

Enantioselective synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide *via* tandem α -aminoxylation-Henry reaction

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Dedicated to Prof. Gordon W. Gribble in recognition of his seminal contributions
to so many aspects of organic chemistry

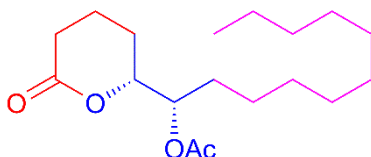
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Abstract

A novel enantioselective synthetic approach of (-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide, an oviposition attractant pheromone of the mosquito *Culex pipiens fatigans* is presented, starting from *n*-dodecanal. The synthesis features tandem α -aminoxylation-Henry and Yamaguchi-Hirao alkylation reactions as key steps.



(-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide

Keywords: δ -lactone, (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide, tandem α -aminoxylation-Henry reaction, regioselective epoxide opening, Yamaguchi-Hirao reaction

Introduction

Functionalized γ - and δ -lactone motifs possess intriguing biological activities and are important building blocks to synthesize a variety of biologically active natural products.¹⁻⁹ In 1982, Laurence and Pickett isolated (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide **1a**, a functionalized δ -lactone, as a major constituent that forms on the mosquito *Culex pipens fatigans* eggs.¹⁰ This mosquito is a possible vector of malaria, West Nile virus and filarial infections.¹¹ The (-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide **1a** attracts other gravid females of the identical and few allied mosquitos tempting them to oviposit in the same place where the original eggs are found. Owing to the potential of (-)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide **1a** in controlling mosquito populations, several enantioselective synthetic approaches for **1a** and its unnatural isomer (+)-6-acetoxy-5-hexadecanolide **1b** (Figure 1) have been disclosed in the literature.¹²⁻²⁹ As part of our research program aimed at developing the asymmetric synthesis of bioactive natural compounds,³⁰⁻³⁷ we turned our attention to developing a flexible and simple approach for the asymmetric synthesis of functionalized δ -lactones and its application to asymmetric synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide **1a**. Herein, we report a new enantioselective synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide **1a** employing tandem α -aminoxylation-Henry reaction as the source of chirality.

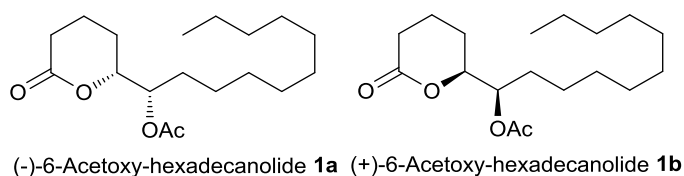
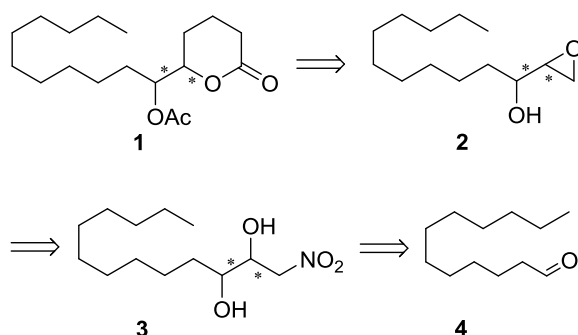


Figure 1. Structures of stereoisomers of 6-acetoxy-hexadecanolide.

