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Asymmetric synthesis of (*R*)-4-hexanolide, the pheromone of *Trogoderma glabrum*

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Abstract—Synthesis of (*R*)-4-hexanolide, a sexual pheromone of *Trogoderma glabrum*, has been achieved with an overall yield of 45.4% in high enantiomeric purity using a chiral auxiliary derived from (*S*)-camphor.

1. Introduction

4-Hexanolide was isolated and identified as a component of the sexual pheromone from the female dermestid beetle *Trogoderma glabrum*,[1] a stored-product pest. Subsequently, Ravid et al.[2] reported the synthesis and bioassay of both the enantiomers, thus determining the absolute configuration of the natural pheromone as (*R*). Early syntheses of optically active 4-hexanolide have been reported from chiral building blocks as well as by chemical or biochemical asymmetric reactions.[3] Mori et al.[4] achieved the synthesis of highly enantiomerically pure enantiomers of 4-hexanolide in 51% overall yield from enantiopure methyl 3-hydroxypentanoate which in turn was prepared in four steps by microbial asymmetric reduction of octyl 3-oxopentanoate. Nuñez et al.[5] reported a synthesis for this pheromone with 17% overall yield from 3-phenyl-1-propanol involving a Sharpless asymmetric epoxidation as a key step. Baker's yeast mediated reduction has been reported for the pheromone antipode[6] in 11% yield from methyl 3-oxo-6-heptenoate. By lipase resolution of the corresponding hydroxysulfone, (*R*)-4-hexanolide was obtained in 15% yield.[7] (*R*)-2,3-*O*-Cyclohexylideneglyceraldehyde, prepared from mannitol, was used to achieve another synthesis in 35% yield.[8] Very recently, through intramolecular asymmetric reduction of 4-oxohexanoic acid with diisopinocampheylborane, a synthesis of the pheromone has been reported in 80% yield.[9]

A new chiral auxiliary **1** (Scheme 1) has been prepared in our group[10] from (1*S*)-camphor and used in highly diastereoselective aldol reactions with excellent results.[11] Now, to expand the use of this auxiliary and continuing our work on the synthesis of optically active insect pheromones[12–15] we have applied this methodology to the synthesis of (*R*)-4-hexanolide **8**.

2. Results and discussion

The synthesis of (*R*)-4-hexanolide was carried out as shown in Scheme 2. Thus, starting with the chiral auxiliary **1**, the asymmetric aldol reaction of its lithium enolate with propanal at −78°C afforded the aldol product **2** in 93% yield as a diastereomeric mixture 97:3 determined by ^{13}C NMR of the crude: *C*HOH signals of both diastereomers at $\delta = 68.9$ (major) and 69.6 (minor). After desilylation, compound **3a** was isolated as a white solid in 96% yield. Protection of secondary hydroxyl group with TBDPS[16] afforded **3b** (94% yield). The diastereomeric ratio was unchanged for these compounds. Cleavage of the chiral auxiliary moiety was accomplished using ceric ammonium nitrate (CAN) to obtain the protected hydroxy acid **4** as a solid in 92% yield along with the recovery of the starting (*S*)-camphor (98%). Compound **4** was reduced with BH_3·THF to give the alcohol **5** which under standard conditions was converted to methanesulfonate **6a**, then iodide **6b** and finally nitrile **6c** (80% yield, three steps). Removal of TBDPS[17] group with Bu_4NF furnished the hydroxy nitrile **7** in 86% yield. Subsequent hydrolysis in aqueous base followed by acidification gave the desired lactone **8** in 90% yield. The analytical and spectral data of the pheromone were in accord with the literature as well as the specific rotation value.[4]

