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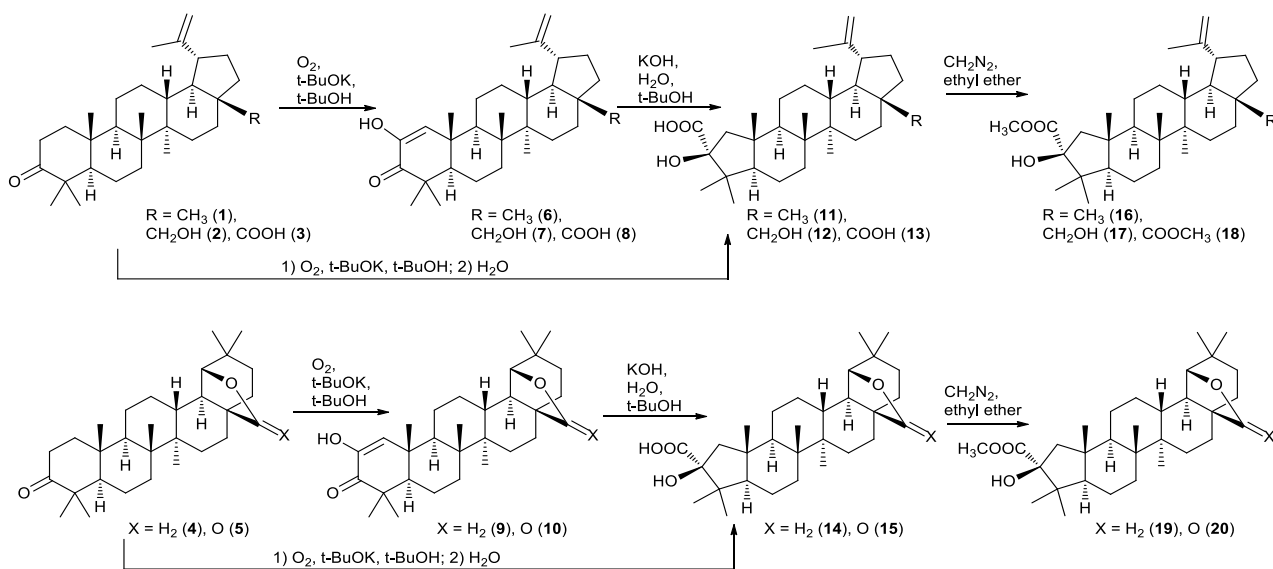
## STEREOSELECTIVITY OF A-RING CONTRACTION FOR 3-OXOTRITERPENOIDS

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The A-ring oxidation/contraction of 3-oxotriterpenoids was developed as a two-step and “one pot” process. A benzylic acid type rearrangement of triterpenoid diosphenols gives (S)- as major and (R)- $\alpha$ -hydroxycarboxylic acids as minor reaction products. The absolute configurations were determined from the X-ray crystal structure analysis.

### Introduction

The development of triterpenoid chemistry over the last ten years<sup>1a,b</sup> was encouraged by the discovery of potential anticancer, antibacterial and antiviral bioactives.<sup>2a-c</sup> The structure/activity relationship led to the development of methods for modification of triterpenoids with different hydrophilic groups (carboxylic, carbonylic, hydroxylic etc.).<sup>3a-c</sup> The modification of the A-ring through a benzylic acid rearrangement of 2,3-dioxo derivatives displays a high potential to the synthesis of new bioactive triterpenoids. Previously reported approaches<sup>4a-d</sup> are cumbersome because they utilize the bromination of 3-oxotriterpenoids followed by the ring contraction of corresponding  $\alpha,\alpha$ -dibromoketones; it is apparent that diosphenols<sup>3b</sup> of lupane and oleanane triterpenoids are more relevant precursors for this purpose.



