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Mn^{III}-Promoted Synthesis of Functionalized γ-Lactones in Acetic and Formic Acids

Laurent Lamarque, Alain Méou and Pierre Brun*

Laboratoire de Synthèse Organique Sélective, associé au CNRS, GCOPL, Université de la Méditerranée, Faculté des Sciences de Luminy, 163 Avenue de Luminy, case 901, F-13288, Marseille Cedex 9, France.

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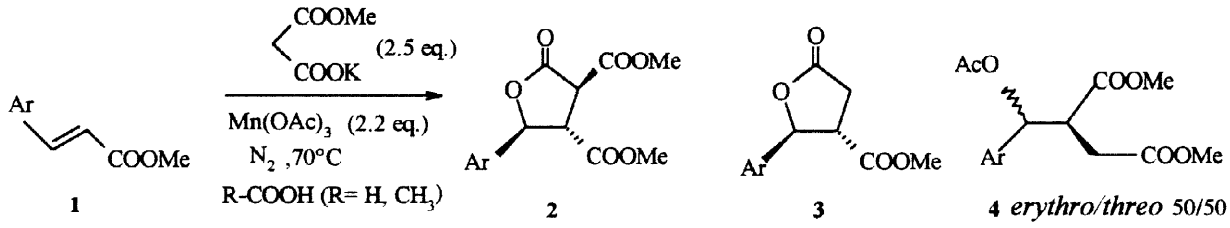
Abstract : The yield of substituted γ-lactones obtained by Mn^{III}-mediated addition of potassium monomethyl malonate on cinnamate esters can be optimized by performing the reaction either in acetic or in formic acid, depending on the substrate.

2,3,4-Trisubstituted γ-lactones can be conveniently synthesized by Mn^{III}-promoted addition of monomethyl malonate on 1,2-disubstituted olefins.[1-5] Provided that one of the substituents on the double bond is aromatic, the reaction is totally regioselective.[2,3] Regarding its diastereoselectivity, the picture was not so clear-cut. Starting from mono-, di- and trimethoxy cinnamate esters, Peterson described in numerous instances the formation of an epimeric mixture of lactones **2** although in a later paper, for one of these substrates, a single (all *trans*) epimer was reported along with an α-decarboxylated lactone as the major side product.[3] Moreover, starting from *trans*-stilbene, Trogolo reported the formation of a single lactone of undetermined stereochemistry.[4,5] In view of our previous results,[6] it seemed very unlikely that aromatic disubstituted olefins would give diastereomeric lactones and that what was considered as a minor epimer of **2** was in fact the α-decarboxylated lactone **3**.

We thus decided to re-examine the addition of monomethyl malonate on a series of *ortho* and/or *para* substituted *trans*-methyl cinnamates. The results are depicted in Figure 1 (R=CH_3) and Table 1.

Figure 1



1 **2** **3** **4** *erythro/threo* 50/50

a : Ar = C_6H_5; **b** : Ar = 4-MeC_6H_4 ; **c** : Ar = 4-$MeOC_6H_4$; **d** : Ar = 2,4-diMeC_6H_3 ; **e** : Ar = 2,4-di$MeOC_6H_3$

Table 1. Addition of potassium monomethyl malonate on cinnamates **1a-e** in acetic acid at 70°C.

Cinnamate	Time (min)	**2** :**3** :**4**	**2** (yield, %)	Unreacted **1** (%)
1a	120	73 :27 :0	29	28
1b	30	92 : 0 :8	44	37
1c	60	85 : 0 :15	51	19
1d	60	59 :37 :4	37	11
1e	30	100 : 0 :0	78	1

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The yields refer to pure isolated products and are based on starting olefin. The major product is always the single epimeric lactone **2**[7] accompanied in all but one case by one or two side products: the α-decarboxylated lactone **3**[8] and/or the acetoxy diester **4**. As expected, the yield of isolated lactone **2** is higher when starting from substituted cinnamates **1b-e** than from **1a**. However, except for **2e**, it remains modest due to the occurrence of **3** and **4**. Consequently, in order to improve the synthetic usefulness of this reaction, the formation of **3** and **4** had to be minimized or, preferably, suppressed. We found that this could be conveniently accomplished, in most cases, by using formic acid instead of acetic acid as the solvent (Figure 1, R=H and Table 2). Furthermore, it happens that the reaction in formic acid, contrary to what is observed with acetic acid, can be conducted at room temperature to give **2** in a yield very similar to the one obtained at 70°C.

Table 2. Addition of potassium monomethyl malonate on cinnamates **1a-e** in formic acid at 25 and 70°C.

Cinnamate	Temp.(°C)	Time (min)	**2** :**3**	**2** (yield, %)[a]	Unreacted **1** (%)
1a	25	180	72 :28	30	29
	70	10	69 :31	31	29
1b	25	135	100 :0	60	18
	70	10	100 :0	61	16
1c	25	135	100 :0	86	-
	70	10	100 :0	84	-
1d	25	90	100 :0	70	8
	70	10	100 :0	74	5
1e	25	240	100 :0	11[b]	3
	70	240	100 :0	2.5[b,c]	-

[a]Pure isolated material. [b]Accompanied by unidentified by-products. [c]Along with 8% of 2,4-dimethoxybenzaldehyde.

In summary, we have shown that lactones **2b-e**, possessing three contiguous stereocenters, can be prepared in good yield (61-86%) by a proper choice of the solvent.

References and notes:

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7. No other epimer could ever be detected by NMR or GC on a capillary column, either on the crude product or in the chromatographic fractions during the purification step.
8. In each case this lactone was independently prepared by addition of acetic acid on appropriate **1**.