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The cyperone route to agarofurans: stereoselective introduction of an hydroxy group at C-4

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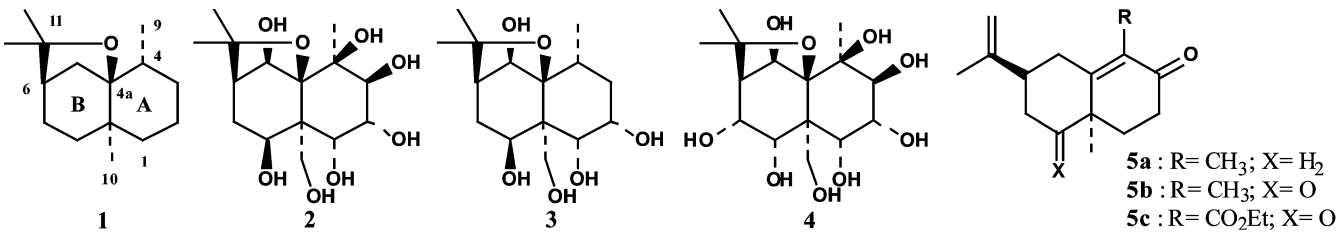
Abstract—In this paper, the construction of the agarofuran tricyclic ring system bearing an hydroxy group at C-4, with the correct configuration at C-4, is described through the rearrangement of the 4,4a α-epoxy 9-benzoyloxy cyperone derivative **11**, readily available from cyperone derivative **5c**, under acidic conditions.

The role of plant secondary metabolites in host plant recognition, especially in oligophagous insects, is of great importance. Substances eliciting feeding responses of the insects have been extensively studied and numerous attempts have also been made in the past decades to isolate antifeedants from plants avoided by insect species. Beside well-known compounds such as azadirachtine[1] or clerodanes,[2] polyesters of agarofurans have been demonstrated to exhibit interesting antifeedant activity.

Indeed, several studies have demonstrated plants of the Celastraceae family to be a rich source of hydroxylated sesquiterpene esters based on the dihydroagarofuran skeleton **1**. These compounds have attracted a great deal of interest on account of their cytotoxic,[3] antitumor,[4] immunosuppressive,[5] but also insect antifeedant activities.[6] The most commonly encountered derivatives of **1** among celastraceous sesquiterpenes are esters of maytol **2**,[7] 3,4-dideoxy-maytol **3**,[8] and euonyminol **4**.[9]

Although several total syntheses of agarofurans have been reported in the literature,[10–12] the main problem of these syntheses remains the introduction of the oxygenated heterocycle with the correct configurations of the asymmetric centers. Indeed, it forces either the hydroxy-isopropyl substituent on cycle B of the agarofuran to be introduced at C-6 in an axial position or the configuration at C-6 to be controlled in the last steps of the synthesis devoted to the heterocycle ring closure.[12] We have already published a new synthetic approach toward the synthesis of highly hydroxylated decalinic systems as putative precursors of agarofurans.[13a] We have also proposed solutions to control the configuration of the asymmetric centers of the heterocycle.[13b] However, even if it has proven possible to alleviate the difficulty of introducing the hydroxy-isopropyl substituent with the correct configuration of the newly created asymmetric center, it was nevertheless useful to design synthetic approaches of agarofurans using as starting material of the synthesis a precursor already incorporating this key feature of the target molecule. Indeed most of the reported synthetic approaches to agarofurans were using either cyperone **5a**, oxo-cyperone **5b**[10a] or santonin[10b] as starting material of the synthesis. The major drawback of the 'cyperone route', which seems to be nevertheless the most versatile route to agarofurans, rests on the lack of stereoselectivity



1 **2** **3** **4**

5a : R= CH_3; X= H_2
5b : R= CH_3; X= O
5c : R= CO_2Et; X= O

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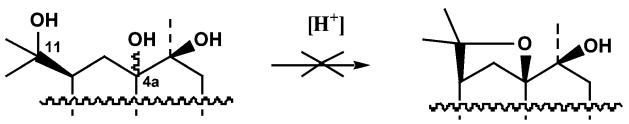
encountered while introducing an hydroxy group at C-4. In order to explore the structure–activity relationships in the antifeedant activity of agarofuran esters, we decided to reinvestigate the 'cyperone route' to have access to a large number of agarofuran polyols with various hydroxylation patterns. As previous interesting reports have shown the 'cyperone route' to be compatible with introduction of hydroxy groups at C-1 and C-2,[14] we focused our efforts on the design of synthetic strategies aimed at the stereoselective introduction of hydroxy groups at C-4.

