J. Braz. Chem. Soc., Vol. 10, No. 5, 363-368, 1999.
Printed in Brazil.

0103 – 5053 $6.00 + 0.00

Article

The Asymmetric Synthesis of (+)-Sitophilure, the Natural Form of the Aggregation Pheromone of *Sitophilus oryzae* L. and *Sitophilus zeamais* M.

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A forma natural do (+)-sitofilure, feromônio de agregação de *Sitophilus oryzae* L. e *Sitophilus zeamais* M., foi preparada em 12 etapas, 18% de rendimento total e 82% de excesso enantiomérico a partir da redução microbiológica de 3-oxopentanoato de metila com *S. cerevisiae* na presença de cloroacetato de etila.

The asymmetric synthesis of (+)-sitophilure, the aggregation pheromone of *Sitophilus oryzae* L. and *Sitophilus zeamais* M., was carried out in 12 steps, 18% overall yield and 82% enantiomeric excess from the enzymatic reduction of methyl 3-oxopentanoate with *S. cerevisiae* in the presence of ethyl chloroacetate.

Keywords: *(+)-sitophilure, pheromone, asymmetric reduction,* S. cerevisiae

Introduction

The weevils of the genus *Sitophilus* are known to cause serious losses of stored cereal grains throughout the world. Effective, cost-efficient grain weevil management could be accomplished by monitoring pest populations with pheromone-baited insect traps and applying control methods only when pest densities reach economic thresholds.

In 1984, Burkholder and coworkers isolated the male-produced aggregation pheromone of the rice weevil (*Sitophilus oryzae* L.) and of the maize weevil (*Sitophilus zeamais* M.), named it sitophilure, and identified it as (4*R**,5*S**)-5-hydroxy-4-methyl-3-heptanone **(1)** (Fig. 1)[1]. The syntheses of the four possible stereoisomers of sitophilure[2] **(1)** and bioassays by Burkholder and coworkers revealed the (4*S*,5*R*) enantiomer as the active form of the pheromone[3]. Somewhat lower but still significant responses were observed for the (4*SR*,5*RS*) mixture while very low responses were elicited by either the (4*R*,5*R*)-isomer or the (4*RS*,5*RS*) racemic mixture. Since effective and cost-efficient control of both maize and rice weevils populations can be foreseen with the aid of the aggregation pheromone, several total syntheses of the racemic and the natural forms of sitophilure **(1)** have been published[4,5].

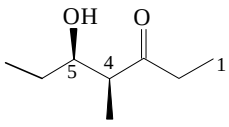

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Figure 1.

Since chiral β-hydroxyesters are versatile and convenient building blocks for the syntheses of biologically important compounds, asymmetric reduction of β-ketoesters by baker's yeast (*Saccharomyces cerevisiae*) has been widely used due to its simplicity, low cost and no need for cofator regeneration. However, it should be emphasized that there are many substrates that afforded low chemical yields and/or low enantioselectivities, and access to both enantiomeric series of a chiral β-hydroxyester from the same prochiral substrate and microorganism is generally not possible. Much effort has been directed towards screening different microorganisms, modifying the substrate and the reaction conditions in order to improve the scope of biocatalyzed β-ketoesters reduction[6].

The incomplete enantioselectivity observed is generally attributed to the existence of several operating oxidoreductases in the baker's yeast cells and in many cases the use of a purified reductase leads to high enantioselectivity[7].

Nakamura and coworkers reported a quite useful method for the reduction of β-ketoesters with baker's yeast. The introduction of a third reagent into the reaction system changes the stereoselectivity of the reduction and allows the

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desired configuration to be obtained in good enantiomeric excess. Thus, the introduction of allyl alcohol or an α, β-unsaturated carbonyl compound shifts the stereoselectivity of the reduction toward the D isomer[8], whereas the introduction of ethyl chloroacetate favors the formation of the L isomer (Scheme 1)[9]. The method is useful because the stereoselectivity can be easily controlled without screening microorganisms or modifying the structure of the subtrate.

We recently took advantage of Nakamura's methodology and developed an efficient preparation of (-)-sericornine, the sex pheromone of the cigarette beetle *Lasioderma sericorne* F., in 9 steps and 12% overall yield from methyl 3-oxopentanoate (**2**). The use of allyl alcohol as an enzymatic inhibitor allowed the preparation of (-)-**3**, in 88% yield and 76% enantiomeric excess[10] which underwent stereoselective Fràter's alkylation[11].

