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Synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide by L-proline-catalyzed asymmetric aldol reactions

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Abstract—The natural mosquito attractant pheromone, (−)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide **1**, was synthesized from readily available aldehyde **3** and cyclopentanone **4** using L-proline catalyzed asymmetric aldol reactions as the key step.

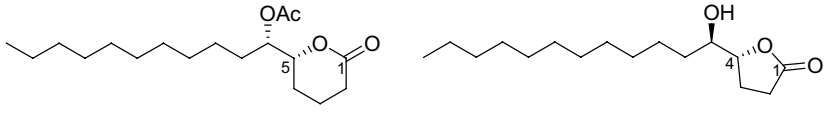
1. Introduction

The mosquito is a vector for filarial diseases and malaria. (−)-(5*R*,6*S*)-6-Acetoxyhexadecan-5-olide **1**, was first isolated by Laurence and Pickett in 1982 from the apical droplet of mosquito eggs.[1] The substance attracts other gravid females of the same and some related mosquito species inducing them to oviposit in the same spot where the original eggs are found. (+)-Muricatacin **2**, a simple active acetogenin derivative, was isolated from the seeds of *Annona muricata*, and shows cytotoxic activity on tumor cell lines (with A-549, lung carcinoma, ED_{50} = 23.3 μg/mL).[2]

Both **1** and **2** have chiral lactone units in the structure; functionalized γ- and δ-lactones have attracted substantial attention in recent years due to their synthetic importance as building blocks in natural products synthesis. Owing to their remarkable physiological activities, much effort has been expanded on the development of methods for their syntheses.[3] Although a great number of synthetic routes to the title compound have been published, a short and efficient route is still needed to be explored. With our interest in L-proline-catalyzed asymmetric aldol reactions,[4] we herein report a short and efficient approach to the synthesis of **1** using L-proline[5] as the catalyst (Fig. 1).

2. Results and discussion

The synthesis started from the known aldehyde **3** and cyclopentanone **4** catalyzed by L-proline (Scheme 1). After purification by flash column chromatography on SiO_2, diastereomers **5a** and **5b** were obtained in 80% yield in a ratio of 85:15. The enantiomeric purity of *syn*-**5a** was determined to be 96% ee by HPLC analysis with a chiral stationary phase column. Protection of the resulting hydroxyl group of the aldol **5a** with Ac_2O at room temperature by a standard method gives ester **7** in a virtually quantitative yield. Baeyer–Villiger oxidation of ketone **7** by *m*-CPBA in anhydrous CH_2Cl_2 at room temperature gave the title compound **1** in 85% yield. Baeyer–Villiger oxidation of aldol **5a** under the same conditions gave



(-)-(5*R*,6*S*)-**1** (+)-(4*R*,5*R*)-**2**

Figure 1. (−)-(5*R*,6*S*)-6-Acetoxyhexadecan-5-olide **1** and (+)-muricatacin **2**.

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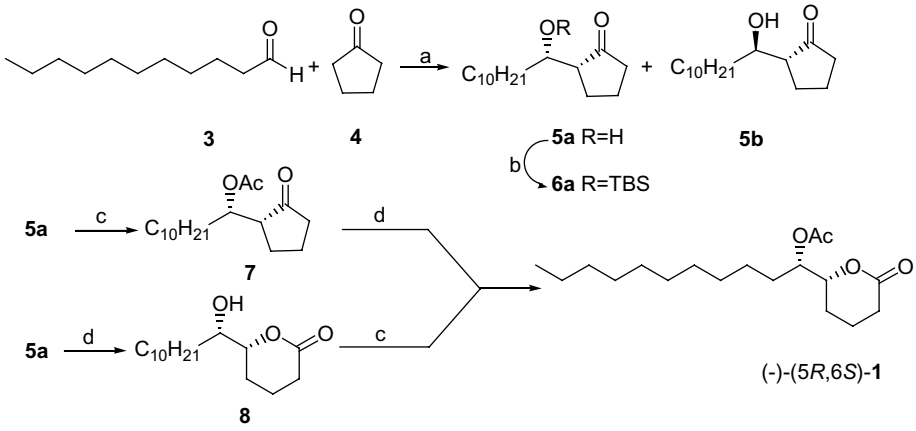

Scheme 1. Reagents and conditions: (a) L-Proline (30 mol %), $CHCl_3$, 24 h, 80%; (b) TBSCl, Imid., DMF; (c) Ac_2O, Py, DMAP, rt, 100%; (d) *m*-CPBA, CH_2Cl_2, $NaHCO_3$, rt, 82–85%.

the desired compound **8** in 82% yield. Synthetic **1** from **7** or **8** showed identical spectral data with those of natural product **1** reported, while the specific rotation of synthetic **1** {$[\alpha]_D = -36.9$ (*c* 1.05, $CHCl_3$)} is comparable with that of natural **1** {lit.[3c] $[\alpha]_D = -38.5$}.

