

TRANSESTERIFICATION REACTIONS WITH Mg^0/I_2 FOR THE SYNTHESIS OF SITOPHILATE, (2R*, 3S*) 1-ETHYLPROPYL-2-METHYL-3-HYDROXPENTANOATE, AN AGGREGATION PHEROMONE FOR *SITOPHILUS GRANARIUS* LINNAEUS, 1785 (COLEOPTERA: CURCULIONIDAE)

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ABSTRACT

The concern to minimize the environmental impacts caused by the use of pesticides in agriculture has led researchers to develop new pest control methods. Thus, the technology based on the use of pheromones has been noted for being highly specific substances, that is act only on individuals of the same species. In this context, we describe the synthesis of sitophilate, aggregation pheromone of *Sitophilus granarius*, a important pest of stored cereal grains. The sitophilate was obtained by

transesterification of methyl-2-methyl-3-oxopentanoate with 3-pentanol mediated by Mg^0/I_2 , with subsequent reduction of the ketone group of 1-ethylpropyl-2-methyl-3-oxopentanoate using $NaBH_4$ in the presence of a Lewis acid ($ZnCl_2$, $MgCl_2$, $CaCl_2$ and $MnCl_2$). The experimental results showed that the $MnCl_2$ is the most effective for the formation of *syn* diastereoisomers, since these are the compounds that exert biological activity on the insect.

KEYWORDS: Synthesis, pheromone, sitophilate, *Sitophilus granarius*, β -keto ester.

REAÇÕES DE TRANSESTERIFICAÇÃO COM Mg^0/I_2 MEDIANDO À SÍNTESE DO SITOFILATO, (2R*, 3S*)-2-METIL-3-HIDROXIPENTANOATO DE 1-ETILPROPILA, FEROMÔNIO DE AGREGAÇÃO DO *SITOPHILUS GRANARIUS* LINNAEUS, 1785 (COLEOPTERA: CURCULIONIDAE)

RESUMO

A preocupação em minimizar os impactos ambientais ocasionado pelo uso de agrotóxicos na agricultura tem levado pesquisadores a desenvolver novos métodos de controle de pragas. Assim, a tecnologia baseada no uso de feromônios tem se destacado por serem substâncias altamente específicas, ou seja, agem apenas sobre indivíduos de uma mesma espécie. Neste contexto, descrevemos a síntese do sitofilato, feromônio de agregação do *Sitophilus granarius*, uma importante praga de grãos de cereais armazenados. O sitofilato foi obtido

através da transesterificação do 2-metil-3-oxopentanoato de metila com 3-Pentanol mediada por Mg^0/I_2 , com posterior redução do grupo cetona do 2-metil-3-oxopentanoato de 1-etilpropila utilizando $NaBH_4$ na presença de um ácido de Lewis ($ZnCl_2$, $MgCl_2$, $CaCl_2$ e $MnCl_2$). Os resultados experimentais mostraram que o $MnCl_2$ é o mais efetivo para a formação dos diastereoisômeros *syn*, uma vez que estes compostos são os que exercem atividade biológica no inseto.

PALAVRAS-CHAVE: Síntese, feromônio, sitofilato, *Sitophilus granarius*, β -cetoésteres.

1 INTRODUCTION

The β -keto esters are important intermediates in organic synthesis, as they are used in the preparation of various natural products in research laboratories, for the pharmaceutical and agrochemical industries, and for polymers manufacture (MA *et al.*, 2016, NOVACEK *et al.*, 2016, MINAMI *et al.*, 2016, WANG *et al.*, 2011, SAIRRE *et al.*, 2005, BO *et al.*, 2003, CHAVAN *et al.*, 2002, WEST & GUNAWARDENA, 1993, HOLMQUIST & ROSKAMP, 1990, KLIPA & HART, 1981, BARCO *et al.*, 1980, BECKET *et al.*, 1978). The transesterification reaction (Figure 1) is an important methodology for the transformation of one ester to another (LIU *et al.*, 2016, SRIDHARAN *et al.*, 2010, IWASAKI *et al.*, 2008, YADAV *et al.*, 2007). This may be carried out spontaneously at high temperature or by using homogeneous or heterogeneous catalysis in an acidic, basic (KIM & KIM, 2016, NAGANAWA *et al.*, 2015, RAFIEE & EAVANI, 2012, PANDEY & KUMAR, 2007) or enzymatic (RAVIA *et al.*, 2013, DHAKE *et al.*, 2011, KALAITZAKIS *et al.*, 2007, CORDOVA & JANDA, 2001, PUNTAMBEKAR & NAIK, 1998) medium by using a Dean Stark apparatus.

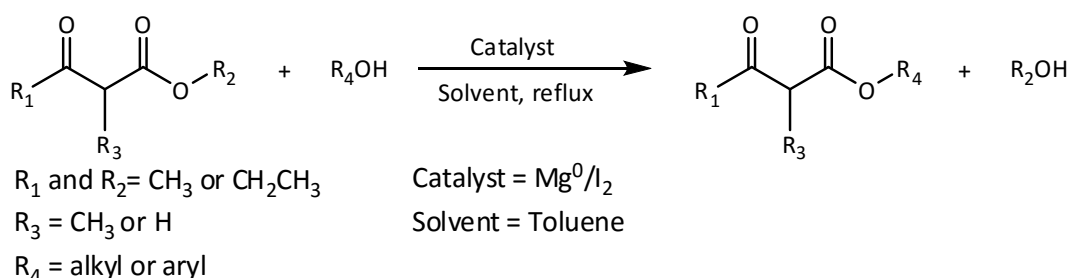


Figure 1: General transesterification reaction.

In this study, some β -keto esters were prepared using ethyl acetoacetate as the substrate, and iodine and magnesium metal as the catalysts, in order to verify the feasibility and the best experimental conditions for the reaction. Afterward, this methodology was applied to the synthesis of *syn* stereoisomers of sitophilate, ($2R^*$, $3S^*$) 1-ethylpropyl-2-methyl-3-hydroxypentanoate (**1a** and **1b**) (Figure 2). These compounds are major components of the aggregation pheromone of grain weevil *Sitophilus granarius* (KALAITZAKIS & SMONOU, 2008, PHILLIPS *et al.*, 1987), an insect that severely damages wheat, barley, corn and other cereals. Such damage causes annual losses of millions of dollars to farmers in many countries (MATEUS *et al.*, 2001, CHAMBERS *et al.*, 1996).

