, 6.45.

3.1.13. 3-Amino-3-(2-hydroxy-3-methoxy)phenylpropionic acid (13). White crystals of **13** were obtained, mp 200–201°C; IR (KBr) 2999, 1616 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.66–6.76, 6.49–6.41 (m, 3H), 4.46 (t, J=7.30 Hz, 1H), 3.62 (s, 3H), 2.51 (d, J=7.25 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.6, 156.1, 153.8, 134.0, 130.0, 125.6, 124.9, 55.6, 36.7, 14.0. Anal. calcd for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.20; N, 6.63. Found: C, 57.05; H, 6.41; N, 6.55.

3.1.14. 3-Amino-3-(2,5-dimethoxy)phenylpropionic acid (14). Compound **14** as white crystals was obtained, mp 206–208°C; IR (KBr) 2944, 1630 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.70–6.88 (m, 3H), 4.30 (t, J=7.89 Hz, 1H), 3.64–3.68 (m, 6H) 2.21–2.54 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 172.3, 154.2, 151.4, 124.5, 115.2, 114.95, 112.6, 55.5, 55.3, 48.9, 36.6. Anal. calcd for $C_{11}H_{15}NO_4.H_2O$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.05; H, 6.85; N, 5.66.

3.1.15. 3-Amino-3-[2-fluoro-3-(trifluoromethyl)]phenylpropionic acid (15). Compound **15** was obtained as white crystals, mp 206°C; IR (KBr) 2948, 1625 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.45–7.58 (m, 2H), 7.20 (t, J=7.91 Hz, 1H) 4.44 (t, J=7.30 Hz, 1H,), 2.51 (d, J=7.38 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.3, 159.5, 133.5, 128.6, 125.6, 125.4, 124.7, 121.1, 45.4, 36.9. Anal. calcd for $C_{10}H_9NO_2F_4$: C, 47.82; H, 3.61; N, 5.58. Found: C, 47.90; H, 4.00; N, 5.90.

3.1.16. 3-Amino-3-(4-phenoxy)phenylpropionic acid (16). White crystals of **16** were obtained, mp 214–215°C; IR (KBr) 3066, 1615 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.89–7.33 (m, 9H), 4.12 (t, J=7.23 Hz, 1H), 2.44 (dd, J=7.12, 2.39 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 172.9, 162.4, 160.4, 131.9, 131.1, 130.2, 125.2, 120.5, 119.8, 52.6, 39.0. Anal. calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.79; H, 5.64; N, 5.38.

3.1.17. 3-Amino-3-(4-phenyl)phenylpropionic acid (17). Compound **17** was obtained as white crystals, mp 244°C; IR (KBr) 3029, 1615 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.19–7.46 (m, 9H), 4.16 (t, J=6.7 Hz, 1H), 2.41 (d, J=7.2 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.0, 158.1, 154.3, 135.4, 129.0, 128.0, 127.8, 127.0, 124.2, 52.0, 37.9. Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.47; H, 6.35; N, 5.80.

3.1.18. 3-Amino-3-[3-(4-methylphenoxy)]phenylpropionic acid (18). White crystals of **18** were obtained, mp 206–208°C; IR (KBr) 3030, 1608 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.77–7.28 (m, 8H), 4.08 (t, J=7.30 Hz, 1H), 2.40 (d, J=7.29 Hz, 2H,), 2.19 (s, 3H); ^{13}C NMR (D_2O/K_2CO_3) δ 171.8, 159.0, 154.5, 138.4, 133.9, 130.9, 130.6, 121.6, 119.5, 118.8, 117.2, 51.9, 38.1, 19.9. Anal. calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.10; N, 5.10.

3.1.19. 3-Amino-3-[3-(4-chlorophenoxy)]phenylpropionic acid (19). Compound **19** was obtained as white crystals, mp 202–203°C; IR (KBr) 3099, 1616 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 7.22–7.29, 7.03–7.06, 6.88–6.91 (m, 8H), 4.09 (t, J=7.29 Hz, 1H), 2.40 (d, J=7.25 Hz, 2H); ^{13}C NMR (D_2O/K_2CO_3) δ 172.7, 159.0, 156.9, 139.7, 132.1, 131.0, 129.9, 123.4, 121.5, 120.6, 118.8, 52.8, 39.0. Anal. calcd for $C_{15}H_{14}NO_3Cl$: C, 61.76; H, 4.84; N, 4.80. Found: C, 61.95; H, 5.02; N, 4.81.

