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From eudesmanes to eudesmanes: rearrangement of a cyperone derivative with introduction of oxygenated substituents at C-10 and C-4

Josiane Beauhaire and Paul-Henri Ducrot*

Unité de Phytopharmacie et Médiateurs Chimiques, Inra, Route de Saint-Cyr, F-78026 Versailles, France

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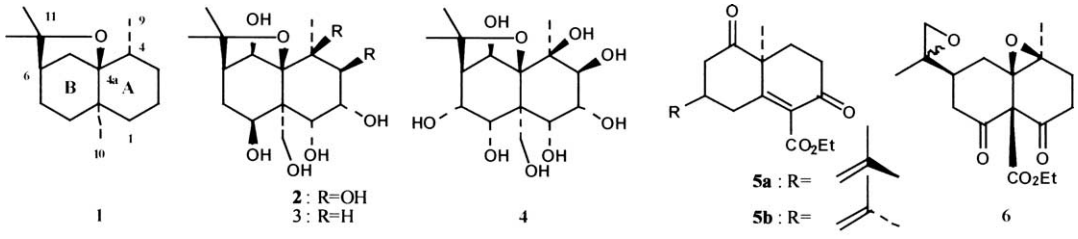
Abstract—In this paper, transformation of cyperone derivative **5b** in diketo epoxide **6**, a potential intermediate for agarofuran sesquiterpenes syntheses, is described in two steps and 36% yield.

Agarofuran esters have attracted a great deal of interest on account of their cytotoxic,[1] antitumor,[2] immunosuppressive,[3] but also insect antifeedant activities.[4] The most commonly encountered derivatives of dihydroagarofuran **1** among celastraceous sesquiterpenes are esters of maytol **2**,[5] 3,4-dideoxy-maytol **3**,[6] and euonyminol **4**.[7]

In a precedent paper,[8] we have tried to show the usefulness of cyperone derivatives as precursors of the agarofuran skeleton. Our efforts were designed to form a C-4 hydroxylated agarofuran starting from cyperone derivative **5a**. However, the synthesis of this useful starting material had to be achieved through Robinson annelation of hydroxy carvone with Nazarov's reagent, which afforded a mixture of both isomers **5a** and **5b** (Scheme 1). We thus decided to consider the possibility of using the undesired product **5b** in a synthesis of C-10 hydroxylated agarofuran sesquiterpenes through rearrangement of the eudesmane skeleton. We indeed have described in an earlier report[9] the possible dienone–phenol like rearrangement, without aromatization, of Wieland–Misher ketone derivatives, involving regioselective Baeyer–Villiger reaction, followed by an intramolecular aldol or Dieckmann ring closure reaction. Taking advantage of the pseudo symmetry of the substrate, this strategy, applied to cyperone derivative **5b**, would indeed afford compounds with an eudesmane skeleton but exhibiting oxygenated functionalities at C-10 and C-4 (Scheme 2) and formal inversion of the configuration at C-6. In the expected product of the reaction sequence, stereogenic centers C-4 and C-6 would therefore have the required relative configurations for the synthesis of natural agarofuran polyols, while the stereochemistry of the ring junction would be putatively controlled during the reduction of the double bond and the thermodynamic ring closure.

In this paper, we want to report our preliminary results toward this goal emphasized by the straightforward synthesis of diketo epoxide **6** in two steps from **5b** and 36% overall yield.



* Corresponding author. Tel.: +33 (0)1 30 83 36 41; fax: +33 (0)1 30 83 31 19; e-mail: ducrot@versailles.inra.fr

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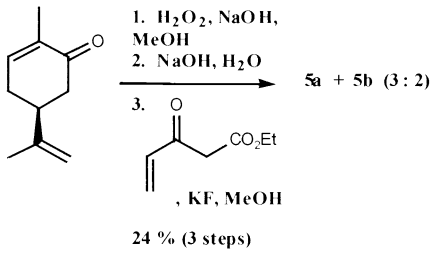
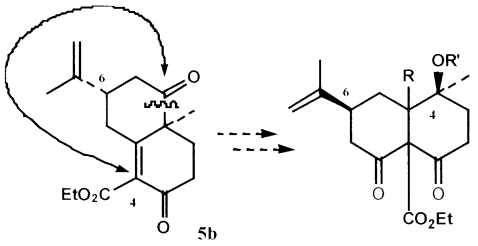


Scheme 1.



Scheme 2.

