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Efficient synthesis and biological evaluation of epiceanothic acid and related compounds

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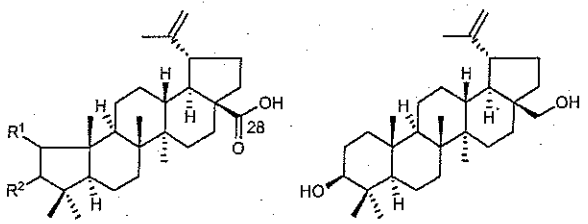
ABSTRACT

Epiceanothic acid (**1**) is a naturally occurring, but very rare pentacyclic triterpene with a unique pentacyclic triterpene (PT) structure. An efficient synthesis of **1** starting from betulin (**3**) has been accomplished in 12-steps with a total yield of 10% in our study. Compound **1** and selected synthetic intermediates were further evaluated as anti-HIV-1 agents, inhibitors of glycogen phosphorylase (GP), and cytotoxic agents. Compound **1** exhibited moderate HIV-1 inhibition. Most importantly, compound **5**, with an opened A-ring, showed significant GP inhibitory activity with an IC_{50} of 0.21 μM, suggesting a potential for development as an anti-diabetic agent. On the other hand, compound **12**, with a closed A-ring, showed potent cytotoxicity against A549 and MCF-7 human tumor cell lines, with IC_{50} values of 0.89 and 0.33 μM, respectively. These results suggest that the A-ring of PTs is an important pharmacophore that could be modified to involve different biological activities.

Pentacylic triterpenes (PTs), a group of widespread natural compounds, possess several intriguing biological activities, such as anti-HIV, antitumor, anti-diabetic, anti-inflammatory, antibacterial, antiviral, antiparasitic, hepatoprotective, wound healing, antioxidant, antipruritic, antiangiogenic, antiallergic, and immunomodulatory activities.[1–5] In recent years, PTs have been the focus of much interest due to their significant therapeutic potentials. The anti-HIV and antitumor activities of PTs have received the most attention, as several synthetic PT derivatives have advanced into clinical trials [e.g., PA-457 (DSB, Bevirimat, MPC-4326)[6,7] and PA-1050040 for AIDS therapy, and betulinic acid, CDDO, and CDDO-Me for cancer therapy]. Our previous investigation also showed that PTs represent a new class of glycogen phosphorylase (GP) inhibitors, which may be a key contributing mode of action in their anti-diabetic activity.[8–10]

Epiceanothic acid (EA, **1**) (Fig. 1) is a naturally occurring ceanothane-type PT isolated from the seeds of the traditional Chinese medicine *Ziziphus jujuba* var. *spinosa* (Bunge) Hu and the stings of *Gleditsia sinensis* Lam.[11–13] It is reported to possess strong anti-HIV-1 replication activity in HIV-1_{IIIB} infected C8166 cell lines (EC_{50} <0.064 μg/mL).[12,13] Compound **1** has two natural configurational isomers, ceanothic acid (**2a**)[14–18] and isoceanothic acid (**2b**).[19] Their structures differ from that of **1** only in the orientations



Epiceanothic acid (**1**): R^1=β-COOH, R^2=β-OH
Ceanothic acid (**2a**): R^1=α-COOH, R^2=β-OH
Isoceanothic acid (**2b**): R^1=β-COOH, R^2=α-OH

Betulin (**3**)

Figure 1. Structures of epiceanothic acid (**1**) and related PT compounds (**2a**, **2b**, **3**).

of the 2-carboxylic acid (**2a**) and 3-hydroxy group (**2b**) in the A-ring. Compound **2a** was reported to possess anti-microbial and cytotoxic activity,[20–22] and its derivatives were found to be potent cancer chemopreventive agents.[23]

Despite its obvious potential, only limited research has been reported on **1**, because it is very rare in nature. Therefore, it is highly desirable to establish a reliable access to **1**-analogs for biological evaluation. Herein, we report an efficient synthetic route to **1** in 12-steps with a total yield of 10% starting from betulin (**3**), which is easily available at a low price. Compound **1** and the pentacyclic triterpene intermediates[24] were then evaluated for anti-HIV-1, GP inhibitory, and cytotoxic activities.

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