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First Total Synthesis of the Linear Abietane Diterpenoid Orthoquinone Umbrosone

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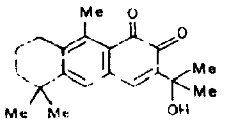
Abstract : The first total synthesis of the rearranged linear abietane diterpenoid orthoquinone, umbrosone (1), was accomplished through a simple convergent route via the tricyclic ketone 11.

The unusual rearranged linear abietane diterpenoid orthoquinone, umbrosone (1)[1], isolated from *Hyptis umbrosa* Slazm (Lamiaceae), exhibited[1] significant activity against gram-positive bacteria. A few other structurally related quinones, pygmaeocine E (2)[2], aegyptinone A (3)[3] and aegyptinone B (4)[3] have been isolated from a number of medicinal plants, some of which are linear homologous structures[3] related to the cytotoxic tanshinones. The potential bioactivity of these new diterpenoid quinones makes them attractive synthetic targets. We report herein the first total synthesis of umbrosone (1), employing a simple flexible and convergent route[4], suitable for the preparation of the other members of this family.



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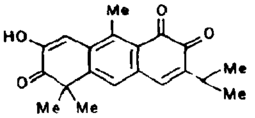

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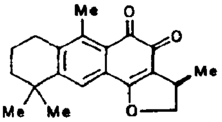

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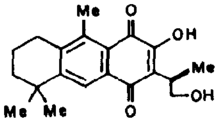

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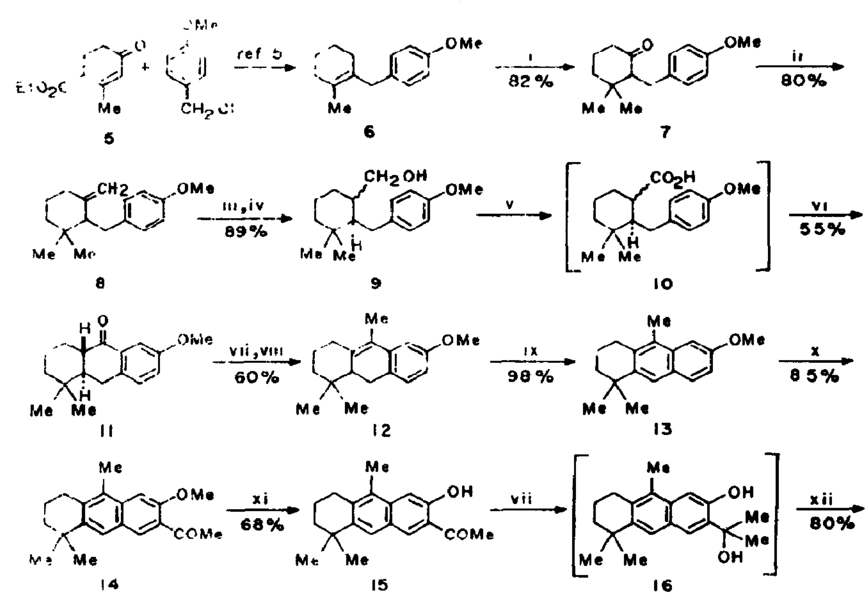
The gem-dimethylcyclohexanone 7[5] (Scheme), obtained in excellent yield from Hagemann's ester (5), through the known[6] cyclohexenone 6, was transformed to the alkene 8. Hydroboration of 8 followed by oxidation with alkaline hydrogen peroxide gave the epimeric mixture of alcohols 9, which on further oxidation with Jones reagent afforded the epimeric acids mixture 10. The direct cyclization of the acids 10 with polyphosphoric acid gave a ketonic product which on chromatography over acidic alumina column afforded a single crystalline epimer 11, mp 118°C assigned as the stable trans-stereoisomer from analogies.[7] The condensation of methylmagnesium iodide with the ketone 11 followed by dehydration gave the styrene 12, which underwent smooth dehydrogenation leading to the tetrahydroanthracene ether 13, mp 110°C. Friedel-Crafts acylation of 13 gave the light yellow oxo-ether 14, mp 91°C. Demethylation of 14 afforded the oxo-phenol 15, mp 210°C. This on condensation with methylmagnesium iodide (3eq) gave the relatively unstable phenolic alcohol 16 which on oxidation with freshly prepared Fremy's salt[8] afforded umbrosone (1), as shining dark red needles, mp 163°C (lit.[1] mp 163-165°C) after chromatography over silica gel (EtOAc-n-hexane). The spectroscopic data obtained for the synthetic 1 were in all respects identical to those reported[1] for the natural product.

Scheme



Reagents : i, $LiMe_2$ Cu-$BF_3.Et_2O$ (-50°C, 1h); ii, sodium tert-pentoxide-$Ph_3P^+MeI^-$-toluene (60-65°C, 3h); iii, B_2H_6-THF; iv, NaOH-H_2O_2; v, Jones reagent-CH_3COCH_3(0°C 1h); vi, PPA (85°C, 2h); vii, MeMgI-Et_2O; viii, $KHSO_4$ (140°C, 30 min); ix, Pd-C (10%)-xylene (reflux 7h); x, CH_3COCl (1.5eq)-$AlCl_3$ (1.6eq)-CH_2Cl_2 (0°C, 1h, r.t. overnight); xi, $AlCl_3$ (1.2eq)-EtSH (2.5eq)-CH_2Cl_2 (0°C, 1h, r.t. overnight); xii, Fremy's salt (2eq)-KH_2PO_4 (2eq)-MeOH (0°C, 1h, r.t. overnight).

In conclusion, the first total synthesis of the rearranged tetrahydroanthraquinonoid diterpene, umbrosone has been realized through a simple route.

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