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Studies on the catalytic hydrogenation of Baylis Hillman derivatives of substituted isoxazolecarbaldehydes[§#]

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Abstract—Results of the catalytic hydrogenation of Baylis-Hillman adducts obtained from substituted 3-, 4- and 5-isoxazolecarboxaldehydes and their corresponding acetates in the presence of Raney-Ni and Pd-C are presented. The hydrogenation of Baylis-Hillman adducts of substituted 5-isoxazolecarbaldehydes and 3-isoxazolecarbaldehydes in the presence of Raney-Ni furnishes diastereoselectively *syn* enaminones over *anti* and in the presence of boric acid as an additive further enhancement of diastereoselectivity in favor of *syn* isomer is observed. The Pd-C-promoted hydrogenation of these substrates is also diastereoselective in favor of *syn* isomer but occurs without the hydrogenolysis of isoxazole-ring. The presence of boric acid as additive in this hydrogenation exhibits no pronounced effect on diastereoselectivity. The Raney-Ni-mediated hydrogenation of Baylis-Hillman adducts of substituted 4-isoxazolecarbaldehydes yield pyridone derivatives and Pd-C-promoted hydrogenation of the same substrate is diastereoselective to afford the *anti* isomer of the resulting products. The enaminones derived from Baylis-Hillman adducts of 3- and 5-isoxazolecarbaldehydes serve as versatile precursors for α'-hydroxy-1, 3-diketones, which undergo acid-catalyzed ring-closure reaction to afford the furanone derivatives in excellent yields.

1. Introduction

The isoxazole heterocycle represents masked β-enaminone and 1, 3-dione systems because of the lability of the N-O bond towards catalytic and chemical reductions under mild conditions.[1-5] This ability of the isoxazole-ring besides making it a useful synthetic intermediate also evokes interest to understand reasons for biological activity because our interest in the Baylis-Hillman chemistry of isoxazolecarbaldehydes has not only led us to generate novel isoxazole-based synthetic intermediates but has also led to identification of bioactive compounds.[6-10]

The hydrogenation studies of the Baylis Hillman adduct and their corresponding derivatives under heterogeneous catalytic conditions with Pd-C and rhodium have been earlier reported.[11-14] While these detailed studies address the issue of diastereoselectivity in the reduced product under different additives and solvent conditions, the fate of the Baylis-Hillman adducts during hydrogenation in the presence of Raney-Ni remains unreported. Since the isoxazole ring is known to undergo hydrogenolysis in the presence of Raney-Ni and Pd-C,[15-18] it was desired to evaluate the effect of these catalysts on the Baylis-Hillman adducts of substituted isoxazolecarbaldehydes. During the course of this study we have noted some unusual and interesting observations, which prompt us to report our findings

2. Results and Discussion

The hydrogenation of the Baylis-Hillman adducts **2a-c** and **3b**, originating from substituted 5-isoxazolecarbaldehydes **1a-c**, in the presence of Raney-Ni in appropriate solvent led to diastereoisomeric mixtures of the enaminones **4a-c** and **5b**, respectively (Scheme 1). Beside other spectroscopic evidence, the opening of the isoxazole-ring was characterized by the presence of two broad singlets for NH_2 protons and an upfield shift of the isoxazole =CH proton from δ 6.5 to δ 5.5 of enaminone in the ^{1}H NMR spectrum. The hydrogenation of **3b** in particular aimed to understand the influence of the ester group on the outcome of hydrogenation. The analyses of the stereochemistry of the hydrogenation products were based on their ^{1}H NMR spectra, which revealed *syn* selectivity over the *anti* products in the range of 2-2.5:1. Compared to these observations, the Pd-C promoted catalytic hydrogenation of

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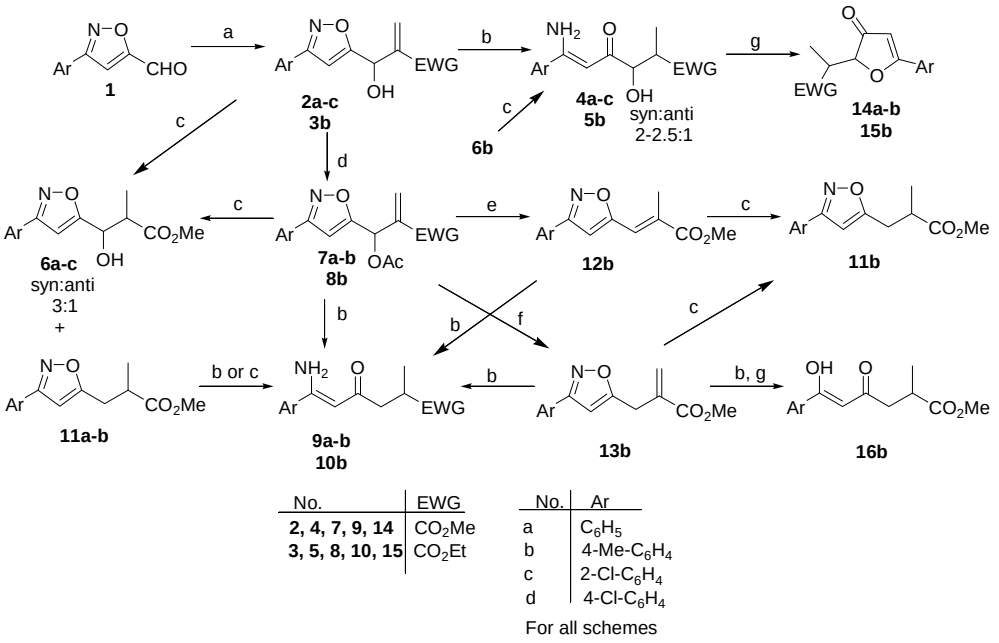
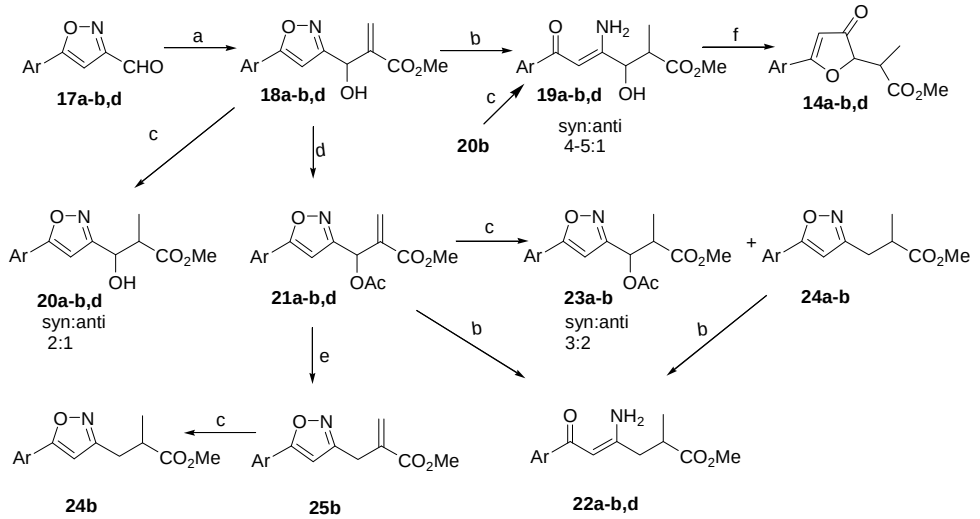
compounds **2a-c** using methanol or ethyl acetate as solvent gave diastereoisomeric mixture of products **6a-c**. The



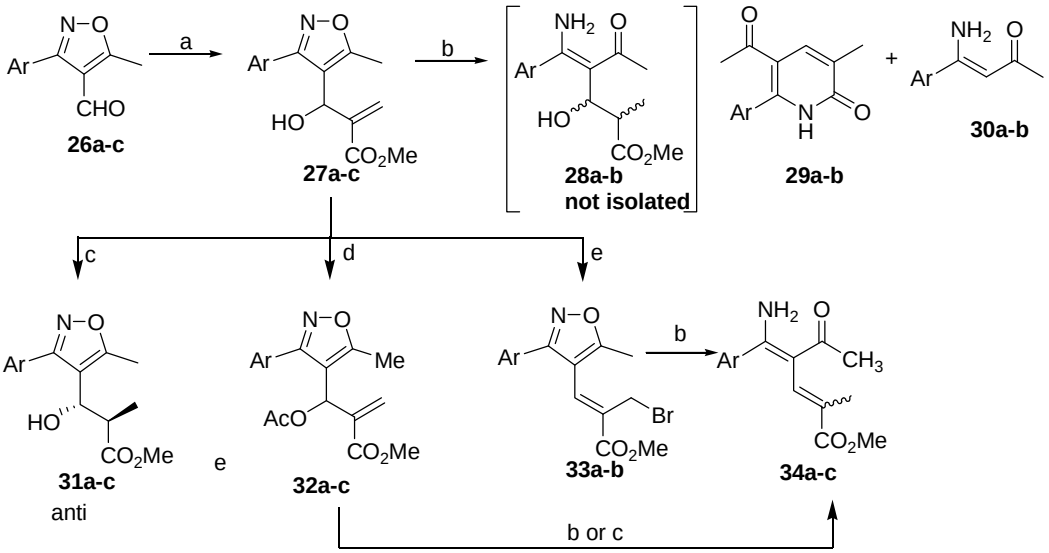
Scheme 1: *Reagents and conditions*-a) CH_2=CHEWG, DABCO, 30 min. b) Raney-Ni, H_2 (Balloon at rt or Parr assembly at 30psi), MeOH, 3h; c) Pd-C, H_2, (Balloon at rt or Parr assembly at 30psi), MeOH or EtOAc, 2-2.5h (**6b** to **4b**, 10h); d). CH_3COCl, Pyridine, CH_2Cl_2, rt, 3-5h; e). $NaBH_4$, MeOH, rt, 2h; f) DABCO, $NaBH_4$, THF: H_2O (1:1), rt, 15 min; g). H^+ (HCl, H_2SO_4, CH_3CO_2H at rt, or mixture of HCO_2H and CH_3CO_2H at 60°C), 24h.



