

Convenient synthesis of substituted α -methylene- δ -valerolactones in aqueous medium using Baylis-Hillman chemistry¹

Vijay Singh and Sanjay Batra*

Medicinal Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001.

Fax: +91-522-2623405, 2623938

E-mail: batra_san@yahoo.co.uk

Abstract: A mild and convenient synthesis of substituted α -methylene- δ -valerolactones was achieved by S_N2 nucleophilic substitution of the acetates of the Baylis-Hillman adducts with acetyl acetone followed by one-pot saponification of the ester, reduction of the keto group and subsequent intramolecular ring closure in aqueous medium.

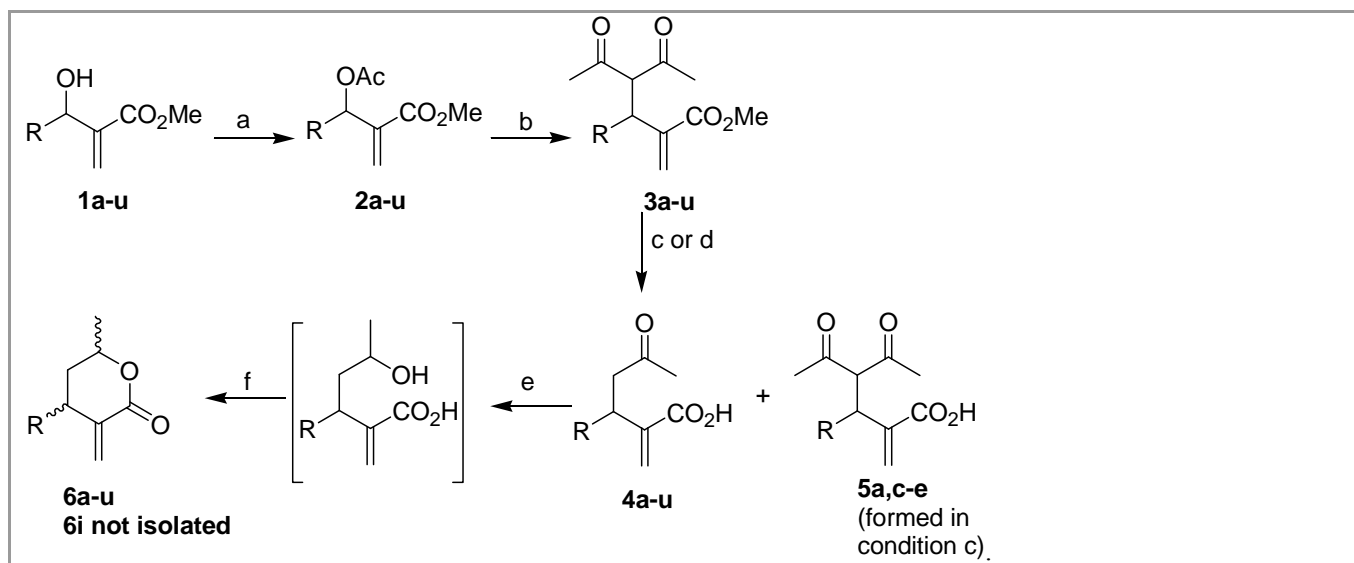
Key words: Baylis-Hillman, α -methylene- δ -valerolactone, nucleophilic substitution, aqueous medium.

The α -methylene- δ -valerolactone moiety is a substructural component of several natural products of biological interest such as vernolepin,² vernomenin,² artemisitene,³ pentalenolactone E,⁴ teucrum lactone⁵ and crassin.⁶ The importance of α -methylene- δ -valerolactone for the synthesis of α -saturated- δ -valerolactones and C-C bond forming transformations have been widely demonstrated.⁷ These considerations possibly led to several elegant approaches towards the synthesis of variety of α -methylene- δ -valerolactones.⁸ The state of art of the synthesis of this class of compounds, however, still requires a strategy which would permit a mild and efficient synthesis of α -methylene- δ -valerolactone. It would be an advantage if such synthesis could be carried out in one-pot and does not require elaborate reaction conditions.⁹ In continuation of our studies on Baylis-Hillman reaction, we perceived such a possibility and details of this study is presented here.

The property of Baylis-Hillman reaction to afford β -hydroxy- α -methylene-ester in a single-step has been efficiently utilized by several workers for the synthesis of variety of α -alkylidene-lactones. The constructions of these lactones have either resulted directly from the Baylis-Hillman products¹⁰⁻¹² or through acetates and bromides obtained from the Baylis-Hillman adducts.¹³⁻¹⁸ In principle, Baylis-Hillman reaction can be utilized for one-pot synthesis of α -methylene-valerolactones by carrying out S_N2 nucleophilic substitution of the acetates of Baylis-Hillman adducts by acetyl acetone followed by the saponification of the ester, reduction of the keto group and subsequent intramolecular ring closure leading to lactonization. Various observations in this study are being described now.

The Baylis-Hillman adducts **1a-u**, generated through methods described in literature¹⁹ upon acetylation in the presence of pyridine and acetyl chloride yielded the acetates **2a-u** (Scheme 1). Subsequent S_N2 nucleophilic addition of acetyl acetone on the acetates **2a-u** in the presence of DABCO in THF: H₂O led to the synthesis of diketo derivatives **3a-u** in excellent yields. Initially during optimization studies, though the tandem deacetyla-

tion and saponification of the esters **3a,c-e** with 15% aqueous KOH or NaOH in methanol furnished the mono keto-acid **4a,c-e** as the major products, minor amounts of diketocids **5a,e** were also formed. The separation of these acids (**4** and **5**) through column chromatography was tedious and the need arose for a process which could eliminate the formation of compound **5**. It was discovered that unlike the reaction in the medium containing methanol, if the saponification is carried out in aqueous medium the mono keto acid is afforded exclusively. Therefore, the saponification with 15% aqueous NaOH at ambient temperature for 4-5h yielded exclusively the acid **4** and the formation of this acid can be expedited if the reaction mixture was refluxed for 10 min. In a parallel study the mono keto acid **4** was subjected to sodium borohydride reduction in the presence of NaOH to yield the hydroxy acid in 2h. Subsequent intramolecular cyclization in the presence of HCl at ambient temperature after 48h gave the desired lactone **6** in high yields. At this stage it occurred to us that one-pot procedure for obtaining the α -methylene- δ -valerolactones is possible. Accordingly, we treated the ketoester **3** with aqueous NaOH at reflux temperature for 10 min. followed by sodium borohydride treatment in the same flask. On completion of the reduction as evident from tlc, the HCl was added to the reaction mixture and it was then refluxed for 1h. Modification of the reaction process in this fashion expedited the reaction sequence without the need of separating and purifying the products at every stage. While this synthetic strategy worked very well for the conversion of variety of ketoesters (**3a-u**) to α -methylene- δ -valerolactones (**6a-u**) (Table 1), the reaction failed to yield the desired product with nitro substituted phenyl derivative (**3i**, entry 9). The lactones were obtained as diastereoisomeric mixtures as evident from the analytical HPLC and spectroscopic analysis and therefore the separation of the diastereoisomers was attempted. Interestingly, the separation was possible only for products **6f**, **6g**, **6h**, **6j** and **6k** where the substituent R was either 2-halo phenyl moiety, furan or a thiophene ring. In all other cases separations of the mixtures were unsuccessful (even with semi-prep. HPLC system). The relative stereochemistry for products **6** where the diastereoisomers were separated was assigned on the basis of nOe experiments. It was found conclusively through nOe experiment that in the less polar diastereoisomer the relative stereochemistry between the hydrogen on C-4 and C-6 was *syn* while in the more polar compound it was *anti* (Fig. 1).



Scheme 1. Reagents and conditions: a) AcCl, Pyridine, CH₂Cl₂, rt, 2-6h. b) Acetyl acetone, DABCO, THF:H₂O. c) 15% KOH or NaOH, methanol, 4h. d) 15% aq. NaOH, reflux, 10 min. e) NaBH₄, aq. NaOH, 2h, rt. f) aq. HCl, reflux, 1h.

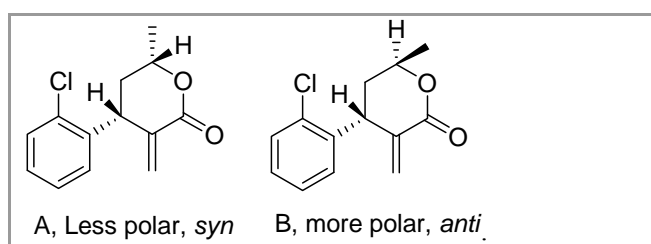
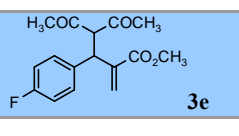
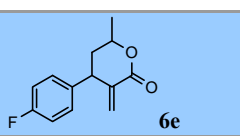
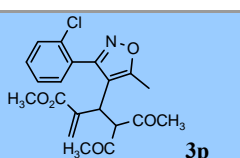
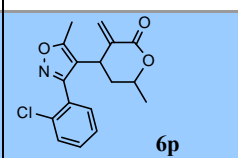
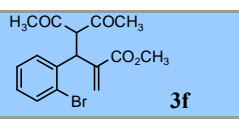
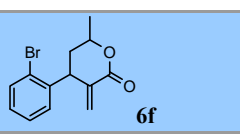
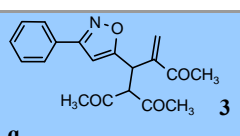
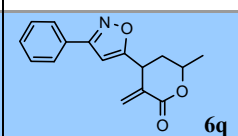
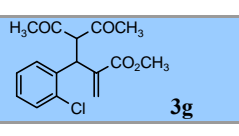
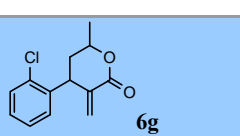
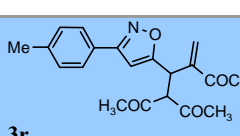
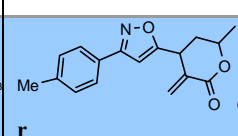
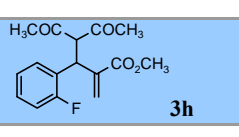
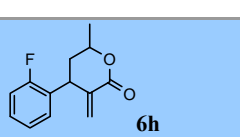
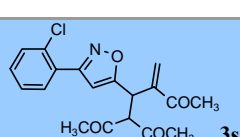
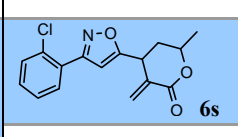
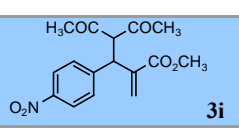
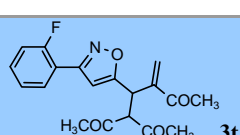
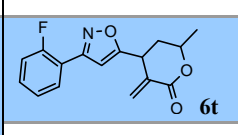
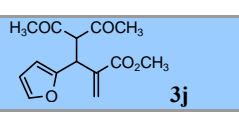
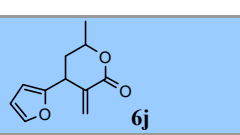
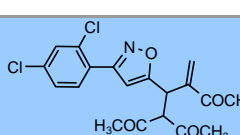
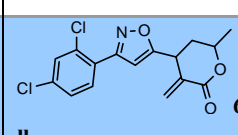
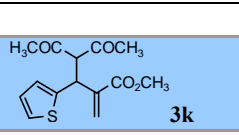
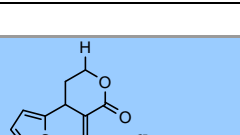