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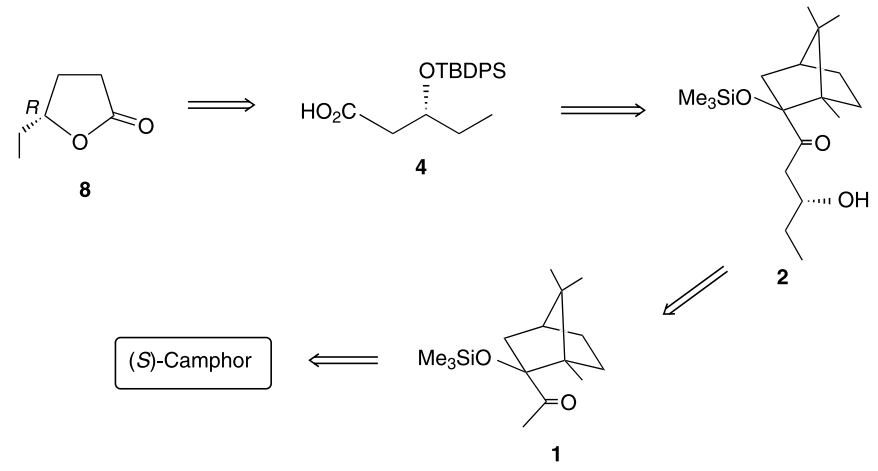
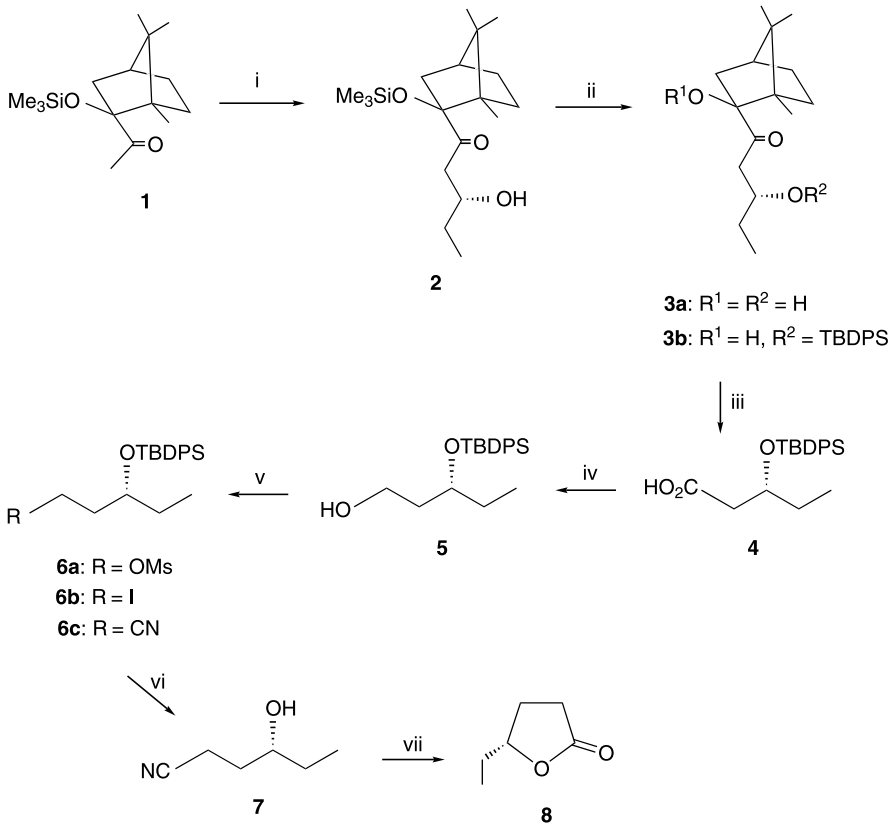


Scheme 1. Retrosynthetic analysis of (*R*)-4-hexanolide.



Scheme 2. *Reagents and conditions*: (i) LDA, −78°C, then CH_3CH_2CHO, 3 h (93%); (ii) a. HF aq., rt, 1.5 h (96%), b. TBDPSCl, imidazole, DMF, rt, 12 h (94%); (iii) CAN, acetonitrile, 0°C, 20 min (92%); (iv) BH_3·THF, 0°C, then rt 4 h (95%); (v) a. MsCl, Et_3N, 0°C, 3 h, b. NaI, acetone, reflux, 12 h, c. NaCN, DMSO, rt, 12 h (80% from **5**); (vi) Bu_4NF, THF, rt, 4 h (86%); (vii) NaOH, 2-methoxyethanol, reflux, 21 h, then HCl (90%).

