An improved synthesis of sitophilure[1]

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Abstract: The asymmetric synthesis of sitophilure was carried out in 8 steps, with 42% overall yield and 97% enantiomeric excess from propionaldehyde. The synthesis relied on an approach employing an asymmetric acyl-thiazolidinethione propionate aldol reaction to establish two stereogenic centers.

Key words: sitophilure, thiazolidinethione, chiral auxiliary, synthesis.

Résumé : Utilisant le propionaldéhyde comme produit de départ, on a réalisé une synthèse asymétrique du sitophilure en huit étapes, avec un rendement global de 42% et un excès énantiomérique de 97%. La synthèse repose sur une approche dans laquelle on utilise une réaction asymétrique aldolique acyl-propionate de thiazolidinethione pour générer deux centres stéréogéniques.

Mots-clés : sitophilure, thiazolidinethione, auxiliaire chiral, synthèse.

[Traduit par la Rédaction]

Introduction

The rice weevil *Sitophilus oryzae L.* and the maize weevil *Sitophilu zeamaais M.* are both pests that cause commercially serious damage to stored cereal grains. Effective, cost-efficient grain weevil management could be accomplished by monitoring the pest populations with pheromone-baited insect traps and applying control methods only when pest densities reach economic thresholds. Their common aggregation pheromone, sitophilure, was identified by Schmuff et al. (1) as (4*R*, 5*S*)-5-hydroxy-4-methyl-3-heptanone. A synthesis of the four sitophilure stereoisomers was reported by Mori (2) to clarify the stereochemistry–bioactivity relationship. Bioassay of Mori's samples by Walgenbach et al. (3) revealed (4*S*,5*R*) stereoisomer **1** to be the pheromone sitophilure (Fig. 1). 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).

Carbon–carbon bond-forming reactions involving asymmetric aldol additions have emerged as powerful tools in organic synthesis. As demonstrated by the pioneering work of Evans et al. (5), Heathcock and co-workers (6), and Crimmins et al. (7), additions of enolates of acyl oxazolidinones, oxazolidinethiones, and thiazolidinethiones to aldehydes can be highly effective at selectively generating enantiomerically pure *syn* and *anti* aldol products. Among these chiral auxilaries, 4-mono substituted thiazolidinethiones derived from natural amino acids are more useful in asymmetric synthesis because they can be removed from the thiazolidinthiones after completion of the chiral induction easily (8). For these reasons, we have chosen to pursue this line of work and applied this system to the synthesis of the pheromone sitophilure using 4-monosubstituted thiazolidinethiones as chiral auxiliary (Scheme 1). In comparison with the published syntheses, this synthesis is very short and the overall yield very high.

Results and discussion

As shown in Scheme 1, we used 4-benzyl-1,3-thiazolidine-2-thione as starting material. Acylation of thiazolidinethione by propionyl chloride using DMAP as catalyst at room temperature afforded *N*-acylthiazolidinthiones **2** in 95% yield (7*a*). Compound **2** was treated with $TiCl_4$, *N*,*N*-diisopropylethylamine (DIPEA), and *N*-methylpyrrolidone (NMP) in turn, and the resulting complex reacted with propionaldehyde to give alcohol **3** in 98% yield (7*c*). The aldol product could be easily protected with *tert*-butyldimethylsilyl chloride (TBDMSCl) using lutidine as base (9). The compound, obtained by the protection of **3**, was reduced to alcohol **4** with sodium borohydride in the presence of ethanol. Oxidation of alcohol **4** with $Py{\cdot}O_3$ in the presence of DIPEA gave aldehyde **5** in 84% yield. Compound **5** was treated with excess EtMgBr to give a diastereoisomeric mixture of alcohols **6** (4*c*). The diastereoisomeric mixtures were not separated and were directly treated with pyridinium chlorochromate (PCC) and anhydrous sodium acetate in CH_2Cl_2, affording a ketone. Deprotection of the TBS group with tetrabutylammonium fluoride afforded sitophilure **1** (89% yield, 42% overall yield, and 97% ee, based on the reported rotation of +27.0) (2).

