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Studies on New Synthetic Pathways to $\Delta^{\alpha,\beta}$-Butenolides from α-Methylbutanolides. II.[1] Electrolytic Oxidation of Simple α-Carboxy-α-methylbutanolides

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A new approach to the synthesis of $\Delta^{\alpha,\beta}$-butenolides from γ-butanolides by means of the electrolytic oxidation of α-carboxy-α,γ-dimethyl-γ-butyrolactone (**3b**) and its α-carboxy-α-methyl analog (**3d**) resulted in predominant formation of the endocyclic $\Delta^{\alpha,\beta}$-isomers, α-methyl-$\Delta^{\alpha,\beta}$-γ-valerolactone (**5a**) and α-methyl-$\Delta^{\alpha,\beta}$-γ-butenolide (**5c**), accompanied by the exocyclic $\Delta^{\alpha,\beta}$-isomers, α-methylene-γ-valerolactone (**5b**) and α-methylene-γ-butanolide (**5d**), respectively, under various conditions.

The conventional oxidation of α-phenylseleno- (**4a**) and α-phenylthio-α-methyl-γ-valerolactone (**4b**) was found to yield a mixture of **5a** and **5b**.

The regiospecific preparation of the *endo*-isomer (**5a**) was ultimately achieved by the use of sequential reactions reported earlier, starting from α-methyl-γ-valerolactone (**1a**) *via* α-methoxycarbonyl- (**3a**), α-carboxy- (**3b**), and α-bromo-α-methyl-γ-valerolactone (**3c**).

Keywords——simple α-methyl-$\Delta^{\alpha,\beta}$-butenolides; electrolytic oxidation; α-carboxy-α-methyl-γ-butanolides; regiospecific preparation; phenylselenenylation method; simple α-methylene-γ-butyrolactones

Various substances possessing a $\Delta^{\alpha,\beta}$-butenolide moiety have been found in nature; for example, protoanemonin,[3a] patulin,[3b] ascaridol,[3c] lichesterinic acid,[3d] penicillic acid,[3e] and cardenolide.[3f] Since most of these α,β-unsaturated lactones are biologically active,[3] the transformation of butanolides to $\Delta^{\alpha,\beta}$-butenolides has received considerable attention. The conversion of simple and fused γ-butyrolactones to the corresponding endocyclic α,β-unsaturated derivatives seems to require rather drastic conditions.[4a,4b] However, in our previous synthesis of α-methyl-$\Delta^{\alpha,\beta}$-butenolide (**5c**) from α-methylbutanolide (**1c**) through sequential alkoxycarbonylation, decarboxylative bromination, and dehydrobromination,[1] α-methoxycarbonyl-α-methyl-γ-valerolactone (**3a**) was converted to α,γ-dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**5e**) *via* the α-bromo intermediate (**3c**), starting from γ-valerolactone (**1b**). In order to compare the above method with the known phenylsulfenylation or phenylselenenylation method,[5] we attempted to utilize the phenylselenenylation method for the formation of the endocyclic isomer (**5a**) from the simple α-methyl-γ-valerolactone (**1a**); exocyclic isomers are predominantly produced in the cases of certain fused α-methylbutanolides. The *endo*-type isomer (**5a**), accompanied by the *exo*-type isomer, α-methylene-γ-valerolactone (**5b**), was obtained by the conventional method. However, the separation of the desired *endo*-isomer

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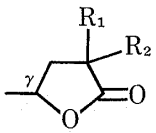
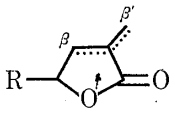

1a: $R_1=CH_3$, $R_2=H$
1b: $R_1=H$, $R_2=H$
1c: 1a(γ-H)
2a: $R_1=H$, $R_2=COOCH_3$
2b: $R_1=H$, $R_2=COOH$
2c: $R_1=H$, $R_2=Br$
3a: $R_1=CH_3$, $R_2=COOCH_3$
3b: $R_1=CH_3$, $R_2=COOH$
3c: $R_1=CH_3$, $R_2=Br$
3d: 3b(γ-H)
4a: $R_1=CH_3$, $R_2=SeC_6H_5$
4b: $R_1=CH_3$, $R_2=SC_6H_5$
5a: $R=CH_3(\Delta^{\alpha,\beta})$
5b: $R=CH_3(\Delta^{\alpha,\beta'})$
5c: $R=H(\Delta^{\alpha\beta,})$
5d: $R=H(\Delta^{\alpha,\beta'})$

Chart 1

from the mixture with the *exo*-isomer is often difficult in the preparation of simple α-methyl-$\Delta^{\alpha,\beta}$-butenolides.

