Highly Regioselective α-Alkylation of γ-Acetoxy-α,β-enoates by Reduction–Alkylation with Lithium Dibutylcuprate–Alkyl Halides: Application to the Synthesis of Spirovetivanes

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Reaction of γ-acetoxy-α,β-enoates with lithium dibutylcuprate followed by alkyl halides results in the predominant or exclusive formation of α-alkyl-β,γ-enoates in high yields under mild conditions; a synthetic route to (±)-α-vetispirene is also presented.

The regioselective α- or γ-alkylation of α,β-unsaturated carbonyl compounds and of allylic acetates is a long-standing synthetic problem which continues to receive much attention.[1] γ-Oxygenated-α,β-unsaturated carbonyl compounds are important intermediates for the syntheses of many natural products[2] and the γ-oxygen functions are eliminated by reducing agents such as zinc amalgam in the presence of hydrochloric acid[2d] and zinc in acetic acid[2e] to yield β,γ-unsaturated carbonyl compounds. However, trapping of a zinc enolate intermediate by electrophiles would be impossible since both the above reduction conditions involve a proton source. Previously, we[3a] and Yamamoto *et al.*[3b] reported the reaction of the γ-oxygenated-α,β-enoate (**1**) with Lewis acid-mediated organocopper reagents to yield a mixture of the α-alkylated-β,γ-enoate (**2**) and the γ-alkylated-α,β-enoate (**3**), γ-alkylation being favoured (Method A).[3]

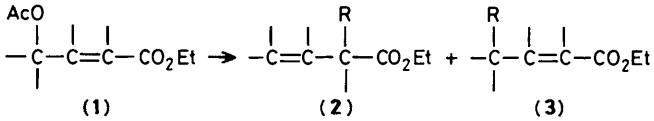


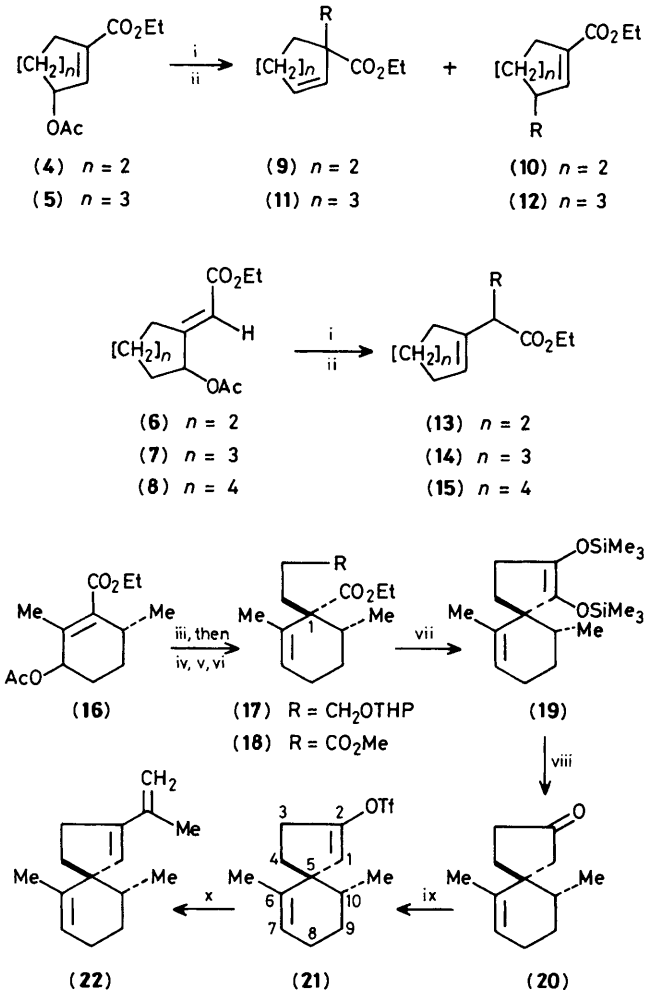
Table 1. Yields of α- and γ-alkylated products in the reaction of γ-acetoxy-α,β-enoates with lithium dibutylcuprate and alkyl halides.[a]

