First Synthesis of Mosquito Larvicidal Butenolides I and II

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Utilizing aldol condensation and β-elimination as the key steps, butenolides I and II in excellent enantiomeric purity have been concisely synthesized for the first time. According to the rotation difference between synthetic samples and natural products, the rotations were corrected by the calculation upon HPLC measurements. In addition, an efficient way to synthesize methyl pentadec-14-enoate was developed.

Keywords butenolides I and II, aldol condensation, methyl pentadec-14-enoate

Introduction

Very recently, two new mosquito larvicidal butenolides I (**1**) and II (**2**) were isolated by Karunaratne *et al*.[1] from the leaves of all three species of *Hortonia* (family *Monimiaceae*) (H. *angustifolia*, H. *floribunda* and H. *ovalifolia*). Both butenolides exhibited mosquito larvicidal activity with LC_{50} values of δ 0.41 and δ 0.47 respectively. The butenolide unit is widespread in a plenty of natural products including marine animals and territorial plants. Among these, *annonaceous* acetogenins are the most famous representative member of the butenolide family.[2] Usually the butenolide segment in *annonaceoua* acetogenins is a 3-substituted 5(*S*)-methyl-2(5*H*)-furanone, which is believed to be the essential subunit for the bioactivities of these acetogenins.[2] As part of our interest on the synthetic program of *annonaceoua* acetogenins, we developed a chiron approach to construct the optically active 3-subtituted 5-methyl-2(5*H*)-furanone[3] through aldol condensation of an ester with *O*-protected-lactaldehyde followed by lactonization and β-elimination. This strategy was again successfully applied in the syntheses of both enantiomers of the butenolides I (**1**) and II (**2**).

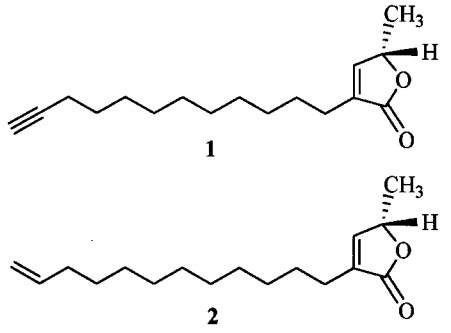

Fig. 1 Structures for butenolides I (**1**) and II (**2**).

Results and discussion

Synthesis of butenolide II (**2**)

Reduction of commercially available 10-undecenoic acid (**3**) with LAH gave 10-undecene-1-ol (**4**),[4] which was further treated with PPh_3/I_2/imidazole to afford 11-iodo-undecene (**5**).[5] Methyl pentadec-14-enoate (**6**) was prepared by a reductive Michael-type addition of methyl acrylate with 1.0 equivalence of **5** in the presence of zinc dust and $NiCl_2 \cdot 6H_2O$ in pyridine.[6] According to our previous procedures,[3] treatment of **6** with LDA produced lithium enolate, which was reacted with freshly prepared (*S*)-*O*-tetrahydropyranyl lactaldehyde to give a mixture of diasteeomeric β-hydroxyl esters. This mixture was subjected to acidic cleavage to deblock THP protection and

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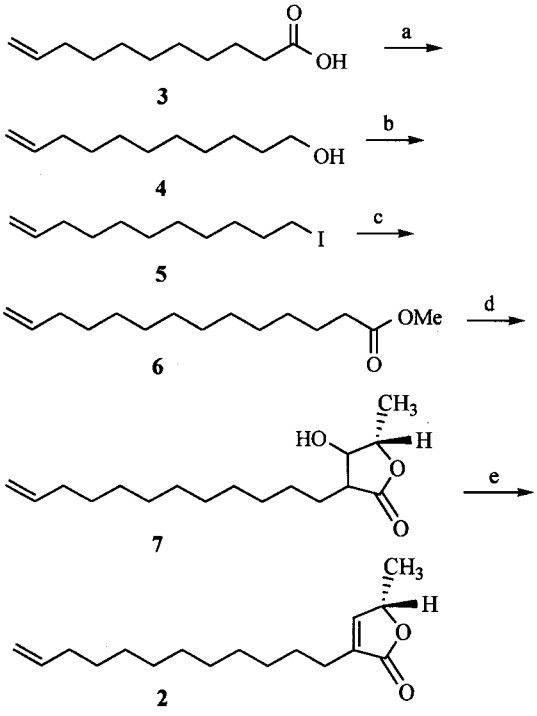
lactonize the aldol adduct to give β-hydroxyl lactones (**7**). Dehydration of **7** with trifluoroacetic anhydride and triethylamine afforded **2** in 26% overall yield. The ^{1}H NMR data of **2** were identical to those of the natural one. However the measured optical rotation value [+33.1 (*c* 1.05, $CHCl_3$)] was much lower than that reported [+80 (*c* 0.0028, $CHCl_3$)]. In order to confirm the results and enantiomeric purity of the synthetic sample, the enantiomer of **2** was synthesized according to the same procedures. With both enantiomers of **2** in hand, the enantiomeric excess values were measured by HPLC method and the results showed synthetic **2** has an *ee* value of 94%. According to these figures, the optical rotation of pure **2** should be +35.2, and the high value reported might be error because of low concentration (Scheme 1).