3.1.20. Hydrochloride of 3-amino-3-[3-(3,4-dichlorophenoxy)]phenylpropionic acid (20). Compound **20** as white crystals was obtained, mp 164–165°C; IR (KBr) 3193, 1609 cm^{-1}; ^1H NMR (D_2O) δ 6.96–7.31, 6.83, 6.57–6.62 (m, 7H), 4.03 (t, J=7.88 Hz, 1H), 2.29–2.41 (m, 2H); ^{13}C NMR (D_2O) δ 171.8, 157.1, 156.79, 139.0, 133.2, 131.6, 131.3, 126.9, 123.3, 120.6, 120.2, 118.6, 118.6, 51.8, 38.1. Anal. calcd for $C_{15}H_{14}NO_3Cl_3$: C, 49.68; H, 3.89; N, 3.86. Found: C, 49.34; H, 3.87; N, 3.93.

3.1.21. Hydrochloride salt of 3-amino-3-(3,4-dibenzyloxy)phenylpropionic acid (21). White crystals of **21** was obtained, mp 198–200°C; IR (KBr) 3133, 1604 cm^{-1}; ^1H NMR (D_2O) δ 7.19–7.40 (m, 10H), 6.87–7.08 (m, 3H), 5.06 (s, 4H), 4.43 (t, J=8.35 Hz, 1H), 2.65–2.85 (m, 2H); ^{13}C NMR (D_2O) δ 173.6, 149.9, 149.6, 137.5, 129.8, 128.5, 128.1, 128.0, 128.0, 127.6, 120.7, 115.3, 114.4, 71.5, 71.1, 52.3, 38.9. Anal. calcd for $C_{23}H_{24}NO_4Cl$: C, 66.74; H, 5.84; N, 3.38. Found: C, 66.96; H, 6.00; N, 3.41.

3.2. Part II

3.2.1. Preparation of ammonium salt of 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa). A mixture of *p*-tolualdehyde **Ia** (1.0 mL, 8.48 mmol), ammonium acetate (1.50 g, 19.5 mmol) and malonic acid (0.884 g, 8.49 mmol) in EtOH (20 mL) were stirred at room temperature for 48 h. A white solid was then collected by filtration and recrystallised twice from H_2O/EtOH (1:4) to afford **IIIa** (1.41 g, 74%); mp 195–197°C; IR (KBr) 3411, 3058, 1588, 823 cm^{-1}; ^1H NMR (D_2O) δ 7.08–7.22 (m, 4H), 4.49–4.54 (m, 1H), 3.48 (d, J=9.06 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (D_2O) δ 177.5, 177.2, 142.1, 134.5, 132.2, 129.7, 62.3, 57.4, 22.7. Anal. calcd (analytical calculation) for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.62; H, 6.83; N, 11.26.

3.2.2. Preparation of 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa). A mixture of *p*-tolualdehyde **1a** (1.0 mL, 8.48 mmol), malonic acid (1.76 g, 16.9 mmol) and ammonium acetate (0.0057 g, 0.0739 mmol) in EtOH (20 mL) were stirred at room temperature for 48 h. A white solid was obtained by filtration, followed by recrystallization from EtOAc to give **VIa** (1.34 g, 77%); mp 212–213°C (lit.[10] 203–204°C); IR (KBr) 3036, 1710, 1693, 830, 811 cm^{-1}; ^1H NMR (CD_3OD) δ 7.53 (s, 1H), 7.38 (d, J=8.18 Hz, 2H), 7.14 (d, J=8.17 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (CD_3OD) δ 173.5, 169.9, 145.1, 144.6, 134.0, 133.3, 133.2, 130.0, 24.0. Anal. calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.22; H, 4.91.

*Preparation of 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (**VIa**) by microwave.*[9] *p*-tolualdehyde **Ia** (1.0 mL, 8.48 mmol), malonic acid (2.71 g, 26.1 mmol) and aluminum oxide (basic, activity type I; 4.92 g, 48.2 mmol) was mixed thoroughly with a vortex mixer. The mixture was then subjected to microwave (conventional microwave) for 7 min. Once the reaction mixture was cooled to room temperature, it was sequentially washed three times (50 mL) with the following solvents: (i) hexane, (ii) ice cold H_2O, (iii) MeOH. The MeOH washes were combined and evaporated to dryness to yield a white solid. The resulting white solid was then recrystallised from EtOAc to afford **VIa** (1.06 g, 61%).

3.2.3. Reaction of 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) with ammonium acetate and malonic acid. Preparation of 3-amino-3-(4-methyl)-phenylpropanoic acid (IVa), 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) and 4-methylcinnamic acid (VIIa). IIIa (0.195 g, 0.873 mmol), ammonium acetate

