STEREOSELECTIVE SYNTHESIS OF (*Z*)-α-ALKYLIDENE-γ-BUTYRO-LACTONE FROM 2-ALKYN-1-ONE

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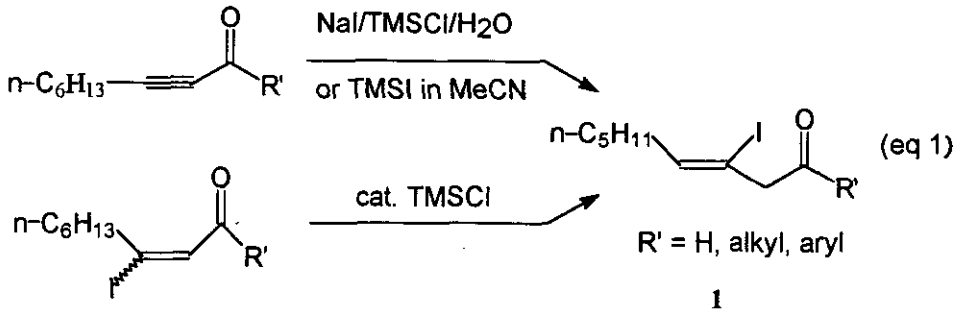
Abstract - A preparation of (*Z*)-α-alkylidene-γ-butyrolactone with or without alkyl or aryl substituent at γ-position from 2-alkyn-1-one is provided.

Efficient methods for the preparation of lactones containing both saturated and unsaturated five or six-membered rings have been considerable interest for synthetic organic chemists in view of their recognized biological activities, for example, fungicidal, herbicidal, antibiotic, and antitumor properties.[1] Usually, synthetic procedures to the α-alkylidenelactones generally involve either (a) conversion of an existing group at the α-position on a preformed lactone ring to the corresponding α-methylene or α-alkylidene group[2] or (b) formation of the α-methylene- or α-alkylidenelactone from acyclic precursors containing all of the desired functional groups *via* a ring closure reaction.[3] Recently, the stereoselective synthesis of (*Z*)-α-alkylidene-γ-butyrolactone has become attractive since these compounds can be used as a plant growth regulator,[4] or as an important intermediate to the synthesis of obtusilactone isolated from *Lindela obtusiloba*, a cytotoxic natural product.[5] Although several methods have been reported for the introduction of an alkylidene group at the α-position of a γ-butyrolactone,[2] there is no general procedure being reported in the literature for the stereoselective synthesis of the exocyclic double bond with the (*Z*)-configuration. Recently, we have reported that (*Z*)-3-iodo-3-alken-1-one system can be easily obtained either by treatment of a conjugated ynone with sodium iodide/trimethylsilyl chloride/water or trimethylsilyl iodide in acetonitrile,[6] or by treatment of conjugated 3-iodo-2-alken-1-one with catalytic amount of trimethylsilyl chloride[7] (Eq 1). Herein, we report that (*Z*)-3-iodo-3-alken-1-one (**1**) can be easily applied to the synthesis of (*Z*)-α-alkylidene-γ-butyrolactones with or without substituent at the γ-position as shown in **Table 1**. Reduction of **1** with sodium borohydride in methanol at room temperature gave (*Z*)-3-iodo-3-alken-1-ol (**2**) in good yield (> 90 %) with no loss of stereochemistry as judged by ^{1}H nmr spectral analyses. In the presence of $Pd(PPh_3)_4$ catalyst, triethylamine, and carbon monoxide in toluene, intramolecular cyclization of (*Z*)-3-iodo-3-alken-1-ol afforded (*Z*)-α-alkylidene-γ-butyrolacton in 18 h and in good yields. Using tetrahydrofuran as the



