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Note

Efficient Synthesis of Akolactone A *via* Pd-Catalyzed Carbonylation

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The first synthesis of (+)- and (−)-akolactone A is described by using Pd-catalyzed carbonylation. A comparison of the optical rotation of both enantiomers of akolactone A and the natural compound suggests that the absolute configuration at the 4-position of akolactone A is *R*.

Key words: Pd-catalyzed carbonylation; α,β-unsaturated-γ-lactone

Akolactone A, an α,β-unsaturated butanolide derivative that has shown cytotoxicity toward human tumorial cell lines, has recently been isolated by I.-S. Chen and co-workers from the stem bark of *Litsea akoensis*.[1] The isolated material was determined to be α,β-unsaturated-γ-lactone, connected with a *trans*-olefinic group at the C-2 position. However, its absolute configuration at the C-4 chiral center has not yet been determined. We describe in this paper the first synthesis of both enantiomers of akolactone A *via* Pd-catalyzed cross coupling and carbonylation. We also report the determination of its absolute configuration.

The synthetic method used for both enantiomers of akolactone A is shown in Scheme 1. 1-Tetradecyne (**2**) was prepared by alkylating a lithium acetylide ethylenediamine complex with 1-bromododecane.[2] Hydroalumination of **2** with DIBALH and subsequent iodination afforded vinyl iodide **3**. The results of the Sonogashira cross-coupling reaction[3] of **3** with (*R*)-(+)-3-butyn-2-ol are summarized in Table 1. The most effective catalyst system in this reaction is 5 mol% of $Cl_2Pd(PPh_3)_2$ and 10 mol% of CuI in pyrrolidine.[4] Regioselective hydroalumination of **4** with sodium bis(2-methoxyethoxy)aluminum hydride and subsequent iodination gave vinyl iodide **5**. Pd-catalyzed carbonylation[5,6] and spontaneous lactonization of **5** with 1 atmosphere of CO in the presence of 5 mol% of $Cl_2Pd(PPh_3)_2$ and Et_3N at 50°C finally afforded (−)-akolactone A (**1a**) in a 75% yield. In this reaction, CO insertion proceeded even under 1 atmosphere of CO pressure, although it has often been reported that high pressure (45 atmosphere) was necessary.[7] The ^{1}H- and ^{13}C-NMR, and IR spectra of synthetic **1a** are in good agreement with the reported values.[1] The optical rotation of synthetic **1a** ($[\alpha]_D^{22} = -14.9$, *c* 0.55, $CHCl_3$) is similar to the reported value for naturally occurring akolactone A {$[\alpha]_D^{28} = -13.2$, (*c* 0.10, $CHCl_3$)}.[1] We also synthesized (+)-akolactone A (**1b**) by using (*S*)-(−)-3-butyn-2-ol. The optical rotation of **1b** was +14.6 (*c* 0.36, $CHCl_3$). On the basis of these results, we assigned the absolute configuration of natural akolactone A at the C-4 position to be *R*.

(-)-Akolactone (1a) (+)-Akolactone (1b)

Fig. 1. Structures of Both Enantiomers of Akolactone A.

Experimental

All reactions were carried out under an Ar atmosphere. Silica gel column chromatographic separation was performed on 70–230-mesh silica gel 60. ^{1}H- and ^{13}C-NMR spectra were measured in $CDCl_3$ with a Bruker DRX 500 FT-NMR (500 MHz) spectrometer, and IR spectra were taken with a Jasco FT/IR 480 Plus infrared spectrometer. Optical rotation was recorded by a Jasco DIP-1000 spec-

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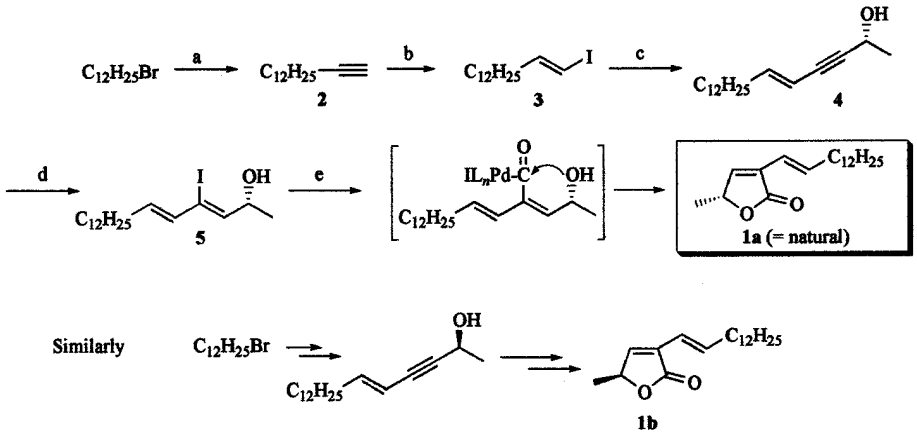
Abbreviations: THF, tetrahydrofuran; DMSO, dimethyl sulfoxide; DIBALH, diisobutylaluminum hydride