The e.e. values for compounds **4**, **5**, **7** and **8** were determined by chiral HPLC analyses comparing retention times with those of racemic samples; the enantiomeric ratio showed to be 96:4 in every case. Regarding **6c** the separation was unsuccessful so the same e.e. value was assumed for this compound by analogy with the rest of the series.

In summary, an efficient synthesis of (*R*)-4-hexanolide has been achieved in high overall yield (45.4% from **1**), high enantiomeric purity (92% e.e.) and suitable for large-scale application since the starting source of chirality, (1*S*)-camphor, is recovered in almost quantitative yield (98%). This procedure allows versatile access to either enantiomer of the key synthon **4** or analogous

in a predictable stereochemistry. In this way starting with the enantiomer of chiral auxiliary **1** and employing ethanal in the aldol reaction step, (*S*)-3-hydroxybutanoic acid would be obtained which is another valuable chiral building block for the synthesis of pheromones and other natural products.

3. Experimental

3.1. General

Solvents were dried by distillation from drying agents as follows: THF, Et_2O (Na–benzophenone); dichloromethane (P_2O_5); MeOH (Mg). Separations by flash chromatography were performed on 230–400 mesh silica gel. Melting points were recorded on a microscopic apparatus. Microscale distillations were performed in a bulb-to-bulb Kugelröhr oven Büchi B-580. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200. Elemental analyses were performed in a Perkin–Elmer 240C Analyzer. Infrared spectra were recorded on a Nicolet–Avatar 360 FT-IR. Optical rotations were measured in a JASCO-DIP-370 polarimeter. High-performance liquid chromatography (HPLC) analyses were carried out on a Waters chromatograph equipped with a diode-array UV detector. Mass spectra were recorded on a API Agilent-SL ion trap using the APCI technique.

3.2. (1*S*)-2-*endo*-[(3*R*)-Hydroxypentanoyl]-2-trimethylsilyloxy-1,7,7-trimethylbicyclo[2.2.1]heptane 2

To a cooled (−78°C) solution of diisopropylamine (0.84 mL, 6 mmol) in dry THF (15 mL) a 2.5 M solution of BuLi in THF (2.4 mL, 6 mmol) was added dropwise under nitrogen. After 30 min of stirring, a solution of methyl ketone **1** (1.34 g, 5 mmol) in 10 mL of THF was added keeping the temperature below −70°C during the addition. The mixture was maintained for 1 h at the same temperature and then freshly distilled propanal (0.74 mL, 10 mmol) was added dropwise. After 3 h at −78°C the reaction mixture was quenched with a saturated solution of NH_4Cl (25 mL) and extracted with CH_2Cl_2 (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent removed in vacuum to afford the crude aldol **2** as a mixture of diastereomers 97:3. Purification by flash chromatography (hexane–ethyl acetate, 45:1) gave 1.52 g (93%) of a colorless syrup: $[\alpha]_D^{25}$ −10.0 (*c* 1, CH_2Cl_2). Data for major isomer: IR *v* 3510 (OH), 1698 (C=O) cm^{-1}; ^1H NMR: δ 3.96–3.84 (m, 1H), 3.52 (bs, 1H), 2.74 (dd, $J=2.6$, 17.9 Hz, 1H), 2.66–2.46 (m, 2H), 1.81–1.06 (m, 8H), 1.04 (s, 3H), 0.98 (s, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 0.82 (s, 3H), 0.10 (s, 9H); ^{13}C NMR: δ 214.0, 90.7, 68.9, 51.8, 50.9, 45.2, 44.9, 40.3, 30.2, 29.6, 25.8, 20.9, 20.3, 11.4, 9.8, 1.7; MS: $m/z=327$ $(MH)^+$.