3. Conclusion

In summary, we have achieved a versatile procedure for the synthesis of enantiomerically pure (−)-(5*R*,6*S*)-6-acetoxy-hexadecan-5-olide **1,** in 57.8% overall yield starting from aldehyde **3** in three steps, using L-proline as catalyst. The synthetic route reported here makes available the chiral lactones that may be of interest for structure-activity studies of this group of compounds.

4. Experimental

Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 BB spectrometer and Bruker AM-400 spectrometer in $CDCl_3$ solution using TMS as an internal reference. IR spectra were obtained using a FT-170SX spectrophotometer. Low resolution mass spectra were measured on a HP-5988 mass spectrometer and high resolution mass spectra (HRMS) were determined on a Bruker Daltonics APEX II 47e Fourier Transform spectrometer with ESI ionization method. Specific rotations were determined using sodium D line on a Perkin–Elmer 341 polarimeter at 20 °C. All solvents were freshly purified and dried by standard techniques. Purification of products was conducted by flash column chromatography (FCC) on silica gel (200–300 mesh) purchased from Yan Tai Yuan Bo Silica Gel Co.

4.1. (2*R*)-2-[1′-(*S*)-Hydroxyundecyl]cyclopentanone 5a

A mixture of 5.1 g (30 mmol) of **3**, 1.03 g (9 mmol) of L-proline, and 5 mL of cyclopentanone **4** in 20 mL of anhydrous $CHCl_3$ was stirred at room temperature for 24 h. The mixture was extracted with Et_2O. The organic layer was washed successively with aq $NaHCO_3$, water, and brine, and dried. After removal of the solvent, the crude product was purified by flash chromatography (petroleum/ethyl acetate = 4:1, v/v) to afford 5.1 g of **5a** ($R_f = 0.50$) and 0.9 g of **5b** ($R_f = 0.45$) in 80% yield. The enantiomeric purity of **5a** was determined to be 96% on a Chiralpak AD-H column (hexane/2-propanol = 95/5, 275 nm).

Compound **5a** $[\alpha]_D = -33.5$ (*c* 0.7, $CHCl_3$); IR (film): 3448, 2956, 2925, 2854, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.6$ Hz, 3H, Me), 1.23 (br s, 2H), 1.34–2.38 (m, 22H), 3.65–3.69 (dt, $J_1 = 6.6$ Hz, $J_2 = 3$ Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.5, 22.6, 24.7, 26.7, 29.3–29.6 (5 C), 31.9, 35.1, 38.4, 53.8, 72.1, 224.2; EIMS *m*/*z*: 254 (M^+, 1.6), 236 (M^+-H_2O, 35), 152 ($M^+-C_5H_{10}O_2$, 35); HRMS (ESI): calcd for $C_{16}H_{30}O_2$+Na (M^++Na) 277.2138, found 277.2141.

Compound **5b** $[\alpha]_D = +36.9$ (*c* 1.05, $CHCl_3$); IR (film): 3448, 2956, 2925, 2854, 1734, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (t, $J = 6.6$ Hz, 3H, Me), 1.23 (br s, 2H), 1.37–2.28 (m, 22H), 4.02–4.04 (dt, $J_1 = 6.6$ Hz, $J_2 = 3$ Hz, 1H, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.6, 22.8, 26.0, 29.3–29.6 (5 C), 31.8, 34.8, 39.1, 54.4, 69.5, 221.7; EIMS *m*/*z*: 254 (M^+, 1.6), 236 (M^+-H_2O, 13), 152 ($M^+-C_5H_{10}O_2$, 35); HRMS (ESI): calcd for $C_{16}H_{30}O_2$+Na (M^++Na) 277.2138, found 277.2141.

4.2. (2*R*)-2-[1′-(*S*)-*tert*-Butyldimethylsilyloxylundecyl]cyclopentanone 6a

To a solution of 170 mg (2.5 mmol) imidazole and 254 mg (1 mmol) of **5a** in 0.5 mL of DMF was added 165 mg (1.1 mmol) of TBDMSCl. The reaction mixture was stirred at room temperature for 4 h and extracted with Et_2O. The organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography (petroleum/ethyl acetate = 16:1, v/v) to afford the pure product **6a** in quantitative yield. $[\alpha]_D = -49.0$ (*c* 1.70, $CHCl_3$); IR (film): 1740, 1250 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$): δ 0.02 (s, 3H, Me), 0.05 (s, 3H, Me), 0.83 (s, 9H, *t*-Bu), 0.88 (t, J = 6.6 Hz, 3H, Me),1.22 (br s, 22H), 1.38–2.33 (m, 2H), 3.97–3.99 (m, 1H, C*H*OTBS); ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.8, –4.6, 14.0, 18.0, 20.8, 22.6, 24.7, 25.1, 25.5, 25.6, 25.8, 26.3, 29.0, 29.3, 29.5, 31.9, 33.7, 36.0, 39.6, 54.5, 72.2, 218.1; EIMS *m*/*z*: 367 (M^+-1, 0.1), 353 (M^+-Me, 109), 311 (M^+-t-Bu, 100); HRMS (ESI): calcd for $C_{22}H_{44}O_2Si$+H (M^++H) 369.3183, found 369.3184.

