Synthesis of Natural α-Methylene Butyrolactones via Tungsten−π-Allyl Complexes. Total Synthesis of (−)-Methylenolactocin

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The synthesis of optically pure α-methylene butyrolactones has received considerable attention because of their wide occurrence in bioactive natural products.[1] This structural unit is also synthetically interesting as it is a useful building block for natural products such as alkaloids, macrocyclic antibiotics, and pheromones.[2] Numerous synthetic methods[1,2] have been developed for the synthesis of chiral α-methylene butyrolactones. We recently reported[3] the synthesis of racemic α-methylene butyrolactones via tungsten−π-allyl compounds **1a** as shown in Scheme 1 (eq 1). Ligand substitution of this dicarbonyl π-allyl complex with NO^+ and X^- generated a reactive allyl species[4] (**1b**) which reacted with R″CHO to yield *trans*-methylenebutyrolactones in high yields.[3b,4] This synthetic method starts with cheap and easily prepared chloropropargyl derivatives.[4] In this paper, we report application of this method for the synthesis of natural (−)-methylenolactocin **2**, which was first isolated from the culture filtrate of *Penicillium* sp. in 1988.[5] Its enantioselective synthesis[6] is currently receiving considerable attention because of its antibacterial and antitumor activities.

Our synthetic protocol is depicted in Scheme 2. The starting (2*S*-*trans*)-3-pentyloxiranemethanol **3** is readily prepared from Sharpless asymmetric epoxidation of 2-octenol.[7] After fractional crystallization, the ee value of compound **3** is estimated to be 98% according to GC analysis of its Mosher ester derivative. This alcohol is subsequently transformed into alkyn-3-ol **4** in 56% yield according to the method reported by Takano.[8] Treatment of **4** with TBSCl and imidazole in DMF gave the 3-siloxyalkyne **5** in 93% yield. Alkylation of **5** with paraformaldehyde followed by tosylation gave an 83% yield of propargyl tosylate **6**. Metalation of compound **6** with $NaCpW(CO)_3$ proceeded smoothly at 23 °C to yield chiral tungsten−propargyl complex **7** in 91% yield. Acidification of **7** with CF_3SO_3H catalyst (0.20 equiv) in cold CH_2Cl_2 (−20 °C) led to intramolecular alkoxycarbonylation, giving chiral tungsten−*syn*-π-allyl complex **8** in 70% yield. The *syn*-configuration of this π-allyl complex was indicated[3b] by the coupling constant J_{34} = 3.6 Hz and further confirmed by X-ray diffraction study;[9] its ORTEP drawing is shown in Figure 1. The C(12) carbon configuration of **8** revealed that the intramolecular alkoxycarbonylation for conversion of **7** to **8** proceeded with retention of stereochemistry. Substitutiion of the two

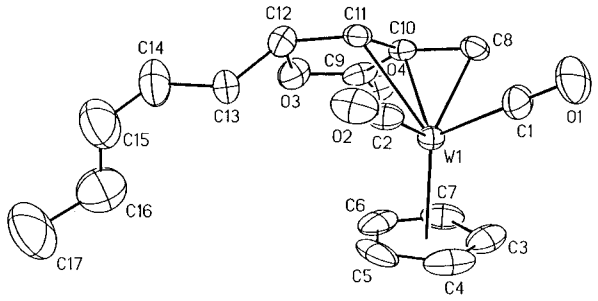
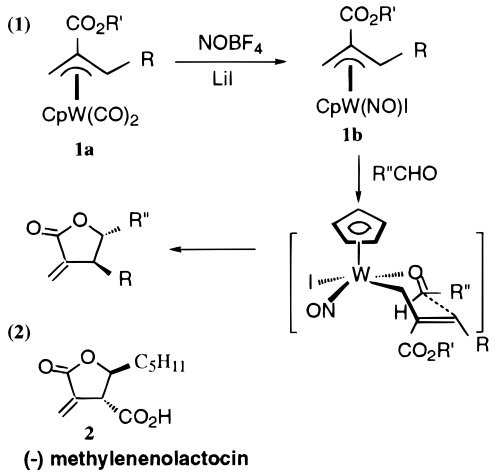


Figure 1. Molecular structure of optically active tungsten−π-allyl complex **8**.

Scheme 1



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(9) Compound **8** crystallizes in the monoclinic space group $P2_12_12_1$, orthorhombic, a = 7.2500(1) Å, b = 11.0386(2) Å, c = 21.4606(2) Å, V = 1717.5(6) Å^3, Z = 4. Data were collected on a Siemens R3m/V diffractometer, using Mo Kα radiation. Final R = 0.0268, R_w = 0.0250 for 9202 reflections >3.0σ(I) out of 10 107 unique reflections.