Figure 1. Structures of the separated diastereoisomers in compound **6g**.

Thus, in summary we have described a convenient and practical synthesis of α -methylene- δ -valerolactones in which all reactions were performed in water, an environment friendly and benign medium and in one flask without the need of work up at every step. The operational simplicity of this synthetic route will be helpful to elaborate the chemistry and bioactivity of α -methylene- δ -valerolactones which still remains unexplored.

Table 1 Structure and yields^a of α -methylene- δ -valerolactones prepared during the study via scheme 1.

Entry	Diketoester	Lactone	Yield %	Entry	Diketoester	Lactone	Yield %
1			81	12			76
2			79	13			77
3			78	14			79
4			78	15			75

5	 3e	 6e	83	16	 3p	 6p	78
6	 3f	 6f	77 ^b	17	 3	 6q	77
7	 3g	 6g	78 ^b	18	 3r	 6	76
8	 3h	 6h	81 ^b	19	 3s	 6s	72
9	 3i	Nil 6i	Nil	20	 3t	 6t	74
10	 3j	 6j	73 ^b	21	 3u	 6	77
11	 3k	 6k	79 ^b				

^aThe yields reported herein are of the α -methylene- δ -valerolactones (**6**) obtained through one pot reaction from diketoesters (**3**); ^bsyn and anti isomer were separated

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. The HPLC were carried out on Agilent 1100 system having DA detector ($\lambda_{\max} = 220\text{nm}, 254\text{nm}$) using a gradient run of 10-100% acetonitrile in water containing 0.1% TFA in 30 min on a RP-18e column (250 X 4.6 mm) having particle size of 5 μm . IR spectra were recorded using a Perkin Elmer RX I FTIR spectrophotometer. ¹H NMR and ¹³C 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 General procedures are exemplified by specific compounds. The spectroscopic data for all products obtained as diastereoisomeric mixtures are presented as such while for compounds **6f**, **6g**, **6h**, **6j** and **6k** where *syn* and *anti* diastereoisomers were separated, the data is presented separately as **A** and **B**, respectively. Ratio of *syn*: *anti* was approx. 50: 50 as evident from the analytical HPLC and ¹H-NMR data.

General Procedure for the synthesis of compounds 3a-u. To the solution of acetate **2a** (8.0g, 34.18 mmol) in THF:water (30mL, 1:1, v/v) was added DABCO (4.61g, 40.97 mmol) and the reaction was allowed to proceed at rt. As soon as the solution becomes clear (ca 30 min),

acetyl acetone (3.57mL, 34.18 mmol) in THF was added dropwise with stirring. The reaction was complete in 2h, after which the reaction mixture was extracted with EtOAc (2X100mL). The organic layers were combined, dried over anhyd. Na₂SO₄ and evaporated to obtain a residue that after chromatography on silica gel using hexane: EtOAc (70:30, v/v) as eluent yielded 6.55g (83%) of **3a** as white solid.

4-Acetyl-2-methylene-5-oxo-3-phenyl-hexanoic acid methyl ester (3a)

mp 100-102°C; R_t= 17.3 min

ν_{\max} (KBr) 1694 (2 X C=O), 1724 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.88 (s, 3H, COCH₃), 2.20 (s, 3H, COCH₃), 3.68 (s, 3H, CO₂CH₃), 4.57 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.79 (d, 1H, *J*= 12.4 Hz, CHAr), 5.74 (s, 1H, 1H of =CH₂), 6.30 (s, 1H, 1H of =CH₂), 7.25 (s, 5H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 28.8, 31.0, 46.7, 52.5, 73.8, 125.5, 127.8, 128.8, 129.1, 139.0, 141.3, 166.7, 202.9; mass (FAB+) *m/z* 275 (M⁺+1).

Anal. Calcd for C₁₆H₁₈O₄: C, 70.06, H, 6.61. Found: C, 69.97, H, 6.52.

4-Acetyl-2-methylene-5-oxo-3-*p*-tolyl-hexanoic acid methyl ester (3b)

84 %, White solid, mp 108-110°C; R_t= 18.5 min

ν_{\max} (KBr) 1693 (2 X C=O), 1722 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.89 (s, 3H, COCH₃), 2.19 (s, 3H, COCH₃), 2.28 (s, 3H, ArCH₃), 3.68 (s, 3H, CO₂CH₃), 4.54 (d, 1H, *J*= 12.6 Hz, CH(COCH₃)₂), 4.75 (d, 1H, *J*= 12.4 Hz, CHAr), 5.71 (s, 1H, 1H of =CH₂), 6.26 (s, 1H, 1H of =CH₂), 7.06 (d, 2H, *J*= 8.2 Hz, ArH), 7.13 (d, 2H, *J*= 8.2 Hz, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 21.4, 28.8, 31.0, 46.3, 52.5, 73.8, 125.2, 128.6, 135.9, 137.4, 141.4, 166.8, 203.1; mass (FAB+) *m/z* 289 (M⁺+1).

Anal. Calcd for C₁₇H₂₀O₄: C, 70.81, H, 6.99. Found: C, 71.04, H, 7.05.

4-Acetyl-2-methylene-5-oxo-3-(4-trifluoromethyl-phenyl)-hexanoic acid methyl ester (3c)

81 %, White solid, mp 114-115°C; R_t= 19.5 min

ν_{\max} (KBr) 1696 (2 X C=O), 1722 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.94 (s, 3H, COCH₃), 2.19 (s, 3H, COCH₃), 3.70 (s, 3H, CO₂CH₃), 4.60 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.87 (d, 1H, *J*= 12.4 Hz, CHAr), 5.79 (s, 1H, 1H of =CH₂), 6.34 (s, 1H, 1H of =CH₂), 7.38 (d, 2H, *J*= 8.2 Hz, ArH), 7.54 (d, 2H, *J*= 8.2 Hz, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 28.7, 30.9, 46.3, 52.6, 73.5, 125.9, 126.1, 126.5, 129.2, 140.5, 143.3, 166.4, 202.1, 202.2; mass (FAB+) *m/z* 343 (M⁺+1).

Anal. Calcd for C₁₇H₁₇F₃O₄: C, 59.65, H, 5.01, Found: C, 59.42, H, 5.27.

4-Acetyl-3-(4-chloro-phenyl)-2-methylene-5-oxo-hexanoic acid methyl ester (3d)

84%, White solid, mp 138-140°C; R_t= 18.9 min;

ν_{\max} (KBr) 1694 (C=O), 1722 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.93 (s, 3H, COCH₃), 2.18 (s, 3H, COCH₃), 3.69 (s, 3H, CH₃), 4.54 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.77 (d, 1H, *J*= 12.5 Hz, CHAr), 5.73 (s, 1H, 1H of =CH₂), 6.29 (s, 1H, 1H of =CH₂), 7.16-7.27 (m, 4H, ArH); mass (FAB+) *m/z* 309 (M⁺+1).

Anal. Calcd for C₁₆H₁₇ClO₄: C, 62.24, H, 5.55. Found: C, 62.20, H, 5.62.

4-Acetyl-3-(4-fluoro-phenyl)-2-methylene-5-oxo-hexanoic acid methyl ester (3e)

82%, White solid, mp 68-70°C; R_t= 17.6 min

ν_{\max} (KBr) 1697 (2 X C=O), 1719 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.92 (s, 3H, COCH₃), 2.19 (s, 3H, COCH₃), 3.70 (s, 3H, CO₂CH₃), 4.54 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.78 (d, 1H, *J*= 12.4 Hz, CHAr), 5.73 (s, 1H, 1H of =CH₂), 6.30 (s, 1H, 1H of =CH₂), 6.92-7.00 (m, 2H, ArH), 7.19-7.27 (m, 2H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 28.7, 31.0, 45.9, 52.5, 73.8, 115.8, 116.2, 125.6, 130.3, 130.5, 134.7, 141.1, 159.8, 164.8, 202.6; mass (FAB+) *m/z* 293 (M⁺+1).

Anal. Calcd for C₁₆H₁₇FO₄: C, 65.74, H, 5.86. Found: C, 65.49, H, 6.00.