The lack of selectivity of the introduction of an hydroxy group at C-4 in the previous reports has to be related to the fact that the heterocycle ring closure has to be effected through acidic treatment of a 4a,11-diol, and is therefore incompatible with the presence of an unprotected tertiary hydroxy group at C-4 (Scheme 1).[15] The functionalization at C-4 had therefore to be achieved after the formation of the agarofuran backbone and its stereochemistry is controlled by steric factors generated by the tetrahydrofuran ring.

In this paper, we report that the presence of an hydroxy group on the carbon atom C-9 of cyperone allows the control of the introduction of the C-4 hydroxy group, before heterocycle formation, through the rearrangement of the 4,4a α-epoxy 9-benzoyloxy cyperone under acidic conditions, leading to the formation of a 4β-benzoyloxy cyperone derivative with inversion of the configuration at C-4, which allows a subsequent acido-catalyzed formation of the tetrahydrofuran ring.

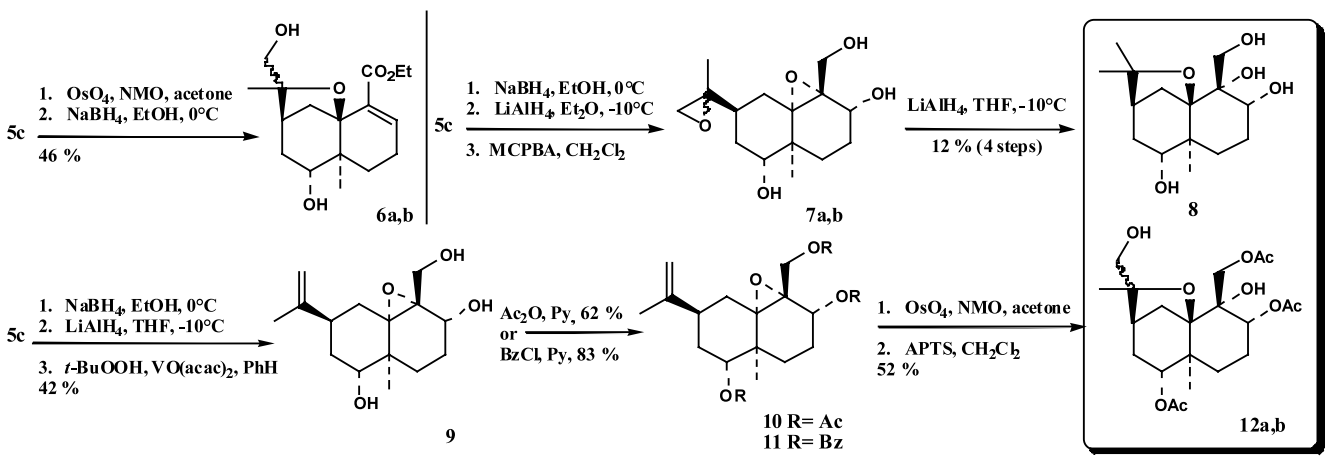
Introduction of an hydroxy group at C-9 of cyperone required us to start the synthetic scheme from easily obtained cyperone derivative **5c**, which is readily available, as a racemate, through Robinson annelation of



Scheme 1.

hydroxycarvone with Nazarov's reagent. First of all, we decided to optimize the already reported agarofuran formation procedures to substrate **5c** (Scheme 2). According to previous reports, osmylation occurred regioselectively on the double bond of the isopropenyl substituent without stereoselectivity and subsequent reduction of both ketones ($NaBH_4$) led to the formation of the agarofuran backbone through spontaneous S_N2' attack of the hydroxy group at C-11 on the allylic alcohol. A mixture of **6a** and **6b** was thereby obtained in 46% overall yield. We then turned to the consecutive reduction of all carbonyl groups of **5c**. Consecutive treatment of **5c** by sodium borohydride and lithium aluminohydride, followed by classical epoxidation of both double bonds (MCPBA) led to a mixture of diepoxy triols **7a**,**b**. Reductive opening of the less substituted 11,12-epoxide then occurred with concomitant tetrahydrofuran formation through opening of the 4,4a-epoxide by the newly generated hydroxy group at C-11. Agarofuran **8** was thereby obtained in 12% overall yield from **5c**.