Entry	Substrate	Alkyl halide	α-Alkylated product (yield, %)	
1	(4)	BuBr	(9) R = Bu	(92%)[b]
2	(4)	MeI	(9) R = Me	(94%)
3	(4)	$Br[CH_2]_3Br$	(9) R = $[CH_2]_3Br$	(75%)
4	(4)	$Br[CH_2]_3OTHP$	(9) R = $[CH_2]_3OTHP$	(52%)
5	(5)	BuBr	(11) R = Bu	(94%)[b]
6	(5)	MeI	(11) R = Me	(89%)
7	(6)	BuBr	(13) R = Bu	(91%)
8	(7)	BuBr	(14) R = Bu	(66%)
9	(7)	EtBr	(14) R = Et	(50%)
10	(8)	BuBr	(15) R = Bu	(87%)

[a] All yields are unoptimised but refer to pure material. All new compounds reported exhibited satisfactory spectroscopic and analytical and/or mass spectral data consistent with the structures. The following procedure is representative. To a stirred solution of Bu^n_2CuLi (1.5 mmol) in a mixture of dry THF (3 ml) and HMPA (0.26 ml, 1.5 mmol) under argon at −70 °C was added dropwise a solution of the γ-acetoxy-α,β-enoate (**4**) (0.5 mmol) in dry THF (2 ml) and the mixture was stirred for 20 min. n-Butyl bromide (3 mmol) was added to the stirred mixture at −70 °C, the temperature was gradually increased to room temperature, and the mixture was stirred for 20 h. After the usual work-up, the α- and γ-butylated mixture was separated by silica gel column chromatography or preparative gas chromatography (1.5% FFAP on Chromosorb W, 2 m, column temp., 130 °C) to yield the pure α-butyl (**9**) R=Bu (92%) and γ-butyl derivatives (**10**) R=Bu (<0.8%). Both the products were fully characterised by ^1H n.m.r., i.r., and combustion analysis and/or mass spectrometry. [b] Plus γ-alkylated product (**10**) or (**12**) (<0.8%).

We describe here a new highly regioselective α-alkylation of the presumed copper enolates derived from the γ-acetoxy-α,β-enolates (**1**) by treatment with lithium dibutylcuprate followed by alkyl halides in a one-pot reaction (Method B). It appears that no general method for the efficient regioselective α-alkylation of such γ-oxygenated-α,β-enoates by reduction–alkylation was available. As can be seen from Table 1, reaction of a variety of γ-acetoxy-α,β-enoates[3,4] with lithium dibutylcuprate at −70 to −40 °C for 10—30 min followed by alkyl halides at room temperature for 15—20 h afforded α-alkylated-β,γ-enoates in high yields and in high regioselectivity. The present regioselective α-alkylation is opposite to the selective γ-alkylation with Lewis acid-mediated organocopper reagent reported earlier.[3] Successful reaction requires both an aprotic solvent, usually diethyl ether or, preferably, THF and HMPA, (2—3 mol. equiv. relative to substrate). Since a substantial amount of starting material was recovered with use of 1 mol. equiv. of the cuprate reagent, at least 2 mol. equiv. of the cuprate are also necessary. The enoates (**4**) and (**5**) with a endocyclic double bond gave, in some cases (entries 1 and 5), a small amount of γ-alkylation product, whereas the substrates (**6**)—(**8**) with an exocyclic double bond afforded exclusively α-alkylation products (entries 7—10). Entry 3 shows selective α-monoalkylation of the substrate (**4**) with 9 mol. equiv. of 1,3-dibromopropane. We were unable to detect any of the bis-alkylated product(s), although we cannot conclusively rule out its presence.