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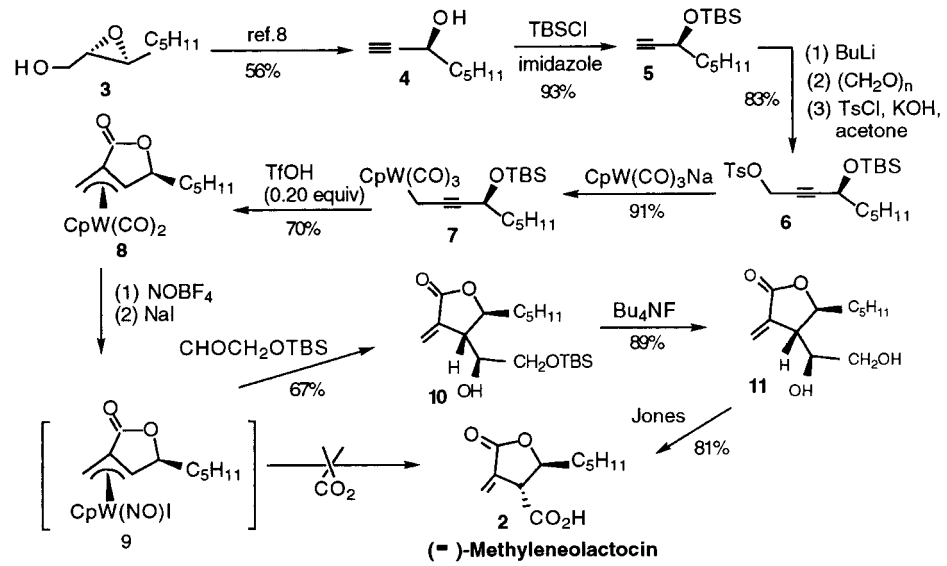
Scheme 2



carbonyls of **8** via sequential treatment with $NOBF_4$ and NaI in CH_3CN (0 °C) generated the corresponding CpW(NO)I(π-allyl)[3,4] derivative **9** which was used in situ to achieve better yields of reaction products. Compounds such as **9** can undergo highly diastereoselective condensation with aldehydes and ketones.[3b,4] Attempts to perform carboxylation of species **9** with flowing CO_2 were unsuccessful, and no (−)-methylenolactocin could be found over the temperature ranges −40 to 23 °C.

To circumvent this synthetic problem, species **9** was treated with $TBSOCH_2CHO$ in CH_3CN at 23 °C (6 h) to yield *trans*-α-methylenebutyrolactone **10** as a single stereoisomer in 67% yield. The *trans*-configuration of **10** was determined by a proton NOE experiment. Although the CH(OH) configuration of **10** is not determined, it is presumbly to have *anti* configuration according to our previous studies on closely related system.[3a−c] The reaction of this type has been elucidated to involve a chairlike transition state to control the stereochemistry of the products.[3a−c,4] Desilylation of compound **10** was achieved in the presence of Bu_4NF to give the diol **11** in 89% yield, and Jones oxidation of **11** effected oxidative cleavage[10] of the 1,2-diol **11** to form (−)-methylenolactocin **2** in 81% yield. Spectral data of **2** {$[\alpha]^{25}_D = -6.77$ (c = 0.52, MeOH)} in this synthesis are virtually identical to those of the authentic sample {$[\alpha]^{25}_D = -6.8$ (c = 0.5, MeOH)} reported in the literature.[5,6]

In conclusion, we have demonstrated that tungsten−π-allyl complexes can be used for total synthesis of natural (−)-methylenolactocin **2**. This route proves to be efficient because only a few steps were involved based on chiral propargyl tosylate that was easily prepared according to literature papers.[8,11] The key step in this synthesis relies on intramolecular alkoxycarbonylation of tungsten-propargyl compounds to yield chiral tungsten−π-γ-lactonyl complex, ultimately preceding to (−)-methylenolactocin according to chemistry of tungsten−π-allyl compounds.

Experimental Section

Unless otherwise noted, all reactions were carried out under nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. Dichloromethane was dried over CaH_2 and distilled before use. $W(CO)_6$, sodium, dicyclopentadiene, tosyl chloride, triflic acid, *tert*-butyl hydroperoxide, $Ti(OPr^i)_4$, (+)-diethyl tartarate, 2-octenol, and sodium were obtained commercially and used without purification. $NaCpW(CO)_3$ was prepared[12] by stirring of $[CpW(CO)_3]_2$ with sodium amalgam in THF for 8 h and it was used in situ. The syntheses of organic substrates **3**−**5** followed the methods in the literature reports,[7,8] and spectral data were identical to those of the authentic samples.

