An efficient synthesis of tetramic acid derivatives with extended conjugation from L-Ascorbic Acid[#]

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Abstract: A straightforward synthesis of tetramic acid derivatives with dienyl susbstituents at C-5 from L-ascorbic acid is reported. The synthesis involves the PCC oxidation of allylic alcohol followed by olefination and subsequent reaction with different amines to give 5-hydroxy lactams, which underwent pTSA catalysed dehydration to give the required tetramic acid derivatives.

1. Introduction

Tetramic acid derivatives constitute an important class of nitrogen heterocyles with pyrrolidine-2,4-dione moiety and are core component of many natural and marine products (Fig. 1). [1, 2] They are associated with a diverse range of biological activities such as potent antibiotic, antiviral, antifungal and cytotoxic activities. [3-5] Very recently many antibiotics with 3- acetyl tetramic acid moiety were reported as anti HSV and anti HIV agents with potent tyrosine phosphatase inhibitory activities.[6] Most of the biologically active tetramic acid antibiotics with dienyl or polyenyl units (Fig. 1) has recently attracted the attention of many chemists as a challenging field of synthetic organic chemistry.[7] Several synthetic teams have been striving to synthesize this class of molecule in quantities sufficient to study its in vivo activity and prove the unique anticancer activity via telomerase inhibition. A variety of multistep solid and solution

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Key words: Ascorbic acid; DBU; Tetramic acid; Wittig Reaction; Pyridinium chlorochromate

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phase syntheses exist for the preparation of both achiral and chiral tetramic acid derivatives [8-12] We have recently embarked upon a programme to synthesize tetramic acid analogues having an extended alkenyl unit at C-5 as new antitubercular agents. Our reasoning is based on the reports that thiolactomycins, [13] a class of thiotetronic acid with alkenyl chain at C-5 posses very good antitubercular activity; and also a current report that tetramic acid possess anti HCV and anti HIV activities.[14,15]

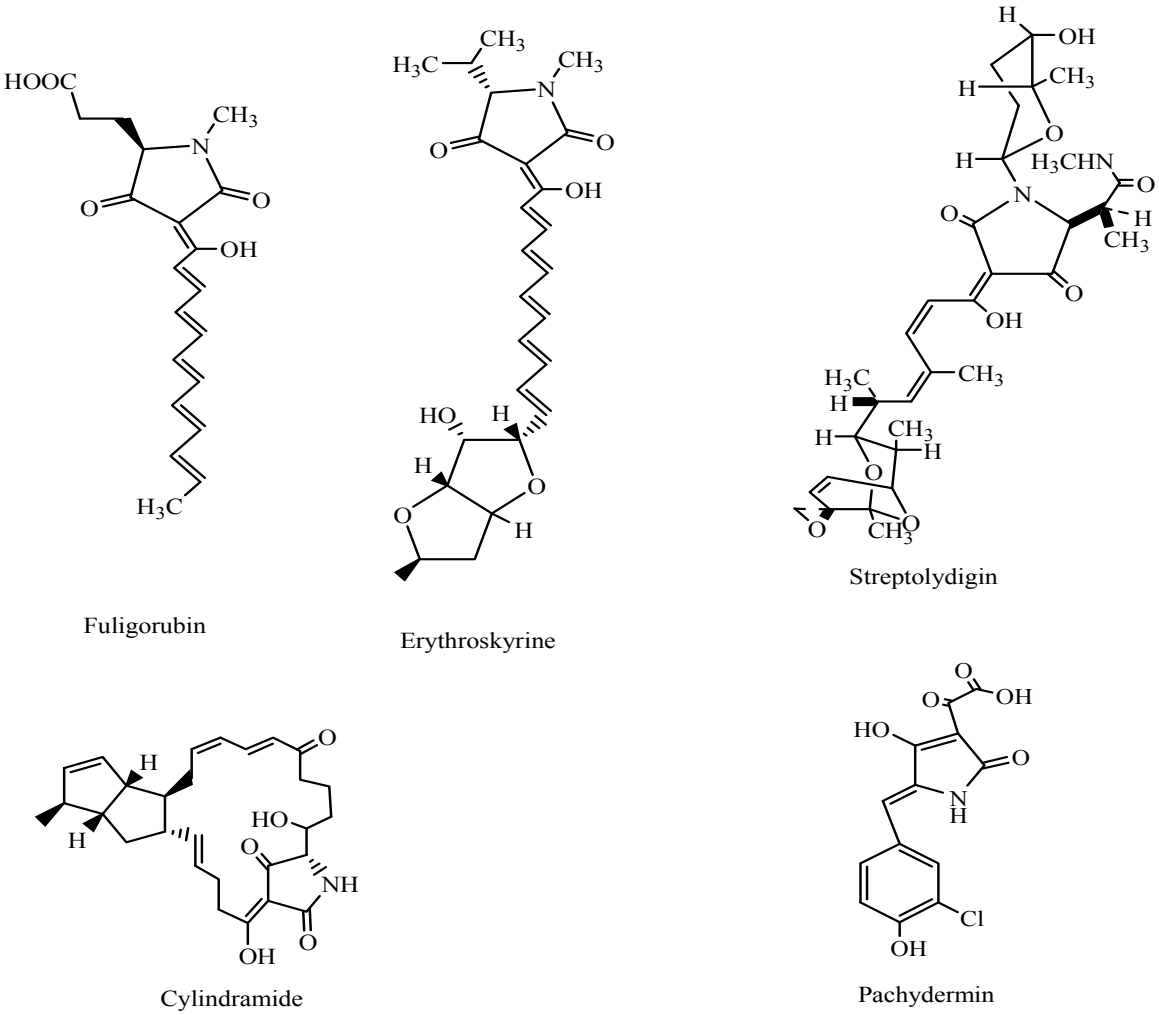


Fig 1 Polyenyl tetramic acid antibiotics

2. Results and discussion

Recently we have started work on the synthesis of tetramic acid starting from ascorbic acid involving protection of 5,6-diol with acetone followed by DBU catalysed one pot synthesis of tetramic acid derivatives as shown in Fig 2.[16] However, none of these compounds possess significant antitubercular or antifungal activity. This led us to synthesisize tetramic acid with dienyl chain at C-5 as thiolactomycin possess alkenyl chain at C-5.

