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A Palladium-Catalyzed Construction of Enantiomerically Pure α-Methylene-γ-butyrolactones. Enantiospecific Synthesis of Both Enantiomers of Methylenolactocin

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Abstract: Optically active β,γ-disubstituted-α-methylene-γ-butyrolactones were synthesized by palladium(II)-catalyzed cyclization reactions of homochiral allylic 2-alkynoates. The reaction was applied to the total synthesis of methylenolactocin in both enantiomeric forms.

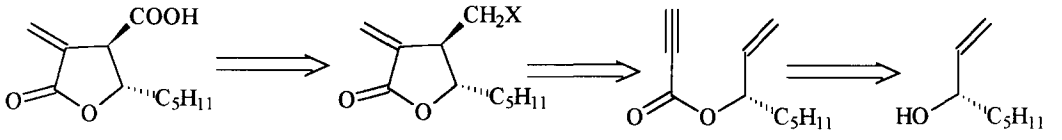
INTRODUCTION

Optically active α-methylene-γ-butyrolactones are an interesting class of compounds not only because of their intrinsic reactivity, which was shown in their use as chiral building blocks for the synthesis of natural products such as alkaloids, macrocyclic antibiotics, lignan lactones, and pheromones,[1] but also because of their occurrence in a large variety of natural products and biologically active compounds.[2] The physiological activity of these α-methylene-γ-butyrolactones often depends on the enatiomeric purity and absolute configuration.[3] Therefore, many methods have been developed for the synthesis of functionalized α-methylene-γ-butyrolactone derivatives in optically active form.[4]

(-)-Methylenolactocin, isolated from the culture filtrate of penicillium *sp.*,[5] is a densely functionlized and isomerization-prone antitumor antibiotic. There has been only one report on its total synthesis involving an asymmetric [2+2] cycloaddition reaction as a key step by Greene and his coworkers[2] and another formal synthetic route was reported by Honda.[6] While for the synthesis of (+)-enantiomer of methylenolactocin, there is no report in literature up to now.

For our interest in palladium-catalyzed cyclization of allylic 2-alkynoates, we have developed some methodologies for the stereoselective synthesis of α-methylene-γ-butyrolactone derivatives.[7] As an extension of

our work we developed an efficient way for the enantiospecific synthesis of the β,γ-disubstituted-α-methylene-γ-butyrolactones[8] and report here a successful enantiospecific synthesis of both enantiomers of methylenolactocin as shown in the retrosythetic route in **Scheme I**.



