Total Synthesis of (4SR, 5RS)-5-Hydroxy-4-Methyl-3-Heptanone, the Racemic Form of the Aggregation Pheromone of *S. orizae* and *S. zeamais*

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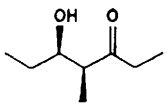
A síntese estereoseletiva de (4RS,5RS)-5-hidroxi-4-metil-3-heptanona(**1**), feromônio de agregação de *S. orizae* e *S. zeamais* é descrita utilizando-se a adição do enolato de lítio da 2-metil-2-trimetilsililóxi-3-pentanona ao propionaldeído, seguida de adição de etilítio e clivagem oxidativa com ácido periódico. A adição do enolato de boro da 3-pentanona ao propionaldeido, seguida de tratamento oxidativo, forneceu uma mistura de (4SR,5RS) - e (4SR,5SR)-5-hidroxi-4-metil-3-heptanona, na proporção de 9:1, respectivamente.

The stereoselective total synthesis of (4SR,5RS)-5-hydroxy-4-methyl-3-heptanone(**1**), the racemic form of the aggregation pheromone of *S.orizae* and *S.zeamais,* is described using the addition of the lithium enolate of 2-methyl-2-trimethylsilyloxy-3-pentanone to propionaldehyde, followed by ehtyllithium addition and oxidative cleavage with periodic acid. The addiciton of the boron enolate of 3-pentanone to propionaldehyde, followed by oxidative treatment, afforded a 9:1 mixture of (4SR,5RS)- and (4SR,5SR)-5-hydroxy-4-methyl-3-heptanone, respectively.

Key words: *sitophilure, pheromone,* S.zeamais, S.orizae.

Introduction

In 1984, Schmuff *et alli*[1] reported the isolation and chemical identification of the aggregation pheromone of *S. orizae* (rice weevil) and *S.zeamais* (maize weevil) which are responsible for major losses of stored grains. Both maize and rice weevils respond most strongly to (4S,5R) - 5-hydroxy-4-methyl-3-heptanone (**1**), known as sitophilure, which was proven to be the major component of the aggregation pheromone of both species. Somewhat lower but still significant responses were observed for the (4SR, 5RS)mixture while very low responses were elicited by either the (4R,5R)-isomer or the (4RS,5RS) racemic mixture[2]. Since effective and cost-efficient control of both maize and rice weevils populations can before seen for the aggregation pheromone, several total syntheses for the racemic and the natural forms of sitophilure (**1**) have being published[3,4].



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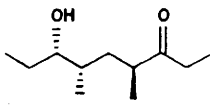

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Experimental

Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone immediately prior to use. Diisopro-pylamine, triethylamine, dichloromethane and disopropyle-thylamine were distilled from calcium hydride. All reactions involving organometallic reagents and di-n-butylboron triflate were carried out under an argon atmosphere. ^{1}H-NMR spectra were determined in CCl_4 or $CDCl_3$ solution at 80 and 300 MHz and ^{13}C-NMR in $CDCl_3$ solution at 75.46 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane and ^{1}H-NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; t, triplet;dt, double triplet; q, quartet; m, multiplet, number of protons and coupling constants in Hertz. Infrared spectra were determined with a Perkin Elmer 399B spectrophotometer. GC-MS data were obtained a with GC-MS HP 5988A and the elemental analyses with a Perkin-Elmer 2400 CHN analyzer.

(4SR,5RS)-5-O-(1'-Ethoxyethyl)-2,5-dihydroxy-2,4-dimethyl-2-O-trimethylsilylheptan-3-one(5): solution of β-hydro-xyketone **4**[5] (0.130g, 0.53 mmol) dissolved in CH_2Cl_2(3 ml) was treated with ethyl vinyl ether (0.52 ml, 5.3 mmol) and catalytic amount of pyridinium p-toluenesulfonate (PPTS). The solution was stirred at room temperature for 3 hours and diluted with CH_2Cl_2 (15ml). The organic phase was washed with aqueous sodium bicarbonate (5%), dried over $MgSO_4$ and the solvent was removed under reduced pressure to afford ketone **5**(0.121 g, 0.38 mmol) as a

colorless oil, in 72% yield, which was used without further purification. A sample was purified (PTLC in SiO_2, 5% ether in hexanes) for elemental analysis.