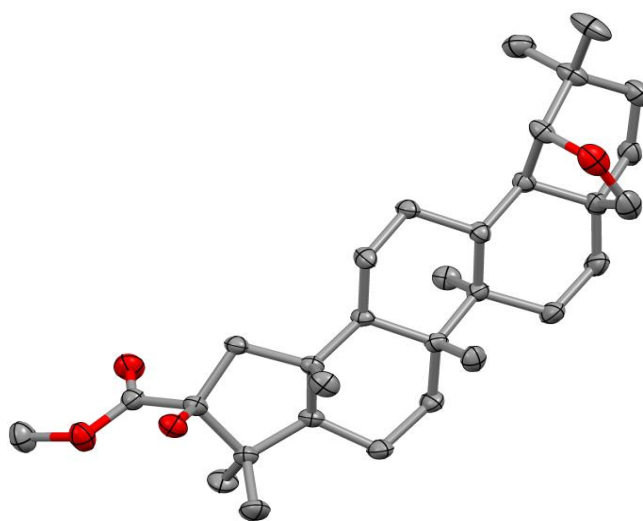
**Scheme 1** Oxidation and A-ring contraction triterpenones

This work is focused on the development of a convenient stereoselective method for A-ring contraction of triterpenones using oxygen and t-BuOK in t-BuOH. In particular, combining the first-step

oxygen oxidation with the second-step benzoic acid rearrangement (BAR) or benzoic ester rearrangement (BER) could lead to the development of a “one pot” ring contraction of 3-oxotriterpenoids into corresponding  $\alpha$ -hydroxycarboxylic acids (BAR) or their esters (BER). Such combination would be successful only if the further oxidation of diosphenols to 2-oxa-2-nortriterpenoids<sup>3b</sup> is avoided. The other goal of this work was to clarify the stereoselectivity of A-ring contraction that could lead to the formation of (S)- and (R)- isomers of tertiary acids or their esters. As ring contraction for 3-oxotriterpenoids was previous studies,<sup>3b</sup> the conditions was also our

(R)- isomers of tertiary acids or their esters. As ring contraction for 3-oxotriterpenoids was not disclosed by influence of reaction matter of interest.

**Fig. 1** The X-ray structure of methyl 19 $\beta$ ,28-epoxy-3 $\beta$ -18 $\alpha$ -oleanan-2-oate (**19**)



structure of methyl hydroxy-1(2 $\rightarrow$ 3)-abeo-

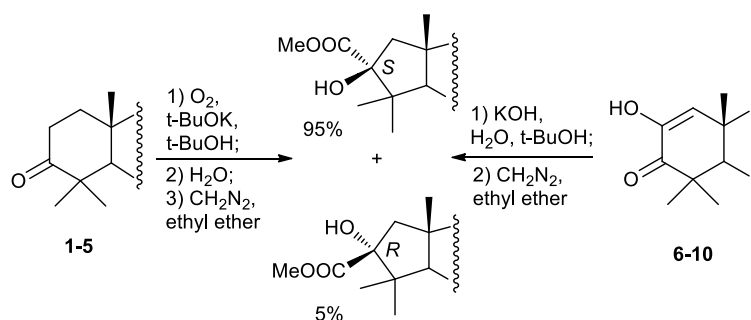
discussion

#### Diosphenols contraction

Starting triterpenoids – lupenone (**1**), betulone (**2**), betulonic acid (**3**), allobetulone (**4**), 3-oxo-18 $\alpha$ -oleanan-28,19 $\beta$ -olide (**5**) and corresponding diosphenols **6–10** (Scheme 1) – were synthesized from commercial lupeol<sup>7</sup> and betulin. Diosphenols **6–10** form smoothly for one hour under these reaction conditions. Stereoselective benzoic acid rearrangement of diosphenols **6–10** into corresponding (S)-hydroxy acids **11–15** occurs with a good yield in KOH/t-BuOH/water over 24 hours at 75 °C. Hydroxy acids **11–15** were esterified with diazomethane into corresponding methyl esters **16–20**. The configurational determination (Fig. 1) was performed by X-ray analysis of the monocystal for ester **19**. Analogous reaction conditions for the oxidation and contraction prompted the possibility of combining the two-step process into a “one-pot” oxidation/contraction process to avoid anisolation of intermediate diosphenols **6–10** (Scheme 1). The introduction of oxygen was interrupted after the complete conversion of starting 3-oxotriterpenoids **1–5** and then the consequent contraction was carried out for 22 hours at 75 °C after adding water to give hydroxy acids **11–15** in >85% overall yields.

