Stereoselective Synthesis of β,γ-Unsaturated Esters and Lactones. Application to Pyrenophorol Synthesis

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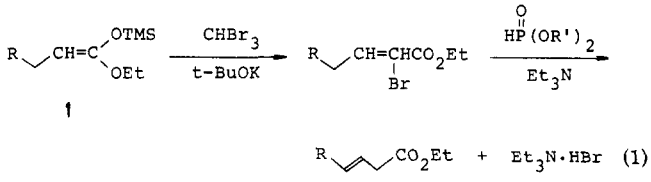
β,γ-Unsaturated ester (carboxylic acid) or lactone has been noted as an important functional group in naturally occurring compounds[1] and is readily transformed to γ-hydroxy or γ-oxo α,β-unsaturated carbonyl compound,[2] which also constitutes a key component of natural products, especially macrolides.[2-4] The common method for the preparation of β,γ-unsaturated esters is based on deprotonation and reprotonation of α,β-unsaturated esters.[5] In our previous papers,[6] we have developed a unique reductive deconjugation of α-bromo α,β-unsaturated ketones to β,γ-unsaturated ketones with a combination of diethyl phosphonate (commercially named, diethyl phosphite) and triethylamine. The present paper describes the highly stereoselective synthesis of β,γ-unsaturated esters or lactones, being accompanied by one-carbon homologation of starting saturated esters or lactones.

The α-bromo α,β-unsaturated ester **2**, easily prepared by the addition of dibromocarbene to the silyl ketene acetal **1**, was treated with dialkyl phosphonate and triethylamine affording the β,γ-unsaturated ester **3** with the deposition of Et_3N·HBr (eq 1, Table I).

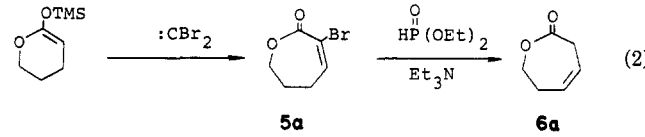


Triethylamine worked well as compared with the other bases such as tributylamine and *N*-methylmorphorine. Pyridine and *N,N*-diethylaniline did not induce the reaction. The effect of various alkyl substituents was examined to show that diethyl phosphonate is superior to the isopropyl or butyl one. A variety of α-bromo α,β-unsaturated esters were allowed to undergo reductive deconjugation. When R^1 of the ester **2** is longer than methyl, the selective formation of β,γ-unsaturated esters was observed. This result is in contrast with the synthesis of β,γ-unsaturated ketones, which contain a small amount of the corresponding α,β-unsaturated isomers. Another interesting feature is the high stereoselectivity of the present transformation. For example, a mixture of ethyl (*E*)- and (*Z*)-2-bromo-2-hexenoates was consumed in the same rate giving ethyl (*E*)-3-hexenoate exclusively. No *Z* isomer was detected in the NMR spectrum of the crude reaction mixture.

The present reaction was unsuccessful in the case of the ester having an alkyl group at the γ-position like ethyl 2-bromo-4-methyl-2-pentenoate. On the other hand, reductive deconjugation of ethyl 2-bromo-4-phenyl-2-butenoate took place very fast even at room temperature. This large difference suggests the γ-proton abstraction at an initial step and the high acidity of the benzylic proton promotes the reaction.

The isomerization of the α,β-unsaturated ester **4** having no α-bromine atom into the β,γ-unsaturated ester did not proceed under the conditions employed here. The reaction course remains speculative, but the α-bromo β,γ-unsaturated ester might be proposed to be an intermediate. It is considered to be reduced to the β,γ-unsaturated ester **3** because reduction of a bromine atom α to the carbonyl group is easily performed with diethyl phosphonate and triethylamine.[7] The active agent might be $(EtO)_2PO^-$ as explained in the previous papers.[8]

The α-bromo α,β-unsaturated lactone **5a**, derived from the silyl ketene acetal of 5-pentanolide, was subjected to reductive deconjugation with diethyl phosphonate (2 equiv) and triethylamine (4 equiv) in benzene at 80 °C for 0.5 h to yield 3-hexen-6-olide (**6a**, 92%). No detectable α,β-unsaturated lactone existed in the reaction mixture (eq 2).