(0.135 g, 1.75 mmol) and malonic acid (0.091 g, 0.87 mmol) were refluxed in EtOH (20 mL) for 24 h. The reaction mixture was allowed to cool to room temperature and the resulting white solid was collected by filtration. This solid was then washed twice with 20 mL of EtOH and then triturated three times with hot MeOH (20 mL) to give **IVa** (0.105 g, 67%); mp 231–232°C (lit. 226°C,[6b] 231°C[6f]); IR (KBr) 3443, 3013, 1623, 1586, 815 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) δ 6.98–7.09 (m, 4H), 4.00 (t, J=7.45 Hz, 1H), 2.30–2.35 (m, 2H), 2.09 (s, 3H); ^{13}C NMR (D_2O/K_2CO_3) 172.4, 138.7, 134.5, 131.7, 128.5, 50.1, 38.1, 18.7. Anal. calcd for $C_{11}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.70; H, 7.61; N, 7.75. The MeOH filtrates were combined and evaporated to dryness to afford **VIa** (0.0086 g, 5%). The EtOH filtrate (from the reaction mixture) was evaporated to dryness and dissolved in 1.0N aqueous NaOH (10 mL). The aqueous solution was then acidified to pH 3 with 1.0N HCl added dropwise to obtain **VIIa** as a white solid (0.0358 g, 25%); mp 199–200°C (lit.[6c] 196–198°C); IR 3032, 1681, 988, 813; ^1H NMR ($CDCl_3$) δ 7.79 (d, J=16.01 Hz, 1H,), 7.47 (d, J=8.15 Hz, 2H), 7.22 (d, J=8.16 Hz, 2H), 6.42 (d, J=16.01 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 146.4, 142.1, 133.1, 130.7, 129.3, 118.2, 21.5. Anal. calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.01; H, 6.39.

3.2.4. Control experiment: reaction of 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) with ammonium acetate and malonic acid. IIIa (0.121 g, 0.499 mmol), ammonium acetate (0.077 g, 1.0 mmol), malonic acid (0.053 g, 0.51 mmol) and water (0.009 mL, 0.5 mmol) were refluxed in EtOH (15 mL) for 24 h to give **IVa** (0.063 g, 66%), **VIa** (0.0051 g, 5%) and **VIIa** (0.020 g, 25%).

3.2.5. Reaction of 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) with ammonium acetate. Preparation of 3-amino-3-(4-methyl)phenylpropanoic acid (IVa), 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) and 4-methylcinnamic acid (VIIa). IIIa (0.207 g, 0.929 mmol) and ammonium acetate (0.143 g, 1.86 mmol) were refluxed in EtOH (20 mL) for 24 h. The reaction mixture was allowed to cool to room temperature and a white solid was then collected by filtration. Subsequently, the solid was washed twice with 20 mL of EtOH followed by trituration with hot MeOH (3×20 mL) to afford **IVa** as a white solid (0.105 g, 63%). The MeOH filtrates were combined and evaporated to yield **VIa** (0.0138 g, 7%). The EtOH filtrate (from the reaction mixture) was evaporated to dryness and dissolved in 1.0N aqueous NaOH (10 mL). The aqueous was then acidified to pH 3 with 1.0N HCl added dropwise to obtain **VIIa** as a white solid (0.0429 g, 29%).

3.2.6. Control experiment: reaction of 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) with ammonium acetate. IIIa (0.116 g, 0.483 mmol), ammonium acetate (0.074 g, 0.966 mmol) and water (0.0087 mL, 0.48 mmol) were refluxed in EtOH (15 mL) for 24 h to give **IVa** (0.060 g, 65%), **VIa** (0.0060 g, 6%) and **VIIa** (0.021 g, 27%).

3.2.7. 3-Amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) refluxed in ethanol. Preparation of 3-amino-3-(4-methyl)phenylpropanoic acid (IVa) and 4-methylcinnamic acid (VIIa). IIIa (0.196 g, 0.877 mmol) was refluxed in ethanol (20 mL) for 24 h. The reaction mixture was allowed to cool to room temperature before a white solid was collected by filtration. The solid was then washed twice with 20 mL of EtOH to give **IVa** (0.0973 g, 62%). The EtOH filtrate was evaporated to dryness and taken up in 10 mL of 1.0N aqueous NaOH. Subsequently, **VIIa** (0.0451 g, 32%) precipitated out of solution following acidification to pH 3 with 1.0N HCl (added dropwise).

3.2.8. Control experiment: 3-amino-3-(4-methylphenyl)-2-carboxy-propanoic acid (IIIa) refluxed in ethanol. IIIa (0.123 g, 0.512 mmol) and water (0.0092 mL, 0.51 mmol) were refluxed in EtOH (15 mL) for 24 h to give **IVa** (0.061 g, 62%) and **VIIa** (0.027 g, 32%).

3.2.9. Reaction of 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) with ammonium acetate. Preparation of 3-amino-3-(4-methyl)phenylpropanoic acid (IVa) and 4-methylcinnamic acid (VIIa). VIa (0.102 g, 0.495 mmol) and ammonium acetate (0.0763 g, 0.991 mmol) were refluxed in ethanol (15 mL) for 24 h. The reaction was then worked up as before to afford **IVa** (0.0241 g, 27%) and **VIIa** (0.0577 g, 72%).

