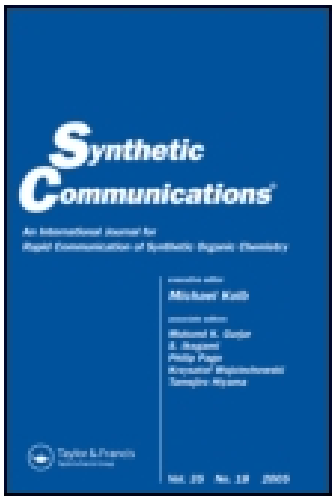

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STEREOSELECTIVE SYNTHESIS OF *TRANS*-β-METHOXYCARBONYL-γ-ARYL-γ-BUTYROLACTONES

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ABSTRACT

Stereoselective synthesis of *trans*-β-methoxycarbonyl-γ-aryl-γ-butyrolactones (**5**) by the reaction of methoxycarbonylmethyl triphenyl arsonium bromide (**1**) and 2,2-dimethyl-5-substituted-benzal-1,3-dioxa-4,6-dioxa-4,6-dione (**2**) is carried out in the presence of potassium carbonate and trace water in dimethoxyethane. 1,2-*Cis*-cyclopropane **3** is formed as an intermediate. The stability of compound **3** in water is related to the property of the aryl substituent. With strong electron-donating groups [**2a–c**, Ar=4-CH_3O–C_6H_4; 3,4-OCH_2O–C_6H_3 or 4-$(CH_3)_2N$–C_6H_4] at room temperature **3** is formed in situ and transformed to γ-butyrolactones **5a–c** immediately, whereas when the aryl substituent is H or a weak electron-donating or electron-withdrawing group (**2d–g**, Ar=4–CH_3-C_6H_4; C_6H_5; 4-Cl–C_6H_4 or 4-NO_2–C_6H_4), **3** is stable to water

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at room temperature. On further heating in acetone, **3** is transformed to γ-butyrolactones **5d–g** (stepwise synthesis). One-pot synthesis of **5d–g** from the reaction of **1** with **2d–g** is also studied.

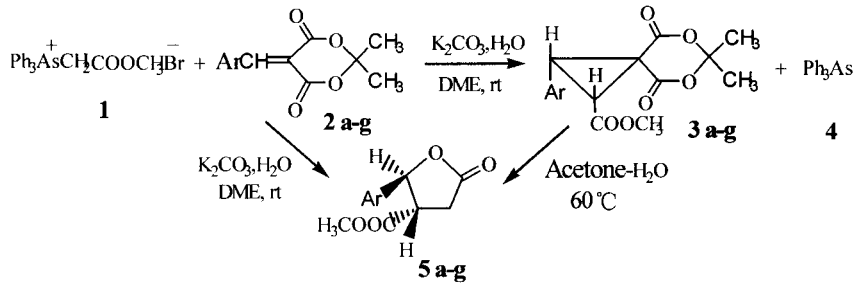
Key Words: Arsenic ylide; Stepwise synthesis; One-pot synthesis; γ-Butyrolactone; Stereoselective synthesis

Compounds containing γ-butyrolactone substructure show antiviral and physiological activities.[1] Therefore, the synthesis of such compounds is of current interest in synthetic organic chemistry. However, simple and highly stereoselective synthetic methods to prepare such compounds are rare. Recently, such a synthetic approach has been described by us.[2] Further study on the stereoselective synthesis of *trans*-β-methoxycarbonyl-γ-aryl-γ-butyrolactone (**5**) is reported here as well as a convenient one-pot process.