Mori and Ebata[2] also reported the use of Fràter's alkylation of methyl (*R*)-2-hydroxypentanoate, prepared by oxidation of pentanoic acid with *Candida rugosa*, to synthesize the four possible stereoisomers of sitophilure **(1)**, in 13-15 steps and 2.0-9.1% overall yield (natural form: 4.3% overall yield and 13 steps).

Here we report an enantioselective synthesis of (+)-sitophilure **(1)** which features the use of ethyl chloroacetate during the microbiological reduction of methyl 3-oxopentanoate with *S. cerevisiae* to control the stereochemical course of the baker's yeast reduction.

Experimental

^{1}H-NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and ^{13}C-NMR spectra in $CDCl_3$ solution at 75.5 MHz (unless otherwise noted) with a Varian Gemini 2000 or a Bruker AC-300P instrument. Chemical shifts are expressed in ppm relative to tetramethylsilane followed by multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qt, quintet; m, multiplet), coupling constant (Hz) and number of protons. Infrared spectra were recorded on a Perkin-Elmer 399B or 1600 series spectrophotometer. Optical rotations were measured at 25 °C in a Polamat A (Carl Zeiss) at 546 nm (mercury line) and corrected to 589 nm (sodium D line).

GC analyses were performed in a Hewlett-Packard 5890 series II chromatograph equipped with flame ionization detector, nitrogen as the carrier gas and capillary columns (30 m x 0.53 mm) with 1% phenylmethylsilicone (HP-1) or cross-linked polyethyleneglycol (Carbowax 20M) as stationary phases. Chiral GC analyses were performed with capillary columns (0.25 mm i.d, 25 m length) packed with heptakis-(2,6-methyl-3-pentyl)- β-cyclodextrine/OV-17 as stationary phase.

Column chromatography was performed using silicagel (70-230 Mesh), except when stated otherwise, and reactions were monitored by TLC (plates from Macherey-Nagel, Germany).

Baker's yeast employed was purchased from Sigma -Aldrich (YSC-2, type 2).

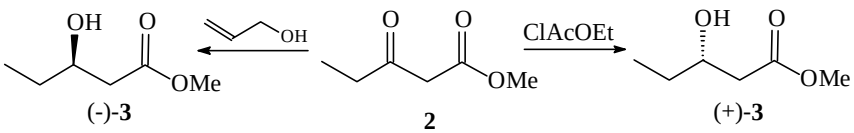
Tetrahydrofuran was treated with sodium/benzophenone and distilled immediately prior to use. Dichloromethane, triethylamine, diisopropylamine and benzene were treated with calcium hydride and distilled immediately prior to use. Oxalyl chloride and dimethyl sulfoxide were distilled prior to use. The remaining reagents employed were purchased from commercial suppliers and used without further purification. The reactions involving anhydrous solvents were carried out under argon atmosphere.

*(+)-(S)-Methyl 3-hydroxypentanoate (**3**)*

To a suspension of Sigma Aldrich dry baker's yeast (20 g) in water (60 mL) at 30 °C was added ethyl chloroacetate (0.43 mL, 4.0 mmol) and the whole mixture was stirred for 1 h at 30 °C. Methyl 3-oxopentanoate **(2)** (0.13 mL, 1.0 mmol) and glucose (20 g) were added and the mixture was stirred 1 day at 30 °C. Celite was added to the suspension and the mixture was filtered. The filtrate was extracted with Et_2O (3 X 15 mL), the organic phase was washed with water (10 mL), brine (10 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by Kugelrohr distillation (70-80 °C, 1 mmHg) to afford 0.093 g (0.70 mmol) of (+)-**3** (70% yield, 82% ee) as a colorless oil. ^{1}H-NMR (CCl_4, 300 MHz): δ 0.96 (t, 3H, *J* = 7 Hz); 1.43-1.49 (m, 2H); 2.33 (dd, 1H, *J* = 16 and 8 Hz); 2.41 (dd, 1H, *J* = 16 and 4 Hz); 3.08 (br s, 1H); 3.67 (s, 3H); 3.81-3.84 (m, 1H). ^{13}C-NMR (CCl_4, 75.5 MHz): δ 9.8; 29.3; 40.7; 51.0; 68.6; 172.4. IR (film): 3431; 1736 cm^{-1}. $[\alpha]_D$ +33.4 (c1.31, $CHCl_3$); lit (-)-**3**[14]: $[\alpha]_D$ -36.9 (c1.31, $CHCl_3$).

