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# REGIOSELECTIVE CYCLOADDITION OF γ,γ-DIMETHYLACONIC ACID WITH ISOPRENE.

# A NOVEL SYNTHESIS OF dl-MENTHONE

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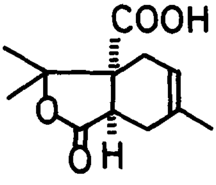
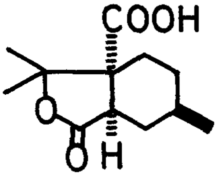
In the course of a study of β-carboxy-α-butenolides, [1,2] it was found that the butenolide C=C bond undergoes a facile 1,3-dipolar addition to give the corresponding cycloadduct. [1] This discovery prompted an investigation of the reaction of butenolides with dienes. [3] We wish to report here the regioselective cycloaddition of γ,γ-dimethylaconic acid with isoprene to give a lactone derivative of dl-4,5-dicarboxy-α-terpineol (1), an intermediate of potential utility in monoterpene synthesis such as dl-menthone.

Reaction of γ,γ-dimethylaconic acid [4] with 3 equivalents of isoprene in benzene in a sealed tube at 140-150° for 3 days gave (1), mp 198-202°, 91% yield, after recrystallization from benzene-acetone, ir (Nujol) 1746 (C=O) $cm^{-1}$. Esterification of (1) with diazomethane afforded the methyl ester of (1), bp 127° (2 mm); ir (neat) 1782 (lactone C=O), 1736 (ester C=O) $cm^{-1}$; nmr ($CDCl_3$) τ 4.65 (m, 1H, =CH), 6.26 (s, 3H, $CH_3O$), 6.40 (m, 1H, COCH), 7.30-7.85 (m, 4H, $2CH_2$), 8.32 (bs, 3H, $CH_3C$=C), 8.50, 8.66 (2s, 6H, $2CH_3$). The elemental analysis and mass spectrum (70 eV, m/e 238 ($M^+$)) of the methyl ester were in agreement with the formula $C_{13}H_{18}O_4$. Glpc analysis of the methyl ester showed a single peak (Rt 10.0 min, SE-30, 4 ∅, 3 m long, at 175°, $H_2$ 30 ml/min).

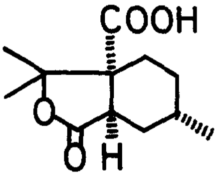
Hydrogenation of the crystalline lactone acid (1) was carried out in dioxane in the presence of Adams catalyst and was followed by thermal decarboxylation at 220-240° to afford the γ-lactone (3), bp 133-135° (5 mm), in 80-82% yield. Fractional distillation of (3) gave (3a) (75%), (3b) (19%), and (3c) (6%). Reduction of (3a) with lithium aluminum hydride



1



2a



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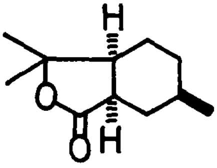
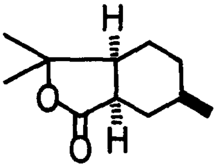
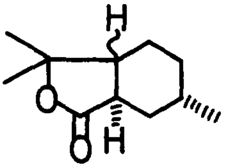