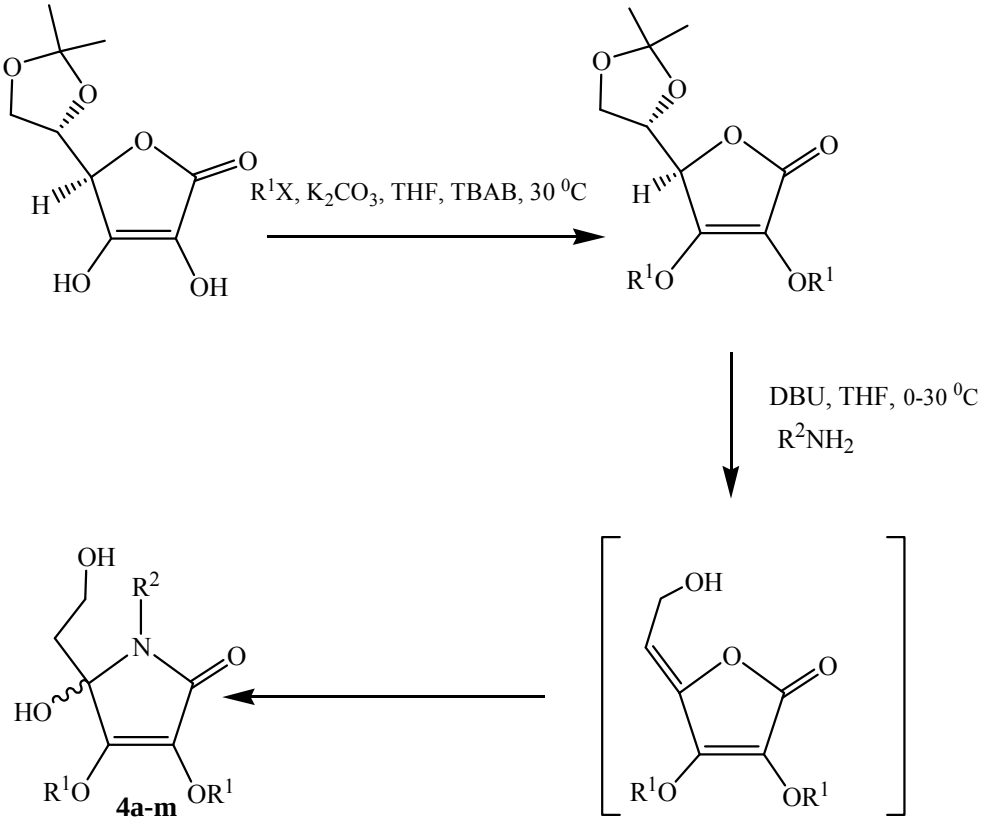


Figure 2

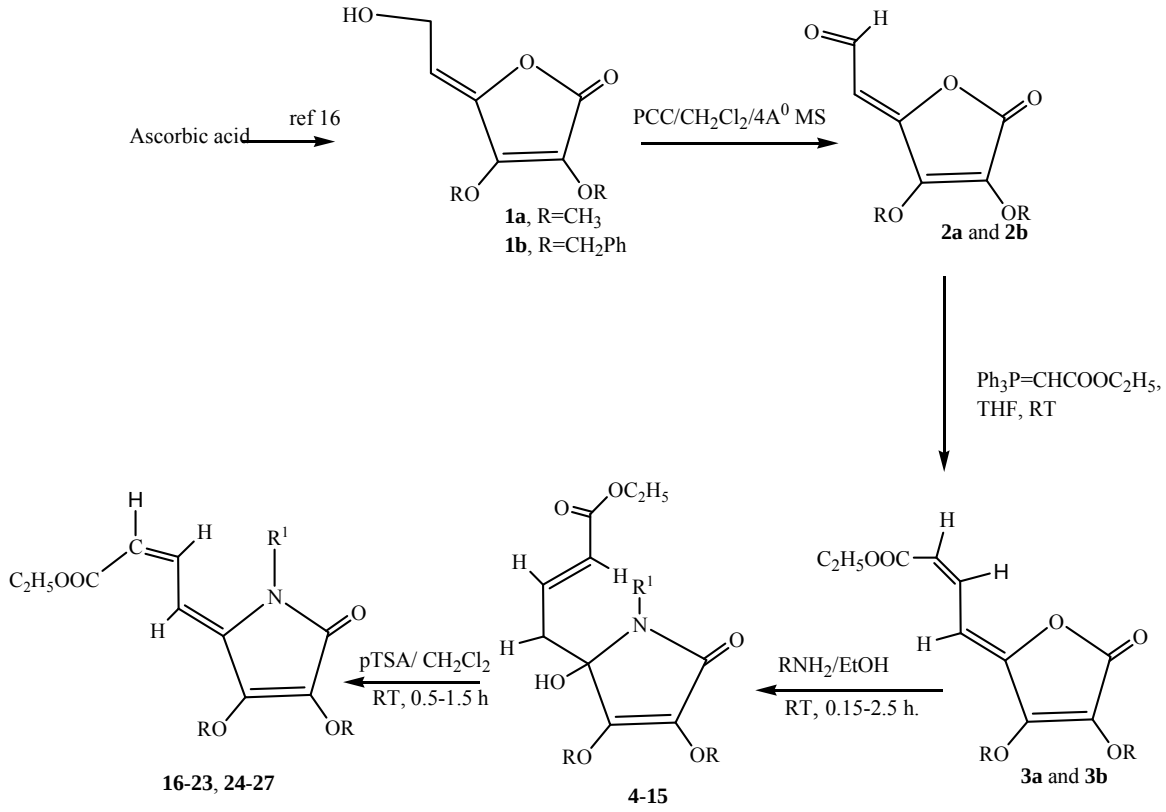
To start with 5,6-*O*-isopropylidene ascorbates were converted into allylic alcohols **1a** and **1b** by our earlier protocol[16] in good yields. Pyridinum chlorochromate (PCC)

oxidation of **1a** and **1b** separately led to the formation of respective aldehydes **2a** and **2b** in good yields. Wittig olefination of these aldehydes **2a** and **2b** with carbethoxymethylene triphenylphosphorane in THF at ambient temperature led to formation of respective exo-dienyl ester of tetronic acid **3a** and **3b** as a mixture of *ZZ* and *ZE* isomers. The two isomers in each case were separated by column chromatography; the ratio (17:3) and the structure of the individual isomers in the above compounds was determined on the basis of spectroscopic studies. In such an earlier study[17] BuLi at -78 ^{0}C was used as catalyst for Wittig olefination with less yields and poor stereoselection as compared to our uncatalysed ambient temperature reaction where *ZZ* isomer is predominantly obtained. The *Z* configuration of the allylic alcohol was already established. However, the geometry of the newly generated double bond in **3a** was decided on the basis of ^{1}H NMR spectroscopic data wherein the H-7 in the major isomer appeared as dd (δ=7.57) with *J*= 11.9 Hz each; while the same proton in minor isomer appears as dd at δ=7.0 with J= 11.3 Hz and 11.4 Hz respectively indicating *E* and *Z* relationship of H-7 with H-8 in the above two isomers. The ^{1}H NMR spectra of the *ZZ* and *ZE* isomers were similar to those reported earlier[17] and the chemical shifts of H-6 and H-8 were almost similar inspite of he close proximity of H-8 with carbethoxy group. The low chemical shift of H-8 in minor isomer may be due to its locked hydrogen bonded six memebred ring conformation. The low chemical shift of H-7 in ZZ isomer may again be explained in terms of a conformation II as proposed by Khan et al.[17] where H-7 is hydrogen bonded to lactone ring oxygen. Similarly, the structure and geometrical stereochemistry of the two isomers of **3b** was established.

In the next step of sequential synthesis of desired molecules, the trienyl derivatives obtained above were reacted with different amines separately to give intermediate 5-hydroxy tetramates. Thus reaction of **3a** first with ethanolic ammonia led to the formation of 5-hydroxy lactam derivative **4** in excellent yield. The structure elucidation of compound **4** was based on its spectroscopic data and microanalysis. ESI MS of the compound showed $[M+Na]^{+1}$ at 294.1 corresponding to its molecular formula. In ^{1}H NMR spectrum of compound **4**, H-6 appeared as a multiplet at δ 2.60-2.77 integrating for two H; and H-7(δ 6.81) was shifted. The exchangeable C5-OH appeared as singlet at δ

1.9, while H-8 appeared at its usual chemical shift of δ 5.87 as doublet. The geometry of the double bond between C-7/C-8 was unaffected and it was *Z* only. That the compound is a racemic mixture of was proved as the optical rotation was found to be zero. Further, we did not observe any conjugate addition product in the above reaction as the possibility existed because of presence of C-7/C-8 double bond conjugated with carbethoxy group. This possibility is ruled out probably because of its conjugation with another C-5/C-6 double bond which deactivates the positive character of C-7 during this reaction.
Similarly, reaction of **3a** with n-propyl-, cyclopropyl-, butyl-, isobutyl-, hexyl-, octyl- and benzyl amines led to the formation of respective N- butyl lactams (**5-11**) in good to very good yields. However, reaction of compound **3b** having 3, 4-dibenzyloxy susbtitutent on reaction different amines used above separately under the similar experimental conditions led to the formation respective 5-hydroxy lactam derivatives (**12-15**) in very good yields.

