A Facile Method for the Preparation of γ-Alkenyl-γ-butyrolactones

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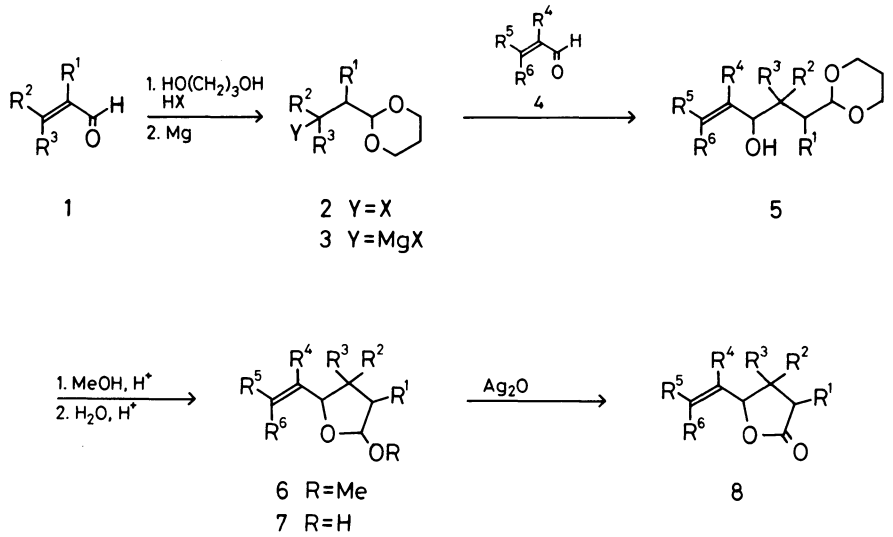
Synopsis. Methyl substituted γ-alkenyl-γ-butyrolactones were prepared from easily available α,β-unsaturated aldehydes such as acrylaldehyde, methacrylaldehyde, crotonaldehyde, and 3-methyl-2-butenal.

The structure of γ-alkenyl-γ-butyrolactones belongs to a kind of allylic esters and the lactones have been utilized to many synthetic reactions. For example, allylic substitutions of the lactones with organocopper reagents,[1] with ester enolate,[2] and with allylsilanes[3] leading to 4-alkenoic acids and 4,8-alkadienoic acid esters have been developed. Moreover γ-alkenyl-γ-butyrolactones have been incorporated in important key compounds for the synthesis of natural products such as ipsdienol,[4] biotin,[5] urinary metabolites of retinoic acid,[6] chrysanthemic acid,[7] avenaciolide,[8] marmelo oxide,[9] and dihydromevinolin.[10] The lactones have been prepared by many methods[11] such as condensation of vinyl epoxide with ethyl cyanoacetate and with diethyl malonate, decarboxylation of 2-vinyl-1,1-cyclopropanedicarboxylic acid prepared from 1,4-dibromo-2-butene and diethyl malonate, and reaction of 1,3-diene with carboxylic acid in the presence of metal oxide, however, these methods seem to have a limitation at the point of generality in which the kinds of applicable starting materials are confined. Here we wish to report the convenient method for the synthesis of methyl-substituted γ-alkenyl-γ-butyrolactones by the combination of easily available starting materials, two molecules of α,β-unsaturated aldehydes such as acrylaldehyde, methacrylaldehyde, crotonaldehyde, and 3-methyl-2-butenal.[12] General synthetic route was outlined in Scheme 1.

