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New strategy toward the diverted synthesis of oxidized abietane diterpenes via oxidation of 6,7-dehydroferruginol methyl ether with dimethyldioxirane

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ABSTRACT

A series of oxidized abietane diterpenes have been synthesized from 8,11,13-abietanotriene. The reaction of 6,7-dehydroferruginol methyl ether with dimethyldioxirane (DMDO) was carried out under various conditions. In all cases, the oxidation of positions C-6 and C-7 were observed with high selectivity when DMDO was used. When some reaction conditions, such as temperature and time were increased, 6α-hydroxysugiol was obtained. Also an interesting formation of the *cis* aminol derivatives was synthesized from *cis* epoxide **12**.

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Dioxiranes are well known oxidants, that have been extensively used to achieve a wide variety of functional group transformations.[1] Dimethyldioxirane (DMDO) is used in common transformations such as epoxidation of alkenes,[2] oxidations of alkynes,[3] oxyfunctionalization of C–H bonds,[4] oxidative cleavage of lactams,[5] and reactions with heteroatoms possessing non-bonding electron pairs, such as N, S, Se, and P.[6]

Abietane diterpenes are widely distributed in the natural sources (Fig. 1). Representative examples are ferruginol (**1**), and 6-hydroxy-5,6-dehydrosugiol (**2**) isolated from the seeds of *Cephalottaxus harringtonia*, which have exhibited important activities.[7] The 6,7-dehydroferruginol methyl ether (**3**) is an antimicrobial agent that has shown activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE).[8] 6α-Hydroxysugiol (**4**), which was isolated from the cones of *Sequoia sempervirens*, has exhibited inhibition against colon, lung, and breast human tumors.[9] In addition, the sugiol methyl ether (**5**), isolated from the bark of *Juniperus formosana* Hay, has also exhibited interesting biological activity.[8,10] The fact that these metabolites exhibit similar biological activity and chemical structure, led us to hypothesize that the oxygen functionality in rings B and C might be responsible for their biological profile.

As part of our research program in the chemistry of diterpenes and their structural modifications, herein we report a fast and simple route to generate abietane diterpenes oxygenated in the C-6

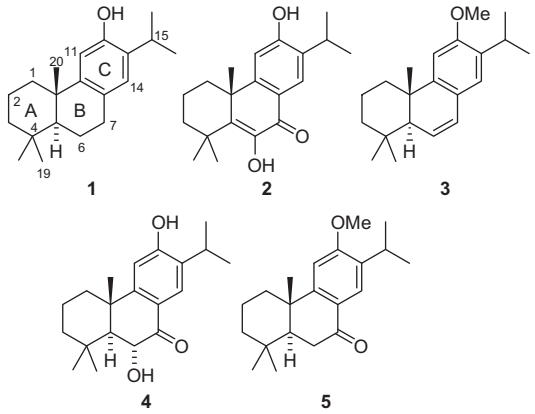

Figure 1. Structure of naturally occurring abietane diterpenes. Ring lettering and relevant atom numbering are shown for compound **1**.

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and C-7 positions with high selectivity, by means of diverse DMDO oxidation conditions.

The synthesis started from the natural diterpene abieta-8,11,13-triene **6** (Scheme 1), which was isolated from *Salvia clevelandii*.[11] Compound **6** was reacted with acetyl chloride in the presence of aluminum chloride to afford ketone **7**. Baeyer–Villiger oxidation of **7** gave compound **8**. A solution of the ester **3** and methanol was treated with potassium carbonate to obtain the known natural diterpene ferruginol **1**, exhibiting spectroscopic data identical to the natural sample. The reaction of **1** with lithium hydroxide in DMF at 0 °C for 4 h afforded the corresponding lithium salt, which was reacted with dimethyl sulfate[12] at 0 °C for 45 min to give the aryl methyl ether **9**. The synthesis of the alcohol **10** was achieved via oxidation of **9** with CrO_3 in acetic acid, followed by reduction of the ketone **5** with sodium borohydride in methanol under inert atmosphere. The resulting diastereomeric mixture of alcohols **10** was then transformed into methyl ether **11** by treatment with mesyl chloride in dry triethylamine at 0 °C.[13] The spectral data of the unsaturated system **11** were in complete agreement with those reported in the literature.[14]

As noted above, a short and efficient procedure was carried out to prepare the key intermediate methyl ether **11** from natural sources. Compound **11** was used as a suitable precursor to have access to oxidized diterpenes through the functionalization of ring B. It is widely known that DMDO is a reagent used in the epoxidation of alkenes in a chemo- and stereoselective manner.[15] Thus, we investigated the scope of the oxidation of abietane diterpens with DMDO. We followed the methodology used by Danishefsky[15] to obtain the unstable epoxide **12** in 80% yield. The epoxide was obtained with high diastereoselectivity (α:β ratio 20:1).[16]

It has been shown that epoxides such as compound **12** are very sensitive to acid conditions and water.[17] To further ascertain the configuration of the epoxide **12**, aminolysis was achieved with $ZnBr_2$ as the catalyst[18] using 4-bromo aniline and 2-iodo aniline to obtain two new β-amine alcohols **13** and **14** in 65% and 54% yields respectively.[19]

