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A novel nonclassical Wittig reaction of dioxolanones: highly facile and concise enantiospecific synthesis of (3*S*,4*S*)-3-hydroxy-4-phenylbutyrolactone†

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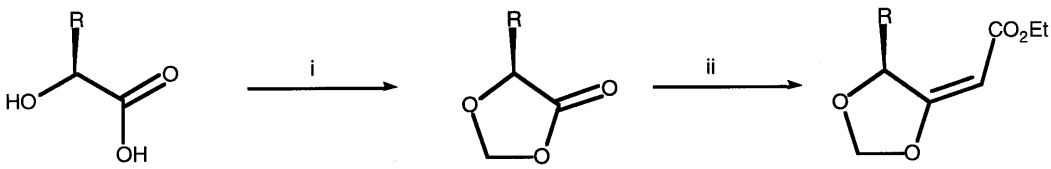
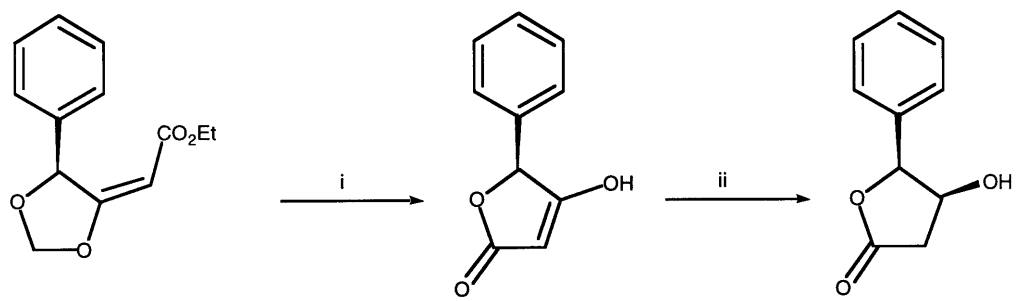
Abstract—A novel and facile Wittig reaction of dioxolanones is described. An application of this protocol to the stereospecific synthesis in an efficient and practical manner of (3*S*,4*S*)-3-hydroxy-4-phenylbutyrolactone is demonstrated.

In recent years, there has been considerable growing interest in the synthesis of functionalized butyrolactones because of their wide occurrence in several natural products, and also their utility as key precursors for the synthesis of various bioactive molecules[1–4] and HIV-protease inhibitors.[5–7] Consequently, a variety of approaches have been developed for their asymmetric[1,2] and racemic[8] synthesis. Among them the Sharpless



1 2 3

Scheme 1. Reagents and conditions: (i) $(CH_2O)n$, PTSA, C_6H_6, reflux, 1 h; (ii) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 2 h.



3a 4 5

Scheme 2. Reagents and conditions: (i) conc. HCl, EtOH, reflux, 4 h; (ii) $NaBH_4$ (1.2 equiv.), CH_3OH, 0°C, 1 h, 86% (for two steps).

Keywords: asymmetric synthesis; dioxolanones; hydroxy acids; Wittig reaction.

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Table 1. Wittig reaction of dioxolanones

Entry	R	Yield[a] (%) **2**	$[\alpha]_D$[b] **2**	Yield[a] (%) **3**	$[\alpha]_D$[c] **3**
a	Ph	93	87	96	−35
b	$PhCH_2$	97	−54	95	−82
c	$(CH_3)_2CH$	92	−27	94	−96
d	$(CH_3)_2CHCH_2$	94	−14	96	−44
e	$CH_3CH_2CHCH_3$	95	−14	94	−10

[a] Isolated yields.
[b] Specific rotations are measured with $c = 1$ in methanol.
[c] Specific rotations are measured with $c = 0.5$ in methanol.

asymmetric dihydroxylation of β,γ-unsaturated esters leading to chiral butyro lactones is of great significance.[1] In view of the synthetic importance of butyrolactone derivatives, we envisioned a new methodology from readily accessible α-hydroxy acids. In this communication, we wish to report a novel and facile Wittig reaction of various dioxolanones (**2** → **3**, Scheme 1) and conversion of the α,β-unsaturated ester **3a** to (3*S*,4*S*)-3-hydroxy-4-phenylbutyrolactone **5** (Scheme 2).

