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SYNTHESIS OF α-ALKYLIDENE-δ-VALEROLACTONES *VIA* THE CONJUGATE ADDITION OF KETONE ENOLATES TO FUNCTIONALIZED ALLYL ACETATES

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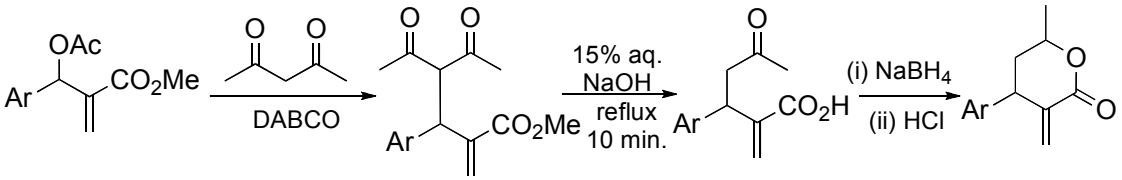
Abstract – Sequential addition of ketone enolates to allyl acetates bearing an ester, followed by reduction and cyclization provides a variety of substituted α-alkylidene-δ-valerolactones.

Butenolides, pyranones, α-alkylidene-γ-butyrolactones and -δ-valerolactones present in multitude of natural products display a variety of biological activities.[1] Although not as prevalent as α-methylene-γ-butyrolactones, the corresponding δ-valerolactones are also essential components and characteristic features of a plethora of natural products.[2] Several of these substrates possess novel pharmacological and interesting biological activities which range from antibiotic to antitumor activity.[2] In addition to the biological significance, α-methylene-δ-valerolactones find applications in carbon-carbon bond forming reactions[3] and methylene-bridged disaccharide synthesis.[4]

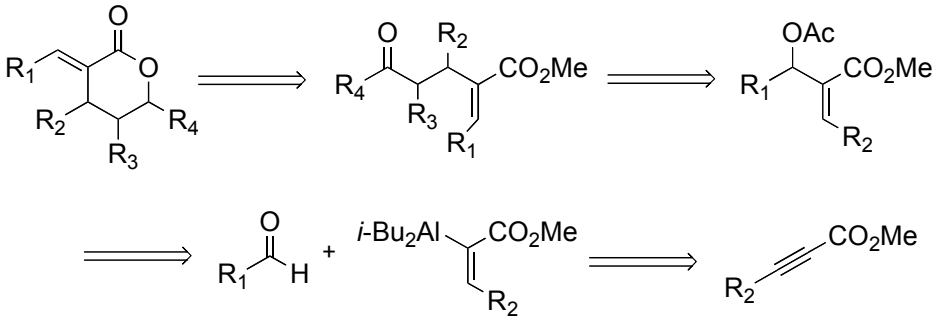
Among the α-alkylidene-δ-valerolactones, the synthesis of α-methylene δ-valerolactones is more common[5] and among the several approaches known in the literature, the metal-mediated cyclization of homoallylic alkynoates[6] and carbonylation[7] are noteworthy. Other processes include synthesis via the Horner-Wadsworth-Emmons reaction of α-phosphonolactones[8] and the trifluoromethanesulfonic acid mediated Friedel-Crafts reaction of diethoxyphosphorylacrylic acids.[9] Shiozaki and coworkers reported the synthesis of α-alkylidene-δ-valerolactones from corresponding ketones via aldol condensation on a δ-valerolactone moiety for the preparation of certain rennin inhibitors.[10] Recently Howell and coworkers reported the synthesis of α-alkylidene-γ-butyrolactones via a cross-metathesis reaction in the presence of Grubbs catalyst and 2,6-dichlorobenzoquinone.[11] However, this process was not effective for the preparation of the corresponding δ-valerolactones. Singh and Batra reported the preparation of a

series of β-aryl-δ-methyl-α-methylene-δ-valerolactones via a nucleophilic substitution (S_N2 process) of Baylis-Hillman acetates (Scheme 1).[12]



