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SYNTHESIS OF 4-epi-GIBBERELLIN A_{12} FROM ENT-7α,18-DIHYDROXY-KAUR-16-ENE

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For some time we have been working on the partial synthesis of diterpenes, using ent-kaurene type tetracyclic diterpenes from Canary species of Sideritis [1] as starting material. One of our objects was the synthesis of compounds with a gibbane skeleton and in this context we carried out a cyclo B reduction via benzylic acid rearrangements [2]. Now we have synthesized 4-epi-gibberellin A_{12} from epicandicandiol [3] (ent-7α,18-dihidroxy-kaur-16-ene)(I).

Jones' oxidation of I gave the keto-acid II which was then methylated with diazomethane yielding the methyl ester III [4] which reacted with oxygen in Kt-BuO/t-BuOH to give the ketolactone IV in good yield (85%): mp 251-253°, $[\alpha]_D$-25°, [λ_{max} 265, ν_{max} 1792, 1675, M^+ 312 (100%)]. When the acid II is auto-oxidated, the yield is lower (40%). Reduction of IV with sodium borohydride in MeOH afforded the alcohol V (80%): mp 199-201°, $[\alpha]_D$-53°, δ 4.38 (s). The chloro-derivative VI: mp 200-202° (70%), was obtained by treating this alcohol with triphenyl phosphine in CCl_4/Py (9:1).

The configurations tentatively assigned to the alcohol in IV and the Cl in VI were based on the facts that reduction of the 7-oxo-kaurene derivatives gives the more stable equatorial alcohol [4] and reaction with Ph_3P/CCl_4 takes place with inversion of configuration in most cases [5].

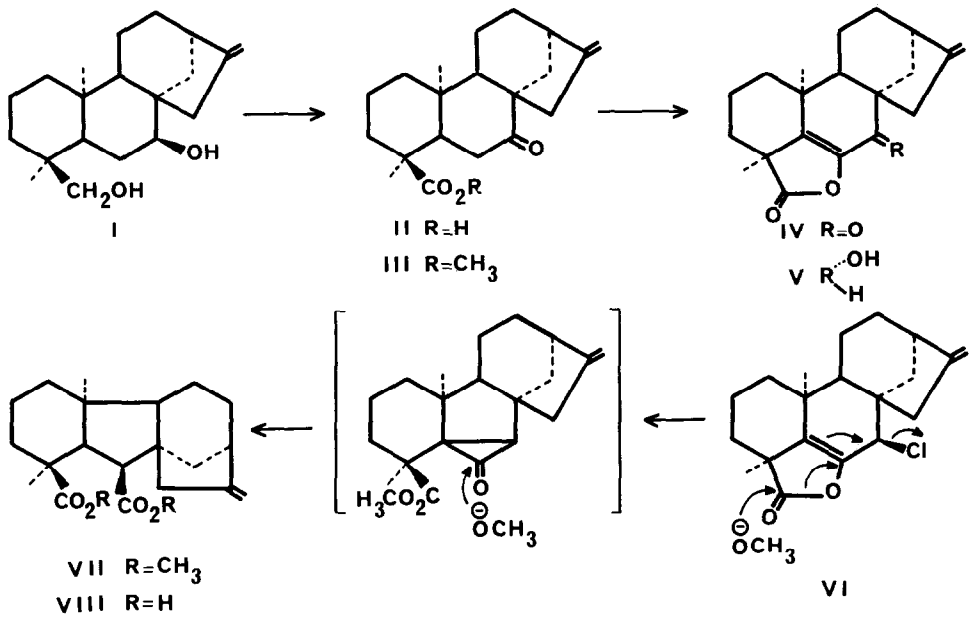
When compound VI was treated with sodium methoxide in dimethoxy ethane [6], a Favorskii rearrangement yielded 4-epi-gibberellin A_{12} dimethyl ester (VII) as a gum (74%) [NMR: δ 4.86 (2H, br s), 3.62, 3.57 (3H each, 2OMe), 3.32, 2.34 (1H each, d, J=12 Hz, H_6 and H_5), 1.32 and 1.12 (3H each, s, 2Me); MS: 360, 328, 300, 285, 270, 251].

The stereochemistry of compound VII was determined on the basis of the spin coupling between the hydrogens at C_5 and C_6 (J=12 Hz) identical to that reported for the GA_{12} dimethyl ester [7] and for other C-20 gibberellins.

Treatment of the dimethyl ester VII with potassium t-butoxide in DMSO afforded

the 4-epi-gibberellin A_{12} (VIII) (83%): mp 233-235°, [NMR: δ 4.85 (2H, d), 3.17, 2.36 (1H each, d, J=12 Hz), 1.40 and 1.13 (3H each, s, 2Me); MS: 314 (M^+-18), 286, 271, 257].

To our knowledge this is the first application of the Favorskii rearrangement conditions to a chloro-enol-lactone and the first synthesis of a 4-epi-gibberellin.



R E F E R E N C E S

1 González A G Fraga B M Hernández M G and Luis J G: Phytochemistry 12 1113 (1973)

2 González A G Fraga B M Hernández M G Larruga F and Luis J G: An Quim 71 733 (1975)

3 Rodríguez B Valverde S and Rocha J M: An Quim 66 503 (1970); Piozzi F Venturella P Bellino A Paternostro M P Rodríguez B and Valverde S: Chem Ind (Lond) 962 (1971)

4 This keto-methyl ester has also been obtained from candicandiol (ent-7β,18-dihydroxy-kaur-16-ene). See 3.

5 Cristol S J Strom R M and Stull D P: J Org Chem 43 1150 (1978) and references cited therein.

6 House H O and Frank G A: J Org Chem 30 2949 (1965)

7 Cross B E and Norton K: J Chem Soc 1570 (1965)