Although all of the aldehydes **1** are easily converted to the corresponding bromo acetal according to the published method for the preparation of 2-(2-bromoethyl)-1,3-dioxane (**2a**) from acrylaldehyde, 1,3-propanediol, and anhydrous hydrogen bromide,[13] crotonaldehyde and 3-methyl-2-butenal were transformed into the corresponding chloro acetals, which are preferable in the preparation of secondary and tertiary Grignard reagents rather than the corresponding bromo acetal. In the acetalization of 3-methyl-2-butenal, hydrochlorination was carried out in the presence of tetrabutylammonium chloride and Molecular Sieves 3A to improve the yields. These bromo and chloro acetals **2** were converted into the corresponding Grignard reagents **3** by the usual method.[13] Then the reactions of Grignard reagents **3** with aldehydes **4** gave the allylic alcohols **5** in high or moderate yields. An attempt of direct hydrolysis of **5** to lactol **7** in aqueous media unfortunately did not succeed even in a mixed solvent such as acetone–water because of the poor solubility in water except for the case of **5a**. Therefore the alcohols **5** were converted to lactol ether **6** in acidic methanol followed by hydrolysis of **6** in acidic aqueous acetone to give lactol **7** in moderate yields without accompanying a tautomer of the lactol, γ-hydroxy aldehyde. In the last oxidation step of **7** to **8**, silver oxide, prepared in situ from silver nitrate and sodium hydroxide, was used as the suitable oxidant which did not oxidize carbon–carbon double bond. The diastereomer ratios of the lactones **8b** and **8c** were determined by GLC analysis as 43:57 and 79:21, respectively. Unfortunately, assignment of the configurations of these lactones did not succeed. To reveal the utility of this method for the preparation of γ-alkenyl-γ-butyrolactone, a precursor **8e**[7] of chrysanthemic acid was synthesized from 3-methyl-2-butenal as the starting material.



Scheme 1.

Table 1. Preparation of γ-Alkenyl-γ-butyrolactones

Run	R^1	R^2	R^3	R^4	R^5	R^6	Yield/% 2	3	5	6	7	8
a	H	H	H	H	H	H	—	—	46[a]	—	53[b]	90
b	Me	H	H	Me	H	H	60(X=Br)	74	91	71	75	47
c	H	Me	H	Me	H	H	100(X=Cl)	68	74	65	52	41
d	H	H	H	Me	H	H	—	—	70[a]	68	69	83
e	H	Me	Me	H	Me	Me	68(X=Cl)	41	61	66	68	43

a) The yields were calculated from **1a**. b) The yield was calculated from **5a**.

Results for the synthesis of **8** were summarized in Table 1.

As described above, this method for the preparation of γ-alkenyl-γ-butyrolactone has the following advantages; (i) easy availabilities of starting materials and the other reagents, (ii) simple procedure and operations, (iii) generality for the preparation of various substituted γ-alkenyl-γ-butyrolactones.

Experimental

General. Boiling points were measured at the pressure indicated and are uncorrected. Infrared spectra (neat) were recorded on a Hitachi EPI-G2 spectrometer. ^{1}H NMR spectra were recorded on a JEOL JNM-PMX60SI spectrometer with Me_4Si as an internal standard in CCl_4. GLC analysis was performed on a Yanaco G-180 Gas Chromatograph.

Materials. Acrylaldehyde, methacrylaldehyde, crotonaldehyde, 3-methyl-2-butenal, 2-(2-bromoethyl)-1,3-dioxane, and the other reagents were commercially available.

Acetalization of Aldehydes 1b,c,e to 2b,c,e. According to the reported procedure[13] for the preparation of **2a**, 2-(2-bromo-1-methylethyl)-1,3-dioxane (**2b**) was prepared from methacrylaldehyde, 1,3-propanediol, and anhydrous HBr. In the similar manner as the preparation of **2b**, the other chloro acetals **2c** and **2e** were prepared from crotonaldehyde and 3-methyl-2-butenal, respectively, by the treatment with 1,3-propanediol saturated with anhydrous HCl in the presence of a half mole of tetrabutylammonium chloride. **2b**: bp 61—62 °C/0.5 mmHg (1 mmHg=133.322 Pa); ^{1}H NMR δ=1.02 (d, J=7 Hz, 3H), 0.83—2.43 (m, 3H), 3.08—4.28 (m, 6H), and 4.39 (d, J=5 Hz, 1H); IR 1145 (s), 1110 (s), and 1015 (s) cm^{-1}; Found: C, 40.46; H, 6.48%. Calcd for $C_7H_{13}BrO_2$: C, 40.21; H, 6.27%. **2c**: bp 63—64 °C/5 mmHg; ^{1}H NMR δ=1.05—2.53 (m, 2H), 1.48 (d, J=7 Hz, 3H), 1.93 (dd, J=5 Hz, 6 Hz, 2H), 3.47—4.50 (m, 5H), and 4.68 (t, J=5 Hz, 1H); IR 1140 (s), 1105 (s), 1080 (s), 1030 (s), 1000 (s), and 620 (s) cm^{-1}; Found: C, 50.94; H, 8.00%. Calcd for $C_7H_{13}ClO_2$: C, 51.07; H, 7.96%. **2e**: bp 68—70 °C/1.5 mmHg; ^{1}H NMR δ=0.82—2.43 (m, 2H), 1.55 (s, 6H), 1.96 (d, J=4.5 Hz, 2H), 3.40—4.21 (m, 4H), and 4.65 (t, J=4.5 Hz, 1H); IR 1145 (s), 1130 (s), 1115 (s), 1085 (s), and 990 (s) cm^{-1}; Found: C, 53.84; H, 8.46%. Calcd for $C_8H_{15}ClO_2$: C, 53.78; H, 8.46%.