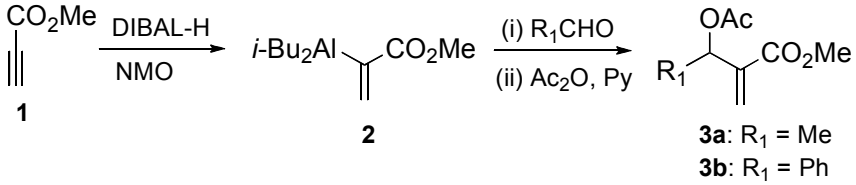
Scheme 1. Batra synthesis of β-aryl-α-methylene-δ-methyl-δ-valerolactones

As part of our ongoing projects on vinylalumination,[13] we envisaged a terse general synthesis of variantly substituted α-alkylidene-δ-valerolactones via the conjugate addition-elimination of functionalized allylic acetates (an overall S_N2' process) with enolate nucleophiles as delineated in Scheme 2. As can be seen, this process allows for the incorporation of substitutions at β, γ, and δ-positions. The successful synthesis of a variety of γ- and δ-substituted α-alkylidene-δ-valerolactones, including the construction of fused bicyclic valerolactone moieties[14] is reported herein.



Scheme 2. Retrosynthesis for α-alkylidene-δ-valerlactones

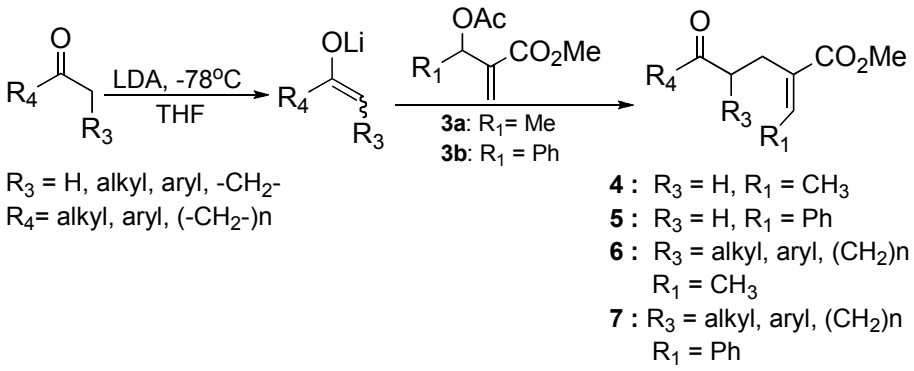
The required allyl acetates for the present study were prepared via the vinylalumination[13] of acetaldehyde and benzaldehyde, followed by esterification of the resulting alcohols with acetic anhydride in the presence of pyridine (Scheme 3). These derivatives can be prepared via Baylis-Hillman reaction[12,15] as well.



Scheme 3. Preparation of α-alkylidene acetates

Initially, the enolates from various methyl ketones were generated under kinetic conditions (LDA, -78 ^{o}C), which was followed by the addition of a solution of **3a** or **3b** (Scheme 4). The conjugate addition-elimination process is only initiated at or above 0 ^{o}C. Subsequent warming of the reaction mixture to ambient condition and stirring overnight ensures complete consumption of **3a** or **3b**. It is to be noted

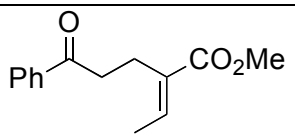
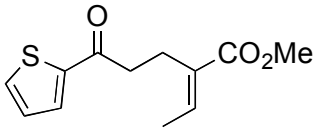
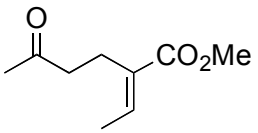
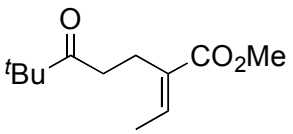
that the reaction is prohibitively slow even at 0 °C. Extensive experimentation confirmed that the presence of excess base or HMPA does not have any beneficial effect on the reaction and that THF is the solvent of choice.

