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CATALYTIC TRANSFER HYDROGENATION OF MYCOEPOXYDIENE

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*Catalytic transfer hydrogenation with hydrogenolysis of mycoepoxydiene (**1**) by ammonium formate/10% Pd-C gave a new compound, deacetylhexahydromycoepoxydiene (**2**), whose structure was determined by spectroscopic and X-ray diffraction experiments. In the primary bioassay, **1**, **2** and hexahydromycoepoxydiene (**3**) showed anticancer activities against HeLa in vitro. The IC_{50} (μg/mL) values were 5.5, 50, and >100, respectively.*

Key words: mycoepoxydiene, catalytic transfer hydrogenation, hydrogenolysis, deacetylhexahydromycoepoxydiene, anticancer activities.

Mycoepoxydiene (**1**) was first isolated from the solid-state fermentation of a rare fungus designated as OSF66617 [1] and later from the liquid-state fermentation of a marine mangrove entophytic fungus (No. 1893) [2]. The first total synthesis [3] and asymmetric total synthesis [4] of **1** has been completed. Compound **1** was found to show cytotoxicity with an IC_{50} (μg/mL) of 2.3 against K562, and of 3.1 against HepG2 [4].

In the ongoing research on the structure-activity relationship of this compound, we prepared hexahydromycoepoxydiene (**3**) by catalytic hydrogenation [5]. In this paper we report another structural modification of **1** by the catalytic transfer hydrogenation reaction.

Compound **1**, $C_{16}H_{18}O_5$, was hydrogenized in EtOH by the catalysis of 10% Pd-C at room temperature to give hexahydromycoepoxydiene, **3**, yield 97%. However, using ammonium formate in MeOH as the source of hydrogen, the catalytic transfer hydrogenation of compound **1** produced a new hexahydrogenation product with deacetylation **2**, yield 90%. In both cases, catalytic hydrogenation and catalytic transfer hydrogenation, hydrogenolysis of the δ-lactone and the other partial was not observed.

The catalytic transfer hydrogenation reaction is attractive especially for small-scale production of diverse products as it requires no special equipment and avoids the handling of potentially hazardous gaseous hydrogen.

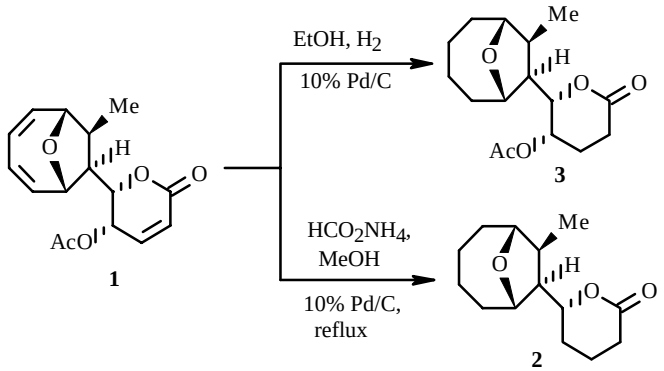

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TABLE 1. NMR Data of **1** and **2** ($CDCl_3$, δ, ppm, J/Hz)

PMR		^{13}C NMR (75.5 MHz)	
1 (500 MHz)	**2** (300 MHz)	**1** (DEPT)	**2** (DEPT)
7.02 (1H, dd, 10, 6.0)	4.33 (1H, td, 2.4, 9.3)	170.00 (C)	171.30 (C)
6.21 (1H, d, 10)	4.07 (1H, t, 4.5)	162.10 (C)	84.18 (CH)
6.09 (1H, bdd, 11, 6)	3.96 (1H, dd, 3.0, 8.1)	140.20 (CH)	79.87 (CH)
6.03 (1H, bdd, 11, 6)	2.63 (1H, m)	137.5 (CH)	78.44 (CH)
5.92 (1H, m)	2.49 (1H, m)	136.9 (CH)	49.67 (CH)
5.89 (1H, m)	2.33 (2H, m)	126.3 (CH)	43.10 (CH)
5.07 (1H, dd, 6.0, 2.4)	2.07 (2H, m)	125.1 (CH)	35.50 (CH_2)
4.48 (1H, dd, 10, 2.4)	1.86 (5H, m)	124.4 (CH)	33.52 (CH_2)
4.31 (1H, d, 4.4)	1.55 (4H, m)	86.40 (CH)	29.45 (CH_2)
4.27 (1H, dd, 6, 5.6)	1.28 (1H, m)	77.60 (CH)	27.49 (CH_2)
3.05 (1H, m)	1.11 (3H, d, 6.9)	75.90 (CH)	25.40 (CH_2)
3.01 (2H, m)		63.10 (CH)	24.36 (CH_2)
2.03 (3H, s)		52.60 (CH)	18.71 (CH_2)
1.13 (3H, d, 6.9)		50.10 (CH)	15.42 (CH_3)
		20.60 (CH_3)	
		14.10 (CH_3)	