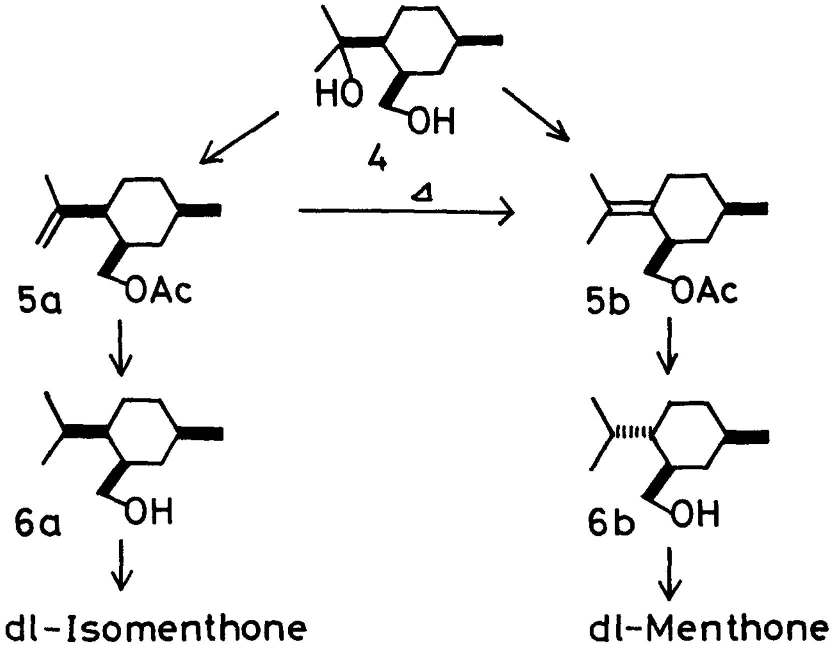
3a



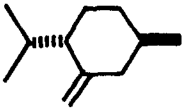
3b



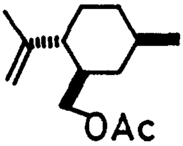
3c



provided the diol (4) in good yield. When (4) was treated with an excess of acetic anhydride at 130-140° for ca. 1 hr, the acetate (5a) was isolated together with 20-30% of its isomer (5b).[5] The isopropenyl derivative (5a) was converted into (5b) after prolonged heating at 140-150° for 3 hr yielded (5b), bp 85-90° (2 mm) bath temperature, in 84% yield. Catalytic hydrogenation of (5b) using platinum oxide gave the saturated alcohol (6b), bp 73-74° (2 mm), in 95% yield after hydrolysis of the saturated acetate, bp 88 (3 mm).[6] Conversion of (6b) to the corresponding xanthate, followed by pyrolytic elimination, produced the olefin (7), bp 83° (20 mm) bath temperature, in ca. 70% yield based on (6b).[7] Ozonolysis of (7) in methylene chloride at -70° gave dl-menthone in ca. 90% yield.[8] dl-Isomenthone was obtained by an analogous sequence from the acetate (5a) <u>via</u> the alcohol (6a). The structure of (3b) was established by reduction with lithium aluminum hydride followed by dehydration with acetic anhydride to give the acetate (8), from which the alcohol (6b) was obtained upon hydrogenation.[9]

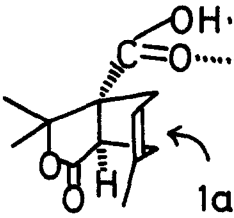


**7**

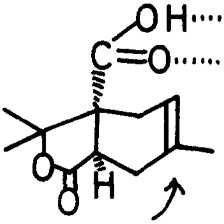


**8**

With regard to the hydrogenation of (1), it would be expected that two isomers (2a and 2b) could be produced. Stereoselective hydrogenation, giving a (2a : 2b) ratio of 94 : 6, is consistent with preferred addition of hydrogen to the less hindered *α* side of the $\pi$ system of (1) in either an endo (1a) or exo (1b) conformation. Decarboxylation of (2a), giving (3a)



**1a**



**1b**

and (3b), occurs with predominant retention of configuration leading to the more stable cis fused lactone. The overall process therefore provides a convenient means of access to an all cis 1,2,4-trisubstituted cyclohexane. Stereoselective hydrogenation of (5b), giving the acetate of (6b), was also observed when the pure acetate (5b), isolated by preparative glpc, was hydrogenated in dry ethanol.

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8. Synthetic dl-menthone and dl-isomenthone were identified by comparison of their spectral data with those of authentic specimens.
9. The purified products were characterized by infrared, nuclear magnetic resonance, and mass spectrometric analyses, which were in accordance with the assigned structures. Satisfactory elemental analyses were obtained for all new compounds.