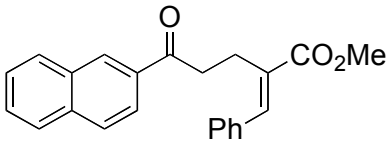
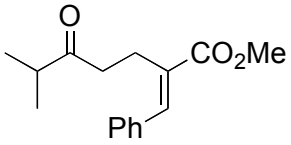
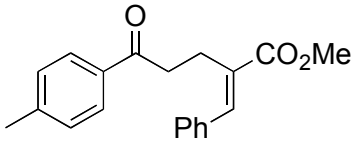


Scheme 4. Preparation of α-alkylidene-δ-keto esters

The oxoesters (**4a-d** and **5a-5c**) from methyl ketones (R_3=H, Scheme 4) were obtained in moderate (52-65%) yields. The ^{1}H NMR analysis of all of the products (**4a-d** and **5a-c**) indicated 90% *E* geometry for the olefin. The C_2-symmetric bis-adducts derived from the deprotonation of **4** or **5** were also obtained in 10-20% yield. The availability of the base for the deprotonation of **4** or **5** could be presumably from the reversibility of the enolate formation. The formation of the bis adduct could be considerably controlled under optimum conditions (1.2 equivalent of LDA), although it could not be completely suppressed. The results are summarized in Table 1.

Table 1. Conjugate addition-elimination of methyl ketone enolates.[a]

entry	acetate	R_2COCH_3	keto ester		
	#	R_2	#	structure[b]	% yield[c]
1	**3a**	Ph	**4a**		65
2	**3a**	2-Thiophenyl	**4b**		52
3	**3a**	Me	**4c**		57
4	**3a**	*t*-Bu	**4d**		63

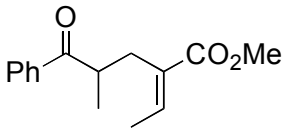
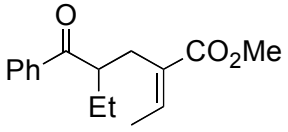
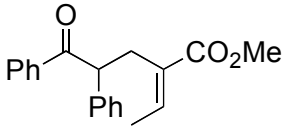
5	**3b**	2-Naphthyl	**5a**		54
6	**3b**	*i*-Pr	**5b**		61
7	**3b**	*p*-Tol	**5c**		56

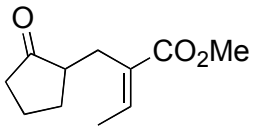
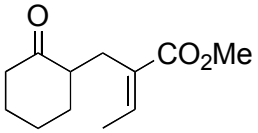
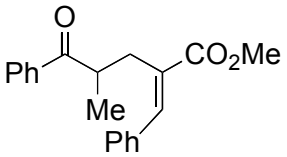
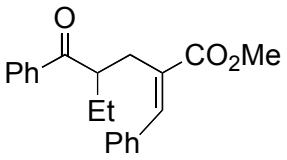
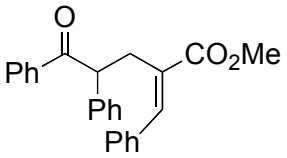
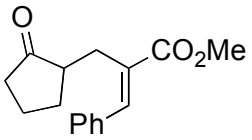
[a]The additions were carried out at -78 °C and warmed overnight to rt.

[b]*E*:*Z* ratio 90:10. The diastereomer ratio was determined by ^{1}H NMR. [c]Isolated yield.

