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Tetrahedron: *Asymmetry* 18 (2007) 2479–2483

Stereoselective synthesis of (−)-6-acetoxyhexadecanolide: a mosquito oviposition attractant pheromone

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Received 3 September 2007; accepted 3 October 2007

Abstract—The stereoselective synthesis of (−)-6-acetoxyhexadecanolide was achieved from the readily available chiral pool compound, L-(+)-tartaric acid. The synthetic sequence includes the elaboration of an α-benzyloxy aldehyde derived from tartaric acid with ring closing metathesis as the key step.

1. Introduction

(−)-6-Acetoxyhexadecanolide **1** is an oviposition attractant pheromone of the female mosquito, *Culex pipiens fatigans*.[1] The mosquito *Culex pipiens fatigans* (=*quinquefasciatus*) is distributed worldwide and in hot climate can be a vector for filarial disease, malaria as well as having the ability to transmit the West Nile virus.[2] Egg laying is influenced by a pheromone,[3] which, if identified, could lead to an effective method of controlling the disease. Laurence and Pickett in 1982 identified (−)-6-acetoxyhexadecanolide **1** as the major component of the attractant pheromone of the mosquito.[1] Although, several approaches for the enantioselective synthesis of **1** have been disclosed in the literature,[4] a versatile strategy for the synthesis of the pheromone is of continuing interest. Our interest in the synthesis of natural products from the chiral pool tartaric acid resulted in the synthesis of various bio-active lactones.[5] The pivotal strategy in our approach is the synthesis and elaboration of an α-benzyloxy aldehyde derived from chiral pool tartaric acid.

2. Results and discussion

As shown in Scheme 1, the synthesis of (−)-6-acetoxyhexadecanolide **1** was anticipated from the unsaturated lactone **2**, the synthesis of which was envisaged from the homoallylic alcohol **3** by ring closing metathesis. The stereoselective allylation of α-benzyloxy aldehyde **4** was envisioned for the formation of **3**. The synthesis of **4** from the bis-Weinreb amide of tartaric acid is a procedure optimized by us in our laboratory.[6]

Accordingly, by utilizing a procedure described by us, bis-Weinreb amide **5** was converted to benzyloxy aldehyde **4**, which on allylation under Keck allylation conditions furnished *threo* alcohol **3** in good yields.[7] Reaction of homoallylic alcohol **3** with acryloyl chloride and triethylamine in dichloromethane at 0 °C furnished acryloyl ester **6** in 73% yield. Treatment of **6** with a Grubbs second generation catalyst in refluxing toluene furnished the expected product **2** albeit in 27% yield (Scheme 2).[8]

Due to the low yield of lactone **2** in the ring closing metathesis reaction, the synthetic sequence was modified as described below. Accordingly, the reaction of homoallylic alcohol **3** with acrolein diethyl acetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate in refluxing benzene afforded acetal **7** as an inseparable mixture of diastereomers. Since the acetal formed will be converted to lactone at a later stage, chirality at the acetal center is of no consequence and the diastereomeric mixture was used as such in the subsequent transformations. Thus, the ring closing metathesis reaction of **7** with Grubbs first generation catalyst in toluene at 60 °C smoothly furnished the RCM adduct **8** in 86% yield. Catalytic hydrogenation of **8** with 10% Pd/C in methanol under a hydrogen atmosphere resulted in alcohol **9** in excellent yield. The secondary hydroxyl group in **9** was epimerized under Mitsunobu