3.2.10. Control experiment: reaction of 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) with ammonium acetate. VIa (0.110 g, 0.533 mmol), ammonium acetate (0.0822 g, 1.067 mmol) and water (0.0096 mL, 0.53 mmol) were refluxed in ethanol (15 mL) for 24 h to give **IVa** (0.025 g, 25%) and **VIIa** (0.063 g, 73%).

3.2.11. 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) refluxed in ethanol. Preparation of 4-methylcinnamic acid (VIIa). VIa (0.0966 g, 0.469 mmol) was refluxed in EtOH (15 mL) for 24 h. The reaction was then worked up as before to yield **VIIa** (0.0708 g, 93%).

3.2.12. Control experiment: 3-(4-methylphenyl)-2-carboxy-2-propenoic acid (VIa) refluxed in ethanol. VIa (0.108 g, 0.527 mmol) and water (0.0094 mL, 0.52 mmol) were refluxed in EtOH (15 mL) for 24 h to give **VIIa** (0.0799 g, 94%).

3.2.13. Preparation ammonium salt of 3-amino-3-(4-methoxyphenyl)-2-carboxy-propanoic acid (IIIb). *p*-Anisaldehyde **Ib** (2.0 mL, 16.44 mmol), ammonium acetate (3.08 g, 40.0 mmol) and malonic acid (1.81 g, 17.4 mmol) in EtOH (25 mL) were stirred at room temperature for 17 h. A white solid was then collected by filtration and recrystallised twice from H_2O/EtOH (1:4) to afford **IIIb** (3.331 g, 85%); mp 158–159°C; IR (KBr) 3459, 1591, 1262, 826 cm^{-1}; ^1H NMR (D_2O) δ 7.29 (d, J=6.42 Hz, 2H), 6.93 (d, J=6.41 Hz, 2H), 4.54–4.59 (m, 1H), 3.74 (s, 3H), 3.52 (d, J=9.20 Hz, 1H); ^{13}C NMR (D_2O) δ 177.6, 177.1, 161.7, 131.3, 130.0, 117.0, 62.3, 57.8, 57.1. Anal. calcd for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.60; H, 6.47; N, 10.82.

3.2.14. Preparation of 3-(4-methoxyphenyl)-2-carboxy-2-propenoic acid (VIb). *p*-Anisaldehyde **Ib** (2.0 mL,

16.4 mmol), malonic acid (3.50 g, 33.7 mmol) and ammonium acetate (0.0105 g, 0.136 mmol) in EtOH (25 mL) were stirred at room temperature for 4 d. The reaction mixture was evaporated to dryness and dissolved in 1.0N aqueous NaOH (10 mL). The aqueous was then acidified to pH 3 with 1.0N HCl added dropwise to give an 'off-white' solid. Subsequent recrystallization of this solid from EtOAc then afforded **VIb** (2.43 g, 67%); mp 204–205°C (lit.[10] 184–185°C); IR (KBr) 3052, 1719, 1278, 844 cm^{-1}; ^1H NMR (CD_3OD) δ 7.45 (s, 1H), 7.41 (d, J=2.08 Hz, 1H), 7.35 (d, J=1.96 Hz, 1H), 6.82 (d, J=2.06 Hz, 1H), 6.79 (d, J=1.95 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (CD_3OD) 171.1, 167.5, 163.2, 141.9, 132.7, 126.5, 125.6, 115.3, 55.9. Anal. calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.46; H, 4.51.

3.2.15. Reaction of 3-amino-3-(4-methoxyphenyl)-2-carboxy-propanoic acid (IIIb) with ammonium acetate and malonic acid. Preparation of 3-amino-3-(4-methoxy)-phenylpropanoic acid (IVb), 3-(4-methoxyphenyl)-2-carboxy-2-propenoic acid (VIb) and 4-methoxycinnamic acid (VIIb). IIIb (0.135 g, 0.562 mmol), ammonium acetate (0.114 g, 1.482 mmol) and malonic acid (0.0585 g, 0.562 mmol) were refluxed in EtOH (20 mL) for 24 h. The work up for this reaction was the same as described for **IIIa**. **IVb** was then obtained as a white solid (0.0803 g, 73%); mp 239°C (lit. 232°C,[6d] 240–241°C[6l]); IR (KBr) 3440, 3046, 1607, 1591, 823 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) 7.11 (dd, J=2.58, 8.75 Hz, 2H), 6.77 (dd, J=2.59, 8.76 Hz, 2H), 3.96 (t, J=7.85 Hz, 1H), 3.61 (s, 3H), 2.31–2.36 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) 172.4, 150.1, 134.4, 129.8, 116.5, 52.9, 50.4, 38.2. Anal. calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.46; H, 6.74; N, 7.20 along with **VIb** (0.0064 g, 5%) and **VIIb** (0.0204 g, 20%); mp 172–173°C (lit.[6e,13] 169–170, 171°C); IR (KBr) 3030, 1687, 1255, 936, 826 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (d, J=16.01 Hz, 1H), 7.53 (d, J=6.77 Hz, 2H), 6.94 (d, J=6.76 Hz, 2H), 6.32 (d, J=16.01 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$) 170.8, 163.1, 146.2, 130.9, 128.4, 116.6, 115.4, 55.8. Anal. calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.20; H, 5.52.