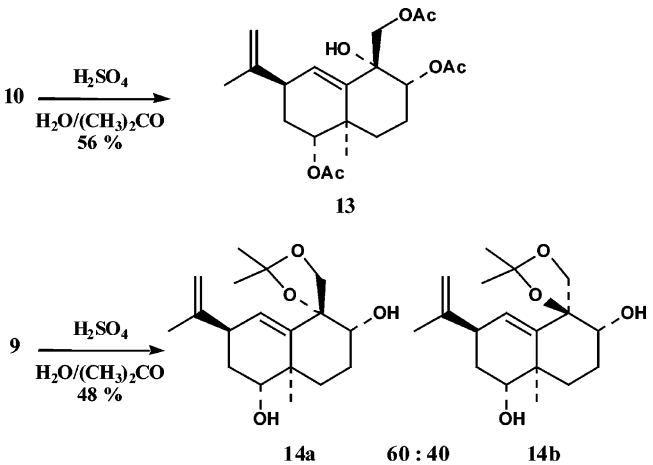
Moreover, the presence of an hydroxy group at C-3 allowed us to perform the regioselective epoxidation of the $\Delta^{4,4a}$ double bond ($VO(acac)_2$, t-BuO_2H), leading to epoxide **9**, the hydroxy groups of which can be protected as acetyl or benzoyl esters. Osmylation of **10** and acidic treatment led to a mixture of agarofuran tetraol **12a**,**b**. In both latter synthetic sequences, the 4,4a-epoxyde acted as a masked hydroxy group at C-4, introduced before the heterocycle ring closure and thus allowed us to avoid the problems depicted on Scheme 1. However, in both **8** and **12**, the relative configuration at C-4 obtained was in fact the opposite of that encountered in most of the natural products, because of the selectivity of the $\Delta^{4,4a}$ epoxidation step, which cannot be inverted, whatever the experimental conditions used. Nevertheless, the presence of the tetrasubstituted 4,4a α-epoxide in compounds **10** and **11** prompted us to investigate their behavior when treated with various acids. Indeed, one could assume that the acidic treatment of such an epoxide could lead to the formation of a carbocation either at C-4 or C-4a, trapping of which by water should allow the formation of the correspond-



Scheme 2.

ing 4,4a-diol with possible inversion of configuration at the carbon atom, where the cation would have been formed. Treatment of triacetate **10** with sulfuric acid in acetone indeed led to the formation of dehydrated compound **13**, which resulted from the carbocation formation at C-4a, trapping of this cation by water and dehydration. In this case, no control on the regiochemistry of the carbocation formation was possible. However, the same experimental procedure using unprotected triol **9** as substrate led to the formation of a diastereomeric mixture of acetals **14a** an **14b** (Scheme 3). While formation of **14a** is explained by the formation of a carbocation at C-4a, quenching of this cation with water, dehydration and protection of the resulting diol, the obtention of acetal **14b**, with inversion of configuration at C-4 should necessarily result from the epoxide ring opening at C-4 in an intramolecular process involving, as the first step of the sequence, formation of a hemiacetal of the hydroxy group at C-9 with acetone (Scheme 4). Indeed, formation of a carbocation at C-4 before hemiacetal formation would have allowed formation of the unobserved 4,9-epoxide through a Payne-like rearrangement.

