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STEREOSELECTIVE SYNTHESIS OF SOME DIALKYL (E)-2-BROMOMETHYLENE GLUTARATES

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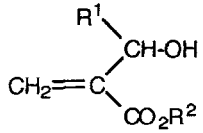
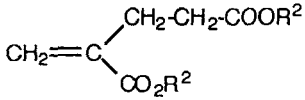
Abstract: *Reaction of 2-bromo-2-bromomethyl glutaric acid esters with tetraalkylammonium fluoride in HMPA, conveniently provides the corresponding dialkyl (E)-2-bromomethylene derivatives in good yields.*

α-Hydroxyalkyl acrylic esters **1**[1] and their analogues (ketones and nitriles) still widely used intermediates because of their ability to function as excellent Michael acceptors[2]. Thus, it has previously been reported that the dimerization of alkyl acrylate in the presence of catalytic amount of trialkyl phosphines[3], leads to the corresponding dialkyl α-methylene glutarates **2** (Scheme 1). In our case, we found that compounds **2** may be obtained from the substitution reaction of α-acetoxymethyl acrylic esters by lithium esters enolates in the presence of copper(I) at low temperature[4].



1



2

Scheme 1

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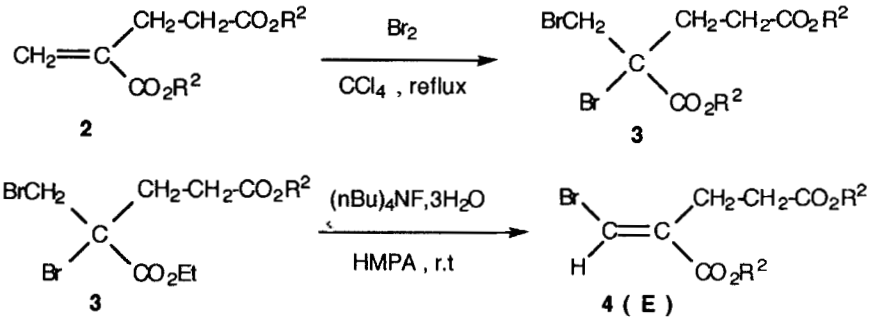
In this communication we describe a convenient stereoselective preparation of dialkyl (E)-2-bromomethylene glutarates **4** from the corresponding dialkyl 2-methylene glutarate **2** (Scheme 2).



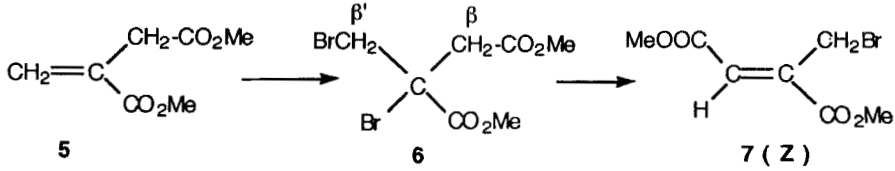
Scheme 2

Table 1: Synthesis of some dialkyl (E)-2-(bromomethylene) glutarates **4a-c**

R^2	Substrates **3a-c**	Yield (%)	Products **4a-c**	Yield (%)
CH_3	**3a**	84	**4a**	83
CH_3-CH_2	**3b**	78	**4b**	76
$(CH_3)_3C$	**3c**	88	**4c**	73

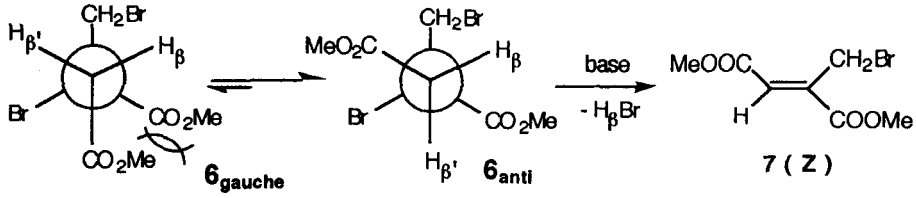
As shown in Scheme 2, treatment of a refluxed carbon tetrachloride solution of **2** with bromine produces the corresponding dibromide adducts **3**. The reaction of compounds **3** mentioned above under mild conditions using HMPA solution of tetrabutylammonium fluoride[5] $(nBu)_4NF,3H_2O$ as base[6-8] gave the desired vinylic bromides **4** in high yields (Table 1).