Finally, the hydroxyl lactams, so obtained were dehydrated to the respective triene derivatives via *p*-toluenesulphonic acid (pTSA) catalysed reaction at ambient temperature. Thus reaction of the above 5-hydroxy lactam **4** with pTSA in CH_2Cl_2 at room temeperature led to the formation of dienyl tetramic acid **16** in quantitative yield. The *ZZ* geometry of the two double bonds in this triene was established based on the basis of its ^{1}H NMR spectrum. Similarly, other dienyl tetramic acid derivatives **17-23** were prepared from the respective lactams in good yields. Similarly dehydration of the hydroxy lactam derivatives **12-15** with pTSA in CH_2Cl_2 initially led to the formation of dienyl lactam derivatives **24-27** in good yields. The structures of all the compounds were determined on the basis of spectroscopic data and microanalysis.



Scheme 1 **Synthesis of Dineyl Tetramic acid Derivatives from Ascorbic Acid**

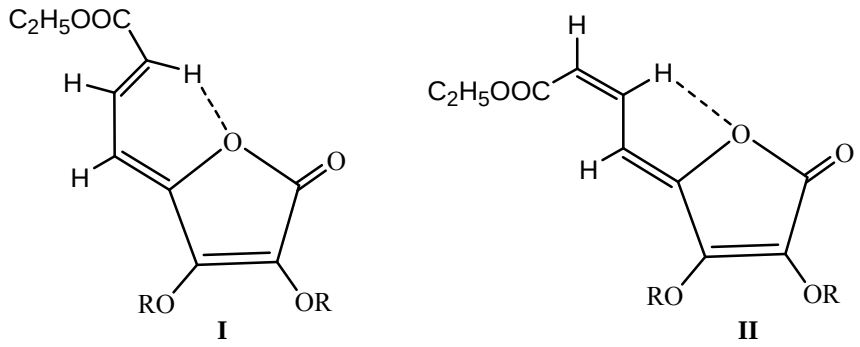


Figure 3

A reaction mechanism proposed (*Figure 4)* for dienyl teramate formation from dienyl esters is similar to earlier proposed by us. It involves most probably ring-opening reaction of the dienyl esters with amines to give the enol-keto amides. The latter

undergoes intramolecular ring closure to give the hydroxy lactams or teramates, which in turn is dehydrated with pTSA to give the required compound.

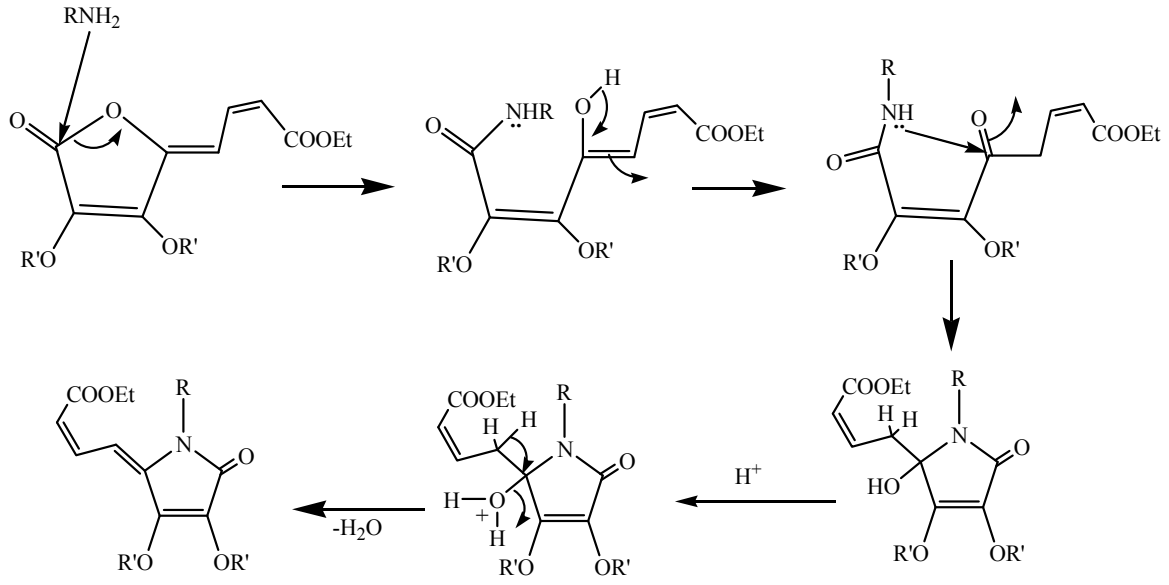


Figure 4 Proposed Reaction Mechanism

3. Conclusion

In conclusion, we have developed an efficient and practical method for the synthesis of dienyl teramic acid derivatives from ascorbic acid. The method involves Wittig olefination of the allylic aldehydes derived from ascorbic acid followed by reaction of the resulting esters with amines leading to formation of intermediate 5-hydroxy lactam. The latter on p- toluene sulphonic acid catalysed dehydration yielded the dienyl tetramic acid derivatives. The compounds bear the structural similarity to the tetramic acid based polyenic antibiotics and the method paves the way for synthesis of a variety of tetramic acid derivatives with different susbstitutents. Detailed bioevaluation of these compounds for different activities is under way.

4. Experimental

4.1 General

Commercially available reagent grade chemicals were used as received. All reactions were followed by TLC on Merck Kieselgel 60 F_{254}, with detection by UV light and/or spraying 20% $KMnO_4$ agueous solution. Column chromatography was performed on Silica Gel (230–400 mesh, Merck). IR spectra were recorded as thin films or neat chloroform solution with a Perkin-Elmer Spectrum RX-1 (4000-450 cm^{-1}) spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded on a Brucker DRX -300 in (*D*) chloroform, shift values in ppm relative to $SiMe_4$ as internal reference, unless otherwise stated; signals are reported as s (singlet), d (doublet), t (triplet), m (multiplet); *J* in Hz. Fast atom bombardement mass spectra (FABMS) were performed by the Mass Spectrometer Jeol SX-102(FAB). Elemental analyses were performed on a Perkin-Elmer 2400 II elemental analyzer. The optical rotations were measured in a 1.0 dm tube with a Rudolf Autopol III polarimeter in chloroform. Solvents were dried and stored over activated 4Å molecular sieve.

