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3-ALCOXY-ALLENYLLITHIUM REAGENTS AS β-ACYL VINYL ANION EQUIVALENTS. A NEW SYNTHESIS OF PYRENOPHORIN.

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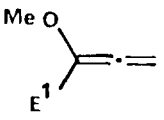
SUMMARY : *Reactions of 3-alcoxy-allenyllithium reagents with electrophiles led to (Z) or (E) keto compounds 3 or 4 after mild acid hydrolysis. Carboxylation led to the 4-oxo-2-alkenoate unit. This reaction was applied to a short synthesis of the macrolide antibiotic, pyrenophorin.*

In a previous study of 3-alcoxy-allenyllithium reagents, we have shown that the ethers 1 are easily metalated by n-butyllithium at -70° and that alkylation of the derivatives 2 led to trans conjugated ketones after acid hydrolysis [1].

We now wish to report that the reagents 2 give compounds cis 3 or/and trans 4 depending upon the nature of the electrophile and upon the experimental conditions of the acid hydrolysis. Thus, when treated with carbon dioxide at -78° and then with methyl iodide in HMPA, followed by mild acid hydrolysis at 0° for 5 mn, 2 gave pure methyl 4-oxo-2(Z)-nonenoate 3c in 65% yield.

Under the same conditions, derivatization with dimethyldisulfide or trimethylchlorosilane led to a mixture of (Z) and (E) isomers 3 and 4. The pure E isomers 4 were obtained by carrying out the acid hydrolysis at room temperature (method A) or by heating the crude work-up mixture in xylene in the presence of a catalytic amount of 2-pyridine-thiol (method B). The time for the conversion of the (Z) isomer into the (E) isomer increases from 3a to 3c [4].

The carboxylation of allenic compounds 2 appears to be a promising reaction since it leads to the 4-oxo-2-alkenoate unit 5 which exists in a wide variety of natural products with interesting biological properties [5]. Of the methods [6] which have been devised for the synthesis of this synthon 5, ours turns out to be a relatively simple and direct route : three reactions (carboxylation, esterification, hydrolysis at room temperature) carried out in "one pot" afford the ester 5 (E^1 = nC_5H_{11}, R = Me) in 50% overall yield from the appropriate allenic ether 1.



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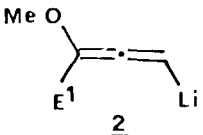
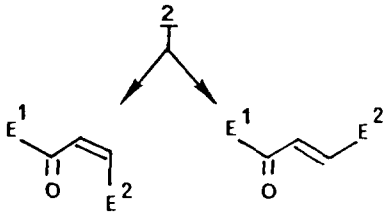


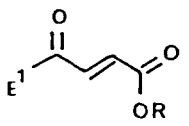


2

$E^1 = n\text{-}C_5H_{11}$

3 4

	Reagents	E^2	overall yield [2]	3 (%)	4 (%)
a	Me_2S_2 [3a]	SMe	60	19	81
b	$ClSiMe_3$ [3b]	$SiMe_3$	60	63	37
c	(i) CO_2 [3c] (ii) MeI	CO_2Me	65	100	0



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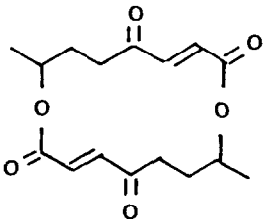

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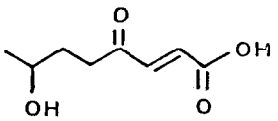

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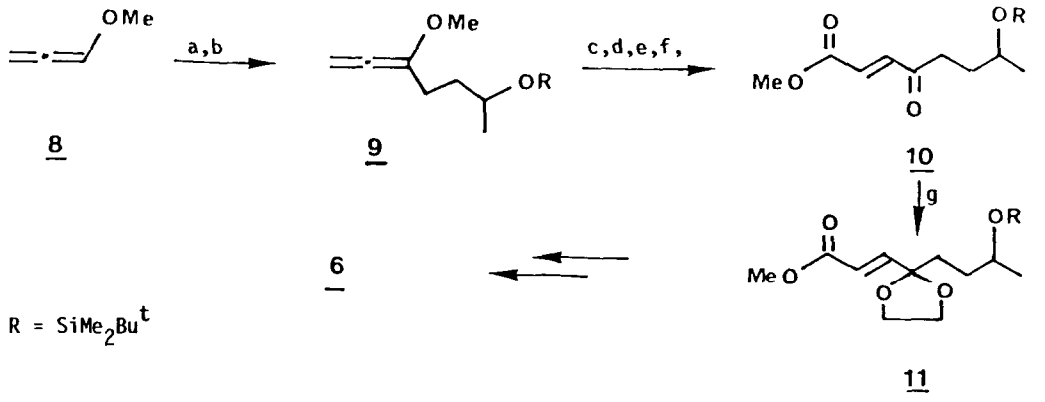
The utility of this new procedure is demonstrated in an efficient short-step synthesis of pyrenophorin 6, a diolide antibiotic produced by the plant pathogenic fungus *Pyrenophora avenae* [7,8]. This bislactone is characterized by a 16-membered ring derived by head to tail dimerization of unit 7. Thus, 9 was easily prepared from 8. Metalation of 9 by n-butyllithium in THF, carboxylation, esterification, hydrolysis, equilibration by 2-pyridine thiol in xylene led to the pure (E)-ketoester 10 in 30% yield. Subsequent ketalization [8f] produced 11, a known intermediate [8c] which has already been converted into (±) pyrenophorin 6. Since the (R) and (S) enantiomers of 3-hydroxy-butan-1-ol are both commercially available, it is possible to prepare optically active 11 and therefore to synthesize all diastereoisomers of 6 [9].