Scheme 1. Reagents and Conditions.
(a) 2.0 equivalent of lithium acetylide-ethylenediamine complex (100%). (b) i) DIBALH, hexane; ii) I_2, THF (85%). (c) 5 mol% $Cl_2Pd(PPh_3)_2$, 10 mol% CuI, pyrrolidine, (*R*)-(+)-3-butyn-2-ol (85%). (d) i) sodium bis(2-methoxyethoxy)aluminum hydride, THF; ii) I_2 (87%). (e) 5 mol% $Cl_2Pd(PPh_3)_2$, 1 atm of CO, 2.0 equiv. of Et_3N, 50°C (75%).

Table 1. Sonogashira Cross Coupling of **3** with (*R*)-(+)-3-Butyn-2-ol

Catalyst (5 ml%)[a]	Solvent/Base	Yield (%)
$Pd(PPh_3)_4$	pyrrolidine	18
$Pd(PPh_3)_4$/CuI	pyrrolidine	38
$Pd(PPh_3)_4$/CuI	THF/Et_3N	42
$Cl_2Pd(PPh_3)_2$/CuI	THF/Et_3N	53
$Cl_2Pd(PPh_3)_2$/CuI	pyrrolidine	85

[a] The amount of CuI was 10 mol%.

trometer, and MS spectra were recorded with a Jeol JMS 700 mass spectrometer.

1-Tetradecyne (2). To a suspension of a lithium acetylide-ethylenediamine complex (1.84 g, 20 mmol) in DMSO (10 ml) was added 1-bromododecane (2.49 g, 10 mmol) at 0°C. The reaction mixture was stirred for 12 h at 23°C. After the reaction had been completed, sat. NH_4Cl (10 ml) was added to the mixture. The mixture was extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed over silica gel (hexane) to afford **3** (1.94 g, 100%) as a colorless oil. IR (film) ν_{max} cm^{-1}: 3314, 2925, 2854, 2119, 1466, 629. ^{1}H-NMR ($CDCl_3$, Me_4Si) δ: 0.88 (3H, t, J= 6.9 Hz), 1.25–1.30 (16H, m), 1.93 (1H, t, J=2.6 Hz), 2.18 (2H, dt, J=7.1, 2.6 Hz). ^{13}C-NMR ($CDCl_3$, Me_4Si) δ: 14.11, 18.42, 22.70, 28.53, 28.79, 29.13, 29.36, 29.52, 29.62, 29.64, 29.67, 31.93, 68.01, 84.84.

(E)-1-Iodo-1-tetradecene (3). Compound **2** (1.94 g, 10 mmol) was treated with DIBALH (2.2 ml, 12 mmol) in dry hexane. The reaction mixture was stirred for 12 h at 20°C. After the reaction had been completed, hexane was evaporated, and I_2 (3.05 g, 12 mmol) in THF (10 ml) was added at 0°C. The reaction mixture was treated with 1 N HCl (20 ml) and then extracted with ether. The organic layer was successively washed with sat. $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated. The residue was filtered through silica gel (hexane) to afford **3** (2.74 g, 85%) as a pale yellow oil. This product was used for the next step without further purification. IR (film) ν_{max} cm^{-1}: 3049, 2955, 2924, 2853, 1466, 944. ^{1}H-NMR ($CDCl_3$, Me_4Si) δ: 0.88 (3H, t, J=6.9 Hz), 1.25–1.45 (20H, m), 2.05 (2H, m), 5.97 (1H, d, J= 14.3 Hz), 6.51 (1H, dt, J=14.3, 7.1 Hz). ^{13}C-NMR ($CDCl_3$, Me_4Si) δ: 14.11, 22.70, 28.38, 28.98, 29.13, 29.36, 29.55, 29.64, 29.67, 31.93, 33.83, 36.05, 74.20, 146.85.

