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Anionic Oxy-Cope Reaction of a Divinyl Cyclobutanol, Pleuromutilin Model Study

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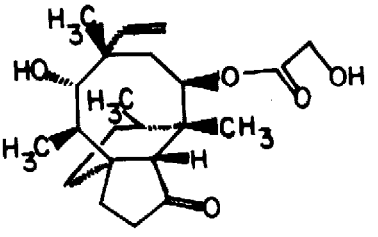
SUMMARY: An approach to the pleuromutilin skeleton via the use of an anionic oxy-Cope[1a,b,c,d] reaction in the construction of an eight membered ring is described.

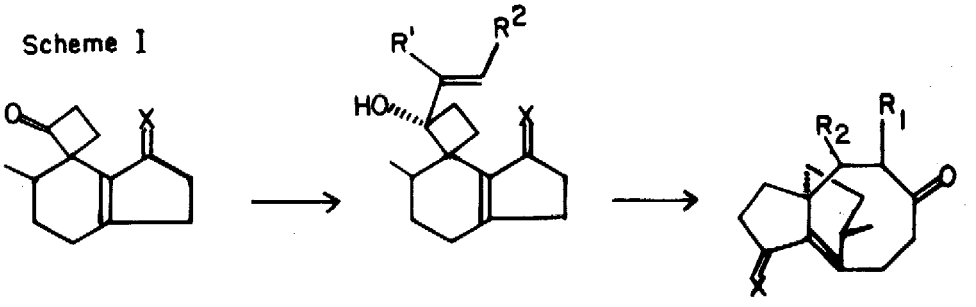
The antibiotic pleuromutilin[2,3](1), isolated from the Basidiomycetes Pleurotus mutilus, is active against gram-positive bacteria. It is most unusual in that its biosynthesis does not follow established patterns.

(1)



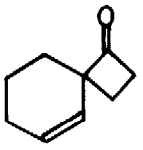
An approach to the synthesis of pleuromutilin[4] is outlined in Scheme I. A spirocyclobutanone derivative[5a] would be coupled with a vinylanion fragment and this system would then rearrange via the oxy-Cope reaction to provide an entry to the skeleton of pleuromutilin.

Scheme I



Below we report some encouraging experiments in this regard. Spiroannulation of cyclohexenone, according to Trost[5a] with 1-lithiocyclopropyl phenyl sulfide,[5b] rearrangement and hydrolysis with fluoboric acid afforded spirocyclobutanone 2 in 58% yield. Treatment of 2 with vinylmagnesium bromide afforded the tertiary allylic alcohol 3[6], which without purification was rearranged via its potassium alkoxide in tetrahydrofuran[1a] (55°, 30 min) to give a 35% yield of 4[7], after purification by chromatography on silica gel.[8] Diimide reduction of 4 and subsequent Jones oxidation gave 5[7] in 88% yield.

Further work directed towards the total synthesis of pleuromutilin as well as more general applications of the divinyl cyclobutanol to cyclooctenone rearrangement is being investigated.



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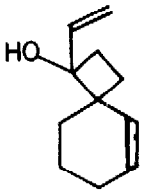

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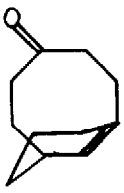

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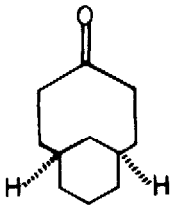

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6. The structure of all new compounds is consistent with their IR, NMR and MS data.
7. Selected spectral data for compound 4 IR (CCl_4) 1705 cm^{-1} MS m/e 165.1 (M + 1), 164.1 (M), 136.1 (-CO) ^1H NMR ($CDCl_3$) (270 MHz) δ 5.17 (bs, 1H), δ 3.07-1.03 (m, 15H) ^{13}C NMR ($CDCl_3$) δ 21.37, 25.67, 29.38, 33.63, 36.24, 38.15, 38.45, 48.04, 128.61, 142.04, 217.33 and 5 IR (CCl_4) 1705 cm^{-1} MS m/e, 166.2 (M) ^1H NMR ($CDCl_3$) 90 MHz δ 2.89-1.3 (m, 18H) ^{13}C NMR ($CDCl_3$) δ 16.46, 28.70, 29.41, 30.39, 31.78, 42.90, 215.24
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