*(2S,3S)-Methyl 3-hydroxy-2-methylpentanoate (**4**)*

A solution of LDA was prepared by the dropwise addition of a 1.55 M solution of n-BuLi in hexane (15.0 mL, 23.3 mmol) to a stirred solution of ^{i}Pr$_2$NH (3.27 mL, 23.3



(-)-**3** **2** (+)-**3**

D-isomer L-isomer

Scheme 1.

mmol) in THF (8 mL) at 0 °C under an argon atmosphere. The mixture was stirred 30 min at 0 °C and then cooled to -78 °C. A solution of (+)-**3** (1.53 g, 11.6 mmol) in THF (5 mL) was added dropwise and the mixture was stirred 45 min at 0 °C. A solution of MeI (1.08 mL, 17.4 mmol) in DMPU (4.7 mL) was added dropwise to the solution at -40 °C. After stirring 45 min at this temperature, the reaction temperature was allowed to reach room temperature. The mixture was quenched with satd. aq. NH_4Cl (7 mL) at 0 °C and extracted with Et_2O (3 X 10 mL). The organic phase was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated to afford 1.19 g of a mixture of **4** and its C-2 epimer (8:1 ratio) which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.98 (t, 3H, *J* = 7 Hz); 1.20 (d, 3H, *J* = 7 Hz); 1.41-1.58 (m, 2H); 2.56 (quint, 1H, *J* = 7 Hz); 2.72 (br s, 1H); 3.58-3.67 (m, 1H); 3.71 (s, 3H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 9.7; 14.2; 27.4; 44.8; 51.7; 74.5; 176.4. IR (film): 3426; 1735 cm^{-1}.

*(-)-(2R,3S)-2-Methyl-1-O-tert-butyl-dimethylsilyl-1,3-pentanediol (**6**)*

To a suspension of $LiAlH_4$ (0.630 g, 16.3 mmol) in THF (20 mL) at 0 °C was added a solution of **4** (1.61 g, 11.0 mmol) in THF (8 mL). The reaction mixture was stirred overnight at room temperature, diluted with Et_2O (20 mL) and successively treated at 0 °C with water (0.63 mL), 10% aqueous NaOH (0.63 mL) and water (1.88 mL). The inorganic solids were filtered and washed with Et_2O (40 mL). The organic extracts were dried over $MgSO_4$ and concentrated to afford (-)-**5** (1.30 g) which was taken up in CH_2Cl_2 (12 mL) and treated with triethylamine (1.69 mL, 12.1 mmol), catalytic amount of N,N-dimethyl-4-aminopyridine (0.008 g, 0.07 mmol) and TBSCl (1.82 g, 12.1 mmol). The mixture was stirred 1 h at room temperature and poured into water. The layers were separated and the organic phase was washed with saturated NH_4Cl solution (3 mL), brine (3 mL), dried over $MgSO_4$ and concentrated. Silica gel chromatography (2% AcOEt in hexanes, v/v) of the crude product afforded (-)-**6** (2.40 g, 10.3 mmol) in 89% overall yield from (+)-**3**, as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.08 (s, 6H); 0.84 (d, 3H, *J* = 7 Hz); 0.90 (s, 9H); 0.95 (t, 3H, *J* = 7 Hz); 1.36-1.50 (m, 1H); 1.50-1.65 (m, 1H); 1.65-1.78 (m, 1H); 3.41-3.51 (m, 1H); 3.59 (dd, 1H, *J* = 10 and 8 Hz); 3.79 (dd, 1H, *J* = 10 and 4 Hz); 3.84 (sl, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ -5.7; -5.6; 9.5; 13.6; 18.1; 25.8; 27.8; 39.0; 68.5; 77.9. IR (film): 3442, 1255, 1083 cm^{-1}. $[\alpha]_D$ -13.1 (c1.3, $CHCl_3$).