Scheme 1

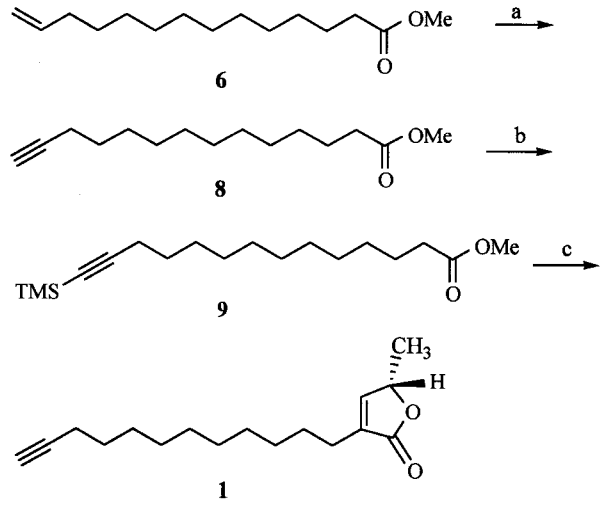


Reagents and conditions: (a) LAH, dry ether, reflux, 86%. (b) PPh_3, imidazle, I_2, dry bezene, 0 ℃, 81%. (c) $NiCl_2 \cdot 6H_2O$, Zn dust, methyl acrylate, py, rt, 74%. (d) (i) LDA, THF-HMPA, −78 ℃; (ii) (*S*)-*O*-tetrahydropyranyl lactal, −78 ℃; (iii) 10% H_2SO_4, rt, 55% in three steps. (e) $(CF_3CO)_2O$, Et_3N, dry CH_2Cl_2, 0 ℃, 90%.

Synthesis of butenolide I (**1**)

First of all, **6** was coverted into the corresponding acetylenic ester (**8**) by bromination and subsequent dehydrobromination with ethanolic potassium hydroxide under reflux.[7] No reaction occurred when protecting **8** with TMSCl using NaH as the base, while *t*-BuOK and LDA gave the complicated systems. According to the reference, a direct silylation of **8** with chlorosilanes afforded the TMS protected acetylenic ester (**9**) in the presence of zinc powder in MeCN.[8] Following the same route as in the preparation of **2**, **1** was finally synthesized in 8% overall yield. The ^{1}H NMR spectrum was identical to that reported.[1] The measured optical rotation of **1** [+30.6 (*c* 0.5, $CHCl_3$)] was a little bit smaller than that reported [+38 (*c* 0.0026, $CHCl_3$)]. For the same reason, the enantiomer of **1** was synthesized and the enantiomeric excess values were measured by HPLC. The *ee* value of synthetic **1** is 92.3%. According to these figures, the optical rotation of pure **1** should be +33.2 (Scheme 2).

Scheme 2



Reagents and conditions: (a) (i) Br_2, $CHCl_3$; (ii) alcohol KOH; (iii) CH_2N_2, ether, 85% in 3 steps. (b) TMSCl, Zn powder, acetonitrile, 120 ℃, sealed tube, 45%. (c) (i) LDA, THF-HMPA, −78 ℃; (ii) (*S*)-*O*-tetrahydropyranyl lactal, −78 ℃; (iii) 10% H_2SO_4, rt; (iv) $(CF_3CO)_2O$, Et_3N, dry CH_2Cl_2, 0 ℃, 39% in four steps.

