Chinese Chemical Letters 24 (2013) 617–618

Contents lists available at SciVerse ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

A convenient synthesis of 2β,3α-dihydroxyurs-12-en-28-oic acid as a natural diastereoisomer of corosolic acid

Shi-Sheng Wang *, Li-Juan Luo, Zhi-Gang Gao, Tong-Wei Guan, Wei-Jie Zhao

School of Pharmaceutical Science and Technology, Dalian University of Technology, Dalian 116023, China

ARTICLE INFO

Article history:
Received 10 January 2013
Received in revised form 25 March 2013
Accepted 28 March 2013
Available online 18 May 2013

Keywords:
2β,3α-Dihydroxyurs-12-en-28-oic acid
Ursolic acid
Glycogen phosphorylase
Corosolic acid

ABSTRACT

2β,3α-Dihydroxyurs-12-en-28-oic acid (**6**) is a naturally occurring diastereoisomer of corosolic acid with glycogen phosphorylase inhibitory activity. A new strategy for the semi-synthesis of **6** was developed. Using the commercially available ursolic acid (**1**) as the starting materials, **6** was synthesized through five facile reactions with a high stereoselectivity and an overall yield of 47.3%. The structure of **6** was confirmed by optical rotation, ESI-MS, ^{1}H NMR and ^{13}C NMR data.

1. Introduction

2β,3α-Dihydroxyurs-12-en-28-oic acid (**6**), a naturally occurring pentacyclic triterpene, was first isolated from *Lagerstroemia floribunda* (Lythraceae) [1]. Compound **6** is the 2β,3α-isomer of corosolic acid that has recently attracted much attention due to its various biological properties, such as glucose lowering effect [2], anti-inflammatory [3], anti-tumor [4], antiviral [5] and cardiovascular activities [6]. Corosolic acid is known as a 'plant insulin' for its remarkable ability in reducing blood glucose level post glucose challenge, which can be probably attributed to its glycogen phosphorylase (GP) inhibitory activity [7–9]. Compound **6** was reported to be a more potent GP inhibitor (IC_{50} 1.1 μmol/L) than corosolic acid (IC_{50} 20 μmol/L), which means that the configuration of 2,3-dihydroxy at the ring A is a critical factor for GP inhibitory activity and 2β,3α-configuration is more favorable than the 2α,3β-configuration [10,11].

Unlike oleanolic acid or ursolic acid, **6** and corosolic acid have very limited distribution and low abundance in nature. Thus, their semi-syntheses from available pentacyclic triterpenes have been investigated [12,13]. For the synthesis of **6**, Sun *et al.* reported a five-step semi-synthetic method starting from the 2β-isomer of corosolic acid [11], which was not commercially available and synthesized from ursolic acid in six steps [10] in an overall yield of 8.8%. Herein, we present a more practical and convenient method for the synthesis of **6** starting from ursolic acid in five steps and a 47.3% overall yield.

2. Experimental

Chemicals for the synthesis were analytical grade. Ursolic acid (**1**) was purchased from Shanxi Yongjian Pharmaceutical Co., Ltd. The reference compound, corosolic acid (2α,3β-dihydroxyurs-12-en-28-oic acid), was purchased from Shanghai Yuanye Technology Co., Ltd. The purity of the compounds was checked by thin layer chromatography and high performance liquid chromatography (HPLC) analyses. The known compounds were characterized by comparing their spectral data with those reported in the literature.