Preparation of Grignard Reagents 3a—e. Grignard reagents **3a—e** were prepared from **2a—e**, respectively, by the treatment with magnesium turning in gently refluxing THF in the similar manner to the published procedure[13] and standardized by titration with 2-butanol using 1,10-phenanthroline as an indicator.[14]

Preparation of the Allylic Alcohols 5a—e. To the THF solution of **3a** (145 ml, 170 mmol) was added a solution of **1a** (10.0 g, 178 mmol) in THF (50 ml) at 0 °C and stirred at the same temperature for 3 h. Then the mixture was quenched by pouring into saturated aq. NH_4Cl and the layer were separated. The aqueous phase was washed three times with ether and the combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated. Distillation of the residue under a reduced pressure gave 2-(3-hydroxy-4-pentenyl)-1,3-dioxane (**5a**) (18.6 g, 108 mmol): bp 100—102 °C/1.5 mmHg; ^{1}H NMR δ=1.00—2.48 (m, 6H), 3.17 (s, 1H), 3.40—4.30 (m, 5H), 4.30—4.73 (m, 1H), and 4.85—6.14 (m, 3H); IR 3450 (s), 1145 (s), 1090 (s), 990 (s), and 925 (s) cm^{-1}; Found: C, 62.92; H, 9.48%. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36%.

In exactly the same manner as above, methyl-substituted analogues **5b—e** were prepared. **5b**: bp 125—127 °C/1.5 mmHg; ^{1}H NMR δ=0.75—2.47 (m, 5H), 0.93 (d, J=6 Hz, 3H), 1.70 (br s, 3H), 3.10 (s, 1H), 3.40—4.56 (m, 6H), 4.75 (br s, 1H), and 4.88 (br s, 1H); IR 3450 (s), 1145 (s), 1120 (s), 1100 (s), 1050 (s), 1000 (s), and 890 (s) cm^{-1}; Found: C, 65.68; H, 10.17%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%. **5c**: bp 102—104 °C/0.4 mmHg; ^{1}H NMR δ=0.83 (d, J=6 Hz, 3H), 1.05—2.45 (m, 5H), 1.63 (s, 3H), 3.04 (s, 1H), 3.28—4.25 (m, 5H), 4.51 (t, J=5 Hz, 1H), and 4.65—5.00 (m, 2H); IR 3425 (s), 1140 (s), 1105 (s), 1070 (s), 1015 (s), 990 (s), and 890 (s) cm^{-1}; Found: C, 65.70; H, 10.17%. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07%. **5d**: bp 116—118 °C/1 mmHg; ^{1}H NMR δ=0.77—2.47 (m, 9H), 2.83 (s, 1H), 3.30—4.30 (m, 5H), 4.33—4.63 (m, 1H), 4.76 (d, J=1.5 Hz, 1H), and 4.88 (d, J=1.5 Hz, 1H); IR 3450 (s), 1140 (s), 1085 (s), 990 (s), and 890 (s) cm^{-1}; Found: C, 64.56; H, 9.90%. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%. **5e**: bp 135—138 °C/1.5 mmHg; ^{1}H NMR δ=0.75—2.47 (m, 4H), 0.90 (s, 3H), 0.93 (s, 3H), 1.67 (s, 3H), 1.75 (s, 3H), 2.91 (s, 1H), 3.47—4.33 (m, 5H), 4.67 (t, J=5 Hz, 1H), and 5.25 (d, J=9 Hz, 1H); IR 3500 (s), 1140 (s), 1085 (s), 1035 (s), 1000 (s), 985 (s), and 820 (m) cm^{-1}; Found: C, 68.08; H, 10.66%. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.60%.