Conclusion

Starting from commercially available lactic acid ester and 10-undecenoic acid, utilizing aldol condensation and β-elimination as the key steps, butenolides **1** and **2** have been concisely synthesized for the first time in excellent

enantiomeric purity. According to the rotation difference between synthetic samples and natural products, the rotations were corrected by the calculation upon HPLC measurements. In addition, an efficient way to synthesize methyl pentadec-14-enoate was developed.

Experimental

General

Flash column chromatography was performed on a silica gel H column (10—40 μm) with mixture of petroleum ether and ethyl acetate as eluent. Microanalyses were carried out in the Micro-analytical Laboratory at Shanghai Institute of Organic Chemistry. *O*-THP-(*S*)-lactaldehyde and *O*-THP-(*R*)-lactaldehyde were prepared from corresponding (*S*) and (*R*)-ethyl lactate.

10-*Undecene*-1-*ol* (**4**)

To a pre-refluxed solution of lithium aluminum hydride (11.43 g, 0.30 mol) in absolute ether (500 mL) was added dropwise 10-undecenoic acid (33 g, 0.20 mol) in dry ether (53 mL) with vigorous stirring in an ice-water bath. After completing the addition, the ice-bath was removed and stirring was continued for 30 min. The mixture was hydrolyzed by cautiously adding dilute sulfuric acid (108 mL of 10% and 108 mL of 20%) with a cool bath. The ether layer was separated, washed with water, and dried over sodium sulfate. Filtration and distillation of the organic layer (114—115 ℃ at 798 Pa) afforded **4**[4] (26.3 g, 86%). IR (neat) ν: 3338, 3078, 2928, 1642, 1465, 1057, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.21—1.62 (m, 14H), 1.94—2.11 (m, 2H), 3.61 (t, J = 6.6 Hz, 2H), 4.86—5.01 (m, 2H), 5.73—5.87 (m, 1H).

11-*Iodo*-1-*undecene* (**5**)

To a solution of **4** (15 g, 0.088 mol), imidazole (20.4 g, 0.3 mol) and Ph_3P (39.5 g, 0.15 mol) in dry bezene (130 mL) was added iodine (38.1 g, 0.15 mol) in portions at 0 ℃ under N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 h. Excess of iodine was removed by the addition of aqueous sodium thiosulfate. The mixture was then transferred to a separating funnel and the organic layer was diluted with benzene. The benzene layer was washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was precipitated by adding diethyl ether and the solid triphenylphosphine oxide was filtered. The filtrate was concentrated and then subjected to column chromatography (petroleum ether: EtOAc, 10:1) to yield the title compound[9] (20.01 g, 81%). ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.26—1.38 (m, 12H), 1.77—1.87 (m, 2H), 2.01—2.08 (m, 2H), 3.18 (t, J = 7 Hz, 2H), 4.93—4.99 (m, 2H), 5.76—5.86 (m, 1H).

Methyl pentadec-14-*enoate* (**6**)

A mixture of powdered $NiCl_2 \cdot H_2O$ (1.19 g, 5 mmol), activated zinc dust (1.64 g, 25 mmol), pyridine (10 mL) and methyl acrylate (2 mL, 22.5 mmol) was well stirred under nitrogen atmosphere at 60 ℃ for 30 min until a dark-red suspension was got. To this cooled mixture was then added the solution of **5** (1.4 g, 5 mmol) in pyridine (5 mL), and the reaction was then stirred overnight at room temperature. The mixture was diluted with EtOAc (20 mL) and filtered through a pad of celite. The pad was washed with EtOAc (10 mL × 3). The combined organic layers were washed successively with HCl (1.0 mol/L, 25 mL × 4), EDTA (1 mol/L, 20 mL), brine (20 mL × 2) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (petroleum ether: EtOAc, 50:1) to give a colorless liquid[7] (0.88 g, 74%). ^1H NMR ($CDCl_3$, 300 MHz) δ: 1.28—1.41 (m, 18H), 2.02—2.09 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 3.68 (s, 3H), 4.92—5.04 (m, 2H), 5.79—5.88 (m, 1H).