(-)-methylenolactocin **optically active**

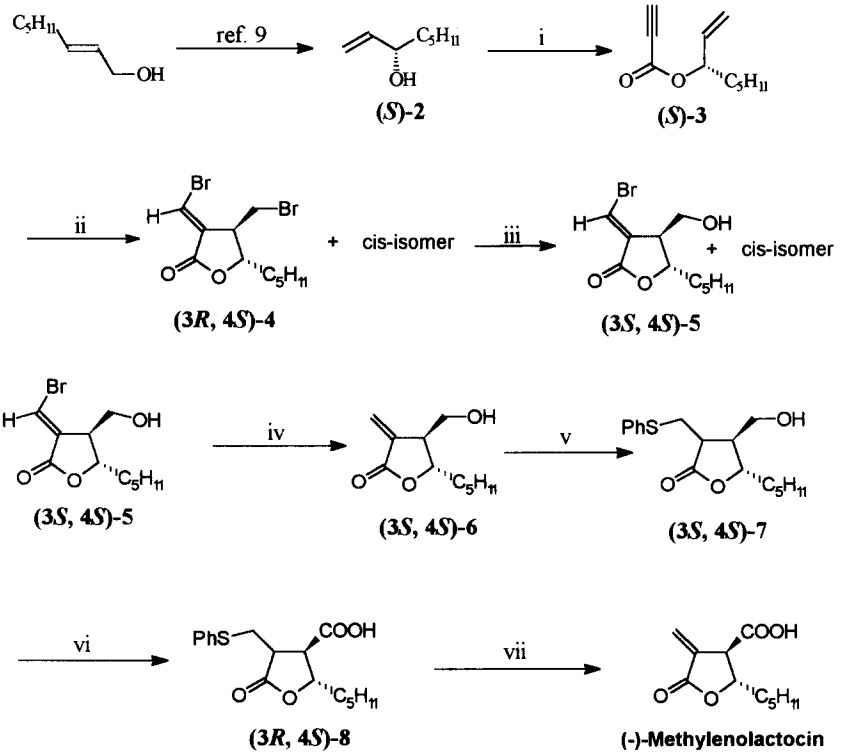
Scheme I

RESULTS AND DISCUSSION

In our synthetic strategy (Scheme II), the starting material, optically active allylic alcohol is easily available from Sharpless asymmetric epoxidation of 2-octen-1-ol and subsequent reduction.[9] The ester **(*S*)-3** was obtained by esterification in the presence of DCC and a catalytic amount of DMAP (70%). The palladium-catalyzed cyclization of allylic propynoate **(*S*)-3** was carried out as follows. To a solution of $CuBr_2$, LiBr and $Pd(OAc)_2$ (5 mmol%) in HOAc, the ester **(*S*)-3** was added, then the mixture was stirred at rt. After the reaction was complete, the cyclic products **4** were purified by column chromatography on silica gel in 90% yield with 71:29 (*trans:cis*) diastereoselectivity. While difficulties were encountered in the direct separation of **(3*R*,4*S*)-4** from its diastereomer, the two diastereomers could be separated by column chromatography on silica gel after further transformation of **4** to **5**.

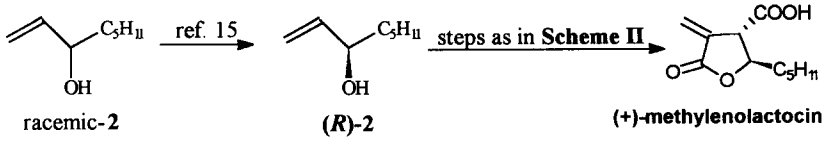
Since the basic skeleton for methylenolactocin was constructed, we focused our attention on the further elaboration of the C-Br bond into the natural product. Due to the base sensitive lactone ring, the hydrolysis condition for the alkyl bromide unit is critical, e. g., the lactone ring was perfectly opened in many ways using NaOH, LiOH or $NaHCO_3$ as bases. Finally according to Dibble's method[10] (but dioxane was replaced by DMSO), the hydrolysis of **4** in refluxing DMSO/H_2O solution with $CaCO_3$ provided the α-bromomethylene β-hydroxymethyl-γ-butyrolactone **(3*S*, 4*S*)-5** together with its diastereomer **(3*R*, 4*R*)-5** in 55% yield, which were easily separated by column chromatography on silica gel. Reduction of the vinyl bromide of **(3*S*, 4*S*)-5** with Zn-Ag couple under Heathcock's condition[11] afforded the **(3*S*, 4*S*)-6** in 90% yield. The direct oxidation of the hydroxyl group in **5** or **6** to a carboxyl group failed under many oxidation conditions. The exocyclic carbon-carbon double bond was believed to make the oxidation reaction complex. Protection of the exocyclic double bond using PhSH (91%),[12] followed by oxidation of the hydroxyl group with PDC in DMF solution[13] did afford the β-carboxyl lactone **(3*R*, 4*S*)-8**. Finally, after deprotection,[14] (-)-methylenolactocin was

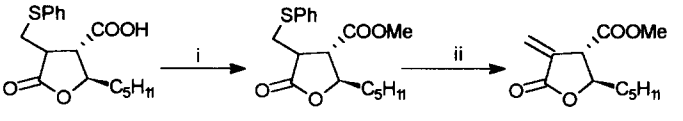
obtained in 75% yield from 7. $\{[\alpha]_D^{25} = -6.78$ (c = 0.53, $CH_3OH)\}$, which is spectroscopically indistinguishable from the literature data $\{[\alpha]_D^{25} = -6.8$ (c = 0.5, $CH_3OH)\}$[2].



Scheme II *Reagents and conditions:* i, propynoic acid, DCC, DMAP, Et_2O, -20°C–rt; ii, $CuBr_2$, LiBr, $Pd(OAc)_2$(5 mol%), HOAc, rt; iii, $CaCO_3$, DMSO-H_2O, 100°C; iv, Zn-Ag, MeOH, 70°C; vi, PDC, DMF, 0°C to rt; vii, $NaIO_4$, MeOH-benzene-H_2O, 0°C–rt, then reflux in toluene.

