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A Short and Stereoselective Synthesis of the (-)-(5*R*, 6*S*)-6-Acetoxy-hexadecane-5-olide

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Abstract: (-)-(5*R*, 6*S*)-6-Acetoxyhexadecan-5-olide **1**, a natural mosquito attractant pheromone, was synthesized from readily available aldehyde **2** and cyclopentanone **3** using L-proline-catalyzed asymmetric aldol reaction as the key step.

Keywords: 6-Acetoxyhexadecan-5-olide, Baeyer-Villiger oxidation, aldol reaction, L-proline.

(-)-(5*R*, 6*S*)-6-Acetoxyhexadecan-5-olide **1,** a natural mosquito attractant pheromone, was first isolated by Laurence and Pickett in 1982 from the apical droplet of the mosquito eggs[1]. Owing to its remarkable physiological activities, much effort has been expanded on the development of the method for its synthesis[2]. More attention has been paid on the topic of L-proline-catalyzed asymmetric aldol reaction[3], we report herein a short and efficient approach to the synthesis of **1** using L-proline as the catalyst.

The synthesis commenced from the known aldehyde **2** and cyclopentanone **3** catalyzed by L-proline (**Scheme 1**). The *syn* aldol **4a** along with its *anti* isomer **4b** were isolated by flash column chromatography on SiO_2, obtained in 80% yield in a ratio of 85:15. The *e.e.* of **4a** was shown to be 96%, estimated by chiral shift reagent. Protection of the resulting hydroxyl group of the aldol **4a** with Ac_2O at r.t. by a standard method gives the ester **5** in virtually quantitative yield. Baeyer-Villiger oxidation of the ketone **5** by *m*-CPBA in anhydrous CH_2Cl_2 at r.t. gave the title compound **1** in 85% yield. Baeyer-Villiger oxidation of the aldol **4a** under the same conditions gave the desired compound **6** in 82% yield. Synthetic **1** from **5** or **6** showed identical spectral data with those of natural product **1** reported, and the optical property of synthetic **1** { $[\alpha]_D^{20}$ –36.9 (*c* 1.05, $CHCl_3$)} is comparable with that of natural **1** {$[\alpha]_D^{20}$ –38.5[2]}[1].

In summary, we have achieved a versatile procedure for the synthesis of enantiomerical pure (-)-(5*R*, 6*S*)-6-acetoxyhexadecan-5-olide **1,** in 65% overall yield starting from aldehyde **2** in three steps, using L-proline as catalyst. The synthetic route reported here makes available the chirailty lactones that may be of interest for structure-activity studies of this type of compounds.

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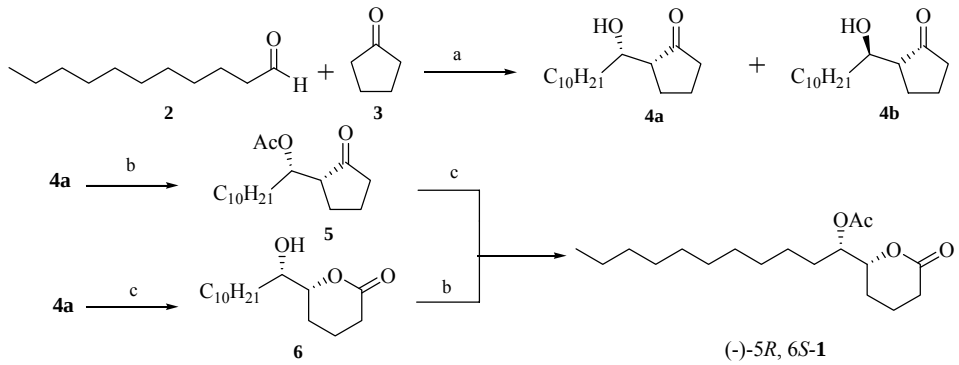
Scheme 1



Reagents and conditions: a. L-Proline (20 mol%), $CHCl_3$, 24 h, 80%; b. Ac_2O, Py, DMAP, r.t., 100%; c. *m*-CPBA, CH_2Cl_2, $NaHCO_3$, r.t., 82~85%.

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References and Notes

1. B. R. Laurence, J. A. Pickett, *J. Chem. Soc., Chem. Commun.,* **1982,** 59.
2. (a) G. Q. Lin, H. J. Xu, B. C. Wu, *et al., Tetrahedron Lett.,* **1985,** *26,* 1233; (b) W. L.Wu, Y. L. Wu, *J. Chem. Research (S),* **1990**, 112; (c) G. Q. Lin, Y. Y. Jiang, G. Z. Guo, K. M. Xia, *Acta Chim. Sin.,* **1987,** *45,* 602; (d) S. Ramaswamy, A. C. Oehlschlager, *Tetrahedron,* **1991,** *47,* 1145; (e) C. Gravier-Pelletier, M. Saniere, I. Charvet, *et al.*, *Tetrahedron Lett.,* **1994,** *35,* 115; () C. Bonini, M. Checconi, G. Righi, L. Rossi, *Tetrahedron,* **1995,** *51,* **4111**.
3. (a) P. Pojarliev, C. Castello, *Org. Lett.,* **2001**, *3*, 573; (b) B. List, *Tetrahedron,* **2002**, *58*, 5573; (c) L. Z. Peng, H. W. Liu, T. Zhang, *et al., Tetrahedron Lett.*, **2003,** *44,* 5107.
4. Selected spectral data:
   4a, $[\alpha]_D^{20}$ –33.5 (*c* 0.7, $CHCl_3$); IR (film): 3448, 2956, 2925, 2854, 1734, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ_{ppm}): 0.86 (t, 3 H, *J* = 6.6 Hz, Me), 1.23 (brs, 2H), 1.34–2.38 (m, 22 H), 3.65–3.69 (dt, 1 H, J_1 = 6.6 Hz, J_2 = 3 Hz, C*H*OH); ^{13}C NMR (75 MHz, $CDCl_3$, δ_{ppm}): 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. **1,** $[\alpha]_D^{20}$ –36.9 (*c* 1.05, $CHCl_3$); IR (film): 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, δ_{ppm}): 0.88 (t, 3 H, *J* = 6.8 Hz, Me), 1.10–1.1.98 (m, 22 H), 2.08 (s, 3 H, CH_3CO), 2.36-2.64 (m, 2 H), 4.32-4.38 (m, 1 H, C*H*OAc), 4.94–4.99 (m, 1 H, C*H*OCO); ^{13}C NMR (75 MHz, $CDCl_3$, δ_{ppm}): 171.0 170.7, 79.8, 73.8, 31.8, 29.9, 29.5–29.2 (6 C), 25.3, 24.0, 22.6, 20.9, 18.3, 14.0; 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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