The present process achieves a synthetically useful method for the stereoselective introduction of a carbon–carbon double bond β,γ to esters or lactones together with one-carbon homologation. This method is applied to the synthesis of (±)-pyrenophorin[2,3] (Scheme I). The silyl ketene acetal of 6-heptanolide prepared by the regioselective Baeyer–Villiger oxidation of 2-methylcyclohexanone underwent the addition of dibromocarbene to give 2-bromo-2-octen-7-olide (**5b**, 46%). Reductive deconjugation was carried out with diethyl phosphonate (2 equiv) and triethylamine (4 equiv) at 80 °C for 3 h leading to the formation of 3-octen-7-olide (**6b**) and 2-octen-7-olide (**7b**) in 86% yield (70:30).[9] Use of tributylamine raised the ratio of the desired β,γ-unsaturated lactone **6b** (**6b**/**7b** = 78:22) although the yield was lowered (55%). The isomer **6b** was separated by flash chromatography and hydrolyzed to **8** with KOH in MeOH–H_2O. The corresponding *trans* isomer has been known as a key intermediate for the preparation of pyrenophorin.[2] The macrolactonization of **8** with Mitsunobu reagent gave the cyclic dimer **9** (50%). The cyclic dimer **9** underwent epoxidation with MCPBA followed by ring opening with LDA to produce (±)-pyrenophorol (**10**) (50%). Oxidation of **10** to (±)-pyrenophorin (**11**) has been reported.[2]

(1) Millar, J. M.; Oehlschlager, A. C.; Wong, J. M. *J. Org. Chem.* **1983**, *48*, 4404. Oehlschlager, A. C.; Wong, J. M.; Verigin, V. G.; Pierce, H. D., Jr. *Ibid.* **1983**, *48*, 5009.

(2) (a) Mali, R. S.; Pohmakotr, M.; Weidmann, B.; Seebach, D. *Liebigs Ann. Chem.* **1981**, 2272. (b) Fujisawa, T.; Takeuchi, M.; Sato, T. *Chem. Lett.* **1982**, 1795.

(3) Labadie, J. W.; Stille, J. K. *Tetrahedron Lett.* **1983**, *24*, 4283. Bates, G. S.; Ramaswamy, S. *Can. J. Chem.* **1983**, *61*, 2466. Hase, T. A.; Ourila, A.; Holmberg, C. *J. Org. Chem.* **1981**, *46*, 3137. Asaoka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, *22*, 735. Seuring, B.; Seebach, D. *Liebigs Ann. Chem.*, **1978**, 2044, and references cited therein.

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(7) Hirao, T.; Kohno, S.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1881.

(8) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745. Steinberg, G. M. *Ibid.* **1950**, *15*, 637.

(9) The formation of the α,β-unsaturated lactone **7b** partially depends on the isomerization of the β,γ-unsaturated lactone **6b**, which was confirmed by the experiment under the conditions employed here.

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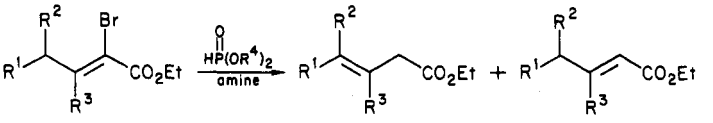
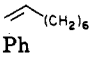
Table I. Preparation of β,γ-Unsaturated Esters