From the optically active allylic alcohol **(*R*)-2** obtained by the kinetic resolution method,[15] the first synthesis of (+)-methylenolatocin $\{[\alpha]_D^{25} = +6.78$ (c = 0.51, $CH_3OH)\}$ was achieved in a similar way as shown in Scheme II. If **(3*S*, 4*R*)-8** was esterified by CH_2N_2, then deprotected using Barbier's method,[16] the methyl ester of (+)-methylenolactocin (**10**) {90%, $[\alpha]_D^{25} = -7.35$ (c = 0.4, $CHCl_3)\}$ was also successfully synthesized (**Scheme III**).





(3*S*, 4*R*)-8 **(3*S*, 4*R*)-9** **(3*S*, 4*R*)-10**
methyl ester of (+)-methylenolactocin

Scheme III *Reagents and conditions:* i, CH_2N_2, Et_2O, rt; ii, a) m-CPBA, CH_2Cl_2, -10°C; b) toluene, reflux.

In summary, we have developed a method to synthesize optically active β,γ-disubstituted α-methylene-γ-butyrolactone in both enantiomeric forms from easily available allylic alcohols. This methodology seems to be widely applicable to the synthesis of this type of natural products.

EXPERIMENTAL SECTION

Infrared spectra were obtained with a Shimadzu IR-440 instrument. Proton magnetic resonance spectra were recorded with a Varian EM-390 or Bruker AM-300 spectrometer and were reported in ppm downfield of internal tetramethylsilane (δ units); ^{19}F magnetic resonance spectra were recorded with a JEDL FX-90Q (36.2 MHz) spectrometer. Mass spectral data were taken on a Finnigan 4021 spectrometer and HRMS data were obtained on an Finnigan MAT 8430 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC instrument. The analytical samples were further purified by Kugelrohr distillation at the specified oven temperatures (ot).

(*S*)-1-Octen-3-ol [**(*S*)-2**] was synthesized according to reported procedure.[8] (*R*)-1-Octen-3-ol [**(*R*)-2**] was obtained from racemic 1-octen-3-ol by kinetic resolution according to Sharpless's method.[15] The enantiomeric purity of **(*S*)-2** and **(*R*)-2** were determined from 300 MHz ^1H NMR and ^{19}F NMR spectra of their Mosher esters, no enantiomer was found in the NMR spectra respectively.

Synthesis of optically active 1'-pentyl propenyl 2-propynoates

1'-(S)-Pentyl propenyl 2-propynoate [**(*S*)-3**] To a solution of 2-propynoic acid (1.88g, 26.8mmol), (*S*)-1-octen-3-ol [**(*S*)-2**] (4.12g, 32.1mmol) in ether (20mL) was added dropwise a solution of DCC (5.53g, 26.8mmol) and DMAP (4-N,N-dimethylaminopyridine) (330mg, 3mmol) in ether (20mL) at -20°C. After the addition, the mixture was stirred at rt for 24h. The mixture was filtered and the filter cake was washed with small portions of ether. The ether solution was concentrated and the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=15/1). The product **(*S*)-3** was obtained (2.18g, 70% based on **(*S*)-2,** 1.9g of **(*S*)-2** was recovered.). $[\alpha]_D^{25}$ = +3.86 (c=1.0, $CHCl_3$). ot 75°C/5mmHg. ^1H NMR(60 MHz/CCl_4) δ 6.1-5.5 (m, 1H), 5.35-5.05 (m, 3H), 2.8 (s, 1H), 1.6-1.1 (m, 8H), 0.9 (t, J = 6 Hz,

3H) ppm; IR (neat): 3300, 2200, 1720, 1230, 990, 910, 760 cm^{-1}; MS m/e: 181(M^++1), 151, 137, 111, 95, 71, 69, 57, 53, 43. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.25; H, 9.02.

1'-(R)-Pentyl propenyl 2-propynoate [**(*R*)-3**] was synthesized similarly from (***R***)-**2**. $[\alpha]_D^{25}$ = -3.85 (c=1.0, $CHCl_3$) for **(R)-3**.