As shown in Scheme 1, ursolic acid was reacted with benzyl chloride to protect the 28-COOH as a benzyl ester. Then the dehydration product **3** [15] was obtained by treating alcohol **2** with methanesulfonyl chloride. Compound **3** was mixed with *m*-chloroperoxybenzoic acid (*m*CPBA) in $NaHCO_3/CH_2Cl_2$ to produce 2α,3α-epoxyurs-12-en-28-oic acid benzyl ester (**4**) [16]. 2β,3α-Dihydroxyurs-12-en-28-oic acid benzyl ester (**5**) [17] was obtained by a ring-cleaving reaction of **4** with THF/H_2O (3/1, (v/v)) as the solvent and $HClO_4$ as the catalyst. Thereafter, the final product **6** was obtained as a white powder after deprotection in 96.2% yield. $[\alpha]_D^{22}$ +62.9 (*c* 0.062, pyridine). ESI-MS (*m*/*z*): 471.4 $[M-H]^-$. ^{1}H NMR (400 MHz, pyridine-d_5): δ 0.94, 1.06, 1.17, 1.21 (s, each 3H), 0.99 (d, 3H, *J* = 4.8 Hz), 1.28 (s, 6H), 2.63 (d, 1H, *J* = 11.0 Hz), 3.98 (d, 1H, *J* = 6.7 Hz), 4.34 (dd, 1H, *J* = 6.4, 13.2 Hz), 5.49 (s, 1H). ^{13}C NMR (100 MHz, pyridine-d_5): δ 18.6, 18.7, 20.9,

* Corresponding author.
E-mail address: wangss@dlut.edu.cn (S.-S. Wang).

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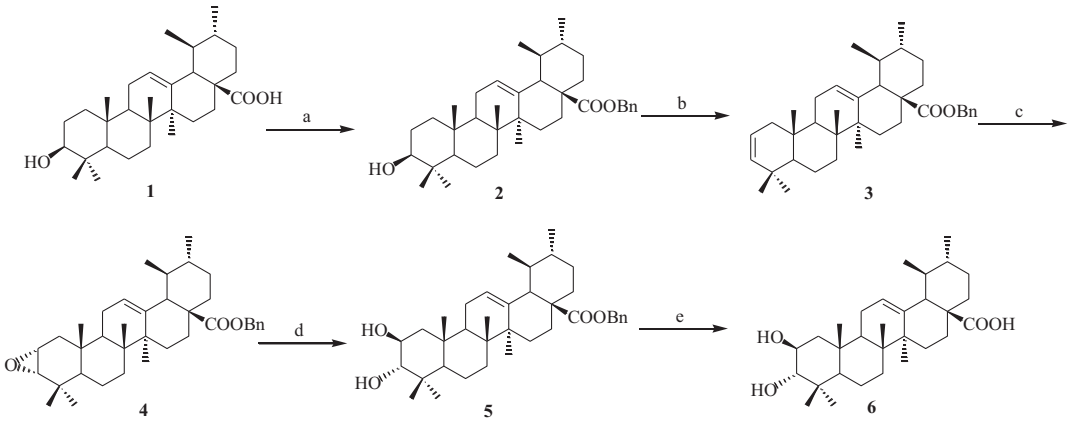
http://dx.doi.org/10.1016/j.cclet.2013.04.022



Scheme 1. Synthesis of 2β,3α-dihydroxyurs-12-en-28-oic acid. (a) BnCl, DMF, 50 °C, 93.7%; (b) methanesulfonyl chloride, DMAP, pyridine, reflux, 89.1%; (c) $NaHCO_3$, *m*CPBA, CH_2Cl_2, 71.5%; (d) $HClO_4$, THF, H_2O, r.t., 82.4%; (e) 10% Pd/C, H_2, THF, 96.2%.

21.1, 22.6, 24.7, 25.0, 25.1, 26.2, 28.4, 29.8, 32.3, 34.5, 38.7, 38.8, 39.1, 40.6, 40.7, 41.4, 44.0, 47.1, 49.3, 49.8, 52.0, 54.9, 71.9, 79.5, 127.1, 140.4, 181.2.

