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Generating Diversity in Natural Product Scaffolds. Efficient C-17 Alkylations of *ent*-Kaur-16-enic Derivatives

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Abstract. The current work presents the first results on the application of the radical addition methodology for the simultaneous attachment of a C-2 synthon and a functional group to the *ent*-kaurenoic acid methyl ester and its C-15 hydroxylated derivative at the C-17 carbon atom.

Key words: *Carboazidation, radical chemistry, diterpene, kaurane.*

Introduction. Many representatives of tetracyclic *ent*-kauranic diterpenoids, which occur broadly in the plant kingdom, display a diverse biological activity. Investigations of active principles of medicinal plants, especially those used in non-traditional Chinese medicine, have shown that a large spectrum of biological activities, including anti-microbial, anti-inflammatory, the cardio-vascular, diuretic, cytotoxic and ant-AIDS are conditioned by the presence in these plants of *ent*-kauranic diterpenoids [1]. The diversity of this family of compounds is impressive and it stems on a whole plethora of functional groups attached to the *ent*-kauranic backbone. Surprisingly, very recent studies have revealed a group of totally unprecedented hybrids of *ent*-kauranic skeleton with highly oxygenated sesquiterpenes [2]. This example has prompted us to initiate an investigation towards the synthesis of *ent*-kauranic alkylated conjugates through a linkage, involving the C-17 carbon atom.

Material and methods. *Ent*-Kaur-16-en-19-oic **1** and 15α-angeloyl-*ent*-kaur-16-en-19-oic **2** acids were isolated from the wastes of sunflower (*Helianthus Annuus*) as described previously [3, 4]. Methyl-ent-kaurenoate **3** and 15α-angeloyl-methyl-*ent*-kaur-16-en-19-oate **4** were obtained on methylation of **1** and **2** with an etherial solution of diazomethane. Synthesis of 15α-hydroxi-methyl-*ent*-kaur-16-en-19-oate **5** was performed on refluxing **4** with a ethanolic solution of sodium hydroxide. Radical carboiodination or carboazidation of **3** and **5** was performed according to the described procedures [5, 6]. Shortly, the substrate was treated under reflux with ethyl iodoacetate (excess) in the presence of a radical initiator (Bu_6Sn_2 or dilauroyl peroxid, DLP) and an azide source (phenylsulfonylazide). Catalytic amounts of a second initiator (di-tert-butyl hyponitrite, DTBHN) was added periodically to the reaction mixture in the case of carboazidation. The reaction course was monitored by TLC. Usual aqueous workup and flash chromatography provided pure reaction products. Their structural characterization was performed based on spectral data.

Results and discussion. Formation of new C-C bonds remains one of the major challenges in organic synthesis. The apparently simple synthetic problem has a separate significance in the natural product chemistry. Usually, compounds isolated from natural sources represent relevant structural complexity and sometimes, high chemical reactivity. In consequence, elaboration of selective methods for new C-C bond formation requires considerable efforts involving long sequence of transformations and protective group manipulations. Therefore, elaboration of new mild and selective alkylation methods represents a permanent scientific priority.

Among the vast arsenal for selective alkylations, methods based on free radical chemistry are emerging now as powerful tools for mild and selective functional group transformations. Visible light - catalyzed red-ox processes and remote functionalizations of inactivated C-H bonds are among the „hottest” area of research in this context. But in the same time, free radical processes can be also efficiently used for generation of new C-C bonds, introducing new functionalities in the molecules of

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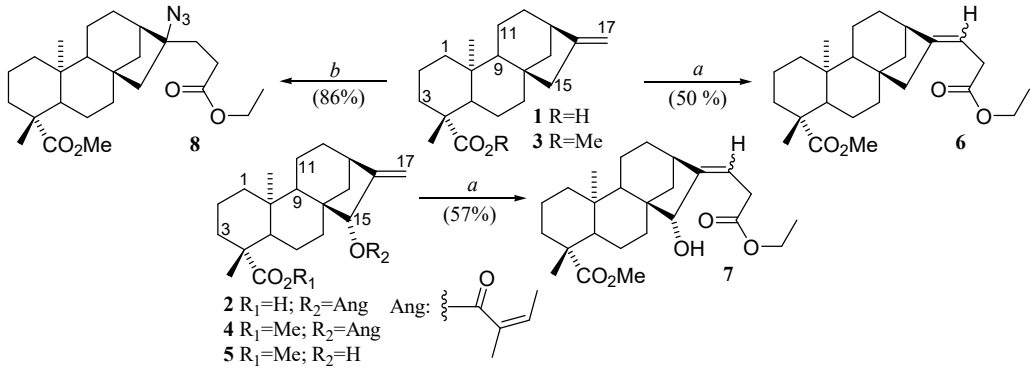
interest under mild reaction conditions that do not affect other functional groups. Such methods are very relevant tools for natural product modifications within diverse SAR studies. *Ent*-Kaurenoic acid **1** can be readily isolated from the wastes of sunflower (*Heliathus Annuus L.*), along with other functionalized derivatives, like C-15 hydroxylated compound **2**. Following chemical modifications of such *ent*-kauranes can bring about new compounds with unknown bioactivities. Using radical chemistry processes for such purposes represents an approach which is underexplored for this class of diterpenoids. Therefore, we embarked on a research project aimed to the modification of readily available *ent*-kauranes with free radical processes. We report here our preliminary results on carboiodination and carboazidation of *ent*-kaurenic esters **3** and **5** (scheme below).



Reagents and conditions: (a) ICH_2CO_2Et, DLP, Ph-H, 24 hrs. reflux; *(b)* ICH_2CO_2Et, Bu_6Sn_2, $PhSO_2N_3$, DTBHN, Ph-H, 2 hrs. reflux.

Carboiodination of both substrates **3** and **5** was relatively sluggish and expected tertiary iodides were not isolated. The basic alkylation products from both substrates were compounds **6** and **7**, which represent products of dehydroiodination of the initially formed iodides.

On the contrary, carboazidation of **3** proceeded with an excellent yield over a much shorter period of time. The obtained products **6** - **8** will be used for following structural modifications.

Conclusions. The present work demonstrates utility of the free radical transformations for efficient structural modification of *ent*-kauranic derivatives. Very convenient alkylation processes based on radical carboiodination and carboazidation can be used for spanning the structural diversity of this class of compounds. This functionalization method allows a one step, high yielding generation of a new C-C bond with simultaneous introduction of an additional functional group. Both can be used for following transformations within diverse SAR investigations.

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