Electrolytic oxidation of α-carboxy-α-methyl-γ-butyrolactones was therfore examined, with the aim of developing a regiospecific reaction favoring the formation of the *endo*-isomer.

Results and Discussion

Treatment of γ-valerolactone (**1b**) with dimethyl carbonate in the presence of sodium bydride gave α-methoxycarbonyl-γ-valerolactone (**2a**), which, on hydrolysis with dilute acid, afforded the lactone acid (**2b**) in nearly quantitative yield. Alkylation of **2a** with methyl iodide furnished α-methoxycarbonyl-α-methyl-γ-valerolactone(**3a**), which was smoothly hydrolyzed with dilute acid or alkali to α-carboxy-α-methyl-γ-valerolactone (**3b**). Subsequent decarboxylative bromination of **3b** by the action of bromine in hot carbon tetrachloride in the presence of mercuric oxide afforded α-bromo-α-methyl-γ-lactone (**3c**) in almost quantitative yield.[1] The steric relationship between the newly introduced α-bromine atom and γ-methyl group in **3c** was assumed to be *cis*, since the γ-methyl and γ-hydrogen signals in the proton nuclear magnetic resonance (PMR) spectrum were shifted towards lower and higher field (Δ +0.19 and −0.26), respectively, compared with those of the non-brominated α-methyl-γ-lactone (**1a**). When the bromolactone (**3c**) was dehydrobrominated with diazabicycloundecene (DBU) in benzene, the desired *endo*-type $\Delta^{\alpha,\beta}$-butenolide (**5a**) was obtained without formation of the undesired *exo*-type $\Delta^{\alpha,\beta}$-isomer (**5b**), as indicated by the absence of the characteristic PMR signals of the *exo*-methylene group. The overall yield of **5a** from **1b** or **1a** *via* **3a**, **3b** and **3c** was approximately 30% on average.

The reaction of α-methyl-γ-valerolactone (**1a**) with diphenyl diselenide in the presence of lithium diisopropylamide at −78° afforded phenylselenolactone (**4a**). As in the case of the bromo analog (**3c**), the introduced α-phenylseleno group and γ-methyl group in **4a** are considered to be in a *cis* relationship because of the shifts of the γ-methyl and γ-hydrogen signals (Δ +0.11 and −0.40) in its PMR spectrum. This phenylseleno derivative (**4a**) was further treated with 30% hydrogen peroxide at room temperature to give a hard-to-separate mixture of **5a** and **5b** (*endo*/*exo*=9/1) in about 20% overall yield from **1a**.[6] Thus, our synthetic method, involving a modified Hunsdicker reaction,[1] seems to be more effective than the conventional method[5,6] for the preparation of the *endo*-type product without concomitant production of the *exo*-type isomer.

As far as we are aware, there has been no report on the application of electrolysis to the α-carboxy-γ-butyrolactone system.[7] This starting material is easily prepared by the

6) B.M. Trost and T.N. Salzmann [*J. Am. Chem. Soc.*, **95**, 6840 (1973)] stated that a mixture of **5a** and **5b** (*endo*/*exo*=7/1) was obtained by thermolysis of the α-methylthio derivative of **1a** in 70% overall yield.
7) S. Torii, T. Okamoto, and H. Tanaka [*J. Org. Chem.*, **39**, 2486 (1974)] described the electrolysis of the β-carboxy-γ-butyrolactone system.

reaction of epoxides with sodiomalonates or sodiomethyl malonates.[8] On the other hand, when an α-methyl-γ-butyrolactone system is readily available, α-carboxy-lactones can be directly prepared as described above by means of α-alkoxycarbonylation[1,9] or α-carboxylation[9] of α-methylbutanolides. α-Carboxy-α-methyl-γ-butanolides thus obtained were subjected to electrolytic oxidation as described below for the preparation of α-methyl-$\Delta^{\alpha,\beta}$-butenolides.

Table I. Electrolytic Oxidation of α-Carboxy-α-methyl-butanolides

Compd.	Solvent ratio			Product ratio			Yield (%)
	Pyridine	H_2O	Et_3N	**5a**	**5b**	**1a**	
3b-Na	30	4	0.3	3	1	0	40
3b-Na	30	4	0.4[a]	18	6	1	40
3b-K	30	4	0.4[a]	2.5	1	0	37
3d-Na[1]	30	4	0.4	3[b]	1[c]	0[d]	44

a) Crown ether, *b*) **5c**, *c*) **5d**, *d*) **1c**.

