
# A remarkably simple and convergent partial synthesis of pomolic acid

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# A remarkably simple and convergent partial synthesis of pomolic acid

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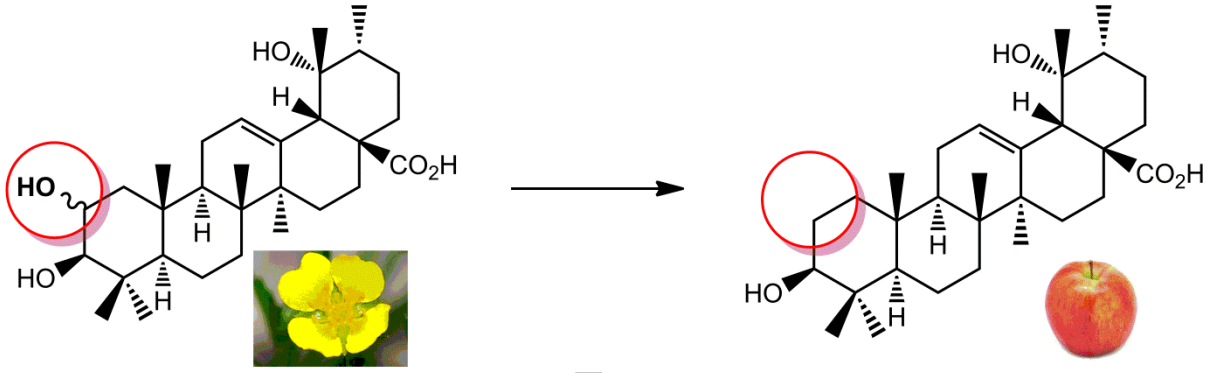
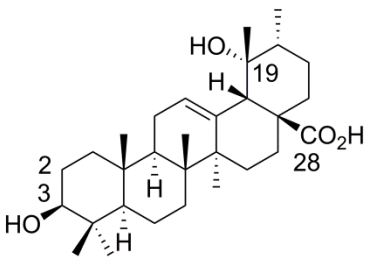
Graph abstract

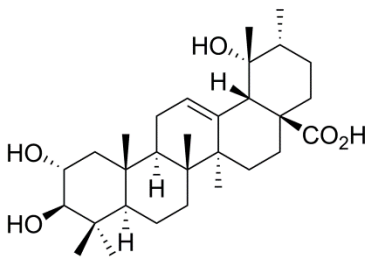



The daily consumption of vegetables and fruits seems to have a positive impact on health. This finding is supported by epidemiological studies correlating the consumption of this foodstuff with a lowered risk of developing cardiovascular diseases and cancer.[1-6] While the over-all risk of getting a cardiovascular disease can be reduced by a variety of known changes in personal lifestyle, the prevention of cancer and its treatment remains difficult, since the high mortality of cancer is often due to metastasis.[7]

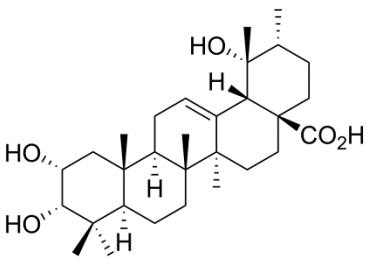
Migration of cancer cells has been associated with CXC chemokine receptor type 4 (CXCR4) signaling,[8-10] and the development of CXCR4 inhibitors is an alternative to classical treatment of cancer by chemotherapy. Quite recently, pomolic acid (**PA**, Fig. 1) was identified as a novel inhibitor of CXCR4.[7] In addition, **PA** triggered apoptosis in human ovarian cancer cells,[11] and it inhibited the growth of K562 leukemia cells.[12-14]




**pomolic acid (PA)**




**tormentic acid (TA)**

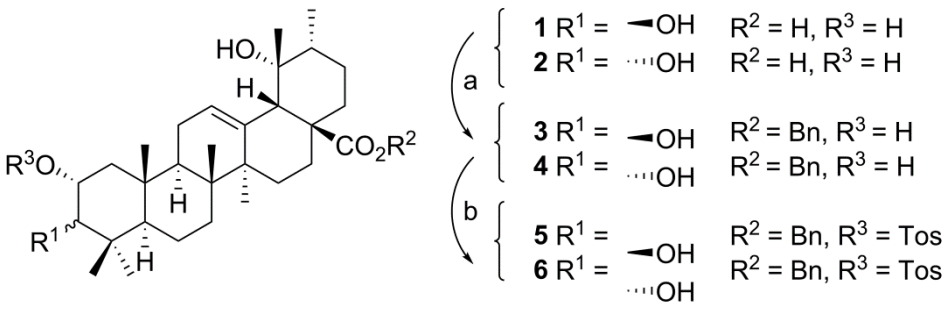



**euscaphic acid (EA)**

Fig. 1 Structure of pomolic acid, tormentic acid and euscaphic acid.