a) nBuli , THF ; b) $Br(CH_2)_2CH(Me)OSiMe_2Bu^t$; c) nBuLi, THF ; d) CO_2 then MeI, HMPA [3c] ; e) H_2SO_4 10% ; f) 2-pyridinethiol,xylene,reflux ; g)$(CH_2OH)_2$,$HC(OEt)_3$,BF_3-Et_2O,benzene, reflux.

Typical procedure : preparation of methyl 7- [(t-butyl)dimethylsilyloxy] -4-oxo-(E)2-octenoate 10 :

A solution of 6- [(t-butyl) dimethylsilyloxy]-3-methoxy-1, 2-heptadiene 9 [10] (7.5g ; 29,3mmol) in dry THF (80ml) was treated with n-butyllithium in hexane (20ml, 30mmol) under nitrogen at - 38° for 2.5h. After cooling to - 78°, a stream of dry CO_2 was bubbled through the solution for 1hr. The reaction mixture was stirred for an additionnal 2hr (-78° to 0°C), then HMPA (20ml) was added. Hexane and THF were removed under reduced pressure at 0°. Methyl iodide (20g, 140 mmol) was added and the solution was stirred overnight at room temperature. The mixture was transferred to a flask containing H_2SO_4 (10%, 250 ml) and ether (100 ml) cooled to 0° and kept under nitrogen. The mixture was stirred at 0° for 1hr. The organic phase was separated and the aqueous phase was extracted with ether. The combined ether layers were washed with brine, dried with magnesium sulfate and evaporated. The residue obtained was dissolved in xylene (80 ml) and heated under reflux in the presence of 2-pyridinethiol (84 mg ; 0.7 mmol) for 4 hr. Removal of xylene under reduced pressure followed by flash chromatography of the residue (ether : pentane, 10 : 90) gave pure (E) isomer 10 (2.64 g) in 30% overall yield from 9. NMR ($CDCl_3$), δ : -0.04 (s,3H) ; - 0.02 (s,3H) ; 0.81 (s,9H) ; 1.07 (d,3H, J=6Hz) ; 3.77 (s,3H) ; 3.83 (m,1H) ; 6.67 (d,1H, J=16Hz) ; 7.07 ppm(d, 1H, J=16Hz).

N O T E S and R E F E R E N C E S

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2. All reported yields are based on compounds purified by flash-chromatography. The new compounds were identified by satisfactory analytical and spectral data.

3. a) the addition of Me_2S_2 was carried out at -78°, the reaction mixture was slowly warmed up to 0° within 2hr.
   b) 30 mn at -78°
   c) anhydrous carbon dioxide was bubbled at -78° for 1 hr. ; the reaction mixture

was then warmed up to 0° and the lithium carboxylate was quenched with methyl iodide in HMPA.

4. Isomer 4b was obtained in 80% yield by heating pure 3b in xylene for 0.5 hr (method B). The trans methyl 4-oxo-2-nonenoate 4c was obtained in 50% overall yield from 1 by following method A for 7 hr or method B for 2 hr.

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9. The dimerizing cyclization of 7 using diethylazodicarboxylate and triphenyl phosphine occurs with inversion of configuration at the carbinol C-atom ; O. Mitsunobu, Synthesis, 1 (1981) ; see also ref. 8b .

10. prepared in 75% yield from 3- [(t.butyl) dimethyl silyloxy] -1-bromobutan [8c] and 1-methoxy-1,2-propadiene, S. Hoff, L. Brandsma and J.F. Arens, Recueil, Trav. Chim. Pays-Bas, 87, 916 (1968) ; L. Brandsma and H.D. Verkruijsse in "Synthesis of acetylenes, allenes and cumulenes", Elsevier Ed., Amsterdam, 1981, p. 38.

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