*(+)-(2R,3R)-2-Methyl-1-O-tert-butyl-dimethylsilyl-1,3-pentanediol (**7**)*

To a solution of (-)-**6** (0.517 g, 2.22 mmol), PPh_3 (2.04 g, 7.77 mmol) and p-nitrobenzoic acid (1.29 g, 7.77 mmol) in benzene (9 mL) at 0 °C was added a solution of diethyl azodicarboxylate (1.22 mL, 7.77 mmol) in benzene (6 mL). The ice-bath was removed and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo and purification by silica gel chromatography (5% AcOEt in hexanes, v/v) of the crude product afforded 0.69 g of the p-nitrobenzoate derivative which was dissolved in MeOH (20 mL) and treated with a solution of K_2CO_3 (1.73 g, 12.6 mmol) in water (5 mL). The mixture was stirred 15 h at room temperature, the solvent was removed and the crude mixture was diluted with Et_2O (20 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 x 5mL). The combined organic phases were washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (2% AcOEt in hexanes, v/v) of the crude product afforded (+)-**7** (0.414 g, 1.78 mmol) as a colorless oil, in 80% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.07 (s, 6H); 0.90 (s, 9H); 0.92 (d, 3H, *J* = 7 Hz); 0.95 (t, 3H, *J* = 7 Hz); 1.32-1.61 (m, 2H); 1.66-1.79 (m, 1H); 3.05 (br s, 1H); 3.68 (dd, 1H, *J* = 10 Hz and 5 Hz); 3.65-3.79 (m, 1H); 3.76 (dd, 1H, *J* = 10 Hz and 4 Hz). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ -5.7; -5.6; 10.0; 10.6; 18.1; 25.8; 26.9; 38.3; 68.5; 76.4. IR (film): 3442, 1255, 1083 cm^{-1}. $[\alpha]_D$ +6.55 (c1.3, $CHCl_3$).

*(+)-(2R,3R)-2-Methyl-1,3-O-di-tert-butyl-dimethylsilyl-1,3-pentanediol (**8**)*

To a solution of (+)-**7** (0.334 g, 1.44 mmol) and 2,6-lutidine (0.34 mL, 2.9 mmol) in CH_2Cl_2 (6.5 mL) at 0 °C was added TBSOTf (0.58 mL, 2.2 mmol). The mixture was stirred 30 min at 0 °C and water (2 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated. Silica gel chromatography (5% AcOEt in hexanes, v/v) of the crude product afforded (+)-**8** (0.468 g, 1.35 mmol) in 94% yield, as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 12H); 0.86 (s, 9H); 0.88 (s, 9H); 0.81 (d, 3H, *J* = 7 Hz); 0.86 (t, 3H, *J* = 7 Hz); 1.36-1.56 (m, 2H); 1.65-1.77 (m, 1H); 3.40 (dd, 1H, *J* = 10 and 7 Hz); 3.56 (dd, 1H, *J* = 10 and 6 Hz); 3.63-3.70 (m, 1H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ -5.3; -4.7; -4.2; -2.9; 10.2; 10.4; 18.2; 18.3; 25.7; 25.9; 27.3; 39.5; 65.6; 73.5. IR (film): 1471, 1089, 1049 cm^{-1}. $[\alpha]_D$ +4.1 (c2.1, $CHCl_3$).

*(+)-(2R,3R)-3-O-tert-Butyl-dimethylsilyl-2-methyl-1,3-pentanediol (**9**)*

To a solution of (+)-**8** (0.398 g, 1.15 mmol) in THF (20 mL) in a Nalgene tube was added freshly prepared buffered pyridinium hydrofluoride (19.0 mL) (stock solution prepared from 2.0 g of Aldrich pyridinium hydrofluoride, 4.0 mL of pyridine and 16 mL of THF). After 3 h at room temperature, satd. aq. $NaHCO_3$ (20 mL) was added. The

layers were separated, the aqueous layer was extracted with Et_2O (3 x 5 mL), the combined organic layers were washed with brine (7 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Silica gel chromatography (10% AcOEt in hexanes, v/v) afforded (+)-**9** (0.220 g, 0.95 mmol) in 83% yield, as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ -0.01 (s, 6H); 0.71 (d, 3H, *J* = 7 Hz); 0.80 (t, 3H, *J* = 7 Hz); 0.80 (s, 9H); 1.30-1.50 (m, 2H); 1.81-1.95 (m, 1H); 2.56 (br s, 1H); 3.38-3.48 (m, 1H); 3.51-3.66 (m, 2H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ -4.5; -4.4; 10.8; 11.9; 18.0; 25.1; 25.8; 36.2; 66.1; 76.6. IR (film): 3355, 1253, 1049, 1022 cm^{-1}. $[\alpha]_D$ +6.65 (c1.3, $CHCl_3$).