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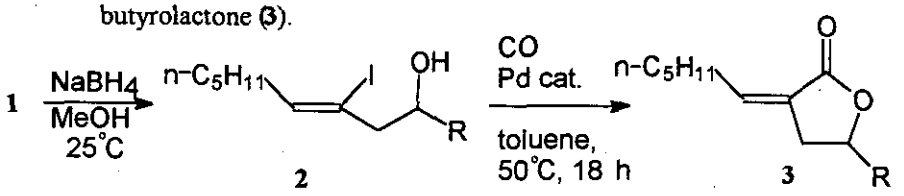
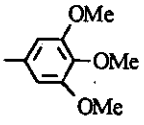
solvent in the cyclization process gave lower yields of the desired product along with some unidentified by-products. Using 5 mol % of bis(dibenzylideneacetone)palladium and 10 mol % of triphenylphosphine similar results could be also obtained. The stereochemistry of the exocyclic double bond was determined by 2D NOESY (phase sensitive) ^{1}H nmr spectral analyses. For example, the 2D NOESY spectrum of compound (**3a**) (**Figure 1**) shows cross peaks due to positive NOEs between the vinylic proton and two allylic protons in the lactone ring (marked with an →).

Table 1. Conversion of (*Z*)-3-iodo-3-alken-1-one (**2**) into (*Z*)-α-alkylidene-γ-butyrolactone (**3**).



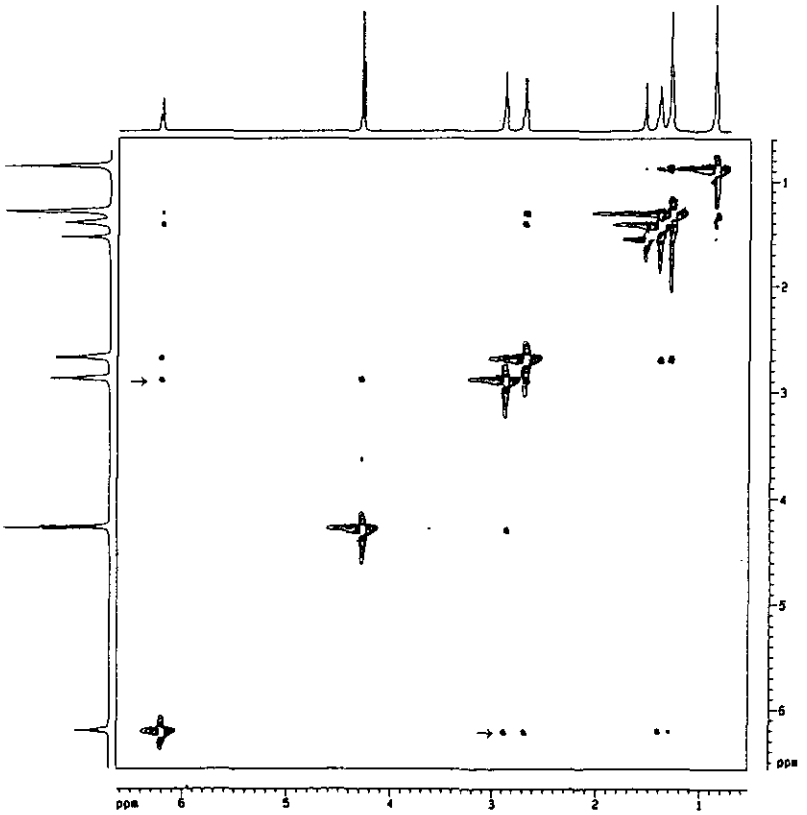
Entry	R =		Yield (%)	
1	-H	**2a**	67	**3a**
2	-Me	**2b**	62	**3b**
3	-Et	**2c**	63	**3c**
4	-C_5H_{11}-n	**2d**	68[a]	**3d**
5	-Ph	**2e**	72	**3e**
6		**2f**	66	**3f**
7		**2g**	56	**3g**

[a] *Z*/*E* ratio was 97/3 as determined by ^{1}H-nmr spectral analysis.

