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Synthesis of a Novel α-Methylene-β-carboxy-γ-thiobutyrolactones

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Abstract: A new series compounds, α-methylene-β-carboxy-γ-thiobutyrolactones, have been prepared and their biological evaluation *in vitro* and *in vivo* have been described. The structures of these compounds were confirmed by ^{1}H NMR and FAB-MS spectra.

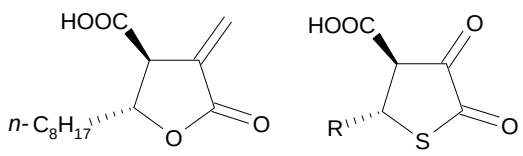
Keywords: Fatty acid synthase, α-methylene-β-carboxy-γ-thiobutyrolactones, synthesis.

Obesity is one of the most common metabolic pathologies in contemporary society, that is associated with increased risk of type II diabetes, cardiovascular and cerebrovascular diseases. Fatty acid synthase(FAS) is the key enzyme in *de novo* lipogenesis, which has been proved to be a new appetite and body weight regulation pathway in mice. C75(**1)** (**Figure 1**) is a novel inhibitor of FAS[1], which can lead a distinct decrease of food intake and body weight of mice without significant toxity[2].

Our interest was initially kindled by the novel mechanism and the structure of C75. As a part of our program aimed at discovering new fatty acid synthase inhibitors, expected to find new agents for the treatment of obesity, we designed a novel *trans*-isomer α-methylene-β-carboxy-γ-thiobutyrolactones (**2**) as our target compounds. Herein we describe the new successful synthesis of these compounds(**Scheme 1**).

In a general procedure, the yieldes of the condensation of succinate esters with aldehydes, known as the Stobbe reaction, are variable and from them a number of other products can arise. To improve the selectivity and yield of this reaction, we sought an activated succinate esters **4**. The anion of **4**, created with NaH or LDA, underwent the expected reaction with aldehydes to give diethyl itaconates, the crude products were cleaved with NaOH/H_2O to give the desired products **5**[3].

Figure 1



1 **2**

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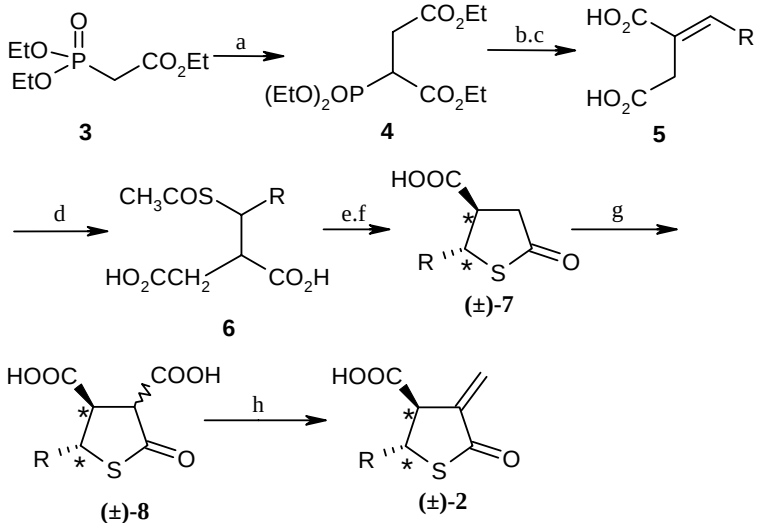
Scheme 1 The synthesis of α-methylene-β-carboxy-γ-thiobutyrolactones



Reagents and conditions: a. NaH/THF; $BrCH_2CO_2Et$ 76.5%; b. LDA/THF; *n*-RCHO; c. NaOH / H_2O b+c 48-57%; d. CH_3COSH 80-85°C/3 days; e. 6 mol/L HCl reflux; f. TFA/reflux d+e+f 39-48.5%; g. $CH_3OCO_2MgOCH_3$ 1.8 mol/L DMF 135-140℃ 3 days; h. Stock solution g+h 29-50.4%

