A Palladium(II)-Catalyzed Construction of α-Methylene-γ-butyrolactones in Optically Active Form. Total Synthesis of (−)-Methylenolactocin

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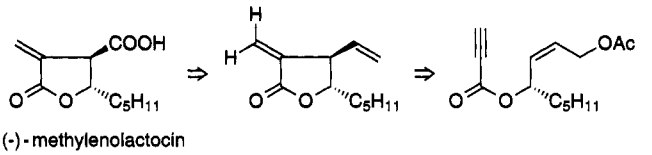
The synthetic challenge of optically active α-methylene-γ-butyrolactone derivatives has stimulated much activity because the α-methylene-γ-butyrolactone is found as a basic structural unit in a wide range of important, naturally occurring compounds.[1] Also, γ-butyrolactones are versatile intermediates in organic synthesis and are widely used in the synthesis of natural products.[2] Much effort has been focused on the enantioselective entry to functionalized γ-butyrolactones, and several such methods have been developed.[1-3]

Methylenolactocin, a small but richly functionalized and isomerization-prone antibiotic, has attracted renewed interest because of its selective antibacterial activity against Gram-positive bacteria and its antitumor activity.[4] Methylenolactocin was first isolated from the culture filtrate of Penicillium sp. by Nakayama and co-workers in 1988.[4] The only example of its total synthesis was reported by Greene in 1992.[5] The key intermediate in this approach was chiral 3-phenylcyclobutanone, which was obtained by an asymmetric [2 + 2] cycloaddition reaction. Recently, Honda and co-workers prepared this chiral key intermediate by employing an enantioselective deprotonation strategy and achieved the formal synthesis of (−)-methylenolactocin.[6]

In this paper, we wish to report the total synthesis of (−)-methylenolactocin, starting from an optically active, functionalized allylic alcohol.

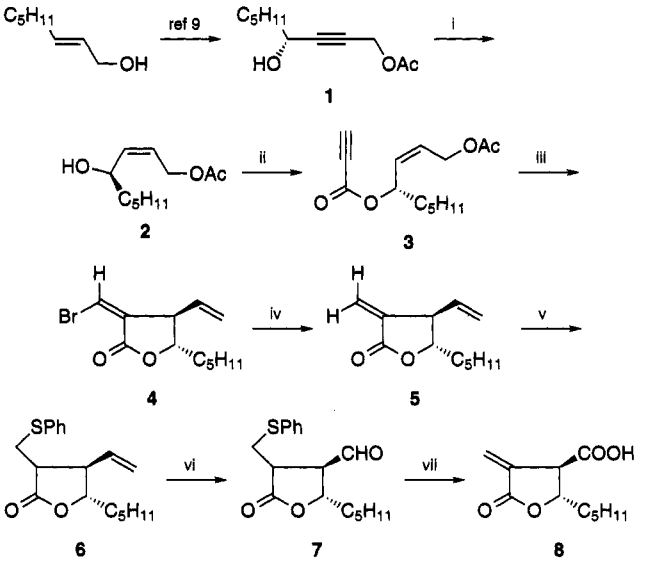
Our approach (retrosynthetic plan: Scheme 1) is based to a large extent on our recent results on the stereochemistry of the palladium(II)-catalyzed ring closure of acyclic allylic 2-alkynoates.[7] This reaction constitutes a highly efficient method for constructing a stereodefined α-methylene-γ-butyrolactone in a single operation via an intramolecular Pd(II)-catalyzed cyclization.

Scheme 1



(-)-methylenolactocin

Scheme 2[a]



[a] Reagent and conditions: (i) P_2–Ni, $NH_2CH_2CH_2NH_2$, EtOH (95%), H_2 (1 atm), rt; (ii) propynoic acid, DEAD, PPh_3, THF, rt; (iii) LiBr, $Pd(OAc)_2$ (0.05 eq), HOAc, rt; (iv) Zn–Ag, MeOH; (v) NEt_3, PhSH, THF, rt; (vi) O_3, MeOH–CH_2Cl_2, −78 °C; (vii) (a) PDC, DMF, 0 °C to rt; (b) $NaIO_4$, MeOH–benzene–H_2O, rt; (c) toluene, reflux.