RESULT AND DISCUSSION

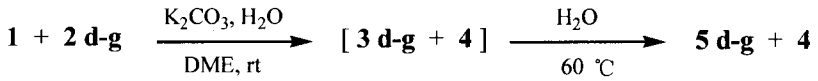
In the stereoselective synthesis of *trans*-β-methoxycarbonyl-γ-aryl-γ-butyrolactone (**5**), the reaction of methoxycarbonylmethyl triphenyl arsonium bromide (**1**) and 2,2-dimethyl-5-substituted-benzal-1,3-dioxa-4,6-dione (**2**) in the presence of potassium carbonate and trace water in dimethoxyethane leads to form 1,2-*cis*-cyclopropane **3** first. The stability of compound **3** to water is related to the property of the substituent on aryl group. When the substituent on aryl is a strong electron-donating group [**2a–c**, Ar=4-CH_3O–C_6H_4; 3,4-OCH_2O–C_6H_3 or 4-$(CH_3)_2N$–C_6H_4], **3** is formed in situ and transformed to γ-butyrolactone **5a–c** immediately (Scheme 1, Table 1). Whereas when the aryl substituent is H, weak electron-donating or electron-withdrawing (**2d–g**, Ar=4-CH_3–C_6H_4; C_6H_5; 4-Cl–C_6H_4 or 4-NO_2–C_6H_4), **3d–g** is stable to water at room temperature. The γ-butyrolactone **5d–g** could be obtained from the isolated **3d–g** by heating in acetone–water (stepwise synthesis, Scheme 1). Moreover, the γ-butyrolactone **5d–g** can also be obtained without the isolation of the reaction product **3d–g** by directly heating in DME–H_2O (one-pot synthesis, Scheme 2). Compared with stepwise synthesis, one-pot synthesis is simpler and gives higher yield (Table 1).

The structures and configurations of compounds **3e–g**, **5a**, **5e,f** have been reported previously.[2,3] The structures of **3d**, **5b–d**, **5g** were confirmed by IR, ^{1}H NMR, MS and elemental analyses (Table 2 and Table 3).



a: Ar=4-CH_3O-C_6H_4 **b**: Ar=3,4-OCH_2O-C_6H_3 **c**: Ar=4-$(CH_3)_2N$-C_6H_4
d: Ar=4-CH_3-C_6H_4 **e**: Ar=C_6H_5 **f**: Ar=4-Cl-C_6H_4 **g**: Ar=4-NO_2-C_6H_4

Scheme 1.



Scheme 2.

Table 1. Preparation of Compounds **5a–g**

Product	Ar	Yield (%) (One-Pot Synthesis)	Yield (%)[a] (Stepwise Synthesis)
5a	4-CH_3O–C_6H_4	64	/
5b	3,4-OCH_2O–C_6H_3	74	/
5c	4-$(CH_3)_2N$–C_6H_4	67	/
5d	4-CH_3–C_6H_4	55	44 = 74% × 60%
5e	C_6H_5	43	30 = 53% × 57%
5f	4-Cl–C_6H_4	56	46 = 74% × 62%
5g	4-NO_2–C_6H_4	48	40 = 83% × 48%

[a]Yield (%) of **5d–g** (stepwise synthesis) = yield of **3d–g** × yield of **5d–g**[b].
[b]The compound **3d–g** was heated in acetone–water to give γ-butyrolactones **5d–g**.

The *trans*-configuration of β-H and γ-H of compound **5e** was determined by the 2D NOESY. The reaction mechanism shown in Scheme 3 would account for the high stereoselectivity. The 1,2-*cis*-cyclopropane **3** is attacked by a molecule of water at C_a from the less hindered side of the cyclopropane ring, resulting in cleavage of the C_a–C_c bond of compound **3** to yield the intermediate **A**. Intermediate **A** transforms into intermediate **B** after the rotation

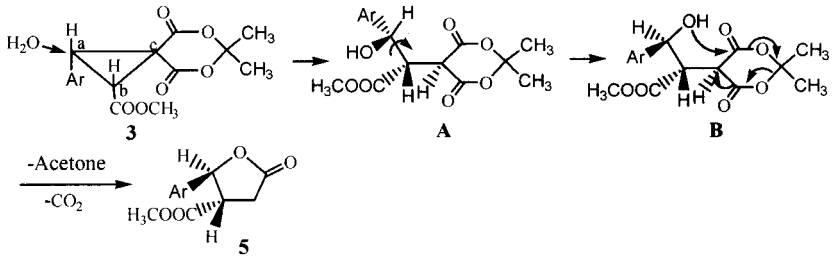
Table 2. MS, IR, ^{1}H NMR Spectra Data and Elemental Analyses of Products **5** or **3**