Compared to the methyl ketones, other classes of ketones such as ethyl, *n*-propyl, benzyl and alicyclic ketones generated keto esters in much better yields with similar *E*:*Z* ratio as observed for **4** and **5**. The keto-adducts from propiophenone (**6a**,**7a**), *n*-butyrophenone (**6b**,**7b**), deoxybenzoin (**6c**,**7c**), cyclopentanone (**6d**,**7d**), and cyclohexanone (**6e**) are among the representatives. The alicyclic derivatives of keto esters (**6d**, **6e** and **7d**) could be successfully generated under analogous reaction conditions. The formation of the bisadducts, as observed for **4a-d** and **5a-c**, does not occur for keto-adducts **6a-d**, **7a-d**, presumably due to the steric congestion at the newly generated ternary stereocenter in these adducts. The results are summarized in Table 2.

Table 2. Conjugate addition-elimination of several classes of ketone enolates.[a]

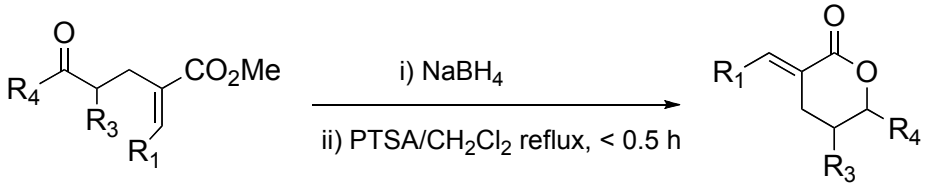
entry	acetate	$R_2COCH_2R_3$		keto ester		
	#	R_2	R_3	#	structure[b]	% yield[c]
1	**3a**	Ph	Me	**6a**		82
2	**3a**	Ph	Et	**6b**		85
3	**3a**	Ph	Ph	**6c**		91

4	**3a**	-CH_2-	(CH_2-)$_2$	**6d**		76
5	**3a**	-CH_2-	(CH_2-)$_3$	**6e**		62
6	**3b**	Ph	Me	**7a**		61
7	**3b**	Ph	Et	**7b**		73
8	**3b**	Ph	Ph	**7c**		80
9	**3b**	-CH_2-	(CH_2-)$_2$	**7d**		69

[a]The additions were carried out at -78 °C and warmed overnight to rt.

[b]*E*:*Z* ratio 90:10. The diastereomer ratio was determined by ^{1}H NMR. [c]Isolated yield.

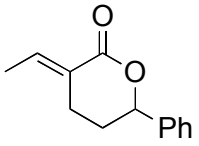
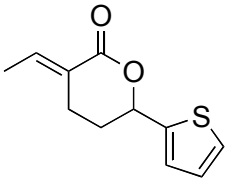
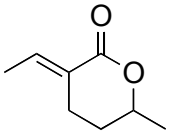
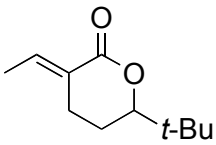
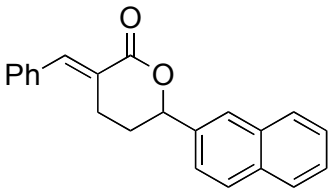
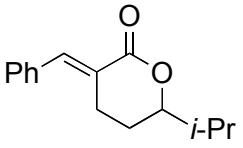
Chemoselective reduction of the α-alkylidene oxoesters to the corresponding hydroxyesters could be effected quantitatively with Sodium borohydride. Substrates **6a-e** and **7a**, **7c** and **7d** underwent reduction with varied diastereoselectivity. The diastereoselectivity was not determined at this point since the alcohol has a tendency to lactonize during aqueous workup. Attempted silica-gel chromatography resulted in partial lactonization of the hydroxyl ester. As a consequence, they were submitted to an acidic environment without further purification and the cyclization to the lactones occurred instantaneously.