(5*S*)-3-*Dodec*-11-*enyl*-4-*hydroxy*-5-*methyl*-*dihydro*-*furan*-2-*one* (**7**)

To a well-stirred solution of diisopropylamine (1.11 g, 11 mmol) in anhydrous THF (10 mL) was added *n*-BuLi solution in hexane (2.0 mol/L, 3.7 mL, 7.4 mmol) at −78 ℃ under N_2 atmosphere. After stirring for 30 min, anhydrous HMPA (2.5 mL, 14.1 mmol) was added and the mixture was stirred for an additional 30 min. A solution of **6** (0.88 g, 3.7 mmol) in THF (10 mL) was added, and the mixture was stirred for 20 min at −78 ℃. The freshly prepared (2*S*)-*O*-tetrahydropyranyl lactaldehyde (0.87 g, 5.5 mmol) in THF (5 mL)

was added and the mixture was stirred for 2 h until the saturated aqueous NH_4Cl (5 mL) was added to quench the reaction. After usual workup, the crude product (1.40 g) was obtained as a clear oil which was used for next step without further purification. The resulting residue in THF (15 mL) was treated with 10% H_2SO_4 (7 mL) at 0 ℃. The reaction mixture was stirred at room temperature for 12 h. The solution was saturated by adding NaCl, then was extracted with ether. The organic phase was washed with brine, dried over $NaSO_4$ and concentrated. Silica gel column chromatography (petroleum ether:EtOAc, 5:1) gave a white-powdered solid **7** (mixture of diastereomers, 0.57 g, 55%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.24—1.47 (m, 21H), 2.01—2.08 (m, 2H), 2.57—2.59 (m, 1H), 4.17—4.21 (m, 1H), 4.91—5.02 (m, 3H), 5.77—5.86 (m, 1H); IR (neat) ν: 3438, 3078, 2927, 2856, 1755, 1641, 1459, 1363, 1181, 1106, 1026, 961, 910 cm^{-1}; EIMS: 282 $[M]^+$; HRMS (EI) calcd for $C_{17}H_{30}O_3$ $[M]^+$ 282.2194, found 282.2192.

(5S)-Butenolide II (**2**)

To a mixture of **7** (36 mg, 0.128 mmol) and Et_3N (0.054 mL, 0.383 mmol) in CH_2Cl_2 (1.0 mL) was added $(CF_3CO)_2O$ (0.027 mL, 0.191 mmol) at 0 ℃. The reaction mixture was stirred at 0 ℃ for 20 h, quenched with aqueous $NaHCO_3$ and extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (elution with 5.0% EtOAc in hexane) to afford **2** (31 mg, 90%). $[\alpha]_D^{23}$ + 33.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.27—1.38 (m, 14H), 1.40 (d, J = 6.6 Hz, 3H), 1.47—1.56 (m, 2H), 1.99—2.06 (m, 2H), 2.22—2.27 (m, 2H), 4.96 (dd, J = 10.1, 2.0 Hz, 1H) 4.98 (dd, J = 17.0, 2.0 Hz, 1H), 4.99—5.02 (m, 1H), 5.80 (ddt, J = 17.0, 10.1, 6.7 Hz, 1H), 7.04 (dd, J = 3.0, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.9, 148.9, 139.3, 134.4, 114.1, 77.4, 33.9, 29.6, 29.6, 29.5, 29.4, 29.2, 29.1, 29.0, 27.5, 25.2, 19.3; IR (neat) ν: 3074, 2964, 2916, 2851, 1745, 1652, 1471, 1261, 1093, 1019, 799 cm^{-1}; EIMS (*m/z*): 264 $[M]^+$; HPLC: 94% *ee* (a chiralcel OD column; UV-detector: 214 nm; 1% *i*-PrOH in hexanes; flow rate 0.7 mL/min).

Tetradec-13-ynoic acid methyl ester (**8**)

To a solution of olefin **6** (1.5 g, 6.25 mmol) in chloroform (3 mL), an excess of bromine (1.5 g, 9.38 mmol) was added and the mixture was stirred for 1 h at room temperature. After usual workup, the product was subjected to react with potassium hydroxide (1.61 g) in absolute ethanol (32 mL) under reflux for 6 h. After being acidified, the acid was extracted with hexane and methylated with CH_2N_2, and then the crude product was purified by chromatography on silica gel (petroleum ether :EtOAc, 15:1) to afford an oil **8**[7] (1.27 g, 85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.44—1.50 (m, 14H), 1.54—1.69 (m, 4H), 2.0 (t, J = 2.7 Hz, 1H), 2.24 (td, J = 6.9, 3.0 Hz, 2H), 2.36 (t, J = 7.8 Hz, 2H), 3.73 (s, 3H).