4-Acetyl-3-(2-bromo-phenyl)-2-methylene-5-oxo-hexanoic acid methyl ester (3f)

85%, Colorless oil; R_t= 18.3 min;

ν_{\max} (Neat) 1696 (2 X C=O), 1720 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.95 (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.68 (s, 3H, CO₂CH₃), 4.92 (d, 1H, *J*= 12.0 Hz, CH(COCH₃)₂), 5.17 (d, 1H, *J*=12.0 Hz, CHAr), 5.93 (s, 1H, 1H of =CH₂), 6.31 (s, 1H, 1H of =CH₂), 7.07-7.57 (m, 4H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 29.8, 30.2, 46.6, 52.4, 72.3, 125.8, 128.1, 129.2, 129.3, 130.1, 134.2, 137.7, 138.7, 166.67, 202.5, 202.9; mass (ES+) *m/z* 376.60 (M⁺+Na).

Anal. Calcd for C₁₆H₁₇BrO₄: C, 54.41, H, 4.85. Found: C, 54.71, H, 5.24.

2-[2-Acetyl-1-(2-chloro-phenyl)-3-oxo-butyl]-acrylic acid methyl ester (3g)

79%, Pale yellow oil; R_t= 17.9 min

ν_{\max} (Neat) 1704 (2 X C=O), 1721 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.95 (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.68 (s, 3H, CO₂CH₃), 4.92 (d, 1H, *J*= 12.2 Hz, CH(COCH₃)₂), 5.20 (d, 1H, *J*=12.2 Hz, CHAr), 5.89 (s, 1H, 1H of =CH₂), 6.30 (s, 1H, 1H of =CH₂), 7.14-7.40 (m, 4H, ArH); mass (ES+) *m/z* 331.00 (M⁺+Na).

Anal. Calcd for C₁₆H₁₇ClO₄.H₂O: C, 58.81; H, 5.86. Found: C, 58.52, H, 6.14.

4-Acetyl-3-(2-fluoro-phenyl)-2-methylene-5-oxo-hexanoic acid methyl ester (3h)

81%, White solid, mp 92-94°C; R_t= 17.3 min

ν_{\max} (KBr) 1696 (2 X C=O), 1720 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200MHz) δ = 1.99 (s, 3H, COCH₃), 2.21 (s, 3H, COCH₃), 3.69 (s, 3H, CO₂CH₃), 4.81 (d, 1H, *J*= 12.2 Hz, CH(COCH₃)₂), 5.01 (d, 1H, *J*=12.4 Hz, CHAr),

5.82 (s, 1H, 1H of =CH₂), 6.31 (s, 1H, 1H of =CH₂), 6.94-7.33 (m, 4H, ArH); mass (ES+) *m/z* 315.07 (M⁺+Na).

Anal. Calcd for C₁₆H₁₇FO₄: C, 65.74; H, 5.86. Found: C 65.37 H, 5.93.

4-Acetyl-2-methylene-3-(2-nitro-phenyl)-5-oxo-hexanoic acid methyl ester (3i)

83%, Brown solid, mp 40-42°C; R_t= 16.7 min

ν_{\max} (KBr) 1697 (2 X C=O), 1725 (CO₂Me) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.04 (s, 3H, COCH₃), 2.23 (s, 3H, COCH₃), 3.67 (s, 3H, CO₂CH₃), 4.89 (d, 1H, *J*= 11.8 Hz, CH(COCH₃)₂), 5.43 (d, 1H, *J*= 11.8 Hz, CHAr), 5.85 (s, 1H, 1H of =CH₂), 6.32 (s, 1H, 1H of =CH₂), 7.35-7.41 (m, 1H, ArH), 7.53 (d, 2H, *J*= 4.2 Hz, ArH), 7.76 (d, 1H, *J*= 7.8 Hz, ArH); mass (FAB+) *m/z* 320 (M⁺+1).

Anal. Calcd. for C₁₆H₁₇NO₆: C, 60.18, H, 5.37, N, 4.39. Found: C, 59.88, H, 5.53, N, 4.03.

2-(2-Acetyl-1-furan-2-yl-3-oxo-butyl)-acrylic acid methyl ester (3j)

80%, White solid, mp 50-52°C; R_t= 16.1 min

ν_{\max} (KBr) 1720 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.10 (s, 3H, COCH₃), 2.17 (s, 3H, COCH₃), 3.76 (s, 3H, CO₂CH₃), 4.66 (d, 1H, *J*= 12.0 Hz, CH(COCH₃)₂), 4.90 (d, 1H, *J*= 12.0 Hz, HetCH), 5.79 (s, 1H, 1H of =CH₂), 6.11 (d, 1H, *J*= 2.8 Hz, HetH), 6.26 (s, 1H, HetH), 6.33 (s, 1H, 1H of =CH₂), 7.29 (s, 1H, HetH); mass (FAB+) *m/z* 265 (M⁺+1).

Anal. Calcd for C₁₄H₁₆O₅: C, 63.63, H, 6.10. Found: C, 63.34, H, 6.14.

4-Acetyl-2-methylene-5-oxo-3-thiophen-2-yl-hexanoic acid methyl ester (3k)

84%, White solid, mp 90-92°C; R_t= 17.0 min

ν_{\max} (KBr) 1715 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.06 (s, 3H, COCH₃), 2.18 (s, 3HCOCH₃), 3.75 (s, 3H, CO₂CH₃), 4.69 (d, 1H, *J*= 12.2 Hz, CH(COCH₃)₂), 5.10 (d, 1H, *J*= 12.2 Hz, HetCH), 5.77 (s, 1H, 1H of =CH₂), 6.30 (s, 1H, 1H of =CH₂), 6.90 (s, 2H, HetH), 7.15-7.18 (m, 1H, HetH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 29.1, 30.8, 45.0, 52.6, 74.3, 125.7, 126.4, 126.6, 127.3, 141.0, 142.6, 166.5, 202.0, 202.3; mass (FAB+) *m/z* 281 (M⁺+1).

Anal. Calcd. for C₁₄H₁₆O₄S: C, 59.98, H, 5.75, S, 11.44. Found: C, 59.63, H, 5.83, S, 11.27.

2-(2-Acetyl-3-oxo-1-pyridin-3-yl-butyl)-acrylic acid methyl ester (3l)

72%, Dark brown solid, mp 55-57°C; R_t= 10.4 min

ν_{\max} (KBr) 1717 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.19 (s, 3H, COCH₃), 2.25 (s, 3H, COCH₃), 3.70 (s, 3H, CO₂CH₃), 4.61 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.80 (d, 1H, *J*= 12.5 Hz, HetCH), 5.83 (s, 1H, 1H of =CH₂), 6.35 (s, 1H, 1H of =CH₂), 7.18-7.35 (m, 1H, HetH), 7.59-7.68 (m, 1H,

HetH), 8.46-8.59 (m, 2H, HetH); mass (ES+) *m/z* 276.47 (M⁺+1), 298.33 (M⁺+Na).

Anal. Calcd for C₁₅H₁₇NO₄: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.78; H, 6.43; N, 4.71.

4-Acetyl-2-methylene-5-oxo-3-(5-phenyl-isoxazol-3-yl)-hexanoic acid methyl ester (3m)

85%, White solid, mp 45-47°C; R_t= 18.9 min

ν_{\max} (KBr) 1697 (2 X C=O), 1719 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.20 (s, 3H, COCH₃), 2.33 (s, 3H, COCH₃), 3.79 (s, 3H, CO₂CH₃), 4.95 (d, 2H, *J*= 3.6 Hz, CH(COCH₃)₂ and HetCH), 5.88 (s, 1H, 1H of =CH₂), 6.39 (s, 1H, 1H of =CH₂), 6.41 (s, 1H, HetH), 7.41-7.44 (m, 3H, ArH), 7.69-7.74 (m, 2H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 29.4, 30.8, 39.3, 52.8, 71.2, 99.7, 126.2, 127.6, 129.3, 129.6, 130.7, 138.5, 163.9, 166.6, 170.8, 201.8; mass (ES+) *m/z* 363.93 (M⁺+Na).

Anal. Calcd for C₁₉H₁₉NO₅: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.51, H, 5.88, N, 3.85.

2-(2-Acetyl-1-[5-(4-bromo-phenyl)-isoxazol-3-yl]-3-oxo-butyl)-acrylic acid methyl ester (3n)

80%, White solid, mp 124-126°C; R_t= 20.9 min

ν_{\max} (KBr) 1695 (2 X C=O), 1716 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.20 (s, 3H, COCH₃), 2.33 (s, 3H, COCH₃), 3.79 (s, 3H, CO₂CH₃), 4.95 (s, 2H, 1H of CH(COCH₃)₂ and 1H of HetCH), 5.88 (s, 1H, 1H of =CH₂), 6.41 (s, 2H, 1H of =CH₂ and 1H of HetH), 7.58 (s, 4H, ArH); mass (ES+) *m/z* 443.80 (M⁺+Na).

Anal. Calcd for C₁₉H₁₈BrNO₅: C, 54.30; H, 4.32; N, 3.33. Found: C, 54.16, H, 4.33, N, 3.65.

2-[2-Acetyl-1-(5-methyl-3-phenyl-isoxazol-4-yl)-3-oxo-butyl]-acrylic acid methyl ester (3o)

80%, Pale yellow oil; R_t= 17.8 min

ν_{\max} (Neat) 1720 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.02 (s, 3H, COCH₃), 2.07 (s, 3H, COCH₃), 2.56 (s, 3H, HetCH₃), 3.68 (s, 3H, CO₂CH₃), 4.39 (d, 1H, *J*= 12.4 Hz, CH(COCH₃)₂), 4.74 (d, 1H, *J*= 12.4 Hz, HetCH), 5.07 (s, 1H, 1H of =CH₂), 6.10 (s, 1H, 1H of =CH₂), 7.47 (s, 5H, ArH); mass (ES+) *m/z* 356.80 (M⁺+1), 378.07 (M⁺+Na).

Anal. Calcd for C₂₀H₂₁NO₅: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.94, H, 6.29, N, 3.99.

