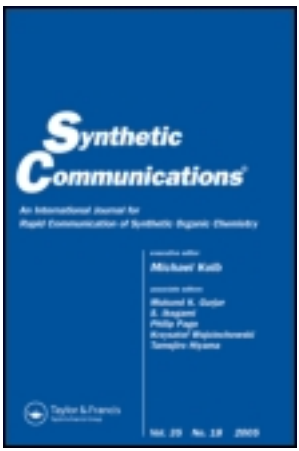

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A Versatile Approach Towards Enantiopure α-Methyl β-Hydroxy Ketones. Application to the Synthesis of (4R,5S) Sitophilure and of Its Stereoisomers

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A VERSATILE APPROACH TOWARDS ENANTIOPURE α-METHYL β-HYDROXY KETONES. APPLICATION TO THE SYNTHESIS OF (4R,5S) SITOPHILURE AND OF ITS STEREOISOMERS

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Abstract: Rice weevil pheromone sitophilure ((4R,5S)-5-hydroxy-4-methyl-3-heptanone) and its three diastereomers were synthesized in three steps, starting from 3-(trimethylsilyloxy)-1,3-pentadiene and propionaldehyde. Other optically active α-methyl β-hydroxy ketones can also be synthesized by the reported procedure.

A short and efficient synthesis of small optically active molecules are often difficult to realize. The existing multi-step methods (up to ten steps) for preparing the pheromone sitophilure, ((4R,5S)-5-hydroxy-4-methyl-3-heptanone), and/or of its stereoisomers are significant in this respect.[1] On the basis of our previous work,[2] we reported herein on a practical and short procedure for the preparation of these compounds. Furthermore, the procedure can be applied to the synthesis of other optically active α-methyl β-hydroxy ketones.

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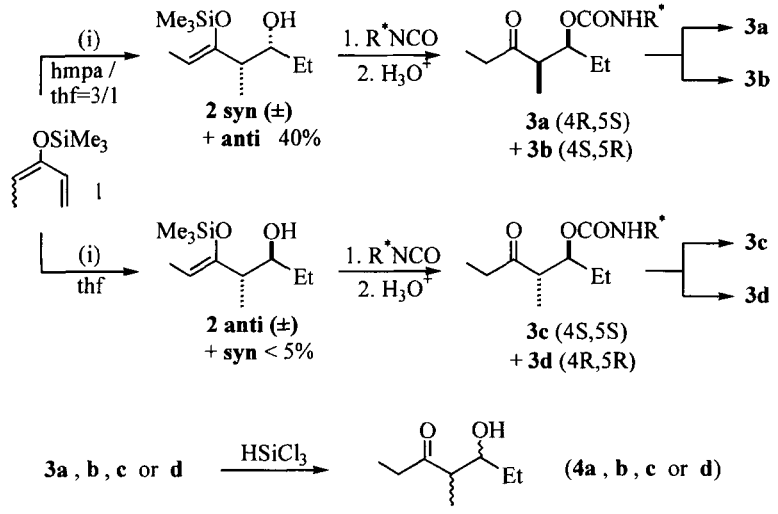


(i) $Cp_2TiCl^{\$}$, iPrMgCl , -20°C ; $^{\$}$ = Cp_2TiCl_2 + ^{i}PrMgCl, r.t., then EtCHO
R^* =(S)Ph(Me)CH-

Scheme 1

The synthetic entry to all of the four stereoisomeric 5-hydroxy-4-methyl-3-heptanones is based on the following previously obtained results: (i) *Anti*-configurated α-methyl β-hydroxy enolsilanes were synthesized in a one-pot reaction, through addition of silyloxylated crotyltitanium reagents to aldehydes.[2a,b] (ii) Optically active, *anti* α-methyl β-hydroxy (carbamate protected) enolsilanes could be isolated, using a chiral isocyanate.[2c] (iii) The reversal of *anti* to *syn* diastereoselectivity in crotyltitanation reaction might be achieved with a choice of HMPA/THF=3/1 (v:v) instead of pure THF as a solvent.[3]

Thereafter, sitophilure (4R,5S)-**4a** as well as its stereoisomers (4S,5R)-**4b**, (4S,5S)-**4c** and (4R,5R)-**4d** were obtained in three steps (Scheme 1). Starting from