3.3.(1*S*)-2-*endo*-[(3*R*)-Hydroxypentanoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 3a

Compound **2** (4.55 g, 14 mmol) was dissolved in MeOH (70 mL) and treated with 48% aq. HF (15 mL). The mixture was stirred at rt for 1.5 h and then saturated aqueous $NaHCO_3$ solution (150 mL) was added. After extracting with ethyl acetate (3×75 mL), the combined organic layers were dried with $MgSO_4$ and the solvent removed under reduced pressure to give a syrup that was purified by flash chromatography (hexane–ethyl acetate, 10:1) affording 3.41 g (96% yield) of product as a white solid: mp 46–49°C; $[\alpha]_D^{25}$ −14.0 (*c* 1, CH_2Cl_2). Data for major isomer: IR *v* 3400 (OH), 1699 (C=O) cm^{-1}; ^1H NMR: δ 3.93 (m, 1H), 3.06 (s, 1H), 2.95 (dd, $J=10$, 16 Hz, 1H), 2.84 (s, 1H), 2.49 (dd, $J=2.6$, 15.8 Hz, 1H), 2.27 (m, 1H), 1.85–1.16 (m, 8H), 1.12 (s, 3H), 0.98 (s, 3H), 0.96 (t, $J=7.3$ Hz, 3H), 0.84 (s, 3H); ^{13}C NMR: δ 214.0, 87.7, 70.4, 52.1, 50.8, 45.6, 45.0, 41.3, 30.3, 29.9, 26.3, 20.9, 20.6, 11.1, 9.9. Anal. calcd for $C_{15}H_{26}O_3$: C, 70.81; H, 10.32. Found: C, 70.79; H, 10.39.

3.4. (1*S*)-2-*endo*-[(3*R*)-*tert*-Butyldiphenylsilyloxypentanoyl]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol 3b

Imidazole (2.34 g, 34.5 mmol) and *tert*-butyldiphenylsilyl chloride (5.43 mL, 20.7 mmol) were added to a stirred solution of **3a** (3.51 g, 13.8 mmol) in anhydrous DMF (41 mL). The mixture was stirred overnight at rt and then poured into ice-water and extracted with Et_2O (3×50 mL). The organic phase was washed with brine, $NaHCO_3$, dried ($MgSO_4$) and the solvent removed. The crude product was purified by column chromatography (hexane–ethyl acetate, 50:1) to give a colorless syrup (6.4 g, 94%): $[\alpha]_D^{25}$ −5.0 (*c* 1, CH_2Cl_2). Data for major isomer: IR *v* 3444 (OH), 1702 (C=O) cm^{-1}; ^1H NMR: δ 7.70–7.66 (m, 4H), 7.40–7.34 (m, 6H), 4.27–4.10 (m, 1H), 3.28 (s, 1H), 3.16 (dd, $J=8.4$, 14.6 Hz, 1H), 2.32 (dd, $J=4.8$, 14.6 Hz, 1H), 2.11 (m, 1H), 1.83–1.17 (m, 8H), 1.12 (s, 3H), 0.99 (s, 9H), 0.95 (s, 3H), 0.83 (s, 3H), 0.65 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 211.98, 135.86, 135.74, 134.12, 133.03, 129.71, 129.51, 127.56, 127.41, 87.74, 73.06, 52.18, 50.78, 45.49, 41.31, 30.29, 27.00, 26.38, 20.90, 20.51, 19.38, 11.16, 9.39; MS: $m/z=475$ $(MH-H_2O)^+$.

