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A SHORT LARGE SCALE SYNTHESIS OF (±) SARKOMYCIN ESTERS.

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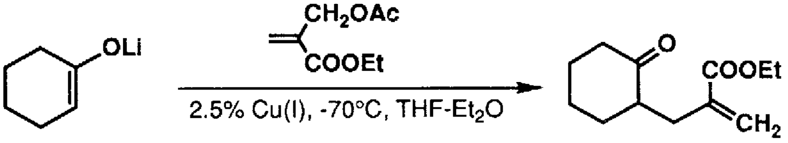
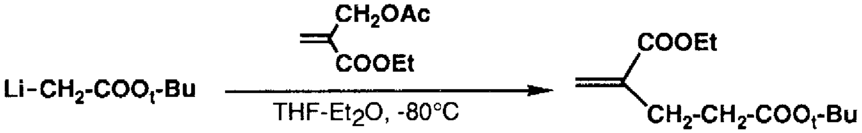
Abstract : *(±) Sarkomycin ethyl ester has been prepared in four steps from ethyl acrylate.*

We have previously described the substitution of α-functionnal acrylic esters by Grignard reagents in the presence of a catalytic amount of copper (I) (1). This reaction can be applied to lithium enolates (ester or ketone). It gives then rise to new α-substituted functional acrylates which are of great interest for the synthesis of biological active compounds (α-methylene δ-valerolactone, (±)-sarkomycin).



Yield 83%

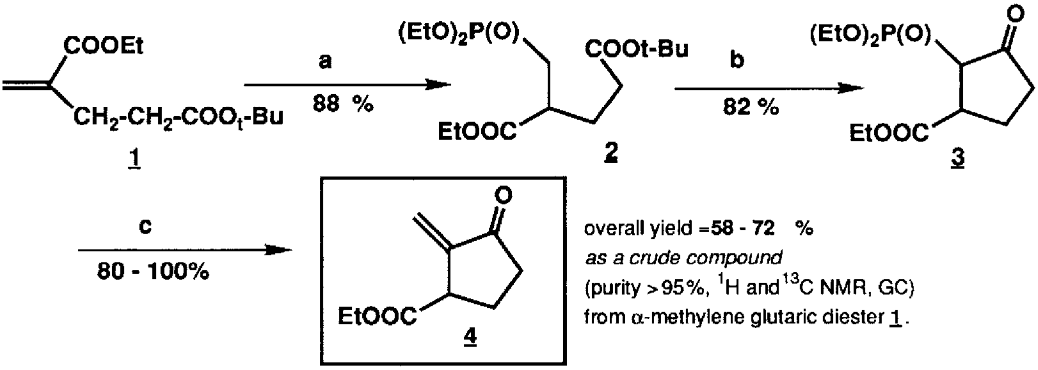


1 Yield 66%

A recent publication (2) on the synthesis of (±) sarkomycin including the same phosphonate 3 as a key intermediate prompts us to describe here our results. Many other preparations of (±) sarkomycin (or its esters) have been reported by multi step syntheses (2, 3) with low overall yields.

We report here a **very short, large scale and improved synthesis of *two* (±) sarkomycin esters** using low cost products and methodology. α-Methylene glutaric acid diester 1 can be included in a very short (3 steps -Michael addition, Dieckman cyclization, Wittig-Horner methylenation-) regiospecific synthesis of the antitumor agent (±) sarkomycin ethyl (or t-butyl)ester.

The addition of diethyl phosphite to the Michael acceptor 1 is performed using solid state potassium carbonate as the base and tetrabutylammonium hydrogen sulfate as a phase transfer reagent in the absence of any solvent. The Dieckman-like cyclization is then performed in THF in the presence of sodium hydride. It leads to the formation of the key β-ketophosphonate intermediate 3 that, under heterogenous low basic Wittig-Horner reaction of paraformaldehyde in THF (or aqueous formaldehyde in water), gives (±)-sarkomycin ethyl ester in 58-72% yields from 1. All these reactions can be performed on a large scale and 3 g of 4 have been prepared for the first time.



overall yield =**58 - 72** %
as a crude compound
(purity >95%, ^{1}H and ^{13}C NMR, GC)
from α-methylene glutaric diester 1.

a) $(EtO)_2P(O)H$, K_2CO_3, $HSO_4N(nC_4H_9)_4$ (2%), 70°C, 8h ; **b)** HNa, THF, Reflux ,1h .

c) (HCHO)n, K_2CO_3, THF, reflux, or aqueous HCHO (30%), K_2CO_3, 20°C, 20 minutes.

This synthesis can be improved using the direct dimerization of acrylates with trisdimethylaminophosphine (TDAP) as a catalyst. It gives 1 in one step.

TDAP

R = **Et**	TDAP 0.2 eq. , 2h, 60°C	Rdt **61** %
R = $_t$**-Bu**	TDAP 0.1 eq. , 16h, 20°C	Rdt **72** %

This reaction have been previously described (4,5) for the selective oligomerization of acrylates and acrylonitrile.

Reactions **a** and **b** can performed in a *one pot procedure* where sodium hydride is added to the heterogeneous mixture after completion of reaction **a** (checked by G.L.C.), giving 3 in 72 % yield. Reaction **c** gives rise either to ethyl or t-butyl esters 4, the selective hydrolysis of which to (±) sarkomycin is now being studied.

Studies on nucleophilic additions to α-methyleneglutaric esters in heterogenous low basic media are in progress.

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