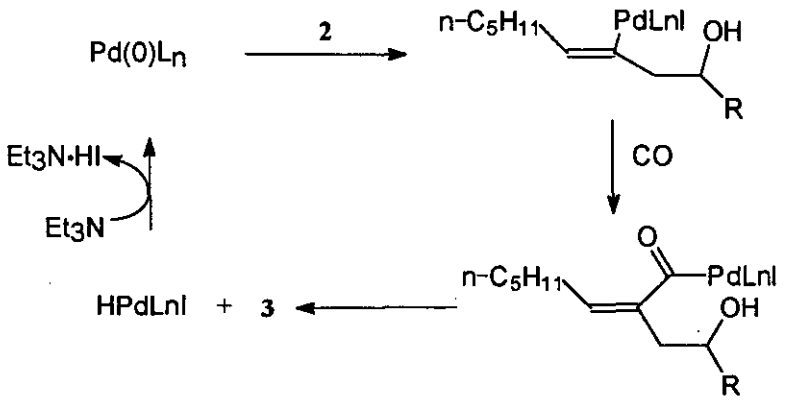
A stoichiometric amount of tributyltin hydride was found to be a good reducing agent to replace triethylamine in the above reaction to shorten the reaction time to about 2.5 h. Similar reaction conditions have been reported in the formylation of organic halides.[8,9] However, it is needed to know that under similar reaction conditions, 2-iodobenzyl alcohol only undergoes a transmetallation and reductive elimination of the acylpalladium hydride to form aldehyde, rather than direct reductive elimination to form the lactone.[7] Attempts to carry out the deconjugation reaction for 5-phenyl-3-pentyn-2-one to prepare (*Z*)-3-benzylidene-5-methyldihydrofuran-2-one failed under conditions in Eq 1. Only (*E*)- and (*Z*)-4-iodo-5-phenyl-3-penten-2-one were isolated in 45 and 42% yields, respectively. However, an aryl or heteroaryl group at the1-position of conjugated ynone could undergo deconjugation, reduction, carbonylation, and alcoholysis to give satisfactory results (Entries 5, 6, and 7).

The mechanism details of the reaction have not yet been clarified. However, the following **Scheme 1** predicted the structure of the only cyclic product (**3**) from the oxidative addition of **2** with palladium(0) catalyst to yield vinylpalladium iodide complex, followed by the carbon monoxide insertion into the palladium-carbon σ bond, and reductive elimination induced by the alcohol to afford **3** and regenerate the palladium(0) catalyst. It is worth noting that reports of the preparation of α-alkylidenelactones with high stereoselectivity and in high yield are scarce.

Figure 1. Phase-sensitive NOESY spectrum of compound (**3a**).



Scheme 1. Proposed mechanism for Pd-catalyzed CO insertion and cyclization of **2**.



EXPERIMENTAL SECTION

The general precedures for the preparation of ynones or ynal were followed according to the literature.[10]

General Procedure for the Conversion of 2 into 3: To a dry flask was charged under nitrogen with 1 mmol of **2**, 1 mmol of triethylamine, 5 mol % of tetrakis(triphenylphosphine)palladium(0), and 3 ml of toluene. A balloon was flushed three times with carbon monoxide and connected to a condenser attached to the reaction flask. The system was flushed with a gentle steam of carbon monoxide for 1 min and then placed in an oil bath at 50 °C for another 18 h. Upon completion of the reaction, the reaction mixture was quenched with 10 % ammonium hydroxide solution. Extraction (ether), washing (aqueous sodium chloride), drying (magnesium sulfate), concentration, and chromatography (silica gel, hexane/ethyl acetate = 9/1 and Chemcosorb 5-ODS-H, MeOH) to give **3**.

(*Z*)-3-Iodo-3-nonen-1-ol (2a): oil; 86 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.90 (t, J = 7 Hz, 3 H), 1.3 - 1.5 (m, 6 H), 2.12 (q, J = 7 Hz, 2 H), 2.70 (t, J = 7 Hz, 2 H), 3.75 (t, J = 7 Hz, 2 H), 5.65 (t, J = 7 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.98, 22.49, 27.98, 31.37, 36.49, 47.95, 60.99, 103.94, 138.58 ppm; ir (neat) 3480 (bs), 1010 (s) cm^{-1}; ms m/z 268 (M^+), 198, 181, 168; HRms calcd for $C_9H_{17}OI$ 268.0324, found 268.0321. Anal. Calcd for $C_9H_{17}OI$: C, 40.31; H, 6.39. Found: C, 40.50; H, 6.55.