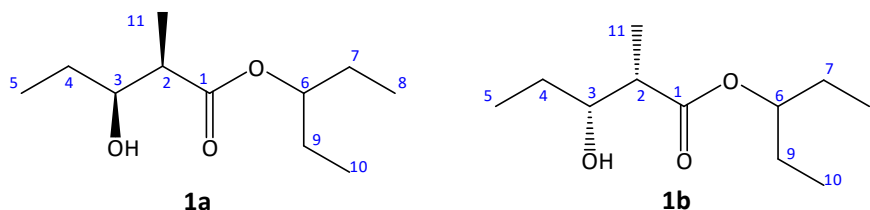


Figure 2: Structure of the *syn* stereoisomers of sitophilate.

In the biological studies, a racemic mixture of sitophilate (*syn* stereoisomers) showed attractiveness similar to the natural product, and unlike the *anti* stereoisomers (pure or racemic

mixture), which was shown to be less attractive (MATEUS *et al.*, 2001, BERGMANN *et al.*, 2009, GIL *et al.*, 2005, CHAVAN *et al.*, 1996, RAZKIN *et al.*, 1996, MORI & ISHIKURA, 1989, CHONG, 1989).

2 EXPERIMENTAL

2.1 General procedure for transesterification reactions

In a 125-mL bi-tubular flask coupled to a reflux condenser and under an inert atmosphere, activated metallic magnesium (1.2 g; 50 mmol) was introduced, and then the starting ester (volume and mass dependent on the respective esters; 7.7 mmol) in 10 mL of dry toluene, was slowly added. Under magnetic stirring, the alcohol (mass and volume dependent on the respective alcohols, 21 mmol) was slowly added. After 10 min, I₂ (0.3 g; 1.2 mmol) was added. The mixture was heated to reflux at the conditions shown in Table 1. The reactions were monitored by thin-layer chromatography and the plates were developed with the chromogen agent KMnO₄ in acidic solution. At the end of the reaction, 20 mL of saturated NH₄Cl solution was added. The reaction products obtained were extracted with three portions of 30 mL of ethyl ether, and the organic phase were poured together and washed three times with 40 mL of saturated solution of NaCl and dried over anhydrous Na₂SO₄, filtered and the solvent was then evaporated. The crude products were purified by column chromatography on silica gel by elution with a gradient of increasing polarity with hexane/ethyl acetate (5%, 10%, 15%, and 20%). The fractions corresponding to the transesterified products were analyzed and characterized by ¹H NMR, ¹³C NMR and GC-MS.

Pentyl-3-oxobutanoate (**2**)

Yield = 77 %, (mass = 1.01 g ± 0.02).

¹H NMR (400 MHz, CDCl₃) δ 0.91 (t, 3H, *J* 6.8 Hz, CH₃), 1.35–1.32 (m, 4H, CH₂), 1.65 (qt, 2H, *J* 6.9 Hz, CH₂), 2.27 (s, 3H, CH₃), 3.46 (s, 2H, CH₂), 4.14 (t, 2H, *J* 6.8 Hz), 4.99 (s, 1H, CH_{enolic}), 12.12 (s, 1H, OH). ¹³C NMR (100 MHz, CDCl₃) δ 13.95, 22.30, 27.99, 28.21, 30.13, 50.14, 65.54, 89.79, 167.26, 172.77, 175.42, 200.68. MS *m/z* (%) 172 ([M]⁺, 0.28), 130 (0.32), 115 (1.08), 103 (31.41), 85 (44.18), 70 (55.65), 55 (45.24), 43 (100.00), 42 (65.24).

Hexyl-3-oxobutanoate (**3**)

Yield = 72 %, (mass = 1.01 g ± 0.04).

¹H NMR (400 MHz, CDCl₃) δ 0.89 (t, 3H, *J* 6.9 Hz, CH₃), 1.31 (sl, 6H), 1.64 (qt, 2H, *J* 7.0 Hz, CH₂), 2.27 (s, 3H, CH₃), 3.45 (s, 2H, CH₂), 4.13 (t, 2H, *J* 6.8 Hz, CH₂), 4.99 (s, 1H, CH_{enolic}); 12.13 (s, 1H, OH). ¹³C NMR (100 MHz, CDCl₃) δ 14.01, 22.57, 25.55, 28.52, 30.10, 31.44, 50.12, 65.51, 89.77, 167.26, 172.76, 175.42, 200.62. MS *m/z* (%) , not observed [M]⁺, 158 (0.04), 129 (0.05), 103 (13.81), 85 (17.71), 69 (9.87), 56 (24.37), 55 (17.92), 43 (100.00), 41 (19.71).

1-Ethylpropyl-3-oxobutanoate (**4**)

Yield = 66 %, (mass = 0.87 g ± 0.03).

¹H NMR (400 MHz, CDCl₃) δ 0.92–0.88 (m, 6H, CH₃), 1.61–1.57 (m, 4H, CH₂), 2.28 (s, 3H, CH₃), 3.46 (s, 2H, CH₂), 4.83–4.79 (m, 1H, CH), 4.99 (s, 1H, CH_{enolic}), 12.20 (s, 1H, OH). ¹³C NMR (100 MHz, CDCl₃) δ 9.56, 26.38, 26.59, 30.14, 50.44, 78.12, 90.03, 167.04, 172.70, 175.27, 200.74. MS *m/z* (%) 172 ([M]⁺, 0.13), 157 (0.01), 143 (1.26), 114 (0.39), 103 (19.93), 101 (11.06), 85 (66.96), 70 (23.24), 59 (29.12), 43 (100.00), 42 (24.22), 41 (23.97).

1-Methylpropyl-3-oxobutanoate (**5**)

Yield = 87 %, (mass = 1.13 g ± 0.02).