(2R,5E)-Octadec-5-en-3-yn-2-ol (4). To a mixture of compound **3** (161 mg, 0.5 mmol) and $Cl_2Pd(PPh_3)_2$ (35 mg, 0.025 mmol) in pyrrolidine (5 ml), (*R*)-(+)-3-butyn-2-ol (36 mg, 0.5 mmol) and CuI (9.5 mg, 0.05 mmol) were added. The reaction mixture was stirred for 12 h at 20°C. After the reaction had been completed, 1 N HCl (20 ml) was added to the mixture. The mixture was extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed over silica gel (hexane/AcOEt=5/1) to afford **4** (112 mg, 85%) as a colorless oil, $[\alpha]_D^{22}$ +13 (*c* 1.5, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3410, 3344, 3021, 2996, 2955, 2919, 2849, 1469, 1092, 958, 607. ^{1}H-NMR ($CDCl_3$, Me_4Si) δ: 0.88 (3H, t, J=6.9 Hz), 1.25–1.45 (20H, m), 1.46 (3H, d, J=6.5 Hz), 1.72 (1H, d, J= 5.2 Hz), 2.10 (2H, m), 4.63 (1H, m), 5.47 (1H, dd, J=15.8, 1.6 Hz), 6.14 (1H, dt, J=15.8, 7.0 Hz). ^{13}C-NMR ($CDCl_3$, Me_4Si) δ: 14.11, 22.70, 24.46, 28.69, 29.11, 29.36, 29.44, 29.58, 29.65, 29.68 (2× C), 31.94, 33.06, 58.89, 82.94, 89.38, 108.77, 145.57.

HREIMS: calcd. for $C_{18}H_{32}O$, 264.2453; found, 264.2471.

(2R,3Z,5E)-4-Iodo-3,5-octadien-2-ol (5). To a solution of compound **4** (132 mg, 0.5 mmol) in THF (3 ml), sodium bis(2-methoxyethoxy) aluminum hydride (0.5 ml, 60% in toluene, 1.7 mmol) was added at 0°C. The reaction mixture was stirred for 5 h, before a solution of iodine (460 mg, 1.8 mmol) in THF (5 ml) was added dropwise. The reaction mixture was stirred for 30 min at 0°C, allowed to warm to 20°C, and quenched with a sat. $Na_2S_2O_3$ solution. The mixture was extracted with ether. The organic solution was successively washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (hexane/AcOEt = 5/1) to give **6** (171 mg, 87%) as a pale yellow oil. This product was used for the next step without further purification; $[\alpha]_D^{26}$ +2.9 (*c* 1.6, $CHCl_3$). IR (film) ν_{max} cm^{-1}: 3346, 2925, 2853, 1637, 1465, 1060, 947. ^{1}H-NMR ($CDCl_3$, Me_4Si) δ: 0.88 (3H, t, J = 6.9 Hz), 1.20–1.60 (20H, m), 1.34 (3H, d, J = 6.6 Hz), 1.79 (1H, br., –OH), 2.17 (2H, m), 4.66 (1H, m), 5.69 (1H, dd, J = 14.5, 0.9 Hz), 5.83 (1H, d, J = 7.5 Hz), 6.04 (1H, dt, J = 14.5, 7.2 Hz) . ^{13}C-NMR ($CDCl_3$, Me_4Si) δ: 14.11, 22.05, 29.24, 29.30, 29.36, 29.47, 29.52, 29.58, 29.61, 29.66, 29.68, 31.93, 31.98, 72.42, 106.02, 131.18, 140.24, 140.60.

(−)-Akolactone A (1a). To a solution of **5** (98 mg, 0.25 mmol) in THF (2 ml) were sequentially added Et_3N (0.14 ml, 0.5 mmol) and $Cl_2Pd(PPh_3)_2$ (9 mg, 12.5 μmol) under 1 atm of CO. The mixture was stirred for 6 h at 50°C. After cooling, the mixture was worked up with ether and brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 5/1) to give **1a** (55 mg, 75%) as a pale yellow oil, $[\alpha]_D^{22}$ −14.9 (*c* 0.55, $CHCl_3$), {natural akolactone A, $[\alpha]_D^{28}$ = −13.2, (*c* 0.10, $CHCl_3$)}.[1] IR (film) ν_{max} cm^{-1}: 3030, 2925, 2853, 1760, 1466, 1318, 1084, 974. ^{1}H-NMR ($CDCl_3$, Me_4Si) δ: 0.88 (3H, t, J = 6.9 Hz), 1.20–1.60 (20H, m), 1.42 (3H, d, J = 6.8 Hz), 2.15 (2H, m), 5.02 (1H, qd, J = 6.7, 1.2 Hz), 6.09 (1H, d, J = 15.9 Hz), 6.79 (1H, dt, J = 15.9, 7.0 Hz), 7.02 (1H, d, J = 1.2 Hz). ^{13}C-NMR ($CDCl_3$, Me_4Si) δ: 14.12, 19.21, 22.70, 28.80, 29.26, 29.37, 29.49, 29.59, 29.66, 29.67, 29.69, 31.94, 33.44, 76.89, 118.31, 129.54, 138.92, 146.76, 172.03. HREIMS: calcd. for $C_{19}H_{32}O_2$, 292.2402; found, 292.2390.

(+)-Akolactone A (1b). $[\alpha]_D^{25}$ +14.6 (*c* 0.36, $CHCl_3$). The ^{1}H- and ^{13}C-NMR, IR, and HRMS spectra were identical with those of **1a**.

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