(4*S*)-1-Toluene-*p*-sulfonyloxy-4-(*tert*-butyldimethylsiloxy)non-2-yne (6). To a cold (−78 °C) stirred solution of compound **5** (2.80 g, 20.0 mmol) in THF (15.0 mL) was added BuLi (12.5 mL, 1.60 M solution in hexane, 20.0 mmol) under N_2, and the mixture was stirred for 30 min. To this solution was added paraformaldehyde (1.20 g, 40.0 mmol) in THF (10 mL), and the mixture was warmed to 23 °C and stirred for an additional 45 min. The resulting mixture was filtered through a Celite pad, and to the filtrate was added brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated to afford a crude alcohol as a yellow oil (4.59 g, 85%) which was subjected to tosylation without further purification. The above alcohol in acetone (10 mL) was added to a solution of TsCl (3.2 g, 17.1 mmol) dissolved in 25 mL of acetone. To the resulting cooled (0 °C) solution was added slowly a solution of KOH (1.42 g, 25.5 mmol) dissolved in 3 mL of H_2O; stirring was continued for 6 h. The solvent was removed in vacuo, and the residue was dissolved in Et_2O (50 mL), washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated. The resulting crude solid was purified by silica gel chromatography using hexane/ether (9/1) as eluent to afford **6** (7.03 g, 83%): $[\alpha]^{22}_D = -29.0$ (c 0.82; $CHCl_3$); IR (neat) 2112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 4.70 (d, J = 1.4 Hz, 2 H), 4.19 (t, J = 6.4 Hz, 1 H), 2.41 (s, 3 H), 1.47 (m, 2 H), 1.35−1.15 (m, 6 H), 1.84 (m, 12 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 133.1, 129.7, 127.9, 91.1, 75.4, 62.5, 58.0, 38.0, 31.2, 25.6, 24.6, 22.4, 21.5, 18.0, 13.9, −4.6, −5.2; HRMS calcd for $C_{22}H_{36}O_4SSi$ 424.2103, found 424.2108.

Tungsten−η^1-Propargyl Compound (7). To a THF (50 mL) solution of $CpW(CO)_3Na$[12] (5.0 mmol) was slowly added

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compound **6** (2.12 g, 5.0 mmol) in THF (5 mL). The mixture was stirred for 5 h at 23 °C. The solution was evaporated to dryness, and the resulting residue was chromatographed over a short neutral alumina column under medium pressure to yield compound **7** as a yellow oil (2.66 g, 91%): $[\alpha]^{21}_D = -30.5$ (*c* 0.74; $CHCl_3$); IR (neat) 2015, 1915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.47 (s, 5 H), 4.35 (t, $J = 6.6$ Hz, 1H), 1.99 (s, 2 H), 1.68−1.53 (m, 2 H), 1.48−1.20 (m, 6 H), 0.89 (m, 12 H), 0.11 (s, 3 H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.3, 216.4, 216.3, 93.2, 92.7, 82.3, 63.7, 39.6, 31.6, 25.8, 25.1, 22.7, 16.3, 14.1, −4.3, −4.9, −32.1; MS (75 eV, *m/e*) 586 (M^+). Anal. Calcd for $C_{23}H_{34}WSiO_4$: C, 47.09; H, 5.85. Found: C, 47.13; H, 5.87.

Synthesis of CpW(CO_2)(π-γ-lactonyl) Compound (8). To a CH_2Cl_2 (20 mL) solution of **7** (2.90 g, 5.0 mmoL) at −40 °C was slowly added CF_3SO_3H (0.09 mL, 1.0 mmol), and the mixture was stirred for 1 h before the temperature was raised to 0 °C. To the resulting solution was added a saturated $NaHCO_3$ solution (3 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried ($MgSO_4$), concentrated, and eluted through a silica column (diethyl ether/hexane = 1/2) to give **8** as a yellow solid (1.65 g, 70%): $[\alpha]^{26}_D = +68.6°$ (*c* 1.12; $CHCl_3$); IR (Nujol) 1950, 1867, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (s, 5 H), 5.03 (m, 1 H), 3.68 (d, $J = 3.2$ Hz, 1H), 3.07 (d, $J = 3.5$ Hz, 1 H), 1.78−1.22 (m, 9 H), 0.91 (t, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 224.5, 219.7, 175.5, 93.3, 80.7, 70.0, 69.3, 38.5, 31.3, 25.4, 22.2, 19.5, 13.7; MS (75 eV, *m/e*) 472 (M^+). Anal. Calcd for $C_{17}H_{20}WO_4$: C, 43.21; H, 4.27. Found: C, 43.25; H, 4.32.