Readily available, optically active ynol 1-acetoxy-2-nonyn-4(*R*)-ol **1**,[8] prepared in a manner similar to the method reported by Kibayashi and co-workers,[9] was converted conventionally in 90% yield to the corresponding enol **2** (Scheme 2). Enol **2** was directly esterified with propynoic acid, by the Mitsunobu method, in the presence of DEAD and PPh_3, to afford acyclic substrate **3** in 85% yield with inversion of configuration of the secondary carbinol center.[10]

The intramolecular cyclization of **3** was accomplished under mild conditions (LiBr (4 equiv), $Pd(OAc)_2$ (0.05 equiv), HOAc, rt). The ring product **4** was obtained in 65% yield with extremely high diastereoselectivity. No other stereoisomer was isolated or detected. Having the basic skeleton and the defined stereochemistry of our target, we next turned our attention to the selective oxidation of the carbon–carbon double bond at the β-position of the lactone ring. First, the vinyl bromide of **4** was reduced with Zn–Ag couple in almost quantitative yield, under Heathcock's conditions.[11] The direct oxidation of this reduction product, by many methods, failed to afford the desired product. To differentiate the two carbon–carbon double bonds in the lactone ring, a Michael addition reaction with PhSH in the presence of

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a weak base (NEt_3) was performed.[12] A single addition product **6**, in which only the electron-deficient C=C bond was protected, was produced in good yield (93%).

Ozonolysis of **6** in a mixture of MeOH and CH_2Cl_2 at −78 °C afforded an unstable aldehyde **7** with retention of the sulfide, which was further oxidized to the carboxylic acid with PDC in DMF,[13] without further purification. Completion of the synthesis of methylenolactocin was accomplished via deprotection of the C=C double bond. The α-methylene unit was unmasked by sodium metaperiodate oxidation in aqueous methanol followed by sulfoxide thermolysis in toluene to give (−)-methylenolactocin (60% from **6** to **8**). The synthetic **8** ($[\alpha]^{25}_D$ = −6.85° (*c*, 0.54; MeOH) provided characterization data that were identical with reported data ($[\alpha]^{25}_D$ = −6.8° (*c*, 0.5; MeOH))[5] in all respects (^{1}H NMR, MS, IR).[4]

In conclusion, enantiopure (−)-methylenolactocin has been synthesized starting from an acyclic ester precursor. This approach, in which stereoselectivity relies on the template role of the palladium(II) in an intramolecular cyclization reaction, should find further application in natural product synthesis. It is worthy of note that this method permits the synthesis of the target molecule in either enantiomeric form, by simply starting with one or the other configuration of the same allylic alcohol.

Experimental Section

Materials. 1-Acetoxy-2-nonyn-4(*R*)-ol (**1**)[9] was prepared as reported.

1-Acetoxy-2(*Z*)-nonen-4(*R*)-ol (2). To a solution of Ni(OAc)$_2$·4H$_2$O (2.73 g, 11 mmol) in 95% ethanol (190 mL) was added a suspension of $NaBH_4$ (0.9 g, 24 mmol) in 95% ethanol (15 mL) under hydrogen atmosphere. Then ethylenediamine (4 mL) was added dropwise, the reaction mixture was stirred under H_2 for 10 min, and the alcohol **1** (23.6 g, 0.11 mmol) was added into the reaction mixture. After the mixture was stirred under 1 atm of hydrogen at rt for 24 h, the catalyst was filtered off and the solvent was removed. The residue was added to 20 mL water, extracted with ethyl acetate, and dried by $MgSO_4$. The pure product **2** was obtained by flash column chromatography: yield 19.5 g (90%); $[\alpha]^{25}_D$ = 22.1° (*c*, 2.0; $CHCl_3$); IR (neat) 3400, 2920, 2850, 1740, 1460, 1370, 1240, 1030, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.67−5.56 (m, 2H), 4.85−4.78 (m, 1H), 4.57−4.45 (m, 2H), 2.13−2.02 (br, 1H), 2.04 (s, 3H), 1.62−1.23 (m, 8H), 0.89 (t, *J* = 6.93 Hz, 3H); MS *m/e* 201 (0.08), 183 (M^+ − OH, 13.85), 141 (M^+ − OAc, 4.00), 129 (M^+ − C_5H_{11}, 1.86), 123 (M^+ − OAc − H_2O, 18.31), 99 (20.34), 81 (10.40), 71 (14.44), 69 (100.00), 55 (12.19); HRMS calcd for $C_9H_{16}O$ (M^+ − HOAc) 140.1201, found 140.1187.

