

Diastereoselective Synthesis of Dimethyl Cyclopropane-1,1-Dicarboxylates from a γ -Alkoxy-Alkylidene Malonate and Sulfur and Phosphorus Ylides

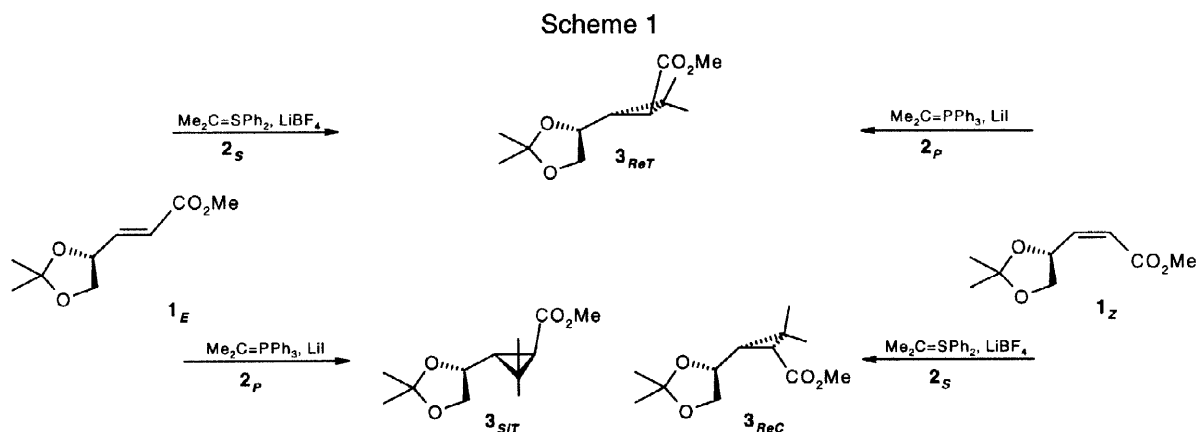
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Abstract: Isopropylidene diphenylsulfurane and isopropylidene triphenylphosphorane react by the same (*Re*) face of the alkylidene malonate derived from the acetonide of (*d*)-glyceraldehyde to produce almost exclusively a single diastereoisomer of the corresponding dimethyl cyclopropane-1,1-dicarboxylate. © 1998 Elsevier Science Ltd. All rights reserved.

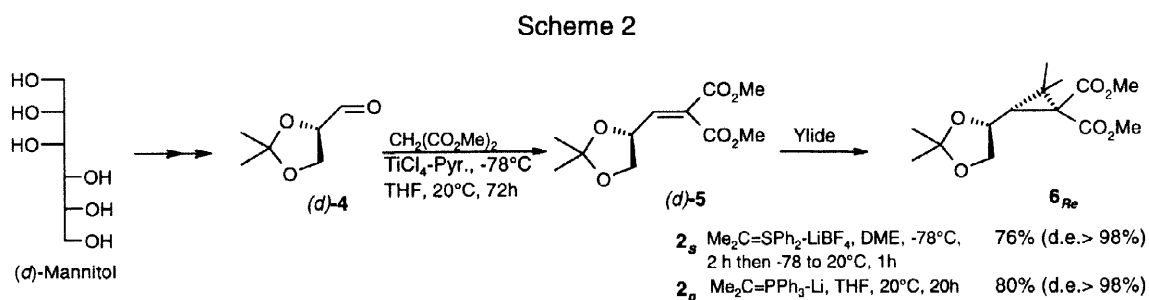
Addition reactions to γ -heterosubstituted- α,β -unsaturated esters **1** bearing an asymmetric centre in the γ -position have been extensively studied and used in synthesis.¹⁻³ Although high to very high asymmetric induction has been observed, the face of attack cannot be predicted accurately. It depends not only upon the nature of the reagent used but often upon the stereochemistry of the C,C double bond of the unsaturated esters.¹⁻³ We found for example that although very closely related isopropylidene diphenylsulfurane **2_S** and isopropylidene triphenylphosphorane **2_P** add both on the same *Re* face² of the *Z*-unsaturated ester **1_Z** leading to **3_{ReC}** and to **3_{ReT}** respectively, they react in a stereodivergent manner with its *E*-stereoisomer **1_E** producing the cyclopropyl esters **3_{ReT}** and **3_{SiT}** resulting from the attack on the *Re* face² with the sulfur ylide and the *Si* face with the phosphorus ylide³ respectively. These reactions have been used for the synthesis of optically active pyrethroid insecticides.⁴