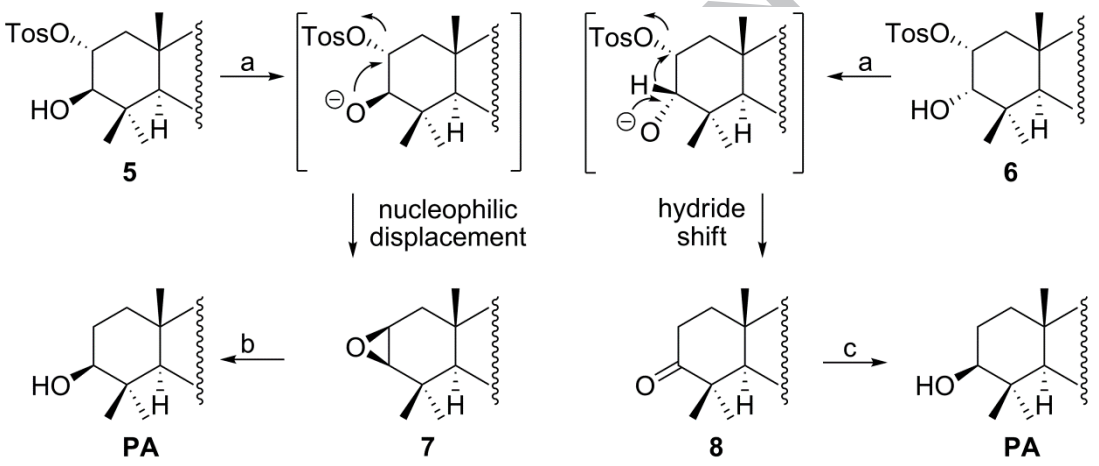
Pomolic acid is an ursolic acid derived triterpene carrying an extra hydroxyl group at position 19. It was first isolated in 1966 from apple peels by Brieskorn and Wunderer.[15, 16] Since then, **PA** has been detected and isolated from many different plants, among them *Perilla frutescens*,[17, 18] *Euscaphus japonica*[19] and *Rosmarinus officinals*.[20, 21] Although **PA** is widespread in many plants and trees, the amount of **PA** is always low, and its extraction from these natural sources remains laborious and not rewarding. Several years ago a partial synthesis of **PA** from rotungenic acid (this starting material (< 60 mg) was obtained from the extraction of 2 kg (!) of the fruits from *Ilex rotunda* followed by HPLC separation) has been reported.[22] These procedures, however, are not suitable to obtain larger amounts of **PA**.

Hence, we decided to look for an alternative approach to access this valuable triterpenoic acid. Retrosynthetic analysis revealed either tormentic acid (**1**, **TA**) or euscaphic acid (**2**, **EA**) as a suitable stating material for a partial synthesis of **PA**. Looking out for a natural source for **TA** and **EA** we came across the plant common tormentil (septfoil, *Potentilla erecta*).[23] This low plant is almost ubiquitous in many parts of Europe and Western Asia, and the rhizomes of this plant are known to contain a mixture of **TA**/**EA** in significant amounts (0.2 to 0.3 %). In a first approach, finely grounded rhizomes from *Potentilla erecta* were extracted with diethyl ether,[24] and **TA** and **EA** were isolated by column chromatography. Esterification (Scheme 1) of **TA** or **EA** with benzyl bromide/potassium carbonate in DMF at room temperature furnished the benzyl esters **3** and **4**, respectively. Esterification of the **TA**/**EA** mixture under the same conditions gave a mixture of **3** and **4** (that could also be separated by chromatography). Reaction of **3** or **4** or a mixture of **3**/**4** with *p*-TsCl/pyridine gave the tosylates **5** or **6** or the mixture **5**/**6** in good yields (again, the mixture **5**/**6** can be separated by chromatography).



**Scheme 1.** a) BnBr, $K_2CO_3$, DMF, 24 h, 25 °C, 83–86%; b) *p*-TosCl, pyridine, 24 h, 25 °C, 70–85%

Reaction of tosylates **5**, **6** or of the **5**/**6** mixture with sodium methoxide in methanol (Scheme 2) gave epoxide **7** (from tosylate **5**) and 3-oxo compound **8** (from **6**) in good yields. While the (deprotonated) β-oriented hydroxyl group at C-3 in **5** favors the formation of an epoxide by intramolecular nucleophilic displacement reaction, this reaction is hampered for **6**. After deprotonation of OH-C(3) in **6** a C-2 → C-3 hydride shift takes places instead,[25] and finally ketone **8** is formed. The separation of acids **TA**/**EA**, esters **3**/**4** or of the tosylates **5**/**6** might be laborious, but the separation of **7** from **8** can be done by chromatography very easily even in large scale preparations.




**Scheme 2.** a) MeOH, NaOMe, reflux, 1 h, 72–86%; b) Pd/C(10%), $H_2$ (5 atm), 25 °C, 5 h, 84 %; c) $NaBH_4$, MeOH, microwaves, 10 min, 85 °C, 81% followed by Pd/C (10%), $H_2$ (5 atm). 25 °C, 5h, 86%

Microwave assisted stereoselective reduction [26] of **8** with sodium borohydride in MeOH [27-27] furnished **9** whose hydrogenation in MeOH/THF in the presence of catal. amounts of Pd/C (10%) gave **PA** in excellent yield.

Reduction of **7**, however, with Pd/C/$H_2$ allowed a direct access to **PA**. Under these conditions a cleavage of the benzyl ester occurred but also a stereoselective ring opening of the epoxide [29] took place, and allowed the isolation of **PA** in good yields.

Thus, all synthetic transformations can be performed with the **TA**/**EA** mixtures (or mixtures of the derivatives, where appropriate) as well as with the analytically pure compounds. At present, this approach constitutes the best and shortest route to **PA**.

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Highlights

- Pomolic acid is an ursolic acid derived triterpene of biological importance
- Its extraction from natural resources is laborious and not rewarding
- Mixtures of tormentic/euscaphic acid are easily obtained in larger amounts
- These mixtures can be easily transformed into pomolic acid in high yields