4-Acetyl -3-[3-(2-chloro-phenyl)-5-methyl-isoxazol-4-yl]-2methylene-5-oxo-hexanoic acid methyl ester (3p)

82%, White solid, mp 130-132°C; R_t= 18.6 min

ν_{\max} (KBr) 1714 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.01 (s, 3H, COCH₃), 2.15 (s, 3H, COCH₃), 2.64 (s, 3H, HetCH₃), 3.72 (s, 3H, CO₂CH₃), 4.30 (d, 1H, *J*= 12.6 Hz, CH(COCH₃)₂), 4.70 (d, 1H, *J*= 12.6 Hz, HetCH), 4.76 (s, 1H, 1H of =CH₂), 5.98 (s, 1H, 1H of =CH₂), 7.24-7.50 (m, 4H, ArH); mass (ES+) *m/z* 390.13 (M⁺+1), 411.80 (M⁺+Na).

Anal. Calcd for C₂₀H₂₀ClNO₅: C, 61.62, H, 5.17, N, 3.59. Found: C, 61.97, H, 5.22, N, 3.57.

2-[2-Acetyl-3-oxo-1-(3-phenyl-isoxazol-5-yl)-butyl]-acrylic acid methyl ester (3q)83%, White solid, mp 108-110°C; $R_t = 18.5$ min

ν_{\max} (KBr) 1721 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.20$ (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.78 (s, 3H, CO₂CH₃), 4.83 (d, 1H, $J = 12.0$ Hz, CH(COCH₃)₂), 5.10 (d, 1H, $J = 12.0$ Hz, HetCH), 5.94 (s, 1H, 1H of =CH₂), 6.41 (s, 1H, 1H of =CH₂), 6.43 (s, 1H, HetH), 7.41-7.47 (m, 3H, ArH), 7.72-7.81 (m, 2H, ArH); mass (ES⁺) m/z 351.93 (M⁺+Na).

Anal. Calcd for C₁₈H₁₈NO₅: C, 65.84; H, 5.53; N, 4.27. Found: C, 65.91, H, 5.60, N, 4.28.

4-Acetyl-2-methylene-5-oxo-3-(3-p-tolyl-isoxazol-5-yl)-hexanoic acid methyl ester (3r)70%, White solid, mp 136-138°C; $R_t = 19.6$ min

ν_{\max} (KBr) 1726 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.19$ (s, 3H, COCH₃), 2.23 (s, 3H, COCH₃), 2.38 (s, 3H, ArCH₃), 3.78 (s, 3H, CO₂CH₃), 4.82 (d, 1H, $J = 12.0$ Hz, CH(COCH₃)₂), 5.08 (d, 1H, $J = 12.0$ Hz, HetCH), 5.93 (s, 1H, 1H of =CH₂), 6.38 (s, 1H, 1H of =CH₂), 6.43 (s, 1H, HetH), 7.23 (d, 2H, $J = 8.0$ Hz, ArH), 7.63 (d, 2H, $J = 8.0$ Hz, ArH); mass (ES⁺) m/z 377.73 (M⁺+Na).

Anal. Calcd for C₂₀H₂₁NO₅: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.79, H, 5.98, N, 3.38.

2-(2-Acetyl-1-[3-(2-chloro-phenyl)-isoxazol-5-yl]-3-oxo-butyl)-acrylic acid methyl ester (3s)84%, White solid, mp 82-84°C; $R_t = 19.3$ min

ν_{\max} (KBr) 1694 (2 X C=O), 1728 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.20$ (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.78 (s, 3H, CO₂CH₃), 4.85 (d, 1H, $J = 11.8$ Hz, CH(COCH₃)₂), 5.09 (d, 1H, $J = 11.8$ Hz, HetCH), 5.95 (s, 1H, 1H of =CH₂), 6.44 (s, 1H, 1H of =CH₂), 6.56 (s, 1H, HetH), 7.33-7.45 (m, 3H, ArH), 7.66-7.68 (m, 1H, ArH); mass (ES⁺) m/z 398.07 (M⁺+Na).

Anal. Calcd for C₁₉H₁₈ClNO₅: C, 60.72; H, 4.83; N, 3.73. Found: C, 60.93, H, 4.87, N, 3.84.

2-(2-Acetyl-1-[3-(2-fluoro-phenyl)-isoxazol-5-yl]-3-oxo-butyl)-acrylic acid methyl ester (3t)70%, White solid, mp 94-96°C; $R_t = 18.8$ min

ν_{\max} (KBr) 1696 (2X C=O), 1725 (CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.20$ (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.78 (s, 3H, CO₂CH₃), 4.83 (d, 1H, $J = 11.8$ Hz, CH(COCH₃)₂), 5.10 (d, 1H, $J = 11.8$ Hz, HetCH), 5.94 (s, 1H, 1H of =CH₂), 6.43 (s, 1H, 1H of =CH₂), 6.54 (d, 1H, $J = 3.6$ Hz, HetH), 7.15-7.24 (m, 2H, ArH), 7.39-7.43 (m, 1H, ArH), 7.89-7.92 (m, 1H, ArH); mass (ES⁺) m/z 381.87 (M⁺+Na).

Anal. Calcd for C₁₉H₁₈FNO₅: C, 63.50; H, 5.05; N, 3.90. Found: C, 63.43 H, 4.95, N, 3.99.

2-(2-Acetyl-1-[3-(2,4-dichloro-phenyl)-isoxazol-5-yl]-3-oxo-butyl)-acrylic acid methyl ester (3u)74%, Yellow oil; $R_t = 21.3$ min

ν_{\max} (Neat) 1723 (br, 2 X C=O and CO₂CH₃) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.20$ (s, 3H, COCH₃), 2.24 (s, 3H, COCH₃), 3.78 (s, 3H, CO₂CH₃), 4.84 (d, 1H, $J = 11.9$ Hz, CH(COCH₃)₂), 5.09 (d, 1H, $J = 11.9$ Hz, HetCH), 5.95 (s, 1H, 1H of =CH₂), 6.44 (s, 1H, 1H of =CH₂), 6.56 (s, 1H, HetH), 7.29-7.35 (m, 1H, ArH), 7.49 (d, 1H, $J = 1.8$ Hz, ArH), 7.64 (d, 1H, $J = 8.4$ Hz, ArH); mass (ES⁺) m/z 431.67 (M⁺+Na).

Anal. Calcd for C₁₉H₁₇Cl₂NO₅: C, 55.63; H, 4.18; N, 3.41. Found: C, 55.86 H, 4.55, N, 3.58.

General Procedure for the synthesis of compounds 4a,c-e.

To a solution of **3a** (5.0g, 18.25mmol) in methanol (20mL) was added 15% aq. KOH soln. (10ml) and stirred at rt for 4h. Thereafter methanol was evaporated from the reaction mixture and 10% aq. HCl soln. (10mL) at 0-5°C was added to neutralize the base and the reaction mixture was extracted with EtOAc (2X80mL). The organic layers were combined, dried over Na₂SO₄ and evaporated under vacuum to yield an oily residue. This residue was purified through column chromatography over silica gel using hexane: EtOAc (60:40, v/v) as eluent to yield 0.2g (4%) of diketoacid **5a** (impure as it was contaminated with product 4) as white solid followed by 3.18g (80%) of **4a** also as white solid.

2-methylene-5-oxo-3-phenyl-hexanoic acid (4a)mp 98-100°C; $R_t = 14.8$ min

ν_{\max} (KBr) 1624 (C=O), 1678 (CO₂H) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.09$ (s, 3H, COCH₃), 2.96-3.02 (m, 2H, CH₂COCH₃), 4.45 (t, 1H, $J = 7.5$ Hz, CHCH₂), 5.67 (s, 1H, 1H of =CH₂), 6.43 (s, 1H, 1H of =CH₂), 7.19-7.28 (m, 5H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) $\delta = 30.6, 41.8, 48.8, 127.3, 127.4, 128.3, 129.0, 141.6, 142.5, 172.1, 207.1$; mass (FAB⁺) m/z 219 (M⁺+1).

Anal. Calcd for C₁₃H₁₄O₃: C, 71.54, H, 6.47, Found: C, 71.58, H, 6.49.

2-methylene-5-oxo-3-(4-trifluoromethyl-phenyl)-hexanoic acid (4c)88%, White solid, mp 106-108°C; $R_t = 16.9$ min

ν_{\max} (KBr) 1690 (C=O), 1699 (C=O) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.11$ (s, 3H, COCH₃), 2.99-3.04 (m, 2H, CH₂COCH₃), 4.51 (t, 1H, $J = 7.1$ Hz, CHCH₂CO), 5.72 (s, 1H, 1H of =CH₂), 6.47 (s, 1H, 1H of =CH₂), 7.34 (d, 2H, $J = 8.0$ Hz, ArH), 7.54 (d, 2H, $J = 8.0$ Hz, ArH); ¹³C NMR (CDCl₃, 50.3 MHz) $\delta 30.6, 41.4, 48.3, 125.9, 127.9, 128.7, 141.8, 145.9, 171.7, 206.2$; mass (FAB⁺) m/z 287 (M⁺+1)

Anal. Calcd. for C₁₄H₁₃F₃O₃.1/2H₂O: C, 56.57, H, 4.74, Found: C, 56.08, H, 4.56.

3-(4-Chloro-phenyl)-2-methylene-5-oxo-hexanoic acid (4d)87%, White solid, mp 99-101°C; $R_t = 15.9$ min

ν_{\max} (KBr) 1680 (CO₂H), 1715 (C=O) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) $\delta = 2.09$ (s, 3H, COCH₃), 2.94-3.00 (m, 2H, CH₂COCH₃), 4.42 (t, 1H, $J = 7.4$ Hz, CHCH₂CO), 5.68 (s, 1H, 1H of =CH₂), 6.43 (s, 1H, 1H of =CH₂),

=CH₂) 7.14 (d, 2H, *J* = 8.4Hz, ArH), 7.25 (d, 2H, *J* = 8.4Hz, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 30.6, 41.2, 48.5, 127.5, 129.1, 129.7, 133.0, 140.2, 142.2, 171.8, 206.4; mass (FAB+) *m/z* 253 (M⁺+1).

Anal. Calcd for C₁₃H₁₃ClO₃: C, 61.79, H, 5.19. Found: C, 61.70, H, 5.29.