1′(*S*)-Pentyl-4′-acetoxy-2′(*Z*)-butenyl 2-Propynoate (3). A solution of PPh_3 (2.23 g, 8.5 mmol) in THF (10 mL) was added dropwise to a solution of DEAD (1.6 g, 9 mmol), propynoic acid (0.63 g, 9 mmol), and **2** (0.89 g, 4.5 mmol) in THF (5 mL) at room temperature. After the mixture was stirred overnight at rt, the solvent was evaporated in vacuo. Et_2O was added into the residue, the precipitate was removed by filtration, and the filtrate was evaporated in vacuo. Then the crude product was submitted to chromatography on silica gel using petroleum ether/ethyl acetate (15:1) as the eluent to afford **3**: yield 0.98 g (85%); $[\alpha]^{25}_D$ = 47.5° (*c*, 1.0; $CHCl_3$); IR (neat) 3250, 2850, 2100, 1740, 1720, 1460, 1380, 1240, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.74−5.69 (m, 1H), 5.58−5.52 (m, 2H), 4.76−4.70 (m, 2H), 2.88 (s, 1H), 2.06 (s, 3H), 1.85−1.5 (m, 2H), 1.4−1.25 (m, 6H), 0.89 (t, *J* = 5.79 Hz, 3H); MS *m/e* 209 (M^+ − 43, 0.22), 195 (0.22), 193 (M^+ − OAc, 10.59), 183 (100.00), 149 (1.65), 125 (11.23), 123 (79.65), 109 (8.45), 69 (15.55), 53 (38.59); HRMS calcd for $C_{12}H_{16}O_2$ (M^+ − HOAc) 192.1150, found 192.1120.

3(*S*)-Pentyl-2(*R*)-vinyl-1(*Z*)-(bromomethylene)-γ-butyrolactone (4). To a solution of **3** (0.25 g, 1 mmol) and LiBr (0.35 g, 4 mmol) in HOAc (5 mL) was added $Pd(OAc)_2$ (12 mg, 0.05 mmol) with stirring at rt. The reaction was carried out at rt for 27 h (monitored by TLC on silica gel). After the reaction was complete, ethyl acetate was added, and then the organic layer was washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude product was submitted to column chromatography to yield **4**: yield 0.19 g (65%); $[\alpha]^{25}_D$ = −86.4° (*c*, 1.2; $CHCl_3$); IR (neat) 3050, 2950, 2850, 1770, 1630, 1260, 1180, 1100, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 6.74 (d, *J* = 2.75 Hz, 1H), 5.73−5.61 (m, 1H), 5.35−5.25 (m, 1H), 4.13 (td, J_1 = 7.56 Hz, J_2 = 4.8 Hz, 1H), 3.26 (td, J_1 = 8.04 Hz, J_2 = 2.74 Hz, 1H), 1.70 (m, 2H), 1.36−1.30 (m, 6H), 0.89 (t, *J* = 6.76 Hz, 3H); MS *m/e* 275 (M^+ (^{81}Br) + 1, 11.18), 274 (M^+ (^{81}Br), 1.67), 273 (M^+ (^{79}Br) + 1, 11.30), 203 (M^+ (^{81}Br) − C_5H_{11}, 2.81), 201 (M^+ (^{79}Br) − C_5H_{11}, 2.57), 193 (M^+ − Br, 6.60), 174 (M^+ (^{81}Br) − $C_5H_{11}CHO$, 55.85), 172 (M^+ (^{79}Br) − $C_5H_{11}CHO$, 55.98), 146 (12.41), 144 (12.47), 113 (4.72), 93 (100.00), 71 (0.87), 66 (10.45). Anal. Calcd for $C_{12}H_{17}BrO_2$: C, 52.71; H, 6.27. Found: C, 52.30; H, 6.45.

3(*S*)-Pentyl-2(*R*)-vinyl-1(*Z*)-methylene-γ-butyrolactone (5). Aqueous 10% hydrochloric acid (3.5 mL) was added to Zinc dust (0.71 g, 11 mmol) with stirring. After 5 min, the liquid was decanted and the zinc was washed with acetone (2 × 5 mL) and ether (5 mL). A suspension of silver acetate (24.5 mg, 0.15 mmol) in boiling HOAc (3.5 mL) was added under stirring. After 1 min, the supernatant was decanted and the Zn−Ag couple was washed with HOAc (5 mL), ether (4 × 5 mL) and MeOH (5 mL). To this couple was added a solution of **4** (0.6 g, 2.2 mmol) in MeOH (1 mL), and the reaction was complete after 5 min. The Zn−Ag couple was filtered off and washed with MeOH. The filtrate was evaporated, and the residue was dissolved in ethyl acetate and washed with 5% hydrochloric acid. The solution was dried and then evaporated to yield **5** (0.42 g). The reduction product was not stable but was pure enough for further reaction.

