A Convenient Method for the Preparation of 3-Substituted Glutarate Diesters

Gus J. Leotta, III,[1a] Larry E. Overman,* and Gregory S. Welmaker[1b]

Department of Chemistry, University of California, Irvine, California 92717-2025

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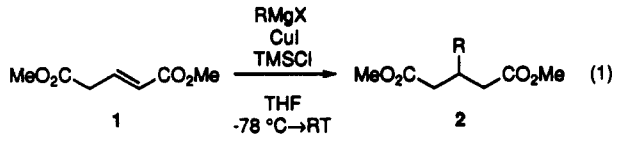
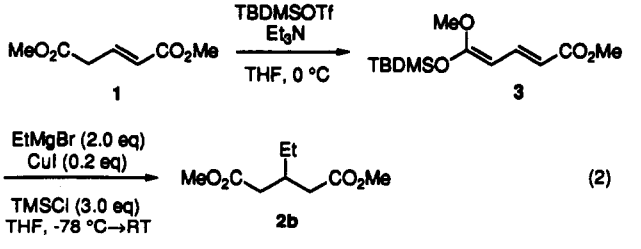
Enzymatic hydrolysis of prochiral 3-substituted glutarate diesters **2** provides ready access to a variety of enantioenriched intermediates for asymmetric synthesis.[2] The recent enantioselective synthesis of the macrolide antibiotic rhizoxin by Ohno and co-workers provides a representative example.[3] Unfortunately, no general, convenient procedure for preparing 3-substituted glutarate diesters is available. Previous attempts to prepare these diesters by conjugate addition of organocuprates to commercially available glutaconate diesters were unsuccessful, presumably due to the acidity of glutaconate diesters.[3c] Herein we report that treatment of dimethyl glutaconate (**1**) with Grignard reagents in the presence of catalytic CuI and excess TMSCl affords the corresponding 3-substituted glutarate diesters **2** in good yields (eq 1).



(1)

The synthesis of 3-substituted glutarate diesters **2** from the reaction of **1** with a Grignard reagent (3–4 equiv) in the presence of CuI (0.3 equiv) and TMSCl (3–5 equiv) was evaluated with five representative Grignard reagents. Results are summarized in Table 1. In the absence of TMSCl, no conjugate addition was observed. Yields of **2** were lower when 1–2 equiv of TMSCl was employed.

It is believed that **1** is first deprotonated and the derived enolate trapped with TMSCl. The resulting ketene silyl acetal intermediate then undergoes conjugate addition in the presence of TMSCl to afford the corresponding 3-substituted glutarate diester.[4] To test this proposal, we prepared the ketene *tert*-butyldimethylsilyl acetal **3** from dimethyl glutaconate and TBDMSOTf (eq 2). When **3**



(2)

was treated with EtMgBr in the presence of CuI (0.2 equiv) and TMSCl (3 equiv), glutarate diester **2b** was obtained in 77% yield. In the absence of TMSCl, no reaction was observed under identical conditions.

Table 1

entry	RMgX	product	isolated yield (%)
1	MeMgCl	**2a**	82
2	EtMgBr	**2b**	85
3	*i*-PrMgCl	**2c**	81
4	PhMgBr	**2d**	77
5	(*Z*)-MeCH=CHMgBr	**2e**	83

In summary, various 3-substituted glutarate diesters can be prepared from glutaconate diesters in high yield by copper-catalyzed addition of Grignard reagents in the presence of excess TMSCl. The trimethylsilyl analog of ketene silyl acetal **3** is a likely intermediate in this process.[5]

Experimental Section

General Procedure. Under a nitrogen atmosphere, a solution of the Grignard reagent (3–4 equiv) was added dropwise to a stirring suspension of CuI (0.3 equiv) in THF (0.1 M). The resulting mixture was stirred at room temperature until a dark color persisted (2–10 min). The mixture then was cooled to −78 °C, and TMSCl (3–5 equiv, freshly distilled from CaH_2) and the diester (1 equiv) were introduced sequentially. The reaction mixture was stirred at −78 °C for 1–2 h and then allowed to warm to ambient temperature over 4–8 h. The reaction then was quenched with saturated aqueous NH_4Cl and diluted with EtOAc. The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography through silica gel (elution with 5% ethyl acetate–hexanes).

Dimethyl 3-[(*Z*)-1-Propenyl]glutarate (2e). Dimethyl glutaconate (5.0 g, 32 mmol) was allowed to react with (*Z*)-1-propenylmagnesium bromide according to the general procedure to afford 5.2 g (83%) of **2e**: IR (film) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (dq, J = 10.9, 6.9 Hz, 1H), 5.13 (dd, J = 10.8, 10.4 Hz, 1H), 3.61 (s, 6H), 3.35 (m, 1H), 2.41 and 2.26 (ABX, J_{AB} = 15.1 Hz, J_{AX} = 6.2 Hz, J_{BX} = 8.0 Hz, 4H), 1.62 (dd, J = 6.9, 1.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 131.1, 126.1, 51.5, 39.4, 30.6, 12.9; HRMS (CI) calcd for $C_{10}H_{17}O_4$ (MH) 201.1126, found 201.1137. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.96; H, 8.07.

Methyl (2*E*,4*E*)-5-(*tert*-Butyldimethylsiloxy)-5-methoxy-2,4-pentadienoate (3). To a stirring, cooled (0 °C) solution of 100 mg (63 μmol) of diester **1** and 5 mL of THF was added sequentially 0.26 mL (1.9 mmol) of Et_3N and 0.17 mL (74 μmol) of TBDMSOTf. The resulting solution was allowed to warm to ambient temperature over 1 h. The reaction then was concentrated under reduced pressure, and the residue was dissolved in 10% ethyl acetate–hexanes and then filtered through Celite. The crude product was purified by flash chromatography through silica gel (elution with 5% ethyl acetate–hexanes) to afford 0.15 g (88%) of **3**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (dd, J = 15.3, 11.2 Hz, 1H), 5.55 (d, J = 15.3 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 0.96 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 163.3, 142.7, 109.5, 78.9, 55.2, 50.7, 25.4, 17.9, −4.5; HRMS (CI) calcd for $C_{13}H_{25}O_4Si$ (MH) 273.1522, found 273.1529.

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