3-(4-Fluoro-phenyl)-2-methylene-5-oxo-hexanoic acid (4e)

89%, White solid, mp 138-140°C; R_t = 14.7 min

*v*_{max} (KBr) 1704 (br, C=O and CO₂H) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 2.09 (s, 3H, COCH₃), 2.94-3.00 (m, 2H CH₂COCH₃), 4.43 (t, 1H, *J* = 7.5 Hz, C HCH₂CO), 5.67 (s, 1H, 1H of =CH₂), 6.42 (s, 1H, 1H of =CH₂), 6.93-6.99 (m, 2H, ArH), 7.15-7.20 (m, 2H, ArH); mass (FAB+) *m/z* 237 (M⁺+1).

Anal. Calcd. for C₁₃H₁₃FO₃: C, 66.09, H, 5.55. Found: C, 66.29, H, 5.63.

General Procedure for the synthesis of compounds 6a,c-e from 4a,c-e

Method I: To the suspension of compound **4d** (2.7g, 10.71 mmol) in water (3mL) was added NaOH (0.471g, 11.78 mmol) and the mixture was stirred for 30min. Thereafter, NaBH₄ (0.407g, 10.71 mmol) was added and the reaction was allowed to stir at rt for another 2h. Finally, conc. HCl was added to the mixture at 0°C till the pH reached 2.0 and the reaction was refluxed for 1h. or stirred at rt. for 48h. On completion as evident from TLC, the reaction mixture was extracted with EtOAc (2X40mL) and water (80mL). The organic layers were combined, washed with brine, dried over anhyd. Na₂SO₄ and evaporated to give an oily residue. This residue was purified through column chromatography over silica gel using hexane: EtOAc (85:15, v/v) as eluent to furnish 2.06g (82%) of pure **6d** as pale yellow oil.

General Procedure for the synthesis of compounds 6a-u from 3a-u

Method II: A mixture of ketoester **3b** (2.0g, 69.4mmol) and 15% aq. NaOH (20ml) was refluxed for 10 min. After cooling to rt, NaBH₄ (0.263g, 69.4mmol) was added and the mixture was stirred at ambient temperature for 2h. Finally the reaction mixture was acidified to pH 2.0 with conc. HCl at 0°C and refluxed for 1h. On completion, the mixture was extracted with EtOAc (2X50mL) and water (100mL). The organic layers were combined, washed with brine, dried over anhyd. Na₂SO₄ and evaporated to obtain an oily residue. The residue was purified through column chromatography over silica gel using hexane:EtOAc (85:15, v/v) as eluent to afford 1.18g (78.7%) of **6b** as colorless oil.

6-Methyl-3-methylene-4-phenyl-tetrahydro-pyran-2-one (6a)

Pale yellow oil; R_t = 17.6 and 17.9 min

*v*_{max} (Neat) 1718 (C=O) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.35 (d, 3H, *J* = 6.2 Hz, CH₃CH), 1.44 (d, 3H, *J* = 6.2 Hz, CH₃CH), 1.99-2.18 (m, 2X2H, CH₂CHCH₃), 3.78-3.85 (m, 1H, CHAr), 4.12 (t, 1H, *J* = 4.6 Hz,

CHAr), 4.45-4.62 (m, 2X1H, CHCH₃), 5.25 (t, 1H, *J* = 1.2 Hz, 1H of =CH₂), 5.56 (s, 1H, 1H of =CH₂), 6.58 (d, 1H, *J* = 2.0 Hz, 1H of =CH₂), 6.68 (s, 1H, 1H of =CH₂), 7.17-7.38 (m, 2X5H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 21.7, 22.1, 37.9, 39.2, 42.3, 45.1, 73.3, 76.1, 127.4, 127.7, 128.1, 128.4, 129.2, 129.3, 130.6, 131.3, 136.8, 139.1, 142.6, 142.9, 166.1, 166.2; mass (ES+) *m/z* 203.07 (M⁺+1), 224.93 (M⁺+Na).

Anal. Calcd. for C₁₃H₁₄O₂: C, 77.20; H, 6.98. Found: C, 77.00, H, 6.77.

6-Methyl-3-methylene-4-p-tolyl-tetrahydro-pyran-2-one (6b)

R_t = 19.1 and 19.5 min

*v*_{max} (Neat) 1716 (CO)cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.35 (d, 3H, *J* = 6.4Hz, CH₃CH), 1.43 (d, 3H, *J* = 6.3Hz, CH₃CH), 2.03-2.13 (m, 2X2H, CH₂CHCH₃), 2.34 (s, 2X3H, ArCH₃), 3.65-3.87 (m, 1H, CHAr), 4.06-4.10 (m, 1H, CHAr), 4.45 (m, 1H, CHCH₃), 4.52-4.73 (m, 1H, CHCH₃), 5.25 (m, 1H, 1H of =CH₂), 5.55 (s, 1H, 1H of =CH₂), 6.66 (d, 1H, *J* = 2.0Hz, 1H of =CH₂), 6.66 (s, 1H, 1H of =CH₂), 7.04-7.17 (m, 2X4H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 21.3, 21.4, 21.7, 22.1, 38.0, 39.2, 41.9, 44.7, 73.3, 76.2, 127.9, 128.3, 129.9, 130.0, 130.6, 131.2, 136.9, 137.1, 137.3, 139.3, 139.6, 139.9, 166.2, 166.3; mass (FAB+) *m/z* 217 (M⁺+1).

Anal. Calcd for C₁₄H₁₆O₂: C, 77.75, H, 7.46. Found: C, 77.52, H, 7.26.

6-Methyl-3-methylene-4-(4-trifluoromethyl-phenyl)-tetrahydro-pyran-2-one (6c)

Colorless oil; R_t = 19.7 and 19.9 min

*v*_{max} (Neat) 1720 (C=O) cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ = 1.38 (d, 3H, *J* = 6.4 Hz, CH₃CH), 1.46 (d, 3H, *J* = 6.4 Hz, CH₃CH), 1.92-2.18 (m, 2X2H, CH₂CHCH₃), 3.89-3.96 (m, 1H, CHAr), 4.20 (t, 1H, *J* = 1.2Hz, CHAr), 4.40-4.67 (m, 2X1H, CHCH₃), 5.23 (d, 1H, *J* = 1.8 Hz, 1H of =CH₂), 5.57 (s, 1H, 1H of =CH₂), 6.61 (d, 1H, *J* = 2.2 Hz, 1H of =CH₂), 6.73 (s, 1H, 1H of =CH₂), 7.33 (d, 2X2H, *J* = 8.0 Hz, ArH), 7.62 (d, 2X2H, *J* = 8.0 Hz, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 21.6, 21.9, 37.7, 39.0, 42.2, 44.9, 73.1, 75.9, 126.2, 128.5, 128.8, 130.9, 131.9, 136.0, 138.3, 146.7, 146.9, 165.6, 165.8; mass (FAB+) *m/z* 271 (M⁺+1).

Anal. Calcd. for C₁₄H₁₃F₃O₂·1/2H₂O: C, 60.21; H, 5.05. Found: C, 60.30, H, 4.79.

4-(4-Chloro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6d)

R_t = 19.3 and 19.6 min; *v*_{max} (Neat) 1718 (CO)cm⁻¹

¹H NMR (CDCl₃, 300 MHz) δ = 1.37 (d, 3H, *J* = 6.3 Hz, CH₃CH), 1.45 (d, 3H, *J* = 6.3 Hz, CH₃CH), 2.05-2.11 (m, 2X2H, CH₂CHCH₃), 3.78 (d, 1H, *J* = 2.1Hz, CHAr), 4.09 (d, 1H, *J* = 4.8Hz, CHAr), 4.43-4.44 (m, 1H, CHCH₃), 4.61-4.64 (m, 1H, CHCH₃), 5.24-5.25 (m, 1H, 1H of =CH₂), 5.55-5.56 (m, 1H, 1H of =CH₂), 6.58 (d, 1H, *J* = 2.7Hz, 1H of =CH₂), 6.69 (s, 1H, H of =CH₂), 7.13 (m, 2X2H, ArH), 7.32 (m, 2X2H, ArH); ¹³C NMR (CDCl₃, 50.32 MHz) δ = 21.7, 22.1, 37.8, 39.1, 41.8,

44.6, 73.2, 76.0, 129.4, 129.8, 130.9, 131.7, 133.5, 136.3, 138.7, 141.3, 165.8; mass (ES+) m/z 236.80 ($M^+ + Na$).

Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97, H, 5.54. Found: C, 65.45, H, 5.49.

4-(4-Chloro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6d)

Colorless oil; $R_t = 19.3$ and 19.6 min

ν_{max} (Neat) 1718 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) $\delta = 1.37$ (d, 3H, $J = 6.3$ Hz, CH_3CH), 1.45 (d, 3H, $J = 6.3$ Hz, CH_3CH), 2.05-2.14 (m, 2X2H, CH_2CHCH_3), 3.78 (d, 1H, $J = 2.1$ Hz, $CHCH_3$), 4.09 (d, 1H, $J = 4.8$ Hz, $CHCH_3$), 4.43-4.44 (m, 1H, CHAr), 4.61-4.64 (m, 1H, CHAr), 5.24-5.25 (m, 1H, 1H of =CH₂), 5.55-5.56 (m, 1H, 1H of =CH₂), 6.58 (d, 1H, $J = 2.7$ Hz, 1H of =CH₂), 6.69 (s, 1H, 1H of =CH₂), 7.13 (m, 2X2H, ArH), 7.32 (m, 2X2H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 21.7, 22.1, 37.8, 39.1, 41.8, 44.6, 73.2, 76.0, 129.4, 129.8, 130.9, 131.7, 133.5, 136.3, 138.7, 141.3, 165.8$; mass (ES+) m/z 236.80 ($M^+ + 1$).

Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97, H, 5.54. Found: C, 65.65, H, 5.56.

