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A HIGHLY STEREOSELECTIVE SYNTHESIS OF ENOL-δ-LACTONES BY THE WITTIG REACTION OF GLUTARIC ANHYDRIDES WITH α-ALKOXYCARBONYLETHYLIDENETRIPHENYLPHOSPHORANE[1)]

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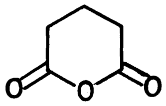
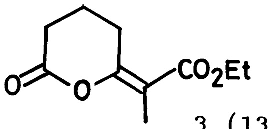
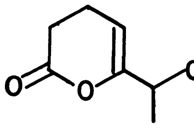
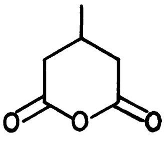
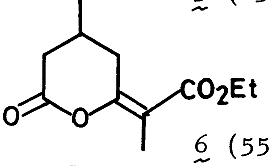
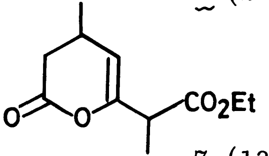
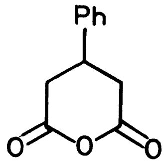
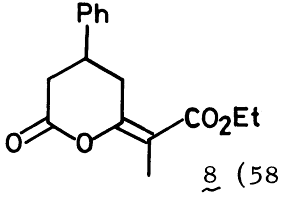
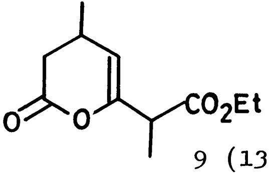
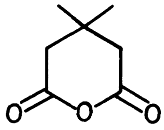
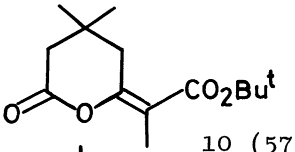
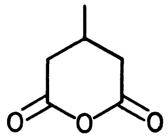
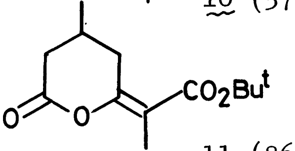
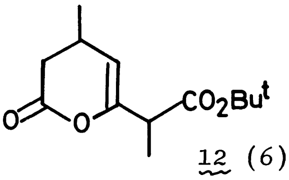
Enol-δ-lactones were prepared stereoselectively by the title reaction.

Enol-lactones occurring in nature often exhibit strong antibiotic activity and carcinogenic properties.[2)] One of the most important methods for the synthesis of enol-lactones is the Wittig reaction between stabilized phosphoranes and cyclic anhydrides.[2b)] Although this method was successfully adapted to the synthesis of enol-γ-lactones, the effort to prepare enol-δ-lactones in the similar way failed and resulted in the formation of the ring-opened products.[3)]

This communication describes the first, highly stereoselective synthesis of enol-δ-lactones by the Wittig reaction of glutaric anhydrides **1** with α-alkoxycarbonylethylidenetriphenylphosphorane. Most of the reactions of **1** with the phosphorane gave exo-enol-δ-lactone and/or endo-enol-δ-lactone as condensation products. This Wittig reaction gave exclusively one of two stereoisomers of exo-enol-δ-lactone. The stereochemistry of the exo-enol-δ-lactone was tentatively assigned as E-configuration due to the coupling constant ($J = 1.5$ Hz) between methylene protons of C_4 and methyl protons of the ethylidene group.[4)] Several examples were examined and the results are shown in Table 1.[5)] Treatment of glutaric anhydride (**1a**) with an equimolar amount of α-ethoxycarbonylethylidenetriphenylphosphorane (**2**) in refluxing chloroform for 16 h and the subsequent separation with column chromatography gave (E)-6-ethoxycarbonyl-5-hepten-5-olide (**3**)(13%) and 6-ethoxycarbonyl-4-hepten-5-olide (**4**)(20%). The reaction of **2** with β-substituted glutaric anhydrides such as **1b** and **1c** gave exo-enol-δ-lactones predominantly. However, the reaction of 3,3-dimethylglutaric anhydride (**1d**) with α-t-butoxycarbonylethylidenetriphenylphosphorane (**5**) afforded exo-enol-δ-lactone **10** in 57% yield as a single product. The Wittig reaction of **1b** with **5** gave exo-enol-δ-lactone **11** in 86% yield along with the endo-isomer **12** (6%).