^{1}H-NMR(CCl_4, 80 MHz) δ 0.15(s,9H), 0.90(t,J=6.0,3H), 1.05 (d,J=7.0,3H), 1.18(t,J=8.0,3H), 1.22 (s,6H), 1.3-1.4(m, 5H), 3.14(m, 1H), 3.55(m, 3H),5.05(q,J=8.0, 1H).

IR(film): 2980,1715,1085 cm^{-1}. Elemental analysis calcd. for $C_{16}H_{34}O_4Si$:C-60.33%; H-10.76%. Observed: C-66.77%; H-11.05%.

(4SR, 5RS)-5-Hydroxy-4-methyl-3-heptanone(1): i. to a solution of ketone **5** (0.095g, 0.30 mmol) in THF (2 ml) was added a 1.0M ethyllithium solution in ether (1 ml), prepared according to Masamune and Choy[6]. The reaction was let to stirred at room temperature for 4 hours when it was quenched by addition of saturated aqueous NH_4Cl solution (2 ml). The reaction mixture was extracted with ether (2x10 ml), the extracts were dried over $MgSO_4$ and the solvent removed under reduced pressure to yield 0.120 g of a pale yellow oil which was used without further purification. This material was dissolved in methanol (5ml) and treated with H_5IO_6(0.275 g, 1.2 mmol). After being stirred overnight at room temperature it was diluted with water and extracted with ether (3 x 10 ml). The combined extracts were washed with brine 2 x 10 ml), dried over Mg SO_4 and the solvent was removed under reduced pressure to yield 0.028g of a pale yellow oil. Purification by preparative thin layer chromatography on SiO_2 (5% ether-hexanes) afforded 0.012 g (28% yield) of (4SR,5RS)-5-hydroxy-4-methyl-3-heptanone(**1**).

ii. To a solution of 3-pentanone (0.43 g, 0.50 ml, 5.0 mmol) in ether (10.0 ml), at -78°C, were added diisopropylethylamine (1.13 ml, 6.50 mmol) and a 1.0 M solution of di-n-butylboron triflate (5.5 ml, 5.5 mmol). After 45 min. at -78°C, propionaldehyde (0.78 ml, 8 mmol) was added dropwise and the reaction was kept at -78°C for 2 hours when it was quenched by the addition of 20 ml of a phosphate buffer, followed by the addition of ether (20 ml). The mixture was let to warm up to room temperature, the organic phase was separated, the aqueous phase was extracted with ether (2 x 20 ml) and the combined organic phases were dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the residue was taken up in methanol (20 ml) and treated with 30% hydrogen peroxide (5 ml). The reaction was let at room temperature for 30 min. and extracted with ether (2 x 20 ml), washed with saturated aqueous NaCl and dried over $MgSO_4$. The organic solvent was removed under reduced pressure and the oily residue was purified by Kugelrohr distillation (1.0 mm, 98-101°C) to yield 0.30 g (2.15 mmol, 43% yield) of a colorless oil.

GC-MS analysis on a 5% phenyl silicone capillary column (oven parameters-initial temperature: 80°C, final temperature: 200°C, rate: 8°C min^{-1}; injection temperature: 250°C; detection temperature:250°C; carrier gas: H_2, split: 25:1; mass detection range: 10-200 a.m.u) showed a 9:1 ration of isomers.

IR(film): 3450(br), 2975, 2940, 2885, 1700, 1460 and 970 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300MHz) δ 0.95(t,3H,J=7.5), 1.05 (t, 3H, J=7.8), 1.12 (d, 3H, J=7.2), 1.3-1.6 (m, 2H), 2.4-2.7 (m, 3H), 2.9 (s, br, 1H), 3.82 (m, 1H).

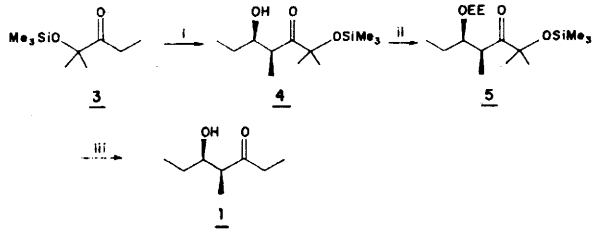
^{13}C-RMN($CDCl_3$, 75.46 MHz) δ 7.54, 10.09, 10.48, 27.09, 35.27, 49.71, 73.01, 217.43.

MS(70 eV) m/z 126 (9%, M^+ - H_2O), 115(4%), 86(20%), 70(14%), 57(100%), 41(14%) and 29(43%).