Scheme 2: *Reagents and conditions*- a) CH_2=$CHCO_2Me$, DABCO, 30 min. b). Raney-Ni, H_2 (Balloon at rt or Parr assembly at 30psi), MeOH, 3h; c). Pd-C, H_2, (Balloon at rt or Parr assembly at 30psi), MeOH or EtOAc, 2-2.5h, (**20b** to **19b**, 10h); d). CH_3COCl, Pyridine, CH_2Cl_2, rt, 2-3h; e). DABCO, $NaBH_4$, THF: H_2O (1:1), rt, 15 min; f). H^+ (HCl, H_2SO_4, CH_3CO_2H at rt, or mixture of HCO_2H and CH_3CO_2H at 60°C), 24h.

absence of the signal for the amino group of the enamine and the unchanged chemical shift of the =CH proton of the isoxazole-ring in the ^{1}H NMR spectra coupled with mass spectra of these compounds indicated that only the reduction of the methylene group had occurred with retention of isoxazole-ring. This result was contrary to the previous literature reports where hydrogenolysis of the isoxazole ring under similar conditions has been reported.[19-21] In these cases, the reaction was also diastereoselective in favor of *syn* isomer over *anti* (ratio of

3:1). In our attempts to understand this unusual behavior, the Pd-C-mediated hydrogenation was carried out under different conditions. In the first instance in a representative example, the Pd-C promoted hydrogenation of compound **2b** was continued for more than 24h but no hydrogenolysis was observed and compound **6b** was isolated exclusively. Thereafter, the reaction was carried out with an excess of catalyst (ca 3-5 fold) without any success. Successively, the compound **6b** was again subjected to hydrogenation in the presence of Pd-C. Interestingly this reaction was completed within 10h to yield the hydrogenolysis products **4b** exclusively. In view of these results, we next examined the hydrogenation of the Baylis-Hillman adducts of 3- and 4-isoxazolecarb-aldehydes. Similar to reactions of the Baylis-Hillman adducts of 5-isoxazolecarbaldehydes, the hydrogenation of the Baylis-Hillman adducts **(18a-b, d)**, derived from substituted 3-isoxazolecarbaldehydes **(17a-b, d)** in the presence of Raney-Ni led to isolation of envisaged enaminones **(19a-b, d)** in good yields (Scheme 2). The observed diastereoselectivity in favor of *syn* isomer over the *anti* isomer was slightly better as compared to the enaminones derived from Baylis-Hillman derivatives of 5-isoxazolecarbaldehydes because the ratio ranged from 4-5:1. The hydrogenation of adducts **18a-b, d** in the presence of Pd-C afforded diastereoisomeric mixtures (*syn*: *anti*, 2:1) of products **20a-b, d** without the hydrogenolysis of the isoxazole ring. However when compound **20b** was again subjected to hydrogenation, the hydrogenolysis of the isoxazole-ring did occur to afford enaminone **19b**. Interestingly when the Baylis-Hillman adducts **(27a-b)**, derived from substituted 4-isoxazolecarbaldehydes, were subjected to hydrogenation in the presence of Raney-Ni; the envisaged enaminones **(28a-b)** could not be isolated. The two products isolated from the reaction were identified as substituted pyridones **29a-b** and enaminones **30a-b** (Scheme 3). The formation of the minor product namely the pyridone derivative **(29a-b)** can be rationalized on the



Scheme 3: *Reagents and conditions*- a) CH_2=$CHCO_2Me$, DABCO, 2d. b) Raney-Ni, H_2 (Balloon at rt or Parr assembly at 30psi), MeOH, 3h; c). Pd-C, H_2, (Balloon at rt or Parr assembly at 30psi), MeOH or EtOAc, 2-2.5h; d). CH_3COCl, Pyridine, CH_2Cl_2, rt, 1h; e). PBr_3, CH_2Cl_2, rt, 45 min.

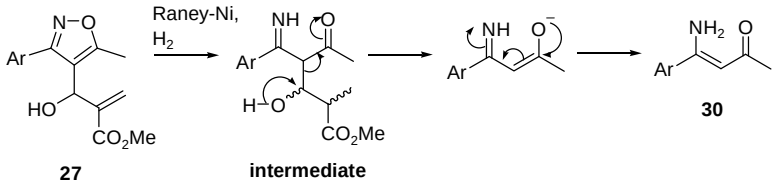


Fig. 1

basis of hydrogenolysis of the isoxazole ring followed by ring closure involving the amino and the ester group followed by dehydration.[22] The plausible explanation for the formation of compound **30** is shown in fig. 1. However the hydrogenation of compounds **27a-c** in the presence of Pd-C was stereospecific to afford the *anti* isomer of products **31a-c** without the cleavage of the isoxazole-ring. Since enaminones **28a-b** were not isolated during the hydrogenolysis of compounds **27a-b**, no attempts were made to carry out Pd-C-promoted hydrogenolysis of compounds **31a-c**.

In the next stage of the study we directed our attention towards evaluating the effect of hydrogenation on the

acetates derived from the Baylis-Hillman adducts of substituted isoxazolecarbaldehydes. The Raney-Ni promoted hydrogenolysis of acetates **7a-b** and **8b** led to enaminones **9a-b** and **10b**, respectively (Scheme 1). Such products may have resulted via hydrogenolysis of the isoxazole-ring with simultaneous loss of acetic acid followed by the reduction of the double bond in the intermediate. In principle, a product similar to compound **9** could be generated from compound **12** or **13**, which in turn can be easily synthesized through reaction of sodium borohydride with the acetate **(7)** under appropriate conditions.[9, 10] In order to obtain chemical evidence for the formation of compounds **9-10**, compounds **12b** and **13b** were subjected to hydrogenation in the presence of Raney-Ni. As envisaged both reactants led to the product **9b** in good yield. To evaluate the fate of hydrogenation in the presence of Pd-C, acetates **7a-b** were subjected to hydrogenation in the presence of this catalyst. Unlike the corresponding Baylis-Hillman adduct **(2a-b)**, the acetates **(7a-b)** invariably furnished a separable mixture of two products. The non-polar products were identified as **11a-b** while the polar products were **6a-b** (Scheme 1). The formation of compounds **11a-b** could be rationalized based on a similar mechanism for compounds **9-10** except for the cleavage of the isoxazole-ring. As reported earlier[13] compound **6** may have resulted from simple reduction of the double bond with simultaneous deacetylation. In accordance with the literature precedence,[13] we too did not observe diastereoselectivity during the formation of product **6**. The additional chemical evidence for the formation of product **11** was achieved by Pd-C-mediated hydrogenation of compounds **12b** and **13b**, which furnished the product **11b**. Further evidence for the assigned structure to compound **11** came from the Raney-Ni promoted hydrogenolysis of **11b** to furnish compound **9b**. In addition, when compound **11b** was subjected to hydrogenation in the presence of Pd-C the hydrogenolysis of the isoxazole-ring does occur to yield compound **9b**.

The Raney-Ni catalyzed hydrogenation of acetates **21a-b, d** yielded exclusively the expected enaminones **22a-b, d** in good yields (Scheme 2). However the Pd-C promoted hydrogenation of these acetates **(21a-b)** gave a mixture of two products. Based on the spectroscopic evidence these products were identified as **23a-b** and **24a-b**. Contrary to the observation with the corresponding derivatives obtained from 5-isoxazolecarbaldehydes **(7)**, the deacetylation does not occur during the process and only the reduced products **23** are obtained. Further the stereochemistry of compounds **23** was in favor of the *anti* isomer over *syn* by 7:3. To unambiguously confirm the formation of products **24a-b**, hydrogenation of compound **24b** in the presence of Raney-Ni led to isolation of product **22b**. The Pd-C promoted hydrogenation of compound **25b**, that was in turn generated from the sodium borohydride-promoted S_N2' nucleophilic substitution of hydride on the acetate **21b**, yielded the product **24b**.

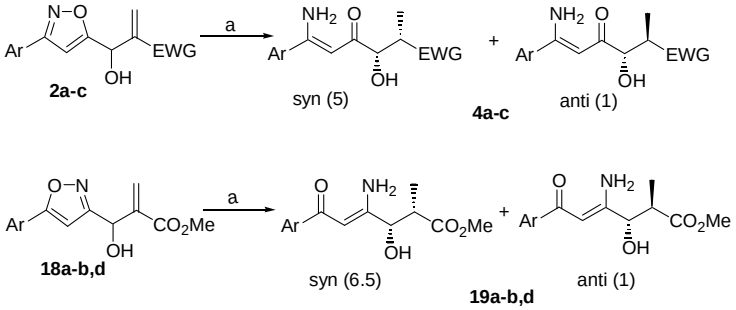
The hydrogenation of acetates **(32a-c)** generated from Baylis-Hillman adducts of substituted 4-isoxazolecarb-aldehydes was found to be significantly different. The hydrogenolysis of compounds **32a-c** in the presence of Raney-Ni invariably led to isolation of enaminones **34a-c** (Scheme 3). Unlike the reaction of other acetates described earlier in this text, the hydrogenolysis of the isoxazole ring here may have proceeded with simultaneous reduction of the methylene group and elimination of acetic acid. However, it seems that further reduction of double bond possibly did not occur because of the steric impedance. On the basis of NOE studies the stereochemistry of the product **34** was assigned as Z. In our efforts to gain further insight into the formation of product **34**, the allylic bromide **33b** was generated and subjected to hydrogenolysis in the presence of Raney-Ni. This reaction also afforded compound **34b**. Similarly, the Pd-C catalyzed hydrogenation of acetates **31a-c** also led to the isolation of products **34a-c**. The formation of compounds **34a-c** was in contrast to other Pd-C mediated reactions carried out during this study where the ring-cleavage did not take place. Thus the extensive hydrogenation studies carried out herein indicate that the behavior of the Baylis-Hillman derivatives of 5- and 3-isoxazolecarbaldehydes is very much similar during the Raney-Ni and the Pd-C-promoted reactions whereas the Baylis-Hillman derivatives obtained from 4-isoxazolecarbaldehydes yields significantly different products. The change in the ester group does not affect the outcome of the hydrogenation reaction. At this point of time the present investigations do not impart any explanation for the stability of the isoxazole ring during Pd-C-promoted hydrogenation of derivatives of Baylis-Hillman reaction of isoxazolecarbaldehydes. Nevertheless, once the double bond present in the side-chain is saturated the hydrogenolysis of the isoxazole-ring does take place in the presence of Pd-C.