In order to clarify the difference between reactivities of α-alkoxycarbonylethylidenetriphenylphosphoranes (**2** and **5**) and ethoxycarbonylmethylenetriphenylphosphorane (**13**),[3)] we reinvestigated the reaction of glutaric anhydride with **13** in chloroform and 1,2-dimethoxyethane,[3)] and obtained the same results as those reported.[3)] Therefore, it would be necessitative for the formation of the desired enol-δ-lactones that an alkylidenephosphorane has no hydrogen atom on the α-position. General applicability of the present reaction for other alkylidenephosphoranes and acid anhydrides of larger ring is currently investigated.

Table 1. Reaction of glutaric anhydrides with α-alkoxycarbonylethylidenetriphenylphosphorane, $Ph_3P{=}\underset{CH_3}{C}CO_2R$ (**2**: R = Et, **5**: R = Bu^t).

Glutaric anhydride	Phosphorane	Products$^{5)}$ (isolated yield, %)		
 **1a**	**2**	 **3** (13)	+	 **4** (20)
 **1b**	**2**	 **6** (55)	+	 **7** (12)$^{a)}$
 **1c**	**2**	 **8** (58)	+	 **9** (13)$^{b)}$
 **1d**	**5**	 **10** (57)		
 **1b**	**5**	 **11** (86)	+	 **12** (6)$^{a)}$

a) Diastereomeric mixture (by ^{13}C NMR). b) Sole product (by ^{13}C NMR).

References

1) Presented at the 43rd National Meeting of the Chemical Society of Japan, Tokyo, March 31, 1981; Abstr. 2, 907.

2) For example, see a) M. Yamamoto, Yuki Gosei Kagaku Kyokai Shi, 39, 25 (1981); b) C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, and W. D. Thorpe, Aust. J. Chem., 28, 2499 (1975), and literatures cited therein.

3) P. A. Chopard, R. J. G. Searle, and F. H. Devitt, J. Org. Chem., 30, 1015 (1965).

4) H. O. House and V. Kramar, J. Org. Chem., 28, 3362 (1963).

5) All products are new and gave satisfactory spectral data and elemental analyses. Representative data are as follows.
3: IR (neat) 1770, 1705, 1640 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.30 (t, J=7 Hz, 3), 1.90 (t, J=1.5 Hz, 3), 1.59-2.14 (m, 2), 2.61 (t, J=6 Hz, 2), 3.09 (t, J=6 Hz, 2), 4.14 (q, J=7 Hz, 2); ^{13}C NMR (CDCl$_3$) δ 11.8, 14.3, 18.0, 25.4, 30.8, 60.6, 110.0, 158.8, 167.4, 168.2.
4: IR (neat) 1770, 1740, 1700 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.21 (t, J=7 Hz, 3), 1.30 (d, J=7 Hz, 3), 2.04-2.86 (m, 4), 3.25 (q, 1), 4.10 (q, J=7 Hz, 2), 5.23 (t, J=4 Hz, 1); ^{13}C NMR (CDCl$_3$) δ 14.1, 14.5, 18.7, 28.3, 43.2, 61.1, 101.6, 151.4, 168.5, 172.0.
12: IR (neat) 1730, 1705 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.19 (d, J=6 Hz, 3), 1.43 (s, 12), 2.06-2.78 (m, 4), 3.30 (q, J=7 Hz, 1); ^{13}C NMR (CDCl$_3$) δ 12.7, 20.3, 25.8, 28.0, 40.7, 47.9, 54.1, 81.7, 169.7, 205.0.

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