4.1.2.1.(Z) – 3,4-dimethoxy-5-(2-hydroxyethylidene)-5H-furan-2-one(1a): General Procedure

To a magnetically stirred solution of 3,4-dimethoxy-5,6-*O*-isopropylidene ascorbic acid 20g (81.96 mmol) in THF (mL), DBU (6.2 mL, 50 mol%) was slowly added and the reaction mixture was stirred for 18 h at room temperature. The solvent was evaporated under reduced pressure and the residue, thus obtained, was dissolved in ethyl acetate (100ml), washed with water (25 ml). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford a crude mass, which was chromatographed over silca gel (230-400 mesh) using a gradient of hexane-EtoAc (9:1→ 3:1) as eluent to give the above compounds as colourless solid(10g, 65.7%), m.p 60^0C , IR (Neat) 3391, 1688 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$) δ = 1.39 (*bs*, 1H), 3.92 (*s,* 3H, $-OCH_3$), 4.16 (*s*, 3H, $-OCH_3$), 4.41((d, *J* = 7.0, 2H, $-OCH_2$), 5.50 (*t*, *J* = 7.0 Hz, 1H, =CH-); ^{13}C NMR (50 MHz, $CDCl_3$) 56.6, 59.9, 60.6, 108.1, 125.0, 142.3, 149.1, 164.7; MS (FAB) $187(M+H)^+$.

4.1.2.2.(Z) – 3,4-dibenzyloxy-5-(2-hydroxyethylidene)-5H-furan-2-one (1b).

It was obtained by reaction of 3,4-dibenzyloxy-5,6-*O*-isopropylidene ascorbic acid 20g (50.5 mmol) and DBU 3.9 ml (50 mol%) as described above. Colourless oil, yield (11g, 64.7%); IR (Neat) 3389, 1676 cm^{-1}; ^{1}NMR (200 MHz, $CDCl_3$) δ = 1.42 (*bs*, 1H), 4.40 (*d*, *J* = 7.0 Hz, 2H, -CH_2O-), 5.16 (s, 2H, -OCH_2Ph), 5.22 (*s*, 2H, -OCH_2Ph), 5.51 (*t*, *J* = 7.0 Hz, 1H, =CH-), 7.21- 7.37(*m*, 10H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 56.9, 73.6, 74.4, 108.0, 124.1, 128.0 (2x C), 129.0 (2xC), 129.1 (3xC), 129.3 (3xC), 135.8, 136.1, 142.7, 148.7, 167.5; MS (FAB) 339 $(M+H)^+$.

4.1.3.1.(*Z*)–(3,4-Dimethoxy-5-oxo-*5H*-furan-2-ylidene)-acetaldehyde (2a):General Procedure

To a magnetically stirred mixture of powdered dried molecular sieve (4Å, 10g) and PCC (11.6 g, 51.6 mmol) in dry CH_2Cl_2 (120 ml), a solution of the above allyl alcohol **1a** (8.00 g, 43.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise at 0 °C and stirring continued for half an hour. The reaction mixture was filtered over a short pad of celite and celite cake was washed with more dichloromethane. The filtrate was evaporated to yield a crude mass which was purified by flash chromatography using a gradient of hexane-EtoAc (9:1→ 4:1) to give compound **2a** as a light yellow solid, m.p 61-63^{0}C Yield (4.20 g, 53%). IR (Neat) 1788, 1656cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) *δ* = 4.05 (3H, s, -OCH_3), 4.18 (3H, s, -OCH_3), 5.65 (1H, d, J= 8 Hz, =CH-), 10.08 (1H, d, J= 8Hz, -CH=O); MS (ESI) 207 $(M+Na)^+$.

4.1.3.2. (*Z*)–(3,4-Dibenzyloxy-5-oxo-5H-furan-2-ylidene)-acetaldehyde(2b).

It was obtained as above by reaction of a mixture of powdered dried molecular sieve (4Å ,11g), PCC (6.3 g, 31.9 mmol) and compound **1b** (9.00 g, 26.6 mmol) in dry CH_2Cl_2 (120 ml) as a Light yellow solid (5.9 g, 54%); IR (Neat) 1790, 1656cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) *δ* = 5.27 (2H, s, -OCH_2Ph), 5.30 (2H, s, -OCH_2Ph), 5.67 (1H, d, J= 8 Hz, =CH-), 10.06 (1H, d, J= 8Hz, -CH=O); MS (ESI): 337 $(M+H)^+$.

4.1.4.1. 4-(3,4-Dimethoxy-5-oxo-*5H*-furan-2-ylidene)-but-2-enoic acid ethyl ester(3a): General Procedure:

A solution of vinylic aldehyde **2a** (4.0 g, 21.73 mmol) and carbethoxymethylenetriphenyl phosphorane (8.3 g, 23.9 mmol) in anh. THF (mL) was magnetically stirred for 1.5 h. The solvent was evaporated and residue was dissolved in ethylacetate (100 ml) and washed with water (2 x 25 ml), organic layer was dried (Na_2SO_4) and evaporated under reduced pressure to afford a crude mass. The latter on column chromatography over silica gel (60-120 mess) using a gradient of hexane:EtoAc (19:1→ 7:1) as eluent gave the above compound as a (Z,Z) and (Z,E) isomer in the ratio of 9:1.

Z, Z-isomer: IR (neat): 1780, 1596 cm-1; ^{1}H NMR(200MHz, CDCl3) *δ* 1.31(t, J= 7.1 Hz, 3H, C*H*$_3$), 3.98 and 4.15 (s, 6H, -OCH_3), 4.20 (q, J= 7.1 Hz, 2H, OC*H*$_2$), 5.91(d, J= 11.9 Hz, 1H, 6-H), 5.96 (d, J= 11.9 Hz, 1H, 8-H), 7.57 (dd, J= 11.9Hz each, 1H, 7-H); MS (FAB) 255 $(M+H)^+$;

Z, E-isomer: m.p. 65^0C; IR (neat): 1777, 1707, 1602 cm-1; ^{1}H NMR (300MHz, CDCl3) δ 1.32(t ,3H, J= 7.1 Hz, CH_3), 3.99 (s,3H, OCH_3), 4.16 (s, 3H, OCH_3), 4.22 (q, s,2H, J= 7.1 Hz, -OCH_2), 5.82 (d, J= 11.2 Hz, 1H, H-6), 7.0 (dd, J= 11.4 & 11.3, 1H, H-7), 7.27 (d, J= 11.1 Hz, 1H, H-8); MS (FAB): 255 $(M+H)^+$.

4.1.4.2. 4-(3, 4-Dibenzyloxy-5-oxo-5H-furan-2-ylidene)-but-2-enoic acid ethyl ester (3b):

It was obtained by reaction of vinylic aldehyde **2b** (4.5 g, 13.4 mmol) and carbethoxymethylene triphenyl phosphorane (5.1 g, 23.9 mmol) as above and purified by column chromatography over silica gel (60-120 mess) using a gradient of hexane:EtoAc (19:1→ 7:1) as eluent gave the above compound as a (Z,Z) and (Z,E) isomer in the ratio of 9:1

Z,Z-isomer: IR (neat) 1778, 1711, 1651 cm^{-1}; ^{1}H NMR(200MHz, CDCl3) δ 1.30 (t, J= 7.0 Hz, 3H, CH_3), 4.22 (t, J= 7.0 Hz, 2H, CH_2), 5.23 (s, 4H, 2x OCH_2), 5.89 (d, J= 11.9 Hz, 1H, 6-H), 5.99 (d, J= 15.4 Hz, 1H, 8-H), 7.20-7.36 (m, 10H, 2x –C_6H_5), 7.55(dd, J= 11.9 Hz each,1H, 7-H); MS (ESI): 429 (M+ Na)$^+$

