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SYNTHESIS OF PROSTAGLANDIN-LIKE ACIDS FROM CHROMOLAENA MORII

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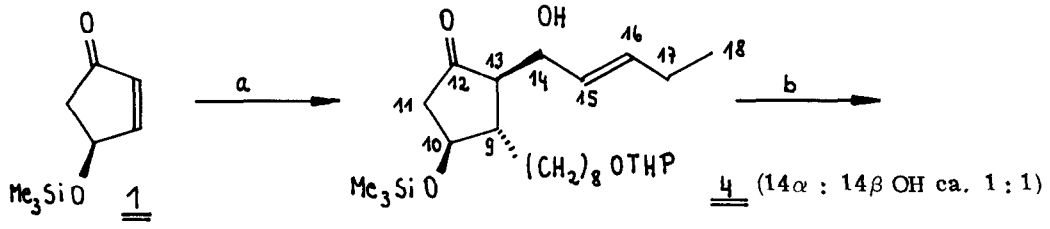
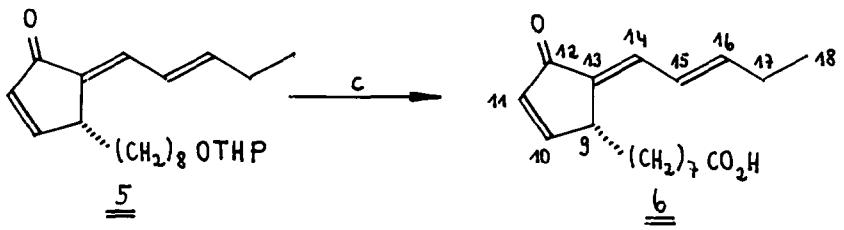
Abstract – Two prostaglandin-like acids were synthesized starting with 4-hydroxycyclopentenone and 2-(pent-2'-in-1'-yl)-cyclopentanone respectively.

From the aerial parts of Chromolaena morii several prostaglandin-like acids were isolated [1,2]. As these compounds only were present in minute amounts a synthesis of some of these acids was desirable for a more detailed study of their biological activities. Inspection of the structure of 6 indicated that a three component-coupling process [3] starting with the silyl ether 1 should be promissing, especially as the corresponding carbinol has been used successfully for other synthetic applications [4]. Furthermore chiral 1 is available [5] which would allow the preparation of the optically active acid.

Several methods are available for producing 4-hydroxycyclopent-2-enone, but the shortest way is the acid catalyzed rearrangement of furfuryl alcohol which is described in a patent [6]. As the reported yield could not be obtained, the conditions were modified. Boiling of furfuryl alcohol for two days in deionisized water at P_H 5.5 gave a crude product which by reaction with hexamethyldisilazane and trimethylchlorosilane gave satisfactory yields of 1. While the corresponding alcohol was very unstable the silylether easily could be purified by distillation. The necessary two other components were pent-2E-enal and a organometallic reagent of a derivative of 8-halooctan-1-ol. While no lithium derivative could be prepared the Grignard reagent was obtained from the chloro compounds in good yield. Addition of this reagent in the presence of cuprous iodide to 1 followed by quenching

the enolate with pent-2E-enal afforded 4. Reaction with tetrabutylammonium fluoride led to elimination of the oxygen function at C-10. The dienone 5 was obtained by reaction with methanesulfochloride and triethyl amine together with about 10 % of the 14Z-isomer. Separation was possible by flash chromatography. The configuration of the double bonds followed from the ^{1}H NMR spectra. The desired acid 6 was obtained after hydrolysis of the tetrahydropyranyl ether 5 followed by PCC oxydation to the corresponding aldehyde and further by Jones-oxidation. Direct Jones-oxidation of the primary alcohol was unsuccessful. The ^{1}H NMR spectrum of 6 was superimposable with that of the natural product, where, however, a 14Z-configuration erroneously was assigned. As the minor isomer of 5 afforded the corresponding 14Z-isomer of 6 the ^{1}H NMR data now allowed a clear assignment of the configurations (6: 7.52 dd (H-10), 6.36 dd (H-11), 6.93 br d (H-14), 6.29 br dd (H-15), 6.25 br dt (H-16); 14Z-6: 7.43 dd (H-10), 6.28 dd (H-11), 6.38 br d (H-14), 7.66 br dd (H-15), 6.10 br dt (H-16) (J [Hz]: 9,10 = 2.5; 9,11 = 2; 10,11 = 6; 14,15 = 10; 15,16 = 15.5; 16,17= 7).