*(3R,4R,5S)-5-O-tert-Butyl-dimethylsilyl-4-methyl-3,5-pentanediol (**11**) and (3R,4R,5R)-5-O-tert-Butyl-dimethylsilyl-4-methyl-3,5-pentanediol (**12**)*

To a solution of oxalyl chloride (0.078 mL, 0.88 mmol) in CH_2Cl_2 (2.5 mL) at -78 °C was added dimethyl sulfoxide (0.12 mL, 1.8 mmol) dropwise. The solution was stirred 10 min at -78 °C and a solution of (+)-**9** (0.103 g, 0.443 mmol) in CH_2Cl_2 (2.5 mL) was added. The mixture was stirred 1.5 h at -78 °C and then triethylamine (0.36 mL, 2.6 mmol) was added. The reaction mixture was allowed to warm to room temperature and quenched with water. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL), the combined organic layers were washed with brine (3 mL), dried over $MgSO_4$ and concentrated to give the crude aldehyde. To a solution of the crude aldehyde (0.087 g, 0.38 mmol) in Et_2O (6 mL) at 0 °C was added 1.0 M ethylmagnesium bromide solution in Et_2O (0.76 mL, 0.76 mmol). The mixture was stirred 30 min at 0 °C and then aq. NH_4Cl solution (1.5 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. Silica gel chromatography (10% AcOEt in hexanes, v/v) of the crude product afforded a 5:1 mixture of diastereomeric alcohols **11** and **12** (0.091 g, 0.35 mmol) in 79% yield, as a colorless oil. An analytically pure sample of alcohol **11** was isolated and characterized. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.09 (s, 6H); 0.77-0.95 (m, 9H); 0.90 (s, 9H); 1.40-1.62 (m, 5H); 2.87 (br s, 1H); 3.64 (ddd, 1H, *J* = 8, 6 and 2 Hz); 3.76 (ddd, 1H, *J* = 9, 6 and 3 Hz). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ -4.6; -3.7; 5.2; 9.8; 10.5; 18.0; 25.8; 27.5; 27.9; 38.2; 76.6; 79.3. IR (film): 3423, 1461, 1105, 1004 cm^{-1}. $[\alpha]_D$ -21.3 (c0.82, $CHCl_3$).

*(+)-(4S,5R)-5-Hydroxy-4-methyl-3-pentanone (**1**)*

To a solution of oxalyl chloride (0.013 mL, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at -78 °C was added dimethyl sulfoxide (0.020 mL, 0.31 mmol) dropwise. The solution was stirred 10 min at -78 °C and a solution of a mixture of **11** and **12** (0.023 g, 0.089 mmol) in CH_2Cl_2 (1.0 mL) was added. The mixture was stirred 1.5 h at -78 °C, and treated with triethylamine (0.06 mL, 0.46 mmol). After warming to room temperature, the reaction was quenched with water, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic phases were washed with brine (4 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue (0.019 g) was dissolved in THF (1 mL) at room temperature and treated with 1.0 M solution of TBAF (0.1 mL, 0.1 mmol) in THF. The mixture was stirred 1 day at room temperature, diluted with Et_2O (10 mL) and treated with aq. NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 4 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Silica gel chromatography (30% AcOEt in hexanes, v/v) afforded (+)-**1** (0.0074 g, 0.052 mmol) in 60% yield, as a colorless oil. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.96 (t, 3H, J = 7 Hz); 1.06 (t, 3H, J = 7 Hz); 1.14 (d, 3H, *J* = 7 Hz); 1.37 (ddq, 1H, *J* = 15, 7 and 3 Hz); 1.51 (ddq, 1H, *J* = 15, 8 and 7 Hz); 2.42-2.70 (m, 3H); 2.86 (br s, 1H); 3.83 (ddd, 1H, *J* = 8, 5 and 3 Hz). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 7.6; 9.9; 10.4; 26.8; 35.1; 49.3; 72.6; 216.8. IR (film): 3453; 1701; 1460 cm^{-1}. $[\alpha]_D$ +24.8 (c1.24, Et_2O). lit.[2]: $[\alpha]_D$ +27.0 (c1.24, Et_2O).

