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SIMPLE SYNTHESES OF (±)-ß-COPAENE, (±)-ß-YLANGENE AND LEMNALOL.

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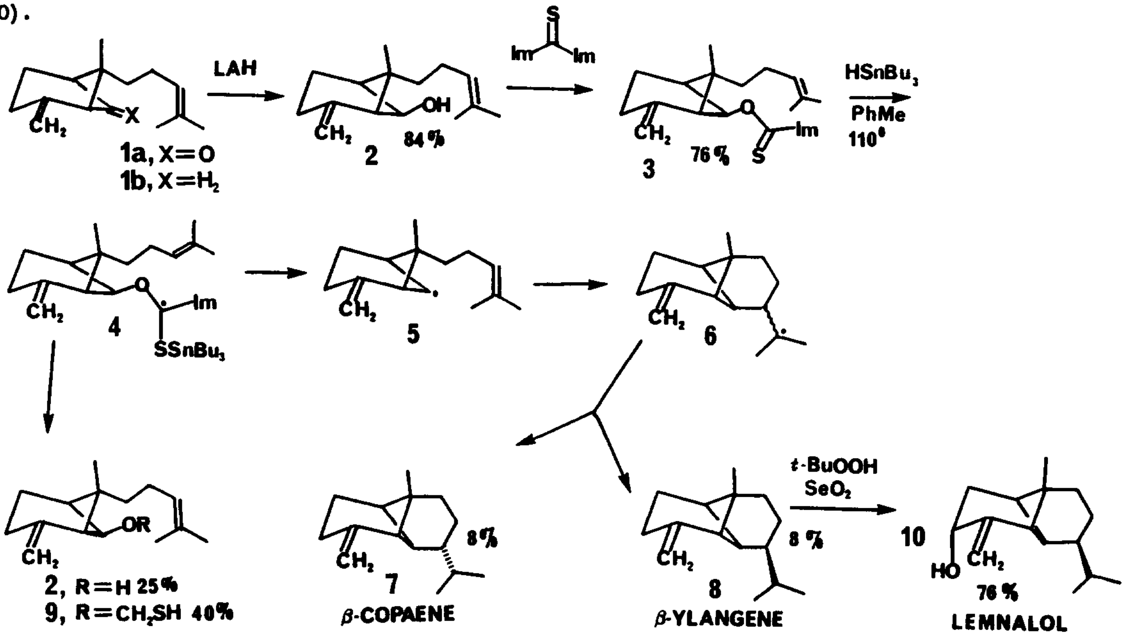
Abstract: The ketone 1a, which we have prepared from geranylacetone in 38% yield by a four step sequence, has been converted to ß-copaene and ß-ylangene by a three step sequence. Oxidation of ß-ylangene with SeO_2 gives lemnalol in 76% yield.

We have recently reported the four step synthesis of 1a from geranylacetone in 38% overall yield and the conversion of 1a to ß-trans-bergamotene (1b) by a Wolff-Kishner reduction.[1,2] The key step in the synthesis of 1a was a novel intramolecular [2 + 2] cycloaddition of a vinylketene. We report here a simple method for the conversion of the versatile intermediate 1a to the tricyclic sesquiterpenes ß-copaene (7), ß-ylangene (8) and lemnalol (10).



The conversion of 1a to ß-copaene and ß-ylangene required a four electron reduction and the formation of a bond between the carbonyl carbon and the proximal end of the trisubstituted double bond. This transformation appeared to be most readily accomplished by the Barton-McCombie method for the deoxygenation of secondary alcohols.[3,4] This procedure should generate the cyclobutyl radical 5 which should cyclize to 6 faster than it reacts with tri-n-butyltin hydride to give **1b**. The cyclization of related radicals is precedented in Bakuzis' syntheses of sativene and copacamphene.[5]

Reduction of **1a** with lithium aluminum hydride (THF, 10 h, 25 °C) gave the alcohol **2** in 84% yield, which was treated with thiocarbonyldiimidazole (2 equiv., CH_2Cl_2, 12 h) followed by flash chromatography to give the imidazolide **3** in 76% yield. Reaction of **3** with tri-n-butyltin hydride in toluene at reflux for 3 hours gave a 1:1 mixture of ß-copaene (**7**) and ß-ylangene (**8**) in 15% yield, accompanied by recovered alcohol **2** in 25% yield and hemithioacetal **9** in 40% yield. ß-trans-Bergamotene (**1b**), which would be formed by the direct reduction of **5**, was not observed. Since **9** can be hydrolyzed to **2** in good yield (1:1:1 THF-H_2O-AcOH, 48 h, 25 °C) the yield of ß-copaene and ß-ylangene is 43% based on recovered starting material.

ß-Copaene and ß-ylangene were readily separated by preparative GC on XF-1150 at 90 °C (t_r = 26 and 23 min, respectively). This is a marked improvement over the procedures reported in previous syntheses of these compounds[6] and their α-isomers.[6,7] The H NMR and IR spectra of **7** and **8** are identical to those previously reported.[6]

Oxidation of ß-ylangene with SeO_2 and t-butyl hydroperoxide[8] gave a 76% yield of the anti-tumor agent lemnalol (**10**) which was identical to an authentic sample by H and ^{13}C NMR and IR spectral and TLC comparison.[9] The selective formation of the axial alcohol has previously been observed in the related oxidation of ß-pinene.[8]

The low yield of **7** and **8** in the Barton deoxygenation is probably a result of the instability of the strained cyclobutyl radical **5**, which slows down the fragmentation of **4** allowing the competing reduction to give **9** to become an important side reaction. Reduction of the imidazolide in xylene at reflux[10] or the xanthate in toluene at reflux gave comparable results. Reduction of the phenyl thionocarbonate ester[11] gave no tricyclic products.

The simple syntheses reported here further demonstrate the utility of the intramolecular cycloaddition of ketenes in organic synthesis. We are continuing to exploit these reactions and are examining alternate approaches to tricyclic systems.

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