Z,E-isomer: m.p. 55^0C ; IR (neat) 1775, 1710, 1648 cm^{-1}; ^{1}H NMR(200MHz, CDCl3) δ 1.27 (t, J= 7.1 Hz, 3H, -CH_3), 4.12 (q, J= 7.1 Hz, 2H, -OCH_2), 5.19 (s, 2H, -OCH_2), 5.26 (s, 2H, -OCH_2), 5.79 (d, J= 11.1 Hz, 1H, 6-H), 7.03 (t, J= 11.1 Hz, 1H, H-7), 7.22-7.37 (m, 11H, H-8 & 2x –C_6H_5); MS (ESI): 429.1 (M+ Na)$^+$

4.1.5.1. (*Z*) 4-(2-Hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (4): General Procedure:

A solution of the above compound **3a** (1g, 3.93 mmol) in ethanolic ammonia (15 ml) was magnetically stirred for 15 min. in a sealed vessel. The excess of ammonia and solvent were evaporated under reduced pressure to give a residual mass. The latter was chromatographed over silica gel (60-120 mess) column using a gradient of hexane:EtoAc (2:3) to give **4** as oily solid, (1g, 98 %); IR (neat) 3431, 1684, 1564 cm-1; ^{1}H NMR(200MHz, CDCl3) δ 1.27 (t, J=7.1Hz, 3H, CH_3), 1.85(s,1H, -OH), 2.60-2.77(m, 2H, CH_2), 3.77 and 4.09 (s, 6H, -OCH_3), 4.15(q, J=7.1Hz, 3H, - OCH_2CH_3), 5.87 (d, J= 15.6Hz, 1H, H-8), 6.81 (m, 2H, H-7 & -NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5,39.4, 59.4, 60.7, 61.3, 83.3, 96.5, 125.6, 141.8, 155.0, 166.5, 170.2; EI MS: 294.1 $(M+Na)^+$; Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16, Found: C, 53.15; H, 6.35; N, 5.14

4.1.5.2. (*Z*) 4-(1-*n*-Benzyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)- but-2-enoic acid ethyl ester (5): A solution of 3a (0.8g, 3.14 mmol) in ethanol and benzyl amine (0.35 ml, 3.14 mmol) was magnetically stirred for 2.5 hrs. Solvent evaporated under reduced pressure and residue was extracted by ethylacetate (25 ml) and water (10 ml). organic layer was evaporated under reduced pressure to give crude mass which was chromatographed over silicagel (60-120 mess) column using a gradient of hexane:EtoAc (1:4) to give **5** as light brown solid, (0.82g, 72.5 %); m.p. 82-84^0C;
IR (neat) 3387,1674, 1598 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 1.24 (t, J= 7.0 Hz, 3H, -OCH_2CH_3), 1.58 (s, 1H, -OH), 2.52 (m, 2H, H-6), 3.82 and 4.06 (s, 6H, -OCH_3), 4.11 (q,

J= 7.0 Hz, 2H, OC*H*$_2$CH$_3$), 4.28 and 4.65 (d, J= 15.2 Hz, 2H, -NC*H*$_2$Ph), 5.32 (d, J= 15.4 Hz,1H, H-8), 6.15-6.23 (m,1H, H-7);^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 37.3, 41.3, 59.4, 60.4, 60.9, 61.1, 86.8, 125.11, 127.8, 128.3, 128.4, 129.0, 138.7, 140.6, 153.0, 166.0, 168.5; MS (ESI): 384.1 $(M+Na)^+$; Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88, Found: C, 63.12; H, 6.40; N, 3.90.

4.1.5.3. (*Z*) 4-(1-*n*-Butyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-5-hydroxy but-2-enoic acid ethyl ester (6): It was obtained by the reaction of 3a (0.9g, 3.54 mmol) and butyl amine (0.26ml, 3.54 mmol) as an oil (0.92g, 79.8%).
: IR (neat) 3333, 1684 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.93 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1Hz, 3H), 1.55-1.65 (m, 4H, 2x -CH_2), 2.72-2.75 (m, 2H, -C*H*$_2$), 3.01-3.40 (m, 2H, -NCH_2), 3.40 (s,1H), 3.78 and 4.06 (s, 6H, -OCH_3), 4.18 (q, J= 7.1Hz, 2H, -OCH_2), 5.82 (d, J= 15.6Hz, 1H, H-8), 6.49-6.57 (m, 1H, H-7); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 14.6, 20.9, 32.0, 37.2, 38.2, 59.3, 60.6, 60.9, 86.3, 108.2, 125.3, 125.9, 141.1, 152.2, 166.0, 168.0; MS (ESI): 350.1 ($M+Na)^+$; Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28, Found: C, 58.67; H, 7.72; N, 4.26.

4.1.5.4. (*Z*) 4-(1-*n*-Cyclopropyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (7): It was obtained by the reaction of 3a (0.5g, 1.96 mmol) and cyclopropyl amine (0.2ml, 1.96 mmol) as an oil (0.43g, 79.8%).
: IR (neat) 3419, 1688, 1596 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.65-0.88 (m, 4H), 1.27 (t, J=7.1Hz, 3H), 2.31-2.36 (m, 1H), 2.83-2.95 (m, 2H), 3.11 (s, 1H), 3.78 and 4.07 (s, 6H), 4.18 (q, J= 7.1Hz, 2H), 5.85 (d, J= 15.6Hz), 6.51-6.59((m,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 3.7, 6.0, 14.6, 21.1, 30.0, 37.0, 59.4, 60.7, 61.0, 87.1, 125.3, 125.9, 141.3, 152.4, 166.0, 169.0; MS (ESI): 334.0 ($M+Na)^+$; Anal. Calcd for $C_{15}H_{21}NO_6$: C, 57.87; H, 6.80; N, 4.50, Found: C, 57.90; H, 6.81; N, 4.52.

4.1.5.5. 4(*Z*) 4-(1-*n*-*iso*-butyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (8): It was obtained by the reaction of 3a (0.6g, 2.36 mmol) and isobutyl amine (0.24ml, 2.36 mmol) as an oil (0.43g, 65.1%). IR (neat) 3385, 1683 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.89 (d, J= 6.6 Hz,6H), 1.26 (t, J=7.2Hz, 3H), 1.6(bs, 1H), 1.96-2.03 (m,1H), 2.71-2.95 (m, 3H), 3.17-3.27 (m,1H), 3.78 and 4.07 (s, 6H), 4.17 (q, J= 7.1Hz, 2H), 5.81 (d, J= 15.6Hz, 1H), 6.48-6.56 ((m,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 20.9, 28.8, 37.2, 45.9, 59.4, 60.6, 60.9, 86.4, 125.3, 126.1, 141.1, 152.0, 166.0, 168.3; MS (FAB) 328 $(M+H)^+$; Anal. Calcd for $C_{16}H_{25}NO_6$: C, 58.70; H, 7.70; N, 4.28, Found: C, 58.72; H, 7.71; N, 4.29

4.1.5.6. (*Z*) 4-(1-n-Hexyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (9):: It was obtained by the reaction of 3a (1.1g, 4.33 mmol) and hexyl amine (0.57ml, 4.33 mmol) as an oil (1.2g, 77%). IR (neat) 3353, 1682, 1596 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.88 (t, J=7.0 Hz , 3H), 1.23-1.30 (m, 7H), 1.46-1.57 (m , 3H), 2.71-2.80 (m, 2H), 3.11-3.30 (m, 4H), 3.78 and 4.06 (s, 6H),