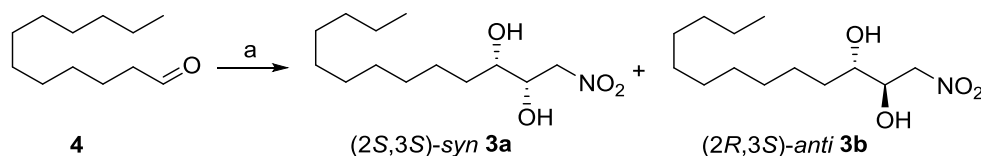
Results and Discussion

Our retrosynthetic route to the synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide is displayed in Scheme 1. The epoxy alcohol **2** was envisioned as a key intermediate from which δ -lactone **1** and 6-acetoxy-5-hexadecanolide **1a-1b** could be synthesized via a Yamaguchi-Hirao alkylation reaction followed by standard organic transformations. The key fragment **2** could in turn be prepared from the diol **3** in simple steps including oxidation, reduction and epoxide formation. Subsequently, compound **3** could be envisaged from commercially available *n*-dodecanal **4** via a tandem α -aminoxylation-Henry reaction.

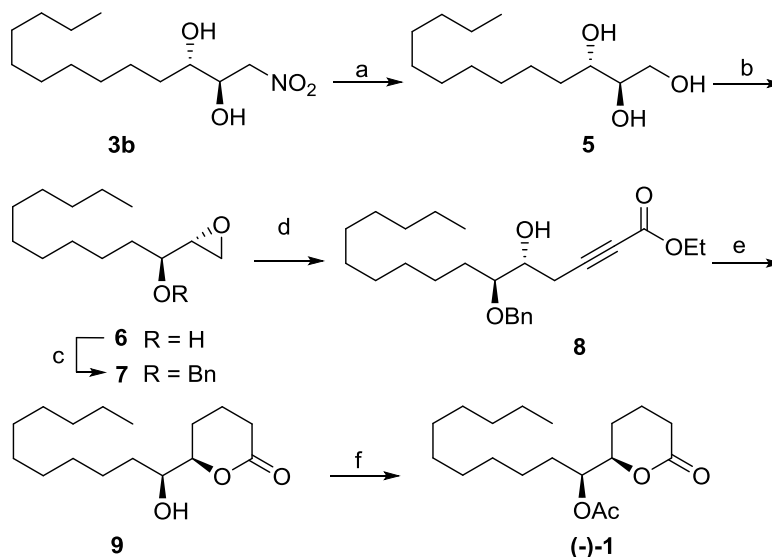


Scheme 1. Retrosynthetic strategy for 6-acetoxy-hexadecanolide **1**.

As illustrated in Scheme 2, the synthetic endeavor towards (-)-(5*R*,6*S*)-6-acetoxylhexadecanolide **1a** commenced with commercially available *n*-dodecanal **4**. Compound **4**, on tandem α -aminoxylation-Henry reaction³⁸ in the presence of catalytic amount of *D*-proline and without ligand, furnished the *syn*- β,γ -dihydroxynitrotridecane **3a** along with its *anti*-diastereomer **3b** in 1:1 ratio with 62% overall yield and excellent enantioselectivities (>99% ees for both *syn*- and *anti*-diastereomers).³⁹ Both (2*S*,3*S*)-*syn* **3a** and (2*R*,3*S*)-*anti* **3b** diastereomers were carefully separated by silica gel column chromatography.



Scheme 2. Reagents and conditions: (a) i) PhNO, *D*-proline (30 mol%), DMSO, rt, 30 min, ii) CH₃NO₂, aq. NaOH, MeOH, Cu(OAc)₂·H₂O, rt, 12 h, 62%.



Scheme 3. Reagents and conditions: (a) i) NaNO₂, AcOH, DMSO, 35 °C, 24 h, ii) LiAlH₄, THF, 0 °C to rt, 3 h, 62% (over two steps); (b) i) TsCl, Bu₂SnO, Et₃N, CH₂Cl₂, 0 °C to rt, 1 h; ii) K₂CO₃, MeOH, rt, 30 min, 76% (over two steps); (c) NaH, BnBr, DMF, 0 °C, 4 h, 92%; (d) *n*-BuLi, BF₃·OEt₂, HCCCO₂Et, dry THF, -78 °C, 2 h, 81%; (e) i) H₂, Pd/C (10%), MeOH, rt, 12 h; ii) *p*-TSA, benzene, reflux, 1 h, 91% (over two steps); (f) Ac₂O, DMAP, DCM, 30 min, 95%.