3.5. (*R*)-3-*tert*-Butyldiphenylsilyloxypentanoic acid 4

To a cooled solution (0°C) of **3b** (5.91 g, 12 mmol) in acetonitrile (146 mL) a solution of CAN (19.7 g, 36 mmol) in water (72 mL) was added dropwise. After stirring for 20 min at the same temperature, water was added (75 mL) and the reaction mixture was extracted with CH_2Cl_2 (5×15 mL). Usual workup yielded 6.21 g of a syrup containing the carboxylic acid **4** and the chiral auxiliary. Purification by column chromatography (hexane–ethyl acetate, from 25:1 to 1:1) allowed the recovery of the starting camphor (1.8 g, 98%) along with **4** (3.94 g, 92%) as a white solid. Mp 69–72°C; IR: *v* 1710 (C=O) cm^{-1}; ^1H NMR: δ 7.70–7.64 (m, 4H), 7.48–7.33 (m, 6H), 4.13–4.01 (m, 1H), 2.49 (d, $J=6.2$ Hz, 2H), 1.59–1.45 (m, 2H), 1.04 (s, 9H), 0.76 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 176.85, 135.78, 135.76, 133.74, 133.44, 129.61, 129.63, 127.49, 127.46, 71.34, 40.90, 29.62, 26.94, 19.33, 9.18; $[\alpha]_D^{25}$ +4.0 (*c* 1, CH_2Cl_2). HPLC: Chiralcel OD-R, methanol/water 80:20, flow rate 0.5 mL/min, R_t 43.8 min (determined as methyl ester derivative). Anal. calcd for $C_{21}H_{28}O_3Si$: C, 70.75; H, 7.91. Found: C, 70.85; H, 8.02.

3.6. (*R*)-3-*tert*-Butyldiphenylsilyloxy-1-pentanol 5

To a cooled solution (0°C) of **4** (1.54 g, 4.31 mmol) in anhydrous THF (13 mL), 1 M BH_3·THF complex (17.3 mL, 17.3 mmol) was added dropwise under nitrogen. After stirring for 15 min at 0°C, the mixture was then gradually allowed to warm to rt and stirred for 4 h. The reaction mixture was cooled to 0°C and MeOH was added dropwise until neutralization. The solvent was removed and the crude product was purified by column chromatography (hexane–ethyl acetate, from 20:1) to afford 1.40 g (95%) of **5** as a colorless syrup. IR: ν 3357 (OH) cm^{-1}; ^1H NMR: δ 7.76–7.69 (m, 4H), 7.50–7.39 (m, 6H), 3.95–3.70 (m, 3H), 2.06 (s, 1H), 1.92–1.40 (m, 4H), 1.08 (s, 9H), 0.73 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 135.80, 135.77, 134.09, 133.70, 129.61, 129.55, 127.53, 127.42, 73.34, 59.76, 37.03, 29.12, 27.04, 19.32, 9.44; $[\alpha]_D^{25}$ −7.0 (*c* 1, CH_2Cl_2). HPLC: Chiralcel OD-H, hexane/isopropanol 99:1, flow rate 0.5 mL/min, R_t 11.5 min. MS: $m/z=343$ $(MH)^+$.

3.7. (*R*)-3-*tert*-Butyldiphenylsilyloxypentyl methanesulfonate 6a

To a cooled solution (0°C) of **5** (3.36 g, 9.8 mmol) in CH_2Cl_2 (88 mL) was added triethylamine (2.75 mL, 19.6 mmol) and then methanesulfonyl chloride (1.55 mL, 19.6 mmol). The mixture was stirred at the same temperature for 3 h, then quenched with water (10 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated under reduced pressure to give 4.20 g (quantitative) of **6a** as a syrup that was employed in the next step without further purification.

3.8. (*R*)-3-*tert*-Butyldiphenylsilyloxypentyl iodide 6b

NaI (15 g, 100 mmol) was added to a solution of **6a** (4.20 g, 9.8 mmol) in dry acetone (100 mL) and the mixture was heated under reflux for 12 h. Water was added (70 mL) and then the mixture was extracted with dichloromethane (3×50 mL). After usual workup, **6b** was obtained (3.97 g, quantitative) as a syrup.

