SYNTHETIC ROUTE TO α-PHOSPHONO-γ-BUTYROLACTONES : SYNTHESIS OF γ-SUBSTITUTED α-METHYLENE-γ -BUTYROLACTONES

Chi-Wan Lee, Jun Mo Gil, and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and
Technology,373-1, Kusung-Dong, Yusung-Gu, Taejon, 305-701, Korea
Tel. 82-42-869-2859 Fax. 82-42-869-2810

Abstract - Treatment of lithiated homoallylic phosphonates with dimethyl carbamyl chloride gave 2-amidophosphonate derivatives. A solution of 2-amidophosphonate in DME-H_2O (2:1 vol) reacted with 2 eq. iodine at room temperature to give α-phosphono-γ-iodoalkyl-γ-butyrolactones in good yield, although the products are mixture. Wadsworth-Emmons reaction of α-phosphono-γ-iodoalkyl-γ-butyrolactones with aldehydes gave α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactone derivatives.

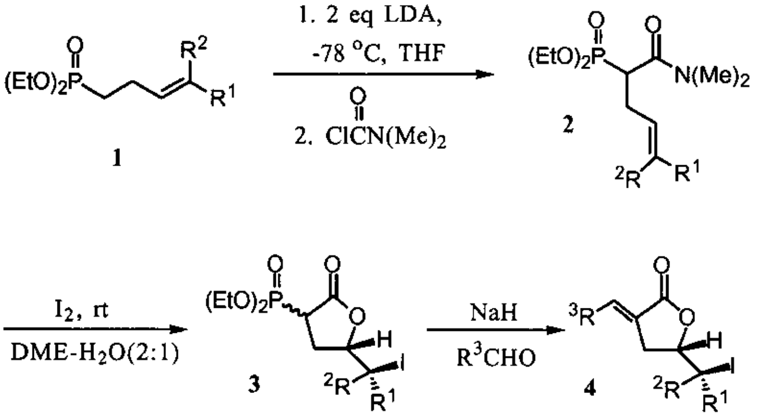
Recently there has been an increasingly large amount of research devoted to developing synthetic routes to α-methylene-γ-butyrolactones.[1] This has been due in large part to interest in several biologically active natural products, which have the α-methylenelactone moiety as a major structural feature.[2]

A general method for construction of the α-methylene-γ-butyrolactone structural units might be one in which a preformed lactone ring is converted directly *via* an "α-methylenation sequence" into the desired α-methylene-γ-butyrolactone.[3]

Much attention has been focused on the synthesis of the α-methylene unit from α-phosphono-γ-butyrolactone (**3**) which can serve as a versatile reagent not only for the introduction of the γ-butyrolactone ring, but for the syntheses of furoquinoline alkaloids and related compounds consisting of furan ring systems.[4]

There are only two literatures about the method for the preparation of α-phosphono-γ-butyrolactone (3) to our knowledge. In Buechel's report,[5] α-phosphono-γ-butyrolactone (**3**) were obtained through Arbuzov reaction from trialkyl phosphites and α-halo-γ-lactones. But this method requires a high temperature and α-halo-γ-lactones as starting material, and some of these are not easily available. And Wiemer *et al.*[6] reported a synthetic method for α-phosphonolactones, but it apparently suffers from the limitation that functional groups which are vulnerable to the organolithium reagent(LDA) may not be present.

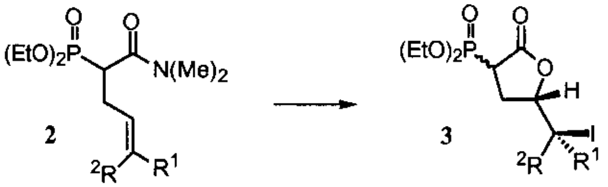
Recently, we have demonstrated that iodocyclization method is effective for the synthesis of 3-furylphosphonate,[7] 2,4-disubstituted furans[8] and β,γ-unsaturated ketones.[9] As an extension of this methods we investigated a new route to α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactones (Scheme).