Results and Discussion

The microbiological reduction of methyl and ethyl 3-oxopentanoate in the presence of ethyl chloroacetate, as described by Nakamura and coworkers[9], afforded (+)-**3** in good enantiomeric excess (Table 1). The nature of the alkoxy moiety (ethyl or methyl) does not significantly affect the enantiomeric excess of the reduction, whereas the use of only 2 equivalents of ethyl chloroacetate surprisingly leads to lower conversion. Having determined the optimal conditions for the reduction of β-ketoester, we were able to isolate gram quantities of (+)-**3** in 70% yield and 82% ee, after purification by Kugelrohr distillation (1mmHg, 70-80 °C) when baker's yeast was previously inactivated at 30 °C for 30 min with 4 equivalents of ethyl chloroacetate.

The stereogenic center at C-4 (sitophilure numbering) was established after alkylation of the lithium dianion derived from (+) **3**, according to Fràter conditions.[10] A 8:1 mixture of (*S,S*)-3-hydroxy-2-methylpentanoate **4** and its C-2 epimer was obtained and the configuration of the major isomer was confirmed to be 2*S*,3*S* by analysis of its ^{1}H-NMR spectrum which displayed a coupling constant (JH_{2-3} = 7.0 Hz) and a deshielding effect at C-2 and C-3 (27.4 and 74.5 ppm, respectively) in the ^{13}C-NMR spectrum characteristic of its *anti* relative configuration[12] (the same carbons in the minor component appeared at 26.7 and 73.2 ppm, respectively).

Attempts to gain direct access to hydroxy ester (+)-**4** through the reduction of methyl 2-methyl-3-oxopentanoate with *S. cerevisiae* in order to simplify the synthetic scheme met with failure: esters of 2-methyl-3-oxopentanoic acid

Table 1. Conversions and enantiomeric excesses in the reduction of methyl and ethyl 3-oxopentanonate with baker's yeast in the presence of ethyl chloroacetate.

Entry	(R)	Equivalents of ClAcOEt	Conversion (%)[a]	Enantiomeric excess of (+)-3 (%)[b]
1	Me	4	100	82
2	Me	2	12	n.d.
3	Et	4	100	87
4	Et	2	30	n.d.

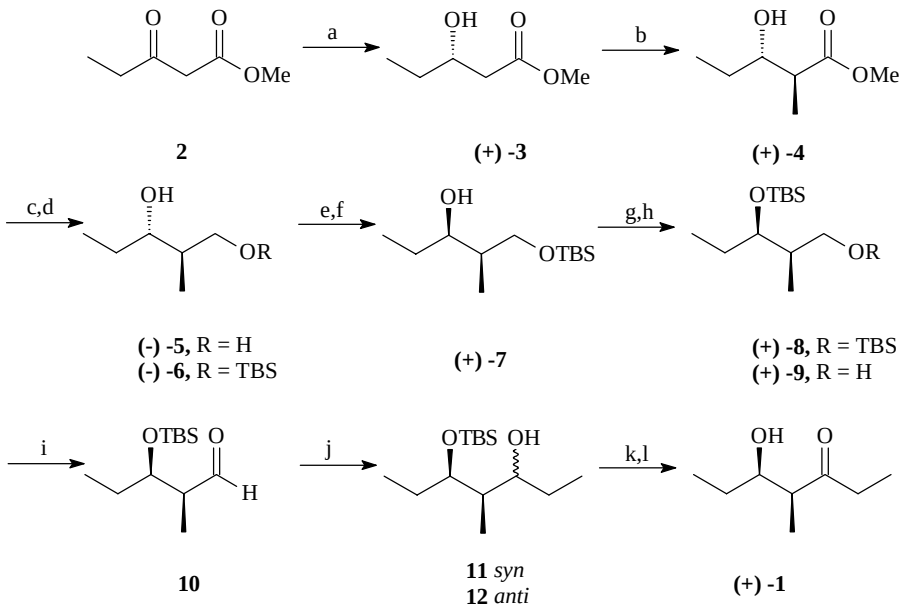
a- Conversion determined by capillary CG analysis after 24h at 30 °C; b- Enantiomeric excess determined by CG on capillary column having heptakis-(2,6-methyl-3-pentyl)- β-cyclodextrin as stationary phase; n.d. = not determined.

are slowly converted by *S. cerevisiae* to the corresponding hydroxyesters in low yields and very poor diastereoselection. At this point it seems that a more straightforward route to (+)-**4** or even to (+)-**1** requires microbial screening.