14-*Trimethylsilanyl-tetradec-13-ynoic acid methyl ester* (**9**)

To a suspension of zinc powder (0.99 g, 15.1 mmol) in dry acetonitrile (4 mL) was added acetylenic ester **8** (0.9 g, 3.78 mmol) and chlorotrimethylsilane (0.54 g, 7.56 mmol). The resulting mixture was heated at 120 ℃ for 10 h in a sealed tube. After removal of excess zinc by filtration, the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (petroleum ether: EtOAc, 30 :1) to afford an oil **9** (0.526 g, 45%). IR (neat) ν: 2929, 2856, 2175, 1742, 1464, 1436, 1363, 1249, 1172, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.15 (s, 9H), 1.2—1.5 (brs, 14H), 1.51—1.65 (m, 4H), 2.16—2.22 (m, 2H), 2.31 (t, J = 7.4 Hz, 2H), 3.67 (s, 3H); EIMS (*m/z*): 310 $[M]^+$; HRMS (EI) calcd for $C_{18}H_{34}O_2Si$ $[M]^+$ 310.2328, found 310.2311.

(5S)-Butenolide I (**1**)

To a solution of DIPEA (0.93 mL, 5.09 mmol) in anhydrous THF (6.0 mL) was added *n*-BuLi (1.7 mL, 2.0 mol/L in hexane, 3.4 mmol) at 0 ℃. The mixture was stirred at 0 ℃ for 30 min, and allowed to cool to −78 ℃. After stirring for further 30 min, anhydrous HMPA (1.48 mL, 8.47 mmol) was added and the mixture was stirred for an additional 30 min. A solution of **9** (526 mg, 1.70 mmol) in THF (6 mL) was injected into

the above mixture. After stirring for 30 min, a solution of *O*-THP-(*S*)-lactal (524 mg, 3.32 mmol) in THF (10 mL) was introduced and the reaction mixture was stirred for 2 h at −78 ℃. The mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvents afforded a crude oil, which was treated with 10% H_2SO_4 (9 mL) in THF (16 mL) for 18 h at room temperature. The reaction mixture was diluted with ether, washed with saturated aqueous $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to give a crude oil. To the mixture of the above oil and Et_3N (0.54 mL, 3.84 mmol) in CH_2Cl_2 (6.8 mL) at 0 ℃ was added $(CF_3CO)_2O$ (0.27 mL, 1.92 mmol). The reaction was stirred at 0 ℃ for 12 h and at r.t. for 6 h, quenched with saturated NH_4Cl and extracted with CH_2Cl_2. After being dried (Na_2SO_4), the extracts were filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (petroleum ether : EtOAc, 10 : 1) to afford the pure **1** (0.19 g, 20%). $[\alpha]_D$ +30.6 (*c* 0.50, $CHCl_3$) {lit.[2] $[\alpha]_D^{22}$ + 38 (*c* 0.0026, $CHCl_3$)}; ^{1}H NMR (CD-Cl_3, 300 MHz) δ: 1.20—1.36 (brs, 12H) 1.41 (d, J = 6.9 Hz, 3H), 1.48—1.57 (m, 4H), 1.94 (t, J = 2.7 Hz, 1H), 2.18 (td, J = 7.1, 2.7 Hz, 2H), 2.27 (t, J = 7.3 Hz, 2H), 5.00 (dq, J = 6.9, 1.6 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 173.8, 148.9, 134.4, 84.8, 77.4, 68.1, 29.5, 29.4, 29.3, 29.2, 29.1, 28.9, 28.5, 27.5, 25.2, 19.3, 18.4; IR (neat) ν: 3312, 2928, 2856, 1756, 1654, 1464, 1374, 1320, 1200, 1120, 1075, 1027, 862, 630 cm^{-1}; EIMS (*m*/*z*): 263 $[MH]^+$; HPLC: 92.3% *ee* (a chiralcel OD column; UV-detector: 214 nm; 1% *i*-PrOH in hexanes; flow rate 0.7 mL/min).

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