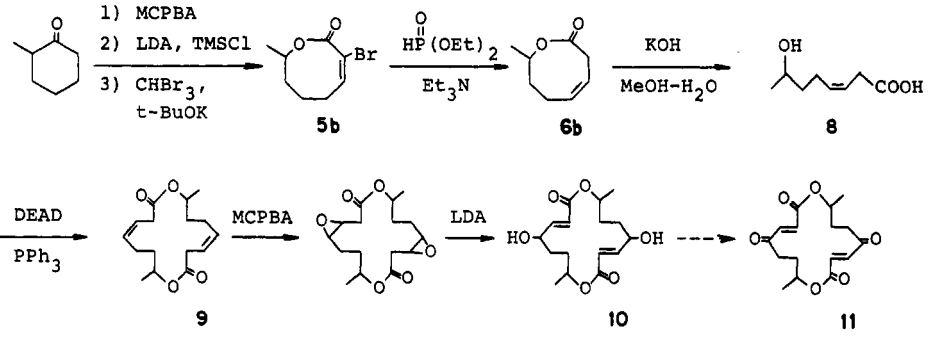


2 3 4

2			$HP(O)(OR^4)_2$				reaction		products	
R^1	R^2	R^3	R^4	equiv	amine	equiv	temp (°C)	time (h)	yield (%)	3:4
n-Pr	H	H	Et	1.2	Et_3N	1.2	80	18	44	
				1.2		4	80	6	60	
				2		4	80	9	75	>99:1
				4		4	80	6	84	>99:1
				2	*n*-Bu_3N	4	80	9	18	
				2		4	80	9	37	
				2		4	80	9	8	
				2	$PhNEt_2$	4	80	9	0[a]	
				2		4	80	9	0[b]	
			i-Pr	2	Et_3N	4	80	9	63	>99:1
			n-Bu	2		4	80	9	58	>99:1
H	H	H[c]	Et	2		4	50	6	55	83:17
				2		4	80	2	78	64:36
Me	H	H	Et	2		4	80	10	61	>99:1
H	H	Me	Et	2		4	80	30	43	31:69
Me	Me	H	Et	2		4	80	28	0	
Et	H	H[c]	Et	2		4	80	8	65	96:4
	H	H	Et	2		4	80	8	55	>99:1
Ph	H	H	Et	2		4	rt	0.5	78	92:8

[a] The starting material (65%) was recovered. [b] The starting material (76%) was recovered. [c] *E* and *Z* mixture.

Scheme I



Experimental Section

Commercially available dialkyl phosphonates were purified by distillation. The α-bromo α,β-unsaturated esters **2** and lactones **5** were prepared in good or moderate yields by the addition of dibromocarbene to the corresponding silyl ketene acetals according to the reported method,[10] although the intermediary *gem*-dibromocyclopropane derivatives spontaneously underwent ring opening into **2** or **5**. Purification of **2** and **5** was carried out by flash chromatography. Ethyl (*E*)- and (*Z*)-2-bromo-2-hexenoates were prepared by dehydrobromination of ethyl 2,3-dibromohexanoate with DBU.

General Procedure for the Preparation of the β,γ-Unsaturated Ester 3 or Lactone 6. A solution of **2** or **5** (1 mmol), dialkyl phosphonate (2 mmol), and triethylamine (4 mmol) was stirred at 80 °C for 2–30 h unless otherwise stated in Table I. In the case of the solid starting material **5a**, benzene (0.5 mL) was used as a solvent. The reaction proceeded with the deposition of Et_3N·HBr. Ether (5 mL) was added to the resultant mixture. The salt was removed by filtration and washed with ether (3 × 5 mL). After evaporation of the filtrate and washings, the residue was flash chromatographed to give **3** or **6**. The products were identified by IR, ^1H NMR, MS, GC analyses (conditions; PEG 2.1 m column, 130 °C) and comparison with those of the authentic data.[5,11]

Preparation of (±)-Pyrenophorol (10). The Baeyer–Villiger oxidation of 2-methylcyclohexanone gave 6-heptanolide regioselectively in 73% yield. Treatment of 6-heptanolide with lithium diisopropylamide in THF at −78 °C followed by the addition of chlorotrimethylsilane and triethylamine produced 7-methyl-2-(trimethylsiloxy)-1-oxacyclohept-2-ene in 68% yield.[12] To a suspension of dry KOBu-*t* (3.4 g, 30 mmol) in hexane (30 mL) was added thus obtained silyl ketene acetal (3.0 g, 15 mmol) at −20 to −15 °C followed by dropwise addition of bromoform (5.3 g, 21 mmol) in hexane (11 mL) over 45 min at the same temperature. After further stirring for 0.5 h, 50 mL of water was added to the resultant mixture, which was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was flash chromatographed, eluting with 10% EtOAc–hexane to give 1.5 g of 2-bromo-2-octen-7-olide (**5b**, 46%): IR (neat) 1720, 1630 cm^{-1}; ^1H

(10) On the contrary, the *gem*-dibromocyclopropanes derived from silyl enol ethers have been reported to be isolated: Amice, P.; Blanco, L.; Conia, J. M. *Synthesis* **1976**, 196.

(11) Hubert, A. J.; Reimlinger, H. *Synthesis* **1969**, 97, and references cited therein.

(12) Ainswarth, C.; Chen, F.; Kuo, Y.-n. *J. Organomet. Chem.* **1972**, *46*, 59.

NMR (60 MHz, $CDCl_3$) δ 1.31 (d, 3 H, J = 6.4 Hz), 1.4–1.9 (m, 4 H), 2.0–2.5 (m, 2 H), 4.5–5.1 (m, 1 H), 6.51 (t, 1 H, J = 5.6 Hz); MS, m/e 220, 218 (M^+).