Electrolysis of the sodium or potassium salt of α-carboxy-α,γ-dimethylbutanolide (**3b**) in a mixture of pyridine and water, using triethylamine as a supporting electrolyte, with a graphite electrode, afforded the corresponding *endo*-type isomer (**5a**) (30%) together with the *exo*-type isomer (**5b**) (10%). Authentic samples of **5a** and **5b** were prepared from **3c** by our method[1] and by the known procedure for **5d**.[10] The results are shown in Table I, including that for the γ-normethyl analog, α-carboxy-α-methylbutanolide[1] (**3d**), where the corresponding *endo*-isomer[1] (**5c**), predominates over the *exo*-isomer[10] (**5d**). The ratio of *endo* to *exo* isomers (*ca.* 3: 1) was determined by comparison of the peak area of the *exo*-methylene protons appearing as doublets (J=3 Hz) at 5.64 and 6.23 ppm with that of the olefinic proton at 7.04 ppm in the PMR spectra.

The use of a catalytic amount of a crown ether, dibenzo-18-crown-6,[11] was found to enhance the rate of the electrolytic reaction, but did not affect the product ratio. Since the reaction product is very soluble in water and is sensitive to acid and base, a reasonable yield cannot be expected in the simple α-carboxy-butanolide system. Further studies on suitable materials such as electrodes, solvents supporting electrolytes, and additives may improve the yield and selectivity. The use of the latter method with the fused α-methyl-γ-butyrolactone system (*e.g.*, certain santanolides), resulting in the regiospecific introduction of the *endo*-type double bond into the lactone moiety, will be reported in the following paper.

Experimental

Melting points and boiling points are uncorrected. Infrared (IR) spectra were run on a Hitachi EPI-G3 spectrometer. PMR spectra were recorded on a JEOL JMN MH-100 spectrometer in $CDCl_3$ solutions, using tetramethylsilane (TMS) as an internal standard. The chemical shifts and coupling constants are given in ppm and Hz, respectively, and the following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and c=complex. Mass spectra (MS) were measured on a Hitachi RMS-4 spectrometer. Gas chromatography (GLC) was conducted with a JGC-1100 (FID) gas chromatograph using a glass column (0.4ϕ×50 cm) of 3% OV-17 on Chromosorb W (80—100 mesh) at 85° (injection temperature, 150°).

α-Methoxycarbonyl-γ-valerolactone (**2a**)——NaH (2 g, after washing the oil dispersion twice with dry benzene) in dry benzene (150 ml) was added to a stirred solution of γ-valerolactone (**1b**) (20 g) in anhydrous

8) E.E. van Tamelen and S.R. Bach, *J. Am. Chem. Soc.*, **80**, 3079 (1958) and references cited therein.
9) These results will be reported in the following and a subsequent paper.
10) B.A. Howie, P.E. Manni, and J.M. Cassady, *J. Med. Chem.*, **17**, 40 (1974).
11) C.J. Pederson, *J. Am. Chem. Soc.*, **89**, 7017 (1967).

$(MeO)_2CO$ (250 ml), and the mixture was gently refluxed for 3 hr. MeOH and water were successively added to the reaction mixture. The solution was acidified with dil. HOAc, saturated with NaCl, and extracted with ether. The organic layer was washed with 10% $NaHCO_3$ and satd. NaCl, and dried over $MgSO_4$. Removal of the solvent left an oil, which ,on distillation, yielded 25.05 g (79.1%) of methoxycarbonyllactone (**2a**) as a colorless oil, bp 147—150°/18 Torr. IR ν_{max}^{film} cm^{-1}: 1780, 1745, 1171, 945. *Anal.* Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.33; H, 6.40.

α-Methoxycarbonyl-α-methyl-γ-valerolactone (**3a**)——MeI (150 ml) was added dropwise to a stirred solution of **2a** (20 g) and NaH (10.5 g, after treatment as above) dissolved in dry benzene (80 ml), and the reaction mixture was heated under gentle reflux for 4—5 hr at 80° then kept overnight at room temperature. The reaction mixture was poured into ice-cooled dil. HCl and extracted with ether. The exttact was washed with 10% $Na_2S_2O_3$ (100 ml) and satd. NaCl, and dried over $MgSO_4$. Removal of the solvent left 16.57 g (84.8%) of methoxycarbonyl-lactone (**3a**) as a colorless oil, bp 125—135°/10 Torr. IR ν_{max}^{film} cm^{-1}: 1775, 1745, 1273, 1191, 1102, 1065, 960. *Anal.* Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.82; H, 7.01.

