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1-Acetoxy and 1-Silyloxy-1,3-dienes via Reductive Homologation of α,β-Unsaturated Esters

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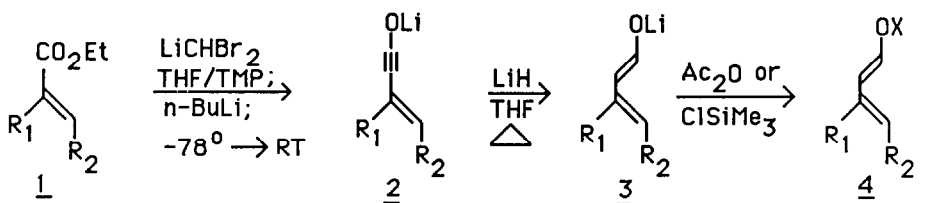
Summary: α, β-Unsaturated esters (1) are stereospecifically converted in a one-pot preparation into 1-oxygenated-E,E-dienes (4). This reductive homologation proceeds via lithium hydride reduction of the ene ynolate anion (2) to the dienolate anion 3, affording 1-acetoxy- or 1-silyloxy-1,3-dienes in yields of about 45-55%.

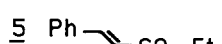
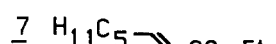
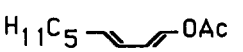
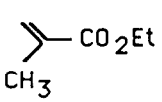
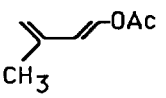
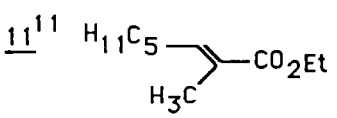
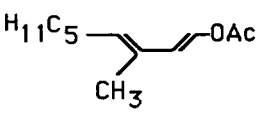
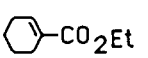
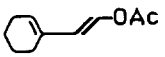
Although E-1-oxygenated-1,3-dienes of structure 4 (R_1,R_2 = H or alkyl, X = acetyl or silyl) have proven useful in synthesis[2], methods for their preparation[3] frequently afford mixtures of geometric isomers. Recently we reported a method for the reductive homologation of esters, which involved reduction of ynolate anions to E-enolate anions on heating with excess 1,3-cyclohexadiene[4]. Attempts to apply this procedure to the known ynolate anion 2 (R_1=H, R_2=Ph), however, to obtain the corresponding E,E-dienolacetate 4 (X=Ac) upon quenching (i.e. 1 → 2 → 3 → 4), had proven unsuccessful. Although the ynolate 2 was



consumed on heating with 1,3-cyclohexadiene, no identifiable product could be isolated. More recently we had found that the actual reducing agent in reductive homologation reactions was lithium hydride (formed in situ)[5]. Since it seemed reasonable that the excess cyclohexadiene, which had been present during reduction of 2, might have resulted in destruction of the desired dienolate anion intermediate 3, the reductive homologation of unsaturated esters 1 was re-examined using lithium hydride under diene-free conditions[5]. This has now resulted in a new synthesis of 1-oxygenated dienes.

Esters 1 were converted to ynolate anions 2 by treatment first with lithiodibromomethane (methylene bromide + lithium tetramethylpiperidide) at -78°C, and then n-butyllithium followed by warming to room temperature. The resulting ynolate anion solutions were then transferred into suspensions of diene-free lithium hydride (prepared from 1,4-cyclohexadiene and excess n-butyllithium) and heated at reflux. The desired dienolate anions 3 were indeed formed under these LiH reduction conditions, as evidenced by their trapping with acetic

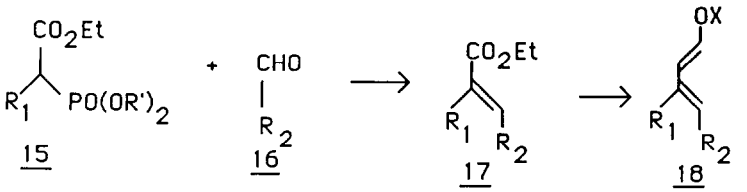
TABLE 1

Starting Ester	Product Diene (yield)*
5 	 6a[8] /X=OAc(51%) b[9a] /X=OSiMe$_3$(55%)
7 	 8[9b] (45%)
9 	 10[10] (39%) (52%)**
11[11] 	 12[9c] (48%)
13 	 14[12] (53%)

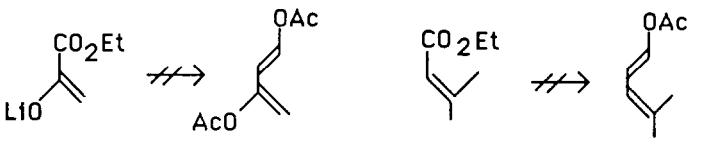
Notes: (*) isolated, purified material unless otherwise noted
(**) GC yield of this rather volatile product.

anhydride to afford E-1-acetoxy-1,3-dienes 4 (X=Ac). Table I shows the results of these experiments. In every case the geometry of the original olefin was preserved (a result of stereoretention in the homologation step[6]), and the newly formed enol double bond had exclusively the trans configuration. Thus the product dienes were formed stereospecifically. The yields (about 50%) were very similar to those obtained from the simple homologation of α, β-unsaturated esters[6], suggesting that the ynolate reduction (2 ⟶ 3) had occurred in high yield.