Recently, the same procedure described above has been applied in one pot to commercially available dimethyl itaconate **5**, furnished dimethyl (Z)-2-bromomethyl fumarate **7**[9] in 73% overall yield (Scheme 3) :



Scheme 3

Regio- and stereoselectivity observed in the case of vinylic bromide derivatives **4** had been studied[10], whereas the regioselective elimination observed in the case of the analogue **7** can be interpreted on the basis of the more acidic proton β then proton β'. However stereoselectivity can be easily rationalized by comparison of the stability of the two conformers $\mathbf{6_{gauche}}$ and $\mathbf{6_{anti}}$. The latter appears to be more favoured with regard to steric and electronic effects (Scheme 4):



Scheme 4

Experimental section

General methods

Preparation of dialkyl-2-methylene glutarate is accomplished by the dimerization of alkyl acrylate in the presence of catalytic amount (2%) of tris dimethylaminophosphine in tetrahydrofuran at 70°C according to the reference 3a. They can be obtained from the substitution reaction of 2-(acetoxymethyl) acrylic esters by lithium esters enolates[4] in the presence of copper(I) as catalyst at -78°C. Reaction progress and purity of products were monitored on an Intersmat 20M gas chromatograph using a 3mx3mm column packed with 10% SE 30. IR spectra were taken on Perkin-Elmer 257 spectrophotometer. ^1H and ^{13}C Nuclear Magnetic Resonance were recorded on a Jeol C-HL 60MHz, FX 90MHz and Bruker 200MHz instruments in $CDCl_3$ solution with TMS as the internal standard.

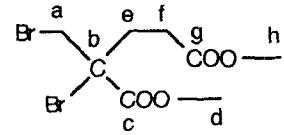
Synthesis of dialkyl 2-bromo-2-bromomethyl glutarates 3a-c

Typical procedure

A 250 mL three-necked round-bottomed flask, fitted with a reflux condenser, magnetic stirring bar, and 100 mL pressure-equalising addition funnel,

is charged with dimethyl-2-methylene glutarate **2a** (25.8g, 0.15mol) and anhydrous carbon tetrachloride (150mL). The mixture is stirred and heated to gentle reflux. The addition funnel is charged with bromine (8mL, 0.155 mol) diluted in anhydrous carbon tetrachloride (40mL) which is added dropwise at a rate such that the bromine colour gradually disappears. The end of the reaction is indicated by the persistence of a brownish colour. The mixture is cooled, and excess bromine is removed by washing with aqueous sodium thiosulfate until the solution is discoloured. The organic layer is separated and washed with water (50mL), dried over anhydrous magnesium sulfate and concentrated. The residue is distilled at reduced pressure yielding (41.80g, 84%) of dimethyl-2-bromo-2-bromomethyl glutarate **3a** as pale yellow oil.

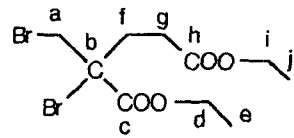
Dimethyl 2-bromo-2-bromomethyl glutarate 3a



b.p.(°C/ torr): 116/0.5
IR($CHCl_3$,vcm^{-1}):1740(C=O) ; 1730(C=O).

^1H NMR($CDCl_3$,TMS): 2.56(s,4H,$2CH_2$) ; 3.70 and 3.83(2m,6H,$2CH_3$) ; 3.96 (AB,2H,J=7Hz,CH_2Br). ^{13}C NMR($CDCl_3$,TMS): f: 24.49 ; e: 31.30 ; a: 34.65 ; h: 50.88 ; d: 52.35 ; b: 58.99 ; g: 167.72 ; c: 170.15.

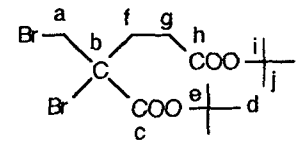
Diethyl 2-bromo-2-bromomethyl glutarate 3b



b.p.(°C/ torr): 120/0.5
IR($CHCl_3$,vcm^{-1}):1740(C=O) ; 1735(C=O).

^1H NMR($CDCl_3$,TMS): 1.30(t,3H,J=7Hz,$2CH_3$) ; 2.51(s,4H,$2CH_2$) ; 3.93(AB,2H,J=7Hz,CH_2Br) ; 4.23(q,J=7Hz,$2CH_2O$-). ^{13}C NMR($CDCl_3$,TMS): j: 13.86 ; e: 14.80 ; g: 30.45 ; f: 31.43 ; a: 35.07 ; b: 60.73 ; i: 60.73 ; d: 62.75 ; h: 167.95 ; c: 172.08.

Di ^{t}butyl 2-bromo-2-bromomethyl glutarate 3c



F : 47 °C
IR($CHCl_3$,vcm^{-1}):1740(C=O) ; 1730(C=O).