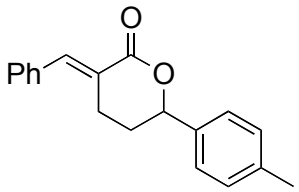
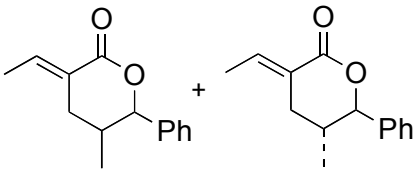
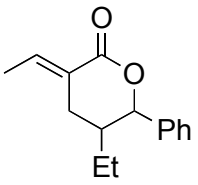
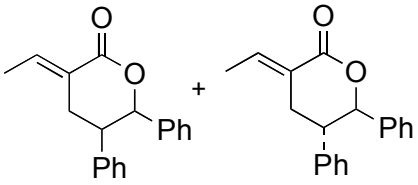
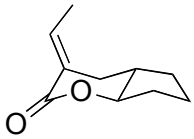
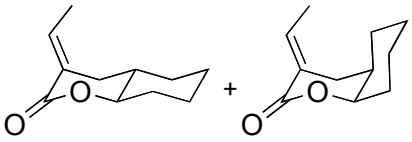
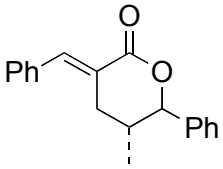
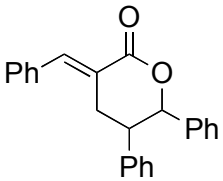
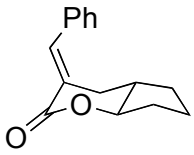


Scheme 5. Preparation of α-alkylidene-δ-valerolactones

Thus, **4a-d**, **5a-c**, **6a-e** and **7a**, **7c**, **7d** generated the lactones **8a-d**, **9a-c**, **10a-e** and **11a**, **11c**, **11d**, respectively, in high yields over two steps (Scheme 5). The alkyl substituent at the α-position predominantly governs the hydride approach from the *si* face of the prochiral carbonyl carbon, thus favoring the formation of the *syn*-alcohol. Thus, while **10a** and **10c** were formed as 2:1 and 1:1 mixture of diastereomers respectively, lactones **10b** and **11b** were generated with high *cis*-selectivity. The diastereomeric ratio was determined from ^{1}H NMR coupling constants. The lactone **11a** and the cyclopentanone-derived lactones **10d** and **11c** were formed excusively as *anti* isomers.[16] The lactone **10e**, obtained from cyclohexanone, was an inseparable diastereomeric mixture in the ratio of 2:1.[14] The yields and the diastereomeric ratios of the lactones are summarized in Table 3.

Table 3. Preparation of α-alkylidene-δ-valerolactones

entry	keto ester	lactone				
	#	#	structure[a]	% yield[b]	dr	
					cis	*trans*
1	**4a**	**8a**		74	na[c]	na
2	**4b**	**8b**		53	na	na
3	**4c**	**8c**		69	na	na
4	**4d**	**8d**		82	na	na
5	**5a**	**9a**		80	na	na
6	**5b**	**9b**		65	na	na

7	**5c**	**9c**		77	na	na
8	**6a**	**10a**		70	2	1
9	**6b**	**10b**		68	>99	<1
10	**6c**	**10c**		74	1	1
11	**6d**	**10d**		63	<1	>99
12	**6e**	**10e**		59	1	2
13	**7a**	**11a**		76	<1	>99
14	**7c**	**11c**		58	24	1
15	**7d**	**11d**		62	<1	>99

[a] *E*:*Z* ratio: 95:5. The diastereomer ratio was determined by ^{1}H NMR.

[b] Isolated yields. [b] Not applicable

In conclusion we have demonstrated a highly convenient synthesis of a variety of α-alkylidene-δ-valerolactones from readily available synthons. The generality of the methodology has been demonstrated via the synthesis of a wide range of δ-alkyl/aryl valerolactones and studies on the stereochemistry at ring junction for fused bicyclic α-alkylidene δ-valerolactones. Current efforts focus on the enantio- and diastereoselective reduction of the keto esters for the preparation of chiral lactones. We are also examining ways to improve the yields in the conjugate addition-elimination step.

