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Synthesis and Characterization of Altaicadispirolactone

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Abstract: Altaicadispirolactone was synthesized via a simple route. In this route, levulinic acid was used as a starting material, and bromination followed by hydrolysis and $BF_3 \cdot OEt_2$-catalyzed cyclization were carried out. A single-crystal ORTEP drawing has been created and more detailed crystallographic data of the compound has been obtained from X-ray analysis.

Keywords: Altaicadispirolactone, 5-hydroxylevulinic acid, lactonization, levulinic acid

INTRODUCTION

In general, synthesis of hydroxy acids or esters and conversion to lactones or macrolides are important processes in organic synthesis[1] because many of these compounds can be used as potential bioactive substances or polymerizable monomers. For an example, compounds containing γ-butyrolactone often show interesting biological activities.[2] Altaicadispirolactone **1**, or 1,6,9,13-tetraoxadispiro[4.2.4.2]tetradecane-2,10-dione, is a dispirolactone with two γ-butyrolactone rings. It was first isolated in 1986 from *Anemone altaica* C.A. May, a traditional Chinese medicinal herb.[3] It is a dimer of 5-hydroxylevulinic acid (5-HLA, **2**), which was isolated from the same plant.[3]

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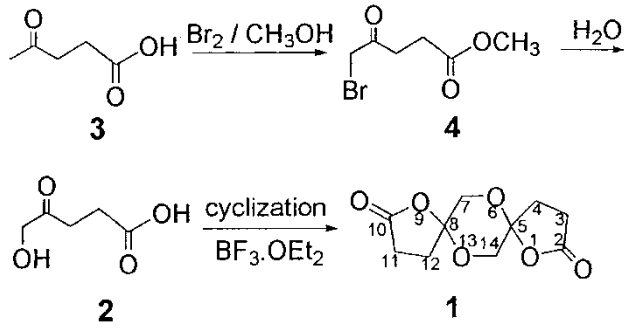
Anemone altaica C.A. May is usually used to decrease the amplitude, frequence, and spike rate of the fast wave and slow wave of gut,[4] and **1** may play a critical role in its therapeutic function. In 1996, S. Li and Y. Li[5] first reported a six-step total synthesis of this compound using succinic anhydride as a starting material. In this article, we report a simple three-step synthesis of **1** using levulinic acid (LA, **3**) as a starting material. Because **3** can be produced from biomass such as cellulose or lignin in large scale and at low cost and can be used to synthesize many useful chemicals, it is frequently proposed as a potential platform chemical derived from biomass.[6] Therefore, our synthesis route may be a more economical and environmentally friendly one. Our synthesis approach is outlined in Scheme 1.

First, **3** was brominated using Br_2 as a bromating agent in methanol at 40°C, a condition under which the methyl is preferentially brominated. Pure methyl 5-bromolevulinate (5-MBL, **4**) was obtained in 38% yield after the bromination reaction and a subsequent low-temperature recrystallization process. Then, **2** was obtained by a one-step hydrolysis of the Br-C and ester bonds of **4** in boiling water in 69% yield. Finally, cyclization of **2** using $BF_3 \cdot OEt_2$ as catalyst gave **1** in 77% yield.

The spectroscopic data of **1** are identical with those of the natural[3] and the previously chemically synthesized[5] products. A single crystal of **1** was cultured in a dilute methylene chloride solution and used for X-ray analysis. The ORTEP drawing of **1** is shown in Fig. 1, which demonstrates that two saturated γ-butyrolactone rings are connected to the dioxane ring in a dispiro arrangement.

Although the first two steps have been reported separately in the literature.[7–9] the reaction and purification processes were both modified in our synthetic route. In the bromination reaction, a methanol-drying procedure reported in literature[7] was omitted for convenience and no unfavorable effect was observed on the yield. In the hydrolysis step, a modified one-step hydrolysis of the Br-C and ester bonds of **4** and a subsequent continuous extraction of



Scheme 1. Synthesis route of **1** using **3** as a starting material.

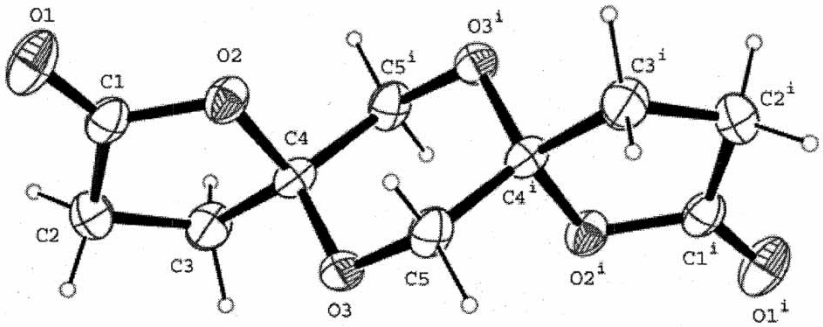


Figure 1. View of the molecule **1** with the atom-labeling scheme.

the concentrated hydrolysis product were performed so that a yield (69%) much higher than the result (38%) of the two-step hydrolysis reported in literature[9] was obtained. In the third step, boron trifluoride etherate ($BF_3 \cdot OEt_2$) was used as catalyst instead of p-toluene sulphonic acid,[5] and consequently a higher yield (77%) was obtained.