¹H NMR (400 MHz, CDCl₃) δ 0.91 (t, 3H, *J* 7.4 Hz, CH₃), 1.25 (d, 3H, *J* 6.3 Hz, CH₃), 1.66–1.52 (m, 2H, CH₂), 2.27 (s, 3H, CH₃), 3.44 (s, 2H, CH₂), 4.91 (st, 1H, *J* 6.3 Hz), 4.99 (s, 1H, CH_{enolic}), 12.19 (s, 1H, OH). **¹³C NMR** (100 MHz, CDCl₃) δ 9.65, 19.36, 28.70, 30.12, 50.51, 73.63, 90.16, 166.84, 172.47, 175.23, 200.78. **MS** *m/z* (%) 158 ([M]⁺, 1), 143 (0.05), 129 (0.43), 114 (0.13), 103 (10.92), 102 (3.37), 85 (34.79), 73 (4.94), 57 (17.85), 56 (15.25), 43 (100.00), 42 (9.58), 41 (19.39).

3-Methylbutyl-3-oxobutanoate (**6**)

Yield = 72 %, (mass = 0.95 g ± 0.08).

¹H NMR (400 MHz, CDCl₃) δ 0.92 (s, 3H, CH₃), 0.93 (s, 3H, CH₃), 1.55 (qt, 2H, *J* 6.9 Hz, CH₂), 1.69 (oct, 1H, *J* 6.7, Hz CH), 2.27 (s, 3H, CH₃), 3.45 (s, 2H, CH₂), 4.18 (t, 2H, *J* 6.9 Hz, CH₂), 4.98 (s, 1H, CH_{enolic}), 12.12 (s, 1H, OH). **¹³C NMR** (100 MHz, CDCl₃) δ 22.41, 24.99, 30.14, 37.16, 50.15, 64.07, 89.79, 167.24, 172.76, 175.42, 200.65. **MS** *m/z* (%) 172 ([M]⁺, 0.06), 157 (0.17), 143 (0.05), 129 (0.93), 115 (1.29), 103 (17.96), 102 (2.85), 85 (36.85), 71 (35.15), 70 (64.72), 69 (23.10), 55 (57.67), 43 (100.00), 42 (33.13), 41 (45.64).

1-Methylethyl-3-oxobutanoate (**7**)

Yield = 83 %, (mass = 0.92 g ± 0.04).

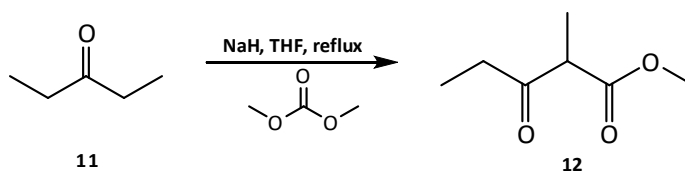
¹H NMR (400 MHz, CDCl₃) δ 1.26 and 1.28 (d, 6H, *J* 6.2 Hz, CH₃), 2.27 (s, 3H, CH₃), 3.42 (s, 2H, CH₂), 4.95 (s, 1H, CH_{enolic}), 5.07 (sp, 1H, CH, *J* 6.3 Hz), 12.18 (s, 1H, OH). **¹³C NMR** (100 MHz, CDCl₃) δ 21.67, 30.08, 50.47, 69.01, 90.17, 166.66, 200.81. **MS** *m/z* (%) 144 ([M]⁺, 0.82), 129 (0.05), 102 (36.45), 87 (18.13), 85 (80.62), 84 (53.56), 69 (42.00), 60 (51.04), 59 (20.97), 57 (2.03), 45 (100.00), 44 (25.94), 42 (80.21).

1-Ethylpropyl-2-methyl-3-oxopentanoate (**10**)

Yield = 61 %, (mass = 0.93 g ± 0.03).

¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, 6H, *J* 7.2 Hz, CH₃), 1.08 (t, 3H, *J* 7.2 Hz, CH₃), 1.34 (d, 3H, *J* 7.1 Hz, CH₃), 1.62–1.54 (m, 4H, CH₂), 2.70–2.48 (m, 2H, CH₂), 3.54 (q, 1H, *J* 7.2 Hz, CH), 4.79 (qt, 1H, *J* 6.2, Hz CH). **¹³C NMR** (100 MHz, CDCl₃) δ 7.71, 9.52, 9.57, 12.95, 26.35, 34.80, 52.88, 77.88, 170.61, 206.57. **MS** *m/z* (%), not observed [M]⁺, 186 (0.22), 172 (0.29), 153 (0.21), 144 (0.68), 130 (11.66), 113 (25.84), 102 (0.87), 83 (1.82), 75 (3.08), 57 (100.00), 43 (40.42).

2.2 Preparation of Methyl-2-methyl-3-oxopentanoate (**12**)



In a 250-mL tri-tubular flask attached to a 25-mL addition funnel, a thermometer and a reflux condenser and under an inert atmosphere, NaH (0.6 g; 25 mmol) and dimethylcarbonate (2.7 g; 30 mmol) in 12 mL of dry THF were introduced. The mixture was brought to reflux at 60 °C under constant stirring. After the start of reflux, a solution of 3-pentanone (**11**) (2.1 mL; 20 mmol) in 2 mL of dry THF was poured in and maintained under reflux for 2 h. After this time, it was cooled to room temperature and the mixture was transferred to a 50 mL extraction funnel. The product obtained was washed successively with three fractions of 5 mL of distilled water, five fractions of 3 mL of 10% NaHCO₃ solution and three fractions of 5 mL of saturated NaCl solution. The organic

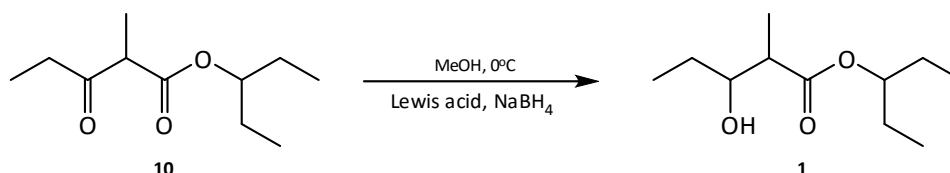
solution was dried over anhydrous Na_2SO_4 , filtered and the solvent evaporated. The crude product was analyzed and characterized by ^1H NMR, ^{13}C NMR and GC–MS.

Methyl-2-methyl-3-oxopentanoate (**12**)

Yield = 90 %, (mass = 2.6 g \pm 0.2).