3. Results and discussion

Using the synthetic route illustrated in Scheme 1, the target product **6** was successfully synthesized in a total yield of 47.3%. The crucial steps of the whole route included the epoxidation of alkene **3** to produce epoxide **4** and the subsequent stereoselective hydrolysis to yield diol **5**. In our research, several oxidants were screened to transform the 2,3-olefinic bonds in **3** to an epoxide, such as hydrogenperoxide, *tert*-butyl hydrogenperoxide, performic acid and *m*CPBA. The reaction with *m*CPBA gave the best results with the fewest by-products, possibly derived from the epoxidation of 11,12-olefinic bond in **3**. The epoxide **4** was obtained using *m*CPBA and its relative configuration was deduced to be 2α,3α according to the configuration of the final product **6**. The stereoselectivity of the epoxidation can be explained by the fact that top face was blocked by two axial methyl groups [14]. In the step of the epoxide opening, reaction solvent with a proper dielectric constant and solubilizing ability was thought to be a pivotal factor for the success of the reaction. After screening several solvents, THF was considered to be optimal and the highly stereoselective ring-opening of epoxide to 2β,3α-dihydroxyl was achieved with $HClO_4$ as an acidic catalyst. Due to the SN_2 nature of the reaction, the 2β,3α-diol **5** was preferentially obtained.

The structure and stereochemistry of **6** were elucidated by comparing its optical rotation, ^{1}H NMR, ^{13}C NMR, MS data with those reported in the literature [11]. According to the spectral data reported in the literatures [10,11], the configurations at 2,3-positions can be established by the coupling constants (*J* values) of the H-3 signal in ^{1}H NMR, which was ~9.4 Hz for 2α,3β, ~2.6 Hz for 2α,3α, ~3.6 Hz for 2β,3β and ~7.5 Hz for 2β,3α, respectively. The optical rotation, MS, ^{1}H NMR and ^{13}C NMR of **6** were consistent with those of 2β,3α-dihydroxyurs-12-en-28-oic acid.

4. Conclusion

We designed a practical route for the synthesis of 2β,3α-dihydroxyurs-12-en-28-oic acid in five steps under mild conditions in high yields and with low cost. The overall yield of the route was much higher than those previously reported. The structure and configuration of the final product were clarified by various spectral techniques.

Acknowledgment

Financial support from the Fundamental Research Funds for the Central Universities (No. DUT12JB08) is greatly appreciated.

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[15] Spectra data of compound **3** (urs-2,12-dien-28-oic acid benzyl ester): ESI-MS: *m*/*z* 529.3 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.71, 1.00, 1.08, 1.10, 1.25 (s, each 3H), 0.86 (d, 3H, *J* = 5.6 Hz), 0.94 (d, 3H, *J* = 6.90 Hz), 4.99 and 5.09 (d, each 1H, *J* = 12.5 Hz), 5.26 (s, 1H), 5.37 and 5.41 (d, each 1H, *J* = 10.2 Hz), 7.33 (m, 5H).
[16] Spectra data of compound **4** (2α,3α-epoxyurs-12-en-28-oic acid benzyl ester): ESI-MS: *m*/*z* 545.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.61, 1.00, 1.08, 1.10, 1.25 (s, each 3H), 0.86 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 5.6 Hz), 2.78 (d, 1H, *J* = 3.5 Hz), 3.18 (1H, m), 4.99 and 5.08 (d, each 1H, *J* = 12.5 Hz), 5.25 (s, 1H), 7.33 (m, 5H).
[17] Spectra data of compound **5** (2β,3α-dihydroxyurs-12-en-28-oic acid benzyl ester): ESI-MS: *m*/*z* 563.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62, 0.99, 1.06, 1.25, 1.27 (s, each 3H), 0.84 (d, 3H, *J* = 6.0 Hz), 0.92 (d, 3H, *J* = 5.6 Hz), 3.63 (d, 1H, *J* = 10.3 Hz), 3.71 (m, 1H), 4.99 and 5.08 (d, each 1H, *J* = 12.5 Hz), 5.25 (s, 1H), 7.33 (m, 5H).