(*Z*)-4-Iodo-4-decen-2-ol (2b): oil; 92 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.90 (t, J = 7 Hz, 3 H), 1.21 (d, J = 7 Hz, 3 H), 1.25 - 1.50 (m, 6 H), 1.88 (s, 1 H), 2.13 (q, J = 7 Hz, 2 H), 2.57 (d, J = 6 Hz, 2 H), 4.09 (sextet, J = 7 Hz, 1 H), 5.62 (t, J = 7 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.92, 21.79, 22.42, 27.30, 31.29, 36.37, 54.41, 65.93, 104.13, 138.49 ppm; ir (neat) 3300 (bs), 1630 (w) cm^{-1}; ms m/z 282 (M^+), 264, 238, 168; HRms calcd for $C_{10}H_{19}OI$ 282.0481, found 282.0483. Anal. Calcd for $C_{10}H_{19}OI$: C, 42.57; H, 6.79. Found: C,

42.68; H, 6.92.

(*Z*)-5-Iodoundec-5-en-3-ol (2c): oil; 88 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H), 1.2 - 1.5 (m, 6 H), 1.53 (quintet, J = 7 Hz, 2 H), 1.62 (s, 1 H), 2.11 (q, J = 7 Hz, 2 H), 2.51 (dd, J = 14, 8 Hz, 1 H), 2.64 (dd, J = 14, 3 Hz, 1 H), 3.79 - 3.87 (m, 1 H), 5.63 (t, J = 7 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 9.93, 13.98, 22.48, 27.96, 28.78, 31.34, 36.45, 52.46, 70.84, 104.47, 138.63 ppm; ir (neat) 3372 (s), 1643 (w) cm^{-1}; ms m/z 296 (M^+), 278, 238, 168; HRms calcd for $C_{11}H_{21}OI$ 296.0637, found 296.0635.

(*Z*)-8-Iodotetradec-8-en-6-ol (2d): oil; 82 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.90 (t, J = 7 Hz, 6 H), 1.25 - 1.6 (m, 14 H), 1.70 (s, 1H), 2.14 (q, J = 7 Hz, 2 H), 2.4 - 2.7 (m, 2 H), 3.8 - 4.0 (m, 1 H), 5.63 (t, J = 7Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.99 (2 x C's), 22.46, 22.56, 25.27, 27.95, 31.32, 31.79, 35.87, 36.42, 52.85, 69.53, 104.50, 138.58 ppm; ir (neat) 3390 (s) cm^{-1}; ms m/z 338 (M^+), 320, 267; HRms calcd for $C_{14}H_{27}OI$ 338.1107, found 338.1105.

(*Z*)-3-Iodo-1-phenyl-3-nonen-1-ol (2e): oil; 90 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.2 - 1.5 (m, 6 H), 1.8 (s, 1 H), 2.13 (q, J = 7 Hz, 2 H), 2.83 (d, J = 7 Hz, 2 H), 5.00 (t, J = 7 Hz, 1 H), 5.59 (t, J = 7 Hz, 1 H), 7.2 - 7.4 (m, 5 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.98, 22.48, 27.89, 31.27, 36.45, 54.99, 72.17, 103.55, 125.94, 127.66, 128.40, 139.29, 142.82 ppm; ir (neat) 3422 (s), 1601 (m), 700 (s) cm^{-1}; ms m/z 326 (M^+ - 18), 238.