^1H NMR (400 MHz, CDCl_3) δ 0.70 (t, 3H, J 7.4 Hz, CH_3), 0.97 (d, 3H, J 7.2 Hz, CH_3), 2.36–2.17 (m, 2H, CH_2), 3.27 (q, 1H, J 7.2 Hz, CH), 3.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3) δ 6.79, 11.99, 33.92, 51.40, 51.45, 170.36, 205.50. MS m/z (%) 144 ($[\text{M}]^+$, 2.63), 129 (0.02), 115 (5.30), 97 (0.06), 88 (10.73), 69 (0.46), 57 (100.00), 43 (6.83).

2.3 Preparation of 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (**1**)



In a 50-mL bi-tubular flask, under an inert atmosphere, 1-ethylpropyl-2-methyl-3-oxopentanoate (0.5 g; 2.5 mmol), compound **10**, 6 mL of methanol, and 5 mmol of Lewis acid (ZnCl_2 , MgCl_2 , CaCl_2 , or MnCl_2) were introduced. The reduction of the carbonyl ketone in the absence of a Lewis acid was also evaluated. The flask was cooled to 0 °C in an ice bath. After 30 min, NaBH_4 (0.19 g; 5 mmol) was slowly added. The reaction was stirred for 2 h, and then 20 mL of a saturated solution of NH_4Cl was slowly added. The product obtained was extracted with three portions of 20 mL of ethyl ether and the organic phases were poured together, washed with three portions of 40 mL of saturated NaCl solution. The organic phase was dried over anhydrous Na_2SO_4 , and then filtered and the solvent was evaporated. The product was purified by chromatography on silica gel with elution by a gradient of increasing polarity with hexane/ethyl acetate (5%, 10%, and 15%). The fractions corresponding to the reduced products were analyzed and characterized by ^1H NMR, ^{13}C NMR and GC–MS. Yield = 89 %, (m = 0.045 g \pm 0.004).

Anti-stereoisomer: 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (**sitophilate**)

^1H NMR (400 MHz, CDCl_3) δ 0.89 (t, 6H, J 7.4 Hz, CH_3), 0.99 (t, 3H, J 7.4 Hz, CH_3), 1.22 (d, 3H, J 7.1 Hz, CH_3), 1.52–1.40 (m, 2H, CH_2), 1.64–1.53 (m, 4H, CH_2), 2.57–2.50 (m, 1H, CH), 2.85 (m, 1H, OH), 3.61–3.56 (m, 1H, CH), 4.84–4.76 (m, 1H, CH). ^{13}C NMR (100 MHz, CDCl_3) δ 9.60, 9.96, 14.57, 26.49, 27.65, 45.10, 74.68, 77.44, 176.18. MS m/z (%), not observed $[\text{M}]^+$, 185 (0.04), 173 (3.95), 155 (0.08), 144 (2.94), 133 (0.69), 115 (64.28), 103 (54.93), 85 (18.02), 74 (100.00), 57 (37.89), 42 (90.03).

Syn-stereoisomer: 1-Ethylpropyl-2-methyl-3-hydroxypentanoate (**sitophilate**)

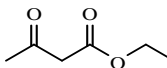
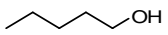
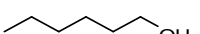


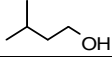

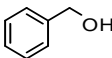

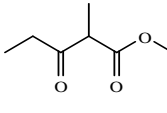

^1H NMR (400 MHz, CDCl_3) δ 0.90 (t, 6H, J 7.4 Hz, CH_3), 0.98 (t, 3H, J 7.4 Hz, CH_3), 1.19 (d, 3H, J 7.1 Hz, CH_3), 1.53–1.43 (m, 2H, CH_2), 1.63–1.54 (m, 4H, CH_2), 2.57–2.51 (m, 1H, CH), 2.87 (sl, 1H, OH), 3.83–3.79 (m, 1H, CH), 4.83–4.76 (m, 1H, CH). ^{13}C NMR (100 MHz, CDCl_3) δ 9.64, 10.41, 10.98, 26.44, 26.85, 44.28, 73.30, 77.48, 176.41. MS m/z (%), not observed $[\text{M}]^+$, 181 (0.02), 173 (1.51), 155 (0.08), 144 (3.33), 132 (0.69), 115 (49.19), 103 (26.91), 85 (10.84), 74 (100.00), 57 (36.95), 42 (74.85).

3 RESULTS AND DISCUSSION

The use of magnesium in organic synthesis gained prominence in the beginning of the 18th century with the work of Professor Victor Grignard (1900). It continues to be used efficiently today in many other synthetic methodologies (SZUROMI, 2000, GOLDBACH *et al.*, 2016, GAIR *et al.*, 2016, FREITAS *et al.*, 2011). Its application as a mediator of transesterification reactions, listed in Table 1 (entries 1–25), served as a model for obtaining the best experimental conditions for the synthesis of 1-ethylpropyl-2-methyl-3-oxopentanoate (**10**), the intermediate ester in the synthesis of sitophilate.

The reaction parameters used for analysis were the reaction time, the use and non-use of toluene as a solvent, as well as the ratio of alcohol to β -keto ester. The most feasible conditions for the synthesis of compound **10** are shown in entry 25.

Table 1: Conditions used for transesterification reactions.

Entry	β -Keto ester	Alcohol	Time of reaction	Purified yield (%)	Ratio (alcohol: β -keto ester)	Product		
1			3 h WO/S	24	1:1	2		
2			3 h WO/S	26	2:1			
3			3 h W/S	33	2:1			
4			6 h W/S	77	2:1			
5			3 h WO/S	24	1:1	3		
6			3 h WO/S	24	2:1			
7			3 h W/S	63	2:1			
8			6 h W/S	72	2:1			
9			3 h WO/S	24	1:1	4		
10			3 h WO/S	24	2:1			
11			3 h W/S	41	2:1			
12			6 h W/S	66	2:1			
13				3 h WO/S	20		1:1	5
14				3 h WO/S	21		2:1	
15				3 h W/S	65		2:1	
16				6 h W/S	87		2:1	
17			3 h W/S	65	2:1	6		
18			6 h W/S	72	2:1			
19			3 h W/S	66	2:1	7		
20			6 h W/S	83	2:1			
21			3 h W/S	No reaction	2:1	8		
22			6 h W/S	No reaction	2:1			
23			3 h W/S	No reaction	2:1	9		
24			6 h W/S	No reaction	2:1			
25			6 h W/S	61	2:1	10		

Reaction carried out without solvent (WO/S).