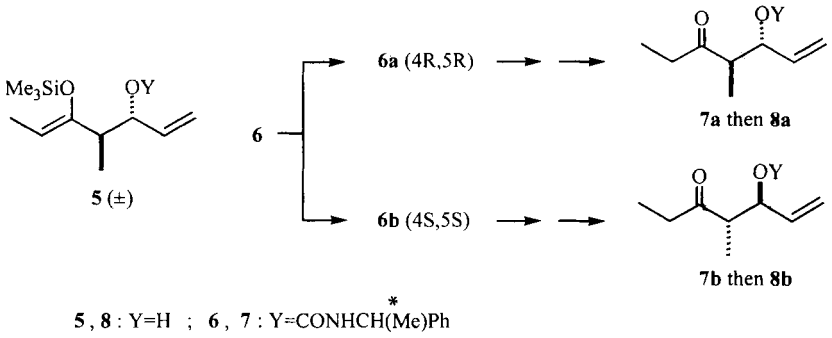
diene **1** and propionaldehyde, racemic functionalized enolsilanes **2** ***anti*** or **2** ***syn*** were formed preferentially,[4] in two solvent-controlled stereoselective crotyltitanation reactions (cf (iii)). The *anti* (*syn*) stereochemistry was assigned to compounds **2** from the ^{1}H NMR vicinal coupling constants and/or ^{13}C NMR resonances using Heathcock rule[5] (see Table I). Compounds **2** then reacted with S-(-)-α-methylbenzyl isocyanate (reflux in toluene, 30 h). After acidic (0.5 M HCl) workup, α-methyl β-hydroxy (carbamate protected) ketones **3** ***anti*** and **3** ***syn*** were obtained directly in almost quantitative yields, as mixtures of two diastereomers, **3a**,**b** and **3c**,**d** respectively. The mixtures **3a**,**b** and **3c**,**d** were easily resolved by flash chromatography, and each of the four stereoisomers deprotected with $HSiCl_3$,[6] to afford α-methyl β-hydroxy ketones **4a-d** in 50-55% overall yields. The enantiomeric stereostructures have been ascertained to **4a**,**4b** and **4c**,**4d**, and the enantiomeric purity of each of the four stereoisomers estimated as >97% by comparison of their specific rotations with literature.[1d]

The reported procedure can be extended to other α-methyl β-hydroxy ketones. An example is depicted in Scheme 2. Enolsilane **5** (±) derived from diene **1** and acrolein reacted with S-(-)-α-methylbenzyl isocyanate to give carbamate-protected **6**, as a mixture of two diastereomers. In contrast to the protocol described above, **6** was isolated by means of a basic ($NaHCO_3$ aq) workup, and separated onto stereoisomers **6a** and **6b** by flash chromatography. Thus, the alternative resolution of the optically active compounds at the enolsilane or the

Table I : ^{1}H and ^{13}C NMR spectra of **2**, **3a-d** (CD_3COCD_3) and **4a-d** (C_6D_6).