Palladium acetate-catalyzed cyclization of allylic 2-propynotes

2-(E)-Bromomethylene-3-bromomethyl-4-pentyl-γ-butyrolactone [**(3*R*, 4*S*)-4** + **(3*S*, 4*S*)-4**] To a solution of **(*S*)-3** (180mg, 1mmol), $CuBr_2$ (895mg, 4mmol), and LiBr (350mg, 4mmol) in HOAc (10mL) was added $Pd(OAc)_2$ (11mg, 0.05mmol). The reaction was then stirred at rt and monitored by TLC (eluent: petroleum ether/ethyl acetate=10/1). After the reaction was complete, ethyl acetate (60 mL) was added and then the mixture was washed with water (1 x 5mL) and brine (2 x 5mL). The ether layer was dried ($MgSO_4$) and concentrated. The yellow residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate=10/1) giving **4** [305mg, 90%, **(3*R*, 4*S*)-4** : **(3*S*, 4*S*)-4** = 71 : 29]. ot 160°C/1mmHg. ^1H NMR (200MHz/$CDCl_3$) δ 7.18 [d, J=1.5Hz, 0.71H (*trans* isomer)], 7.10 [d, J=1.5Hz, 0.29H (*cis* isomer)], 4.58 [quint, J=5.8Hz, 0.29H (*cis* isomer)], 4.40 [td, J=6.0, 4.2Hz, 0.71H (*trans* isomer)], 3.60 [d, J=6.0Hz, 1 42H (*trans* isomer)], 3.52 [m, 0.58H (*cis* isomer)], 3.16 (m, 1H), 1.70 (t, J=7.0Hz, 2H), 1.40 (m, 6H), 0.96 (t, J=6.0Hz, 3H) ppm; IR (neat): 3050, 1770, 1630, 1180, 840, 770, 700, 620, 550cm^{-1}; MS m/e(%): 343 [M^+(^{81}Br)+1] (10), 341 [M^+(^{81}Br, ^{79}Br)+1] (25), 339 [M^+(^{81}Br)+1] (11), 261 (3.9), 259 (4.5), 161 (100), 159 (91), 139 (16), 137 (12), 95, 93, 43. Anal. Calcd for $C_{11}H_{16}Br_2O_2$: C, 38.85; H, 4.74. Found: C, 38.87; H, 4.53.

2-(E)-Bromomethylene-3-bromomethyl-4-pentyl-γ-butyrolactone [**(3*S*, 4*R*)-4** + **(3*R*, 4*R*)-4**] was synthesized similarly starting from (***R***)-**3**.

The Hydrolysis of dibromosubstituted derivatives of α-methylene-γ-butyrolactone

2-(E)-Bromomethylene-3(S)-hydroxymethyl-4(S)-pentyl-γ-butyrolactone **(3*S*, 4*S*)-5.** To a solution of **(3*R*, 4*S*)-4** + **(3*S*, 4*S*)-4** (340mg, 1.0mmol) in DMSO-water (1 : 1) (10mL) was added $CaCO_3$ (500mg, 5.0mmol). After refluxing for 30h, the reaction mixture was cooled to room temperature, filtered through a pad of celite and extracted with ether (10mL × 5). The combined organic solution was washed with brine, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: petroleum ether: ethyl acetate = 7 : 3) to yield **(3*S*, 4*S*)-5** (110mg, 39.1%) and **(3*R*, 4*S*)-5** (45mg, 16%). oil. $[\alpha]_D^{25}$ = -6.82 (c=1.1, $CHCl_3$) for **(3*S*, 4*S*)-5**. ^1H NMR (200MHz/$CDCl_3$) δ : **(3*S*, 4*S*)-5** 7.06(d, J=2Hz, 1H), 4.36-4.24 (q, J=6Hz, 1H), 3.74 (d, J = 6Hz, 2H), 3.30 (brs, 1H), 3.0-2.9 (m, 1H), 1.6-1.1 (m, 8H), 0.90 (t, J=7Hz, 3H) ppm; IR (neat): 3400, 2950, 1760, 1630, 1170, 770, 700cm^{-1}; MS m/e(%): 279 (18), 277 (17), 248 (8.4), 246 (8.9), 207 (13), 205 (13), 167 (46), 97 (100). Anal. Calcd for $C_{11}H_{17}BrO_3$: C, 47.67; H, 6.18. Found: C, 47.81; H, 6.50.