Reaction carried out with solvent (W/S).

The formation of the enolate of 3-pentanone (**11**) with NaH in THF, and subsequent nucleophilic attack to the dimethylcarbonate led to the formation of methyl-2-methyl-3-oxopentanoate (**12**) at a yield higher than 90%.

The carbonyl reduction reaction of **10** to an alcohol proceeded without problems under all experimental conditions at yields higher than 80%.

Taniguchi *et al.* (1993) performed experiments to determine the induction of chirality. The authors investigated the diastereoselectivity of the reduction of some β -keto esters with NaBH_4 when the reaction is performed in the absence and presence of a Lewis acid in the chloride form, such as ZnCl_2 , MgCl_2 , CaCl_2 , and MnCl_2 . The results of this study concluded that when there is no Lewis acid used in the reduction, the main product obtained is the *anti* diastereoisomer (a compound known as a Cram or Felkin product). However, when the reduction reaction is performed with the use of a Lewis acid, the preferential product is the *syn* diastereoisomer (a compound known as a Cram-chelated or *anti*-Felkin product) (EVANS *et al.*, 2001, MENGEL & REISER, 1999, CRAM & ELHAFEZ, 1952).

The studies by Taniguchi *et al.* (1993) and the model proposed by Cram and Elhafez for the α -substituted β -keto ester (**10**) were used in this study to explain the diastereoselective formation of the *syn* isomers of the pheromone of interest, 1-ethylpropyl-2-methyl-3-hydroxypentanoate (**1a** and **1b**), since these are the stereoisomers that exert biological activity on the insect.

When there is no Lewis acid used in the reduction reactions, the structure of **10** does not show a rigid conformation. The groups attached to the stereogenic carbon, are found positioned in such a way that a lowest interaction occurs between them. Accordingly, the hydrogen transfer occurs at the less sterically hindered face, i.e. at the *Si* face of the carbonyl group of the ketone, thus leading to the *anti* product of 1-ethylpropyl-2-methyl-3-hydroxypentanoate (**1c** and **1d**) as the major product (Figure 3). However, when experiments are conducted with the use of a Lewis acid, a chelate is formed between the metal atom and the two oxygen atoms of the carbonyl groups of the ketone and the ester, leaving the molecule with a rigid conformation. The hydrogen transfer also occurs on the less sterically hindered side, the *Re* face, such as in this case. Here, the *syn* diastereoisomers of **1a** and **1b** are preferentially produced (Figure 4).

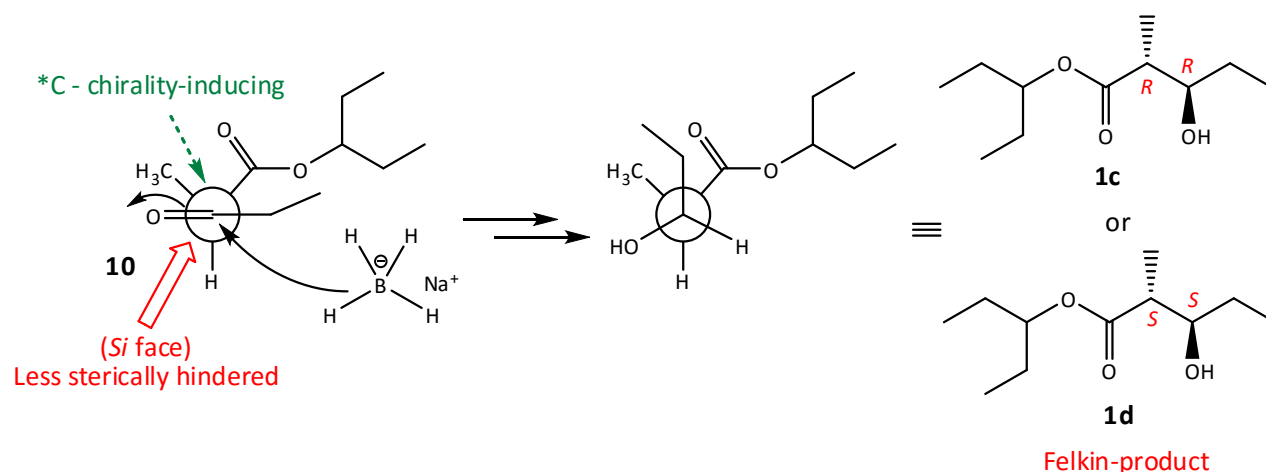


Figure 3: Cram and Elhafez model without the use of Lewis acids for the reduction of 1-ethylpropyl-2-methyl-3-oxopentanoate (**10**) with NaBH_4 .