Preparation of Lactol Ether 6b—e. A solution of **5b** (1.70 g, 8.49 mmol) in MeOH (40 ml) was acidified with 2 drops of 6 M HCl (1 M=1 mol dm^{-3}) and stirred at room temperature for 12 h. After neutralization with saturated aq. $NaHCO_3$, ether was added to the mixture. The organic layer was separated and the aqueous layer was washed three times with ether. The combined extracts were washed with water. After the solution was dried with anhydrous $MgSO_4$ and concentrated, distillation of the residue under the reduced pressure afforded 2-methoxy-3-methyl-5-isopropenyltetrahydrofuran (**6b**) (940 mg, 6.01 mmol): bp 69—71 °C/24 mmHg; ^{1}H NMR δ=1.01 (br d, J=7 Hz, 3H), 1.23—2.37 (m, 3H), 1.69 (br s, 3H), 3.27 (s, 3H), 4.13—4.63 (m, 2H), 4.70 (br s, 1H), and 4.90 (br s, 1H); IR 1100 (s), 1070 (s), 1010 (s), and 895 (s) cm^{-1}; Found: C, 69.11; H, 10.48%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%.

In the same manner as above, methyl-substituted analogues **6c—e** were prepared. **6c**: bp 75—78 °C/22 mmHg; ^{1}H NMR δ=0.63—1.17 (m, 3H), 1.33—2.63 (m, 6H), 3.23 (s, 3H), 3.67—3.97 (m, 0.6H), 4.18—4.45 (m, 0.6H), and 4.67—5.10 (m, 2.8H); IR 1100 (s), 1070 (s), 1030 (s), and 895 (s) cm^{-1}; Found: C, 68.91; H, 10.37%. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32%. **6d**: bp 73—75 °C/30 mmHg; ^{1}H NMR δ=1.42—2.33 (m, 7H), 3.32 (s, 3H), 4.42 (br t, J=7 Hz, 1H), 4.77 (br s, 1H), and 4.85—5.13 (m, 2H); IR 1205 (s), 1105 (s), 1050 (s), 1035 (s), and 895 (s) cm^{-1}; Found: C, 67.33; H,

10.06%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%. **6e**: bp 105—110 °C/33 mmHg; ^{1}H NMR δ=0.85 (s, 3H), 0.98 (s, 3H), 1.47—2.17 (m, 2H), 1.70 (s, 3H), 1.77 (s, 3H), 3.25 (s, 3H), 4.07—4.40 (m, 1H), 4.82 (t, J=5 Hz, 1H), and 5.05 (d, J=8 Hz, 1H); IR 1100 (s), 1050 (s), 1030 (s), 1000 (s), 980 (s), and 840 (s) cm^{-1}; Found: C, 71.98; H, 11.00%. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94%.

Hydrolysis of 5a and 6b—e to Lactol 7a—e. A solution of **5a** (1.34 g, 7.77 mmol) in 10% H_2SO_4 (45 ml) and stirred at room temperature for 12 h. The mixture was extracted three times with ether. After the extracts were washed with brine, dried with anhydrous $MgSO_4$, and concentrated, distillation of the residue under a reduced pressure afforded 2-hydroxy-5-vinyltetrahydrofuran (**7a**) (474 mg, 4.15 mmol): bp 80—100 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.00—2.65 (m, 4H), 3.75 (br s, 1H), 4.17—4.80 (m, 1H), and 4.83—6.25 (m, 4H); IR 3420 (s), 1050 (s), 1020 (s), 990 (s), and 925 (s) cm^{-1}; Found: C, 63.37; H, 9.02%. Calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83%.