2-(E)-Bromomethylene-3(R)-hydroxymethyl-4(R)-pentyl-γ-butyrolactone (**3*R*, 4*R*)-5** was synthesized similarly. $[\alpha]_D^{25}$ = +6.79(c=1.0, $CHCl_3$) for (**3*R*, 4*R*)-5.**

Reduction of vinyl bromide bond of 5 by Zn-Ag

3(S)-Hydroxymethyl-4(S)-pentyl-α-methylene-γ-butyrolactone (**3*S*, 4*S*)-6** Aqueous 10% hydrochloric acid (3.0 mL) was added to zinc dust (0.50 g, 7.8 mmol) with stirring. Five minutes after, the liquid was decanted and the zinc was washed with acetone (2 x 5 mL) and ether (5 mL). A suspension of silver acetate (20.0 mg, 0.12 mmol) in boiling HOAc (3.5 mL) was added under stirring. After 1 minute, the supernatant was decanted and the Zn-Ag couple was washed with HOAc (5 mL), ether (4 x 5 mL) and MeOH (5 mL). To this couple was added a solution of (**3*S*, 4*S*)-5** (0.42 g, 15.2 mmol) in MeOH (2.5 mL), the reaction was complete after 5 h at 70 °C. The Zn-Ag couple was filtered off and washed with MeOH. The filtrate was evaporated, the residue was dissolved in ethyl acetate and washed with 5% hydrochloric acid. The solution was dried and then evaporated to yield (**3*S*, 4*S*)-6** (0.27 g, 90%). oil. $[\alpha]_D^{25}$ = -8.64 (c = 1.1, $CHCl_3$). ^1H NMR (300MHz/$CDCl_3$) δ : 6.33 (d, J = 2.58Hz, 1H), 5.72 (d, J = 2.19Hz, 1H), 4.41 (m, 1H), 3.76 (d, J = 6.25Hz, 2H), 2.88 (m, 1H), 1.70 (m, 2H), 1.55-1.23 (m, 6H), 0.89 (m, 3H) ppm; IR (neat): 3400, 2920, 2850, 1760, 1660, 1465, 1270, 720cm^{-1}; MS m/e(%): 199 (M^++1, 12.25), 181 (6.02), 168 (22.25), 139 (11.09), 127 (43.80), 97 (100.0), 43 (22.44); HRMS for $C_{11}H_{18}O_3$: 198.1256. Found: 198.1286.

3(R)-Hydroxymethyl-4(R)-pentyl-α-methylene-γ-butyrolactone (**3*R*, 4*R*)-6** was synthesized similarly from (**3*R*, 4*R*)-5**. $[\alpha]_D^{25}$ = +8.24 (c=1.0, $CHCl_3$) for (**3*R*, 4*R*)-6**.

Protection of the exo-carbon-carbon double bond in the lactone 6 by PhSH

2-Phenylthiomethyl-3(S)-hydroxymethyl-4(S)-Pentyl-γ-butyrolactone [(**3*S*, 4*S*)-7**] Thiophenol (0.26 mL, 2.54 mmol) and triethylamine (0.28 mL, 2.0 mmol) were added to a stirred solution of (**3*S*, 4*S*)-6** (0.22 g, 11.1 mmol) in THF (6.0 mL) at rt. After 24h, the reaction mixture was treated with acetic acid until pH=7. Water (8 mL) was added, and the mixture was extracted with ether (4 x 10 mL). The organic layer was washed with sat. $NaHCO_3$ and brine, and dried. The solvent was evaporated and column chromatography of the crude products afforded the lactone (**3*S*, 4*S*)-7** (0.31 g, 91%) as an oil. $[\alpha]_D^{25}$ = -19.7 (c=1.5, $CHCl_3$). ^1H NMR (300 Mhz / $CDCl_3$) δ : 7.42-7.23 (m, 5H), 4.25 (m, 1H), 3.90-3.70 (m, 1H), 3.62 (dd, J_1=3.68Hz, J_2= 13.64Hz, 1H), 3.02 (dd, J_1 = 8.72, J_2 = 13.62Hz, 1H), 2.86 (m, 1H), 2.25 (m, 1H), 1.86-1.20 (m, 1H), 0.88 (t, J = 3.33Hz, 3H) ppm; IR (Nujol film): 3450, 2920, 2850, 1760, 1580, 1480, 1440, 1190, 740, 690cm^{-1}; MS m/e(%): 309 (M^+ + 1, 82.38), 308 (M^+, 100.0), 291 (M^+ - OH, 20.16), 199 (M^+ - SPh, 1.70), 123 (37.31), 109 (13.33), 77 (3.51), 65 (5.46); Anal. Calcd for $C_{17}H_{24}O_3S$: C, 66.20; H, 7.84. Found: C, 66.01; H, 8.01.