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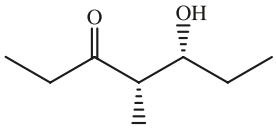
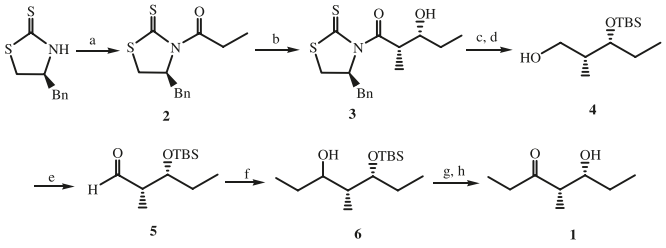
Fig. 1. Sitophilure **1.**



1

Scheme 1. Improved synthesis of sitophilure **1**. Reagents and conditions: a) DMAP (0.2 equiv.), Et_3N (1.2 equiv.), propionyl chloride (1.3 equiv.), CH_2Cl_2, RT, 3 h; b) $TiCl_4$ (1.05 equiv.), DIPEA (1.1 equiv.), NMP (2.0 equiv.), propionaldehyde (1.1 equiv.), CH_2Cl_2, 0 °C, 3 h; c) TBDMSCl (2.5 equiv.), lutidine (1.5 equiv.), CH_2Cl_2, RT, 3 h; d) $NaBH_4$ (4.0 equiv.), EtOH, 0 °C, 1 h; e) Py·SO_3 (3.7 equiv.), DIPEA (2.3 equiv.), CH_2Cl_2, 0 °C, 3 h; f) EtMgBr (2.8 equiv.), Et_2O, –78 °C ~ RT, 2 h; g) PCC (1.5 equiv.), NaOAc (0.3 equiv.), CH_2Cl_2, RT, 4 h; h) Bu_4NF (1.0 equiv.), THF, RT, 18 h.



Conclusion

In summary, an efficient synthesis (8 steps, 42% overall yield, and 97% enantiomeric excess) of enantiomerically enriched sitophilure **1** was developed from propionaldehyde using 4-benzyl-1,3-thiazolidine-2-thione as chiral auxiliary.

Experimental

General

All organic solvents and base were dried by standard methods. TLCs were performed on precoated plates of silica gel HF254 (0.5 mm, Yantai, China). Flash column chromatography was performed on silica gel H (Yantai, China). Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were determined with a PerkinElmer Model 241 MC polarimeter. IR spectra were recorded on an IR-spectrum one (PE) spectrometer. ^{1}H NMR (600 MHz) and ^{13}C NMR (150 MHz) spectra were recorded on a Varian Unity INOVA 600 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Finnigan LCQ DUO MS system.

Synthesis of (*S*)-4-benzyl-3-propionyl-1, 3-thiazolidine-2-thione (2)

To a solution of the thiazolidinethione (7.5 g, 35.89 mmol) in dry CH_2Cl_2 (150 mL) at room temperature was added DMAP (0.88 g, 7.18 mmol) and triethylamine (6.0 mL, 43.06 mmol). Freshly distilled propionyl chloride (4.1 mL, 46.65 mmol) was added dropwise over 5 min and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched into saturated NH_4Cl (25 mL) and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the organic extracts were combined, washed with aqueous saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and the solvent was evaporated. The crude product was recrystallized from CH_3CN to yield a yellow solid **2** (9.03 g, 95%), mp 101.1–101.5 °C. IR (KBr, cm^{-1}): 1703, 1261, 1163, 1033, 759, 706. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.27-7.35 (m, 5H), 5.38 (m, 1H), 3.21 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 3.13 (dd, *J* = 10.8 Hz, 7.2 Hz, 1H), 3.05 (dd, *J* = 10.8 Hz, 2.4 Hz, 1H), 2.88 (dd, *J* = 10.2 Hz, 3.0 Hz, 1H),1.19 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 202.5, 174.8, 137.4, 130.0, 129.3, 69.1, 37.3, 33.0, 32.3, 9.8.