3.2.16. 3-Amino-3-(4-methoxyphenyl)-2-carboxy-propanoic acid (IIIb) refluxed in ethanol. Preparation of 3-amino-3-(4-methoxy)phenylpropanoic acid (IVb) and 4-methoxycinnamic acid (VIIb). IIIb (0.119 g, 0.495 mmol) was refluxed in EtOH (20 mL) for 24 h. The work up was the same as for **IIIa** to yield **IVb** (0.074 g, 76%) and **VIIb** (0.0166 g, 19%).

3.2.17. Reaction of 3-(4-methoxyphenyl)-2-carboxy-2-propenoic acid (VIb) with ammonium acetate and malonic acid. Preparation of 3-amino-3-(4-methoxy)-phenylpropanoic acid (IVb) and 4-methoxycinnamic acid (VIIb). VIb (0.268 g, 1.20 mmol), ammonium acetate (0.205 g, 2.66 mmol) and malonic acid (0.128 g, 1.23 mmol) were refluxed in EtOH (15 mL) for 24 h. The reaction was then worked up as for **VIa** to afford **IVb** (0.0315 g, 13%) and **VIIb** (0.183 g, 85%).

3.2.18. Reaction of 3-(4-methoxyphenyl)-2-carboxy-2-propenoic acid (VIb) with ammonium acetate. Preparation of 3-amino-3-(4-methoxy)phenylpropanoic acid (IVb) and 4-methoxycinnamic acid (VIIb). VIb (0.262 g, 1.18 mmol) and ammonium acetate (0.204 g, 2.65 mmol) were refluxed in EtOH (15 mL) for 24 h. The reaction was then worked up as for **VIa** to give **IVb** (0.0248 g, 11%) and **VIIb** (0.184 g, 88%).

3.2.19. 3-(4-Methoxyphenyl)-2-carboxy-2-propenoic acid (VIb) refluxed in ethanol. Preparation of 4-methoxycinnamic acid (VIIb). VIb (0.249 g, 1.12 mmol) was refluxed in EtOH (20 mL) for 24 h. The reaction was then worked up as for **VIa** to yield **VIIb** (0.198 g, 94%).

3.2.20. Preparation of ammonium salt of 3-amino-3-(4-nitrophenyl)-2-carboxy-propanoic acid (IIIc). *p*-Nitrobenzaldehyde **Ic** (1.53 g, 10.15 mmol), ammonium acetate (1.63 g, 21.17 mmol) and malonic acid (1.11 g, 10.67 mmol) in EtOH (25 mL) were stirred at room temperature for 48 h. A yellowish white solid was then collected through filtration and recrystallised twice from H_2O/EtOH (1:4) to afford **IIIc** (1.40 g, 54%); mp 270–271°C (dec.); IR (KBr) 3426, 3039, 1650, 1583, 1343, 859 cm^{-1}; ^1H NMR (D_2O) δ 8.02 (d, J=8.86 Hz, 2H), 7.40 (d, J=8.86 Hz, 2H), 4.28 (d, J=9.92 Hz, 1H), 3.23 (d, J=9.92 Hz, 1H); ^{13}C NMR (D_2O) δ 177.0, 176.6, 150.5, 144.9, 131.0, 126.8, 62.6, 57.0. Anal. calcd for $C_{10}H_{13}N_3O_6$: C, 44.28; H, 4.83; N 15.49. Found: C, 44.45; H, 4.82; N, 15.24.

3.2.21. Preparation of 3-(4-nitrophenyl)-2-carboxy-2-propenoic acid (VIc). *p*-Nitrobenzaldehyde **Ic** (2.02 g, 13.37 mmol), malonic acid (2.87 g, 27.57 mmol) and ammonium acetate (0.0100 g, 0.130 mmol) in EtOH (25 mL) were stirred at room temperature for 6 d. The reaction mixture was evaporated to dryness and triturated with H_2O (150 mL) twice to yield **VIc** (2.75 g, 87%); mp 294–295°C (dec.); IR (KBr) 3055, 1727, 1696, 1524, 1351, 835 cm^{-1}; ^1H NMR (CD_3OD) δ 8.07 (d, J=8.92 Hz, 2H,), 7.58 (d, J=8.92 Hz, 2H), 7.55 (s, 1H); ^{13}C NMR (CD_3OD) 170.3, 170.1, 149.7, 140.8, 139.2, 132.3, 131.2, 124.8. Anal. calcd for $C_{10}H_7NO_6$: C, 50.64; H, 2.97; N, 5.91. Found: C, 50.64; H, 2.92; N, 5.82.