4-(4-Fluoro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6e)

Yellow oil; $R_t = 17.7$ and 18.0 min

ν_{max} (Neat) 1716 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (d, 3H, $J = 6.4$ Hz, CH_3CH), 1.44 (d, 3H, $J = 6.2$ Hz, $CHCH_3$), 1.90-2.14 (m, 2X2H, CH_2CHCH_3), 3.78-3.85 (m, 1H, CHAr), 4.11 (brs, 1H, CHAr), 4.41-4.54 (m, 1H, $CHCH_3$), 4.56-4.65 (m, 1H, $CHCH_3$), 5.23 (d, 1H, $J = 1.2$ Hz, 1H of =CH₂), 5.55 (s, 1H, 1H of =CH₂), 6.59 (s, 1H, 1H of =CH₂), 6.68 (s, 1H, 1H of =CH₂), 7.00-7.21 (m, 2X4H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 21.6, 22.0, 37.9, 39.2, 41.5, 44.4, 73.2, 76.0, 115.8, 115.9, 116.3, 116.4, 129.5, 129.7, 129.9, 130.0, 130.6, 131.4, 136.8, 138.3, 138.5, 139.1, 159.7, 164.6, 165.8$; mass (FAB+) m/z 221 ($M^+ + 1$).

Anal. Calcd. for $C_{13}H_{13}FO_2$: C, 70.90; H, 5.95. Found: C, 70.79, H, 6.91.

syn-4-(2-Bromo-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6f-A)

White solid, mp 38-40 °C; $R_t = 19.7$ min

ν_{max} (KBr) 1720 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.96-2.24 (m, 2H, CH_2CHCH_3), 4.49 (brs, 2H, 1H of CHAr and 1H of $CHCH_3$), 5.59 (s, 1H, 1H of =CH₂), 6.73 (s, 1H, 1H of =CH₂), 7.07-7.18 (m, 2H, ArH), 7.30 (d, 1H, $J = 7.2$ Hz, ArH), 7.60 (d, 1H, $J = 7.4$ Hz, ArH); mass (ES+) m/z 302.93 ($M^+ + Na$).

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.56, H, 4.77.

anti-4-(2-Bromo-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6f-B)

Yellow oil; $R_t = 19.5$ min

ν_{max} (Neat) 1720 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.45$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.88-2.00 (m, 1H, 1H of CH_2CHCH_3), 2.14-2.21 (m, 1H, 1H of CH_2CHCH_3), 4.39-4.46 (m, 1H, CHAr), 4.57-4.66 (m, 1H, $CHCH_3$), 5.28 (d, 1H, $J = 2.6$ Hz, 1H of =CH₂), 6.59 (s, 1H, $J = 2.8$ Hz, 1H of =CH₂), 7.10-7.32 (m, 3H, ArH), 7.59 (dd, 1H, $J_1 = 2.0$ Hz, $J_2 = 8.0$ Hz, ArH); mass (ES+) m/z 302.93 ($M^+ + Na$).

Anal. Calcd. for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.70, H, 4.90.

syn-4-(2-Chloro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6g-A)

Colorless oil; $R_t = 19.3$ min

ν_{max} (Neat) 1716 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.97-2.26 (m, 2H, CH_2CHCH_3), 4.40-4.54 (m, 2H, 1H of CHAr and 1H of $CHCH_3$), 5.59 (s, 1H, 1H of =CH₂), 6.72 (s, 1H, 1H of =CH₂), 7.09-7.11 (m, 1H, ArH), 7.21-7.27 (m, 2H, ArH), 7.39-7.44 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 21.6, 37.5, 41.3, 73.3, 128.0, 128.9, 129.4, 130.2, 134.1, 137.6, 140.3, 166.2$; mass (ES+) m/z 236.93 ($M^+ + 1$) 258.93 ($M^+ + Na$).

Anal. Calcd. for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54. Found: C, 65.58, H, 5.64.

anti-4-(2-Chloro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6g-B)

Colorless oil; $R_t = 19.1$ min

ν_{max} (Neat) 1720 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.45$ (d, 3H, $J = 6.4$ Hz, CH_3CH), 1.92-2.03 (m, 1H, 1H of CH_2CHCH_3), 2.11-2.19 (m, 1H, 1H of CH_2CHCH_3), 4.38-4.46 (m, 1H, CHAr), 4.60-4.65 (s, 1H, $CHCH_3$), 5.26 (d, 1H, $J = 2.2$ Hz, 1H of =CH₂), 6.57 (d, 1H, $J = 2.6$ Hz, 1H of =CH₂), 7.18-7.31 (m, 3H, ArH), 7.38-7.43 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 21.9, 37.6, 41.3, 76.0, 128.0, 128.9, 129.4, 130.2, 134.2, 137.6, 140.3, 166.3$; mass (ES+) m/z 236.93 ($M^+ + 1$) 258.93 ($M^+ + Na$).

Anal. Calcd. for $C_{13}H_{13}ClO_2 \cdot 1/2H_2O$: C, 63.55; H, 5.74. Found: C, 63.57, H, 5.70.

syn -4-(2-Fluoro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6h-A)

White solid, mp 48-50 °C; $R_t = 17.8$ min

ν_{max} (KBr) 1721 (C=O) cm^{-1} ; 1H NMR ($CDCl_3$, 200 MHz) $\delta = 1.37$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 2.07-2.34 (m, 2H, CH_2CHCH_3), 4.37-4.47 (m, 2H, 1H of CHAr and 1H of $CHCH_3$), 5.57 (s, 1H, 1H of =CH₂), 6.68 (s, 1H, 1H of =CH₂), 7.08 (s, 3H, ArH), 7.26 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50.32 MHz) $\delta = 21.6, 36.3, 36.8, 73.5, 116.0, 116.4, 124.7, 129.2, 129.4, 129.8, 131.3, 135.9, 158.3, 163.2, 165.9$; mass (ES+) m/z 242.93 ($M^+ + Na$).

Anal. Calcd. for $C_{13}H_{13}FO_2 \cdot 1/2H_2O$: C, 68.11; H, 6.15. Found: C, 68.47, H, 6.34.

anti-4-(2-Fluoro-phenyl)-6-methyl-3-methylene-tetrahydro-pyran-2-one (6h-B)

Yellow oil; $R_f = 17.7$ min; ν_{\max} (Neat) 1721 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.45$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.98-2.10 (m, 2H, CH_2CHCH_3), 4.11-4.18 (m, 1H, CHAr), 4.60 (s, 1H, CHCH_3), 5.30 (s, 1H, 1H of =CH₂), 6.58 (s, 1H, 1H of =CH₂), 7.03-7.27 (m, 4H, ArH); mass (ES⁺) m/z 242.93 ($\text{M}^+ + \text{Na}$).

Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{FO}_2 \cdot 1/2\text{H}_2\text{O}$: C, 68.11; H, 6.15. Found: C, 68.47, H, 6.34.

syn-4-furan-2-yl-6-methyl-3-methylene-tetrahydro-pyran-2-one (6j-A)

Yellow oil; $R_f = 15.8$ min

ν_{\max} (Neat) 1717 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200MHz) $\delta = 1.38$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.90-2.05 (m, 1H, 1H of CH_2CHCH_3), 2.31-2.41 (m, 1H, 1H of CH_2CHCH_3), 4.08 (d, 1H, $J = 3.5$ Hz, HetCH), 4.37-4.46 (m, 1H, CHCH_3), 5.72 (s, 1H, 1H of =CH₂), 6.04 (d, 1H, $J = 3.0$ Hz, HetH), 6.30-6.33 (m, 1H, HetH), 6.67 (s, 1H, 1H of =CH₂), 7.37-7.38 (m, 1H, HetH); mass (FAB⁺) m/z 193 ($\text{M}^+ + 1$).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.74; H, 6.29. Found: C, 68.41, H, 6.55.

anti-4-furan-2-yl-6-methyl-3-methylene-tetrahydro-pyran-2-one (6j-B)

Yellow oil; $R_f = 15.6$ min

ν_{\max} (Neat) 1717 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200MHz) $\delta = 1.44$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 2.00-2.22 (m, 2H, CH_2CHCH_3), 3.93-4.02 (m, 1H, HetCH), 4.49-4.56 (m, 1H, CHCH_3), 5.48 (t, 1H, $J = 1.2$ Hz, 1H of =CH₂), 6.15 (d, 1H, $J = 3.2$ Hz, HetH), 6.32-6.35 (m, 1H, HetH), 6.57 (d, 1H, $J = 2.6$ Hz, 1H of =CH₂), 7.36 (t, 1H, $J = 0.8$ Hz, HetH); mass (FAB⁺) m/z 193 ($\text{M}^+ + 1$).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.74; H, 6.29. Found: C, 68.59, H, 6.32.

syn-6-Methyl-3-methylene-4-thiophen-2-yl-tetrahydro-pyran-2-one (6k-A)

Pale yellow solid, mp 104-106 °C, $R_f = 17.2$ min

ν_{\max} (KBr) 1718 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.38$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 2.05-2.27 (m, 2H, CH_2CHCH_3), 4.31 (brs, 1H, HetCH), 4.50-4.57 (m, 1H, CHCH_3), 5.73 (s, 1H, 1H of =CH₂), 6.70 (s, 1H, 1H of =CH₂), 6.81 (s, 1H, HetH), 6.94-6.98 (m, 1H, HetH), 7.24 (d, 1H, $J = 4.8$ Hz, HetH); ^{13}C NMR (CDCl_3 , 50.32 MHz) $\delta = 21.0, 37.8, 72.6, 124.4, 125.1, 126.8, 130.9, 135.2, 145.3, 164.7$; mass (FAB⁺) m/z 209 ($\text{M}^+ + 1$).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.44, H, 5.55, S, 15.01.

anti-6-Methyl-3-methylene-4-thiophen-2-yl-tetrahydro-pyran-2-one (6k-B)

Brown solid, mp 34-36 °C; $R_f = 16.9$ min

ν_{\max} (KBr) 1714 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.45$ (d, 3H, $J = 6.2$ Hz, CH_3CH), 1.90-2.14 (m, 1H, 1H of CH_2CHCH_3), 2.25-2.30 (m, 1H, 1H of CH_2CHCH_3), 4.16 (d, 1H, $J = 10.9$ Hz, HetCH), 4.55-4.62 (m, 1H, CHCH_3), 5.49 (s, 1H, 1H of =CH₂), 6.63 (s, 1H, 1H of =CH₂), 6.93-7.00 (m, 2H, HetH), 7.24 (d, 1H,

$J = 5.0$ Hz, Het); mass (ES⁺) m/z 209.07 ($\text{M}^+ + 1$), 231.07 ($\text{M}^+ + \text{Na}$).

Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2\text{S}$: C, 63.43; H, 5.81; S, 15.40. Found: C, 63.48, H, 5.60, S, 15.08.

6-Methyl-3-methylene-4-pyridin-3-yl-tetrahydro-pyran-2-one (6l)

Yellow oil; $R_f = 8.6$ min (not resolved)

ν_{\max} (Neat) 1716 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.40$ (m, 3H, $J = 6.4$ Hz, CH_3CH), 1.46 (m, 3H, $J = 6.2$ Hz, CH_3CH), 1.94-2.19 (m, 2X2H, CH_2CHCH_3), 3.82-3.97 (m, 1H, HetCH), 4.17 (t, 1H, $J = 1.8$ Hz, HetCH), 4.58-4.86 (m, 2X1H, CHCH_3), 5.25 (d, 1H, $J = 1.0$ Hz, 1H of =CH₂), 5.57 (s, 1H, 1H of =CH₂), 6.62 (d, 1H, $J = 2.8$ Hz, 1H of =CH₂), 6.72 (s, 1H, 1H of =CH₂), 7.27-7.65 (m, 2X1H, HetH), 7.49-7.57 (m, 2X1H, HetH), 8.51-8.57 (m, 2X2H, Het); ^{13}C NMR (CDCl_3 , 75.46 MHz) $\delta = 21.1, 21.6, 37.0, 38.5, 39.5, 42.1, 72.7, 75.6, 123.7, 123.9, 130.6, 131.6, 135.2, 135.4, 137.9, 138.1, 148.4, 148.8, 149.3, 149.6, 165.0, 165.2$; mass (FAB⁺) m/z 204.

Anal. Calcd for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.67, H, 6.75, N, 6.50.

6-Methyl-3-methylene-4-(5-phenyl-isoxazol-3-yl)-tetrahydro-pyran-2-one (6m)

White solid, mp 114-116 °C; $R_f = 18.0$ and 18.4 min

ν_{\max} (KBr) 1711 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.42$ -1.49 (m, 2X3H, CH_3CH), 1.97-2.31 (m, 2X2H, CH_2CHCH_3), 4.16-4.27 (m, 2X1H, HetCH), 4.59-4.66 (m, 2X1H, CHCH_3), 5.59 (d, 1H, $J = 2.2$ Hz, 1H of =CH₂), 5.77 (s, 1H, 1H of =CH₂), 6.38 (s, 2X1H, HetH), 6.68 (d, 1H, $J = 2.6$ Hz, 1H of =CH₂), 6.73 (s, 1H, 1H of =CH₂), 7.45-7.48 (m, 2X3H, ArH), 7.75-7.77 (m, 2X2H, ArH); ^{13}C NMR (CDCl_3 , 75.46 MHz) $\delta = 20.3, 20.5, 33.7, 34.0, 35.0, 35.3, 72.5, 74.2, 96.2, 97.5, 124.8, 126.0, 128.0, 129.5, 129.9, 130.4, 132.9, 133.8, 163.8, 164.0, 169.7$; mass (FAB⁺) m/z 270.

Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 70.99; H, 5.75; N, 4.82.

4-[5-(4-Bromo-phenyl)-isoxazol-3-yl]-6-methyl-3-methylene-tetrahydro-pyran-2-one (6n)

White solid, mp 92-94 °C; $R_f = 20.4$ and 20.8 min

ν_{\max} (KBr) 1708 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) $\delta = 1.42$ -1.50 (m, 2X3H, CH_3CH), 2.01-2.37 (m, 2X2H, CH_2CHCH_3), 4.15-4.27 (m, 2X1H, HetCH), 4.64-4.70 (m, 2X1H, CHCH_3), 5.58 (d, 1H, $J = 2.4$ Hz, 1H of =CH₂), 5.76 (s, 1H, 1H of =CH₂), 6.40 (d, 2X1H, $J = 3.8$ Hz, HetH), 6.67-6.72 (m, 2X1H, =CH₂), 7.62 (s, 2X4H, ArH); ^{13}C NMR (CDCl_3 , 75.46 MHz) $\delta = 21.7, 21.9, 35.1, 35.4, 36.4, 36.7, 73.9, 75.6, 98.1, 99.4, 125.3, 126.3, 127.7, 131.4, 132.0, 132.8, 134.2, 135.1, 165.4, 165.5, 170.1$ mass (ES⁺) m/z 370.13 ($\text{M}^+ + \text{Na}$).

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{BrNO}_3$: C, 55.19; H, 4.05; N, 4.02. Found: C, 55.46; H, 4.34; N, 3.69.

6-Methyl-3-methylene-4-(5-methyl-3-phenyl-isoxazol-4-yl)-tetrahydro-pyran-2-one (6o)

Yellow oil; R_f = 17.2 min (not resolved)

ν_{\max} (Neat) 1717 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.26-1.38 (m, 2X3H, CH_3CH), 1.83-2.03 (m, 2X2H, CH_2CHCH_3), 2.39 (s, 2X3H, HetCH₃), 3.72-3.84 (m, 1H, HetCH), 4.05-4.06 (m, 1H, HetCH), 4.50-4.53 (m, 2X1H, CHCH_3), 5.53 (s, 1H, 1H of =CH₂), 5.59 (s, 1H, 1H of =CH₂), 6.66 (s, 1H, 1H of =CH₂), 6.68 (s, 1H, 1H of =CH₂), 7.48 (s, 2X5H, ArH); mass (FAB+) m/z 284 (M^+).

Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.90; H, 6.31; N, 4.79.

4-[3-(2-Chloro-phenyl)-5-methyl-isoxazol-4-yl]-6-methyl-3-methylene-tetrahydro-pyran-2-one (6p)

White solid, mp 103-105 °C; R_f = 18.2 min (not resolved)

ν_{\max} (KBr) 1717 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.22-1.38 (m, 2X3H, CH_3CH), 1.73-2.04 (m, 2X2H, CH_2CHCH_3), 2.40 (s, 2X3H, HetCH₃), 3.42-3.64 (m, 1H, HetCH), 3.82 (s, 1H, HetCH), 4.46-4.49 (m, 2X1H, CHCH_3), 4.51(d, 1H, J = 1.8 Hz, 1H of =CH₂), 5.62 (s, 1H, 1H of =CH₂), 6.61 (s, 2X1H, =CH₂), 7.34-7.54 (m, 2X4H, ArH); ^{13}C NMR (CDCl_3 , 75.46 MHz) δ = 12.9, 13.0, 21.0, 21.8, 31.3, 33.8, 35.4, 36.8, 73.8, 76.0, 115.7, 127.5, 127.6, 128.6, 128.8, 129.9, 130.4, 130.5, 131.6, 131.9, 132.1, 134.0, 134.2, 135.4, 136.2, 161.7, 161.9, 165.3, 166.7, 166.8; mass (FAB+) m/z 318 (M^+).

Anal. Calcd for $\text{C}_{17}\text{H}_{16}\text{ClNO}_3$: C, 64.26; H, 5.08; N, 4.41. Found: C, 63.96, H, 5.33; N, 4.02.

6-Methyl-3-methylene-4-(3-phenyl-isoxazol-5-yl)-tetrahydro-pyran-2-one (6q)

Yellow oil; R_f = 17.8 and 17.9 min

ν_{\max} (Neat) 1721 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.42 (d, 3H, J = 6.2 Hz, CHCH_3), 1.48 (m, 3H, J = 6.2 Hz, CH_3CH), 1.98-2.18 (m, 2H, CH_2CHCH_3), 2.32-2.52 (m, 2H, CH_2CHCH_3), 4.19-4.28 (m, 2X1H, HetCH), 4.54-4.60 (m, 2X1H, CHCH_3), 5.69 (d, 1H, J = 1.9 Hz, 1H of =CH₂), 5.86 (s, 1H, 1H of =CH₂), 6.35 (s, 1H, HetH), 6.43 (s, 1H, HetH), 6.69 (d, 1H, J = 2.2 Hz, 1H of =CH₂), 6.80 (s, 1H, 1H of =CH₂), 7.46 (s, 2X3H, ArH), 7.77-7.7.80 (m, 2X2H, ArH); mass (ES+) m/z 270.07 (M^+), 292.13 (M^+ +Na).

Anal. Calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_3 \cdot \text{H}_2\text{O}$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.51, H, 6.04; N, 4.83.

6-Methyl-3-methylene-4-(3-p-tolyl-isoxazol-5-yl)-tetrahydro-pyran-2-one (6r)

Yellow oil; R_f = 19.4 and 19.5 min

ν_{\max} (Neat) 1722 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.41 (d, 3H, J = 6.4 Hz, CH_3CH), 1.44 (d, 3H, J = 6.4 Hz, CH_3CH), 2.05-2.17 (m, 2H, CH_2CHCH_3), 2.40 (s, 2X3H, ArCH₃), 2.43-2.65 (m, 2H, CH_2CHCH_3), 4.16-4.27 (m, 2X1H, HetCH), 4.51-4.54 (m, 2X1H, CHCH_3), 5.70 (s, 1H, 1H of =CH₂), 5.86 (s, 1H, 1H of =CH₂), 6.32 (s, 1H, HetH), 6.40 (s, 1H, HetH), 6.69 (s, 1H, 1H of =CH₂), 6.72 (s, 1H, 1H of =CH₂), 7.26-7.28 (m, 2X2H, ArH), 7.66-7.70 (m, 2X2H, ArH); ; mass (FAB+) m/z 284(M^+).