EXPERIMENTAL

The melting point of the purified product **2** was measured by Perkin-Elmer 7 DSC. IR spectra (ν_{max} in cm^{-1}) were recorded on a Nicolet 560 FT-IR spectrometer. ^1H NMR spectra were obtained with a Brucker AVANCE 500-M spectrometer using tetramethylsilane as internal standard. Mass spectra were determined on a Thermofinnigan 1A-1112 spectrometer. A single crystal of compound **2** was measured on a Rigaku RAXIS-RAPID single-crystal diffractometer.

Methyl 5-Bromolevulinate 4

Bromine (160 g, 1 mol) was added to a solution of **3** (116 g, 1 mol) in methanol (500 ml) at 30 °C for 30 min. The reaction mixture was then stirred at 40°C for 8 h. After removing the methanol under reduced pressure, the residue was dissolved in diethyl ether (500 ml) and washed with water and then with sodium bicarbonate aqueous solution. After the ethereal layer was dried (Na_2SO_4 and 4 Å molecular sieve), the ether was distilled off. The residue was dissolved in diethyl ether/cyclohexane (1:1, 800 ml), and the solution was then cooled at −20 to −40°C. After recrystallization for 2 h, filtration, and washing, **4** (80 g) was obtained in 38% yield as colorless acicular crystals. Melting point: 19°C. ν_{max}, (cm^{-1}) 2953, 1735, 594. δ_H ($CDCl_3$) 2.64–2.97 (4H, brs,. CH_2CH_2), 3.68 (3H, s, $COOCH_3$), 3.98 (3H, s, $BrCH_2$).

5-Hydroxylevulinic Acid 2

A mixture of **4** (20 g) and water (300 ml) were heated to reflux for 4 h before evaporation and concentration. The residue mixture was continuously extracted with diethyl ether with a modified extractor for 48 h. The resultant ethereal solution was dried with magnesium sulphate. After evaporation of the ether, a crude crystalline product (12 g) (mp 98.6–99.6°C) was obtained. Recrystallization from chloroform (60 ml/g) gave 9.2 g of colorless crystals (mp 100–101°C). ν_{max} (cm^{-1}) 3427(OH), 1696, 1409. $\delta_H(CDCl_3)$ 2.61–2.81 (2H, dm, CH_2COC), 2.44 (2H, M, CH_2COO), 4.06–4.28 (2H, ds, $COCH_2O$). Calc. for $C_5H_8O_4$: C, 48.13; H, 5.76. Found: C, 48.20; H, 5.84.

Altaicadispirolactone 1

$BF_3 \cdot OEt_2$ (0.5 ml) was added to a solution of **2** (4 g) in CH_2Cl_2 (300 ml), and the mixture was refluxed for 4 h in a 500-ml round-bottomed flask equipped with a Deam–Sbark apparatus. The reaction mixture was washed with deionized water. The organic layer was dried (with Na_2SO_4) and then evaporated to obtain 3.1 g of white powder. After recrystallization in CH_2Cl_2, 3 g of granulous crystals were obtained in 77% yield. ν_{max} (cm^{-1}) 1766, 1226; 1049. δ_H ($CDCl_3$) 2.09–2.14, 2.30–2.35, 2.69–2.75, 2.91–2.97 (8H, 4 m, 3, 4, 11,

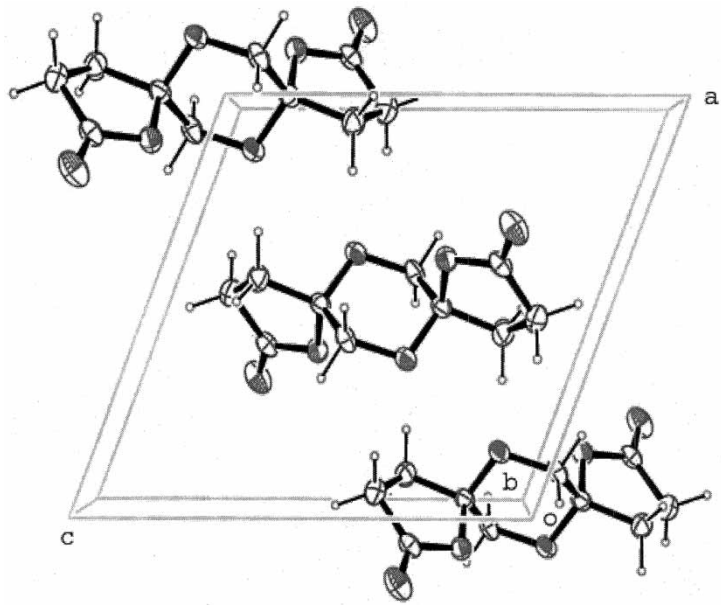


Figure 2. Crystal structure of **1** viewed along the b axis.

12H), 3.83–3.85 (2H, d, 7a, 14a, H), 4.14–4.16 (2H, d, 7a, 14a, H). δ_c ($CDCl_3$) 180.7 (C═O), 105.3 (O–C–O), 77.3 (CH_2–O), 65.3 (CH_2–C═O), 29.8, 28.0. Calc. for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.63; H, 5.27. Crystal data for **1**: monoclinic, space group P21/n, a = 8.898(5)Å, b = 6.010(2)Å, c = 9.897(4)Å, β = 111.70(1)Å, z = 2, radiation = MoK (0.71069 Å), final R = 0.048. The final R is better than that of crystallographic data reported in Ref. 10, where the R = 0.065. Its crystal packing is shown in Fig. 2. Within the crystal lattice, the molecules are arranged along the diagonal of a–c axis in a parallel fashion occupying the crystallographic plane. The crystallographic data for the structures **1** in this article have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC261917.

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