These reactions were successful for α,β -unsaturated starting esters having an α-substituent (9), a trans β-substituent (5 & 7), or both (11 & 13). Such esters with the E-configuration (5, 7, 11) are readily available with high stereoselectivity via the Horner-Emmons reaction of aldehydes (15 + 16 ⟶ 17)[7], providing a general strategy for the stereocontrolled preparation of dienes 18, even when R_1 and R_2 are alkyl groups. It is



also noteworthy that the intermediate dienolate anions (3) can also be trapped with chlorotrimethylsilane to afford 1-silyloxy-1,3- dienes (e.g. 5 ⟶ 6b), also useful Diels-Alder substrates[2]. When the LDA-derived lithium enolate of ethyl pyruvate (19) was subjected to the diene-free reductive homologation sequence, however, none of the 1,3-dioxygenated diene 20 was obtained upon quenching with acetic anhydride; from aliquot quenches, it appeared that little of the intermediate ynolate anion was formed in this case.



19 20 21 22

Similarly, the β-disubstituted ester 21 failed to afford dienolacetate 22, although in this case ynolate formation had clearly proceeded smoothly. Heating with LiH resulted in destruction of the ynolate anion and formation of numerous decomposition products, perhaps due to the presence of protons on an allylic position cis to the ynolate anion (and the intermediate dianion expected during reduction[5]). Since E,E-dienes are generally the most important (for Diel's-Alder chemistry), the failure of ester 22 to be formed represents only a minor limitation to the method's[13] utility.

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1. SK&F Postdoctoral Scientist

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9. (a) For 6b, NMR ($CDCl_3$): δ 7.53-6.93 (m, 6H), 6.76, 6.66, 6.56, 6.53, 6.43 (m, 2H), 6.26, 6.16, 6.03, 5.80, 5.66 (m, 1H), 0.23 (s, 9H); I.R. (film) 3100-2730 (br), 1630, 1590, 1480, 1440, 1400, 1370, 1290, 1280, 1170, 1130, 1040, 960, 850, 740, 680 cm-1; M+ calc'd for $C_{13}H_{18}OSi$ = 218.1126, obs = 218.1130. (b) For 8, NMR ($CDCl_3$): 7.30 (br d, 1H, J = 12 Hz), 6.06, 5.96, 5.85, 5.70, 5,60 (m, 3H), 2.13 (s, 3H), 2.10-1.83 (m, 2H), 1.70-1.10 (m, 6H), 1.10-0.70 (m, 3H); I.R. (film) 3100-2760, 1755, 1660, 1620, 1450, 1370, 1280, 1210, 1070, 970, 890 cm-1; M+ calc'd for $C_{11}H_{18}O_2$ = 182.1316, obs = 182.1306. (c) For 12, NMR ($CDCl_3$): δ 7.24 (d, 1H, J = 13 Hz), 6.06 (d, 1H, J = 13 Hz), 5.43 (t, 1H, J = 7 Hz), 2.13 (s, 3H), 2.20-1.90 (m, 2H), 1.76 (s, 3H), 1.60-1.10 (m, 6H), 1.10-0.70 (m, 3H); I.R. (film) 3100-2700 (br), 1755, 1670, 1450, 1350, 1260, 1140, 1040, 1010, 950, 720 cm-1; M+ calc'd for $C_{12}H_{20}O_2$ = 196.1463, obs = 196.1442.

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13. A general procedure for effecting this new alkoxy diene synthesis is as follows. A solution of 6.6 mmol of n-butyllithium in hexane is added dropwise to a stirred solution of 7.2 mmol of 2,2,6,6-tetramethylpiperidine in 6mL of THF, under a N_2 atmosphere and with ice-bath cooling. This solution is then added dropwise via cannula to a stirred solution of 6.6 mmol of dibromomethane in 6 mL of THF, cooled with a -78° C bath. After 5 min, a solution of 2 mmol of ester in 5 mL of THF is added dropwise, and 10 min later a solution of 16 mmol of n-butyllithium in hexane is added dropwise. The -78°C bath is replaced with a 30°C bath (slowly on larger scales: butane gas evolution), and stirring is continued for 30 min to afford the ynolate anion solution. In a separate flask, a solution of 16 mmol of n-butyllithium in hexane is added dropwise to a solution of 8.0 mmol of 1,4-cyclohexadiene in 4 mL of THF, under N_2 and cooled with a -78°C bath. The mixture is then stirred at room temperature for 45 min, producing a suspension of LiH, and the solution of ynolate anion is added. The mixture is heated at reflux for 1-3 hr, while the reaction is monitored via 50 L aliquots, quenched into 100 L portions of 5:1 ethanol/acetyl chloride and extracted into 1mL of ether; disappearance of the ynolate-derived homologated ester is watched for in the GC analysis of these aliquots. When the reaction is complete (usually after 1hr), the mixture is cooled with a -78°C bath, and 3 mL of acetic anhydride is added. The bath is removed and after 30 min the mixture is diluted with 200 mL of ether, washed with saturated sodium bicarbonate and then brine, and purified by chromatography on silica gel.

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