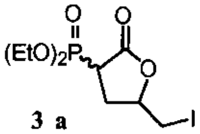


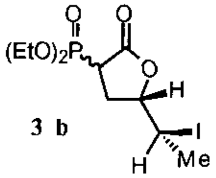
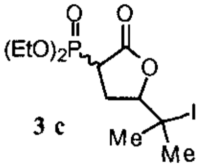
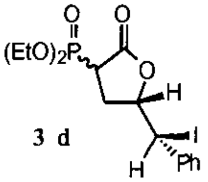
Scheme

Treatment of lithiated diethyl homoallylphosphonates (**1**) with dimethylcarbamyl chloride gave 2-amidophosphonate derivatives (**2**). **2d** was prepared as in the literature.[10] A solution of 2-amidophosphonates in DME-H_2O (2:1 vol) reacted with 2 eq. iodine at room temperature to give the mixture of α-phosphono-γ-iodoalkyl-γ-butyrolactones (**3**) in good yields. The cyclization using *N,N*-dimethylamide derivatives with iodine led to *erythro*-fused γ-butyrolactones arising from *anti* addition across the *trans* double bond. Although we could not characterized about the *erythro*-fused γ-butyrolactones (**3**) directly, we could confirm the *erythro*-fusion by the NMR research (at $R_2 = H_a$, $J_{H\text{-}Ha} = 7.0$ Hz and ^{13}C NMR showed single isomer) of the α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactone derivatives (**4**).[11] But, the stereoseletivity of the 1,3-asymmetric induction of the phosphoryl groups with the iodoakyl groups have not been showed. And, we could not characterized the *cis*- or *trans*-isomers, because the isomers were not seperated by silica gel chromatography. The result of our approach to γ-substituted α-phosphono-γ-butyrolactone (**3**) is summarized in Table 1.

Table 1. The synthesis of α-phosphono-γ-butyrolactones



R^1	R^2	product (**3**)	yield(%)[a]
H	H	 **3 a**	95

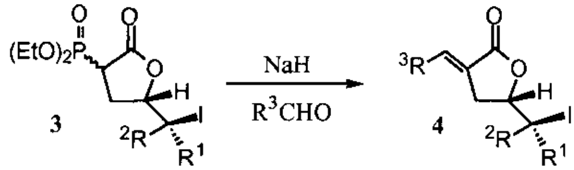
Me	H	 **3 b**	90
Me	Me	 **3 c**	89
Ph	H	 **3 d**	83

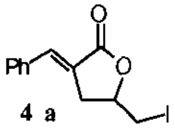
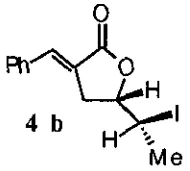
[a] Isolated yield

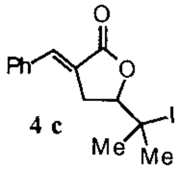
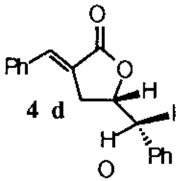
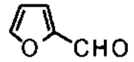
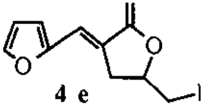
Wadsworth-Emmons reaction of α-phosphono-γ-iodoalkyl-γ-butyrolactones (**3**) with aldehydes gave the α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactone derivatives (**4**) as the single isomer. The results are summarized in Table 2.

When **4c** was treated with 3 eq. of DBU at room temperature for 12 h, dehydroiodination reaction led directly to γ-alkylidenebutenolide (**5**) which is attributed to basic isomerization of α,γ-dimethylene-γ-butyrolactone *in situ* by excess DBU. Except **4c**, however, we have found none of the desired butenolide. Instead, we obtained the complicated mixture.