Thus, the α-hydroxy acids **1** were treated with paraformaldehyde in presence of catalytic PTSA for 1 h to obtain the dioxolanones **2**‡ in excellent yields (92–97%, Table 1).

The Wittig reaction of the dioxolanones **2** with ethoxycarbonylmethylenetriphenyl phosphorane afforded the corresponding α,β-unsaturated esters **3**‡ in quantitative yields (94–96%, Table 1). This reaction is highly facile and clean and was completed in 2 h in all cases. The results obtained with various dioxolanones (**2a**–**e**) demonstrating the generality of this reaction, are summarized in Table 1. Compounds **2** and **3** were fully characterized by ^{1}H NMR, IR, mass spectroscopic data, and microanalysis, which were in good agreement with the assigned structures. Important characteristic signals of **3a**, ^{1}H NMR: δ 1.25 (t, 3H, $J = 6.2$ Hz), 4.15 (q, 2H, $J = 6.2$ Hz), 5.75 (s, 1H) clearly indicated the ethoxycarbonyl and olefin functionalities. In the ^{1}H NMR of all compounds **3a**–**e**, only one set of sharp signals was seen clearly, suggesting the existence of only one stereoisomer. No NOE signal enhancement of the ring protons was observed on irradiation of the vinylic proton and hence the olefin geometry was assumed to have the thermodynamically more stable '*E*' geometry.

The Wittig products obtained in the present study are important key precursors for butyrolactone derivatives. This is demonstrated by subjecting the α,β-unsaturated ester **3a** to acidic hydrolysis to furnish lactone **4**, which was reduced using sodium borohydride to give the hydroxybutyrolactone as a single enantiomer **5** (Scheme 2). From spectroscopic (^{1}H NMR, IR, mass) data and the specific rotation $[\alpha]_D = +36$ ($c = 1$, MeOH), lit.[1] $[\alpha]_D = +36$ ($c = 0.98$, MeOH) data, the structure and absolute configuration was found to be (3*S*,4*S*)-3-hydroxy-4-phenylbutyrolactone (**5**). The exclusive formation of **5** in the sodium borohydride reduction of **4** may be attributed to the diastereofacial selective addition of hydride.

In summary, a novel and facile Wittig reaction of dioxolanones and a synthesis of (3*S*,4*S*)-3-hydroxy-4-phenylbutyrolactone in a stereospecific and efficient manner is described. The Wittig products obtained in the present methodology are a new class of highly useful versatile intermediates for the synthesis of various bioactive molecules. Since both antipodes of chiral α-hydroxy acids are accessible by several methods, the present methodology has wide scope and will be amenable to make all possible stereoisomers and analogous compounds. Further work on the synthesis of natural butyrolactones using this methodology is currently in progress and will be reported in due course.

Acknowledgements

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‡ Selected data: **Compound 2a**: Colorless oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ 5.20 (s, 1H, PhC<u>H</u>), 5.6 (s, 1H, -C<u>H</u>$_2$), 5.7 (s, 1H, -C<u>H</u>$_2$), 7.35–7.50 (m, 5H, -C_6<u>H</u>$_5$); IR (neat): 1786 cm^{-1}; EIMS (*m*/*z*): 164 (M^+); anal. found: C, 65.73; H, 5.03. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91. **Compound 3a**: Colorless syrup; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, $J = 6.2$ Hz, -C<u>H</u>$_3$), 4.15 (q, 2H, $J = 6.2$ Hz, -C<u>H</u>$_2$OCO), 4.60 (s, 1H, -C<u>H</u>), 5.45 (s, 1H, =C<u>H</u>), 5.5 (s, 1H, -C<u>H</u>$_2$), 5.75 (s, 1H, -C<u>H</u>$_2$), 7.30–7.45 (m, 5H, -C_6<u>H</u>$_5$); IR (neat): 1755 cm^{-1}; FABMS (*m*/*z*): 235 ($M+H^+$); anal. found: C, 66.41; H, 6.18. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02.