Having *anti*-diastereomer (2*R*,3*S*)-*anti* **3b** in hand, we then performed an oxidation using NaNO₂/acetic acid in DMSO to provide the acid⁴⁰⁻⁴¹ which on immediate reduction with LiAlH₄ afforded the triol derivative **5** in 62% yield (Scheme 3). Our next goal was to achieve the synthesis of the terminal epoxide moiety. Towards this end, triol **5** on regioselective monotosylation using TsCl/NEt₃ in the presence of a catalytic amount of dibutyltin oxide⁴²⁻⁴³ followed by base treatment, successfully furnished the terminal epoxide **6** in 76% yield, [α]_D²⁵ +16.4 (c 1.0, CHCl₃); {lit.²⁷ [α]_D²⁰ +16.2 [c 1.01, CHCl₃]}. The free hydroxyl group of intermediate **6** was then alkylated with benzyl bromide in the presence of sodium hydride as base to produce the benzyl ether derivative **7** in 92% yield. Next, regioselective ring opening of epoxide **7** with lithium salt of ethyl propiolate under the Yamaguchi-Hirao conditions⁴⁴ afforded homopropargylic alcohol derivative **8** in 81% yield. Subsequently, the

lactone **9** was obtained from compound **8** via a two-step procedure involving catalytic (Pd/C, 10%) hydrogenation and *p*-TSA catalyzed lactonization in 91% yield. Finally, treatment of alcohol **9** with acetic anhydride and catalytic DMAP in dichloromethane at room temperature furnished (-)-(5*R*,6*S*)-6-acetoxyhexadecanolide **1a** in 95% yield; $[\alpha]_D^{25} -36.89$ (*c* 1.0, CHCl₃); {lit.²⁶ $[\alpha]_D^{32} -36.8$ (*c* 1.0, CHCl₃)}. The physical and spectroscopic data of (-)-(5*R*,6*S*)-6-acetoxyhexa-decanolide **1a** were in full agreement with literature data.

Conclusions

In summary, we have demonstrated a general and flexible synthetic approach for functionalized δ -lactones and its application to the asymmetric synthesis of (-)-(5*R*,6*S*)-6-acetoxyhexadecan-5-olide employing asymmetric tandem α -aminooxylation-Henry reaction on the commercially available *n*-dodecanal. Further extension of the tandem α -aminooxylation-Henry reaction strategy to biologically active molecules of more structural complexity and diversity is in progress.

Experimental Section

General. All reactions were carried out under argon or nitrogen in oven-dried glassware using standard glass syringes and septa. The solvents and chemicals were purchased from Merck and Sigma Aldrich chemical company. Solvents and reagents were purified and dried by standard methods prior to use. Progress of the reactions was monitored by TLC using precoated aluminium plates of Merck kieselgel 60 F254. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of *n*-hexane and EtOAc. Optical rotations were measured on an automatic polarimeter, AA-65. ¹H and ¹³C NMR spectra were recorded in CDCl₃ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. Chemical shifts are reported in δ (ppm), referenced to TMS. HRMS were recorded on Agilent 6530 Accurate-Mass Q-TOF using electrospray ionization. IR spectra were recorded on an Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory.