4.14 (q, J= 7.0 Hz, 2H), 5.89 (d, J= 15.5 Hz, 1H), 6.46-6.61 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 14.5, 22.9, 27.3, 29.7, 29.9, 31.8, 38.5, 59.3, 60.6, 60.9, 86.1, 125.3, 126.1, 141.1, 152.1, 167.1, 169.7; MS (ESI): 356($M+H)^+$; Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94, Found: C, 60.85; H, 8.23; N, 3.94

4.1.5.7. (*Z*) 4-(1-*n*-Octyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (10):: It was obtained by the reaction of 3a (0 .8g, 3.14 mmol) and octyll amine (0.24ml, 3.14 mmol) as an oil (0.88g, 73.3%). IR (neat) 3366, 2930, 1686. cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.87 (t, J=6.7 Hz, 3H), 1.20-1.30 (m,11H), 1.35-1.60(m, 3H), 2.74-2.82 (m, 2H), 2.93-3.32 (m, 4H), 3.79 and 4.06 (s, 6H), 4.14 (q, J= 7.1 Hz, 2H), 5.90 (d, J=15.6, 1H), 6.37-6.62 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 14.5, 22.9, 27.7, 29.6, 30.0, 32.1, 37.2, 38.6, 59.4, 60.7, 61.0, 86.3, 125.4, 126.1, 141.0, 152.1, 166.2, 170.1; MS (ESI): 406 ($M+Na)^+$; Anal. Calcd for $C_{20}H_{33}NO_6$: C, 62.64; H, 8.67; N, 3.65, Found: C, 62.66; H, 8.68; N, 3.64.

4.1.5.8. (*Z*) 4-(1-*n*-Propyl-2-hydroxy-3,4-dimethoxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (11):: It was obtained by the reaction of 3a (0.7g, 2.75 mmol) and propylamine (0.23ml, 2.75 mmol) as an oil (0.7g, 81.3%). IR (neat) 3329, 2974, 1687 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 093 (t, J=7.3 Hz, 3H), 1.28 (t, J= 7.1Hz, 3H), 1.57-1.73 (m, -3H) 2.75-2.85 (m,2H), 3.05-3.15 (m,1H), 3.31-3.41 (m,1H), 3.83 (s, 3H), 4.07 (s,-3H), 4.15 (q, J= 7.1 Hz, 2H), 5.86 (d, J=15 Hz, 1H), 6.54-6.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 15.5, 23.0, 39.4, 40.5, 59.4, 60.9, 61.9, 85.1, 125.5, 126.2, 141.0, 153.5, 166.2, 167.8; MS (ESI): 336 ($M+Na)^+$; Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.50; H, 7.40; N, 4.47, Found: C, 57.49; H, 7.43; N, 4.49.

4.1.5.7. (*Z*) 4-(2-hydroxy-3,4-dibenzyloxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (12): It was obtained by the reaction of 3b (0.65g, 1.6 mmol) and ethanolic ammonia (10ml) as an paste (0.58g, 85.8%).
IR (Neat): 3310, 1709, 1680 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 1.26 (t, J=7.2 Hz, 3H), 2.54-2.74 (m, 2H), 4.14 (q, J= 7.1 Hz, 2H), 4.92 (d, J=12.8, 2H), 5.07 (d, J= 12.4 Hz, 2H), 5.84 (d, J= 15.5 Hz, 1H), 6.76-6.86 (m,1H), 7.17-7.32 (m,10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 30.0, 37.0, 39.5, 60.7, 73.2, 74.9, 93.6, 123.5, 125.9, 127.9, 128.5, 128.8, 128.9, 129.4, 136.5, 136.7, 141.7, 154.8, 166.4, 170.3; MS (ESI): 446 ($M+Na)^+$; Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.07; H, 5.95; N, 3.31, Found: C, 68..09; H, 5.96; N, 3.33.

4.1.5.7. (*Z*) 4-(1-*n*-Butyl-2-hydroxy-3,4-dibenzyloxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (13):: It was obtained by the reaction of 3b (0.5g, 1.24 mmol) and butyl amine (0.12ml, 1.24 mmol) as an white solid (0.43g, 73.5%); m.p. 50-52^{0}C;
IR (Neat): 3277, 1723, 1675, 1598 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.94 (t, J= 7.1 Hz, 3H), 1.25-1.40 (m, 5H), 1.56-1.67 (m, 2H), 2.70-2.77 (m, 2H), 2.94 (s, 1H), 3.15-3.38 (m, 2H), 4.16 (q, 2H, J= 15.6 Hz), 4.80-5.15 (m, 4H), 5.77 (d, J= 15.6 Hz, 1H), 6.40-6.67 (m,1H), 7.15-7.33 (m, 10H);^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 14.7, 20.9,

32.1, 37.3, 38.4, 60.7, 73.2, 74.9, 86.6, 124.0, 125.5, 127.9 128.6, 128.8, 128.9, 129.5, 136.5, 136.6, 141.2, 152.2, 166.0, 168.2; MS (ESI): 502 ($M+Na)^+$, 480 ($M+H)^+$; Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.13; H, 6.94; N, 2.93, Found: C, 70.14; H, 6.96; N, 2.94.

4.1.5.8. (*Z*) 4-(1-*n*-Hexyl-2-hydroxy-3,4-dibenzyloxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (14):: It was obtained by the reaction of 3a (0.5g, 1.24 mmol) and hexylamine (0.16ml, 1.24 mmol) as an white solid (0.45g, 72.5%); m.p. 54-55^{0}C;
IR (Neat) 3270, 1670, 1596 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.88 (t, J= 7.1 Hz, 3H), 1.13-1.28 (m, 9H), 1.54-1.60 (m, 2H), 2.69-2.76 (m, 2H), 3.06-3.32 (m, 2H), 4.16 (q, J=7 Hz, 2H), 4.79-5.15 (m, 4H), 5.77 (d, J=15.5 Hz, 1H), 6.50-6.70 (m,1H), 7.15-7.33 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 14.6, 23.0, 25.1, 27.4, 30.0, 31.8, 37.3, 136.5, 136.6, 141.1, 152.1, 166.0, 168.1; MS (ESI): 530 ($M+Na)^+$; Anal. Calcd for $C_{30}H_{37}NO_6$: C, 70.97; H, 7.35; N, 2.76, Found: C, 70.99; H, 7.38; N, 2.75.

4.1.5.9. (*Z*) 4-(1-*n*-Benzyl-2-hydroxy-3,4-dibenzyloxy-5-oxo-2,5-dihydro-*1H*-pyrrol-2-yl)-but-2-enoic acid ethyl ester (15):: It was obtained by the reaction of 3a (0.78g, 1.93 mmol) and benzylamine (0.21ml, 1.93 mmol) as an brown solid (0.8g, 81.6%); m.p. 66-68^{0}C;
IR (Neat): 3423, 1680, 1592 cm^{-1};
^{1}H NMR (300MHz, CDCl3) δ 1.25 (3H, t, J= 7.1 Hz, -OCH_2CH_3),2.50-2.65 (3H, m, -CH_2, OH), 4.09 (2H, q, J= 7 Hz) 4.28-4.39 (m, 2H), 5.03-5.23 (m, 4H), 5.33 (d, J= 15.6 Hz), 6.23-6.31 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 37.5, 41.5, 60.4, 73.5, 75.1, 87.1, 123.9, 125.2, 127.2, 127.5, 127.9, 128.2, 128.6, 128.8, 129.0, 129.3, 129.6, 136.4, 136.5, 138.8, 140.7, 153.1, 175.9, 168.7; MS (ESI): 536 ($M+Na)^+$; Anal. Calcd for $C_{31}H_{31}NO_6$: C, 72.50; H, 6.08; N, 2.73, Found: C, 72.52; H, 6.11; N, 2.76.