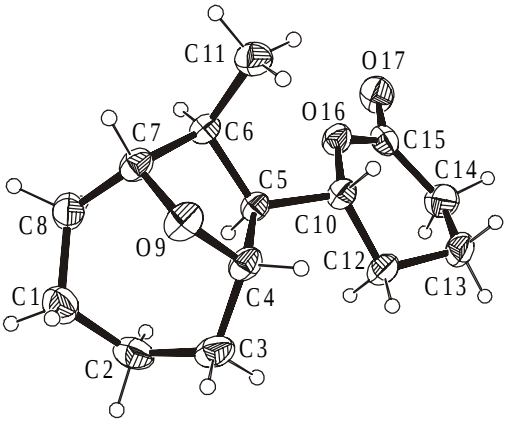

Fig. 1. View of crystal **2** with the atom-labeling scheme.

Compound **2** was obtained as block colorless crystals, mp 213–214°C, $[\alpha]_D^{20}$ +207° (*c* 0.027, MeOH). Mw 238, $C_{14}H_{22}O_3$. The structure of reaction product **2** was elucidated by spectral and single crystal X-ray diffraction techniques. Based on chemical-shift analysis data (Table 1), the 14 signals of the ^{13}C NMR spectrum of **2** were assigned to one methyl, seven methenes, five mono-protonated sp^3-hybridized carbons, and one carbonyl.

The PMR spectrum displayed a total of 22 signals, including one methyl, three carbinols, two methines, and 7 complicated methenes. The signals of the acetyl group disappeared in the NMR of **2**. This indicated that hydrogenolysis occurred in **1**. Moreover, comparing the NMR spectra of **2** with that of **1**, six olefin proton signals (5.9~7.0 ppm) and six sp^2 carbons (120~140 ppm) in the NMR of **1** disappeared, and many complicated peaks at 1.2~2.7 ppm and 7 sp^3 carbons signals (18~36 ppm) appeared in the NMR of **2**. Also in the IR, there was no double bond absorption at 3010 cm^{-1}, and the carbonyl group of the lactone was at 1730 cm^{-1}. All these indicated that the three carbon-carbon double bonds of **1** were hydrogenated. Finally, X-ray diffraction experiments confirmed the structure of **2** (Fig. 1), and the absolute configurations of chiral carbons remained in the reactions.

Primary anticancer assays against HeLa *in vitro* showed that the IC_{50} (μg/mL) values of 1–3 were 5.5, 50, and >100, respectively. The other chemical modifications of **1** are going on.

EXPERIMENTAL

M.p.: uncorrected. IR spectra were recorded on a FT-IR Vector 22 (Bruker) spectrophotometer in KBr disks, in cm^{-1}. ^1H, ^{13}C, and DEPT NMR spectra were obtained on a Varian Inova 500 NB and Mercury 300 spectrometer using 5% solutions in $CDCl_3$. Chemical shifts were determined relative to TMS as internal standard, δ in ppm, J/Hz. UV: Shimadzu UV-3150 spectrophotometer. MS: VG-ZAB-HS mass spectrometer.

Reaction. A solution of **1** (0.1 mmol) and HCO_2NH_4 (0.60 mmol) in 10 ml of absolute MeOH with 10% Pd-C (2.9 mg) was heated to reflux for 12 h (reaction monitored by TLC). The catalyst was filtered off and washed with fresh methanol. The filtrate was evaporated under reduced pressure. The residue was recrystallized from acetonitrile, giving a block colorless crystal of **2** (21.40 mg). Yield 90%, deacetylhexahydromycoepoxydiene, **2**, mp 213–214° (CH_3CN). $[\alpha]_D^{20}$ +207° (*c* 0.027, MeOH). UV ($CHCl_3$, λ_{max}): 269 nm (log ε 3.0). IR spectrum (KBr, cm^{-1}): 2933, 2878, 2858, 1730 (C=O), 1634, 1443, 1371, 1286, 1248, 1200, 1165, 1115, 1056, 1007, 971, 953, 932, 895, 703. Mass spectrum (FAB, *m/z*; I_{rel}, %): 239 (10) $[M+1]^+$, $C_{14}H_{22}O_3$.

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