α-Carboxy-α-methyl-γ-valerolactone (**3b**)——a) Conc. HCl (14 ml) was added to a solution of **3a** (5 g) in dioxane (14 ml), and the mixture was gently refluxed for 1 hr. Removal of the solvent gave an oil, which was dissolved in 10% $NaHCO_3$, and the solution was washed with ether. The aqueous solution was acidified with dil. HCl under ice cooling and extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvent was evaporated off to give 4.13 g (70.4%) of carboxylactone (**3b**) as an oil, IR ν_{max}^{film} cm^{-1}: 2500—3400 (broad), 1700—1787 (broad). b) A solution of **3a** (0.5 g) in 10% KOH—MeOH (10 ml) was stirred for 48 hr at room temperature. After removal of the solvent, 10% HCl was added to the residue and the mixture was extracted with $CHCl_3$. The $CHCl_3$ soln. was dried and concentrated *in vacuo* to give 0.44 g (98%) of **3b**, which was identical with the sample obtained above.

Decarboxylation of α-Carboxy-α-methyl-γ-valerolactone (**3b**)——**3b** (0.58 g) was heated in an oil bath at 165—170° until no further evolution of CO_2 was observed (10 min). The product was distilled to give 0.37 g (64.1%) of α-methyl-γ-valerolactone (**1a**) as a colorless oil, bp 172—174°/23 Torr (bp 204—204.5°[12]). IR ν_{max}^{film} cm^{-1}: 1776, 1771, 1180, 1045, 951. PMR δ: 1.27 (3H, d, J=7), 1.14 (3H, d, J=7), 2.05 (1H, q), 2.63 (2H, m), 5.02 (1H, m). *Anal.* Calcd for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.10; H, 8.78.

α-Bromo-α-methyl-γ-valerolactone (**3c**)——Br_2 (0.63 g) in 20 ml of CCl_4 was added dropwise to a mixture of **3b** (0.63 g), HgO (0.84 g), and CCl_4 (50 ml), and the mixture was refluxed for 1.5 hr. After removal of inorganic solids and the solvent, the residual oil was distilled to give 0.6 g (78%) of bromolactone (**3c**) as a colorless oil. $C_6H_9BrO_2$, MS *m/e*: 192.108 (M^+). bp 80—85°/35 Torr. IR ν_{max}^{film} cm^{-1}: 1785, 1781, 1201, 1190, 1094, 954. PMR δ: 1.46 (3H, d, J=6), 1.94 (3H, s), 1.92 (1H, d, J=8; d, J=15), 2.76 (1H, d, J=4; d, J=15), 4.76 (1H, m).

α,γ-Dimethyl-$\Delta^{\alpha,\beta}$-butenolide (**5a**)——DBU (0.95 mg) was added to a solution of **3c** (0.44 mg) in dry benzene (7 ml), and the mixture was refluxed for 3.0 hr. After filtration, the reaction mixture was extracted with ether, then the ether solution was washed with 10% HCl and satd. NaCl, and dried over $MgSO_4$. The residue obtained by removal of the ether was distilled to give dimethylbutenolide (**5a**) as a colorless oil (0.16 g, 63%), bp 100—103°/45 Torr.[13] *Anal.* Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.09; H, 7.04. PMR δ: 1.40 (3H, d, J=7), 1.89 (3H, br. s), 4.96 (1H, m), 7.02 (1H, br. s). IR ν_{max}^{film} cm^{-1}: 3075, 1761, 1660.

α-Methylene-γ-valerolactone (**5b**)——Triphenyl phosphine (5.24 g) was added to a solution of **2c** (3.3 g) in dry tetrahydrofuran (THF) (8 ml) and the mixture was refluxed for 3 hr under nitrogen. The crystalline phosphonium bromide that precipitated (6.85 g, 80%) was collected. A stirred aqueous suspension of this salt (4.7 g) in water (15 ml) was treated dropwise with 10% NaOH (4.9 ml) under ice-cooling, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with satd. NaCl and dried over $MgSO_4$. After removal of the solvent, a solution of the residue in CH_2Cl_2 was passed through a short column of silica gel, and elution with CH_2Cl_2 afforded α-triphenylphosophonylidene-γ-valerolactone as a crystalline powder (2.9 g, 77%). A solution of this derivative (0.54 g) in acetone (2.25 ml) containing 38% HCHO (0.3 ml) was stirred at room temperature for 23 hr. The solution was mixed with $MgSO_4$, and the organic layer was concentrated to a small volume. The insoluble material was removed by filtration, and distillation of the filtrate *in vacuo* gave α-methylenelactone (**5b**) as a colorless oil (0.08 g, 50%), bp 75°/0.45 Torr (bath temp.). *Anal.* Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.37; H, 7.10. IR ν_{max}^{film} cm^{-1}: 3095, 1756, 1662, 873. PMR δ: 1.40 (3H, d, J=7), 2.65 (2H, m), 4.68 (1H, m), 5.62 (1H, t, J=3), 6.20 (1H, t, J=3).