In the same manner as above, methyl-substituted analogues **7b—e** were prepared. **7b**: bp 60—70 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.05 (br d, J=6 Hz, 3H), 1.23—2.57 (m, 3H), 1.70 (br s, 3H), and 4.05—5.43 (m, 5H); IR 3425 (s), 1075 (s), 1040 (s), 1000 (s), 990 (s), and 895 (s) cm^{-1}; Found: C, 67.47; H, 9.96%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%. **7c**: bp 65—70 °C/1.5 mmHg; ^{1}H NMR δ=0.73—1.17 (m, 3H), 1.17—2.76 (m, 6H), and 3.65—5.75 (m, 5H); IR 3425 (s), 1090 (s), 1070 (s), 1050 (s), 1010 (s), 980 (s), and 895 (s) cm^{-1}; Found: C, 67.37; H, 9.97%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%. **7d**: bp 100—120 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.50—2.17 (m, 7H), 4.10—5.13 (m, 4H), and 5.17—5.73 (m, 1H); IR 3425 (s), 1060 (s), 1045 (s), 1000 (s), 980 (s), and 895 (s) cm^{-1}; Found: C, 65.55; H, 9.47%. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44%. **7e**: mp 65—70 °C; bp 70-85 °C/1.5 mmHg; ^{1}H NMR δ=0.87 (s, 3H), 1.00 (s, 3H), 1.50—2.07 (m, 2H), 1.70 (s, 3H), 1.77 (s, 3H), and 4.12—5.67 (m, 4H); IR 3375 (s), 1095 (s), 1050 (s), 1025 (s), 1000 (s), 985 (s), and 840 (s) cm^{-1}; Found: C, 70.39; H, 10.72%. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%.

Oxidation of 7a—e to γ-Alkenyl-γ-butyrolactone 8a—e. To a solution of silver nitrate (780 mg, 4.59 mmol) in water (1 ml), 6.51 M NaOH solution (1.80 ml, 11.7 mmol) was added at room temperature. The mixture was heated to 50 °C and methanol (1 ml) was added. After being cooled to 0 °C, a solution of **7a** (262 mg, 2.29 mmol) in MeOH (2 ml) was added to the suspension of silver oxide. The reaction mixture was stirred at 40 °C for 12 h. After being cooled to room temperature and acidified with 10% H_2SO_4, the mixture was extracted with $CHCl_3$. The extracts were washed with water and brine, dried with anhydrous $MgSO_4$, and concentrated. Distillation of the residue gave 5-vinyltetrahydro-2-furanone (**8a**)[11b] (232 mg, 2.07 mmol): bp 100—120 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.78—3.15 (m, 4H), 4.78—6.20 (m, 4H); IR 1775 (s) and 980 (s) cm^{-1}.

In the same manner as above, methyl-substituted analogues **8b—e** were prepared. Determination of the diastereomer ratios of the lactones **8b** and **8c** was performed by analytical GLC (0.25 mm×50 m FFAP column, 120 °C, relative retention time was 1.00:1.01 and 1.00:1.07, respectively. **8b**: bp 120—130 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.25 (d, J=7 Hz, 3H), 1.50—3.05 (m, 3H), 1.75 (s, 3H), 4.54—5.20 (m, 3H); IR 1775 (s) and 900 (s) cm^{-1}; Found: C, 68.77; H, 8.55%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%. **8c**: bp 120—130 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=0.79—1.27 (m, 3H), 1.75 (s, 3H), 1.80—2.93 (m, 3H), 4.25—4.60 (m, 1H), 4.98 (br s, 2H); IR 1780 (s) and 910 (s) cm^{-1}; Found: C, 68.36; H, 8.74%. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63%. **8d**: bp 110—130 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.76 (s, 3H), 1.80—2.77 (m, 4H), 4.70—5.18 (m, 3H); IR 1770 (s) and 900 (s) cm^{-1}; Found: C, 66.54; H, 8.11%. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99%. **8e**:[7] mp 45—50 °C; bp 130—150 °C/1.5 mmHg (Kugelrohr); ^{1}H NMR δ=1.00 (s, 3H), 1.12 (s, 3H), 1.73 (s, 3H), 1.80 (s, 3H), 2.31 (s, 1H), 2.34 (s, 1H), 4.78 (d, J=9 Hz, 1H), 5.19 (br d, J=9 Hz, 1H); IR 1775 (s) and 850 (m) cm^{-1}.

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