(*Z*)- 3-Iodo-1-(3,4,5-trimethoxyphenyl)non-3-en-1-ol (2f): oil; 83 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.2 - 1.4 (m, 6 H), 2.13 (q, J = 7 Hz, 2 H), 2.80 - 2.83 (m, 2 H), 3.83 (s, 3 H), 3.87 (s, 6 H), 4.92 (dd, J = 7, 5 Hz, 1 H), 5.61 (t, J = 7 Hz, 1 H), 6.60 (s, 2 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.92, 22.42, 27.86, 30.85, 31.27, 36.42, 54.93, 56.08, 60.77, 72.30, 102.76, 103.47, 137.25, 138.58, 139.27, 153.19 ppm; ir (neat) 3466 (s), 1595 (s) cm^{-1}; ms m/z 434 (M^+), 416, 289, 197. Anal. Calcd for $C_{18}H_{27}O_4I$: C, 49.78; H, 6.27. Found: C, 49.89; H, 6. 42.

(*Z*)-1-Furan-2-yl-3-iodonon-3-en-1-ol (2g): oil; 79 % yield; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.2 - 1.5 (m, 6 H), 1.7 (s, 1 H), 2.12 (q, J = 7 Hz, 2 H), 2.99 (d, J = 7 Hz, 2 H), 5.01 (t, J = 7 Hz, 1 H), 5.64 (t, J = 7 Hz, 1 H), 6.27 (d, J = 3 Hz, 1 H), 6.32 (dd, J = 3, 2 Hz, 1 H), 7.38 (s, 1H) ppm; ^{13}C nmr ($CDCl_3$,TMS) δ 13.98, 22.48, 27.86, 31.25, 36.42, 50.93, 66.18, 102.26, 106.78, 110.14, 139.56, 142.18, 154.70 ppm; ir (neat) 3389 (s) cm^{-1}; ms m/z 334 (M^+), 316; HRms calcd for $C_{13}H_{19}O_2I$ 334.0430, found 334.0432. Anal. Calcd for $C_{13}H_{19}O_2I$: C, 46.72; H, 5.73. Found: C, 46.78; H, 5.88.

(*Z*)-3-Hexylidenedihydrofuran-2-one (3a): oil; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.3 - 1.5 (m, 6 H), 2.68 (q, J = 7 Hz, 2 H), 2.90 (td, J = 7, 2 Hz, 2 H), 4.31 (t, J = 7 Hz, 2 H), 6.23 (tt, J = 7, 2 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.95, 22.45, 27.44, 28.76, 29.12, 31.39, 65.23, 123.29, 144.44, 170.12 ppm; ir (neat) 1767 (s) cm^{-1}; ms m/z 168 (M^+), 139, 125; HRms calcd for $C_{10}H_{16}O_2$ 168.1150, found 168.1148. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.68.

(*Z*)-3-Hexylidene-5-methyldihydrofuran-2-one (3b): oil; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.35 - 1.50 (m with one doublet at δ 1.39, 9 H), 2.49 (ddd, J = 16, 4, 2 Hz, 1 H), 2.69 (q, J = 7 Hz, 2 H), 3.00 (ddd, J = 16, 7, 2 Hz, 1 H), 4.56 - 4.66 (m, 1 H), 6.18 (tt, J = 7, 2 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.97, 21.81, 22.47, 27.56, 28.81, 31.41, 36.91, 73.67, 124.71, 144.15, 169.81 ppm; ir (neat) 1766 (s) cm^{-1}; ms m/z 182 (M^+), 167, 153, 139; HRms calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1305. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.58; H, 10.11.

(*Z*)-5-Ethyl-3-hexylidenedihydrofuran-2-one (3c): oil; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 3 H), 0.99 (t, J = 7 Hz, 3 H), 1.25 - 1.50 (m, 6 H), 1.60 - 1.80 (m, 2 H), 2.49-2.57 (m, 1 H), 2.69 (q, J = 7 Hz, 2 H), 2.92 - 3.00 (m, 1 H), 4.39 (quintet, J = 7 Hz, 1 H), 6.17 (tt, J = 8, 2 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 9.04, 13.92, 22.40, 27.47, 28.74, 28.97, 31.34, 34.70, 78.40, 124.52, 143.99, 169.84 ppm ; ir (neat) 1751 (m) cm^{-1}; ms m/z 196 (M^+), 167, 153; HRms calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1464. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.53; H, 10.42.