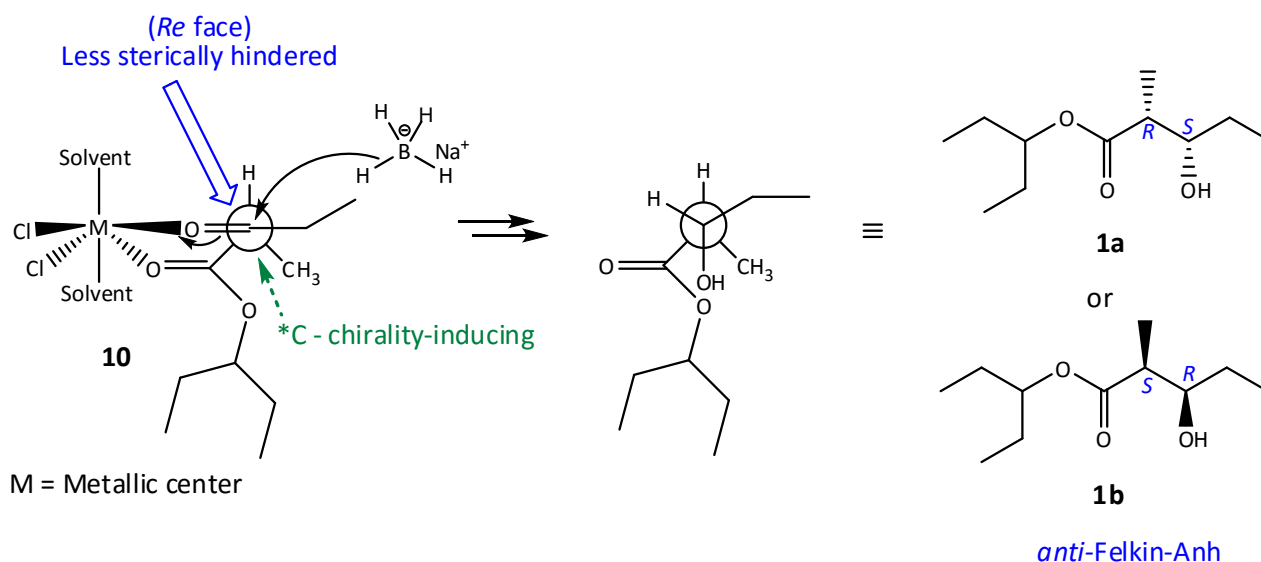


Figure 4: Cram and Elhafez model with the use of Lewis acids for the reduction reaction of 1-ethylpropyl-2-methyl-3-oxopentanoate (**10**) with NaBH₄.

Table 2 indicates the Lewis acid, the reaction yield and the relative proportion of each pair of diastereoisomers determined by GC–MS.

Table 2: Yields and diastereoisomeric excess obtained in the reduction reactions with NaBH₄ to form sitophilate (**1**).

Entry	Lewis Acid	Reaction yield	* Diastereoisomeric excess <i>anti/syn</i>
1	-----	85 %	70 / 30
2	ZnCl ₂	77 %	40 / 60
3	MgCl ₂	81 %	34 / 66
4	CaCl ₂	81 %	24 / 76
5	MnCl ₂	89 %	13 / 87

*Proportions calculated by the base area relative to each peak in GC–MS analysis.

According to data presented in Table 2, the more effective chloride in this transformation is MnCl₂ (entry 5), because in addition to having provided the best reaction yield, it led to the highest extent of formation of *syn* diastereoisomers. In this case, there was a near reversal of diastereoselectivity compared with that obtained in the reaction without the use of a Lewis acid (entry 1). These results are consistent with those reported by Taniguchi *et al.* (1993).

Figure 5 shows a comparison between the chromatograms of the products obtained using different Lewis acids in the reduction reactions.

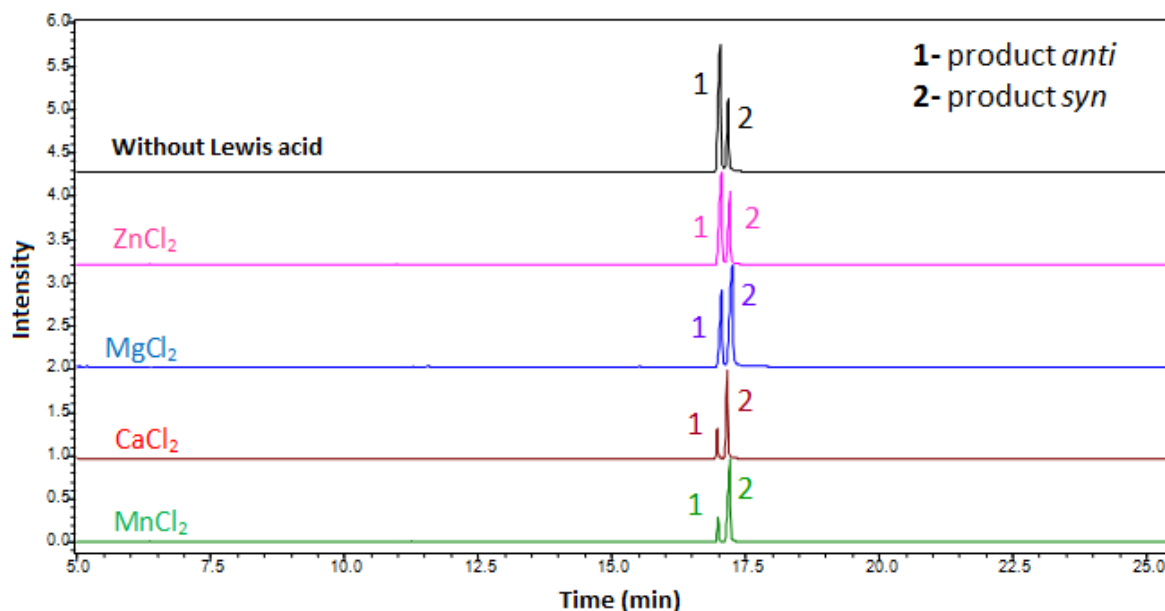


Figure 5: Comparison between the chromatograms of the products obtained in the reduction reactions of 1-ethylpropyl-2-methyl-3-oxopentanoate (**10**).

4 CONCLUSIONS

The transesterification reactions were considered satisfactory, with yields ranging from 61 to 87 %. The choice of Mg^0/I_2 to mediate such reactions came from the work of Chavan *et al.* (2002) who conducted transesterifications of β -keto esters with different alcohols and phenols using Zn^0/I_2 and applied the coumarin synthesis. These reactions served as a model to establish the best experimental conditions for use in the synthesis of sitophilate.

In respect to the use or not of Lewis acids ($ZnCl_2$, $MgCl_2$, $CaCl_2$ e $MnCl_2$) in the reduction step with $NaBH_4$, we conclude that the non-use of such compounds leads to a majority formation of the *anti* diastereoisomers, while the use $MnCl_2$ takes the majority formation of the *syn* diastereoisomers, since these latter compounds are that exert biological activity on the insect.