A solution of **5b** (153 mg, 0.70 mmol), diethyl phosphonate (194 mg, 1.40 mmol), and triethylamine (283 mg, 2.80 mmol) was stirred at 80 °C for 3 h. Ether (20 mL) was added to the resultant mixture. The separated white deposit (Et_3N·HBr) was filtered off and washed with ether (2 × 10 mL). The filtrate and ethereal washings were concentrated and flash chromatographed, eluting with 10% EtOAc–hexane to give 59 mg (60%) of **6b** as a colorless oil and 25 mg (26%) of **7b**. **6b**: IR (neat) 1730, 1660 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.37 (d, 3 H, J = 6.4 Hz), 1.5–1.9 (m, 2 H), 2.0–2.6 (m, 2 H), 3.1–3.3 (m, 2 H), 4.5–5.0 (m, 1 H), 5.53 (dt, 1 H, J = 11.0, 3.8 Hz), 5.73 (dtt, 1 H, J = 11.0, 7.1, 1.9 Hz); MS, m/e 140 (M^+). Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.90.

Thus obtained β,γ-unsaturated lactone **6b** (59 mg, 0.42 mmol) was treated with 6 N KOH in methanol (0.84 mL) and water (0.41 mL) at room temperature for 1 h. Water (2 mL) was added to the resultant mixture, which was extracted with ether (3 × 5 mL). The aqueous layer was adjusted to pH 2 with concentrated HCl and extracted with ether (3 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give 57 mg of the product **8**, which was pure by TLC (R_f 0.47, EtOAc): IR (neat) 3400 (broad), 1720 cm^{-1} (no peak assigned to the trans isomer); ^1H NMR (90 MHz, $CDCl_3$) δ 1.21 (d, 3 H, J = 6.3 Hz), 1.52 (q, 2 H, J = 6.3 Hz), 2.0–2.3 (m, 2 H), 3.0–3.2 (m, 2 H), 3.84 (sextet, 1 H, J = 6.3 Hz), 5.4–5.8 (m, 2 H), 6.16 (broad s, 2 H); MS, m/e 158 (M^+).

The dimerization of **8** was carried out according to the reported method[2a] to give **9** in 50% yield: IR (neat) 1730, 1660 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (d, 6 H, J = 6.3 Hz), 1.4–1.8 (m, 4 H), 1.9–2.3 (m, 4 H), 2.9–3.2 (m, 4 H), 4.7–5.2 (m, 2 H), 5.3–5.8 (m, 4 H); high-resolution MS calcd for $C_{16}H_{24}O_4$ 280.1673, found 280.1689.

To a solution of **9** (33 mg, 0.12 mmol) in CH_2Cl_2 (2.5 mL) was added MCPBA (78 mg) at 0 °C. Stirring was continued at 0 °C for 0.5 h and at room temperature for 3 h. Ether (30 mL) was added to the mixture, which was washed with ice-cooled 5% $NaHCO_3$ (20 mL), 2% NaOH (10 mL), and brine. The organic phase was dried over $MgSO_4$ and concentrated to give 30 mg of a white solid (no olefinic proton in ^1H NMR). Butyllithium (43 μL, 0.069 mmol) was added to a solution of diisopropylamine (13 μL, 0.092 mmol) in THF (0.37 mL) at −78 °C. The resulting solution was stirred at 0 °C for 0.5 h. The white solid obtained above (7.2 mg, theoretically 0.023 mmol) in THF (0.18 mL) was added dropwise at −78 °C over 15 min. The mixture was stirred at the same temperature for 1 h and quenched with acetic acid (14 μL). After warming up to room temperature, brine (3 mL) was added to the mixture, which was extracted with ether (3 × 5 mL). The combined organic layers were washed with 5% $NaHCO_3$ (3 mL) and brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed on a silica gel column eluting with 40% EtOAc–hexane to give **10** (3.7 mg, 50% based on **9**): IR (neat) 3400 (broad), 1715, 1650, 980 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.25 (broad d, 6 H), 1.4–2.0 (m, 8 H), 4.0–4.6 (m, 2 H), 4.7–5.3 (m, 2 H), 5.98 (d, 2 H, J = 15.6 Hz), 6.83 (dd, 2 H, J = 15.6, 5.1 Hz).