It has been reported earlier that the α'-hydroxy-1, 3-diketones derived from isoxazoles provide a facile synthetic method to obtain 3(2H)-furanones derivatives.[23-25] In a similar observation Chimichi et al. recently reported the synthesis of substituted 3(2H)-furanones through appropriately substituted α'-hydroxy-1, 3-diketones utilizing isoxazoles as the starting substrate. As part of our objectives to demonstrate the synthetic utility of the enaminones synthesized during this study, compounds **4a-b, 5b** and **19a-b, d** were subjected to acid-promoted cyclization-dehydration reaction. The reaction of compounds **4a-c, 5b** and **19a-b, d** with HCl or H_2SO_4 led to the furanones **14a-d** and **15b** in moderate yields only. However excellent yields of furanones (**14a-d** and**15b**) were achieved when the same reaction was carried out in the presence of a mixture of acetic acid and formic acid (Scheme 1 and 2). To provide chemical evidence for the fact that the formation of furanones is via the cyclodehydration of the diketo derivatives afforded by the enaminones in the presence of acid, compound **10b** was treated with acid to yield the diketo-derivative **16b** in quantitative yields. It has been reported[26] earlier that Raney-Ni-promoted hydrogenation of 2-isoxazolines and isoxazoles, in the presence of boric acid leads to diketo-derivatives. To assess the possibility of generating these furanones through one pot reaction we decided to carry out the Raney-Ni-mediated hydrogenation of **2a-c** in the

presence of boric acid.[27] This hydrogenation though did not yield the desired furanones; there was a dramatic change in the degree of diastereoselectivity (Scheme 4). The *syn* isomer was preferentially obtained over *anti* isomer as shown in Table 1. Encouraged by this observation we also subjected the Baylis-Hillman derivatives **2a** and **18a** to Pd-C-promoted hydrogenation in the presence of boric acid. However during the process, we did not observe any significant change in the diastereoselectivity.

Table 1: Ratio of *syn* and *anti* enaminones derivative obtained without and with boric acid during Raney-Ni promoted hydrogenation of Baylis-Hillman adducts of 5 and 3-isoxazolecarbaldehydes

Compound No.	Raney-Ni only (*syn*: *anti*)	Raney-Ni + Boric acid (*syn*: *anti*)
2a	**4a** (2:1)	**4a** (5:1)
2b	**4b** (5:2)	**4b** (6:1)
2c	**4c** (5:2)	**4c** (5:1)
3b	**5b** (4:1)	**5b** (9:1)
18a	**19a** (4:1)	**19a** (7:1)
18b	**19b** (5:1)	**19b** (13:2)
18d	**19d** (5:1)	**19d** (13:2)



Scheme 4: *Reagents and conditions*- a) Raney-Ni, H_2, H_3BO_3, rt, 6h.

3. Conclusions

In summary, we have described some interesting observations made during the Raney-Ni and Pd-C catalyzed hydrogenation of the Baylis-Hillman adducts generated from 3-, 4- and 5-isoxazolecarbaldehydes and their corresponding acetates. For the first time we report here the diastereoselective hydrogenation of the Baylis-Hillman derivatives in the presence of Raney-Ni. During the course of the present study better diastereoselectivity was achieved by carrying out these hydrogenations in the presence of boric acid. Presently, it is difficult to assign reason for preservation of the isoxazole-ring in the Pd-C-promoted hydrogenation of derivatives of Baylis-Hillman reaction during this study. The enaminones generated from the hydrogenation of Baylis-Hillman adducts of isoxazolecarbaldehydes could serve as direct access to substituted α'-hydroxy-1, 3-diketones that are scarcely available.

4. Experimental

4.1. General.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a 300 or a 200 MHz FT spectrometer, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The FABMS were recorded on JEOL/ SX-102 spectrometers and ESMS were recorded through direct flow injections in Merck M-8000 LCMS system. Elemental analyses were performed on a Carlo Erba 1108 microanalyzer or Elementar's Vario EL *III* microanalyzer. The spectroscopic data for all products obtained as diastereoisomeric mixtures are presented as such and no attempts were made to separate them. For preparation of compounds **2, 7, 18, 21, 27** and **32** refer to reference no. 6, 8 and 9.

4.2. Hydrogenation in the presence of Raney-Ni- Representative Procedure

A mixture of compound **2a** (520mg, 2.0 mmol) and Raney-Ni (100mg in ethanol) in methanol (10 mL) was subjected to hydrogenation either in the Parr assembly at 35psi at rt or stirred in a sealed vessel having hydrogen atmosphere maintained by a balloon. The reaction was allowed to continue for 2.5 h. Thereafter, the catalyst was removed by vacuum-filtering the reaction mixture through a celite bed with methanol. The filtrate was evaporated to obtain an oily residue which was taken in ethyl acetate (2x20 mL) and washed with water (20 mL). The organic layers were collected, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to obtain a crude oily

product. Purification of the crude product by column chromatography over silica gel (230-400 mesh) using hexane: ethyl acetate (3:2, v/v) as the eluent furnished compound **4a** as yellow oil.

4.2.1. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-phenyl-hex-5-enoic acid methyl ester (4a).
65% (0.34g from 0.52 g of **2a**); Yellow oil; [Found: C, 63.83; H, 6.19; N, 5.04. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32]. ν_{max} (Neat) 1731 (CO_2Me), 3406 (OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.07 (d, 3H, *J*= 7.0 Hz, -CH-C$\underline{H}_{3anti}$), 1.26 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.90-2.99 (m, 2H, 2 X –C$\underline{H}$-CH_3), 3.69 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.75 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.34 (brs, 1H, -C$\underline{H}$(OH)-$CH_{anti}$), 4.70 (brs, 1H, -C$\underline{H}$(OH)-$CH_{syn}$), 5.47 (s, 1H, =C$\underline{H}_{syn}$), 5.49 (s merged with brs, 3H, =C$\underline{H}_{anti}$ and 2 X 1H of N$\underline{H}_2$), 7.44-7.58 (m, 10H, Ar$\underline{H}$), 9.89 (brs, 2H, 2 X 1H of N$\underline{H}_2$); Mass (FAB+) *m/z* 264 (M^++1).

4.2.2. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-p-tolyl-hex-5-enoic acid methyl ester (4b).
67% (1.34g from 2.0g of **2b**); Yellow oil; [Found: C; 65.23, H, 6.72; N, 4.88. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05]. ν_{max} (Neat) 1730 (CO_2Me), 3402 (OH and NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.07 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.26 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.40 (s, 6H, 2 X Ar-C$\underline{H}_3$), 2.87-2.97 (m, 2H, 2 X –C$\underline{H}$-CH_3), 3.69 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.74 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.34 (t, 1H, *J*= 6.0 Hz, -C$\underline{H}$(OH)-CH_{anti}), 4.68 (d, 1H, *J*= 3.0 Hz, -C$\underline{H}$(OH)-CH_{syn}), 5.45 (s, 1H, =C$\underline{H}_{syn}$), 5.48 (s, 1H, =C$\underline{H}_{anti}$), 5.54 (brs, 2H, 2 X 1H of N$\underline{H}_2$), 7.25 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.45 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$), 9.86 (brs, 2H, 2 X 1H of N$\underline{H}_2$); Mass (ES+) *m/z* 300.73 (M^++Na).

4.2.3. 6-Amino-6-(2-chloro-phenyl)-3-hydroxy-2-methyl-4-oxo-hex-5-enoic acid methyl ester (4c).
63% (0.72g from 1.14g of **2c**); Yellow solid, mp 124-26ºC; [Found: C, 56.85; H, 5.40; N, 4.44. $C_{14}H_{16}ClNO_4$ requires C, 56.48; H, 5.42; N, 4.70]. ν_{max} (KBr) 1730 (CO_2Me), 3402 (OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.07 (d, 3H, *J*= 7.0 Hz, -CH-C$\underline{H}_{3anti}$), 1.25 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.87-2.98 (m, 2H, 2 X -C$\underline{H}$-CH_3), 3.67 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.72 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.28 (brs, 1H, -C$\underline{H}$(OH)-$CH_{anti}$), 4.67 (brs, 1H, -C$\underline{H}$(OH)-$CH_{syn}$), 5.23 (s, 1H, =C$\underline{H}_{syn}$), 5.25 (s, 1H, =C$\underline{H}_{anti}$), 6.18 (s, 2H, 2 X 1H of N$\underline{H}_2$), 7.35-7.47 (m, 8H, Ar$\underline{H}$), 9.85 (brs, 2H, 2 X 1H of N$\underline{H}_2$); Mass (FAB+) *m/z* 298 (M^++1).

4.2.4. 6-Amino-3-hydroxy-2-methyl-4-oxo-6-p-tolyl-hex-5-enoic acid ethyl ester (5b).
62% (0.62g from 1.0g from **3b**); Yellow solid, mp 118-120ºC; [Found: C, 66.03; H, 6.98; N, 4.51. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81]. ν_{max} (KBr) 1726 (CO_2Et), 3402 (OH and NH_2); ^1H NMR (200 MHz, $CDCl_3$) δ = 1.06 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.19-1.32 (m, 9H, -CH-C$\underline{H}_{3syn}$, 2 X $CO_2CH_2C\underline{H}_3$), 2.41 (s, 6H, 2 X Ar-C$\underline{H}_3$), 2.80-2.91 (m, 2H, 2 X –C$\underline{H}$-CH_3), 4.09-4.29 (m, 2q merged, 4H, 2 X $CO_2C\underline{H}_2$), 4.35 (d, 1H, *J*= 6.6 Hz, -C$\underline{H}$(OH)-CH_{anti}), 4.69 (d, 1H, *J*= 3.0 Hz, -C$\underline{H}$(OH)-CH_{syn}), 5.48 (s, 1H, =C$\underline{H}_{syn}$), 5.49 (s, 1H, =C$\underline{H}_{anti}$), 5.60 (s, 2H, 2 X 1H of N$\underline{H}_2$), 7.25 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.45 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$), 9.85 (brs, 2H, 2 X 1H of N$\underline{H}_2$); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ = 9.8, 13.5, 14.5, 21.7, 44.4, 44.8, 60.9, 61.2, 75.3, 76.9, 90.0, 91.2, 126.6, 130.1, 133.9, 134.1, 141.9, 142.0, 163.4, 163.8, 174.4, 195.8, 196.0; Mass (FAB) *m/z* 292 (M^++1).