#### Selectivity and mechanism of A-ring contraction

Though  $\alpha$ -hydroxycarboxylic acids **11–15** were isolated as (3S)- isomers only (Scheme 1) formation of (3R)-isomers also is possible. Stereoselectivity of analogous contraction was explained by steric factors for chair conformation of  $\alpha$ -diketone rings in previous studies of steroids and triterpenoids. However, these studies did not provide an isomeric resolution of reaction mixtures. We performed a study of benzoic acid rearrangement stereoselectivity through analysis of reaction mixture before product isolation.



**Scheme** of contraction for 3-**1–5** and diosphenols **6–10** with KOH in t-BuOH

**2** Stereoselectivity oxotriterpenoids **10** with KOH in t-

The presence of both isomers were indicated when GC/MS and NMR analyses were performed for crude reaction products that had been methylated with diazomethane (Scheme 2). The influence of reaction conditions on stereoselectivity has been studied for benzoic acid rearrangement of diosphenol

**6.** It was determined (GC/MS) that the (S)/(R)-isomeric ratio of methyl 3 $\beta$ -hydroxy-1(2 $\rightarrow$ 3)-abeolup-20-en-2-oate (**16**) to 3 $\alpha$ hydroxy-1(2 $\rightarrow$ 3)-abeolup-20-en-2-oate (**16'**) was 95/5 for the contraction with KOH in tert-butanol and 81/19 for the contraction with KOH in methanol (BAR). A significant decrease of selectivity (78/22 **16** to **16'** ratio) was observed when diosphenol **6** was treated with KOCH<sub>3</sub> in methanol (BER). Isomeric esters of  $\alpha$ -hydroxycarboxylic acids **16** and **16'** were isolated individually by separation on silica.

#### Conclusion

Efficient "one pot" stereoselective A-ring contraction for 3-oxotriterpenoids was developed. Benzilic acid rearrangement of triterpenoid diosphenols is a stereoselective process with the formation of (S)- $\alpha$ -hydroxy acids as major products. For the first time, corresponding (R)- $\alpha$ -hydroxy acids were detected, isolated and characterized. The stereoselectivities for benzilic rearrangement of diosphenols depend on the reaction conditions (reaction solvent and basic reagent). All synthesized triterpenoids are potential bioactive compounds and being tested for antiviral, anticancer, antibacterial activities.

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## ХІМІЧНІ ТЕОРІЇ КОЛІРНОСТІ

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У даній науковій статті розглядаються фізико-хімічні особливості виникнення кольору, механізм сприйняття кольорів людським оком, а також структура молекул забарвлених речовин. Значна увага приділяється вивченню електронних переходів та спектрів поглинання сонячних променів.

Сприйняття кольору це складний фізико-хімічний процес. Колір, який ми сприймаємо, є результатом декількох процесів: взаємодії магнітних коливань, які створюють світловий промінь, із молекулами речовини; вибіркового поглинання, зумовленого особливостями структури молекул; впливу променів, відбитих на сітківку ока [1].

Сонячний промінь містить світлові хвилі різної довжини. Якщо сонячне світло при падінні на речовину не поглинається, а повністю відбивається і розсіюється, то така речовина буде здаватися білою, а якщо всі промені видимої частини спектру будуть поглинатися речовиною, то ми побачимо її чорною. У тому ж випадку, коли речовина поглинає лише частину променів