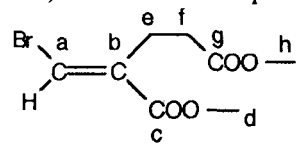
^1H NMR($CDCl_3$,TMS): 1.46(s,9H,C_4H_9); 1.50(s,9H,C_4H_9) ; 2.46(m,4H,$2CH_2$) ; 3.88(AB,2H,J=7Hz,CH_2Br). ^{13}C NMR($CDCl_3$,TMS): j: 27.56 ; d: 28.05 ; g: 31.57 ; f: 31.80 ; a: 35.73 ; b: 61.89 ; i: 80.78 ; e: 83.47 ; h: 166.75 ; c: 171.45.

Synthesis of dialkyl (E)-2-bromomethylene glutarates 4a-c

Typical procedure

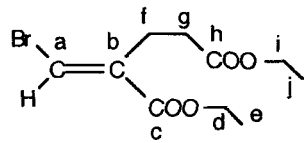
To a 250mL three-necked round-bottomed flask, fitted with an efficient mechanical stirrer, a 100mL pressure equalising addition funnel and reflux condenser protected by calcium chloride drying tube are added tetrabutylammonium fluoride $(nBu)_4NF,3H_2O$ (23,62g, 75mmol, 1.25equiv.) and hexamethylphosphoramide (HMPA, 40mL). The mixture is cooled to 0°C in an ice bath and stirred until it becomes homogeneous. Dimethyl-2-bromo-2-bromomethyl glutarate **3a** (19,92g, 60mmol, 1equiv.) is added via the pressure-equalising dropping funnel over 30 min period. After the addition is complete, the reaction mixture is stirred at 0°C for one hour and is then allowed to warm gradually to room temperature for a period of ten hours until the starting dihalogenated ester disappears. The brown mixture is cooled and quenched with aqueous solution of sulfuric acid (2N, 120mL), then extracted with hexane (80mLx 5). The combined organic extracts are washed with water until neutrality of the aqueous layer and dried over anhydrous magnesium sulfate. The slurry is filtered through a glass filter and the filtrate is concentrated. The residue is distilled at reduced pressure to give dimethyl (E)-2-bromomethylene glutarate **4a** (12.49g, 83 %) as a colourless liquid.

Dimethyl (E)-2-bromomethylene glutarate 4a



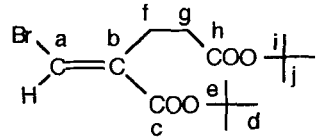
b.p.(°C/ torr): 90/0.3
IR($CHCl_3$,vcm^{-1}):1725(C=O) ; 1715(C=O) ; 1620(C=C).
^1H NMR($CDCl_3$,TMS): 2.60 and 2.73(2m,4H,$2CH_2$) ; 3.66(s,3H,CH_3) ; 3.76(s,3H,CH_3) ; 7.53 (s,1H,=CHBr). ^{13}C NMR($CDCl_3$,TMS): f: 24.52 ; e: 30.84 ; a: 50.54; h: 51.28 ; d: 121.89 ; b: 133.78 ; g: 161.96 ; c: 170.13.

Diethyl (E)-2-bromomethylene glutarate 4b



b.p.(°C/ torr): 78/0.2
IR($CHCl_3$,vcm^{-1}):1725(C=O) ; 1715(C=O) ; 1610(C=C).
^1H NMR($CDCl_3$,TMS): 1.26(t,6H,J=7Hz,$2CH_3$) ; 2.56 and 2.73(2m,4H,$2CH_2$) ; 4.16(q,4H,J=7Hz,$2CH_2O$-) ; 7.42(s,1H,=CHBr). ^{13}C NMR($CDCl_3$,TMS): j: 14.18 ; e: 14.18 ; g: 25,37 ; f: 32.00 ; i: 60,50 ; d: 61.28 ; a: 123.70 ; b: 136,80 ; h: 162.62 ; c: 172.27.

Di ^{t}butyl (E)-2-bromomethylene glutarate 4c



b.p.(°C/ torr): 98/0.25

IR($CHCl_3$,vcm^{-1}):1725(C=O) ; 1710(C=O) ; 1615(C=C).

^{1}H NMR($CDCl_3$,TMS): 1.50(s,9H,tC_4H_9) ; 1.54(s,9H,tC_4H_9) ; 2.43 and 2.66(2m,4H,$2CH_2$) ; 7.43(s,1H,=CHBr). ^{13}C NMR($CDCl_3$,TMS): j: 26.78 ; d: 27.96 ; g: 25.41 ; f: 31.15 ; i: 81.09 ; e: 83.78 ; a: 124,32 ; b: 135.97 ; h: 165.16 ; c: 173.03

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