Synthesis of (*S*)-4-benzyl-3-((2′S, 3′*R*)-3′-hydroxy-2′-methylpentanoyl)-thiazolidine-2-thione (3)

To solution of compound **2** (4.99 g, 18.82 mmol) in anhyd. CH_2Cl_2 (100 mL) at 0 °C under N_2 was added $TiCl_4$ (2.17 mL, 19.76 mmol), and the solution was stirred for 15 min. DIPEA (3.60 mL, 20.70 mmol) was added dropwise to the mixture, and the solution was stirred for 40 min. NMP (3.61 mL, 37.65 mmol) was added at 0 °C and the mixture was stirred for an additional 10 min. Freshly distilled propionaldehyde (1.51 mL, 20.70 mmol) was then added to the enolate. The reaction was allowed to stir for 2 h followed by the addition of satd. NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over anhyd. $MgSO_4$, filtered and concentrated, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 10:1 *v*/*v*) to afford a yellow oil **3** (5.95 g, 98%). $[\alpha]_D^{25}$ = +130.3° (c 1.30, $CHCl_3$). IR (KBr, cm^{-1}): 3344, 2963, 1693, 1260, 1164, 743, 701. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.12–7.27 (m, 5H), 5.25 (m, 1H), 4.43 (m, 1H), 3.77 (m, 1H), 3.31 (dd, *J* = 6.6 Hz, 4.8 Hz, 1H), 3.13 (dd, *J* = 9.6 Hz, 3.6 Hz, 1H), 2.95 (dd, *J* = 10.2 Hz, 2.4 Hz, 1H), 2.80 (d, *J* = 11.4 Hz, 1H), 1.46 (q, *J* = 7.2 Hz, 1H), 1.37 (q, *J* = 6.0 Hz, 1H), 1.16 (d, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 201.2, 178.1, 136.2, 129.3, 128.9, 128.8, 128.7, 127.2, 73.5, 68.7, 42.7, 37.9, 31.9, 27.1, 10.2, 10.1.

Synthesis of (2*R*, 3*R*)-3-(*t*-butyldimethylsilanyloxy)-2-methyl-1-pentanol (4)

To a stirred solution of **3** (4.89 g, 15.13 mmol) in CH_2Cl_2 (50 mL) was added lutidine (2.65 mL, 22.74 mmol) and *t*-butyldimethylsilyl chloride (4.56 g, 37.77 mmol). After stirring for 3 h at room temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with CH_2Cl_2 (50 mL) and brine. The organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuum to give a green oil product (5.30 g). The green oil product (5.30 g, 14.18 mmol) was dissolved in anhyd. ethanol (50mL) and treated with sodium borohydride (2.25 g, 14.25 mmol) with cooling (ice-water bath) and stirring. After stirring for 1 h, 1 N HCl was added to quench the reaction. The reaction mixture was extracted with ethyl acetate and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 5:1 *v*/*v*) to afford a colorless oil **4** (2.92 g, 72%). $[\alpha]_D^{25}$ = +6.68° (c 1.30, $CHCl_3$) [lit. value (4*c*) $[\alpha]_D^{25}$ = +6.65° (c 1.30,

$CHCl_3$)]. IR (KBr, cm^{-1}): 3362, 2959, 1463, 1254. ^1H NMR (600 MHz, $CDCl_3$) δ: 3.61 (m, 2H), 3.44 (m, 1H), 2.43 (s, 1H), 1.91 (m, 1H), 1.44 (m, 2H), 0.83 (s, 9H), 0.74 (t, J = 7.2 Hz, 3H), 0.02 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 66.0, 39.2, 25.8, 25.2, 18.0, 11.8, 10.7, -4.4, -4.6.