2-Phenylthiomethyl-3(R)-hydroxymethyl-4(R)-Pentyl-γ-butyrolactone [**(3*R*, 4*R*)-7**] was synthesized similarly. $[\alpha]_D^{25}$ = +20.1 (c=1.55, $CHCl_3$) for **(3*R*, 4*R*)-7.**

Synthesis of the target molecules

(-)-Methylenolactocin A solution of **(3*S*, 4*S*)-7** (90 mg, 0.3 mmol) in DMF(1 mL) was added dropwise at 0 °C to pyridinium dichromate (1.10g, 3 mmol) in DMF (10 mL). The mixture was stirred at rt for 40 h, diluted with water (20 mL) and extracted with ether. The ethereal extract was washed with brine, dried ($MgSO_4$) and evaporated to give a solid residue which was not further purified. The residue was dissolved in MeOH (4.05 mL) containing benzene (0.13 mL) and water (0.89 mL), which was treated with sodium metaperiodate (43 mg). After stirring for ca. 50 h, the product was extracted with CH_2Cl_2. The extract was concentrated and heated at 110 °C in toluene (4 mL) for 5 h. Evaporation of the solvent under reduced pressure afforded a crude oil. Column chromatography afforded (-)-Methylenolactocin. Yield: 45 mg (75%). $[\alpha]_D^{25}$ = -6.87 (c=0.53; MeOH). Its ^{1}H NMR, IR and MS was identical with the reported data.[5]

(±)-Methylenolactocin was prepared similarly. $[\alpha]_D^{25}$ = +6.78 (c, 0.51; MeOH).

Synthesis of methyl ester of (+)-methylenolactocin [**(+)-10**] A solution of **(3*R*, 4*R*)-7** (180 mg, 0.59 mmol) in DMF (2mL) was added dropwise at 0 °C to pyridinium dichromate (2.20g, 6 mmol) in DMF (20 mL). The mixture was stirred at rt for 40 h, diluted with water (40 mL) and extracted with ether. The ethereal extract was washed with brine, concentrated and treated with CH_2N_2. After usual workup **(3*S*, 4*R*)-9** was obtained by column chromatography as an oil. Yield: 160 mg (82%). $[\alpha]_D^{25}$ = +23.35 (c=0.55, $CHCl_3$). ^{1}H NMR (300MHz/$CDCl_3$) δ : 7.39-7.23 (m, 5H), 4.40 (dt, J_1 = 4.47Hz, J_2 = 8.4Hz, 1H), 3.73 (s, 3H), 3.52 (dd, J_1 = 3.82Hz, J_2 = 13.63Hz, 1H), 3.34 (m, 1H), 3.09 (m, 2H), 1.70 (m, 2H), 1.60-1.20 (m, 6H), 0.89 (t, J = 6.34Hz, 3H) ppm; IR (Nujol film): 2900, 2840, 1760, 1720, 1460, 1380, 1165, 1010cm^{-1}; MS m/e(%): 337 (M^++1, 20.09), 336 (M^+, 59.72), 305 (M^+-OMe, 1.52), 277 (M^+-SPh, 5.30), 180 (100.0), 135 (56.41), 123 (63.64), 94 (35.58), 77 (12.25), 43 (24.07); HRMS Calcd for $C_{18}H_{24}O_4S$: 336.1395 Found: 336.1392.

(3*S*, 4*S*)-9 (70 mg, 0.21 mmol) in CH_2Cl_2 (2.8 mL) was added drop by drop a solution of m-CPBA (49.5 mg, 0.23 mmol) in CH_2Cl_2 (0.7 mL) at -10^{0}C. The mixture was stirred for 10 min. After usual workup, a crude oil was obtained. The residue was heated at 110 °C in toluene (5 mL) for 5h. Evaporation of the solvent under reduced pressure gave a crude oil. Column chromatography afforded methyl ester of (+)-Methylenolactocin [(+)-**10**]. Yield: 45 mg (95%). $[\alpha]_D^{25}$ = -7.35 (c=0.4; $CHCl_3$). ν_{max}(neat)/cm^{-1} 2950, 1770,1740,1660, 1460 and 1260; ^{1}H NMR (300MHz/$CDCl_3$) δ_H (300 MHz, $CDCl_3$) 0.90 (3H, t, *J* =6.91Hz), 1.20-1.60 (6H, m), 1.75 (2H, m), 3.58 (1H, m), 4.80 (1H, q, *J* =5.88 Hz), 5.91 (1H, d, *J* =2.66 Hz), 6.41 (1H, d, *J* =3.05 Hz); MS *m/z* 227 (M^++1), 195, 166, 67; HR-MS (EI): found: 226.1206, calcd. 226.1205 for $C_{12}H_{18}O_4$,

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