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Total Synthesis of 16-Acetoxy-6,7-didehydroferruginyl Methyl Ether

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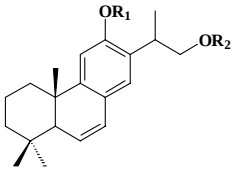
Abstract: An efficient synthetic route have been developed to 16-acetoxy-6,7-didehydroferruginyl methyl ether.

Keywords: Total synthesis, 16-hydroxy-6,7-didehydroferruginol, 16-acetoxy-6,7-didehydro-ferruginyl methyl ether.

16-Hydroxy-6,7-didehydroferruginol **1** was isolated from the root of *Salvia apiana* by Anonio G. *et al*[1]. It is interesting to medicinal and synthetic scientist that the oxidative status of C16 in this molecular. Based on our knowledge, no synthetic way had been conducted to this compound and to further explore the relationship between structure and bioactivities, we here report an efficient synthetic route to the 16-acetoxy-6,7-didehydroferruginyl methyl ether **2**.

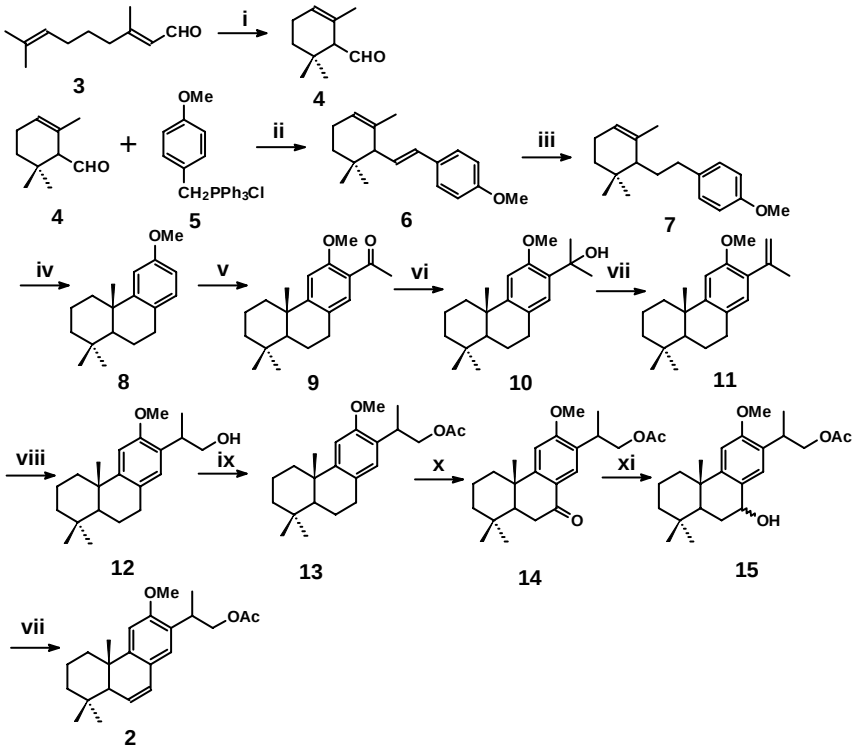


1 **R_1=R_2=H**
2 R_1=Me R_2=Ac

As shown in **Scheme 1**, we used AC→ABC strategy. Acid promoted cyclization of citral **3** gave the (α)-cyclocitral **4**. Condensation of **4** with (4-methoxybenzyl)-triphenylphosphonium chloride **5** (prepared form *p*-anisic acid *via* 3 steps) at the presence of n-BuLi yield the styrene derivative **6** in 60% yield. Partial hydrogenation of **6** in ethanol over 10% Pd/C gave compound **7**. To stereoselectively obtain the compound **8** (A/B ring is *trans* junction), we tested several conditions. Finally, we found that BF_3 Et_2O in CH_2Cl_2 is a better cylcization reagent which gave the *trans* isomer nearly quantitively. Treatment of **8** with acetyl chloride and anhydrous $AlCl_3$ in CH_2Cl_2 gave **9**. The compound **10** was obtained in high yield by treatment of **9** with MeLi in THF. Dehydration of **10** with *p*-Tos/benzene gave the styrene derivative **11** in 90% yield. Hydroboration and oxidation of **11** (BH_3 Me_2S, THF, 0°C; NaOH H_2O_2,

90% yield) gave the alcohol **12**. The compound **14** was obtained *via* protection (Ac_2O/Pyr.) and oxidation (CrO_3 /HOAc) from compound **12**. Reduction of **14** with $NaBH_4$ in CH_3OH gave the alcohol **15** quantitively. The title compound **2**[2]was obtained in high yield by dehydration of **15** with *p*-Tos/benzene.

Scheme 1



i: 95% H_2SO_4 (30%); ii: n-BuLi, hexane, r.t. (60%); iii: 10% Pd/C, (100%); iv: BF_3 Et_2O, CH_2Cl_2, (>95%) ; v: acetyl chloride, $AlCl_3$, overnight, (90%); vi: MeLi, 95%; vii: *p*-Tos, benzene, reflux, (90%); viii: BH_3 Me_2S, THF, NaOH, H_2O_2, 85%; ix: Ac_2O/Pyr, 90%; x: CrO_3/HOAc, r.t. 0.5hr ; xi: $NaBH_4$, CH_3OH. r.t. 95%

In conclusion, we had developed an efficient synthetic way to the 6-acetoxy-6,7-didehydroferruginyl methyl ether.

References

1. G. G. Antonio, E. A. Zahira, A. G. Tersen, G. L. Javier, *Phytochemistry*, **1992** *31*(5), 1691.
2. All compound gave satisfactory elemental analysis and spectroscopic data. Selected spectroscopic data of compound **2** : IR (KBr, cm^{-1}) 2932, 1722, 1500, 1350. MS *m/z* (EI): 342, 327, 121, ^1H NMR (400Mhz $CDCl_3$ δ/ppm) 0.89, 0.95, 0.97(each 3H, s, Me-18, Me-19, Me-20), 1.16 (3H, d, *J*=7.0Hz, H-17), 1.94(3H, s, OAc), 3.37(1H, m, H-15), 3.73 (3H, s, OMe), 4.05 (2H, m H-16), 5.80(1H, dd, *J*=9.5, 2.7Hz H-7), 6.39(1H, dd, *J*=9.5, 2.7Hz H-6), 6.62 (1H, s, H-14), 6.78 (1H, s, H-11),

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