Table 1 Physical data of title compounds **2a-e**

Entry	R	Mp(℃)	^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz)	^{13}C NMR (100 MHz, $CDCl_3$, δ ppm)	FAB-MS *m/z*
2a	*n*-C_6H_{13}	77-79	6.18(d, 1H, J=2.24), 5.61(d, 1H, J=2.0) 4.08(dt, 1H, J= 9.04, 5.28), 3.71(dt, 1H J=2.0, 5.32) 1.1-2.1(m, 10H) 0.88(t, 3H J=6.56)	14.0, 22.4, 27.6, 28.7, 31.5, 37.0, 47.0, 53.01, 120.1, 142.0, 175.8, 195.3	242
2b	*n*-C_8H_{17}	79-81.5	6.18(d, 1H J=2.36), 5.60(d, 1H J=2.12) 4.08(dt, 1H J= 5.08, 9.28), 3.71(dt, 1H J= 2.28, 5.32) .1-2.1(m, 14H) 0.86(t, 3H J=6.68)	14.0, 22.6, 27.6, 28.3, 29.1, 29.2, 31.7, 36.9, 47.0, 53.0, 120.1, 142.1, 175.3, 195.4	270
2c	*n*-C_9H_{19}	81-82.5	6.17(d, 1H J=2.48), 5.59(d, 1H J=2.28) 4.08(dt, 1H J= 9.28, 5.32), 3.72(dt, 1H J= 5.52, 2.04) .1-2.1(m, 16H) 0.88(t, 3H J=6.8)	14.0, 22.6, 27.6, 29.2, 29.3, 29.4, 29.6, 31.8, 37.0, 47.1, 53.0, 120.0, 142.1, 175.6, 195.4	284
2d	*n*-$C_{10}H_{21}$	83-85	6.18(d, 1H J=2.48), 5.61(d, 1H J=2.28) 4.08(dt, 1H J= 9.28, 5.32), 3.71(dt, 1H J= 5.42, 2.14) .1-2.1(m, 18H) 0.89(t, 3H J=6.68)	14.1, 22.6, 27.6, 29.2, 29.3, 29.4, 29.5, 29.6, 31.8, 37.0, 47.1, 53.1, 120.0, 142.2, 175.5, 195.5	298
2e	*n*-$C_{11}H_{23}$	85.5-87	6.18(d, 1H J=2.4), 5.59(d, 1H J= 2.12) 4.08(dt, 1H J=9.28, 5.32), 3.71(dt, 1H J=2.12, 5.32) .1-2.1(m, 20H) 0.86(t, 3H J=6.64)	14.1, 22.6, 27.6, 29.1, 29.3(×2), 29.4, 29.5(×2), 31.8, 37.0, 47.0, 52.9, 120.1, 142.0, 175.4, 195.2	312

1,4-Addition of thioacetic acid to the compound **5** gave the product **6** according to Holmberg. The acetylthio group was hydrolyzed to the thiol[4,5], which then formed the *trans*-thiolactone **(±)-7** by an acid-catalyzed procedure[5].

Stiles´ reagent (methyl methoxymagnesium) had been described that it could make the *trans*-β-carboxy-γ-butyrolactones α-carboxylated efficiently[6,7]. We applied this reagent for the synthesis of our target compounds. The reactions proceeded well without suffering appreciable ring cleavage and that the product **(±)-8** could be converted with diethylamine in formalin (Stock solution) to racemic *trans*-isomer **(±)-2** in about 50% yield. Chiral separation and configuration determination of racemic compounds is in processing.

In total, we have synthesized 5 new target compounds. The structures of these compounds were confirmed by ^{1}H-NMR, ^{13}C-NMR and FAB-MS (data shown in **Table 1**).

Cheerfully, compounds **2a-e** all exhibited more stronger inhibition activity to FAS than C75 *in vitro*. *In vivo*, compounds **2b** produced sustained reduction in body weight of DIO mice as long as the drug was administered, and reduced adipose mass of liver, kidney and other peripheral tissues. It could also normalize the obesity-associated hyperglycemia and hyperinsulinemia.

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