Reduction of (+)-**4** with lithium aluminum hydride, selective monosilylation with TBSCl and separation of the diastereoisomers by silica gel chromatography gave (-)-**6** in 89% overall yield from (+)-**3**. At this stage, we were ready to undertake the configuration inversion at C-5 (sitophilure numbering) required to convert (-)-**6** to sitophilure **(1)**. Mitsunobu inversion[13] followed by basic hydrolysis gave (+)-**7** in 80% yield. Silylation of (+)-**7** with TBSOTf gave (+)-**8** in 94% yield, which was monodeprotected selectively with HF-pyridine to afford (+)-**9** in 83% yield. Swern oxidation of (+)-**9** gave the unstable aldehyde **10** which was immediately treated with EtMgBr to give a diastereoisomeric mixture of alcohols **11** and **12** (4.5:1 *syn:anti* ratio) in 79% yield. Although the stereogenic center at C-3 (sitophilure numbering) would not be necessary in the desired pheromone, the above mixture was separated by silica gel chromatography, and the less polar and more abundant isomer **11**, was fully purified and characterized.

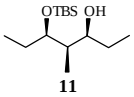
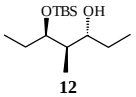
The conversion of the aldehyde **10** to the diastereoisomeric mixture of alcohols **11** and **12** has been previously reported by Mori and Ebata[2]. The ^{1}H- and ^{13}C-NMR spectral data of our less polar isomer were in accord with the values reported by these authors for the *syn* isomer **11**, but the value of the specific optical rotation of our less polar isomer was in accordance with the value reported by Mori and Ebata for the *anti* isomer **12** (Table 2). Since the data were divergent we decided to carry out an NMR analysis of our less polar isomer. After desilylation, its ^{1}H- and ^{13}C-NMR spectra revealed a symmetrical diol (only 5 signals in the ^{13}C-NMR spectrum), fully confirming that our as well as Mori and Ebata's less polar and more abundant isomer displayed all *syn* stereochemistry as depicted in **11**, and that the specific optical rotation of **11** and **12** were erroneously interchanged in Mori and Ebata's paper[2].

Swern oxidation of the diastereoisomeric mixture of alcohols **11** and **12**, followed by deprotection of the TBS group, gave (+)-sitophilure **(1)**, in 60% yield. The ^{1}H- and ^{13}C-NMR spectral data and the optical rotation ($[\alpha]_D$+24.8 (c1.24, Et_2O)), are in good agreement with those reported in the literature for (+)-**1** by Mori and Ebata.[2] The enan-



Scheme 2. a) baker's yeast (YSC-1), ClAcOEt (70% yield, 82% ee); b) i. LDA, THF, -78 °C; ii. MeI, DMPU; c) $LiAlH_4$, THF rt; d) TBSCl, Et_3N, CH_2Cl_2, DMAP(cat.), rt (89% yield, 3 steps); e) p-$NO_2C_6H_4CO_2H$, Ph_3P, DEAD, C_6H_6, rt; f) K_2CO_3, MeOH, H_2O, rt (80% yield, 2 steps); g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C (94% yield); h) HF-Py, THF, rt (83% yield) i) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; j) EtMgBr, Et_2O (79% yield, 2 steps); k) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C; l) TBAF, THF, rt (60% yield, 2 steps).

Table 2. Literature and experimental values of optical rotation of **11** and **12**.

Literature[2]	Literature[2]	Experimental
less polar	 **11**	 **12**
	more polar	less polar
$[\alpha]_D$ +32.8 (c0.81, $CHCl_3$)	$[\alpha]_D$ -21.7 (c0.83, $CHCl_3$)	$[\alpha]_D$ -21.3 (C0.82, $CHCl_3$)

tiomeric excess of (+)-**1** was determined to be 82% after chiral GC analysis (heptakis-2,6-dimethyl-3-pentyl- β-cyclodextrine as stationary phase).

Conclusion

An efficient preparation (12 steps, 18% overall yield and 82% enantiomeric excess) of enantiomerically enriched (+)-sitophilure **(1)** was developed from methyl (*S*)-3-hydroxypentanoate, readily prepared by baker's yeast reduction of methyl 3-oxopentanoate.

Acknowledgements

The authors gratefully acknowledge the financial support from FINEP (Brazil), CNPq (Brazil) and IFS (Sweden).

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Received: April 13, 1999

FAPESP helped in meeting the publication costs of this article