EXPERIMENTAL

General: Unless otherwise noted, reagents were purchased from commercial suppliers. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Diisopropylamine was distilled over calcium hydride or potassium hydroxide and stored over 4 Å molecular sieves. *n*-Butyl lithium (2.5 M solution in hexanes) was procured from Aldrich. Thin layer chromatography was performed on Sorbent Technologies precoated silica gel w/UV254 glass backed (250μm) plates. Silica gel (Sorbent Technologies 230-400 mesh) was used for flash column chromatography. ^{1}H NMR spectra was recorded on a Gemini (300 MHz) or Bruker (200 MHz) spectrometer. Spectra was referenced internally to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm) as the internal standard. Commercially available $CDCl_3$ was stored under 4 Å molecular sieves. Chemical shifts (δ) were reported as parts per million (ppm) in δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Gemini 300 spectrometer and referenced to $CDCl_3$ (δ 77.0 ppm). Coupling constants (*J*) were reported in Hertz. Spectroscopic data is presented for representative compounds.

Typical procedure for preparation of α-alkylidene-δ-valerolactone 8a.

Preparation of 4a: To a solution of diisopropylamine (0.33 mL, 2.4 mmoles) in anhydrous THF (1 mL) at -78 ^{o}C was added *n*-BuLi (0.96 mL, 2.4 mmol, 2.5 M soln. in hexanes) followed by the addition of a solution of acetophenone (0.24 g, 2 mmol dissolved in anhydrous THF (3mL) at the same temperature over a period of 10 minutes. To the resulting mixture was added a solution of **3a** (0.34 g, 2 mmol) dissolved in anhydrous THF (3 mL) and stirred overnight, during which time the reaction mixture warmed upto ambient temperature. This was then quenched with saturated aqueous ammonium chloride, extracted with EtOAc, dried (Na_2SO_4) and concentrated to obtain crude **4a**, which was purified by flash column chromatography using silica-gel (1:9:: EtOAc:hexanes) to obtain 0.30 g (65%) of pure **4a** as an oil. δH(300 MHz; $CDCl_3$): 7.99 (2H, d, J 6.0, ArH), 7.4-7.6 (3H, m, ArH), 6.9 (1H, q, J 7.2, CH_3CH=C), 3.75 (s, 3H, OCH_3), 3.13-3.08 (2H, m, CH_2CH_2), 2.76-2.71 (2H, m, CH_2CO), 1.86 (d, 3H, J 7.14, CH_3) δC(75 MHz; $CDCl_3$): 199.4, 167.9, 138.9, 136.7, 133, 131.7, 128.5, 128, 51.6, 37.7, 21.4 14.3.

Preparation of 8a: To a solution of **4a** (0.1 g, 0.43 mmol) in anhydrous MeOH (3 mL) was added solid $NaBH_4$ (16.3 mg, 0.43 mmol) under ice-cooling and stirred for 2 h. The reaction mixture was quenched

with water. Methanol was removed under reduced pressure and the aqueous layer was extracted with EtOAc, dried (Na_2SO_4) and concentrated. The contents in the flask was dissolved in CH_2Cl_2 (5 mL) and catalytic amount of *p*-toluenesulfonic acid was added and the solution was refluxed for 30 min. The reaction was quenched with water, extracted with CH_2Cl_2, dried (Na_2SO_4), and purified by flash column chromatography using silica-gel (1:9::EtOAc:hexanes) to obtain 0.064 g (74%) of **8a** as a white crystalline solid. δH(300 MHz; $CDCl_3$): 7.4-7.2 (6H, m, ArH, CH_3CH=C), 5.28 (1H, dd, J 2.34, PhCH), 2.76-2.31 (2H, m, CH_2CH_2), 2.28-2.18 (1H, m, CH_2CHO), 2.10-1.86(1H, m, CH_2CHO), 1.83 (d, 3H, J 7.14, CH_3). δC(75 MHz; $CDCl_3$): 166.5, 141.5, 139.6, 128.6, 128.2, 125.9, 125.8 MS (EI) 202(M+), 104, 96, 77.

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