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A NEW SYNTHETIC ROUTE TOWARDS PICEALACTONE A FROM AN ABIETIC ACID

Shengliang Liao,[1] Minggui Shen,[1,2*] Jie Song,[3] Shibin Shang,[1,2] Xiaoping Rao,[1,2] and Zhanqian Song[1*]

A new synthetic route towards picealactone A from an abietic acid, dehydroabietic acid, was introduced in this study. In this synthetic route, the picealactone A was synthesized by a tandem oxide/intramolecular esterification of 7-carbonyl dehydroabietic acid catalyzed by Yb(OTf)$_3$.

Keywords: synthesis, picealactone A, dehydroabietic acid, Yb(OTf)$_3$.

Dehydroabietic acid (DHAA) (**1**), a naturally occurring diterpene resin acid, has received increased interest in recent years because it and its derivatives exhibit a variety of biological activities [1–5]. These features make DHAA a new scaffold in drug design, and further chemical modifications of DHAA have important implications in drug development.

Chemical modifications on ring B of DHAA have been widely reported [6–8]. Previous research showed that some derivatives synthesized by the modification of ring B exhibited potential pharmaceutical activity [7–9]. Hence, studies of new derivatives of DHAA as pharmaceutical agents by structural changes on ring B of DHAA are meaningful and desired.

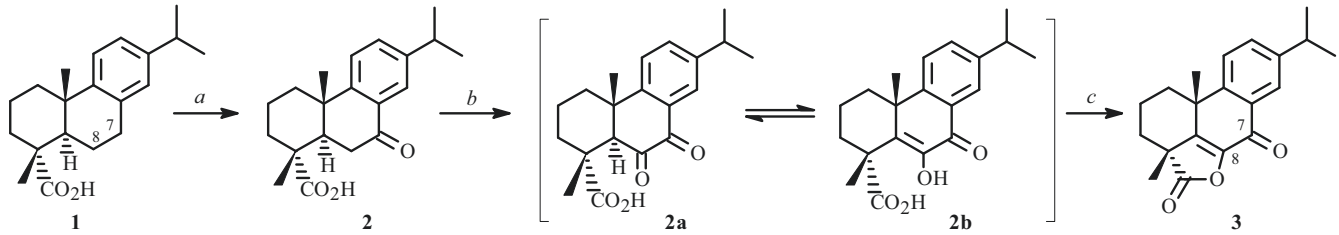
Picealactone is a valuable natural compound with many potential biological activities; it includes three types, picealactone A, B, and C [10]. Among them, picealactone A can be synthesized through modification of ring B of DHAA [11, 12]. However, the existing synthetic method for picealactone A is not satisfactory because of low yield. Therefore, the present work reports a new synthetic route toward picealactone A by modification of ring B of DHAA, which is achieved by a tandem oxide/intramolecular esterification of 7-carbonyl dehydroabietic acid (Scheme 1).

Dehydroabietic acid (DHAA, **1**) was isolated from disproportionated rosin according to the literature [13]. 7-Carbonyl DHAA (**2**) was obtained by oxidation of DHAA (**1**) according to the literature [14]. With 7-carbonyl DHAA (**2**) as the raw material, we propose a method to prepare a dicarbonyl derivative of DHAA (or its enol tautomer) based on the oxidation of 8-carbon to 8-carbonyl, then synthesize the lactone derivative of DHAA through intermolecular esterification.

SeO_2 is believed to be an efficient oxidant for the transformation of the 8-carbon to 8-carbonyl, and Yb(OTf)$_3$ is regarded as an ideal catalyst for promoting this reaction; meanwhile, Yb(OTf)$_3$ is a Lewis acid, which can be used to catalyze the esterification reaction [15]. Accordingly, in this work, the 7-carbonyl DHAA (**2**) was treated with 2 eq of SeO_2 and 0.1 eq of Yb(OTf)$_3$ in a dioxane–H_2O mixture so as to obtained a lactone derivative of DHAA.

As was expected, the tandem oxidation/intramolecular esterification proceeded successfully. Firstly, 7-carbonyl DHAA (**2**) was oxidized to 7,8-dicarbonyl DHAA (**2a**), but the reaction did not stop, since 7,8-dicarbonyl DHAA could transform to an enol tautomer (**2b**), and subsequently intramolecular esterification occurred, catalyzed by the Yb(OTf)$_3$, to yield the lactone compound picealactone A (**3**). The product picealactone A was characterized by mp, ESI-MS, and ^{1}H NMR spectroscopy.