Synthesis of 3-(*t*-butyldimethylsilanyloxy)-2-methylpentanal (5)

A solution of Py·SO_3 (1.88 g, 11.80 mmol) in dry DMSO (15 mL) was added dropwise to a solution of **4** (0.74 g, 3.19 mmol) and DIPEA (4.5 mL, 27.2 mmol) in dry CH_2Cl_2 (5 mL) and stirred in an ice-water bath. The mixture was stirred for 3 h, added to brine, and extracted with ether. The combined organic fractions were dried over $MgSO_4$, filtered and concentrated in vacuum, and the residue was chromatographed on silica gel (*n*-hexane/EtOAc, 10:1 *v*/*v*) to yield a colorless oil **5** (0.62 g, 84%). $[\alpha]_D^{25}$ = +22.9° (c 2.4, $CHCl_3$) [lit. value (10) $[\alpha]_D^{25}$ = +22.7° (c 2.4, $CHCl_3$)]. IR (KBr, cm^{-1}): 2959, 1727, 1463, 1258. ^1H NMR (600MHz, $CDCl_3$) δ: 9.73 (s,1H), 4.01 (m, 1H), 2.42 (m, 1H), 1.49 (m, 2H), 1.02 (m, 3H), 0.84 (s, 9H), 0.03 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 205.3, 73.3, 50.7, 27.3, 25.7, 17.9, 10.0, 7.4, –4.3, –4.8.

Synthesis of (3*R*,4*R*,5*RS*)-5-(*t*-butyldimethylsilanyloxy)-4-methyl-3-heptanol (6)

To a cooled (–78 °C) solution of **5** (0.50 g, 2.17 mmol) in ether (10 mL) was added ethylmagnesium bromide (2 mL, 6 mmol of a 3.0 mol/L solution in Et_2O) over a 5 min period under N_2. After the addition, the cooling bath was removed, the reaction mixture was allowed to warm to room temperature, and stirred for an additional 2 h. Saturated aq. NH_4Cl (10 mL) was added to quench the reaction. The reaction mixture was extracted with CH_2Cl_2 (20 mL) and dried over $MgSO_4$, filtered and concentrated, the crude product was purified by column chromatography (*n*-hexane/EtOAc, 10:1 *v*/*v*) to afford a colorless oil **6** (0.47 g, 83%). IR (KBr, cm^{-1}): 3441, 1463, 1259. ^1H NMR (600 MHz, $CDCl_3$) δ: 3.67 (m, 1H), 3.55 (m, 1H), 2.52 (s, 1H), 1.42–1.46 (m, 5H), 0.83 (t, J = 7.2 Hz, 3H), 0.79 (s, 9H), 0.76 (t, J = 7.2 Hz, 3H), 0.72 (t, J = 7.2Hz, 3H), 0.02 (m, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 79.2, 76.8, 38.2, 27.9, 27.5, 25.8, 18.0, 10.4, 9.8, 5.3, –3.7, –4.6.

Synthesis of (4*S*,5*R*)-5-hydroxy-4-methyl-3-pentanone(1)

To a solution of pyridinium chlorochromate (0.47 g, 2.23 mmol) and anhydrous sodium acetate (0.04 g, 0.44 mmol) in CH_2Cl_2 (10 mL) was added **6** (0.37 g, 1.44 mmol) at room temperature. The reaction was stirred for 4 h, followed by the addition of ether (20 mL). The resulting solution was filtered through a column of silica, dried over $MgSO_4$, and concentrated under reduced pressure. The residue (0.36 g) was dissolved in anhyd. THF (15 mL) and treated with tetrabutyl ammonium fluoride (0.37 g, 1.41 mmol). The resulting solution was stirred for 18 h before being diluted with ether (20 mL). The mixture was washed with satd. aq. NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated, and the crude product was purified by column chromatography (*n*-hexane/EtOAc, 10:1 *v*/*v*) to afford a colorless oil **1** (0.18 g, 89%), $[\alpha]_D^{25}$ = +26.3° (c 1.24, Et_2O) [lit. value (2) $[\alpha]_D^{25}$ = +27.0° (c 1.24, Et_2O)]. IR (KBr, cm^{-1}): 3445, 2959, 2930, 1710, 1462, 1255. ^1H NMR (600 MHz, $CDCl_3$) δ: 3.75 (m, 1H), 3.55 (s, 1H), 2.51 (m, 1H), 1.29–1.50 (m, 4H), 1.06 (d, J = 3.6 Hz, 3H), 0.98 (t, J = 7.2 Hz, 6.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 216.6, 72.5, 49.2, 34.7, 26.7, 11.5, 10.2, 9.9.

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