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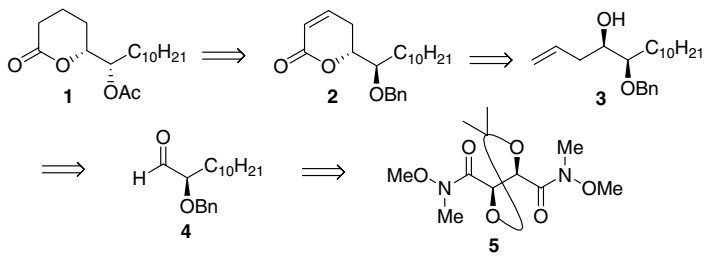
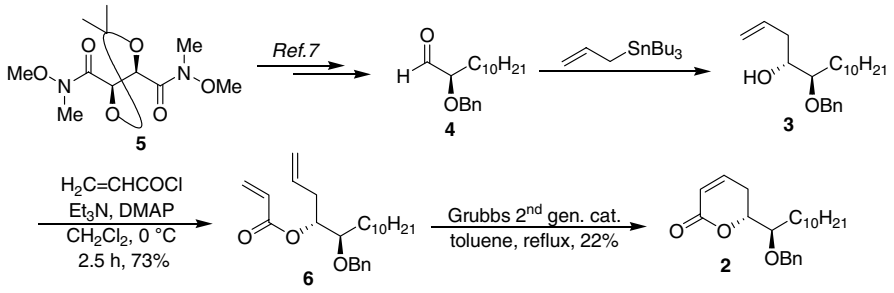
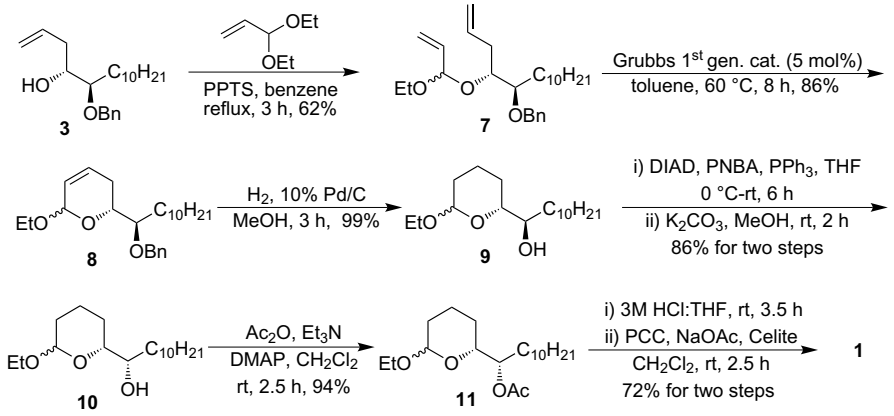
doi:10.1016/j.tetasy.2007.10.006



Scheme 1. Retrosynthesis for the synthesis of (−)-6-acetoxyhexadecanolide **1**.



Scheme 2. Ring closing metathesis of acryloyl ester **6**.



Scheme 3. Stereoselective synthesis of 6-acetoxyhexadecanolide **1**.

conditions, furnishing alcohol **10** in 86% yield. Reaction of **10** with acetic anhydride and triethylamine in dichloromethane at room temperature yielded acetate **11** in 94% yield. Treatment of **11** with 3 M HCl in THF at room temperature furnished the corresponding lactol, which was subjected to oxidation with PCC in dichloromethane at room temperature to afford (−)-6-acetoxyhexadecanolide **1** in 72% yield over two steps (Scheme 3). The spectroscopic and physical data $[\alpha]_D = -37.5$ (c 0.4, $CHCl_3$); lit.[4b] $[\alpha]_D = -36.8$ (c 1.55, $CHCl_3$) are in good agreement with that reported in the literature.

3. Conclusion

In conclusion, a facile stereoselective synthesis of 6-acetoxyhexadecanolide was accomplished from L-(+)-tartaric acid, involving ring closing metathesis reaction as the key step. The synthetic sequence depicted *en route* to the lactone is highly diastereoselective with good overall yield.

4. Experimental

4.1. General procedures

Column chromatography was performed on silica gel, Acme grade 100–200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points are uncorrected. Unless stated otherwise, all reactions were performed under an inert atmosphere. Optical rotations were measured on a JASCO DIP-370 digital

polarimeter measured at 25 °C. Homoallylic alcohol **3** was prepared according to the procedure described by us earlier.[7]