Compd.	^{1}H, ^{13}C NMR (δ, ppm / TMS) data
2 ***syn***	**^{1}H**: 0.20 (s, 9H); 0.94 (t, J=7 Hz, 3H); 0.98 (d, J=7.1 Hz, 3H);1.20-1.35 (m, 2H); 1.52 (d, J=6.6 Hz, 3H); 2.20 (dq, J=7.1 Hz, 5.6 Hz, 1H); 3.05 (d, J=5.1 Hz, D_2O exchangeable); 3.45-3.55 (m, 1H); 4.58 (q, J=6.6 Hz,1H). **^{13}C**: 1.1; 10.1; 11.5; 14.3; 26.7; 47.1; 74.6; 102.7; 154.7.
2 ***anti***	**^{1}H**: 0.20 (s, 9H); 0.97 (t, J=7.2 Hz, 3H); 1.02 (d, J=7.1 Hz, 3H);1.30-1.45 (m, 2H); 1.57 (d, J=7.1 Hz, 3H); 2.62 (dq, J=7.1 Hz, 7.1 Hz, 1H); 2.71 (d, J=6.8 Hz, D_2O exchangeable); 3.32-3.45 (m, 1H); 4.68 (q, J=6.8 Hz, 1H). **^{13}C**: 0.7; 10.8; 12.0; 15.1; 28.5; 39.8; 75.5; 101.5; 154.6.
3a	**^{1}H**: 0.78-0.93 (m, 6H); 0.98 (d, J= 7.1 Hz, 3H); 1.43 (d, J=7.1 Hz, 3H); 1.45-1.55 (m, 2H); 2.40-2.60 (m, 2H); 2.75-2.85 (m, 1H); 4.78 (m, 1H); 4.93 (m, 1H); 6.69 (d, J=8.0 Hz, 1H); 7.25-7.40 (m, 5H). **^{13}C**: 8.1; 10.5; 11.8; 23.2; 26.1; 35.5; 50.0; 51.4; 76.2; 126.8; 126.6; 129.2; 146.0; 156.5; 212.1.
3b	**^{1}H**: 0.80-0.96 (m, 6H); 0.99 (d, J= 7.1 Hz, 3H); 1.41 (d, J=7.1 Hz, 3H); 1.46-1.61 (m, 2H); 2.46-2.54 (m, 2H); 2.75-2.81 (m, 1H); 4.72-4,84 (m, 2H); 6.69 (d, J=8.0 Hz, 1H); 7.25-7.40 (m, 5H). **^{13}C**: 7.9; 9.5; 12.5; 23.2; 24.8; 35.3; 50.0; 51.4; 76.5; 126.8; 127.6; 129.2; 146.1; 156.2; 212.2.
3c	**^{1}H**: 0.78-0.93 (m, 6H); 0.98 (d, J= 6.9 Hz, 3H); 1.40-1.60 (m, 2H); 1.42 (d, J=7.1 Hz, 3H); 2.40-2.60 (m, 2H); 2.75-2.90 (dq, J=7.1 Hz, 7.1 Hz, 1H); 4.80 (m, 1H); 4.93 (m, 1H); 6.69 (d, J=8.0 Hz, 1H); 7.25-7.40 (m, 5H). **^{13}C**: 7.9; 9.5; 12.5; 23.2; 24.8; 35.3; 50.0; 51.4; 76.5; 126.7; 127.6; 129.2; 146.0; 156.5; 212.1.
3d	**^{1}H**: 0.78-0.93 (m, 6H); 0.99 (d, J= 7.1 Hz, 3H); 1.40-1.60 (m, 2H); 1.43 (d, J=7.1 Hz, 3H); 2.40-2.60 (m, 2H); 2.75-2.85 (dq, J= 7.1 Hz, 7.1 Hz,1H); 4.72-4.86 (m, 2H); 6.69 (d, J=8.0 Hz, 1H); 7.25-7.40 (m, 5H). **^{13}C**: 8.0; 10.4; 11.8; 23.1; 26.1; 35.5; 50.1; 51.4; 76.2; 126.7; 127.6; 129.1; 146.1; 156.5; 212.2.
4a-b	**^{1}H**: 0.85 (t, J= 7 Hz, 3H); 0.89 (t, J= 7 Hz, 3H); 0.91 (d, J= 7Hz, 3H); 1.2-1.3 (m, 2H); 2.0-2.1 (m, 2H); 2.4 (m, 1H); 3.4-3.5 (m, 1H). **^{13}C**: 7.7; 10.2; 10.7; 27.4; 34.9; 49.9; 72.7; 214.9. **4a** :(4R, 5S) Sitophilure: $[\alpha]_D$ -26.1° **4b** :(4S, 5R) Sitophilure:$[\alpha]_D$ +25.3°
4c-d	**^{1}H**: 0.79 (d, J= 7.1 Hz, 3H); 0.88 (t, J= 7 Hz, 3H); 0.92 (d, J= 7Hz, 3H); 1.2-1.4 (m, 2H); 1.9-2.0 (m, 2H); 2.0-2.1 (m, 1H); 2.43 (br.s., 1H); 3.58-3.66 (m, 1H). **^{13}C**: 7.7; 10.0; 14.0; 27.9; 36.0; 50.8; 74.9; 214.8. **4c** : (4S, 5S)-5-Hydroxy-4-methyl-3-heptanone : $[\alpha]_D$ +38.2° **4d** : (4R, 5R)-5-Hydroxy-4-methyl-3-heptanone : $[\alpha]_D$ -36.5°

ketone level is indicative of the versatility of the method. The acidic hydrolysis of both **6a** and **6b** produced the corresponding ketones **7a** and **7b**, which can be further deprotected with $HSiCl_3$ to afford hydroxy-free compounds **8a** and **8b**. The absolute configurations of **8a** (4R,5R) and **8b** (4S,5S) were determined by



Scheme 2

hydrogenating the precursor **7a**,**7b** to **3d**,**3c** (Scheme 1), and comparing their specific rotations with that obtained above.