The relative stereochemistry of **13** and **14** was determined by the magnitude of the coupling constants and by ROESY experiments. Thus, protons H-6 and H-7 showed correlation with CH_3-20, indicating a *cis* configuration between H-6 and H-7 in the β-face (Fig. 2). The relative stereochemistry observed was surprising at first sight, considering the high reactivity of the benzylic position of C-7 and the possibility of electronic delocalization generating a carbocation via opening of the epoxide. Further

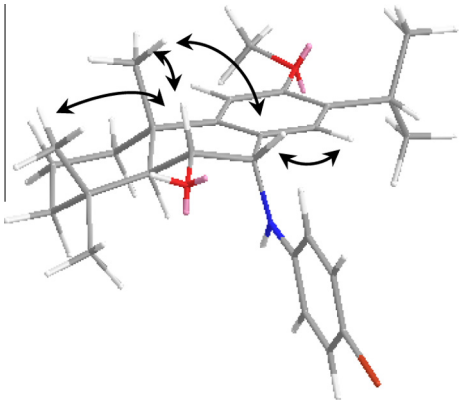
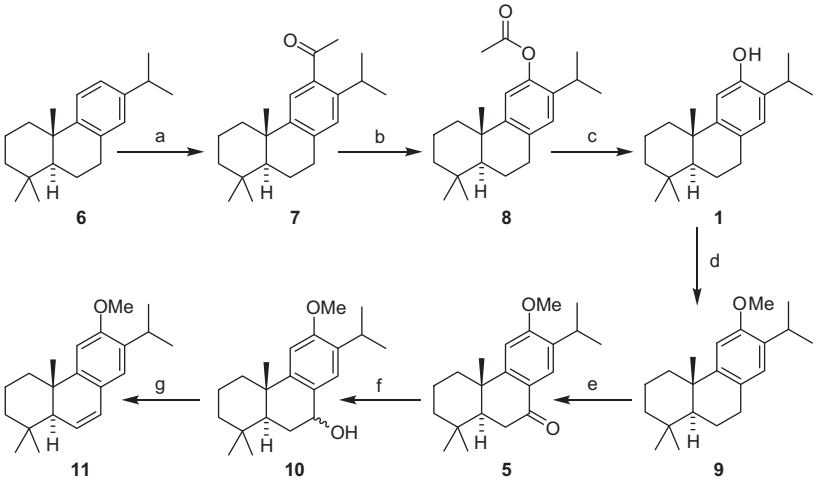


Figure 2. Selected NOESY correlations (double-ended arrows) of **13**.

nucleophilic reaction with an amine on the less hindered face, provided the observed β-amine alcohols with high level of diastereoselectivity.[18] It should occur via amine association with the alkoxide and amine or via zinc binding to alkoxide and amine, delivering the amine in a *cis* fashion.[20]

In order to set the optimal conditions to generate the epoxide **12**, and taking into account the formation of the diol **15** in the presence of water, other derivatives were synthesized under slightly modified conditions (Scheme 2). When the concentration of DMDO was increased by an additional equivalent at −25 °C, the diol **15** yielded 70%. On the other hand, when the temperature, the number of equivalents of DMDO (8.5 equiv), and reaction times were increased, the formation of a 3:1 mixture of **4** and **2**, was observed respectively. As a result, additional oxidation at C-6 and C-7 was observed, in time dependent reaction, similar to what is expected in acetylenic systems.[3] The spectral data of compounds **4** and **2** were in agreement with those reported in the literature.

In conclusion, we are now reporting a simple route to obtain the oxidized abietane diterpenes, similar to that of sugiol which holds great pharmacological interest. DMDO is a convenient reagent for the chemo- and stereoselective oxidation of abietane diterpenes bearing a double bond in position C-6 and C-7. DMDO also represents a mild and effective reagent to provide various desired oxidized derivatives. In addition, aminolysis of epoxide **12** represents an attractive route for the formation of β-amine alcohols. Mechanistic explorations are underway.



Scheme 1. Reagents and conditions: (a) AcCl (5.5 equiv), $AlCl_3$ (5 equiv), CH_2Cl_2, rt, 24 h, under N_2, 92%; (b) *m*-CPBA (2.5 equiv), TsOH (0.1 equiv), $ClCH_2CH_2Cl$, reflux, 5 h, 81%; (c) K_2CO_3 (3 equiv), MeOH/CH_2Cl_2 (2:1), 0 °C, 2 h, 89%; (d) $LiOH{\cdot}H_2O$ (2 equiv), DMF, under N_2, rt, 4 h, then $(MeO)_2SO_2$ (3 equiv), 0 °C, 45 min, 93%; (e) CrO_3 (1.2 equiv), AcOH, rt, 4 h, 63%; (f) $NaBH_4$ (3 equiv), MeOH, rt, 12 h, under N_2, 94%; (g) MsCl (2.5 equiv), Et_3N (4 equiv), CH_2Cl_2, 0 °C, 12 h, under N_2, 79%.

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