3.9. (*R*)-4-*tert*-Butyldiphenylsilyloxyhexanenitrile 6c

To a solution of crude **6b** (3.97 g, 8.8 mmol) in 20 mL of dry DMF, NaCN (0.51 g, 9.8 mmol) was added. The resulting mixture was stirred overnight at rt then poured into ice-water and extracted with ethyl acetate (3×15 mL). The organic layer was washed with 1N NaOH (30 mL), brine, dried ($MgSO_4$) and concentrated in vacuum. The obtained residue was purified by column chromatography (hexane–ethyl acetate, 15/1), to give **6c** as a colorless syrup (2.76 g) in 80% yield from alcohol **5**. IR: ν 2247 (C≡N) cm^{-1}; ^1H NMR: δ 7.71–7.62 (m, 4H), 7.50–7.35 (m, 6H), 3.80–3.69 (m, 1H), 2.44–2.26 (m, 2H), 1.84–1.73 (m, 2H), 1.59–1.41 (m, 2H), 1.07 (s, 9H), 0.76 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 135.67, 135.60, 133.78, 133.47, 129.73, 129.60, 127.62, 127.46, 119.88, 72.59, 31.12, 28.89, 27.00, 19.37, 12.74, 9.26; $[\alpha]_D^{25}$ −4.0 (*c* 1, CH_2Cl_2). MS: $m/z=352$ $(MH)^+$.

3.10. (*R*)-4-Hydroxyhexanenitrile 7

Compound **6c** (0.52 g, 1.5 mmol) was taken up in THF (9 mL) and treated with 1 M Bu_4NF (3 mL, 3 mmol). The mixture was stirred at rt for 4 h, then CH_2Cl_2 (20 mL) was added and the resulting mixture washed with saturated aqueous $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and the solvent removed yielding a syrup, which upon column chromatography (hexane–ethyl acetate, 20/1) afforded 0.146 g (86%) of **7** as a colorless syrup. IR: ν 3433 (OH), 2249 (C≡N). cm^{-1}; ^1H NMR: δ 3.60–3.47 (m, 1H), 3.00 (bs, 1H), 2.44 (dd, $J=6.6$, 7.7 Hz, 2H), 1.98–1.54 (m, 2H), 1.51–1.36 (m, 2H), 0.89 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 119.89, 70.86, 31.83, 29.90, 13.50, 9.67; $[\alpha]_D^{25}$ −45.0 (*c* 1, CH_2Cl_2). HPLC: Chiralcel OD-H, hexane/isopropanol 95:5, flow rate 0.5 mL/min, R_t 6.3 min. MS: $m/z=114$ $(MH)^+$.

3.11. (*R*)-4-Hexanolide 8

To a solution of **7** (0.113 g, 1 mmol) in 2-methoxyethanol (1 mL) 8.5N NaOH (0.5 mL, 4.2 mmol) was added and the reaction mixture was stirred and heated under reflux for 21 h. The mixture was acidified with 3N HCl to pH 2, stirred for 45 min at rt and extracted with Et_2O. The aqueous layer was saturated with NaCl and further extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and the solvent removed to give a yellow oil which upon distillation afforded **8** (0.10 g, 90%) as a light yellow liquid. Bp 105–110°C/26 mm Hg; IR: ν 1766 (C=O) cm^{-1}; ^1H NMR: δ 4.50–4.36 (m, 1H), 2.57–2.49 (m, 2H), 2.36–2.23 (m, 1H), 1.95–1.56 (m, 3H), 1.00 (t, $J=7.3$ Hz, 3H); ^{13}C NMR: δ 177.19, 82.17, 28.90, 28.52, 27.52, 9.50; $[\alpha]_D^{25}$ +50.0 (*c* 1, MeOH) {lit.[4] $[\alpha]_D^{25}$ +53.1 (*c* 1, MeOH)}. HPLC: Chiralcel OB-H, hexane/isopropanol 94:6, flow rate 0.5 mL/min, R_t 40.5 min. MS: $m/z=115$ $(MH)^+$.

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