4.2. Preparation of (4*R*,5*R*)-4-acryloxy-5-benzyloxypentadec-1-ene 6

To a stirred solution of homoallylic alcohol **3** (0.1 g, 0.3 mmol), triethylamine (0.1 mL, 0.6 mmol), and DMAP (7 mg, 0.06 mmol) in 2.5 mL of dichloromethane at 0 °C was added acryloyl chloride (0.04 mL, 0.45 mmol) dropwise. The reaction mixture was stirred for 2.5 h at the same temperature. After the reaction was complete (indicated by TLC), it was poured into water (7 mL) and extracted with diethyl ether (3 × 6 mL). The combined ethereal extracts were washed with brine (10 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/ethyl acetate (95:5) as eluent to yield **6** as a colorless oil in 73% yield (0.085 g). $[\alpha]_D = +13.0$ (*c* 1.0, $CHCl_3$); IR (neat): 2925, 2854, 1726, 1404, 1269, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45–7.28 (m, 5H), 6.46 (dd, $J = 17.3$, 1.5 Hz, 1H), 6.19 (dd, $J = 17.3$, 10.4 Hz, 1H), 5.87 (dd, $J = 10.4$, 1.5 Hz, 1H), 5.79 (ddt, $J = 17.5$, 10.2, 6.7 Hz, 1H), 5.28 (quin, $J = 4.4$ Hz, 1H), 5.18–5.04 (m, 2H), 4.65 (s, 2H), 3.55 (dt, $J = 7.4$, 4.4 Hz, 1H), 2.58–2.49 (m, 1H), 2.47–2.36 (m, 1H), 1.69–1.24 (m, 19H), 0.93 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 138.4, 133.9, 130.7, 128.5, 128.3, 127.9, 127.6, 117.6, 78.8, 73.6, 72.4, 34.3, 31.8, 29.8, 29.6, 29.5, 29.4, 29.3, 25.5, 22.6, 14.1; HRMS calcd for $C_{25}H_{38}O_3$+Na, 409.2719; found, 409.2718.

4.3. Preparation of (*R*)-6-((*R*)-1-(benzyloxy)undecyl)-5,6-dihydropyran-2-one 2

Diene **6** (0.08 g, 0.21 mmol) and Grubbs 2nd generation catalyst (17 mg, 0.02 mmol, 10 mol %) in 10 mL of toluene were heated at reflux, under an argon atmosphere. After 10 h, it was cooled to room temperature. Evaporation of the solvent followed by column chromatography of the resulting residue using petroleum ether/ethyl acetate (85:15) as eluent afforded **2** as a colorless oil in 22% yield (18 mg), along with 54% (48 mg) of recovered starting material. $[\alpha]_D = +61.9$ (*c* 2.1, $CHCl_3$); IR (neat): 2924, 2854, 1727, 1455, 1380, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.23 (m, 5H), 6.89 (ddd, $J = 9.3$, 6.0, 2.1 Hz, 1H), 5.99 (dd, $J = 9.6$, 1.8 Hz, 1H), 4.64 and 4.59 (AB q, $J = 11.4$ Hz, 2H), 4.52 (dt, $J = 12.6$, 4.2 Hz, 1H), 3.55 (quin, $J = 4.5$ Hz, 1H), 2.57–2.42 (m, 1H), 2.32–2.20 (m, 1H), 1.75–1.14 (m, 19H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 145.5, 138.1, 128.4, 127.9, 127.8, 121.2, 79.1, 78.3, 72.9, 31.8, 29.6, 29.5(4), 29.5(1), 29.3, 25.7, 24.8, 22.6, 14.1; HRMS calcd for $C_{23}H_{34}O_3$+Na, 381.2406; found, 381.2405.

4.4. Preparation of (4*R*,5*R*)-5-benzyloxy-4-(1-ethoxyallyloxy)pentadec-1-ene 7

Single neck round-bottomed flask (10 mL) fitted with Dean-Stark apparatus and a condenser was charged with homoallylic alcohol **3** (0.1 g, 0.3 mmol) in 5 mL of benzene. PPTS (5 mg, 0.02 mmol) followed by acroleindiethyl acetal (0.12 mL, 0.75 mmol) was then added at room temperature and further refluxed for 3 h. After the reaction was complete, it was cooled to room temperature and diluted with 20 mL of diethyl ether. The ether layer was washed with satd $NaHCO_3$ (2 × 6 mL), brine (8 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/ethyl acetate (96:4) as eluent to yield the diastereomeric mixture of acetal **7** in 62% (0.78 g, 88% based on 30% of starting material recovery) yield as a colorless oil. IR (neat) 2923, 2856, 1645, 1453, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38–7.23 (m, 5H), 5.98–5.72 (m, 2H), 5.43–5.21 (m, 2H), 5.19–4.88 (m, 3H), 4.70–4.47 (m, 2H), 3.90–3.37 (m, 4H), 2.55–2.38 (m, 1H), 2.32–2.16 (m, 1H), 1.71–1.13 (m, 21H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 135.8(9), 135.8(1), 135.6, 128.3, 127.9, 127.5, 118.1, 118.0, 116.7, 116.5, 102.3, 102.2, 100.5, 80.4, 80.2, 76.7, 76.6, 72.5, 72.4, 60.8, 60.4, 35.1, 34.4, 31.9, 29.6, 29.5, 29.4, 26.2, 25.9, 22.7, 15.2, 15.1, 14.1; HRMS calcd for $C_{27}H_{44}O_3$+Na, 439.3188; found, 439.3184.