3.2.22. Reaction of 3-amino-3-(4-nitrophenyl)-2-carboxy-propanoic acid (IIIc) with ammonium acetate and malonic acid. Preparation of 3-amino-3-(4-nitro)phenyl-propanoic acid (IVc), 3-(4-nitrophenyl)-2-carboxy-2-propenoic acid (VIc) and 4-nitrocinnamic acid (VIIc). IIIc (0.198 g, 0.779 mmol), ammonium acetate (0.127 g, 1.65 mmol) and malonic acid (0.100 g, 0.963 mmol) were refluxed in EtOH (20 mL) for 48 h. The work up for this reaction was the same as described for **IIIa**. **IVc** was then obtained as light-yellow solid (0.0608 g, 40%); mp 229–230°C (dec.); IR (KBr) 3477, 3034, 1607, 1598, 1357, 1283, 847 cm^{-1}; ^1H NMR (D_2O/K_2CO_3) 7.98 (d, J=8.92 Hz, 2H), 7.37 (d, J=8.91 Hz, 2H), 4.16 (t, J=7.35 Hz, 1H), 2.30–2.51 (m, 2H); ^{13}C NMR (D_2O/K_2CO_3) 172.0, 160.2, 150.4, 129.9, 126.4, 50.8, 39.3. Anal. calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.69; H, 4.68; N, 13.21. along with **VIc** (0.0085 g, 5%) and **VIIc** (0.0873 g, 53%); mp 293–294°C (dec.) (lit.[13] 285–286°C, dec.); IR (KBr) 3040, 1696, 1342, 1265, 947, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (d, J=8.90 Hz, 1H), 7.38 (d, J=8.90 Hz, 2H,), 7.03 (d, J=16.30 Hz, 2H,), 6.28 (d, J=16.30 Hz, 1H,); ^{13}C NMR ($CDCl_3$) 169.2, 149.7, 144.6, 140.1, 131.1, 130.8, 126.4.

Anal. calcd for $C_9H_7NO_4$: C, 55.96; H, 3.65; N, 7.25. Found: C, 55.80; H, 3.57; N, 7.10.

3.2.23. 3-Amino-3-(4-nitrophenyl)-2-carboxy-propanoic acid (IIIc) refluxed in ethanol. Preparation of 3-amino-3-(4-nitro)phenylpropanoic acid (IVc) and 4-nitrocinnamic acid (VIIc). IIIc (0.201 g, 0.792 mmol) was refluxed in EtOH (20 mL) for 48 h. The work up was the same as for **IIIa** to yield **IVc** (0.0787 g, 47%) and **VIIc** (0.0717 g, 47%).

3.2.24. Reaction of 3-(4-nitrophenyl)-2-carboxy-2-propenoic acid (VIc) with ammonium acetate and malonic acid. Preparation of 3-amino-3-(4-nitro)phenylpropanoic acid (IVc) and 4-nitrocinnamic acid (VIIc). VIc (0.207 g, 0.874 mmol), ammonium acetate (0.148 g, 1.923 mmol) and malonic acid (0.0956 g, 0.919 mmol) were refluxed in EtOH (20 mL) for 48 h. The reaction mixture was cooled to room temperature before an off white solid was collected by filtration. The solid was then washed twice with EtOH (20 mL) followed by trituration with H_2O (20 mL) twice to afford **IVc** (0.0062 g, 3%). The H_2O filtrates were combined and evaporated to give **IIIc** (0.0158 g, 7%). The EtOH filtrate, from the reaction mixture, was evaporated to dryness and dissolved in 1.0N NaOH (10 mL). The aqueous was then acidified to pH 3 with 1.0N HCl added dropwise to yield **VIIc** (0.148 g, 88%).

3.2.25. Reaction of 3-(4-nitrophenyl)-2-carboxy-2-propenoic acid (VIc) with ammonium acetate. Preparation of 3-amino-3-(4-nitro)phenylpropanoic acid (IVc) and 4-nitrocinnamic acid (VIIc). VIc (0.208 g, 0.879 mmol) and ammonium acetate (0.146 g, 1.90 mmol) were refluxed in EtOH (20 mL) for 48 h. The reaction was then worked up (as the above procedure) to give **IVc** (0.0070 g, 4%), **IIIc** (0.0185 g, 8%) and **VIIc** (0.146 g, 0.754 mmol, 86%).