5 REFERENCES

1. BARCO, A., BENETTI, S., POLLINI, G.P., BARALDI, P.G., GANDOLFI, C. A new, elegant route to a key intermediate for the synthesis of 9(0)-methanoprostacyclin. *J. Org. Chem.*, v.45, n.23, p.4776–4778, 1980.
2. BECKET, D., BRODSKY, N.C., KALO, J. Structure relation of conjugated cycloalkenones and their ketals. *J. Org. Chem.*, v.43, n.13, p.2557–2562, 1978.
3. BERGMANN, J., VILLAR, J., ZARBIN, P.H.G. Synthesis of pheromones: Highlights from 2005-2007. *Current Organic Chemistry*, v. 13, p.683-719, 2009.
4. BO, W., MING, Y.L., SHUAN, S.J. Ionic liquid-regulated sulfamic acid: chemoselective catalyst for the transesterification of β -keto esters. *Tetrahedron Letters*, v.44, n.27, p.5037–5039, 2003.
5. CHAMBERS, J., VAN WYK, C.B., WHITE, P.R., GERRAD, C.M., MORI, M. Grain Weel, *Sitophilus*

- granarius* (L.): Antennal and behavioral responses to male-produced volatiles. *J. Chem. Ecol.*, v.22, n.10, p.1639-1653, 1996.
6. CHAVAN, S.P.; ZUBAIDHA, P.K.; DANTALE, S.W.; KESHAVARAJA, A.; RAMASWAMY, A.V.; RAVINDRANATHAN, T. Use of solid superacid (sulphated SnO₂) as efficient catalyst in facile transesterification of keto esters. *Tetrahedron Letters*, v.37, n.2, p.233-236, 1996.
 7. CHAVAN, S. P.; SHIVASANKAR, K; SIVAPPA, R.; KALE, R. Zinc mediated transesterification of β -ketoesters and coumarin synthesis. *Tetrahedron Letters*, v.43, p. 8583-8586. 2002.
 8. CHONG, J.M. Enantioselective synthesis of sitophilate, the granary weevil aggregation pheromone. *Tetrahedron*, v.45, n.3, p.623-628, 1989.
 9. CORDOVA, A., JANDA, K.D. A Highly Chemo- and Stereoselective Synthesis of β -Keto Esters via a Polymer-Supported Lipase Catalyzed Transesterification. *J. Org. Chem.* v.66, n.5, p.1906-1909, 2001.
 10. CRAM, D.J., ELHAFEZ, F.A.A. Studies in Stereochemistry. X. The Rule of "Steric Control of Asymmetric Induction" in the Syntheses of Acyclic Systems. *J. Am. Chem. Soc.*, v.74, p.5828-5835, 1952.
 11. DHAKE, K.P., TAMBADE, P.J., QURESHI, Z.S., SINGHAL, R.S., BHANAGE B.M. HPMC-PVA Film Immobilized *Rhizopus oryzae* Lipase as a Biocatalyst for Transesterification Reaction. *ACS Catalysis*, v.1, n.4, p.316-322, 2011.
 12. EVANS, D.A.; ALLISON, B.D.; YANG, M. G., MASSE, C.E. The exceptional chelating ability of dimethylaluminum chloride and methylaluminum dichloride. The merged stereochemical impact of α - and β -stereocenters in chelate-controlled carbonyl addition reactions with enolsilane and hydride nucleophiles. *J. Am. Chem. Soc.*, v.123, n.44, p.10840-10852, 2001.
 13. FREITAS, J.D., CAVALCANTE, S.K.M., SANTOS, E.D., FREITAS, A.J.D., ANTUNES, L.O., FREITAS, M.L., GOULART, H.F., SANT`ANA, A.E.G. Padronizaço da sntese dos principais constituintes feromonais de insetos dos gneros *Metamasius* e *Rhynchophorus*. *Holos*, v.2, p.15-27, 2011.
 14. GAIR, J.J., YOUNG, A.J., SCEPANIAC, J.J., SIMONE, P.M., CHAU, C.T., PETERSON, A.A., FERGUSON, E.M.N., OLOO, W.N., WELNA, D.T., SIVERSON, J.I., STAHL, L.M., SCHALLER, C.P. Reaction of a polyphosphino ruthenium(II) acetate complex with Grignard reagents: Halogenation, alkylation and β -elimination. *Journal of Organometallic Chemistry*, v.801, p.42-47, 2016.
 15. GIL, S., PARRA, M., RODRIGUEZ, P., SOTOCA, E. New Synthesis of (\pm)-Sitophilate Using Carboxylic Acid Dianion Methodology - A Stereoselectivity Study. *Synthesis*, n.19, p.3451-3455. 2005.
 16. GOLDBACH, M., DANIELI, E., PERLO, J., KAPTEIN, B., LITVINOV, V. M., BLMICH, B., ASANOVA, F., DUCHATEAU, A.L.L. Preparation of Grignard reagents from magnesium metal under continuous flow conditions and on-line monitoring by NMR spectroscopy. *Tetrahedron Letters*, v.57, p.122-125, 2016.
 17. GRIGNARD, V. *Comptes Rendus de l'Academie des Sciences, Paris*, v.130, II 33, 130, p.1322-1324, 1900.
 18. HOLMQUIST, C.R., ROSKAMP, E.J. The conversion of olefins to β -keto esters: Ozonolysis of olefins followed by *in situ* reduction with tin(II) chloride in the presence of ethyl diazoacetate. *Tetrahedron Letters*, v.31, n. 35, p.4991-4994, 1990.