Results and Discussion

Along with our studies on the diastereoselective total synthesis of (+/-)-sericornine(**2**)[5] we reasoned that the common biogenetic origin of **1** and **2**, i.e. the polyketide biosynthetic pathway, would entitle a common synthetic route based on stereoselective aldol condensation for both of them based on stereoselectivel aldol condensation.

Scheme 1 depicts the preparation of (+/-)-**1** starting from

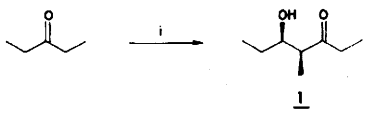


i) LDA, THF, -78°C ; then C_2H_5CHO (75-82%); ii) $C_2H_5OC_2H_3$, PPTS, CH_2Cl_2 (72%); iii) C_2H_5Li, Et_2O, -30°C ; then H_5IO_6, MeOH, RT (28%).

α-trimethylsilyloxy ketone **3**[7], which is prepared in 75%yield from α-hydroxyisobutyronitrile. The kinetic lithium enolate from **3**, which was shown to have the **Z** geometry[7], was prepared in THF at -78°C and let to condense with propionaldehyde to afford (4RS, 5SR) **4** in 75-82% yield[5] after Kugelrohr purification. The racemic mixture obtained was shown to be diastereomerically homogeneous by ^{13}C-NMR (75.1 MHz) and CG-MS analyses. The relative configuration was established through conversion of (+/-)-**4** to the known methyl ester **6**[8,9]. Chain elongation was achieved in a three step sequence: hydroxyketone **4** was uneventfully converted into its ethoxyethyl ether **5** (72% yield), followed by ethyllithium addition and oxidative cleavage with periodic acid. After chromatography on silica gel, (+/-)-**1** was isolated; in *ca.* 28% yield from (+/-)-**5**, as a colorless oil identical by ^{1}H and ^{13}C-NMR spectroscopy with the data reported for (+/-)-sitophilure(**1**)[3].

The low overall yield of the sequence above and the notorious advantage of higher diastereoselectivity of boron enolates lacking a bulky substituent attached to the carbonyl group led us to explore the boron enolate of **3** pentanone as a one-pot methodology for the synthesis of *syn*-α-methyl-β-hydroxyketones. Of the several experimental protocols available to carry out condensations between boron enolates of ketones and aldehydes[10,11], in our hands the best results were achieved when the boron enolate from 3-pentanone was generated in diethyl ether at -78°C using di-n-butylboron triflate and N,N-diisopropylethylamine as base. Condensation with an excess (1.6 equivalents) of propionaldehyde and oxidative treatment of the boron intermediate with hydrogen peroxide in methanol afforded the condensation product, in 43% overall yield after Kugelrohr purification, as a 9:1 mixture of diastereoisomers to which

structures (4SR, 5RS)- and (4SR, 5SR) - 5 - hydroxy-4-methyl-3-heptanonne were assigned based on ^{1}H- and ^{13}C-NMR correlation with known data for the above compounds[4a].



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i) $^{n}Bu_2BOTF$, Et_2O, $^{i}Pr_2NEt$, -78°C; C_2H_5CHO; then 30% H_2O_2, MeOH (43%).

The level of diastereoselection described above correlates well with the results of Enders and Lohray[4b] which have also observed a 9:1 *sin:anti* ratio in the aldol condensation of the boron enolate of (R)-2-tert-butyldimethylsilyl-3-pentanone with propionaldehyde. The sense of diastereo- selection observed both in the reaction of the lithium enolate of α-trimethylsilyloxy ketone **3** and of the boron enolate of 3-pentanone can be rationalized through a six-membered transition state as proposed in the Zimmermann-Traxler model[12].

Molecular mechanics calculations performed with the MM2. UEC force field[13] has confirmed the *anti* isomer as the thermodinamically more stable (0.43 kcal.mol^{-1}) isomer[12] with non-bonded distances of 2.11Å between the oxygen of the carbonyl group and the hydrogen of the hydroxyl group, in both isomers. The diastereoisomeric ratio observed above should then reflect, to some extent, the kinectically controlled addition of the boron enolate of 3-pentanone to propionaldehyde.

The results herein describe two routes to (4SR,5RS)-5-hydroxy-4-methyl-3-heptanone(**1**), the racemic form of the aggregation pheromone of *S. orizae* and *S. zeamais*. The efficiency of the one-pot preparation using the di-n-butylboron enolate of 3-pentanone (80% diastereosomeric excess and 43% overall yield is noteworth and it provided synthetic material for biological evaluation.

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