4.1.6.1. 4-(3, 4-Dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester(16): General Procedure

A solution of the above compound **4** (0.7g, 2.58 mmol) in anh. CH_2Cl_2 (5mL) and *p*-toluene sulphonic acid (0.49g, 2.58 mmol) was stirred magnetically for 30 min. at room temperature during which the starting material disappeared (TLC). The reaction mixture was neutralized (pH 7.0) with solid $NaHCO_3$, filtered and filtrate was concentrated to give a crude mass. The latter was dissolved in ethyl acetate (100 ml), washed with water (2 x 25 mL)., organic layer dried (Na_2SO_4) and evaporated under reduced pressure to give a gummy mass, which was chromatographed over silca gel (60-120 mess) using a gradient of (1:19 → 1:4) as eluent to give compound **16** as colourless solid (0.450g, 68.9%), m.p. 167-169^0; IR (Neat): 1719, 1607 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) *δ* 1.32 (*t*, J= 7.1 Hz, 3H), 4.00 and 4.02 (*s*, 6H), 4.10 (*q*, J= 7.0 Hz, 2H), 5.93 (d, *J*= 12.3 Hz, 1H, H-6), 5.96 (d, J= 15.0 Hz, 1H, H-8), 7.75 (dd, J= 12.4 & 12.5 Hz,1H, H-7), 9.13 (s,

1H). ^{13}C NMR (50 MHz, $CDCl_3$)14.6, 59.7, 60.8, 61.2, 105.1, 122.4, 123.3, 129.5, 136.9, 137.9, 144.6, 167.2, 167.7; MS (ESI): 254 ($M+H)^+$; Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53, Found: C, 56.92; H, 5.99; N, 5.54.

4.1.6.2. 4-(1-*n*-propyl-3, 4-Dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester(17): It was obtained by the reaction of 11 (0.31g, 0.99 mmol) and *p*-toluene sulphonic acid (0.18g, 0.99 mmol) as an oil (0..18g, 62%);
IR (Neat): 1702, 1620, 1219 cm^{-1}; ^{1}H NMR (200MHz, $CDCl_3$) δ 0.91 (t, J= 7.1 Hz, 3H), 1.30 (t, J= 7.0 Hz, 3H), 1.51-1.66 (m, 2H), 3.47-3.55 (m, 2H), 3.96 and 4.13 (s, 6H), 4.20 (q, J= 7.0 Hz, 2H), 5.86 (d, J= 8.6 Hz,1H), 5.92(d, J= 11.7 Hz, 1H), 8.12 (dd, J= 12.0, 12.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.5, 14.5, 22.2, 40.3, 60.0, 60.7, 60.9, 109.2, 123.3, 137.3, 139.8, 165.2, 167.4; MS (ESI): 296 ($M+H)^+$; Anal. Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74, Found: C, 72.84; H, 7.20; N, 4.76.

4.1.6.3. 4-(1-*n*-Butyl-3, 4-Dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester(18): It was obtained by the reaction of 6 (0.6g, 1.83 mmol) and *p*-toluene sulphonic acid (0.34g, 1.83 mmol) as an oil (0.4g, 70.9%).
IR (Neat): 1700, 1620, 1259 cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.91 (t, J= 7.1 Hz, 3H), 1.30 (t, J= 7.1 Hz, 3H), 1.38-1.56 (m, 4H), 3.53 (t, J= 6.9 Hz, 2H), 3.96and 4.13 (s, 6H, OCH_3), 4.23 (q, J= 7.0 Hz, 2H), 5.83 (d, J= 12.0 Hz, 1H) 5.89(d, J= 15.2 Hz, 1H), 8.12 (dd, J= 12Hz,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 14.7, 20.4, 30.0, 31.1, 38.5, 40.7, 59.9, 60.5, 60.6, 104.3, 108.8, 123.1, 129.9, 137.3, 139.8, 144.8, 164.9, 167.1; MS (ESI): 310 ($M+H)^+$; Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53, Found: C, 62.15; H, 7.46; N, 4.54.

4.1.6.4. 4-(1-*iso*-Butyl-3, 4-Dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (19): It was obtained by the reaction of 8 (0.55g, 1.68 mmol) and *p*-toluene sulphonic acid (0.31g, 1.68 mmol) as an brown solid (0.3g, 58%), m.p: 56-58^{0}C
IR (Neat): 1680, 1619 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 0.90 (d, J= 6.7 Hz, 6H,), 1.31 (t, J= 7.1Hz, 3H), 1.84-2.1 (m, 1H), 3.36(d, J= 7.5 Hz, 2H), 3.98 and 4.14(s, 6H,), 4.19(q, J= 7.1Hz,2H), 5.87 (d, J= 12 Hz, 1H), 5.92 (d, J= 15.3 Hz, 1H), 8.16 (dd, J= 12 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 20.4, 28.3, 46.1, 59.9, 60.5, 60.6, 109.1, 123.1, 129.7, 137.7, 139.7, 144.8, 165.1, 167.0; MS (ESI): 310 ($M+H)^+$; Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53, Found: C, 62.13; H, 7.52; N, 4.55.

4.1.6.5. 4- (1- Cyclopropyl-3, 4-dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (20): It was obtained by the reaction of 7(0.54g, 1.73 mmol) and *p*-toluene sulphonic acid (0.32g, 1.73 mmol) as an greenish solid (0.31g, 62%); m.p. 62-64^{0}C;
IR (Neat): 1700, 1620, 1354cm^{-1}; ^{1}H NMR (200MHz, CDCl3) δ 0.87-0.99 (m, 4H), 1.31 (t, J= 7.0 Hz, 3H), 2.73 (m,1H), 3.93 and 4.12(s, 6H), 4.23 (2H, q, J= 7.0 Hz, OCH_2),

5.90 (1H, d, J= 15.3 Hz, CH), 6.26(1H, d, J= 12.23 Hz, CH), 8.07 (1H, dd, J= 12.3 & 12.4Hz, CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 6.7, 14.6, 21.1, 60.0, 60.6, 60.8, 110.1, 123.4, 129.4, 138.5, 139.8, 144.8, 165.6, 167.3; MS (ESI): 294(M+H)$^+$; Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78, Found: C, 61.44; H, 6.56; N, 4.76.

4.1.6.6. 4- (1- *n*-Hexyl-3, 4-dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (21): It was obtained by the reaction of 9(0.4g, 1.12 mmol) and *p*-toluene sulphonic acid (0.21g, 1.12 mmol) as an oil (0.19g, 55%).
IR (Neat): 1700, 1620 cm^{-1};^{1}H NMR (200MHz, CDCl3) δ 0.88 (t, J= 7.0 Hz, 3H), 1.29 (m, 7H), 1.52-1.63 (m, 4H), 3.41-3.55 (m , 2H), 3.96and 4.13 (s, 6H,), 4.23 (q, J= 6.9 Hz, 2H), 5.83 (d, J= 12 Hz, 1H), 5.88 (d, J= 14.6 Hz, 1H), 8.09 (dd, J= 12.2 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3, 14.6, 22.9, 26.8, 28.9, 31.8, 38.8, 60.0, 60.7, 60.9, 109.0, 123.2, 130.0, 137.3, 139.8, 145.0, 165.1, 167.4; MS (ESI): 338.2(M+H)$^+$; Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15, Found: C, 64.09; H, 8.10; N, 4.16.