***syn*-(2*S*,3*S*)-/*anti*-(2*R*,3*S*)-1-Nitrotridecane-2,3-diol (3a)/(3b).** To a DMSO (15 mL) solution of aldehyde **4** (2.0 g, 10.80 mmol) was added nitrosobenzene (1.16 g, 10.8 mmol), followed by D-proline (375 mg, 3.26 mmol, 30 mol%) and the reaction mixture stirred for about 20-30 min at rt. The completion of the reaction was monitored by its color change from green to orange or by TLC until all the nitrosobenzene was consumed and used as such for the next step without further purification. To the above crude solution was added MeOH (15 mL), nitromethane (6.58 g, 5.8 mL, 108 mmol), aq. NaOH (650 mg, 16.2 mmol, 8M), and above synthesized α -aminooxylated aldehyde were added. The reaction mixture was stirred for 30 min, then Cu(OAc)₂·H₂O (3.24 g, 16.2 mmol) was added and the mixture further stirred for additional 12 h at rt. After completion of the reaction (monitored by TLC), the reaction mixture was evaporated, diluted with H₂O, extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, and concentrated. The *syn/anti* diastereomers were separated and purified by silica gel column chromatography (EtOAc/hexane, 1:9 v/v) as eluent, which furnished the *syn*-diastereomer **3a** (874 mg, 31%) as a white solid. $[\alpha]_D^{25} +55.2$ (*c* 0.20, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ : 4.63-4.49 (m, 2H), 4.27-4.18 (m, 1H), 3.75-3.72 (m, 1H), 2.41 (br s, 2H), 1.56-1.20 (m, 18H), 0.86 (t, *J* 8.6 Hz, 3H); ¹³C NMR (100

MHz, CDCl₃) δ : 77.5, 73.1, 72.0, 33.0, 32.2, 29.9, 29.8, 29.7, 29.6, 25.9, 22.9, 14.4. HRMS (ESI) m/z calcd for C₁₃H₂₇NO₄ ([M-H]⁺) 260.1867; found 260.1872.

After separating the *syn*-diastereomer, the quickly eluting *anti*-diastereomer **3b** was then isolated (EtOAc/hexane, 1:5 v/v) as a white solid (874 mg, 31%). [α]_D²⁵ +72.5 (c 1.0, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ : 4.62-4.48 (m, 2H), 4.25-4.21 (m, 1H), 3.59-3.51 (m, 1H), 1.61-1.20 (m, 18H), 0.86 (t, *J* 8.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 78.3, 71.4, 70.4, 33.2, 31.5, 29.3, 29.2, 29.1, 29.1, 29.0, 25.1, 22.3, 13.8.

(2R,3S)-Tridecane-1,2,3-triol (5). To a stirred solution of *anti*-diastereomer **3b** (500 mg, 1.91 mmol) in DMSO (5 mL) at 35 °C were added NaNO₂ (396 mg, 5.75 mmol) and AcOH (1.1 mL, 19.0 mmol). After stirring for 24 h at the same temperature, the reaction mixture was quenched with H₂O and acidified with 10% aq solution HCl (25 mL). The aqueous layer was extracted with Et₂O (3 x 30 mL), dried over anhydrous Na₂SO₄, concentrated in vacuo, and used as such for the next step without further purification. LiAlH₄ (145 mg, 3.82 mmol) was added to a solution of above crude material in THF (5 mL) at 0 °C under N₂ atmosphere. After 5 min, the reaction was allowed to reach rt and stirred for a further 3 h. Then the reaction mixture was quenched with 10% aq NaOH. The aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The residue was subjected to silica gel column chromatography (EtOAc/hexanes, 4:1 v/v) to give triol **5** (274 mg, 62%) as a white solid. [*R*_f = 0.4, EtOAc]; [α]_D²⁵ +40.4 (c 0.8, CHCl₃); IR (CH₂Cl₂) ν : 3415, 2945, 2910, 2863, 1701, 1651 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 3.90-3.48 (m, 3H), 2.64 (br, 1H), 2.74 (br, 1H), 2.26 (br, 2H) 1.70-1.10 (m, 18H), 0.93 (t, *J* 6.88 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ : 73.0, 67.5, 62.8, 33.8, 31.9, 29.6, 29.5, 29.3, 25.3, 22.6, 14.1; HRMS (ESI)⁺ m/z calcd for C₁₃H₂₈O₃Na⁺ [M+Na⁺] 255.1930; found 255.1929.