Table 2. The synthesis of α-methylene-γ-butyrolactones



R^1	R^2	R^3CHO	product (**4**)	yield(%)[a]
H	H	PhCHO	 **4 a**	88
Me	H	PhCHO	 **4 b**	85

Me	Me	PhCHO	 4 c	86
Ph	H	PhCHO	 4 d	82
H	H		 4 e	84

[a] These isolated yields are not optimized.

In summary, we have developed a new alternative and mild route to α-phosphono-γ-butyrolactones (3). Although this procedure involved the well-known halocyclization, the showed route proved to be of a value since it is the first approach to the synthesis of α-phosphono-γ-butyrolactones(3) as a mixture *via* iodocyclization. And this reaction provides a new synthetic method for γ-substituted α-methylene-γ-butyrolactones.

EXPERIMENTAL SECTION

General. All reactions were conducted under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring. THF was distilled from Na/benzophenone ketyl. ^{1}H-NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$ using TMS or residual $CHCl_3$ as internal references. Diethyl butenylphosphonates (1) were synthesized as described in the literature with minor modification.[10]

General procedure for the preparation of α-phosphono-γ-iodoalkyl-γ-butyrolactones (3)
A solution of diethyl 3-butenylphosphonate (1)(0.192 g, 1 mmol) in 5 mL of THF was treated dropwise with a solution (1.1 ml) of 2 M LDA (2.2 mmol) in hexane at -78 °C. After stirring for 1 h at this temperature, a solution of *N,N*-dimethylcarbamyl chloride (0.118 g, 1.1 mmol) in 5 mL of THF was added dropwise and the reaction mixture was stirred at rt for 2 h. To the resultant solution was added saturated ammonium chloride, and the mixture was extracted with CH_2Cl_2. Then the combined organic extracts were concentrated. To a solution of 2-amidophosphonate (**2**)(0.274 g, 1 mmol) in 8 mL of DME-H_2O (2:1 vol) was added iodine (0.508 g, 2 mmol) at rt. The reaction mixture was stirred for 12 h. The resultant solution was treated with saturated sodium thiosulfate, and then extracted with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated in vacuo. The mixture was purified by silica gel chromatography (AcOEt).

α-phosphono-γ-iodomethyl-γ-butyrolactones (3a): oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.54-4.43(m, 1H), 4.16-3.99(m, 4H), 3.33-3.02(m, 3H), 2.69-2.57(m, 1H), 2.26-2.09(m, 1H), 1.23(t, 6H, J=7.02); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.47(d, J=4.15), 77.49,63.48-62.59(m), 40.00(d, J=138.15), 30.65(d, J=3.7), 16.10(d, J=5.7), 7.08 ; HRMS calcd for $C_9H_{16}O_5IP$ 361.9780 (M^+), found 361.9768. Anal. Calcd for $C_9H_{16}O_5IP$: C, 52.93 ; H, 7.89. Found: C, 53.91 ; H, 7.94.

α-phosphono-γ-iodoethyl-γ-butyrolactones (3b): oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.28-4.01(m, 5H), 3.19-3.01(m, 1H), 2.71-2.66(m, 1H), 2.30-2.16(m, 1H), 1.86(t, 3H, J=7.29), 1.26(dt, 6H, J=7.02, J=2.18); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.60(d, J=4.15), 82.52-82.12(m), 63.60-62.65(m), 40.22(d, J=137.3), 30.57(d, J=3.7), 28.6, 23.91, 16.18(m) ; HRMS Calcd $C_{10}H_{18}O_5IP$ 375.9937 (M^+), found 375.9951.

α-phosphono-γ-iodoisopropyl-γ-butyrolactones (3c): oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.27-4.09(m, 4H), 4.04-3.77(m, 1H), 3.30-3.10(m, 1H), 2.73-2.30(m, 2H), 1.93(t, 3H, J=2.76), 1.88(s, 3H), 1.41-1.21(m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.71(d, J=4.45), 86.40-85.97(m), 63.92-63.00(m), 48.99, 45.81, 33.12, 30.1, 40.23(d, J=141.75),16.36(m) ; HRMS Calcd $C_{11}H_{20}O_5IP$ 391.0093 (M^++ 1), found 390.9989.