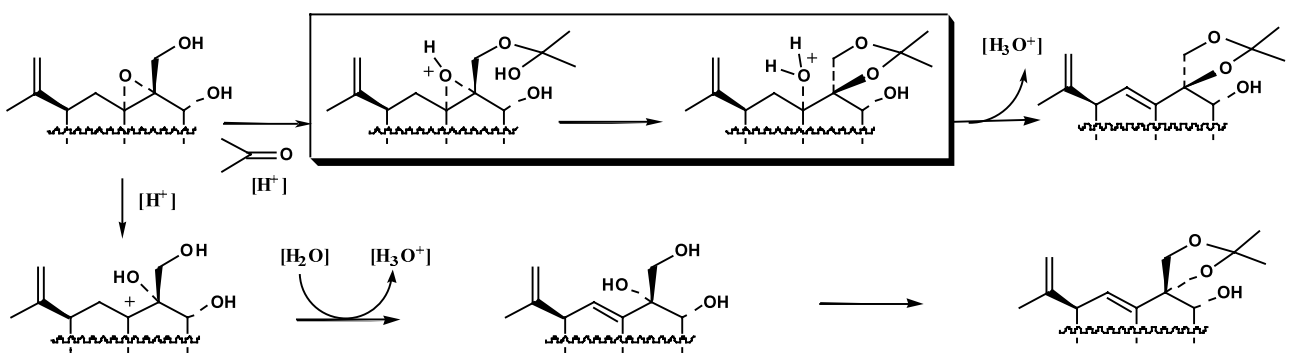
Thus, according to already reported examples of intramolecular acetyl group migration with vicinal epoxide ring opening,[16–19] which should rely on a similar mechanism, we decided to explore the possibility of such an acyl group migration with epoxide ring opening on compounds **10** and **11** under non-aqueous conditions.



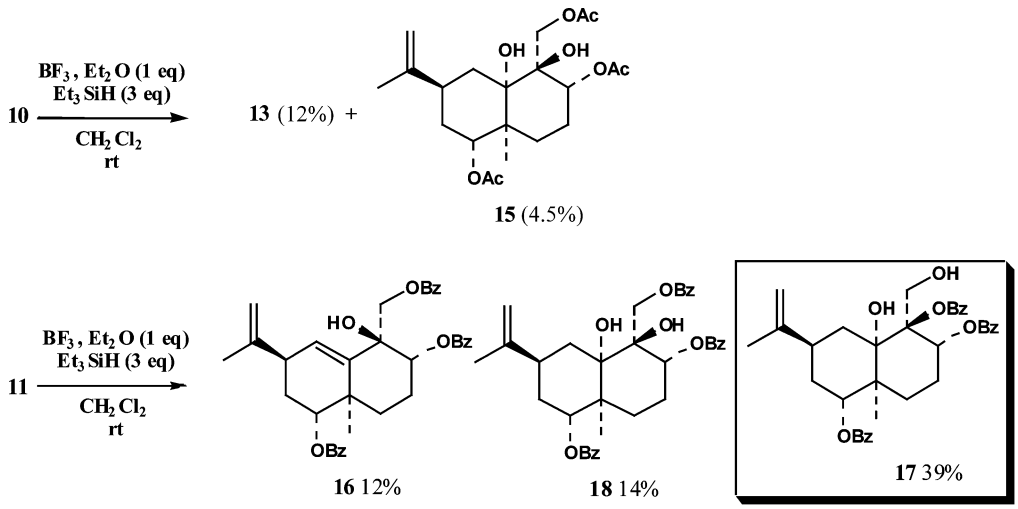
Scheme 3.

We therefore turned to the use of boron trifluoride[19] etherate in various solvents. The results obtained when boron trifluoride was used alone were rather disappointing since the reaction produced as major products, compounds with rearranged carbon skeletons. However, we found that addition of triethylsilane to the reaction mixture was an effective way of preventing these backbone transformations. If the role of triethylsilane in this procedure remains unclear, it definitely did not act as a reducing agent. In these optimized conditions the only factor allowing the control of the course of the reaction was the solvent. Use of a polar solvent like acetonitrile favored the formation of dehydrated compounds similar to those obtained upon treatment with aqueous sulfuric acid. On the other hand, use of apolar solvents allowed the formation of the desired rearranged compounds with acyl migration from carbon 11 to carbon 4. When using dichloromethane as solvent and peracetyled triol **10** as substrate, however, the major product of the reaction remained dehydrated compound **13**. The desired rearranged compound was never observed but opening of the 4,4a-epoxide through formation of a carbocation at carbon 4 was observed in 4.5% yield and was proven to occur with inversion of the configuration at C-4, leading to diol **15**. Finally, the use of **11** as starting material of the reaction, due to the better migrating ability of the benzoyl group, led to the formation of three major compounds. The expected dehydrated alcohol **16** was formed in only 12% yield, while the rearranged benzoate **17** was obtained in 39% yield. Besides these two expected products, compound **18**, similar to **15**, was also obtained in 14% yield (Scheme 5). In both latter cases, inversion of the configuration at C-4 was proven to have occured through examination of the NMR data.[20]