4.2.5. 6-Amino-2-methyl-4-oxo-6-phenyl-hex-5-enoic acid methyl ester (9a).
65% (0.37g from 0.57g of **7a**); Yellow oil; [Found: C, 67.71; H, 7.01; N, 5.67. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66]. ν_{max} (Neat) 1728 (CO_2Me), 3406 (br, NH_2) cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 1.22 (d, 3H, *J*= 6.8 Hz, -CH-C$\underline{H}_3$), 2.32-2.55 (m, 1H, -C$\underline{H}$-CH_3), 2.83-3.06 (m, 2H, -CH-C$\underline{H}_2$), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 5.38 (brs, 1H, N$\underline{H}_2$), 5.42 (s, 1H, =C$\underline{H}$), 7.42-7.56 (m, 5H, Ar$\underline{H}$), 9.89 (brs, 1H, N$\underline{H}_2$); Mass (ES+) *m/z* 270.80 (M^++Na).

4.2.6. 6-Amino-2-methyl-4-oxo-6-p-tolyl-hex-5-enoic acid methyl ester (9b).
67% (0.27g from 0.40g of **7b**); White solid; mp 80-82ºC; [Found: C, 68.54; H, 7.01; N, 5.23. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36]. ν_{max} (KBr) 1720 (CO_2Me), 3394 (br, NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.22 (d, 3H, *J*= 6.8 Hz, -CH-C$\underline{H}_3$), 2.39 (s, 3H, Ar-C$\underline{H}_3$), 2.44-2.55 (m, 1H, -C$\underline{H}$-CH_3), 2.82-3.03 (m, 2H, -CH-C$\underline{H}_2$), 3.69 (s, 3H, $CO_2C\underline{H}_3$), 5.21 (brs, 1H, N$\underline{H}_2$), 5.41 (s, 1H, =C$\underline{H}$), 7.23 (d, 2H, *J*= 8.2 Hz, Ar$\underline{H}$), 7.46 (d, 2H, *J*= 8.2 Hz, Ar$\underline{H}$), 9.90 (brs, 1H, N$\underline{H}_2$); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ = 17.6, 21.7, 36.2, 46.0, 52.1, 94.64, 126.5, 130.0, 134.6, 141.4, 161.5, 177.4, 197.3; Mass (ES+) m/z 284.80 (M^++Na).

4.2.7. 6-Amino-2-methyl-4-oxo-6-p-tolyl-hex-5-enoic acid ethyl ester (10b).
65% (0.33g from 0.5g of **8b**); Yellow oil; [Found: C, 69.94; H, 7.33; N, 5.32. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09]. ν_{max} (Neat) 1727 (CO_2Et), 3409 (br, NH_2) cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 1.21 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_3$), 1.25, (t, 3H, *J*= 7.0 Hz, $CH_2C\underline{H}_3$), 2.39 (s, 3H, Ar-C$\underline{H}_3$), 2.43-2.53 (m, 1H, -C$\underline{H}$-CH_3), 2.81-3.01 (m, 2H, -CH-C$\underline{H}_2$), 4.15 (q, 2H, *J*= 7.0 Hz, $CO_2C\underline{H}_2$), 5.20 (brs, 1H, N$\underline{H}_2$), 5.42 (s, 1H, =C$\underline{H}$), 7.23 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.44 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 9.89 (brs, 1H, N$\underline{H}_2$); Mass (ES+) m/z 298.53 (M^++Na).

4.2.8. 4-Amino-3-hydroxy-2-methyl-6-oxo-6-phenyl-hex-4-enoic acid methyl ester (19a).
70% (0.84g from 1.20g of **18a**); White solid, mp 88-90ºC; [Found: C, 63.57; H, 6.67; N, 4.99. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.36]. ν_{max} (KBr) 1653 (C=O), 1733 (CO_2Me), 3410 (br, OH and NH_2) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.22 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.30 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.85-2.90 (m, 2H, 2 X -C$\underline{H}$-CH_3), 3.75 (s, 6H, 2 X $CO_2C\underline{H}_3$), 4.18 (d, 1H, *J*= 6.6 Hz, -C$\underline{H}$(OH)-CH_{anti}), 4.36 (d, 1H, *J*= 4.6 Hz, -C$\underline{H}$(OH)-CH_{syn}), 5.70 (s, 1H, =C$\underline{H}_{anti}$), 5.72 (s, 1H, =CH_{syn}), 6.10 (brs, 2H, 2 X 1H of N$\underline{H}_2$), 7.39-7.58 (m, 6H, Ar$\underline{H}$), 7.85-7.96 (m, 4H, Ar$\underline{H}$), 10.04 (brs, 2H, 2 X

1H of N$\underline{H}_2$), 11.40 (brs, 2H, 2 X O$\underline{H}$); Mass (FAB+) *m/z* 264 (M^++1).

4.2.9. 4-Amino-3-hydroxy-2-methyl-6-oxo-6-p-tolyl-hex-4-enoic acid methyl ester (19b).

87% (0.35g from 0.40g of **18b**); Yellow oil; [Found: C, 65.08; H, 7.02; N, 4.89. $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05]. ν_{max} (Neat) 1652 (C=O), 1734 (CO_2Me) 3402 (br OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.20 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.27 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.38 (s, 3H, Ar-C$\underline{H}_{3anti}$), 2.41 (s, 3H, Ar-CH_{3syn}), 2.78-2.89 (m, 2H, 2 X –C$\underline{H}$-CH_3) 3.73 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.76 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.12 (d, 1H, *J*= 6.4 Hz, -C$\underline{H}$(OH)-CH_{anti}), 4.34 (d, 1H, *J*= 2.6 Hz, -C$\underline{H}$(OH)-CH_{syn}), 5.56 (s, 1H, =CH_{syn}), 5.70 (s, 1H, =C$\underline{H}_{anti}$), 6.10 (brs, 2H, 2 X 1H of N$\underline{H}_2$), 7.21 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}_{anti}$), 7.25 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}_{anti}$), 7.76 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}_{syn}$), 7.84 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}_{syn}$), 10.05 (brs, 2H, 2 X 1H of N$\underline{H}_2$), 10.72 (brs, 2H, 2 X O$\underline{H}$); Mass (FAB+) *m/z* 278 (M^++1).

4.2.10. 4-Amino-6-(4-chloro-phenyl)-3-hydroxy-2-methyl-6-oxo-hex-4-enoic acid methyl ester (19d).

73% (0.42g from 0.48g of **18d**); sticky solid; [Found: C, 56.24; H, 5.51; N, 5.01. $C_{14}H_{16}ClNO_4$ requires C, 56.48; H, 5.42; N, 4.70]. ν_{max} (Neat) 1730 (CO_2Me), 3406 (br OH and NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.20 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.29 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.82-2.89 (m, 2H, 2 X –C$\underline{H}$-CH_3), 3.73 (s, 3H, CO_2CH_{3syn}), 3.76 (s, 3H, CO_2CH_{3anti}), 4.36 (d, 1H, *J*= 7.4 Hz, -C$\underline{H}$(OH)-CH_{anti}), 4.81 (d, 1H, *J*= 4.6 Hz, -C$\underline{H}$(OH)-CH_{syn}), 5.58 (d, 1H, =C$\underline{H}_{syn}$), 5.65 (s, 1H, =C$\underline{H}_{anti}$), 6.11 (brs, 1H, 1H of N$\underline{H}_2$), 6.52 (brs, 1H, 1H of N$\underline{H}_2$), 7.37 (d, 4H, *J*= 8.6 Hz, Ar$\underline{H}$), 7.78 (d, 4H, *J*= 8.6 Hz, Ar$\underline{H}$), 10.05 (brs, 1H, 1H of N$\underline{H}_2$), 10.32 (brs, 1H, 1H of N$\underline{H}_2$); Mass (FAB+) *m/z* 298 (M^++1).

4.2.11. 4-Amino-2-methyl-6-oxo-6-phenyl-hex-4-enoic acid methyl ester (22a).

83% (0.66g from 0.80g of **21a**); Yellow oil; [Found: C, 68.20; H, 6.79; N, 5.97. $C_{14}H_{17}NO_3$ requires C, 68.00; H, 6.93; N, 5.66]. ν_{max} (Neat) 1734 (CO_2Me); 3396 (br, NH_2) cm^{-1},^1H NMR (200MHz, $CDCl_3$) δ = 1.27 (d, 3H, *J*= 7.0 Hz, -CH-C$\underline{H}_3$), 2.59-2.82 (m, 3H, -C$\underline{H}$-CH_2 and -CH-C$\underline{H}_2$), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.50 (brs, 1H, 1H of N$\underline{H}_2$), 5.69 (s, 1H, =C$\underline{H}$), 7.39-7.58 (m, 3H, Ar$\underline{H}$), 7.85-7.96 (m, 2H, Ar$\underline{H}$), 10.08 (brs, 1H, 1H of N$\underline{H}_2$); Mass (FAB+) *m/z* 248 (M^++1)

4.2.12. 4-Amino-2-methyl-6-oxo-6-p-tolyl-hex-4-enoic acid methyl ester (22b).

85% (0.33g from 0.35g of **21a**); Yellow oil; [Found: C, 69.03; H, 7.17; N, 5.50. $C_{15}H_{19}NO_3$ requires C, 68.94; H, 7.33; N, 5.36]. ν_{max} (Neat) 1734 (CO_2Me); 3497 (br, NH_2) cm^{-1},^1H NMR (200MHz, $CDCl_3$) δ = 1.27 (d, 3H, *J*= 7.0 Hz, -CH-C$\underline{H}_3$), 2.38 (s, 3H, Ar-C$\underline{H}_3$), 2.59-2.82 (m, 3H, -C$\underline{H}$-CH_2 and -CH-C$\underline{H}_2$), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.50 (brs, 1H, 1H of N$\underline{H}_2$), 5.69 (s, 1H, CH), 7.19, 7.23 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.75, 7.79 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 10.10 (brs, 1H, 1H of N$\underline{H}_2$); Mass (FAB+) *m/z* 262 (M^++1).

