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THE CONVERSION OF ASPERULOSIDE TO AN OPTICALLY ACTIVE PROSTAGLANDIN INTERMEDIATE

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Summary: Synthesis of optically active intermediate 1a for PGF$_{2\alpha}$ or (+)-11-deoxy-11α-hydroxymethyl PGF$_{2\alpha}$ from asperuloside is described.

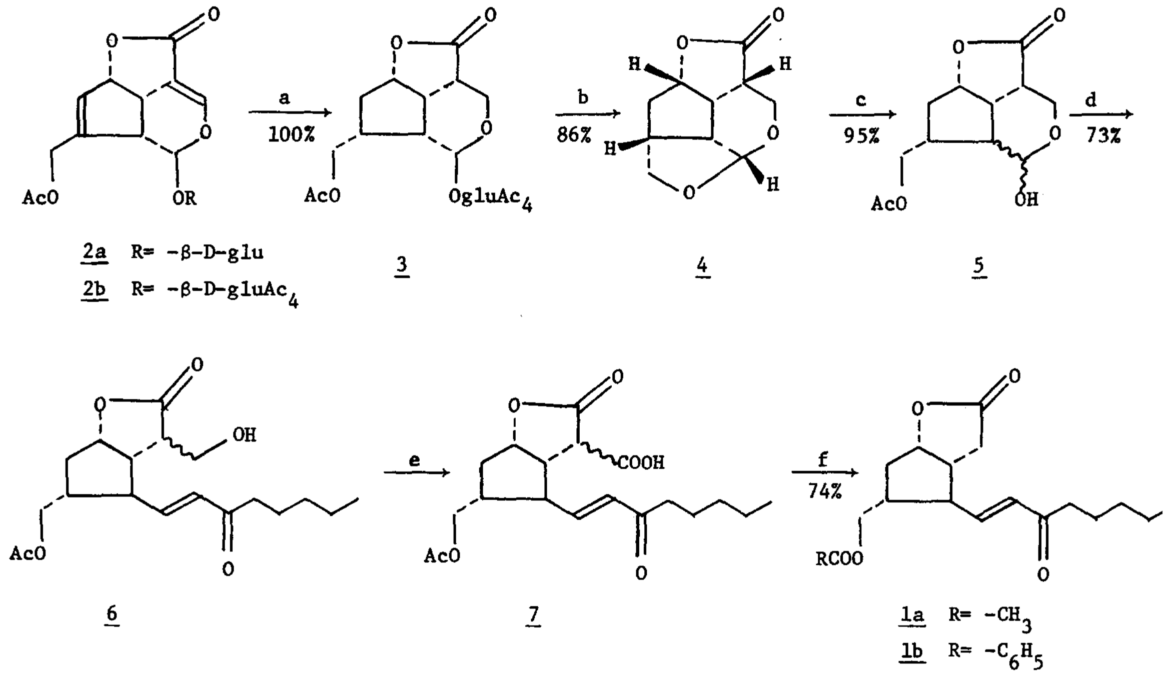
As a continuation of our efforts to convert iridoids[1] to optically active prostanoids, we wish to describe the preparation of a useful intermediate, 1a[2], from asperuloside (2a). Ohno[3] and coworkers have recently converted benzoate 1b into PGF$_{2\alpha}$ and 11-homo PGF$_{2\alpha}$. The use of similar procedures should allow the conversion of the acetate to the same prostanoids.

Crude asperuloside was isolated from Coprosma repens[4] by the procedure of Briggs[5] and converted to its tetraacetate 2b (acetic anhydride/pyridine). This was purified by a combination of chromatography and crystallization and afforded pure tetraacetate, m.p. 150-151°C (lit.[5] m.p. 154°C) in 0.2% yield based on the weight of fresh plant material.

The tetraacetate 2b was hydrogenated over 5% Rhodium on carbon in ethyl acetate at 1 atm. by starting at -30°C and raising the temperature slowly to 0°C during 3 hr.. Tetrahydroasperuloside-tetraacetate (3) m.p. 148-9°C was isolated in virtually quantitative yield. Partial hydrolysis of 3 in refluxing AcOH/H$_2$O (5/1) for three hours afforded a mixture of tetracyclic acetal 4 (m.p. 113-4°C, $[\alpha]_D^{25}$ -61.5°(chloroform)) and hemiacetal 5, m.p. 151-2°C. When the hydrolysis was continued for 8 days at 100-110°C, acetal 4 was produced in 86-92% yield. The all-cis structure of 4 was confirmed by X-ray analysis, most kindly performed by Dr. John Blount of Hoffmann-LaRoche (Nutley, N.J.).

An attempt to attach the lower side chain by Mukaiyama reaction[3] with 2-acetoxy-1-heptene gave 5 as the major product. The same product was made in 95% yield by treating 4 with TiCl$_4$(1.25 equiv.) and acetyl chloride (2.5 equiv.) in methylene chloride for 45 min. at 0°C. Production of 5 from 4 as well as by partial hydrolysis of 3 proves that TiCl$_4$/AcCl opened the 5-membered ring of the tetracyclic acetal 4.

Wadsworth-Emmons reaction of 5 proceeded smoothly with dimethyl 2-oxoheptylphosphonate (6 equiv.) and n-butyllithium or sodium hydride (6 equiv.) in DMSO for approximately 3 hours at 50°C, giving a mixture of hydroxymethyl-enones 6a/b which were isolated by flash chromatography in 73% yield. Separately (hplc) or together 6a and 6b were oxidized by short (60 sec.) exposure to Jones' reagent in refluxing acetone to a crude, unstable carboxylic acid (7), which was decarboxylated without further purification by refluxing in glacial acetic acid, to give 1a ($[\alpha]_D^{25}$ -28°(chloroform)), as an oil in 74% overall yield (from 6a/b mixture).



a) H_2, 5% Rh/C, EtOAc, -30°C to 0°C, 3 hr.; b) 5/1 $AcOH/H_2O$, reflux, 8 days; c) 1.25 eq. $TiCl_4$, 2.5 eq. AcCl, 45 min., 0°C; d) 6 eq. n-BuLi, 6 eq. $(MeO)_2POCH_2COC_5H_{11}$, rt-50°C, 0.5 hr.; 50-55°C, 3 hr.; e) Jones' reagent, refluxing acetone, 60 seconds. f) glacial acetic acid, reflux, 3.5 hr..

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