Compd.	M.p.(°C)	MS (m/z)	IR (cm^{-1})	Microanalyses Found (calcd.)	^{1}H NMR ($CDCl_3$) δ (ppm) *J* (Hz)
5b	98–100	264 (M^+, 51%)	1779	C: 58.81 (59.09)	2.94 (2H, m, α-H)
		233 (3)	1734	H: 4.47 (4.55)	3.31 (1H, m, β-H)
		149 (96)	1210		3.77 (3H, s, OCH_3)
		114 (80)	1143		5.55 (1H, d, $J=7.5$, γ-H)
		86 (16)			5.98 (2H, s, -OCH_2O-)
		55 (100)			6.82 (3H, m, ArH)
5c	110–112	263 (M^+, 70%)	1775	C: 63.79 (63.88)	2.96 (2H, m, α-H)
		160 (26)	1730	H: 6.38 (6.46)	2.97 (3H, s, N-CH_3)
		149 (100)	1198	N: 5.14 (5.32)	2.98 (3H, s, N-CH_3)
		115 (15)	1149		3.38 (1H, m, β-H)
		86 (1)			3.74 (3H, s, OCH_3)
		55 (32)			5.55 (1H, d, $J=7.6$, γ-H)
					7.00 (4H, m, ArH)
5d	92–94	234 (M^+, 11%)	1783	C: 66.65 (66.67)	2.33 (3H, s, 4-CH_3–C_6H_4)
		121 (29)	1736	H: 6.00 (5.98)	2.77 (1H, m, α-H)
		114 (100)	1210		3.06 (1H, m, α-H)
		86 (11)	1184		3.32 (3H, s, OCH_3)
		55 (46)			3.72 (1H, m, β-H)
					5.72 (1H, d, $J=7.9$, γ-H)
					7.12 (2H, d, $J=8.1$, ArH)
					7.16 (2H, d, $J=8.1$, ArH)

5g	164–166	265 (M^+, 1%) 151 (1) 114 (85) 86 (10) 55 (100)	1787 1723 1218 1182	C: 54.02 (54.34) H: 4.09 (4.15) N: 5.15 (5.28)	2.88 (1H, m, α-H) 3.07 (1H, m, α-H) 3.33 (3H, s, OCH_3) 3.72 (1H, m, β-H) 5.82 (1H, d, $J=7.7$, γ-H) 7.49 (2H, d, $J=8.6$, ArH) 8.25 (2H, d, $J=8.6$, ArH)
3d	138–139	319 ($M^+ + 1$, 2%) 260 (11) 140 (100) 129 (23) 82 (22)	1771 1738 1521 1307 912	C: 64.30 (64.10) H: 5.76 (5.66)	1.70 (3H, s, CH_3) 1.75 (3H, s, CH_3) 2.35 (3H, s, 4-CH_3–C_6H_4) 3.81 (3H, s, OCH_3) 3.83 (1H, d, $J=9.5$, ▷–H) 3.90 (1H, d, $J=9.5$, ▷–H) 7.15 (2H, d, $J=8.1$, ArH) 7.23 (2H, d, $J=8.1$, ArH)

Table 3. ^{13}C NMR Spectra Data of Product **5d**

Compd.	^{13}C NMR (d-DMSO) δ(ppm)
5d	21.2(4-CH_3–C_6H_4), 31.4(β-C), 46.7(α-C), 51.9($COOCH_3$), 81.2(γ-C), 125.5(Ar), 129.2(Ar), 132.3(Ar), 138.8(Ar), 170.1(–CO–), 175.1(–CO–, butyrolactone)



Scheme 3.

of C_a–C_c bond. The β,γ-*trans*-γ-butyrolactone **5** is formed through the attacking of the hydroxy group to the ester group to break the Meldrum's acid ring with the elimination of a molecule of acetone and a molecule of carbon dioxide.