(S)-1-((R)-Oxiran-2-yl)undecan-1-ol (6). To a stirred solution of **5** (200 mg, 0.86 mmol) in CH₂Cl₂ (6 mL) under N₂ atmosphere at 0 °C were added Et₃N (0.15 ml, 1.03 mmol), catalytic amount of Bu₂SnO (21 mg, 0.09 mmol) and TsCl (181 mg, 0.94 mmol). The resulting mixture was stirred at rt for 1 h. Then the reaction mixture was quenched with H₂O, extracted with CH₂Cl₂ and the extract dried over Na₂SO₄. The combined organic layers were concentrated under reduced pressure to afford crude tosylate which was used for next step.

K₂CO₃ (237 mg, 1.72 mmol) was added to a solution of above crude product in MeOH (5 mL) at rt and stirred for 30 min. The resulting mixture was diluted with H₂O (10 mL) and EtOAc (20 mL). The organic layer was separated, and aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:4) to give epoxide **6** (140 mg, 76%) as a colourless liquid. [*R*_f = 0.3, EtOAc/hexane 1:4 v/v]; [α]_D²⁵ +16.4 (c 1.0, CHCl₃); {lit.²⁷ [α]_D²⁰ +16.2 [c 1.01, CHCl₃]}; IR (CH₂Cl₂) ν : 3453, 2935, 2856, 1256, 1426 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 3.71-3.68 (m, 1H), 3.01-2.99 (m, 1H), 2.84-2.83 (m, 1H), 2.79-2.77 (m, 1H), 1.69-1.66 (m, 2H), 1.50-1.21 (m, 16H), 0.93 (t, *J* 7.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ : 68.4, 54.5, 43.4, 33.4, 31.9, 29.7, 29.6, 29.5, 29.3, 25.3, 22.7, 14.1; HRMS (ESI)⁺ m/z calcd for C₁₃H₂₇O₂[M+H⁺] 215.2011; found 215.2012.

(-)-(5R,6S)-6-Acetoxyhexadecan-5-olide (1a). To a stirred solution of the alcohol **9** (20 mg, 0.07 mmol) in anhydrous CH₂Cl₂ (3.0 mL) under N₂ atmosphere at rt were added DMAP (51 mg, 0.42 mmol) and Ac₂O (43 mg, 0.42 mmol). The resulting mixture was stirred for 30 min. at rt. Next, the reaction mixture was quenched by addition of cold H₂O and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and solvent was removed in *vacuo*. Silica gel column chromatography of the resultant residue furnished the target compound **1** (20 mg, 95%) as a colorless oil. [*R*_f = 0.4, EtOAc/hexane, 1:4 v/v]; [α]_D²⁵ -36.89 (c 1.0, CHCl₃); {lit.²⁶ [α]_D³² -36.80 (c 1.0, CHCl₃)}; IR (CH₂Cl₂) ν : 2935, 2844, 1740, 1361, 1236 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 4.99-4.95 (m, 1H), 4.38-4.31 (m, 1H), 2.65-2.57 (m, 1H), 2.50-2.41 (m, 1H), 2.08 (s, 3H), 2.00-1.79 (m, 2H), 1.72-1.56 (m, 4H), 1.38-1.20 (m, 16H), 0.88 (t, *J* 6.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃)

δ : 170.9, 170.5, 80.5, 74.3, 31.9, 29.8, 29.7, 29.6, 29.5, 25.2, 23.5, 22.7, 21.0, 18.2, 14.1; HRMS (ESI)⁺ m/z calcd for C₁₈H₃₃O₄[M+H] 313.2379; found 313.2395.

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Supplementary Material

Electronic supplementary information (ESI) available; copies of ¹H and ¹³C NMR spectra of compounds **1a**, Rac-**3**, **3a**, **3b** and **5-9**; HPLC of Rac-**3**, **3a**, **3b**, and HRMS of final compound **1a**. This material can be found *via* the "Supplementary Content" section of this article's webpage.

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