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A Concise Approach to the Synthesis of Carnosic Acid Type Diterpenes

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Abstract: 10-vinyl-8,11,13-podocatriene **8**, which is a model of Carnosic acid type diterpenes, has been synthesized by an expeditious convergent synthetic approach.

Keywords: Carnosic acid, synthesis, diterpenes, cyclization, anti-HIV.

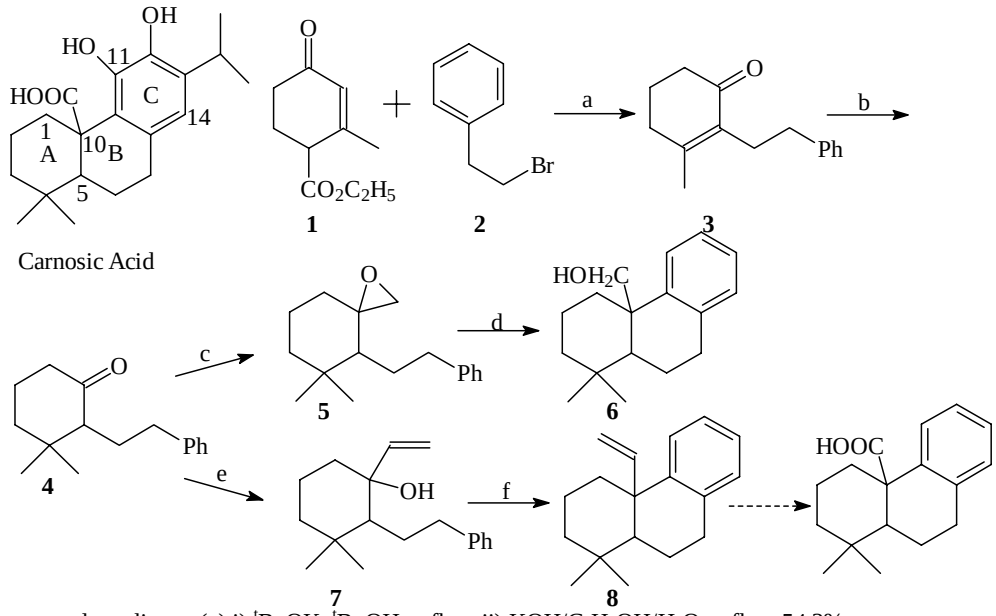
AIDS has seriously affected human being's health and about 13.9 million people have been killed by AIDS in the world. So far, A. Paris *et al*[1] found that Carnosic acid and its analogs posses inhibitory effect on HIV-1 protease and HIV virus replication activity. In order to clarify the structure-active relationship of this kind of compounds, a concise approach was designed, which is a convergent synthesis. Best to our knowledge, it is the first successful convergent route in total synthesis of carnosic acid type diterpenes rather than most A→B→C linear approach which was reported in literature[2]. The outline of this approach is described in **scheme 1**.

Compound **3** was prepared in 54% overall yield by refluxing bromide **2** with a mixture of Hagemann's ester **1** and ^{t}BuOK/^{t}BuOH followed by hydrolysis in refluxing EtOH in the presence of KOH[3]. Treatment of enone **3** with $LiCu(CH_3)_2$ at -30°C gave A/C bicycle intermediate **4** in 87% yield[3]. It is difficult to imagine a more efficient means of synthesis this type compounds by direct epoxy-arene cyclization reaction, especially if the *trans* configuration was required. So at first, the epoxide **5**, which was synthesis in almost quantitative yield by reaction enone **4** with excess $BrCH_2Li$[4] at -80°C, was subjected to epoxy-arene cyclization[5]. Many Lewis Acids were tried. But the compound **6** was obtained in very low yield or no reaction. Consequently, we decided to try to cyclize **7** to **8**. The result showed it was indeed a viable option. By treating **4** at room temperature with excess vinylmagnesium bromide, **7** was obtained in a 92% yield[6]. Then **7** was treated with $TiCl_4$[7] in THF at -90°C to yield the desired compound **8**[8] in 61% yield. **8** can be easily transformed to 10-carboxy aromatic tricycles compound by oxidation.

In conclusion, a short, practical synthesis of carnosic acid type diterpenes has been achieved employing Friedel-Crafts reaction as the key step. Functional group of C-ring to total synthesis of various carnosic acid analogs will be reported in the future

publications.

Scheme 1



Regents and conditons: (a) i) ^{t}BuOK, ^{t}BuOH, reflux; ii) $KOH/C_2H_5OH/H_2O$, reflux, 54.3%; (b) $LiCu(CH_3)_2$, $BF_3 \cdot Et_2O$, THF, -30℃, 87.5%; (c) CH_2Br_2, n-BuLi, THF, -80℃; (d) Lewis Acid, CH_2Cl_2; (e) CH_2=CHBrMg, THF, RT, 92%; (f) $TiCl_4$, THF, -90℃, 61%.

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8. Spectra data of **8**: δ_H (500MHz,$CDCl_3$): 7.03~7.21 (4H,m), 6.27 (1H,dd,J=10.5Hz), 4.98 (1H,dd,J=1,10.5Hz), 4.67 (1H,dd,J=1,10.5Hz), 1.25~2.9 (11H,m), 0.94 (3H,s), 0.88 (3H,s); EI-MS: 240 (M^+,62), 225 (35), 213 (15), 129 (100), 117 (60).

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