3(*S*)-Pentyl-2(*R*)-vinyl-1-[(phenylthio)methyl]-γ-butyrolactone (6). Benzenethiol (0.3 mL, 3.0 mmol) and triethylamine (0.35 mL, 2.5 mmol) were added to a stirred solution of **5** (0.26 g, 1.35 mmol) in THF (6.5 mL) at rt. After 24 h, the reaction mixture was treated with acetic acid until pH = 7. Water (8 mL) was added, and the mixture was extracted with ether (4 × 10 mL). The organic layer was washed with saturated $NaHCO_3$ and brine and dried. The solvent was evaporated, and column chromatography of the crude products afforded the lactone **6** (0.38 g, 93%) as an oil: $[\alpha]^{25}_D$ = 74.7 (*c*, 1.0; $CHCl_3$); IR (neat) 2920, 2860, 1780, 1640, 1300, 1190, 1000, 930 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (m, 2H), 7.33−7.27 (m, 2H), 7.24 (m, 1H), 5.70−5.59 (m, 1H), 5.19−5.02 (m, 2H), 3.36 (dd, J_1 = 4.2 Hz, J_2 = 13.7 Hz, 1H), 3.23 (dd, J_1 = 5.36 Hz, J_2 = 13.7 Hz, 1H), 2.84−2.72 (m, 1H), 1.74−1.53 (m, 4H), 1.35−1.27 (m, 4H), 0.9 (t, *J* = 6.7 Hz, 3H); MS *m/e* 304 (M^+), 259, 195, 181, 135, 123 (100.0), 91, 77, 65; HRMS calcd for $C_{18}H_{24}O_2S$ 304.1497, found 304.1459.

3(*S*)-Pentyl-2(*R*)-carbonyl-1-[(phenylthio)methyl]-γ-butyrolactone (7). Lactone **6** (60 mg, 0.2 mmol) in MeOH (3.5 mL) and CH_2Cl_2 (1.8 mL) was ozonized at −78 °C. On completion of the reaction after 5 min, nitrogen was bubbled through the solution. Me_2S (0.3 mL) was added, and the reaction mixture was stirred at −78 °C for 2 h and warmed to rt. The solvent was evaporated, leaving the crude unstable aldehyde as a liquid, which was used without further purification: ^{1}H NMR (CCl_4, 90 MHz) δ 9.7 (s, 1H), 7.2 (m, 5H), 4.4−4.1 (m, 1H), 3.6−3.4 (m, 1H), 3.1−2.8 (m, 3H), 1.8−1.5 (m, 2H), 1.5−1.1 (m, 6H), 0.9 (t, *J* = 6.0 Hz, 3H).

Methylenolactocin (8). Crude aldehyde **7** in DMF (4 mL) was added dropwise at 0 °C to pyridinium dichromate (1.5 g, 4 mmol) in DMF (15 mL). The mixture was stirred at rt for 24 h, diluted with water (30 mL), and extracted with ether. The extract was dried and evaporated to give a residue. The residue was dissolved in MeOH (3.0 mL) containing benzene (0.1 mL) and water (0.6 mL), which was treated with sodium metaperiodate (30 mg). After being stirred 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 **8**: yield 50 mg (60%); $[\alpha]^{25}_D$ = −6.85° (*c*, 0.54; MeOH); IR (Nujol film) 3360, 3150, 3050, 2930, 1760,

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1710, 1660, 1410, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 6.50 (d, J = 3.0 Hz, 1H), 6.05 (d, J = 3.0 Hz, 1H), 4.85 (m, 1H), 3.65 (m, 1H), 1.7 (m, 2H), 1.5–1.1 (m, 6H), 0.9 (m, 3H); MS *m/e* 213 ($M^+ + 1$), 195, 183, 167, 142 (100.0), 124, 113, 99, 71, 55.

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Supplementary Material Available: ^1H NMR spectra for compounds **2**, **3**, and **6** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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