(*Z*)-3-Hexylidene-5-pentyldihydrofuran-2-one (3d): oil; ^{1}H nmr ($CDCl_3$,TMS) δ 0.89 (t, J = 7 Hz, 6 H), 1.3-1.8 (m, 14 H), 1.6 - 1.8 (m, 2 H), 2.52 (ddq, J = 16, 6, 2 Hz, 1 H), 2.69 (q, J = 7 Hz, 2 H), 2.95 (ddd, J = 16, 7, 1.4 Hz, 1 H), 4.44 (quintet, J = 7 Hz, 1 H), 6.17 (tt, J = 8, 2 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.94, 22.46, 24.55, 27.50, 28.78, 31.37, 31.49, 35.25, 36.09, 77.33, 124.59, 143.98, 169.87 ppm; ir (neat) 1754 (s), 1671 (m), 1185 (s) cm^{-1}; ms m/z 238 (M^+), 195; HRms calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1930. Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.70; H, 11.17.

(*Z*)-3-Hexylidene-5-phenyldihydrofuran-2-one (3e): oil; ^{1}H nmr ($CDCl_3$,TMS) δ 0.90 (t, J = 7 Hz, 3 H), 1.3-1.5 (m, 6 H), 2.75 (q, J = 7 Hz, 2 H), 2.87 (ddd, J = 16, 5, 2 Hz, 1 H), 3.30 (ddd, J = 16, 8, 2 Hz, 1 H), 5.47 (t, J = 7 Hz, 1 H), 6.23 (tt, J = 7, 2 Hz, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 14.00, 22.48, 27.64, 28.78, 31.43,

38.01, 77.86, 124.04, 125.41, 128.36, 128.74, 140.21, 144.68, 169.58 ppm; ir (neat) 1756 (s), 1670 (m) cm^{-1}; ms m/z 244 (M^+), 173; HRms calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1461. Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.77; H, 8.42.

(*Z*)-3-Hexylidene-5-(3,4,5-trimethoxyphenyl)dihydrofuran-2-one (3f): oil; ^1H nmr ($CDCl_3$, TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.3 - 1.5 (m, 6 H), 2.75 (q, J = 7 Hz, 2 H), 2.8 - 2.9 (m, 1 H), 3.29 (ddd, J = 16, 8, 1.3 Hz, 1 H), 5.40 (t, J = 7 Hz, 1 H), 6.26 (tt, J = 8, 2 Hz, 1 H), 6.54 (s, 2 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.86, 22.35, 27.55, 28.65, 31.30, 37.99, 56.07, 60.72, 77.81, 102.16, 123.91, 135.73, 137.71, 144.71, 153.42, 169.42 ppm; ir (neat) 1754 (s), 1669 (m) cm^{-1}; ms m/z 334 (M^+). Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.40; H, 7.96.

(*Z*)-4-Hexylidene-3,4-dihydro-2*H*-[2,2']bifuranyl-5-one (3g): oil; ^1H nmr ($CDCl_3$, TMS) δ 0.89 (t, J = 7 Hz, 3 H), 1.2 - 1.5 (m, 6 H), 2.73 (q, J = 7 Hz, 2 H), 3.16 (dd, J = 7, 2 Hz, 2 H), 5.44 (t, J = 7 Hz, 1 H), 6.28 (tt, J = 7, 2 Hz, 1 H), 6.3 - 6.4 (m, 2 H), 7.42 (s, 1 H) ppm; ^{13}C nmr ($CDCl_3$, TMS) δ 13.94, 22.42, 27.53, 28.68, 31.35, 33.60, 71.09, 109.00, 110.41, 123.56, 143,35, 144.38, 151.35, 168.89 ppm; ir (neat) 1760 (s), 1670 (m) cm^{-1}; ms m/z 234 (M^+), 189; HRms calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1255. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.89; H, 7.87.

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