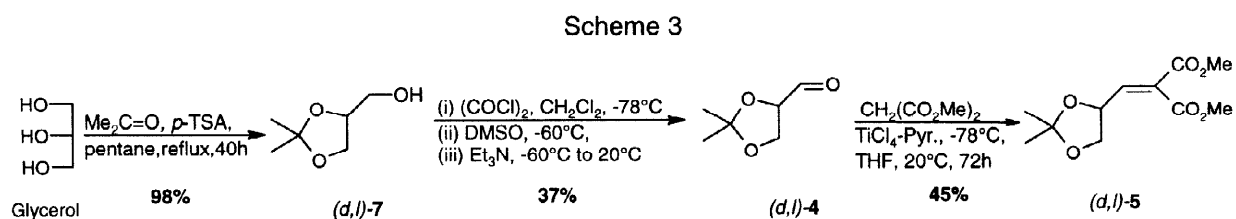
We have been for some time interested to extend this work to the related dimethyl alkylidene malonate **5**, but its synthesis was not obvious. It has been already obtained,⁵ in unspecified yield mixed with its β,γ -regioisomer from glyceraldehyde acetonide (*d*)-**4** via a Knoevenagel reaction catalyzed by piperidine in toluene. Its ethyl ester analogue is known but has been synthesized in only low yield using the same reaction.⁶

We decided to establish a convenient and reliable synthesis of enantiomerically pure **5** and to study its behavior toward the ylides **2_P** and **2_S**. We selected the Knoevenagel reaction⁷ due to the great availability of both partners: glyceraldehyde acetonide (*d*)-**4**⁸ and dimethyl malonate, hoping that one of the various experimental conditions described will avoid epimerisation of (i) the very labile glyceraldehyde acetonide (*d*)-**4**, derived from (*d*)-mannitol, before the reaction took place or of (ii) the alkylidene malonate once formed.

Although a number of conditions did not work properly,⁹ we found that the use of titanium tetrachloride in conjunction with pyridine¹⁰ was a good alternative (Scheme 2), on condition that the reaction is first performed at low temperature (-78°C) then carried out at room temperature for enough time to go to completion (20°C, 72 h, Scheme 2). The yield of enantiopure ($[\alpha]_D^{24^\circ\text{C}} = +20.4$, CHCl_3 ; e.e. > 98 %) distilled product ranges constantly between 50 to 60% on a 3-10 g scale and even reached 70% once.



The chemical and stereochemical purity of (*d*)-**5** derived from mannitol⁸ has been proved, using a chiral HPLC,¹¹ on which it exhibits a single peak whereas its racemate (*d,l*)-**5**, prepared from the acetonide of glycerol (*d,l*)-**7** (Scheme 3),¹² is resolved into two peaks under similar conditions.