In conclusion, the present method appears to be a short and easy procedure for the preparation of optically active α-methyl β-hydroxy ketones.

Experimental Section

All reactions were carried out under argon using vacuum line techniques. THF and toluene were distilled under argon atmosphere from benzophenone ketyl. HMPA was distilled under argon over 13X molecular sieves. Titanocene dichloride[7] and 3-(trimethylsilyloxy)-1,3-pentadiene[8] were prepared according to the described procedures. Other reagents were purchased from Aldrich Chemical Co. Propionaldehyde was distilled under argon prior to use. ^{1}H and ^{13}C NMR

spectra were recorded at 200 and 50 MHz respectively. Column flash chromatography was performed on silica gel 60 (Merk).

Preparation of Enolsilane **2 syn**. Titanocene dichloride (12 mmol) was partly dissolved in 5 ml of THF, ^{i}PrMgCl (6 ml, 2M solution in THF) was added dropwise. After stirring for 15 min., the resulting green solution of Cp_2TiCl was cooled to -20°C. A solution of ^{i}PrMgCl (6 ml, 2M solution in THF) and silyloxydiene **1** (12 mmol, 3 ml) were added slowly and simultaneously by syringe at -20°C. After 15 min., HMPA (50 ml) was added, followed by propionaldehyde (12 mmol) 30 min. later. After an additional 1 hr period the reaction mixture was poured into a separatory funnel containing Et_2O (250 ml) and treated with sat. aq. $NaHCO_3$ (40 ml). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined organics were washed with H_20 and dried ($MgSO_4$) and concentrated in vacuo. Separation by flash chromatography on a silica gel column eluting with hexane/ether (8/1) afforded the crude β-hydroxy enol silyl ether **2** ***syn*** (80%) as a colorless oil.

Preparation of Enolsilane **2** ***anti***. Preparation of allyltitananium complex was performed as described above in 40 ml of THF at -20°C. HMPA was not used. Propionaldehyde was added 30 min. later. The reaction mixture was worked up after an additional 1 hr period as precedently described. Separation by flash chromatography on a silica gel column eluting with hexane/ether (8/1) afforded the crude β-hydroxy enol silyl ether **2** ***anti*** (75%) as a colorless oil.

Preparation of carbamate-protected ketones (**3a-d**). General procedure. Enolsilane **2** ***syn-anti*** (1mmol) was dissolved in toluene (8 ml) and the (S)-(-)-α-methylbenzyl isocyanate (1.3 mmol) was added. The reaction mixture was heated under reflux for 30 hr. After evaporation of the solvent under vacuo the pure product was dissolved in 10 ml of THF. HCl 0.5M (3 ml) was added to the stirring solution at room temperature. After 20 min., the reaction mixture is poured in a separatory funnel contaning Et_2O (50 ml). The Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined organics were washed, dried ($MgSO_4$) and concentrated in vacuo. Compounds **3a,b** and **3c,d** were isolated by flash chromatography on a silica gel column eluting with hexane/Et_2O (1:1) (95%) as colorless oils.

Hydroxy ketones **4a-d**. Cleavage of carbamates **3a-d**. General procedure. Carbamate (1 mmol) is dissolved in THF (6 ml), triethylamine (1.1 mmol) and trichlorosilane (1.1 mmol) was added dropwise. The reaction is conducted at room temperature and monitored by TLC. After 24 hr, the reaction mixture was diluted with 50 ml of Et_2O and was worked up by washing the organic layer with 5 ml of satured aqueous NH_4Cl. The organic layer was washed, dried ($MgSO_4$) and concentrated in vacuo. Compounds **4a-d** were isolated by flash chromatography on a silica gel column eluting with hexane/Et_2O (1:1) (65-75%) as colorless oils.

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4. The *syn* stereoselectivity is lower (*syn/anti*=60/40) than that observed in a similar reaction involving isoprene (syn/anti=88/12).[3] The *syn* and *anti* stereoisomers could be easily separated; see experimental section.

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