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TOTAL SYNTHESIS OF 6-OXO-GRINDELIC ACID METHYL ESTER†)

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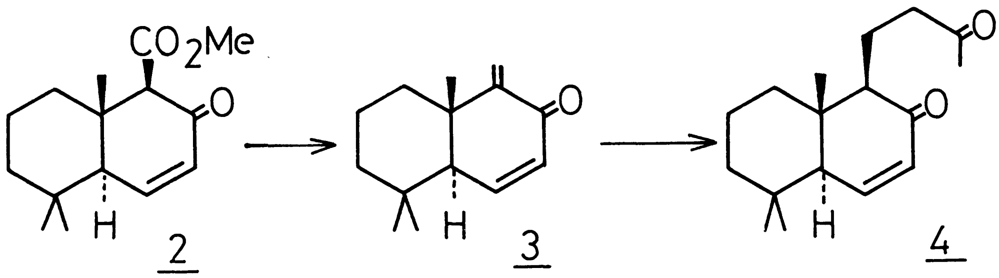
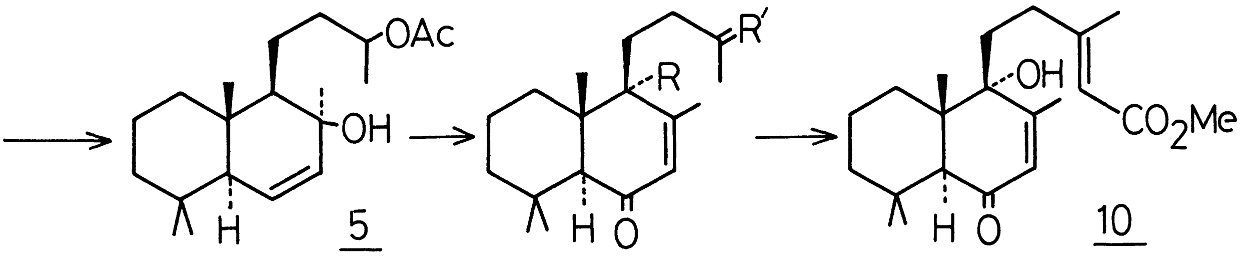
The first synthesis of the methyl ester of 6-oxo-grindelic acid (1) from decalone derivative 2 through γ-hydroxyenone 7 was described.

6-Oxo-grindelic acid (1) isolated from *Grindelica robsta*1) is a highly oxidized labdane type diterpene. The presence of the adjacent oxidized functional groups of this molecule aroused interest of its synthesis.

Recently we have developed2) the two new synthetic methods of 9-carbomethoxy-$\Delta^{6(7)}$-4,4,10-trimethyl decalone (2), one of which is the direct photocyclization of 10-carbomethoxy-β-ionone enolate and the other is the thermal electrocyclic reaction of 7,8-cis-10-carbomethoxy-β-ionone enolacetate followed by methanolysis. Compound 2 bears exactly adequate functional groups accessible to the synthesis of 6-oxo-grindelic acid (1). Thus 6-oxo function could be introduced by the oxidative rearrangement of chromic ester3) of t-8-β-hydroxyl group which is generated by methylation of the carbonyl at C-8, and SeO_2 oxidation of the resulted enone could yield the tertiary hydroxyl function required for the ether linkage at C-9.

Compound 2 was converted to exomethylene enone 34) ($LiAlH_4$, MnO_2, H^+, 88 % yield) which was derived to diketone 4 (methyl acetoacetate/catalytic NaOMe/MeOH, 1.3 equiv. of 1 % NaOH/H_2O-MeOH, H^+-heating, 81 % overall yield). 8-β-Hydroxyl derivative 5 was obtained by reduction ($LiAlH_4$) of 4 followed by selective oxidation (MnO_2), methylation (excess MeLi, ether)5), and acetylation (Ac_2O-Py) (80 % yield from 4). The successful oxidative rearrangement of 5 to enone 6 was achieved by CrO_3-5 % aq H_2SO_4 in ether (0°C, 2 h, 84 % yield) and then SeO_2 oxidation of 6 afforded γ-hydroxyenone 7 in 41 % yield (dioxane, reflux, 30 m)5). C-9-hydroxyl group was protected as tetrahydropyranyl ether (dihydropyran, PPTS) prior to hydrolysis (aq K_2CO_3, MeOH) of acetoxyl group and following oxidation ($CrO_3 \cdot 2Py$) to avoid the formation of hemiacetal 8 which did not react with Wittig-Horner reagent. 9 (48 % from 7) afforded unsaturated ester 10 by Wittig-Horner reaction ($(CH_3O)_2POCH_2CO_2CH_3$, NaH, THF, quantitative yield) followed by removing the protecting group (70 % AcOH, room temp., overnight). The Z isomer of 10 was less than 5 % by the nmr spectrum. Finally the synthesis of 6-oxo-grindelic acid methyl ester (11), mp 71-73°C, was achieved by a treatment of 10 with triethylamine (reflux, 24 h, ~50 % yield for the last two steps)6). The nmr and ir spectra of synthesized 11 were identical with those reported for the methyl ester of natural compound 1.

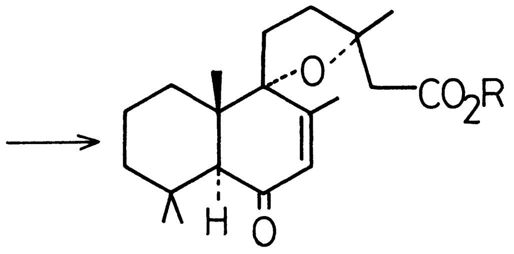




6 R=H, R′=H, OAc

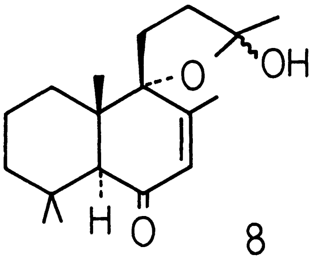
7 R=OH, R′=H, OAc

9 R=OTHP, R′=O



11 R=CH_3

1 R=H



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References

†) Dedicated to Emeritus Professor Takeo Sakan on the occasion of his 70th birthday.

1) L. Mangoni and M. Balardini, Gazz. Chim. Ital., 92, 983 (1962).
2) The details will be reported elsewhere.
3) W. G. Dauben and D. M. Michno, J. Org. Chem., 42, 682 (1977).
4) Satisfactory spectral data were obtained for all new compounds.
5) Both methyl at C-8 and hydroxyl at C-9 must be introduced exclusively from the less hindered α-side.
6) This reaction afforded the one stereoisomer predominantly as a major product. The stereochemistry at the C-13 position of the methyl ester of natural compound (1) is unknown.

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