α-Methyl-α-phenylseleno-γ-valerolactone (**4a**)——BuLi (3.5 ml) and **1a** (0.51 g) in THF (2 ml) were added dropwise to a solution of diisopropylamine (0.55 g) in dry THF (17 ml). The lactone enolate was treated with diphenyldiselenide (1.6 g) in THF (2 ml) containing hexamethylphosphoramide (HMPA) (0.97 g) at −78°. The reaction mixture was stirred for 30 min at the same temperature, then kept at −40° for 90 min, followed by warming to room temperature. The reaction mixture was acidified with 5% HCl and extracted with ether. The ether solution was washed with satd. NaCl and dried over $MgSO_4$. The crude

12) C. Liebermann and C. Scheiber, *Chem. Ber.*, **16**, 1821 (1823).

13) deM C. Armengand [*C. R.*, **254**, 3696 (1962)] did not give any physical data except bp 91—92°/11 Torr for **5a**; his material may not have been in a pure state.

oil (2.44 g) obtained was chromatographed over silica gel to give phenylselenolactone (**4a**) as white crystals (0.38 g, 31.3%). Recrystallization from ether–petr. ether afforded an analytical sample of **4a**, mp 46—48°. IR ν_{max}^{KBr} cm^{-1}: 3050, 1770, 1580, 1440, 1200, 955, 740, 690. PMR δ: 1.38 (3H, d, J=6), 1.50 (3H, s), 1.93 (1H, d, J=9; d, J=12), 2.51 (1H, d, J=5; d, J=13), 4.62 (1H, m), 7.42—7.58 (5H, c). *Anal.* Calcd for $C_{12}H_{14}O_2$: C, 53.53; H, 5.20. Found: C, 53.87; H, 5.17.

Reaction of α-Methyl-α-phenylseleno-γ-valerolactone (4a) with Hydrogen Peroxide——A solution of **4a** (0.14 g) in THF (2.5 ml) containing a catalytic amount of HOAc was treated dropwise with 30% H_2O_2 (0.35 ml) under ice-cooling, and the mixture was stirred for 1 hr. The mixture was poured into ice-cooling satd. $NaHCO_3$ and extracted with ether. Removal of the solvent afforded a mixture of **5a** and **5b** as an oil, 0.33 g (59%). IR ν_{max}^{film} cm^{-1}: 3075, 1760, 1660. PMR δ: 1.40 (3H, d, J=7), 1.90 (3H, d, J=0.5), 4.97 (1H, q, J=7; d, J=2), 7.04 (1H, d, J=2; q, J=0.5) for **5a** in addition to 1.37 (3H, d, J=6), 2.61 (2H, m), 4.64 (1H, m), 5.64 (1H, t, J=3), 6.23 (1H, t, J=3) for **5b** [*endo*/*exo*=9/1].

General Procedure for Electrolysis——The electrolysis was carried out in a water-jacketed beaker (5 cm in diameter and 7.5 cm high) under stirreing with a magnetic stirrer. The current was controlled by manual adjustment to the required voltage. Two graphite plates were immersed into the electrolytic solution to a depth of 2—3 cm and placed parallel to each other, *ca.* 3 mm apart.

Electrolytic Oxidation of α-Carboxy-γ-valerolactone (3b)——A solution of **3b**-Na (0.31 g), Et_3N (0.3 ml), and H_2O (4 ml) in pyridine (30 ml) was electrolyzed using graphite plates as electrodes at a current of 0.01—0.25 A at room temperature for 4 hr. The reaction mixture was acidified with conc. HCl under ice-cooling, then extracted with CH_2Cl_2, and the extract was washed with 10% Na_2CO_3 and Satd. NaCl. The CH_2Cl_2 solution was evaporated to dryness *in vacuo*, and the residue was distilled to give a mixture of **5a** and **5b** as a colorless oil (0.07 g, 37%), bp 120—140°/12 Torr (bath temp.), MS *m*/*e*: 112 (M^+). IR ν_{max}^{film} cm^{-1}: 1767, 1758, 1662. The PMR spectrum was similar to that of the oxidation product of **4a** and showed this material to be a mixture of **5a** and **5b** (3: 1).

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