Anal. Calcd for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 66.89; H, 4.91; N, 4.88. Found: C, 66.66; H, 5.10; N, 5.04.

4-[3-(2-Chloro-phenyl)-isoxazol-5-yl]-6-methyl-3-methylene-tetrahydro-pyran-2-one (6s)

Yellow oil; R_f = 18.9 and 19.1 min

ν_{\max} (Neat) 1722 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.43 (d, 3H, J = 6.4 Hz, CH_3CH), 1.46 (d, 3H, J = 6.4 Hz, CH_3CH), 2.07-2.19 (m, 2H, CH_2CHCH_3), 2.35-2.52 (m, 2H, CH_2CHCH_3), 4.22-4.30 (m, 2X1H, HetCH), 4.42-4.63 (m, 2X1H, CHCH_3), 5.69 (s, 1H, 1H of =CH₂), 5.86 (s, 1H, 1H of =CH₂), 6.50 (s, 1H, HetH), 6.60 (s, 1H, HetH), 6.69 (s, 1H, 1H of =CH₂), 6.79 (s, 1H, 1H of =CH₂), 7.38-7.48 (m, 2X3H, ArH), 7.71-7.72 (m, 2X1H, ArH); mass (ES+) m/z 326.27 (M^+ +Na).

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{ClNO}_3$: C, 63.27; H, 4.65; N, 4.61. Found: C, 63.51, H, 5.04; N, 4.33.

4-[3-(2-Fluoro-phenyl)-isoxazol-5-yl]-6-methyl-3-methylene-tetrahydro-pyran-2-one (6t)

Yellow oil; R_f = 18.3 and 18.5 min

ν_{\max} (Neat) 1720 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.42 (d, 3H, J = 6.2 Hz, CH_3CH), 1.47 (d, 3H, J = 6.2 Hz, CH_3CH), 2.06-2.13 (m, 2H, CH_2CHCH_3), 2.31-2.43 (m, 2H, CH_2CHCH_3), 4.26-4.32 (m, 2X1H, HetCH), 4.42-4.67 (m, 2X1H, CHCH_3), 5.68 (d, 1H, J = 2.4 Hz, 1H of =CH₂), 5.86 (s, 1H, 1H of =CH₂), 6.48 (d, 1H, J = 2.4 Hz, HetH), 6.58 (d, 1H, J = 3.5 Hz, HetH), 6.69 (d, 1H, J = 2.4 Hz, 1H of =CH₂), 6.80 (s, 1H, 1H of =CH₂), 7.14-7.28 (m, 2X2H, ArH), 7.43-7.46 (m, 2X1H, ArH), 7.94-7.98 (m, 2X1H, ArH); ^{13}C NMR (CDCl_3 , 75.46 MHz) δ = 21.2, 21.4, 33.8, 35.2, 36.0, 36.5, 73.2, 75.0, 102.0, 102.2, 103.5, 103.6, 116.2, 116.5, 124.6, 128.9, 130.8, 131.8, 131.9, 132.2, 132.6, 133.6, 157.9, 158.5, 161.8, 172.2; mass (ES+) m/z 310.20 (M^+ +Na).

Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{FNO}_3 \cdot \text{H}_2\text{O}$: C, 62.94; H, 5.28; N, 4.59. Found: C, 63.31, H, 5.04; N, 4.67.

4-[3-(2,4-Dichloro-phenyl)-isoxazol-5-yl]-6-methyl-3-methylene-tetrahydro-pyran-2-one (6u)

Yellow oil; R_f = 21.1 and 21.4 min

ν_{\max} (Neat) 1720 (C=O) cm^{-1} ; ^1H NMR (CDCl_3 , 200 MHz) δ = 1.43 (d, 3H, J = 6.2 Hz, CH_3CH), 1.48 (d, 3H, J = 6.2 Hz, CH_3CH), 2.05-2.20 (m, 2H, CH_2CHCH_3), 2.32-2.44 (m, 2H, CH_2CHCH_3), 4.27-4.31 (m, 2X1H, HetCH), 4.33-4.62 (m, 2X1H, CHCH_3), 5.69 (d, 1H, J = 2.4 Hz, 1H of =CH₂), 5.86 (s, 1H, 1H of =CH₂), 6.49 (s, 1H, HetH), 6.59 (s, 1H, HetH), 6.69 (d, 1H, J = 2.6 Hz, 1H of =CH₂), 6.79 (s, 1H, 1H of =CH₂), 7.32-7.38 (m, 2X1H, ArH), 7.52 (s, 2X1H, ArH), 7.65-7.72 (m, 2X1H, ArH); ^{13}C NMR (CDCl_3 , 75.46 MHz) δ = 21.2, 21.3, 33.8, 35.2, 36.0, 36.5, 73.2, 74.9, 102.7, 104.1, 126.3, 126.4, 127.5, , 129.5, 130.2, 130.9, 131.6, 132.1, 132.6, 133.4, 136.4, 160.2, 164.1, 171.9, 172.2; mass (FAB+) m/z 338 (M^+).

Anal. Calcd for $\text{C}_{16}\text{H}_{13}\text{Cl}_2\text{NO}_3$: C, 56.82; H, 3.87; N, 4.14. Found: C, 56.97, H, 4.10; N, 3.89.

Acknowledgment

One of the authors (VS) acknowledges the financial support from DST in the form of fellowship. This work was supported by the financial grant under DST Project no. SR/SI/OC-04/2003.

References

- (1) CDRI Communication No. **6732**.
- (2) Kupchan, S. M.; Hemingway, R. J.; Werner, D.; Karim, A.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 3596-3597.
- (3) a) Liao, X.-B.; Han, J.-Y.; Li, Y. *Tetrahedron Lett.* **2001**, *42*, 2843-2845. b) Ekthawatchai, S.; Kamchonwongpaisan, S.; Kongsaree, P.; Tarnchompoo, B.; Thebtaranonth, Y.; Yuthavong, Y. *J. Med. Chem.* **2001**, *44*, 4688-4695. c) Avery, M. A.; Alvim-Gaston, M.; Vroman, J. A.; Wu, B.; Ager, A.; Peters, W.; Robinson, B. L.; Charman, W. *J. Med. Chem.* **2002**, *45*, 4321-4335.
- (4) Cane, D. E.; Rossi, T. *Tetrahedron Lett.* **1979**, *20*, 2973-2974.
- (5) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507-14545.
- (6) a) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 2385-2390. b) McMurry, J. E.; Dushin, R. G. *J. Am. Chem. Soc.* **1990**, *112*, 5967-5971.
- (7) a) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820-836. b) Giese, B.; Hoch, M.; Lamberth, C.; Schmidt, R. R. *Tetrahedron Lett.* **1988**, *29*, 1375-1378. c) Takeda, K.; Imaoka, I.; Yoshii, E. *Tetrahedron* **1994**, *50*, 10839-10848. d) Solladie', G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1995**, *51*, 9559-9568. e) Solladie', G.; Boeffel, D.; Maignan, J. *Tetrahedron* **1996**, *52*, 2065-2074.
- (8) a) Grieco, P. A. *Synthesis* **1975**, 67-82. b) Ksander, G. M.; McMurry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180-1185. c) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977-5982. d) Paterson, I.; Fleming, I. *Tetrahedron Lett.* **1979**, *20*, 993-994. e) Ochiai, M.; Fujita, E.; Arimoto, M.; Yamaguchi, H. *Tetrahedron Lett.* **1983**, *24*, 777-780. f) Carlson, M. R.; White, L. L. *Synth. Commun.* **1983**, *13*, 237-241. g) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058-4067. h) Lee, E.; Hur, C. U.; Park, C. M. *Tetrahedron Lett.* **1990**, *35*, 5039-5040. i) Nishitani, K.; Harada, Y.; Nakamura, Y.; Yokoo, K.; Yamakawa, K. *Tetrahedron Lett.* **1994**, *35*, 7809-7812. j) Gupta, A.; Vankar, Y. D. *Tetrahedron* **2000**, *56*, 8525-8531. k) Krawczyk, H.; Sliwinski, M. *Tetrahedron* **2003**, *59*, 9199-9211. l) Krawczyk, H.; Sliwinski, M.; Wolf, W. M.; Bodalski, R. *Synlett* **2004**, 1995-1999.
- (9) Noyori, R. *Chem. Comm.* **2005**, 1807-1811.
- (10) Masuyama, Y.; Nimura, Y.; Kurusu, Y. *Tetrahedron Lett.* **1991**, *32*, 225-228.
- (11) Adam, W.; Salgado, V. O. N.; Peters, E. -M.; Peters, K.; von Schnering, H. G. *Chem. Ber.* **1993**, *126*, 1481-1486.
- (12) Martinez, I.; Andrews, A. E.; Emch, J. D.; Ndakala, A. J.; Wang, J.; Howell, A. *Org. Lett.* **2003**, *5*, 4399-4402.
- (13) Brezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317-4318.
- (14) a) Bauchat, P.; Le Rouille, E.; Foucad, A. *Bull. Chim. Soc. Fr.* **1991**, 267-271. b) Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375-378.
- (15) Choudhury, P. K.; Foubelo, F.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 3581-3584.
- (16) Paquette, L. A.; Mendez-Adino, J. *Tetrahedron Lett.* **1999**, *40*, 4301-4304.
- (17) Schneider, M. F.; Blechert, S.; Matuszak, A.; Pickardt, J. *Synlett* **1999**, 638-640.
- (18) Gonzalez, A. G.; Silva, M. H.; Padron, J. I.; Leon, F.; Reyes, E.; Alvarez-Mon, M.; Pivel, J. P.; Quintana, J.; Estevez, F.; Bermejo, J. *J. Med. Chem.* **2002**, *45*, 2358-2361.
- (19) a) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276-281. b) Cai, J.; Zhou, Z.; Zhao, G.; Tang, C. *Org. Lett.* **2002**, *4*, 4723-4725. c) Roy, A. K.; Batra, S. *Synthesis*, **2003**, 1347-1356. d) Roy, A. K.; Batra, S. *Synthesis*, **2003**, 2325-2330.