Regioselective Allylation of Ketones under Neutral Conditions

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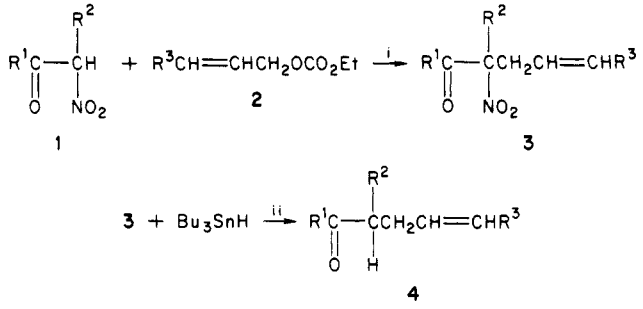
Regioselective allylation of ketones is an important process in organic synthesis and many methods have been devised for this purpose.[1] Among them, palladium-catalyzed allylation of β-keto esters or β-keto sulfones and subsequent removal of the ester or sulfonyl function has been used quite often owing to the high selectivity of these procedures.[2] In this note we report another selective method for the allylation of ketones. Our method consists of two key steps: allylation of α-nitro ketones (**1**) with allylic carbonates (**2**) in the presence of a palladium(0) catalyst[3] and subsequent denitration with Bu_3SnH.[4]



(i) $Pd(PPh_3)_4$ (5 mol %), THF, rt; (ii) AIBN (0.2 equiv), benzene, 80 °C, 2 h

Allylation was carried out by stirring a mixture of **1**, **2**, and $Pd(PPh_3)_4$ (5 mol %) in tetrahydrofuran (THF) at room temperature for 20 h. Allylated products (**3**) were obtained in 70–80% yields. Subsequent denitration was carried out by heating a mixture of **3**, tributylstannane (Bu_3SnH, 1.2 equiv), and azobis(isobutyronitrile) (AIBN, 0.2 equiv) in benzene at 80 °C for 2 h. The results are summarized in Table I. The requisite starting α-nitro ketones were prepared by acylation of nitroalkanes[5] or by oxidation of β-nitro alcohols.[6] Thus, the present method consist of genuinely simple procedures and required neither acidic nor basic conditions, so it affords some advantages over the conventional methods.[1]

Table I. Regioselective Allylation of Ketones

R^1	R^2	R^3	3, yield, %	4, yield, %
n-C_4H_9	Et	Ph	**3a**, 70	**4a**, 85
n-C_4H_9	Et	H	**3b**, 72	**4b**, 87
n-C_3H_7	n-C_3H_7	Ph	**3c**, 72	**4c**, 83
n-C_3H_7	n-C_3H_7	H	**3d**, 81	**4d**, 80
n-C_6H_{13}	Me	Ph	**3e**, 75	**4e**, 80
n-C_6H_{13}	Me	H	**3f**, 72	**4f**, 85

The present method can be applied to allylation of esters. Allylation of ethyl α-nitrobutyrate[3] and subsequent denitration gave the allylated product of ethyl butyrate.

Experimental Section

α-Nitro ketones (**1**) were prepared according to the literatures.[5,6]

Allylation of 1. General Procedure. To a stirred solution of **1** (0.01 mol) and **2** (0.01 mol) in THF (10 mL) under argon was added $Pd(PPh_3)_4$ (0.05 g) at room temperature. The resulting

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(2) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. Tsuji, J. *Organic Synthesis with* Palladium *Compounds*; Springer-Verlag: Berlin, 1980.

(3) Allylic carbonates are excellent electrophiles for the palladium-catalyzed allylic alkylation, see: Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523 and references therein. Allylation of nitro compounds, see: Wade, P.; Morrow, S.; Hardinger, S. *J. Org. Chem.* **1982**, *47*, 365. Aleksandrowicz, Pitrowska, H.; Sas, W. *Tetrahedron* **1982**, 1321. Genet, J. P.; Ferround, D. *Tetrahedron Lett.* **1984**, *25*, 3579. Wade, P.; Hinney, H.; Amin, N.; Vail, P.; Morrow, S.; Hardinger, S.; Saft, M. *J. Org. Chem.* **1981**, *46*, 765.

(4) We have found that Bu_3SnH replaces an aliphatic nitro group by hydrogen without affecting oxo, cyano, sulfonyl, or sulfinyl groups; this is the basis of a new synthetic method: Ono, N.; Miyake, H.; Tamura, R.; Kaji, A. *Tetrahedron Lett.* **1981**, *22*, 1705. Ono, N.; Kamimura, A.; Miyake, H.; Hamamoto, I.; Kaji, A. *J. Org. Chem.* **1985**, *50*, 3692 and references therein.

(5) Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040.

(6) Rosini, G.; Ballini, R.; Sorrenti, P.; Petrini, M. *Synthesis* **1984**, 607.

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