4.2.13. 4-Amino-6-(4-chloro-phenyl)-2-methyl-6-oxo-hex-4-enoic acid methyl ester (22d).

85%; Yellow oil; [Found: C, 59.77; H, 5.99; N, 5.21. $C_{14}H_{16}ClNO_3$ requires C, 59.68; H, 5.72; N, 4.97]. ν_{max} (Neat) 1729 (CO_2Me); 3478 (br, NH_2) cm^{-1},^1H NMR (200MHz, $CDCl_3$) δ = 1.27 (d, 3H, *J*= 7.0Hz, -CH-C$\underline{H}_3$), 2.23-2.48 (m, 1H, -C$\underline{H}$-CH_3), 2.57-2.86 (m, 2H, -CH-C$\underline{H}_2$), 3.71 (s, 3H, $CO_2C\underline{H}_3$), 5.65 (s, 1H, =C$\underline{H}$), 5.70 (brs, 1H, 1H of N$\underline{H}_2$), 7.35, 7.39 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.78, 7.82 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 10.10 (brs, 1H, 1H of N$\underline{H}_2$); Mass (ES+) *m/z* 282.47 (M^++1)

4.2.14. 5-Acetyl-3-methyl-6-phenyl-1H-pyridin-2-one (29a).

15% (0.045g from 0.30g of **27a**); Yellow solid, mp 163-165°C; [Found: C, 73.24; H, 6.62; N, 5.44 $C_{14}H_{13}NO_2$ requires C, 73.99; H, 6.16; N, 5.77]. ν_{max} (KBr) 1697 (COMe), 1667 (CONH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 1.82 (s, 3H, =C-C$\underline{H}_3$), 2.02 (s, 3H, COC$\underline{H}_3$), 7.33-7.51 (m, 5H, Ar$\underline{H}$), 7.70 (s, 1H, C$\underline{H}$=C-CH_3), 10.72 (brs, 1H, N$\underline{H}$); Mass (FAB+) *m/z* 228 (M^++1)

4.2.15. 5-Acetyl-3-methyl-6-p-tolyl-1H-pyridin-2-one (29b).

16% (0.080g from 0.50g of **27b**); Yellow solid, mp 164-166 °C; [Found: C, 74.93; H, 6.45; N, 5.98. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.81]. ν_{max} (KBr) 1699 (COMe), 1668 (CONH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.81 (s, 3H, =C-C$\underline{H}_3$), 2.04 (s, 3H, COC$\underline{H}_3$), 2.41 (s, 3H, Ar-C$\underline{H}_3$), 7.15 (s, 4H, Ar$\underline{H}$), 7.72 (s, 1H, C$\underline{H}$=C-CH_3), 10.72 (brs, 1H, N$\underline{H}$); Mass (FAB+) *m/z* 242 (M^++1)

4.2.16. 4-Amino-4-phenyl-but-3-en-2-one (30a).

58% (0.17g from 0.30g of **27a**); Yellow solid, mp 93-95°C; [Found: C, 66.93; H, 7.51; N, 7.58. $C_{10}H_{11}NO.H_2O$ requires C, 67.02; H, 7.31; N, 7.82]. ν_{max} (KBr) 1697 (COMe), 3395 (NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.15 (s, 3H, COC$\underline{H}_3$), 5.31 (brs, 1H, N$\underline{H}_2$), 5.45 (s, 1H, =C$\underline{H}$), 7.42-7.45 (m, 3H, Ar$\underline{H}$), 7.52-7.57 (m, 2H, Ar$\underline{H}$), 9.98 (brs, 1H, N$\underline{H}_2$), ^{13}C NMR (50.32 MHz, $CDCl_3$) δ = 30.2, 95.6, 126.6, 129.3, 137.7, 161.3, 197.9; Mass (FAB+) *m/z* 162 (M^++1).

4.2.17. 4-Amino-4-p-tolyl-but-3-en-2-one (30b).

58% (0.29g from 0.50g of **27b**); Yellow solid, mp 58-60°C; [Found: C, 71.33; H, 6.79; N, 7.45. $C_{11}H_{13}NO.1/2H_2O$ requires C, 71.71; H, 7.11; N, 7.60]. ν_{max} (KBr) 1694 (COMe), 3402 (NH_2) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 2.15 (s, 3H, COC$\underline{H}_3$), 2.39 (s, 3H, Ar-C$\underline{H}_3$), 5.34 (brs, 1H, N$\underline{H}_2$), 5.44 (s, 1H, =C$\underline{H}$), 7.23 (d, 2H, *J*= 8.0Hz, Ar$\underline{H}$), 7.44 (d, 2H, *J*= 8.0Hz, Ar$\underline{H}$), 10.01 (brs, 1H, N$\underline{H}_2$), Mass (FAB+) *m/z* 176 (M^++1).

4.2.18. (*Z*) 4-Acetyl-5-amino-2-methyl-5-phenyl-penta-2, 4-dienoic acid methyl ester (34a).

65% (0.45g from 0.53g of **32a**); Brown solid, mp 96-98°C; [Found: C, 69.77; H, 6.63; N, 5.55. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40]. ν_{max} (KBr) 1699 (COMe and CO_2Me), 3441 (br, NH_2) cm^{-1}; ^1H NMR(200 MHz, $CDCl_3$) δ = 1.36 (s, 3H, =C-C$\underline{H}_3$), 2.18 (s, 3H,

COC$\underline{H}_3$), 3.67 (s, 3H, $CO_2C\underline{H}_3$), 5.31 (brs, 1H, N$\underline{H}_2$), 7.38 (s, 5H, Ar$\underline{H}$), 7.44 (d, 1H, *J*= 1.2 Hz, C-C$\underline{H}$=C), 10.67 (brs, 1H, N$\underline{H}_2$); Mass (ES+) *m/z* 260.60 (M^++1)

4.2.19. (*Z*) 4-Acetyl-5-amino-2-methyl-5-p-tolyl-penta-2, 4-dienoic acid methyl ester (34b).
85% (0.45g from 0.53g of **32b**); Yellow solid, mp 76-78°C; [Found: C, 70.33; H, 6.76; N, 4.99. $C_{16}H_{19}NO_3$ requires C, 70.31; H, 7.01; N, 5.12]. ν_{max} (KBr) 1705 (COMe and CO_2Me), 3377 (br, NH_2) cm^{-1}; ^{1}H NMR(200 MHz, $CDCl_3$) δ = 1.36 (s, 3H, =C-C$\underline{H}_3$), 2.17 (s, 3H, COC$\underline{H}_3$), 2.35(s, 3H, Ar-C$\underline{H}_3$), 3.68 (s, 3H, $CO_2C\underline{H}_3$), 5.31 (brs, 1H, N$\underline{H}_2$), 7.14 (d, 1H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.22 (m, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.46 (d, 1H, *J*= 1.2 Hz, C-C$\underline{H}$=C); Mass (FAB+) *m/z* 274 (M^++1).

4.2.20. (*Z*) 4-Acetyl-5-amino-5-(2-chloro-phenyl)-2-methyl-penta-2, 4-dienoic acid methyl ester (34c).
80% (0.24g from 0.30g of **32c**); Yellow solid, mp 118-120°C; [Found: C, 61.08; H, 5.82; N, 4.97. $C_{15}H_{16}ClNO_3$ requires C, 61.33; H, 5.49; N, 4.77]. ν_{max} (KBr) 1707 (COMe and CO_2Me), 3369 (br, NH_2) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.58 (s, 3H, =C-C$\underline{H}_3$), 2.14 (s, 3H, COC$\underline{H}_3$), 3.64 (s, 3H, $CO_2C\underline{H}_3$), 7.17-7.38 (m, 4H, Ar$\underline{H}$), 7.49 (d, 1H, *J*= 1.2 Hz, C-C$\underline{H}$=C); Mass (FAB+) *m/z* 294 (M^++1).

4.3. Hydrogenation in the presence of Pd-C- Representative Procedure.

To the methanolic solution of compound **2a** (520mg, 2.0 mmol), 75mg of 10% Pd-C was added under nitrogen atmosphere. The atmosphere of the vessel was replaced by hydrogen gas. The reaction was carried out either on the Parr assembly at 30psi at rt or through stirring in a sealed vessel having hydrogen atmosphere maintained by a balloon. After completion, the reaction mixture was filtered over a pad of celite and the solvent was concentrated under reduced pressure to obtain an oily residue. This residue was purified over silica gel (230-400 mesh) column using hexane: ethyl acetate (80:20, v/v) as eluent.

4.3.1. 3-Hydroxy-2-methyl-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (6a).
78% (0.41g from 0.52g of **2a**); Yellow oil; [Found: C, 64.72; H, 5.98; N, 5.25. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79; N, 5.36]. ν_{max} (Neat) 1732 (CO_2Me), 3429 (br, OH) cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ = 1.22 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.31 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 3.07-3.14 (m, 2H, 2 X -C$\underline{H}$-CH_3), 3.67 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.72 (s, 3H, CO_2CH_{3anti}), 4.96 (t, 1H, *J*= 6.0 Hz, -C$\underline{H}$(OH)-CH_{anti}), 5.34 (d, 1H, *J*= 5.6 Hz, -C$\underline{H}$(OH)-CH_{syn}), 6.59 (s, 1H, =CH_{anti}), 6.62 (s, 1H, =CH_{syn}), 7.43-7.46 (m, 6H, Ar$\underline{H}$), 7.77-7.82 (m, 4H, Ar$\underline{H}$); Mass (FAB+) *m/z* 262 (M^++1).

4.3.2. 3-Hydroxy-2-methyl-3-(3-p-tolyl-isoxazol-5-yl)-propionic acid methyl ester (6b).
80% (0.54g from 0.67g of **2b**); White solid; mp 68-70 ºC; [Found: C, 65.68; H, 6.32; N, 4.70. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22, N, 5.09]. ν_{max} (KBr) 1738 (CO_2Me), 3417 (br, OH) cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ = 1.21 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.31 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3syn}$), 2.39 (s, 6H, 2 X Ar-C$\underline{H}_3$), 3.07-3.14 (m, 2H, 2 X -C$\underline{H}$-CH_3), 3.67 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.72 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.94 (t, 1H, *J*= 6.8 Hz, -C$\underline{H}$(OH)-CH_{anti}), 5.27 (t, 1H, *J*= 1.5 Hz, -C$\underline{H}$(OH)-CH_{syn}), 6.56 (s, 1H, =C$\underline{H}_{anti}$), 6.59 (s, 1H, C$\underline{H}_{syn}$), 7.24 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.68 (d, 4H, *J*= 8.0 Hz, Ar$\underline{H}$); Mass (FAB+) *m/z* 276 (M^++1).