1) Institute of Chemical Industry of Forest Products, China Academy of Forestry; National Engineering Laboratory for Biomass Chemical Utilization; State Forestry Administration′s Key and Open Laboratory for Forest Chemical Engineering; Jiangsu Provincial Key Laboratory for Biomass Energy and Material, 210042, Nanjing, Jiangsu, P. R. China, e-mail: shenminggui@sina.com; lhssxly@hotmail.com; 2) Institute of New Technology of Forestry, China Academy of Forestry, 100091, Beijing, P. R. China; 3) Department of Chemistry and Biochemistry, University of Michigan-Flint, 303E Kearsley Street, Flint, MI 48502, USA. Published in *Khimiya Prirodnykh Soedinenii*, No. 4, July–August, 2017, pp. 560–561. Original article submitted October 31, 2015.



a. CrO_3; *b*. SeO_2, $Yb(OTf)_3$; *c*. $Yb(OTf)_3$

Scheme 1. $Yb(OTf)_3$ catalyzed tandem oxide/intramolecular esterification of 7-carbonyl DHAA.

Since picealactone A is a known compound, the characterization data, including mp, HR-EI-MS, and ^1H and ^{13}C NMR has been reported in the literature [10]. In this work, the tested mp of picealactone A is 182–186°C. The ESI-MS signal at 311 $[M + H]^+$ indicates that the molecular weight of picealactone A is 310. Consequently, the characterization data of picealactone A obtained in this work are in good agreement with the reported data. This study can provide an alternative synthetic method to picealactone A.

EXPERIMENTAL

All reagents were obtained from local commercial suppliers and used without further purification. ^1H NMR spectra was recorded with a Bruker Ascend^{TM} 400 analyzer in DMSO-d_6 with TMS as internal standard. Mass spectra were recorded on an Agilent-5973 spectrometer (ESI source).

Synthesis of 7-Carbonyl DHAA (2). A mixture of dehydroabietic acid (10 mmol), CrO_3 (30 mmol), and AcOH (10 mL) was stirred at room temperature. After 3 h, the mixture was quenched into water (30 mL) and extracted with EtOAc (10 mL × 3). The organic phase was combined and washed with saturated NaCl solution (10 mL × 3), and then the organic phase was dried, concentrated under vacuum, and purified by silica gel chromatography to afford the desired product 7-carbonyl dehydroabietic acid. Sticky liquid. Yield 71%. ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 12.32 (1H, s), 7.71 (1H, d, J = 1.8), 7.51 (1H, dd, J = 8.2, 1.9), 7.41 (1H, d, J = 8.2), 2.93 (1H, dd, J = 13.8, 6.9), 2.81 (1H, dd, J = 17.6, 14.3), 2.49 (1H, d, J = 3.0), 2.39 (1H, d, J = 12.8), 2.19 (1H, dd, J = 17.6, 3.0), 1.92 (1H, s), 1.70 (3H, dd, J = 20.0, 13.0), 1.47 (1H, d, J = 12.8), 1.21 (9H, dd, J = 13.2, 7.0). ESI-MS *m/z* 315 $[M + H]^+$.

Synthesis of Picealactone A (3). A mixture of $Yb(OTf)_3$ (0.1 mmol), 7-carbonyl dehydroabietic acid (10 mmol), 1,4-dioxane (3 mL), H_2O (1 mL), and SeO_2 (20 mmol) was stirred at 90°C for 24 h. Then the mixture was cooled to room temperature and filtered on a short pad of Celite in order to immobilize the unreacted SeO_2. The filtrate was extracted with EtOAc (10 mL × 3). The organic phase was combined and washed with saturated NaCl solution (10 mL × 3), and then the organic phase was dried, concentrated under vacuum, and purified by silica gel chromatography to afford the desired product. White crystals, yield 78%, mp 182–186°C. $[\alpha]_D^{20}$ +14.6° (*c* 0.5, CH_3OH). ^1H NMR (400 MHz, DMSO-d_6, δ, ppm, J/Hz): 7.96 (1H, d, J = 1.9), 7.75 (1H, d, J = 8.2), 7.63 (1H, dd, J = 8.2, 2.0), 3.10–2.89 (1H, m), 2.43 (1H, d, J = 12.8), 2.09 (1H, d, J = 14.1), 1.95 (1H, d, J = 12.6), 1.72 (2H, d, J = 14.7), 1.57 (6H, d, J = 8.0), 1.24 (6H, d, J = 6.9). ESI-MS *m/z* 311 $[M + H]^+$.

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