4.1.6.7. 4-(1-*n*-Octyl-3, 4-Dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester(22): It was obtained by the reaction of 10(0.4g, 1.04 mmol) and *p*-toluene sulphonic acid (0.19g, 1.04 mmol) as an oil (0.23g, 60.5%);
IR (Neat): 1705, 1618 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 0.88 (t, J= 6.9 Hz, 3H), 1.27-1.55(m, 15H), 3.46-3.59 (m, 2H), 3.86, 4.12 (s, 6H,), 4.19 (q, J= 7.2 Hz, 2H), 5.88 (d, J= 12 Hz, 1H), 5.93 (d, J=15.3 Hz, 1H) 8.16 (dd, J= 12.0 & 12.3 Hz, 1H);^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 14.7, 22.9, 27.1, 29.0, 29.5, 32.1, 38.7, 59.9, 60.5, 60.6, 108.8, 123.1, 129.9, 137.3, 139.8, 144.8, 164.8, 167.1. MS (ESI): 366.2 M+H)$^+$; Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83, Found: C, 65.71; H, 8.59; N, 3.86.

4.1.6.8. 4-(1-*n*-Benzyl-3, 4-dimethoxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (23): It was obtained by the reaction of 5(0.65g, 1.8 mmol) and *p*-toluene sulphonic acid (0.34g, 1.8 mmol) as an oily solid (0.4g, 65.5%).

IR (Neat): 1704, 1625cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 1.28(t, J= 7.1 Hz, 3H), 4.02 and 4.17 (s, 6H), 4.21(q, J= 7.1 Hz, 2H), 4,79 (s, 2H), 5.80(d, J= 15.3 Hz, 1H), 5.85 (d, J=11.7 Hz, 1H), 7.18-7.36 (m, 5H), 8.06(dd, J=12 Hz ,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 42.4, 60.0, 60.5, 60.8,109.5, 110.2, 110.6, 123.7,127.0(2xC), 127.8, 29.1 (2xC), 136.9, 139.5, 145.3, 165.1, 167.0; two MS (ESI): 344.1 M+H)$^+$; Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08, Found: C, 66.47; H, 6.19; N, 4.10.

4.1.6.9. 4-(3, 4-Dibenzyloxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (24): It was obtained by the reaction of 12 (0.6g, 1.41 mmol) and *p*-toluene sulphonic acid (0.26g, 1.41 mmol) as an white solid (0.36g, 63.1%); m.p: 101-103^{0}C;

IR (Neat): 3427, 2364, 1625 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 1.31 (t, J= 7.1 Hz, 3H), 4.18(q, J= 7.1Hz, 2H), 5.22 and 5.33 (s, 4H), 5.95 (d, J= 14.0 Hz, 2H), 7.25-7.38 (m, 10H), 7.79 (dd, J= 13.6, 12.4 Hz, 1H), 9.29 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 61.2, 73.5, 74.4, 105.2, 122.6, 128.1(3xC), 128.9(xC), 129.2 (3xC), 136.7, 137.0, 137.7, 144.2, 167.2, 167.7; MS (ESI): 406 $M+H)^+$; Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.10; H, 5.72; N, 3.45, Found: C, 71.12; H, 5.73; N, 3.48.

4.1.6.10. 4-(1-*n*-Butyl-3, 4-dibenzyloxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (25): It was obtained by the reaction of 13 (0.7g, 1.46 mmol) and *p*-toluene sulphonic acid (0.27g, 1.46 mmol) as an oil (0.37g, 55.2%).
IR (Neat): 2960, 2362, 1599 cm^{-1}.^{1}H NMR (300MHz, CDCl3) δ 0.92 (t, J= 7.2 Hz,3H,), 1.18 (t, J= 7.2 Hz, 3H,), 1.23-1.38 (m, 2H), 1.47-1.57 (m, 2H), 3.56 (t, J= 7.2 Hz, 2H), 4.18(q, J= 7.2 Hz, 2H), 5.27 (s, 4H), 5.85 (d, J=1.5 Hz, 1H), 5.89 (d, J= 4.8 Hz, 1H), 8.18 (dd, J= 12.0, 12.3 Hz 1H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 14.3, 20.0, 30.7, 38.1, 60.1, 73.6, 73.9, 108.8, 123.1, 127.6, 128.2, 128.5, 128.5, 128.7, 136.1 136.4, 136.9, 139.2, 143.8, 164.6, 166.5.MS (ESI): 462 ($M+H)^+$; Anal. Calcd for $C_{28}H_{31}NO_5$: C, 72.86; H, 6.77; N, 3.03, Found: C, 72.84; H, 6.80; N, 3.05.

4.1.6.11. 4-(1-*n*-Benzyl-3, 4-dibenzyloxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (26): It was obtained by the reaction of 15 (0.44 g, 0.85 mmol) and *p*-toluene sulphonic acid (0.16g, 0.85 mmol) as an solid (0.22g, 55%); IR (Neat) 2370, 1700, 1620 cm^{-1}.^{1}H NMR (300MHz, CDCl3) δ 1.18 (t, J= 7.2 Hz, 3H,), 4.14 (q, J= 7.2 Hz, 2H,), 5.07-5.37 (m, 6H), 5.75 (d, J= 15 Hz, 1H,), 5.81 (d, J= 12 Hz, 1H), 7.16-7.46 (m, 15H), 8.12 (dd, J= 12.0 Hz ,1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 42.5, 60.5, 74.1, 74.5, 110.5, 124.0, 127.0, 127.9, 128.1, 128.7, 129.0, 129.2, 136.4, 136.9, 139.3, 144.8, 165.3, 166.9.MS (ESI): 496 ($M+H)^+$; Anal. Calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83, Found: C, 75.16; H, 5.92; N, 2.82.

4.1.6.12. 4-(1-n-Hexyl-3, 4-dibenzyloxy-5-oxo-1, 5-dihydro-pyrrol-2-ylidene)-but-2-enoic acid ethyl ester (27): It was obtained by the reaction of 14 (0.31g, 0.61 mmol) and *p*-toluene sulphonic acid (0.11g, 0.61 mmol) as an sticky solid (0.18g, 62%). IR (Neat) 1699, 1620 cm^{-1}; ^{1}H NMR (300MHz, CDCl3) δ 0.92 (t, J= 6.5 Hz, 3H), 1,21 9 t, J= 7.1 Hz, 3H), 1.27-1.58(m, 8H), 3.57 (t, J= 7.1 Hz, 2H), 4.11 (q, J= 7.1 Hz, 2H), 5.29 (s, 4H), 5.86 (d, J= 12 Hz, 1H), 5.92 (d, J= 15 Hz, 1H), 7.27-7.41 (m, 10H), 8.19 (dd, J= 12.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 14.7, 22.9, 26.8, 29.0, 31.8, 38.8, 60.4, 74.0, 74.3, 109.1, 123.5, 128.0, 128.6, 128.9, 129.1, 136.5, 136.8, 137.3, 139.7, 144.2, 164.9, 166.8; MS (ESI): 490 ($M+H)^+$; Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.59; H, 7.21; N, 2.86, Found: C, 73.62; H, 7.24; N, 2.88.

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