The synthesis of the diene 14, was achieved starting with 7 which easily was obtained via alkylation of the enamine of cyclopentanone. Introduction of the required double bond was achieved by bromination of the enol acetate 8 followed by elimination of HBr affording 9 [3.02 dt (H-6, J = 2.5, 1.5)] and small amounts of the exocyclic conjugated ketone [6.38 tt (H-6, J = 2.5, 2.5)]. Addition of the organometallic reagent 2 to the ketone 9 gave the trans-disubstituted cyclopentanone 10 which after hydrolysis of the tetrahydropyranyl ether was transformed by Jones-oxidation to the corresponding acid. Reaction with diazomethane gave 11 which after partial hydrogenation was transformed via the kinetic controlled anion to the silylenolether 12. Reaction with NBS gave the 11-bromo ketone which was transformed to 13 by elimination of HBr. However, isomerization also gave the thermodynamic stable $\Delta^{9(13)}$ ketone (^{1}H NMR: H-14 2.91 dd (J = 7.5, 1.5). Flash chromatography allowed the separation of the isomers (ca. 9 : 4). Saponification of 13 afforded 14, its ^{1}H NMR spectrum was identical with that of the natural product.

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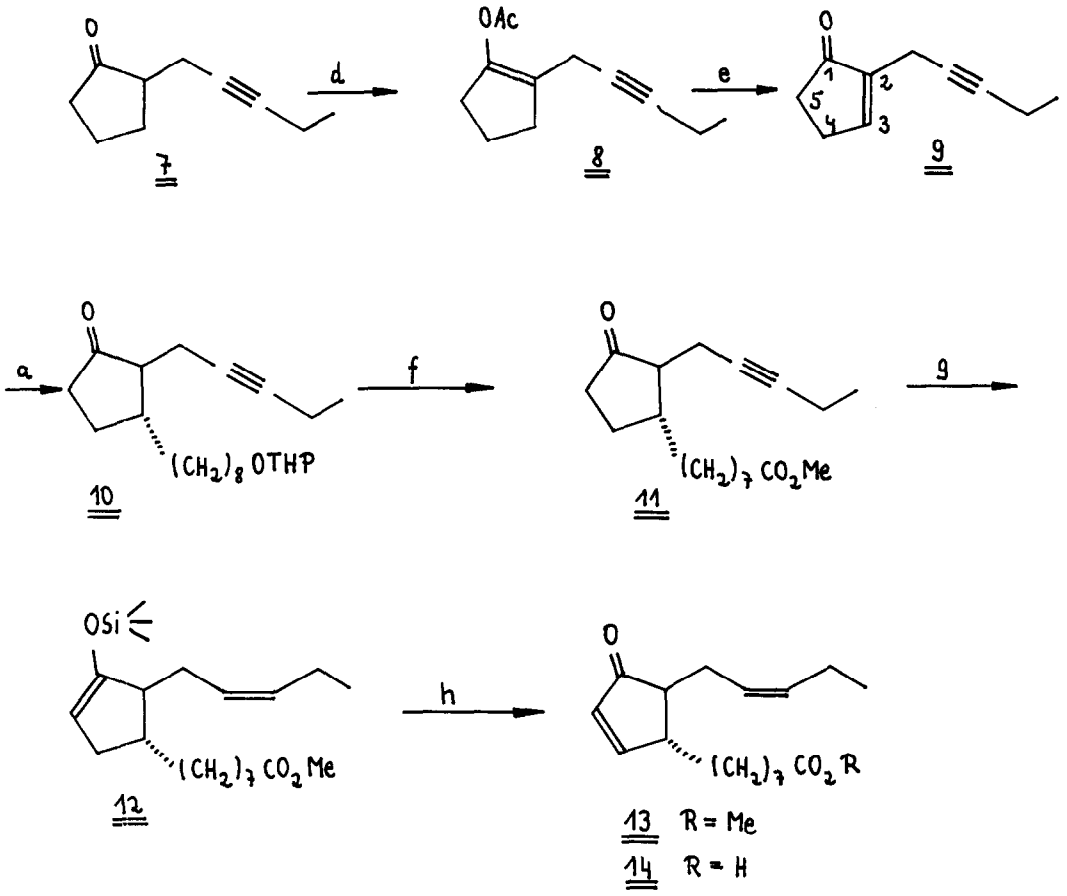

a) $ClMg(CH_2)_8OTHP/Cu_2J_2$ (2)/THF, -45 °C, 4 h; EtCH=CHCHO(E) (3), -78 °C, 15 h; b) TBAF, $MeSO_2Cl/NEt_3$, 43 % 14E, 12 % 14Z; c) pTS, MeOH; PCC/NaOAc/CH_2Cl_2; Jones-oxidation, 35 %; d) Ac_2O, pTS, 86 %; e) $Br_2/CaCO_3/CHCl_3$; LiBr, Li_2CO_3, DMF, 66 %; f) amberlyst H-15/MeOH, 12 h, Jones-oxidation, 91 %, CH_2N_2, 81 %; g) Lindlar catalyst, H_2; $LiN(SiMe_3)_2$, $ClSiMe_3$, 97 %; h) NBS; LiBr, Li_2CO_3, DMF; KOH/MeOH.

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