This work indicates that the reaction of arsonium bromide **1** with electron-deficient alkenes **2** is an efficient approach to synthesize *trans*-β-methoxycarbonyl-γ-aryl-γ-butyrolactone (**5**) with high stereoselectivity and the by-product triphenyl arsine can be reused. One-pot synthesis is simpler with higher yield.

EXPERIMENTAL

Melting points were uncorrected and recorded on a WRS-1 melting point apparatus. IR spectra were measured on a 7400 spectrometer (Shanghai Analytical Instrument Factory, China) with KBr discs. NMR spectra were determined with AC-100SC spectrometers, using solutions in $CDCl_3$ or d-DMSO with tetramethylsilane or d-DMSO as the internal standard for ^{1}H and ^{13}C nuclei respectively. Coupling constants were given in Hz. Mass spectra were run on a HP 5989A spectrometer. Elemental data were obtained from Foss Heraeus CHN-O-RAPID elemental analysis instrument.

Synthesis of *trans*-β-Methoxycarbonyl-γ-aryl-γ-butyrolactone (5a–c) and *cis*-methoxycarbonyl-2-aryl-6,6-dimethyl-5,7-dioxa-spiro [2,5]-4,8-octadiones (3d–g)

General procedure—Methoxycarbonylmethyl triphenyl arsonium bromide **1** (0.459 g, 1 mmol), 2,2-dimethyl-5-substituted-benzal-1,3,-dioxa-4,6-dione **2a–g** (1 mmol) and K_2CO_3 (0.15 g) were stirred in dimethoxyethane (5 mL) in the presence of a drop of water at room temperature. At the end of the reaction (monitored by TLC), the white solid was filtered off and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography (GF_{254}, 200–300 mesh) with petroleum ether–ethyl acetate mixture (v : v = 7 : 3) as eluent. By-product triphenyl arsine (reusable and the product **5a–c** or **3d–g** can be obtained easily. The yields of the products **5a–c** or **3d–g** were illustrated in Table 1.

Synthesis of *trans*-β-Methoxycarbonyl-γ-aryl-γ-butyrolactones (5d–g) (Stepwise Synthesis)

General procedure—*Cis*-1-methoxycarbonyl-2-aryl-6,6,-dimethyl-5,7-dioxaspiro[2,5]-4,8-octadione **3d–g** (1 mmol) was heated in 3 mL of acetone–water (v : v = 2 : 1) at 60°C. At the end of the reaction (monitored by TLC), the white solid was filtered off and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography (GF_{254}, 200–300 mesh) with petroleum ether–ethyl acetate mixture (v : v = 7 : 3) as eluent. Then product **5d–g** can be obtained. The yields of the product **5d–g** were illustrated in Table 1.

Synthesis of *trans*-β-Methoxycarbonyl-γ-aryl-γ-butyrolactone (5d–g) (One-Pot Synthesis)

General procedure—Methoxylcarbonylmethyl triphenyl arsonium bromide 1 (0.459 g, 1 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione **2d–g** (1 mmol) and K_2CO_3 (0.15 g) were stirred in dimethoxyethane (5 mL) in the presence of a drop of water at room temperature. At the end of reaction (monitored by TLC), the white solid was filtered off and 1 mL water was added into the filtered solution. The mixture was heated to 60°C. When the reaction was completed (monitored by TLC), the solvent evaporated under reduced pressure and the residue purified by silica gel column chromatography (GF_{254}, 200–300 mesh) with petroleum ether-ethyl acetate mixture (v : v = 7 : 3) as eluent. By-product triphenyl arsine (reusable) and the

product **5d–g** can be obtained. The yields of the products **5d–g** were illustrated in Table 1.

Analytical data were illustrated in this paper and previous paper.[2,3]

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