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A NEW SYNTHESIS OF dl-MUSCOPYRIDINE BASED ON THE REGIOSELECTIVE CYCLOPENTENONE ANNULATION

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Sulphuric acid catalyzed ring closure of propargyl alcohol dianion adduct of 2-cyclododecenone gives bicyclo[10.3.0]pentadec-1(12),2-dien-13-one. 1,6-Conjugate addition of methyl group followed by ring-expansion and aromatization affords the title compounds.

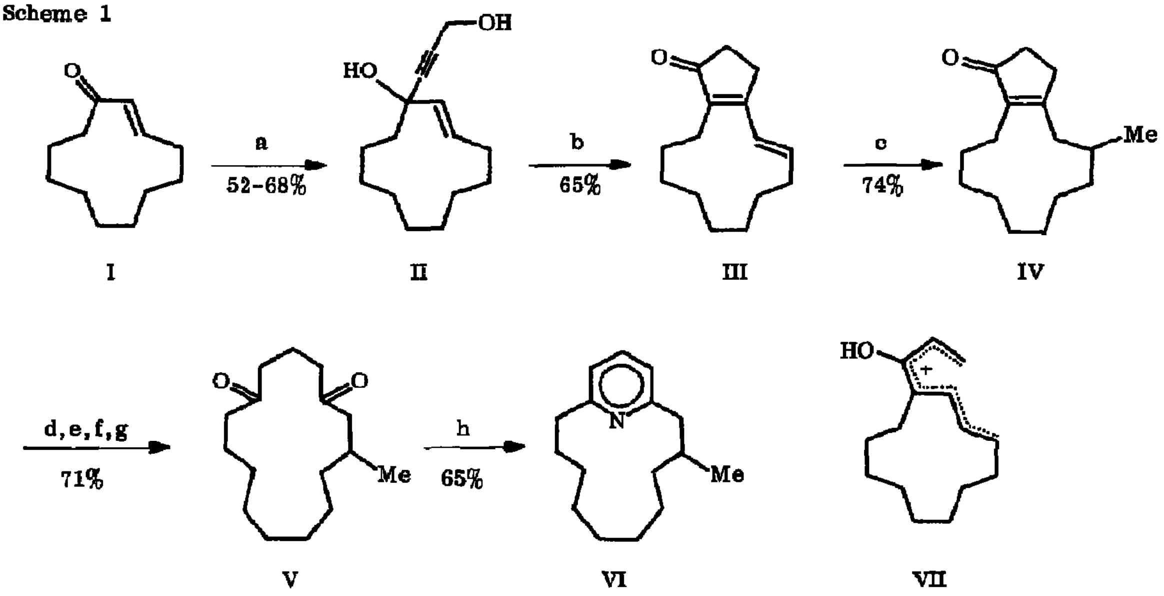
The recently established cyclopentenone annulation[1] involves the conrotatory ring closure of 3-hydroxypentadienyl cation intermediates. An easy access to this end employs propargyl alcohol dianion adducts of cyclic ketones.[1a,b] We have extended the concept to 2-cyclododecenone and found that the annulation takes place likewise regioselectively to give a conjugated dienone III. This was further proved to be a useful intermediate for dl-muscopyridine synthesis (Scheme 1).[2,3]

To a methanol (80 ml) solution of II[4] (1.20 g) was added conc sulphuric acid (40 ml) at the temperature of -20° to -3° and the reaction mixture was allowed to warm to room temperature in 14 hr. Work-up followed by chromatographic purification (silica gel, hexane-AcOEt 5:1 elution) gave the dienone III[4] (0.72 g) in 65% yield as a single product (colorless needles, mp 87-87.5° from hexane; PMR (CCl_4): δ 6.17 (1 H, dt, J = 16.5, 4.5 Hz), 6.68 (1 H, d, J = 16.5 Hz); IR (CCl_4): 1693, 1643, 1596, 972 cm^{-1}; UV max (EtOH): 281 nm, log ε 4.3). These spectral data are fully consistent with the structure III. The formation of the conjugated dienone is reasonably explained in terms of the conrotatory ring closure of the heptatrienyl cation intermediate VII to a vinylcyclopentenyl cation, since the disrotatory ring closure of VII to a cycloheptadienyl cation is sterically hindered by the octamethylene chain. It is worthy to note that the C(2) of 2-cyclododecenone solely is incorporated into the five-membered ring.

Conjugate 1,6-addition of methyl group to the dienone III was selectively effected with methylmagnesium iodide in the presence of copper(I) chloride[5] to give the bicyclic cyclopentenone IV[4] in 74% isolated yield. Subsequent transformation to the diketone V was carried out according to the procedure found by Gray and Dreiding.[6] Thus, the bicyclic cyclopentenone IV was reduced to an allyl alcohol which was then oxidized to an epoxy alcohol. Tosylation followed by solvolysis gave the diketone V[4] in 71% overall yield.

Final treatment of V with hydroxylamine hydrochloride in ethanol at 160° (sealed tube)[7] gave dl-muscopyridine in 65% yield, which exhibited correct spectra.[8,9]

Scheme 1



(a) LiC≡CCH$_2$OLi, THF, -78°-r.t., (b) H$_2$SO$_4$-MeOH (1:2), -20°-r.t., (c) MeMgI-CuCl, THF-Et$_2$O (1:1), 0°, (d) NaBH$_4$, (e) m-Cl-C$_6$H$_4$CO$_3$H, (f) TsCl, pyridine, (g) H$_2$O-dioxane, CaCO$_3$, reflux, (h) NH$_2$OH·HCl, EtOH, 160°

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