α-phosphono-γ-iodobenzyl-γ-butyrolactones (3d): oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41-7.22(m, 5H), 5.25-5.03(m, 1H), 4.27-4.10(m, 4H), 3.24-2.86(m, 4H), 1.39-1.23(m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.60(d, J=4.15), 139.394, 138.798, 128.93-127.64(m), 81.60-81.18(m), 63.91-63.08(m), 40.78(d, J=137.3), 33.89, 31.58(d, J=3.65), 16.47-16.30(m) : HRMS Calcd $C_{15}H_{20}O_5IP$ 438.0093 (M^+), found 438.0097.

General procedure for the synthesis of α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactones (4)

To a mixture of NaH (0.036 g, 1.2 mmol) of a 80 % suspension in oil and α-phosphono-γ-iodoalkyl-γ-butyrolactones (1 mmol) in 5 mL of THF, at rt under nitrogen atmosphere, was added dropwise the carbonyl compound (1.2 mmol, neat for adding, or dissolved in 3 mL of THF for adding). After 1 h saturated NH_4Cl (5 mL) is added and the mixture is extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to give α-(alkyl)methylene-γ-iodoalkyl-γ-butyrolactone which is purified by short pass column chromatography on silica gel (haxane : AcOEt = 6 : 1).

α-(phenyl)methylene-γ-iodomethyl-γ-butyrolactones (4a): mp 101-102 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55-7.32(m, 6H), 4.66-4.58(m, 1H), 3.47-3.26(m, 3H), 2.99-2.90(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.10, 137. 27, 134.21, 129.97, 128.89, 123.49, 75.14, 34.06, 8.82. Anal. Calcd for $C_{12}H_{11}O_2I$: C, 76.99 ; H, 5.92. Found: C, 77.00 ; H, 5.77.

α-(phenyl)methylene-γ-iodoethyl-γ-butyrolactones (4b): mp 104-106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58-7.40(m, 6H), 4.42-4.17(m, 2H), 3.46-2.92(m, 2H), 2.00(d, 3H, J=6.83); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.32, 137. 26, 134.37, 130.10, 128.99, 123.76, 80.43,34.21, 30.05, 23.99.

α-(phenyl)methylene-γ-iodoisopropyl-γ-butyrolactones (4c): mp 110-112 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.36(m, 5H), 4.05(dd, 1H, J=5.48, J=5.46), 3.47-3.06(m, 2H), 2.01(s, 3H), 1.92(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.47, 137.02, 134.39, 130.03, 128.97, 123.81, 84.22, 49.42, 33.63, 33.53, 31.44.

α-(phenyl)methylene-γ-iodobenzyl-γ-butyrolactones (4d): mp 132-137 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.24(m, 11H), 5.19-4.65(m, 2H), 3.49-2.66(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.89, 139.16, 138.87, 137.35, 137.17, 134.27, 130.06, 130.00, 128.99-128.07(m), 123.80, 123.46, 79.39, 35.65, 35.45, 34.68, 33.35.

α-(2-furyl)methylene-γ-iodomethyl-γ-butyrolactones (4e): mp 95-97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56(s, 1H), 7.28-7.26(m, 1H), 6.67-6.65(m, 1H), 6.51-6.49(m, 1H), 4.67-4.55(m, 1H), 3.48-3.26(m, 3H), 3.03-2.90(m, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.92, 150.93, 145.46, 123.26, 120.91, 116.39, 112.50, 75.30, 34.00, 9.03.

α-benzyl-γ-dimethylidenebutenolide (5): mp 82-84 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20(m, 5H), 7.043(s, 1H), 3.65(s, 2H), 1.94(s, 3H), 1.82(s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.63, 144.65, 137.61, 134.36, 131.65, 128.64, 128.72, 126.72,121.16, 31.61, 18.54, 18.40.

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