19. IWASAKI, T., MAEGAWA, Y., HAYASHI, Y., OHSHIMA, T., MASHIMA, K. Transesterification of Various Methyl Esters Under Mild Conditions Catalyzed by Tetranuclear Zinc Cluster. *J. Org. Chem.*, v.73, n.13, p.5147-5150, 2008.
20. KALAITZAKIS, D., KAMBOURAKIS, S., ROZZELL, D.J., SMONOU, I. Stereoselective chemoenzymatic synthesis of sitophilate: a natural pheromone. *Tetrahedron Asymmetry*, v.18, p.2418-2426, 2007.
21. KALAITZAKIS, D.; SMONOU, I. A Convenient Method for the Assignment of Relative Configuration of Acyclic α -Alkyl- β -hydroxy Carbonyl Compounds by ^1H NMR. *J. Org. Chem.*, v.73, n.10, p.3919–3921, 2008.
22. KIM, K.Y., KIM, D.Y. Catalytic Enantioselective Alkylation of beta-keto Esters with Xanthidrol in the Presence of Chiral Palladium Complex. *Bulletin of the Korean Chemical Society*, v.7, p.5-6, 2016.
23. KLIPA, D.K., HART, H. Synthesis of bicyclo[3.3.0]oct-1(2)-en-3-one. *J. Org. Chem.*, v.46, n.13, p.2815-28-16, 1981.
24. LIU, H., CHEN, J., CHEN, L., XU, Y., GUO, X., FANG, D. Carbon Nanotube-Based Solid Sulfonic Acids as Catalysts for Production of Fatty Acid Methyl Ester via Transesterification and Esterification. *ACS Sustainable Chemistry & Engineering*, v.12, 2016.
25. MA, X., ABLAJAN, K., OBUL, M., SEYDIMEMET, M., RUZI, R., LI, W. Facial one-pot, three-component synthesis of thiazole compounds by the reactions of aldehyde/ketone, thiosemicarbazide and chlorinated carboxylic ester derivatives. *Tetrahedron*, v.72, n.18, p.2349-2353, 2016.
26. MATEUS, C.R.; FELTRIN, M.P.; COSTA, A.M.; COELHO, F., ALMEIDA, W.P. Diastereoselectivity in heterogeneous catalytic hydrogenation of Baylis–Hillman adducts. Total synthesis of (\pm)-sitophilate. *Tetrahedron*, v.57, n.32, p. 6901-6908, 2001.
27. MENGEL, A., REISER, O. Around and beyond Cram's Rule. *Chemical Reviews*, v.99, n.5, p.1191–1224, 1999.
28. MINAMI, O. YOSHIHARU, Y., KAZUO, N. Asymmetric alpha-amination of beta-keto esters using a guanidine-bisurea bifunctional organocatalyst. *Beilstein Journal of Organic Chemistry*, v.12, p.198-203, 2016.
29. MORI, K., ISHIKURA, M. Pheromone Synthesis, CXVII Synthesis of Sitophilate, the Aggregation Pheromone of *Sitophilus granarius* L., and Its Antipode. *Liebigs Annalen der Chemie*, v.1989, n.12, 13, p.1263–1265, 1989.
30. NAGANAWA, Y., KOMATSU, H., NISHIYAM, H. Zinc-catalyzed Enantioselective Electrophilic Amination of β -Ketocarbonyl Compounds with Axially Chiral Phenanthroline Ligands. *Chemistry Letters*, v.44, p.1652–1654, 2015.
31. NOVACEK, J., MONKOWIUS, U., HIMMELSBACH, M., WASER, M. Asymmetric alpha-chlorination of beta-keto esters using bifunctional ammonium salt catalysis. *Monatshefte Fur Chemie*, v.147, n.3, p.533-538, 2016.
32. PANDEY, R.K., KUMAR, P. A facile procedure for transesterification of β -keto esters promoted by ceria-yttria based Lewis acid catalyst. *Catalysis Communications*, v.8, n. 7, p.1122-1125, 2007.
33. PHILLIPS, J.K., MILLER, S.P.F., ANDERSEN, J.F., FALES, H.M., BURKHOLDER, W.E. The chemical

- identification of the granary weevil aggregation pheromone. *Tetrahedron Letters*, v.28, n.49, p.6145-6146, 1987.
34. PUNTAMBEKAR, H.M., NAIK, D.G. *Geotrichum candidum* Assisted Synthesis of Sitophilate, Male Aggregation Pheromone of Granary Weevil. *Synthetic Communications*, v.28, n.13, p.2399–2406, 1998.
 35. RAFIEE, E., EAVANI, S. Polyoxometalate-based acid salts with tunable separation properties as recyclable Brønsted acid catalysts for the synthesis of β -keto enol ethers. *Catalysis Communications*, v.25, n.5, p. 64-68, 2012.
 36. RAVIA, S.P., R, MARIELA, KROEGER, S., VERO, S., SEOANE, G.A., GAMENARA, D. A concise and stereoselective chemoenzymatic synthesis of Sitophilate, the male-produced aggregation pheromone of *Sitophilus granarius* (L.). *Tetrahedron-Asymmetry*, v.24, n.19, p.1207-1211, 2013.
 37. RAZKIN, J., GONZÁLES, A., GIL, P. Stereoselective synthesis of sitophilate and sitophilure. *Tetrahedron: Asymmetry*, v.7, n.12, p.3479–3484, 1996.
 38. SAIRRE, M.I., BRONZE-UHLE, E.S.; DONATE, P.M. Niobium(v) oxide: a new and efficient catalyst for the transesterification of β -keto esters. *Tetrahedron Letters*, v.46, n.15, p.2705-2708, 2005.
 39. SRIDHARAN, V. RUIZ, M. MENÉNDEZ, J. C. Mild and High-Yielding Synthesis of β -Keto Esters and β -Ketoamides. *Synthesis*, n.6, p.1053-1057, 2010.
 40. SZUROMI, P. D. Grignard Reactions in Water. *Science*, v.289, n.5488, p.2241, 2000.
 41. TANIGUCHI, M., FUJII, H., OSHIMA, K. Stereoselective reduction of 2-Methyl-3-oxo Ester (or Amides) with sodium borohydride catalyzed by manganese (II) chloride or tetrabutylammonium borohydride. A practical preparation of *erythro* and *threo*-3-hydroxy-2-methyl esters (or Amides). *Tetrahedron*, v.29, n.48, p.11169-11182, 1993.
 42. WANG, X., MA, L.; YU, W. Synthesis of imidazo[1,2-*a*]pyridines by the bis(acetyloxy)(phenyl)- λ^3 -iodane-mediated oxidative coupling of 2-aminopyridines with β -keto esters and 1,3-diones. *Synthesis*, v.15, p.2445–2453, 2011.
 43. WEST, F.G., GUNAWARDENA, G.U. Pseudocine substitution via internal delivery. Formal cyclopentadienone-ketone Michael adducts from 4-hydroxycyclopentenones. *J. Org. Chem.*, v.58, n.19, p.5003–5044, 1993.
 44. YADAV, J.S., REDDY, B.V.S., KRISHNA, A.D., REDDY, C. S.; NARSAIAH, A.V. Triphenylphosphine: An efficient catalyst for transesterification of β -keto esters. *J. Mol. Catal. A: Chem.*, v.261, n.1, p. 93–97, 2007.