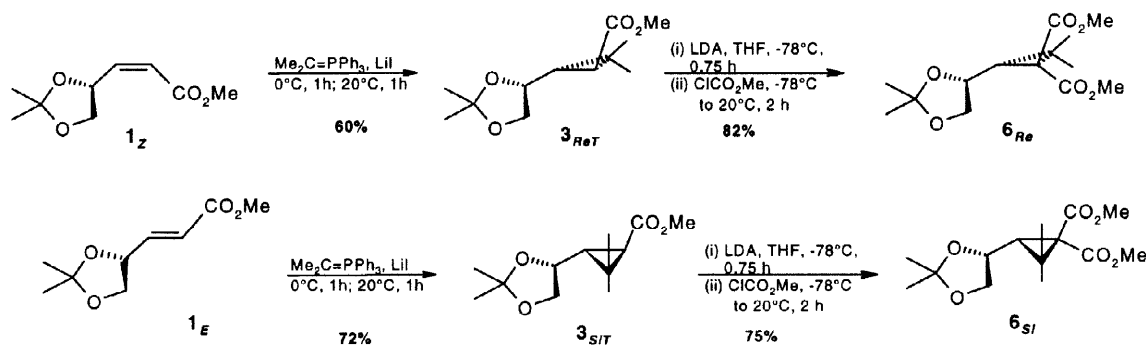


Little is known about the reactivity of phosphorus and sulfur ylides with alkylidene malonates,¹³ but we luckily found that the ylides **2_P** and **2_S** react with the alkylidene malonate (*d*)-**5** and produce both, in very good yield, the same dimethyl cyclopropane-1,1-dicarboxylate **6_{Re}** almost as a single diastereoisomer ($[\alpha]_D^{24^\circ\text{C}} = +0.93$, CHCl_3 ; d.e. > 97%, Scheme 2). As expected the sulfur ylide was the more reactive (DME, -78°C, 1h then -78°C to 20°C, 1h) since the phosphorus analogue required higher

temperature and much longer time to provide **6_{Re}** with the same yield (THF, 20°C, 1h : 46%; 3h : 74%; 20h : 80%).

The relative stereochemistry of the dimethyl cyclopropane-1,1-dicarboxylate **6_{Re}** and its stereochemical homogeneity has been assessed by correlation (¹H and ¹³C NMR) with an authentic sample of **6_{Re}**, prepared by carbomethoxylation of the enolate derived from the cyclopropyl ester **3_{Re}** (Scheme 4), which shows their identity.¹⁴

Scheme 4



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 9. Intractable mixtures of compounds have been obtained if the Knoevenagel reaction is carried out as follows (i) piperidine-AcOH, CH₂Cl₂, 20°C, 1h or 80 h (ii) piperidine, benzene, reflux, 72 h (ii) piperidine, benzene, 20°C, 24 h.
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 11. We used for that purpose a chiral column Chiralcel OD-H from *Daicel Chemical Industries*, 0.5x25 cm, solvent : hexane-isopropanol : 97/3, pressure : 47 bar, 1ml / min., UV detection 254 nm, (*l*)-**5** : Rt = 17.8 min. ; (*d*)-**5** : Rt = 19.2 min..
 12. (a) Oxidation of the acetonide of glycerol (*d,l*)-**7**^{12b} was unsuccessful with PCC even when carried out with AcONa as a buffer, since it provides an intractable mixture of compounds. Swern oxidation leads to the desired aldehyde (*d,l*)-**4** which cannot be fully purified. That is the reason why the yield of (*d,l*)-**5** was so low (b) Newman, M. S.; Renall, M. *J. Am. Chem. Soc.* **1945**, 67, 1621.
 13. (a) We previously found^{13b} that dimethyl ethylidene malonate reacts with isopropylidene triphenyl phosphorane (generated from isopropyl triphenylphosphonium iodide and *n*-BuLi in THF, 20°C, 1 h) to provide the corresponding dimethyl 2-ethyl-cyclopropane-1,1-dicarboxylate (i) in 44 % yield when the reaction is carried out in THF (20°C, 24 h) (ii) in 14% yield when performed in the same solvent but at higher temperature (80°C, 24h) and (iii) in 70 % yield if performed in a THF-DMSO mixture (80°C, 6h) (b) Unpublished results from our laboratory; De Vos M.-J. *Research Report*, July **1984**.
 14. This sample is very different from its diastereoisomer **6_{Sj}** synthesized from **3_{Sj}** according to the same procedure (Scheme 4).