As expected from our previous works, Baeyer–Villiger reaction (2 equiv. MCPBA, 2 equiv. $NaHCO_3$, CH_2Cl_2, rt, 2 h) performed on diketone **5b** regioselectively afforded the desired epoxy caprolactones **7** (70%), beside substantial amounts of caprolactone **8** (11%) (epoxides **9** being observed in very low yield <2%).

Treatment of **7** in methanolic basic solution (3 equiv. AcONa, THF/MeOH/H_2O (4/2/1), rt, 48 h) gave rise, as expected, to the methyl esters **10**, resulting from transesterification of the lactone. However, further treatment in basic conditions did not allow a further evolution of these methyl esters. Moreover, treatment of **10** by various heteroatomic nucleophiles did not permit us to observe Michael addition on the double bond, which would have allowed the Dieckmann ring closure to occur (Scheme 3).

On the other hand, working with conditions similar to those we described earlier,[9] with adding a catalytic amount of base (H_2O_2 (30% in H_2O), 0.1 equiv. NaOH (5% w/w in H_2O), MeOH (substrate concentration: 1.5 M), rt, 2h) gave rise to the formation of diketo epoxide **6** in 51% yield besides acid **11** (20%) and recovered starting material (18%). The structure of **6**[10] was fully elucidated after reduction of both keto groups (4 equiv. $LiAlH_4$, THF, 0°C), which led to epoxy diol **12**. Indeed, besides observation of characteristic nOes, the anisotropic effect of the 4,4a-epoxide oxygen allows the easy observation of both H-5α and H-5β (1.05 and 1.84 ppm, respectively), coupling constants of which with the neighboring H-6 clearly demonstrate the equatorial position of the epoxy isopropyl side chain on a *cis* decalinic system.

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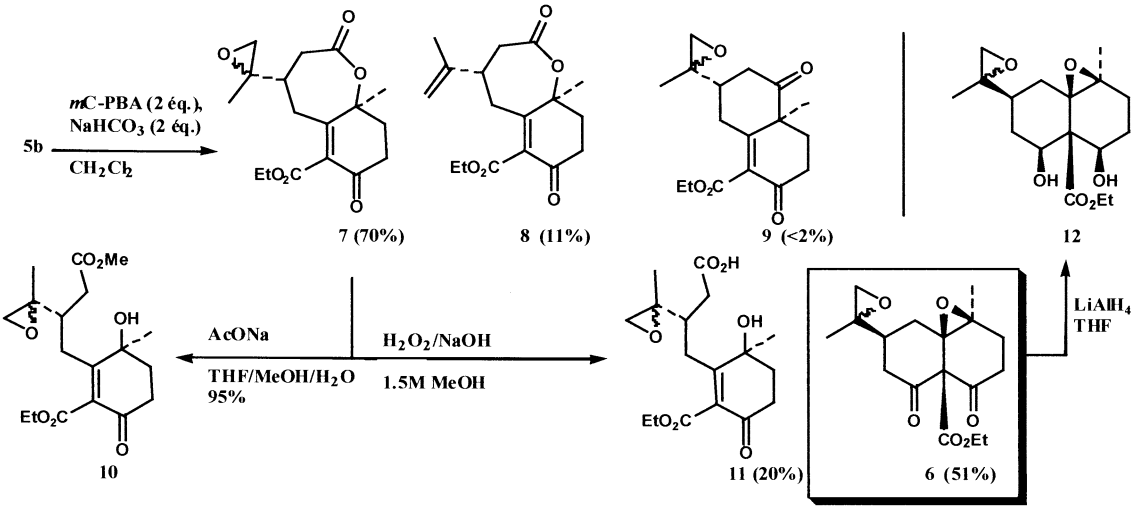

Scheme 3.

10. All new compounds gave satisfactory analytical data: **6** (1:1 mixture of diastereomers): ($C_{17}H_{22}O_6$) calcd: C, 63.34; H, 6.88; O, 29.78; found: C, 63.05; H, 6.94. F= 130°C (AcOEt) ^{13}C (75 MHz) δ (ppm): 208.9 (s), 199.7 (s), 164.2 (s), 72.0 (s), 66.0 (s), 62.2 (t), {57.6, 57.5} (s), {52.8, 52.3} (t), {47.3, 47.2} (s), {39.4, 38.9} (t), {39.1, 38.9} (d), 32.4 (t), {28.3, 27.9} (t), 23.0 (t), 20.9 (q), {18.8, 18.4} (q), 14.1 (q).