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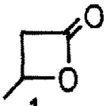
A NOVEL METHOD FOR THE TERPENE SYNTHESIS BY THE RING-OPENING REACTION OF β-METHYL-β-PROPIOLACTONE

Tamotsu Fujisawa,* Toshio Sato, Tatsuo Kawara, Atsunari Noda, and Toshiyuki Obinata
Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan

Summary; *A new route for the terpene synthesis is investigated, which undergoes via terpene carboxylic acids as key intermediates obtained by the regiospecific ring opening of β-methyl-β-propiolactone with a cuprate or with a Grignard reagent in the presence of a copper catalyst.*

We wish to report here a novel method for the terpene synthesis *via* a key intermediate, 3,7-dimethyl-6-octenoic acid (citronellic acid) or 3,7,11-trimethyl-6,10-dodecadienoic acid, which is easily obtained from β-methyl-β-propiolactone (C_4 unit) and homoprenyl (C_6 unit) or homogeranyl Grignard reagent (C_{11} unit). The key step for the terpene synthesis is the regiospecific ring-opening reaction of β-methyl-β-propiolactone with a cuprate or with a Grignard reagent in the presence of a copper(I) catalyst, which has been developed in our laboratory.[1]

One of the starting materials, β-methyl-β-propiolactone (1) is easily available by the hydrogenation of ketene dimer.[2] The reaction of the lactone with bromomagnesium dihomoprenylcuprate (2), prepared from homoprenylmagnesium bromide (3) (2 equiv) and copper(I) iodide (1 equiv) in THF-Me_2S (12:1) at -40 °C, was performed at -40 °C for 1 h, and then the reaction mixture was allowed to warm to -10 °C for over 1 h to result in a formation of citronellic acid (4)[3] in a yield of 87%.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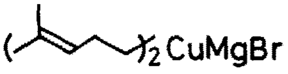

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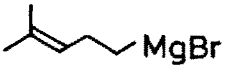

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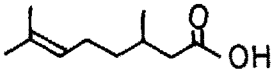

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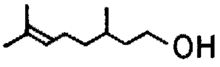
Although one of two homoprenyl groups in the cuprate was in vain, the problem was easily solved by the copper-catalyzed reaction of the lactone with equimolar amount of the Grignard reagent, which was also successful to give the same terpene carboxylic acid. Thus, when homoprenyl Grignard reagent (3) was added to a mixture of the lactone and copper(I) iodide (2 mol %) in THF-Me_2S (20:1) at -15 °C and then the solution was allowed to warm to -3 °C for over 4 h, 4 was obtained in a yield of 90%.

A monoterpene alcohol, citronellol (5) was easily derived from 4 by the esterification with CH_2N_2 followed by the reduction with $LiAlH_4$ in 94% yield. Pulegone (6), a cyclic monoterpene, was also prepared from 4. Intramolecular cyclization of the corresponding acid chloride, prepared by the treatment of 4 with $SOCl_2$ and pyridine, with $BF_3 \cdot OEt_2$ in CH_2Cl_2 at r.t. for two days, followed by the treatment with K_2CO_3 in methanol at r.t. for 3 h, afforded 6 in 63% yield. Synthesis of geraniol (8) and nerol (9) was readily conducted by the introduction of double bond into α,β-position of the ester of 4. According to the procedure by Trost et al.[4], the sulfenylation with dimethyl disulfide furnished α-methylsulfenyl ester in 85% yield. Oxidation with sodium methaperiodate followed by refluxing in toluene for 20 h in the presence of $CaCO_3$ gave methyl geranate (7)[3] (E:Z=1:1,[5] 81% yield). A mixture of 8 and 9 was obtained in 81% yield by the reduction of 7 with $LiAlH_4$.



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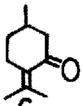

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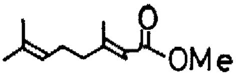

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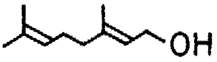

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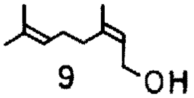

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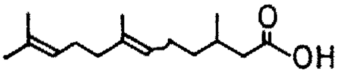
A sesquiterpene alcohol, farnesol (12) was also synthesized *via* the key intermediate, 3,7,11-trimethyl-6,10-dodecadienoic acid (10), by utilizing the ring-opening reaction of β-methyl-β-propiolactone. When the Grignard reagent of homogeranyl bromide (E:Z=72:28)[6] was added to a mixture of the lactone and 2 mol % of copper(I) iodide in THF-Me_2S at -10 °C, and then the solution was maintained at -10~-5 °C for 1 h, 10 was obtained in a yield of 80%. Methyl farnesoate (11)[3] (Z,Z:Z,E:E,Z:E,E=14:14:36:36)[5] was obtained in a yield of 62% by the identical procedure as that described for methyl geranate. Reduction of 11 with $LiAlH_4$ furnished 12[3] in a yield of 85%.



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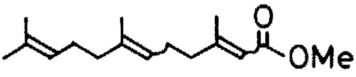

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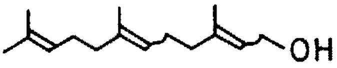

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Thus, the regiospecific ring-opening of β-methyl-β-propiolactone should provide a promising method for the synthesis of a wide variety of terpenes by a combination with various organometallic reagents, and by further transformation of the carboxylic group to other functional groups.

References

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