4.5. Preparation of (2*R*)-2-((*R*)-1-(benzyloxy)undecyl)-6-ethoxy-3,6-dihydro-2*H*-pyran 8

To a solution of **7** (0.08 g, 0.2 mmol) in 5 mL of toluene, Grubbs 1st generation catalyst (8 mg, 0.009 mmol, 5 mol %) was added and heated to 60 °C, under an argon atmosphere. After the reaction was complete (~8 h), it was cooled to room temperature. Evaporation of the solvent followed by column chromatography of the resulting residue using petroleum ether/ethyl acetate (95:5) as eluent afforded **8** as a colorless oil in 86% yield (64 mg, 95% based on 10% recovery of the starting material). IR (neat) 2924, 2857, 1643, 1456, 1094, 1021 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43–7.24 (m, 5H), 6.07–5.92 (m, 1H), 5.78–5.63 (m, 1H), 5.17 and 5.03 (br s, 1H), 4.85–4.59 (m, 2H), 4.09–3.78 (m, 2H), 3.66–3.32 (m, 2H), 2.34–2.08 (m, 1H), 1.96–1.74 (m, 1H), 1.71–1.13 (m, 21H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 129.1, 128.8, 128.3, 128.1, 127.8, 127.5, 127.4, 125.4, 97.9, 94.5, 81.1, 80.4, 75.4, 73.7, 72.7, 67.7, 63.9, 63.1, 31.9, 30.2, 29.9, 29.8, 29.6, 29.5, 29.4, 26.8, 26.4, 25.6, 25.4, 22.7, 15.3, 15.2, 14.1; HRMS calcd for $C_{25}H_{40}O_3$+Na, 411.2875; found, 411.2879.

4.6. Preparation of (2*R*)-2-((*R*)-1-hydroxyundecyl)-6-ethoxytetrahydropyran 9

To a solution of **8** (60 mg, 0.15 mmol) in 2 mL of methanol at room temperature was added activated 10% Pd/C (30 mg). The reaction mixture was stirred for 3 h under a hydrogen atmosphere (balloon) at the same temperature. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/ethyl acetate (9:1) as eluent to yield **9** as a colorless oil in 99% (46 mg) yield. IR (neat): 3438, 2923, 2853, 1458, 1127, 1031, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.87 and 4.5–4.38 (m, 1H),

4.05–3.19 (m, 4H), 2.53 and 2.07 (d, $J = 4.2$ Hz, 1H, exchangeable with D_2O), 1.97–1.15 (m, 27H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 96.9, 74.3, 71.5, 62.2, 32.8, 31.9, 29.6, 29.5, 29.3, 27.1, 25.5, 22.6, 17.6, 15.0, 14.0; HRMS calcd for $C_{18}H_{36}O_3$+Na, 323.2562; found, 323.2560.

4.7. Preparation of (2*R*)-2-((*S*)-1-hydroxyundecyl)-6-ethoxytetrahydropyran 10

In a 10 mL single neck round-bottomed flask was placed **9** (40 mg, 0.13 mmol), triphenylphosphine (87 mg, 0.33 mmol), and *p*-nitrobenzoic acid (56 mg, 0.33 mmol) dissolved in 2 mL of THF, under an argon atmosphere. It was cooled to 0 °C and DIAD (0.07 mL, 0.33 mmol) was added dropwise over a period of 7 min. It was then warmed up to room temperature and stirred for 6 h at the same temperature. After the reaction was complete (indicated by TLC), it was poured into water and extracted with diethyl ether (3×6 mL). The combined ether layers were washed with brine (10 mL) and dried over Na_2SO_4. Column chromatography of the residue obtained after evaporation of the solvent using petroleum ether/ethyl acetate (93:7) as an eluent yielded the *p*-nitrobenzoate along with uncharacterized impurity. This was subjected to the next reaction without further purification.