The utility of the present regioselective reduction–alkylation[5] is demonstrated by its application to the synthesis of the constituents of vetiver oil. Thus, reduction–alkylation of the γ-acetoxy-α,β-enoate (**16**) with lithium dibutylcuprate followed by 3-(tetrahydropyran-2-yloxy)propyl bromide gave the THP-ester (**17**) [i.r. ($CHCl_3$) ν: 1720 cm^{-1}] as the sole isolable product in 25% yield. Although the relative stereochemistry at C-1 in (**17**) has not yet been clarified the α-configuration of the ester group at C-1 was inferred from the synthesis of the spiro-ketone (**20**) and (±)-α-vetispirene (**22**) derived from (**17**). The THP-ester (**17**) was converted into the diester (**18**) [68% overall yield from (**17**); i.r. ($CHCl_3$) ν: 1723 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ: 0.91 (3H, d, *J* 6.3 Hz, sec. Me), 1.25 (3H, t, *J* 7.1 Hz, CH_2Me), 1.54 (3H, m, vinyl Me), 3.67 (3H, s, OMe), and 5.74 (1H, m, olefinic H)] by the reactions in Scheme 1. The modified acyloin condensation of (**18**) was carried out using sodium and chlorotrimethylsilane in refluxing toluene[6] to yield the rather labile bis(trimethylsilyl) ether (**19**) (91% yield) which, without purification, was converted into the spiro-ketone (**20**)[7,8] [i.r. ($CHCl_3$) ν: 1735 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ: 0.90 (3H, d, *J* 7 Hz, sec. Me), 1.65 (3H, m, vinyl Me), and 5.41 (1H, m, olefinic H)], by a standard procedure.[8d] The synthesized ketone (**20**), one of the constituents of vetiver oil,[7] was characterised by comparison of its spectra with those of the authentic compound.[8c,d] The



Scheme 1. *Reagents and conditions:* i, Bu_2CuLi (Table 1); ii, RX (Table 1); iii, Bu_2CuLi (6 equiv.), THF–HMPA (6:1), −70 to 40 °C, 30 min, then $Br[CH_2]_3OTHP$ (6 equiv.), room temp., 16 h; iv, 5% HCl in EtOH, reflux, 2 h; v, DMSO–$(COCl)_2$, Et_3N, −65 °C, 1 h; vi, Ag_2O in MeOH, room temp., 30 min, then ethereal CH_2N_2, room temp., 5 min; vii, Na (6 equiv.), Me_3SiCl (6 equiv.), toluene, reflux, 2 h; viii, ref. 8d; ix, Tf_2O–pyridine, room temp., 3 days; x, (isopropenyl)$_2$CuMgBr (4 equiv.), −70 to 5 °C, 2.5 h.

THF = tetrahydrofuran; HMPA = hexamethylphosphoric triamide; THP = tetrahydropyran-2-yl; DMSO = dimethyl sulphoxide; Tf = CF_3SO_2.

spiro-ketone (**20**) was transformed into (±)-α-vetispirene (**22**) by treatment with trifluoromethanesulphonic anhydride–pyridine at room temperature and followed by silica gel column chromatography to give (**21**) [46% yield, i.r. ($CHCl_3$) ν: 1665, 1416, 1138, and 909 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ: 0.89 (3H, d, *J* 6.5 Hz, sec. Me), 1.61 (3H, m, 6-Me), 5.42 (1H, m, 7-H), and 5.44 (1H, t, *J* 1.8 Hz, 1-H)]. Cross-coupling[9] of (**21**) with the reagent prepared from copper(I) iodide and isopropenylmagnesium bromide in THF gave (±)-α-vetispirene (**22**)[10] [M^+, *m/z* 202.1704 (calc. 202.1721); ^1H n.m.r. ($CDCl_3$) δ: 4.90 (2H, m, $C{=}CH_2$), 5.38 (1H, m, 7-H), and 5.50 (1H, m, 1-H)] in 21% yield.

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