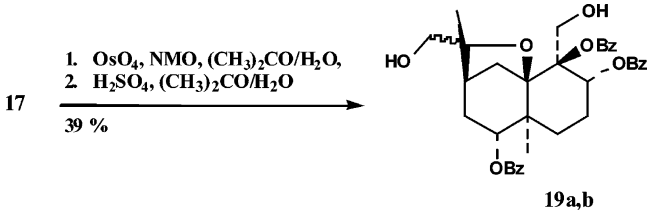
Thereafter, agarofuran formation was achieved through osmylation of the remaining double bond of **17** followed by acidic treatment, resulting in the formation of a mixture of agarofurans **19a**,**b** since the configuration at C-11 was not controlled in this reaction sequence (Scheme 6).



Scheme 4.



Scheme 5.



Scheme 6.

The easy formation of agarofurans **19** shows the formation of protected 4-alcohols to be the key step in the synthesis of highly hydroxylated agarofurans esters through the 'cyperone route'.

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20. All new compounds gave satisfactory analytical data. Selected NMR data ($CDCl_3$): **16**: ^1H NMR (300 MHz) δ (ppm) (J (Hz)): 7.35–8.15 (m, 15H); 5.92 (d, 1H, 4); 5.33 (dd, 1H, 12, 6); 5.07 (dd, 1H, 11, 4); 4.73 (bs, 1H); 4.71 (d, 1H, 13); 4.67 (bs, 1H); 4.35 (d, 1H, 13); 2.98 (td, 1H, 4, 2); 1.77 (s, 3H); 1.62 (s, 3H); 1.5–2.4 (m, 6H); ^{13}C NMR (75 MHz): 166.1 (2C); 165.3; 146.5; 139.0; 128.7; 128.5–133.4 (3*C_6H_5); 112.9; 77.8; 75.5; 74.6; 63.8; 42.2; 39.0; 34.8; 30.3; 27.0; 22.0; 20.6. **17**: ^1H NMR (300 MHz) δ (ppm) (J (Hz)): 7.35–8.10 (m, 15H); 5.82 (t, 1H, 7); 5.24 (dd, 1H, 11, 6); 4.90 (bs, 1H); 4.34 (bs, 1H); 4.13 (d, 1H, 12); 3.92 (d, 1H, 12) (at low concentration, protons at 4.13 and 3.92 ppm exhibit a coupling constant of 7 and 5 Hz, respectively, with an exchangeable proton at 4.75

ppm); 3.46 (d, 1H, 16); 2.61 (m, 1H); 2.56 (m, 1H); 1.8–2.3 (m, 6H); 1.71 (s, 3H); 1.68 (s, 3H); ^{13}C NMR (75 MHz): 166.4; 166.3; 165.9; 147.7; 128.5–133.4 (3*C_6H_5); 111.4; 92.6; 77.3; 75.4; 74.1; 66.8; 44.8; 36.8; 29.1; 27.0; 23.5; 23.1; 22.6; 16.7. **18**: ^{1}H NMR (300 MHz) δ (ppm) (J (Hz)): 7.15–8.15 (m, 15H); 5.43 (dd, 1H, 12 7); 5.18 (d, 1H, 12); 5.15 (bs, 1H); 4.96 (d, 1H, 12); 4.85 (bs, 1H); 4.83 (bs, 1H); 2.72 (bm, 1H); 2.63 (bd, 1H, 14); 1.8–2.1 (m, 7H); 1.81 (s, 3H); 1.28 (s, 3H); ^{13}C NMR (75 MHz): 166.7; 166.4; 165.9; 148.4; 128.2–133.8 (3*C_6H_5); 109.7; 80.5; 79.3; 78.0; 77.4; 63.6; 41.2; 35.6; 34.1; 31.1; 29.9; 24.5; 21.4; 19.4.