4.3. (2*R*)-2-[1′-(*S*)-Acetoxyundecyl]cyclopentanone 7

A mixture of 254 mg (1 mmol) of **5a**, 1 mL of acetic anhydride, 1 mL of pyridine, and 10 mg of DMAP was stirred at room temperature for a period of 0.5 h. The reaction mixture extracted with Et_2O and the organic layer washed with water, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography (petroleum/ethyl acetate = 16:1, v/v) to afford a colorless oil in 100% yield. $[\alpha]_D = -42.0$ (c 0.80, $CHCl_3$); IR (film): 1735, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82 (t, J = 6.6 Hz, 3H, Me), 1.21 (br s, 22H), 1.94 (s, 3H, CH_3CO), 1.50–2.30 (m, 2H), 5.16–5.21 (m, 1H, C*H*OAc); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 20.6, 20.9, 22.6, 24.3, 25.4, 25.5, 25.6, 25.8, 26.3, 29.3, 29.4, 29.5, 31.9, 32.7, 38.7, 51.7, 72.2, 170.1, 218.1; EIMS *m*/*z*: 296 (M^+), 236 (M^+-OAc, 80); HRMS (ESI): calcd for $C_{18}H_{32}O_3$+Na (M^++Na) 319.2244, found 319.2250.

4.4. (5*R*,6*S*)-6-Hydroxyhexadecan-5-olide 8

To a solution of 254 mg (1 mmol) of **5a** in 15 mL of anhydrous CH_2Cl_2, 504 mg (6 mmol) of $NaHCO_3$, and 1.04 g (6 mmol) of *m*-CPBA was added. The reaction mixture was then stirred at room temperature for 4 h, and extracted with Et_2O. The organic layer was washed successively with aq $NaHCO_3$, water, and brine, and dried. After removal of solvent, the crude product was purified by flash chromatography (petroleum/ethyl acetate = 2:1, v/v) to afford 220 mg of compound **8** in 82% yield. Mp 66.5–68 °C; $[\alpha]_D = -11.0$ (c 1.50, $CHCl_3$); IR (film): 3440, 2920, 2850 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J = 6.3 Hz, 3H, Me), 1.33 (br s, 18H, $(CH_2)_9$), 1.49–1.94 (m, 4H), 2.42–2.61 (m, 2H), 3.52–3.58 (m, 1H, C*H*OH), 4.13–4.18 (m, 1H, C*H*OCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.3, 20.8, 22.6, 24.1, 25.4, 29.3–29.5 (6 × C), 31.8, 32.6, 34.0, 73.3, 83.3, 171.7; EIMS *m*/*z*: 252 (M^+-H_2O, 0.12), 100 ($M^+-OC_{11}H_{22}$, 100); HRMS (ESI): calcd for $C_{16}H_{30}O_3$+NH_4 (M^++NH_4) 288.2533, found 288.2538.

4.5. (−)-(5*R*,6*S*)-6-Acetoxy-hexadecan-5-olide 1

A mixture of 296 mg (1 mmol) of **7**, 504 mg (6 mmol) of $NaHCO_3$, and 1.04 g (6 mmol) of *m*-CPBA in 15 mL of anhydrous CH_2Cl_2 was stirred at room temperature for 4 h. The mixture was extracted with Et_2O. The organic layer was washed successively with aq $NaHCO_3$, water, and brine, and dried. After removal of solvent, the crude product was purified by flash chromatography (petroleum/ethyl acetate = 2:1, v/v) to afford 265 mg of title compound **1** in 85% yield.

Compound **8** (270 mg, 1 mmol), 1 mL of acetic anhydride, 1 mL of pyridine, and 10 mg of DMAP were stirred at room temperature for 0.5 h. The reaction mixture was extracted with Et_2O and the organic layer washed with water, brine and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was purified by flash chromatography to afford colorless oil **1** in 100% yield. $[\alpha]_D = -36.9$ (c 1.05, $CHCl_3$); IR (film): 1745 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H, Me), 1.10–1.98 (m, 22H), 2.08 (s, 3H, CH_3CO), 2.36–2.64 (m, 2H), 4.32–4.38 (m, 1H, C*H*OAc), 4.94–4.99 (m, 1H, C*H*OCO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 18.3, 20.9, 22.6, 24.0, 25.3, 29.5–29.2 (6 × C), 29.9, 31.8, 73.8, 79.8, 170.7, 171.0; EIMS *m*/*z*: 312 (M^+, 1.6), 269 (M^+-Ac, 13), 252 (M^+-AcOH, 32), 99 ($M^+-AcOCHC_{10}H_{21}$, 100); HRMS (ESI): calcd for $C_{18}H_{32}O_4$+Na (M^++Na) 335.2193, found 335.2192.

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