3.2.26. 3-(4-Nitrophenyl)-2-carboxy-2-propenoic acid (VIc) refluxed in ethanol. Preparation of 4-nitrocinnamic acid (VIIc). VIc (0.208 g, 0.876 mmol) was refluxed in EtOH (20 mL) for 48 h. The reaction was then worked up as for **VIa** to yield **VIIc** (0.157 g, 0.812 mmol, 93%).

3.2.27. Preparation of 3-amino-3-(4-methyl)phenylpropanoic acid (IVa) and 4-methylcinnamic acid (VIIa) in methanol, ethanol and 2-propanol as solvent systems. *p*-Tolualdehyde **Ia** (1.0 mL, 8.48 mmol), ammonium acetate (1.511 g, 19.60 mmol) and malonic acid (0.892 g, 8.57 mmol) were refluxed in MeOH (30 mL). *p*-Tolualdehyde **Ia** (1.0 mL, 8.48 mmol), ammonium acetate (1.511 g, 19.60 mmol) and malonic acid (0.896 g, 8.610 mmol) were refluxed in EtOH (30 mL). *p*-Tolualdehyde **Ia** (1.0 mL, 8.48 mmol), ammonium acetate (1.519 g, 19.71 mmol) and malonic acid (0.893 g, 8.54 mmol) were refluxed in 2-PrOH (30 mL). The three reactions were carried out in the same oil bath set at 83°C. These reactions were refluxed for 24 h and allowed to cool to room temperature before a white solid was collected (through filtration) from each reaction mixture. The white solid was then triturated with EtOH (50 mL) twice to give **IVa** (methanol; 0.971 g, 64%), (ethanol; 0.822 g, 54%) and (2-propanol; 0.772 g, 51%). The filtrate from each reaction mixture was evaporated to dryness and dissolved in 1.0N NaOH (20 mL). This aqueous solution was then acidified to pH 3 with 1.0N HCl added dropwise to yield **VIIa** (methanol; 0.497 g, 3.062 mmol, 36%), (ethanol; 0.618 g, 3.808 mmol, 45%) and (2-propanol; 0.656 g, 4.045 mmol, 48%).

3.2.28. Preparation of 3-amino-3-(4-methoxy)phenylpropanoic acid (IVb) and 4-methoxycinnamic acid (VIIb) in methanol, ethanol and 2-propanol as solvent systems. *p*-Anisaldehyde **Ib** (1.0 mL, 8.22 mmol), ammonium acetate (1.30 g, 16.84 mmol) and malonic acid (0.858 g, 8.24 mmol) were refluxed in MeOH (30 mL). *p*-Anisaldehyde **Ib** (1.0 mL, 8.22 mmol), ammonium acetate (1.277 g, 16.57 mmol) and malonic acid (0.859 g, 8.26 mmol) were refluxed in EtOH (30 mL). *p*-Anisaldehyde **Ib** (1.0 mL, 8.22 mmol), ammonium acetate (1.279 g, 16.59 mmol) and malonic acid (0.861 g, 8.28 mmol) were refluxed in 2-PrOH (30 mL). The three reactions were carried out in the same oil bath set at 83°C. These reactions were refluxed for 24 h and allowed to cool to room temperature before a white solid was collected (through filtration) from each reaction mixture. The white solid was then triturated with EtOH (50 mL) twice to give **IVb** (methanol; 1.219 g, 76%), (ethanol; 1.034 g, 70%) and (2-propanol; 0.744 g, 51%). The filtrate from each reaction mixture was evaporated to dryness and dissolved in 1.0N NaOH (25 mL). This aqueous was then acidified to pH 3 with 1.0N HCl added dropwise to yield **VIIb** (methanol; 0.352 g, 24%), (ethanol; 0.434 g, 30%) and (2-propanol; 0.700 g, 48%).

3.2.29. Preparation of 3-amino-3-(4-nitro)phenylpropanoic acid (IVc) and 4-nitrocinnamic acid (VIIc) in methanol, ethanol and 2-propanol as solvent systems. *p*-Nitrobenzaldehyde **Ic** (1.007 g, 6.65 mmol), ammonium acetate (1.091 g, 14.16 mmol) and malonic acid (0.697 g, 6.700 mmol) were refluxed in MeOH (30 mL). *p*-Nitrobenzaldehyde **Ic** (1.007 g, 6.65 mmol), ammonium acetate (1.049 g, 13.61 mmol) and malonic acid (0.695 g, 6.68 mmol) were refluxed in EtOH (30 mL). *p*-Nitrobenzaldehyde **Ic** (1.007 g, 6.65 mmol), ammonium acetate (1.068 g, 13.86 mmol) and malonic acid (0.700 g, 6.72 mmol) were refluxed in 2-PrOH (30 mL). The three reactions were carried out in the same oil bath set at 83°C. These reactions were refluxed for 24 h and allowed to cool to room temperature before a white solid was collected (through filtration) from each reaction mixture. The white solid was then triturated with EtOH (50 mL) twice to give **IVc** (methanol; 0.206 g, 15%), (ethanol; 0.374 g, 27%) and (2-propanol; 0.455 g, 33%). The filtrate from each reaction mixture was evaporated to dryness and dissolved in 1.0N NaOH (25 mL). This aqueous was then acidified to pH 3 with 1.0N HCl added dropwise to yield **VIIc** (methanol; 1.081 g, 84%), (ethanol; 0.932 g, 73%) and (2-propanol; 0.851 g, 66%).