4.3.3. 3-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (6c);
81% (0.20g from 0.25g of **3c**); Pale yellow oil; [Found: C, 56.66; H, 5.77; N, 5.74. $C_{14}H_{14}ClNO_4$ requires C, 56.36; H, 5.79; N, 5.36]. ν_{max} (Neat) 1734 (CO_2Me), 3401 (br, OH) cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ = 1.22 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_{3anti}$), 1.31 (d, 3H, *J*= 7.2 Hz, -CH-CH_{3syn}), 3.07-3.14 (m, 2H, 2 X -C$\underline{H}$-CH_3), 3.73 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.76 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.97 (t, 1H, *J*= 6.0 Hz, -C$\underline{H}$(OH)-CH_{anti}), 5.31 (t, 1H, *J*= 1.5 Hz, -C$\underline{H}$(OH)-CH_{syn}), 6.59 (s, 1H, =CH_{anti}), 6.73 (s, 1H, =CH_{syn}), 7.33-7.50 (m, 6H, Ar$\underline{H}$), 7.69-7.82 (m, 2H, Ar$\underline{H}$); Mass (ES+) *m/z* 296.23 (M^++1)

4.3.4. 2-Methyl-3-(3-phenyl-isoxazol-5-yl)-propionic acid methyl ester (11a).
38% (0.21g from 0.55g of **7a**); White solid; mp 94-96 ºC; [Found: C, 68.76; H, 5.89; N, 5.36. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16; N, 5.71]. ν_{max} (KBr) 1733 (CO_2Me) cm^{-1}; ^{1}H NMR (300MHz, $CDCl_3$) δ = 1.26 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_3$), 2.89-2.97 (m, 2H, -CH-C$\underline{H}_2$), 3.19-3.24 (m, 1H, -C$\underline{H}$-CH_3), 3.76 (s, 3H, $CO_2C\underline{H}_3$), 6.35 (s, 1H, =C$\underline{H}$), 7.46-7.53 (m, 3H, Ar$\underline{H}$), 7.81-7.86 (m, 2H, Ar$\underline{H}$); Mass (ES+) *m/z* 246.47 (M^++1).

4.3.5. 2-Methyl-3-(3-p-tolyl-isoxazol-5-yl)-propionic acid methyl ester (11b).
25% (0.16g from 0.65g of **7b**); White solid; mp 78-80 ºC; [Found: C, 69.48; H, 6.61; N, 5.40. $C_{15}H_{17}NO_3$ requires C, 69.64; H, 6.41, N, 5.33]. ν_{max} (KBr) 1726 (CO_2Me) cm^{-1}; ^{1}H NMR (300MHz , $CDCl_3$) δ = 1.27 (d, 3H, *J*= 7.2 Hz, -CH-C$\underline{H}_3$), 2.39 (s, 3H, Ar-C$\underline{H}_3$), 2.89-2.96 (m, 2H, -CH-C$\underline{H}_2$), 3.18-3.21 (m, 1H, -C$\underline{H}$-CH_2), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 6.31 (s, 1H, =C$\underline{H}$), 7.24 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$), 7.67 (d, 2H, *J*= 8.0 Hz, Ar$\underline{H}$); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ = 17.4, 21.8, 30.8, 38.6, 52.3, 100.4, 109.94, 126.7, 127.0, 129.9, 140.4, 162.8, 171.4, 175.7; Mass (FAB+) *m/z* 260 (M^++1).

4.3.6. 3-Hydroxy-2-methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (20a). *syn:anti 2:1*
85% (0.13g from 0.15g of **18a**); White solid, mp 74-76ºC; [Found: C, 64.11; H, 5.99; N, 4.98. $C_{14}H_{15}NO_4$ requires C, 64.36; H, 5.79, N, 5.36]. ν_{max} (Neat) 1731 (CO_2Me), 3403 (br, OH) cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ= 1.24-1.31 (d, 6H, *J*= 7.0 Hz, 2 X -CH-C$\underline{H}_3$), 3.04-3.11 (m, 1H, -C$\underline{H}$-CH_{3syn}), 3.33-3.36 (m, 1H, -C$\underline{H}$-CH_{3anti}), 3.78 (s, 6H, 2 X $CO_2C\underline{H}_3$), 4.91, 4.98 (t, 1H, *J*= 6.53 Hz, -C$\underline{H}$(OH)-CH_{anti}), 5.28 (t, 1H, *J*= Hz, -C$\underline{H}$(OH) -CH_{syn}), 6.60 (s, 2H,

2 X =CH), 7.44-7.49 (m, 6H, ArH), 7.76-7.80 (m, 2H, ArH); Mass (FAB+) *m/z* 262 (M^++1).

4.3.7. 3-Hydroxy-2-methyl-3-(5-p-tolyl-isoxazol-3-yl)-propionic acid methyl ester (20b). *syn: anti 2:1*
89% (0.18g from 0.20g of **18b**); White solid; mp 90-92ºC; [Found: C, 64.75; H, 6.48; N, 5.24. $C_{15}H_{17}NO_4$ requires C, 64.44; H, 6.22, N, 5.09]. ν_{max} (KBr) 1738 (CO_2Me), 3458 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.26 (d, 3H, *J*= 7.2 Hz, -CH-CH$_{3anti}$), 1.28 (d, 3H, *J*= 7.2 Hz, -CH-CH$_{3syn}$), 2.40 (s, 6H, 2 X Ar-CH$_3$), 3.02-3.09 (m, 1H, -CH-CH$_{3syn}$), 3.48-3.74 (m, 1H, -CH-CH$_{3anti}$), 3.74 (s, 3H, 2 X CO_2CH_3), 4.93 (t, 1H, *J*= 6.2 Hz, -CH(OH)-CH$_{anti}$), 5.26 (t, 1H, *J*= 1.5 Hz, -CH(OH)-CH$_{syn}$), 6.54 (s, 2H, 2 X CH), 7.26 (d, 4H, *J*= 8.0 Hz, ArH), 7.66 (d, 4H, *J*= 8.0 Hz, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ = 11.5, 14.6, 21.9, 44.8, 44.9, 52.5, 68.3, 69.5, 97.5, 98.1, 125.0, 126.2, 130.1, 140.9, 165.6, 165.9, 170.9, 175.9, 176.3; Mass (FAB+) *m/z* 276 (M^++1).

4.3.8. 3-[5-(4-Chloro-phenyl)-isoxazol-3-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (20d). *syn: anti 2:1*
87% (0.58g from 0.67g of **18d**); White solid; mp 134-36ºC; [Found: C, 57.04; H, 4.89; N, 4.77. $C_{14}H_{14}ClNO_4$ requires C, 56.86; H, 4.77, N, 4.74]. ν_{max} (KBr) 1733 (CO_2Me), 3427 (br, OH) cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 1.26 (d, 3H, *J*= 7.0 Hz, -CH-CH$_{3anti}$), 1.28 (d, 3H, *J*= 7.0 Hz, -CH-CH$_{3syn}$), 3.03-3.10 (m, 1H, -CH-CH$_{3syn}$), 3.42-3.48 (m, 1H, -CH-CH$_{3anti}$), 3.74 (s, 6H, 2 X CO_2CH_3), 4.93 (t, 1H, *J*= 3.0 Hz, -CH(OH)-CH$_{anti}$), 5.27 (brs, 1H, -CH(OH)-CH$_{syn}$), 6.60 (s, 1H, =CH$_{anti}$), 6.62 (s, 1H, =CH$_{syn}$), 7.43 (d, 4H, *J*= 8.6 Hz, ArH), 7.70 (d, 4H, *J*= 8.6 Hz, ArH); Mass (FAB+) *m/z* 296 (M^++1).

4.3.9. 3-Acetoxy-2-methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (23a). *syn:anti 2:3*
17% (0.097g from 0.58g of **21a**); Yellow oil; [Found: C, 63.55; H, 5.76; N, 4.66. $C_{16}H_{17}NO_5$ requires C, 63.36; H, 5.65; N, 4.62] ν_{max} (Neat) 1745 (COMe and CO_2Me) cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ = 1.20 (d, 3H, *J*=7.2 Hz, -CH-CH$_{3anti}$), 1.32 (d, 3H, *J*=7.2 Hz, -CH-CH$_{3syn}$), 2.09 (s, 3H, COCH$_{3anti}$), 2.16 (s, 3H, COCH$_{3syn}$), 3.17-3.25 (m, 2H, 2 X –CH-CH$_3$), 3.70 (s, 3H, CO_2CH_{3syn}), 3.75 (s, 3H, CO_2CH_{3anti}), 6.16 (d, 1H, J= 9.0 Hz, -CH(OAc)-CH$_{anti}$), 6.31 (d, 1H, J= 6.0 Hz, CH(OAc)-CH$_{syn}$), 6.49 (s, 1H, =CH$_{syn\ i}$), 6.52 (s, 1H, =CH$_{ant}$), 7.44-7.49 (m, 6H, ArH), 7.75-7.79 (d, 4H, ArH); Mass (FAB+) *m/z* 304 (M^++1).