The *p*-nitrobenzoate obtained above was dissolved in 2 mL of methanol and K_2CO_3 was added at room temperature and stirred vigorously at the same temperature for 2 h. After the reaction was complete (TLC), it was poured into water and extracted with diethyl ether (3×5 mL). The combined ether extracts were washed with brine (7 mL) and dried over Na_2SO_4. The residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/ethyl acetate (9:1) as eluent to furnish **10** in 69% (28 mg, 86% yield based on 19% recovery of the starting material) as a colorless oil. IR (neat): 3415, 2923, 2854, 1645, 1549, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.86 (br s, 1H), 3.78–3.29 (m, 4H), 1.98 (d, $J = 3.0$ Hz, 1H, exchangeable with D_2O), 1.94–1.17 (m, 27H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 97.2, 73.6, 71.2, 62.2, 31.9, 31.8, 29.9, 29.7, 29.6, 29.3, 26.0, 23.9, 22.7, 17.5, 15.1, 14.1; HRMS calcd for $C_{18}H_{36}O_3$+Na, 323.2562; found, 323.2558.

4.8. Preparation of (2*R*)-2-((*S*)-1-acetoxyundecyl)-6-ethoxytetrahydropyran 11

To the stirred solution of **10** (30 mg, 0.1 mmol), DMAP (3 mg, 0.02 mmol), and Et_3N (0.5 mL) in 2 mL of dichloromethane was added Ac_2O (0.02 mL, 0.2 mmol) at room temperature. It was then stirred for 2.5 h and quenched with water and extracted with diethyl ether (3×5 mL). The combined ethereal extracts were washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent followed by column chromatography of the resultant residue using petroleum ether/ethyl acetate as eluent yielded acetate **11** as a colorless oil in 94% (32 mg) yield. IR (neat): 2923, 2853, 1744, 1456, 1371, 1238, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.94–4.78 (m, 2H), 3.84–3.63 (m, 2H), 3.57–3.33 (m, 1H), 2.06 (s, 3H), 1.92–1.17 (m, 27H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 96.9, 75.9, 69.5, 62.1, 31.9, 29.8, 29.7, 29.5(6), 29.5(3), 29.3, 26.6, 25.4, 22.7, 21.1, 17.7, 15.1, 14.1; HRMS calcd for $C_{20}H_{38}O_4$+Na, 365.2668; found, 365.2666.

4.9. Preparation of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide 1

To a stirred THF (1 mL) solution of **11** (30 mg, 0.09 mmol) was added 1 mL of 3 M HCl at room temperature and stirred for 3.5 h. After the reaction was complete (indicated by TLC), it was poured into water (5 mL) and extracted with diethyl ether (3×5 mL). The combined ether layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation of the solvent yielded the lactol, which was used in the next step without further purification.

To a solution of the lactol (obtained above) in 1 mL of dichloromethane was added Celite (10 mg) and sodium acetate (22 mg, 0.27 mmol) at room temperature and stirred for 5 min. PCC (58 mg, 0.27 mmol) was then introduced into the reaction mixture at the same temperature. It was stirred at room temperature for 2.5 h. After the reaction was complete (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with diethyl ether (15 mL). The ether layers were combined and the residue obtained after evaporation of the solvent was purified by column chromatography using petroleum ether/ethyl acetate (8:2) as eluent to yield **1** as a colorless oil in 72% (20 mg). $[\alpha]_D = -37.5$ (*c* 0.4, $CHCl_3$); lit.[4b] $[\alpha]_D = -36.8$ (*c* 1.55, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.98 (dt, $J = 7.2$, 5.1 Hz, 1H), 4.35 (ddd, $J = 11.1$, 4.8, 3.6 Hz, 1H), 2.69–2.38 (m, 2H), 2.08 (s, 3H), 2.02–1.76 (m, 2H), 1.74–1.53 (m, 4H), 1.48–1.16 (m, 16H), 0.88 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.5, 80.5, 74.3, 31.9, 29.6, 29.5, 29.4(4), 29.4, 29.3, 25.2, 23.5, 22.7, 21.0, 18.2, 14.1. HRMS calcd for $C_{18}H_{32}O$+Na, 335.2198; found, 335.2198.

Acknowledgments

We thank the Department of Science and Technology (DST), New Delhi for funding of this project. P.A. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi for a fellowship.

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