Acknowledgments

C. Y. K. T. acknowledges a Natural Sciences and Engineering Research Council (NSERC) of Canada Scholarship. D. F. W. acknowledges operating grants from NSERC and Medical Research Council of Canada (MRC).

References

1. (a) Shinagawa, S.; Kanamaru, T.; Harada, M.; Okazaki, H. *J. Med. Chem.* **1987**, *30*, 1458. (b) Oki, T.; Hirano, M.; Tomatsu, K.; Numata, H.; Kamei, H. *J. Antibiot.* **1989**, *42*, 1756. (c) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 6523.
2. (a) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem.* **1994**, 38. (b) Yang, L.; Weber, E.; Greenlee, W. J.; Patchett, A. *Tetrahedron Lett.* **1993**, *34*, 7035.
3. Seebach, D.; Overhand, M.; Kuhnle, F. N.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H. *Helv. Chim. Acta* **1996**, *79*, 913.
4. George, G. I. *The Organic Chemistry of β-Lactams*. Verlag Chemie: New York, 1993.
5. For reviews, see the following and the references thereafter, (a) Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, 117. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517. (c) Juriasti, E. *Enantioselective Synthesis of β-Amino Acids*. VCH: New York, 1997.
6. (a) Mamaev, V. P. *Zh. Obshch. Khim.* **1957**, *27*, 1290. (b) Posner, T.; Schreiben, G. *Ber.* **1924**, *57*, 1129. (c) Dutt, S. *J. Indian Chem. Soc.* **1924**, *1*, 298. (d) Johnson, T. B.; Lival, J. E. *J. Am. Chem. Soc.* **1936**, *58*, 299. (e) Pandya, S.; Vahida, T. *Proc. Indian Acad. Soc.* **1936**, *4A*, 134. (f) Profft, E.; Becker, F. J. *J. Prakt. Chem.* **1965**, *30*, 18. (g) Merz, K. W.; Haller, R. *Pharm. Acta Helv.* **1963**, *38*, 442. (h) Lazar, L.; Martinek, T.; Bernath, G.; Fulop, F. *Synth. Commun.* **1998**, *28*, 219. (i) Preobrazhenskaya, K. P.; Smirnov, S. M. *Zh. Org. Khim.* **1972**, *8*, 2045. (j) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1998**, *63*, 2351. (k) Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhar, V. P.; Savchenko, M. V.; Svedas, V. K. *Tetrahedron: Asymmetry* **1995**, *6*, 1601. (l) Kalvin, D. M.; Woodard, R. W. *J. Org. Chem.* **1985**, *50*, 2259. (m) Dallemagne, P.; Tembo, O.; Rault, S.; Robba, M. *Bull. Soc. Chim. Fr.* **1989**, 98. (n) Ashton, M. J.; Hills, S. J.; Newton, C. G.; Taylor, J. B.; Tondu, S. *Heterocycles* **1989**, *28*, 1015. (o) Laschat, S.; Kunz, H. J. *J. Org. Chem.* **1991**, *56*, 5883. (p) Rault, S.; Dallemagne, P.; Robba, M. *Bull. Soc. Chim. Fr.* **1987**, 1079. (q) Bayston, D. J.; Falque, V.; Scott, R. M. US Patent 6207854, 2001.
7. (a) Rodionow, W. M.; Postovskaja, E. A. *J. Am. Chem. Soc.* **1929**, *51*, 841. (b) Rodionow, W. M. *J. Am. Chem. Soc.* **1929**, *51*, 847.
8. Hann, A.; Lapworth, A. *J. Chem. Soc.* **1904**, *85*, 46.
9. For review, see Jones, G. *Organic Reactions*, Wiley: New York, 1967; Vol. 15. p 204.
10. Kwon, P.; Kim, Y.; Kang, C. J.; Kwon, T.; Chung, S.; Chang, Y. T. *Synth. Commun.* **1997**, *27*, 4091.
11. Corey, E. J. *J. Am. Chem. Soc.* **1952**, *74*, 5897.
12. Patai, S.; Edlitz-Pfeffermann, J.; Rozner, Z. *J. Am. Chem. Soc.* **1954**, *76*, 3446.
13. Knoevenagel, E. *Ber.* **1898**, *31*, 2596.