4.3.10. 3-Acetoxy-2-methyl-3-(5-p-tolyl-isoxazol-3-yl)-propionic acid methyl ester (23b). *syn:anti 1:2*
15% (0.038g from 0.25g of **21b)**; White solid, mp 60-62ºC; [Found: C, 63.96; H, 5.85; N, 4.49. $C_{17}H_{19}NO_5$ requires C, 64.34; H, 6.03; N, 4.41]. ν_{max} (KBr) 1745 (COMe, CO_2Me), cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.20 (d, 3H, *J*= 7.2 Hz, -CH-CH$_{3anti}$), 1.31 (d, 3H, *J*= 7.2 Hz, -CH-CH$_{3syn}$), 2.09 (s, 3H, COCH$_{3anti}$), 2.15 (s, 3H, CH$_{3syn}$), 2.39 (s, 6H, 2 X CH$_3$), 3.15-3.23 (m, 2H, 2 X -CH-CH$_3$), 3.70 (s, 3H, CO_2CH_{3syn}), 3.74 (s, 3H, CO_2CH_{3anti}), 6.13 (d, 1H, *J*= 8.8 Hz, -CH(OAc)-CH$_{anti}$), 6.30 (d, 1H, *J*= 6.0 Hz, -CH(OAc)-CH$_{syn}$), 6.43 (s, 1H, =CH$_{syn}$), 6.45 (s, 1H, =CH$_{anti}$), 7.27 (d, 4H, *J*= 8.0 Hz, ArH), 7.66 (d, 4H, *J*= 8.0 Hz, ArH); Mass (ES+) *m/z* 340.47 (M^++Na).

4.3.11. 2-Methyl-3-(5-phenyl-isoxazol-3-yl)-propionic acid methyl ester (24a).
52% (0.30g from 0.58g of **21a)**; Yellow oil; [Found: C, 68.55; H, 5.91; N, 5.83. $C_{14}H_{15}NO_3$ requires C, 68.56; H, 6.16, N, 5.71]. ν_{max} (Neat) 1735 (CO_2Me), 3456 (br, OH) cm^{-1}; ^1H NMR (200MHz, $CDCl_3$) δ= 1.28 (d, 3H, *J*= 7.0 Hz, -CH-CH$_3$), 2.82-3.12 (m, 3H, -CH-CH$_3$ and -CH$_2$-CH), 3.71 (s, 3H, CO_2CH_3), 6.37 (s, 1H, =CH), 7.42-7.48 (m, 3H, ArH), 7.73-7.77 (d, 2H, ArH); ^{13}C NMR (50.32 MHz, $CDCl_3$) δ = 8.8, 30.2, 39.1, 52.9, 99.87, 126.2, 127.9, 129.3, 130.5, 162.6, 170.2, 176.2; Mass (FAB+) *m/z* 246 (M^++1).

4.3.12. 2-Methyl-3-(5-p-tolyl-isoxazol-3-yl)-propionic acid methyl ester (24b).
49% (0.12g from 0.25g of **21b**); White solid, mp 83-84ºC; [Found: C, 69.52; H, 6.60; N, 5.12. $C_{15}H_{17}NO_3$ requires C, 69.48; H, 6.61; N, 5.40]. ν_{max} (KBr) 1730 (CO_2Me), 3446 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.27 (d, 3H , *J*= 6.6. –CH-CH$_3$), 2.39 (s, 3H, Ar-CH$_3$), 2.81-3.11 (m, 3H, -CH-CH$_3$ and -CH$_2$-CH), 3.71 (s, 3H, CO_2CH_3), 6.31 (s, 1H, =CH), 7.24 (d, 2H, *J*= 8.0 Hz, ArH), 7.64 (d, 2H, *J*= 8.0 Hz, ArH); Mass (ES+) *m/z* 260.36 (M^++1).

4.3.13. 3-Hydroxy-2-methyl-3-(5-methyl-3-phenyl-isoxazol-4-yl)-propionic acid methyl ester (31a). *anti*
60% (0.25g from 0.42g of **27a**); Yellow oil; [Found: C, 65.55; H, 5.91; N, 4.83. $C_{15}H_{17}NO_4$ requires C, 65.44; H, 6.22; N, 5.09]. ν_{max} (Neat) 1733 (CO_2Me), 3411 (br, OH) cm^{-1}; ^1H NMR (200MHz, $DMSOd_6$) δ = 0.69 (d, 3H, *J*= 7.0 Hz, -CH-CH$_3$), 2.52 (s, 3H, =C-CH$_3$), 2.67-2.85 (m, 1H, -CH-CH$_3$), 3.56 (s, 3H, CO_2CH_3), 4.66-4.71 (m, 1H, -CH(OH)-CH), 7.53-7.55 (m, 3H, ArH), 7.73-7.76 (m, 2H, ArH); Mass (FAB+) m/z 276 (M^++1).

4.3.14. 3-Hydroxy-2-methyl-3-(5-methyl-3-p-tolyl-isoxazol-4-yl)-propionic acid methyl ester (31b). *anti*
63% (0.26g from 0.41g of **27b**); Pale yellow solid, mp 100-102ºC; [Found: C, 66.36; H, 6.88; N, 4.72. $C_{16}H_{19}NO_4$ requires C, 66.42; H, 6.62; N, 4.84]. ν_{max} (KBr) 1714 (CO_2Me), 3411 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 0.84 (d, 3H, *J*= 7.2 Hz, -CH-CH$_3$), 2.40 (s, 3H, Ar-CH$_3$), 2.55 (s, 3H, =C-CH$_3$), 2.74-2.83 (m, 1H, -CH-CH$_3$), 3.71 (s, 3H, CO_2CH_3), 4.84, 4.89 (d, 1H, *J*= 9.8 Hz, -CH(OH)-CH), 7.25 (d, 2H, *J*= 8.0 Hz, ArH), 7.60 (d, 2H, *J*= 8.0 Hz, ArH); Mass (FAB+) m/z 290 (M^++1).

4.3.15. 3-[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-3-hydroxy-2-methyl-propionic acid methyl ester (31c). anti
63% (0.32g from 0.50g of **18a**); White solid, mp 108-110ºC; [Found: C, 57.89; H, 5.14; N, 4.27. $C_{15}H_{16}ClNO_4$ requires C, 58.16; H, 5.21; N, 4.52]. ν_{max} (Neat) 1730 (CO_2Me), 3425 (br, OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 0.90 (d, 3H, *J*= 7.2 Hz, -CH-CH$_3$), 2.56 (s, 3H, =C-CH$_3$), 2.65-2.79 (m, 1H, -CH-CH$_3$), 3.67 (s, 3H,

$CO_2C\underline{H}_3$), 4.63 (d, 2H, *J*= 9.8 Hz, -C<u>H</u>(OH)-CH), 7.35-52 (m, 4H, Ar<u>H</u>); Mass (ES+) m/z 310.53 (M^++1).

4.4. Preparation of allylic bromide-Typical Procedure

To the stirred solution of compound **27b** (500mg, 1.74 mmol) in dry dichloromethane (5mL) was added a solution of PBr_3 (0.17mL, 1.74mmol) dropwise at 0°C. The reaction was allowed to proceed for 30 min. at same temperature. Thereafter the reaction mixture was decomposed with ice-cold water and extracted with dichloromethane (2 X 20 mL). The organic layers were combined, dried (Na_2SO_4) and evaporated to furnish a residue that crystallizes on triturating with hexane to yield 0.48g of bromide.

4.4.1. (*E*) 2-Bromomethyl-3-(5-methyl-3-p-tolyl-isoxazol-4-yl)-acrylic acid methyl ester (33b).

95 %; Yellow solid, mp 128-130°C; [Found: C, 54.52; H, 4.60; N, 4.12. $C_{15}H_{17}NO_3$ requires C, 54.87; H, 4.61; N, 4.00;]. ν_{max} (KBr) 1723 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ = 2.37 (s, 3H, Ar-C<u>H</u>$_3$), 2.39 (s, 3H, =CH-C<u>H</u>$_3$), 3.88 (s, 3H, $CO_2C\underline{H}_3$), 4.09 (s, 2H, =C-C<u>H</u>$_2$-Br), 7.25 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>), 7.42 (s, 1H, =C<u>H</u>-C-), 7.50 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>); Mass (ES+) *m/z* 350.80 (M^++1).

4.5. Reaction of enamine ketones with acetic acid-formic acid mixture-Representative Procedure

The compound **4a** (525mg, 2.0 mmol) was stirred in 4 mL of acetic acid-formic acid (80%) mixture (50:50, v/v) at 60 ºC for 24h. After cooling to room temperature, the mixture was partitioned between ethyl acetate (30mL) and water (25mL). The organic layer was separated and successively washed with 10% $NaHCO_3$ aq. solution (until the washing was neutral). The organic layer was finally washed with brine, dried over Na_2SO_4 and evaporated to obtain a residue. This residue upon column chromatography over silica gel using hexane: ethyl acetate (85:15, v/v) furnished the product.

4.5.1. 2-(3-Oxo-5-phenyl-2, 3-dihydro-furan-2-yl)-propionic acid methyl ester (14a).

88% (0.46 from 0.52g of **4a**); Pale yellow oil; [Found: C, 63.23; H, 5.88. $C_{14}H_{14}O_4.H_2O$ requires C, 63.63; H, 6.10] ν_{max} (Neat) 1697 (C=O), 1740 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.13 (d, 3H, *J*= 7.2 Hz, -CH-C<u>H</u>$_{3anti}$), 1.41, 1.44 (d, 3H, *J*=7.2Hz, -CH-C<u>H</u>$_{3syn}$), 3.12-3.21(m, 2H, 2 X C<u>H</u>), 3.69 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.81 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.80 (d, 1H, *J*= 5.6 Hz, -CO-C<u>H</u>-O-$_{anti}$), 5.13, 5.14 (s, 1H, *J*= 3.1 Hz, -CO-C<u>H</u>-O-$_{syn}$), 6.07 (s, 1H, =CH$_{anti}$), 6.08 (s, 1H, CH$_{syn}$), 7.44-7.58 (m, 6H, Ar<u>H</u>), 7.78-7.85 (m, 4H, Ar<u>H</u>); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ = 12.72, 13.94, 41.35, 43.66, 44.16, 46.10, 47.1, 52.8, 53.0, 86.2, 94.5, 99.7, 102.1, 127.7, 127.9, 128.2, 128.7, 128.8, 129.3, 130.5, 133.5, 134.1, 134.9, 171.2, 174.6, 175.5, 189.4, 195.4; Mass (ES+) *m/z* 269.60 (M^++Na).

4.5.2. 2-(3-Oxo-5-p-tolyl-2, 3-dihydro-furan-2-yl)-propionic acid methyl ester (14b).