Condensation of π-Allyl Complex 8 with 2-(*tert*-butyldimethylsiloxy)acetaldehyde. To a stirring CH_3CN (7 mL) solution of π-allyl compound **8** (1.41 g, 3.0 mmol) was slowly added a CH_3CN (2 mL) solution of $NOBF_4$ (0.38 g, 3.3 mmol) at 0 °C. After 30 min, NaI (0.90 g, 6.0 mmol) was added, and the mixture was stirred for additional 30 min and treated with $TBSOCH_2CHO$ (0.57 g, 3.3 mmol) at 0 °C. The solution was warmed to 23 °C and stirred for 4 h to produce a dark orange precipitate. The solution was treated with $NaHCO_3$, concentrated, and eluted on a preparative TLC plate (diethyl ether/hexane = 7/1) to give compound **10** as a yellow oil (0.68 g, 67%): $[\alpha]^{24}_D = -5.4°$ (*c* 0.58; $CHCl_3$); IR (neat) 3450 (br), 1770, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.36 (d, $J = 2.4$ Hz, 1 H), 5.79 (d, $J = 2.4$ Hz, 1 H), 4.43 (m, 1 H), 3.68−3.45 (m, 3 H), 2.91 (m, 1 H), 1.63−1.22 (m, 8 H), 0.88 (13H, 2s + m), 0.07 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 135.3, 124.8, 79.5, 72.7, 63.5, 46.9, 36.3, 31.5, 31.3, 25.7, 25.5, 24.4, 22.4, 18.1, 13.8, −5.4; HRMS calcd for $C_{18}H_{34}SiO_4$ 342.2226, found 342.2231.

Deprotection of TBS Ether. Synthesis of Dihydroxylactone (11). To a stirring THF (5 mL, 0 °C) solution of **10** (0.68 g, 2.0 mmol) was added dropwise a 1 M THF solution of Bu_4NF (2.4 mL, 2.4 mmol). Stirring is continued for 1.5 h. The resulting solution was concentrated, and the residue was dissolved in EtOAc, washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The crude compound was chromatographed on silica column (diethyl ether/hexane = 1/1) to give **11** as a light yellow oil (0.40 g, 89%): $[\alpha]^{24}_D = -5.2$ (*c* 0.36; $CHCl_3$); IR (neat) 3450 (br), 1770, 1470 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.28 (d, $J = 1.9$ Hz, 1 H), 5.75 (d, $J = 1.9$ Hz, 1H), 4.39 (m, 1 H), 3.78−3.42 (m, 5 H), 2.80 (m, 1 H), 1.65−1.49 (m, 2 H), 1.48−1.12 (m, 6 H), 0.85 (t, $J = 6.4$ Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.1, 125.5, 80.6, 72.9, 63.4, 47.0, 36.1, 31.4, 24.4, 22.4, 13.9; HRMS calcd for $C_{12}H_{20}O_4$ 228.1361, found 228.1367.

(−)-Methylenolactocin (2). A solution of the dihydroxylactone **11** (0.22 g, 1.0 mmol) in acetone (4 mL) was treated with freshly prepared Jones reagent at 40 °C until a persistent orange color was observed. After the solution was stirred for 5 min (TLC) and cooled to room temperature, 2-propanol was added to destroy the excess reagent. The reaction mixture was diluted with water (2 mL), and acetone was removed under reduced pressure. The residue was extracted with CH_2Cl_2 (3 × 5 mL). The organic extract was washed with brine (4 mL) and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which was purified by a short column of silica gel (diethyl ether/hexane = 4/1) to give (−)-methylenolactocin **2** (0.17 g, 81%): $[\alpha]^{24}_D = -6.77$ (*c* 0.52, MeOH); IR (neat) 3460, 1750, 1660, 1460 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 6.44 (d, $J = 2.9$ Hz, 1H), 6.00 (d, $J = 2.9$ Hz, 1H), 4.78 (m, 1 H), 3.61 (m, 1 H), 1.73 (m, 2 H), 1.52−1.20 (m, 6 H), 0.86 (t, $J = 3.4$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 168.2, 132.4, 125.8, 78.8, 49.5, 35.6, 31.3, 24.4, 22.3, 13.6; HRMS calcd for $C_{11}H_{16}O_4$ 212.1048, found 212.1052.

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Supporting Information Available: ^1H and ^{13}C NMR of all new compounds; tables of crystal data and thermal parameters and ORTEP drawing of compound **8** (28 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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