88% (0.40 from 0.45g of **4b**); Pale yellow solid, mp 108-110°C; [Found: C, 68.91; H, 5.90. $C_{15}H_{16}O_4$ requires C, 69.22; H, 6.20]. ν_{max} (KBr) 1694 (C=O), 1740 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ= 1.12 (d, 3H, *J*= 7.2Hz, -CH-C<u>H</u>$_{3anti}$), 1.41 (d, 3H, *J*= 7.2 Hz, -CH-C<u>H</u>$_{3syn}$), 2.43 (s, 6H, 2 X Ar-C<u>H</u>$_3$), 3.11-3.20 (m, 2H, 2 X C<u>H</u>), 3.69 (s, 3H, $CO_2C\underline{H}_{3syn}$), 3.80 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.79 (d, 1H, *J*= 5.6 Hz, -CO-C<u>H</u>-O-$_{anti}$), 5.12, (d, 1H, *J*= 3.0 Hz, -CO-C<u>H</u>-O-$_{syn}$), 6.03 (s, 1H, =CH$_{anti}$), 6.04 (s, 1H, =CH$_{syn}$), 7.29 (d, 4H, *J*= 8.0 Hz, Ar<u>H</u>), 7.69 (d, 4H, *J*= 8.0Hz, Ar<u>H</u>), 7.73 (d, 4H, *J*=8.0 Hz, Ar<u>H</u>); ^{13}CNMR (50.32 MHz, $CDCl_3$) δ = 12.8, 14.0, 22.2, 31.3, 43.6, 44.6, 46.1, 47.2, 52.9, 53.1, 94.4, 98.9, 104.7, 125.8, 127.9, 128.3, 130.6, 132.4, 145.3, 170.9, 171.4, 174.6, 189.8, 195.5; Mass (FAB+) *m/z* 261 (M^++1).

4.5.3. 2-[5-(4-Chloro-phenyl)-3-oxo-2,3-dihydro-furan-2-yl]-propionic acid methyl ester (14d).

85% (0.34 from 0.40g of **4d**); Pale yellow sticky solid; [Found: C, 60.00; H, 4.91. $C_{14}H_{13}ClO_4$ requires C, 59.90; H, 4.67]. ν_{max} (Neat) 1694 (C=O), 1738 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ= 1.13 (d, 3H, *J*= 7.2Hz, -CH-C<u>H</u>$_{3anti}$), 1.42 (d, 3H, *J*= 7.2 Hz, -CH-C<u>H</u>$_{3syn}$), 3.16-3.21(m, 2H, 2 X C<u>H</u>), 3.69 (s, 3H, -$CO_2C\underline{H}_{3syn}$), 3.81 (s, 3H, $CO_2C\underline{H}_{3anti}$), 4.79 (d, 1H, *J*= 5.6 Hz, -CO-C<u>H</u>-O-$_{anti}$), 5.14 (d, 1H, *J*= 3.0 Hz, -CO-C<u>H</u>-O-$_{syn}$), 6.03 (s, 1H, =CH$_{anti}$), 6.08 (s, 1H, =CH$_{syn}$), 7.47 (d, 4H, *J*= 8.6 Hz, Ar<u>H</u>), 7.74 (d, 4H, *J*= 8.0 Hz, Ar<u>H</u>), Mass (FAB+) *m/z* 281 (M^++1).

4.5.4. 2-(3-Oxo-5-p-tolyl-2, 3-dihydro-furan-2-yl)-propionic acid ethyl ester (15b).

89% (0.89g from 1.0g of **5b**); Pale yellow oil; [Found: C, 69.87; H, 6.65. $C_{16}H_{18}O_4$ requires C, 70.06; H, 6.61]. ν_{max} (Neat) 1699 (C=O), 1734 (CO_2Me) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.10-1.46 (m, 12H, 4 X -$CH_2C\underline{H}_3$), 2.43 (s, 6H, 2 X Ar-C<u>H</u>$_3$), 3.00-3.20 (m, 2H, 2 X -C<u>H</u>-CH_3), 4.13-4.29 (m, 4H, 2 X -$CO_2C\underline{H}_2$-), 4.76, (d, 1H, *J*= 5.4 Hz, -CO-C<u>H</u>-O-$_{anti}$), 5.13 (d, 1H, *J*= 3.0 Hz, -CO-C<u>H</u>-O-$_{syn}$), 6.02 (s, 1H, =C<u>H</u>$_{anti}$), 6.04 (s, 1H, =C<u>H</u>$_{syn}$), 7.29 (d, 4H, *J*= 8.0 Hz, Ar<u>H</u>), 7.69 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>), 7.73 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>); Mass (FAB+) *m/z* 275 (M^++1).

4.5.5. 6-Hydroxy-2-methyl-4-oxo-6-p-tolyl-hex-5-enoic acid methyl ester (16b).

89 % (0.089g from 0.1g of **9b**); Yellow oil; [Found: C, 68.76; H, 6.77. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92]. ν_{max} (Neat) 1690 (C=O), 1736 (CO_2Me), 3455 (OH) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ = 1.25 (d, 3H, *J*= 7.0 Hz, -CH-C<u>H</u>$_3$), 2.40 (s, 3H, Ar-C<u>H</u>$_3$), 2.41-2.48 (m, 1H, -C<u>H</u>-CH_3), 2.84-3.04 (m, 2H, -CH-C<u>H</u>$_2$), 3.70 (s, 3H, $CO_2C\underline{H}_3$), 6.14 (s, 1H, =CH-CO-), 7.24 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>), 7.77 (d, 2H, *J*= 8.0 Hz, Ar<u>H</u>); Mass (FAB+) *m/z* 263 (M^++1).

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References

1. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857-869.
2. Li, C. S.; Lacasse, E. *Tetrahedron Lett*. **2002**, *43*, 3565-3568.
3. Jones, R. C. F.; Dunn, S. H.; Duller, K. A. M. *J. Chem. Soc. Perkin Trans 1*. **1996**, 1319-1321.
4. Kenar, J. A. *J. Am. Oils Chem. Soc.* **2003**, *80*, 1027-1032.
5. a) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller K. A. M.; Dunn, S. H. *J. Chem. Soc., Perkins Trans.* 1 **1994**, 2513-2515. b) Jones, R. C. F.; Bhalay, G.; Carter, P. A.; Duller K. A. M.; Vulto, S. I. E. *J. Chem. Soc*., *Perkins Trans. 1* **1999**, 765-776. c) Jones, R. C. F.; Dawson, C. E.; O'Mahony, M. J. *Synlett* **1999**, 873-876.
6. a) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276-281. b) Roy, A. K.; Batra, S. *Synthesis*, **2003**, 1347-1356. c) Roy, A. K.; Batra, S. *Synthesis*, **2003**, 2325-2330.
7. Roy, A. K.; Rajaraman, B.; and Batra, S. *Tetrahedron* **2004**, *60*, 2301-2310.
8. a) Patra, A.; Batra, S.; Bhaduri, A. P. *Synlett* **2003**, 1611-1614. b) Saxena, R. A Patra, A.; Batra, S. *Synlett* **2003**, 1439-1442. c) Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P. *Synlett* **2002**, 1819-1822.
9. Batra, S.; Roy, A. K.; Patra, A.; Bhaduri, A. P.; Surin, W. S.; Raghvan, S. A. V.; Sharma, P.; Kapoor, K.; Dikshit, M.. *Bioorg. Med. Chem*. **200**4, *12*, 2059-2077.
10. Patra, A.; Roy, A. K.; Batra, S.; Bhaduri, A. P.; Khanna, A.; Chander, R.; Dikshit, M. *Bioorg. Med. Chem*. **2003**, *11*, 2269-2276.
11. BOuzide, A. *Org. Lett*. **2002**, *4*, 1347-1350.
12. Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901-6908.
13. Mateus, C. R.; Almeida, W. P.; Coelho, F. *Tetrahedron Lett*. **2000**, *41*, 2533-2536.
14. a) Brown, J. M.; Cutting, I.; James, A. P. *Bull. Soc. Chim. Fr*. **1988**, 211-217. b) Brown, J. M., Cutting, I. *J. Chem. Soc., Chem Commun*. **1985**, 578-579.
15. Sainsbury, M. in *Comp. Org. Syn.*, Trost, B. M., Ed.; Pergamon Press, **1991**,Vol 8, pp644-646.
16. Bianchi, G.; DeAmici, M. *J. Chem. Soc. Chem. Comm*. **1978**, 962-963.
17. Amicchio, S.; Morrocchi, S.; Ricca, A. *Tetrahedron Lett*. **1974**, 2793-2796.
18. Stork, G.; Ohashi, M.; Kamachi, H.; Kakisawa, H. *J. Org. Chem.* **1971**, *36*, 2784-2786.
19. Chimichi, S.; Boccalini, M.; Cosimelli, B.; Viola, G.; Vedaldi, D.; Dall' Acqua, F. *Tetrahedron Lett*. **2002**, *43*, 7473-7476.
20. Chimichi, S.; Boccalini, M.; Cosimelli, B.; Dall' Acqua, F.; Viola, G. *Tetrahedron* **2003**, *43*, 5215-5223.
21. Pei, Y.; Wickham, B. O. S. *Tetrahedron Lett*. **1993**, *34*, 7509-7512.
22. Stuyter, M. A. T.; Pandit, U. K.; Speckaamp, W. N.; Huismon, H. O. *Tetrahedron Lett*. **1966,** 87-90.
23. Casnati, G.; Quilico, A.; Vita-Finzi, P. *Gazz. Chim. Ital*. **1966**, *96*, 1073-1083.
24. Casnati, G. Ricca, A. *Tetrahedron Lett* **1967**, 327-330.
25. Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Tetrahedron Lett*. **1984,** *25*, 4313-4316.
26. Kozikowski, A. P.; Goldstein, S. *J. Org. Chem*. **1983**, *48*, 1139-1141. b) Jensen, S.; Torssell, K. B. G. *Acta Chem. Scand*. **1995**, *49*, 53-56.
27. a) Thomsen, I.; Torssell, K. B. G. *Acta Chem. Scand*. **1988**, *B42 (5)*, 309-313. b) Ueno, T.; Oikawa, M.; Oikawa, H.; Ichihara, A. *Biosci. Biotechnol. Biochem*. **1995**, *59*, 2104-2110.