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INVESTIGATIONS INTO THE TOTAL SYNTHESIS OF INSECT ANTIFEEDANT CLERODANES THE TOTAL SYNTHESIS OF ± 4-EPI AJUGARIN

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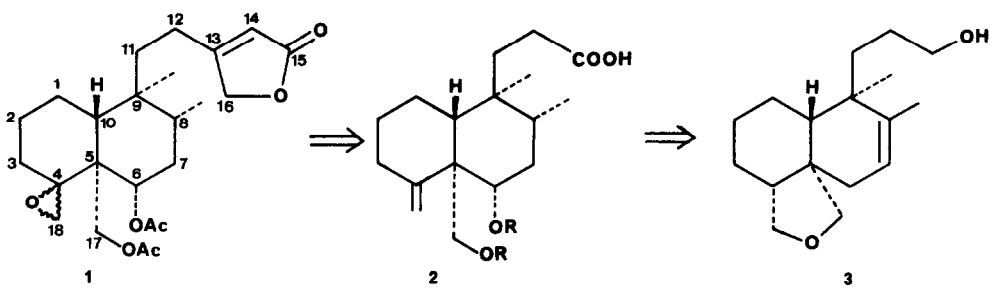
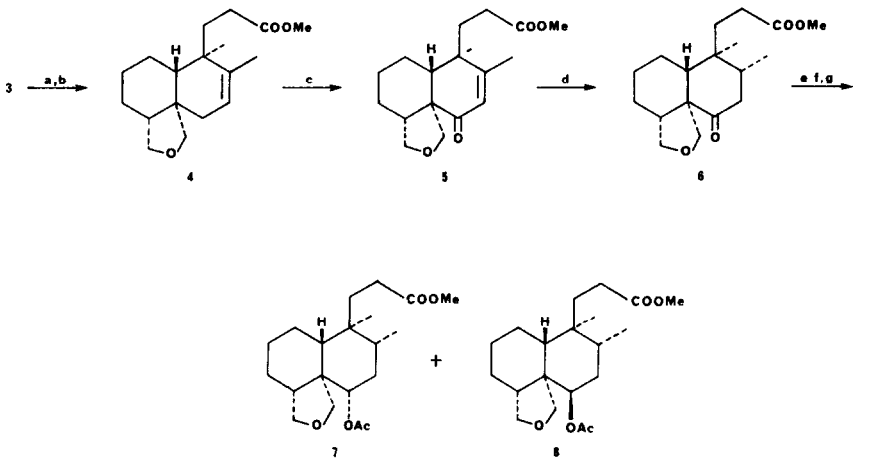
Summary Starting from alcohol 3, a stereospecific synthesis of carboxylic acid 2 is described. This acid 2 is a key intermediate in the total synthesis of ajugarins and its conversion into ± 4-epi ajugarin is reported.

A number of clerodane diterpenes, as represented by ajugarin I[1,2], (1) and clerodin[3], possess insect antifeedant activity. During the last few years several papers on synthetic approaches towards these compounds[4,5,6] and of several types of model compounds[7,8] have appeared. Recently we published the synthesis of an interesting model compound for ajugarin I[9]. The communication of Kende and Roth[6] on the total synthesis of ajugarin IV prompts us to report on our synthesis of 4-epi ajugarin I and on our efforts towards the total synthesis of ajugarin I, following the scheme outlined below.



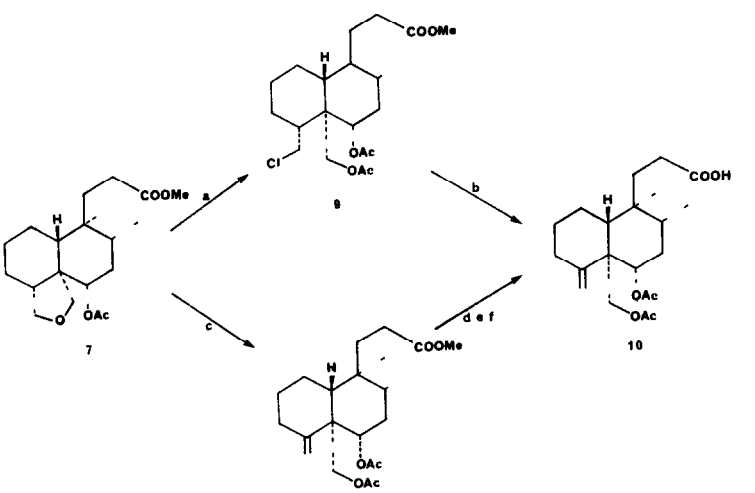
The alcohol 3* was chosen as the starting material[10]. Oxidation with Jones' reagent afforded the carboxylic acid in high yield, which was converted into the methyl ester 4 on treatment with diazomethane Allylic oxidation (chromic acid in acetic acid, 60% yield) of 4 gave the enone 5, which was hydrogenated in quantitative yield (Pd/C) to the ketone 6 Reduction of this compound with lithium tri-*t*-butoxy aluminium hydride gave a mixture of the equatorial and axial alcohols

in a 4 1 ratio. Acetylation and separation on silica gel afforded the equatorial acetate 7 (m p. 86-87°C) in 71% yield and the axial acetate 8 (m p 121-123°) in 18% yield



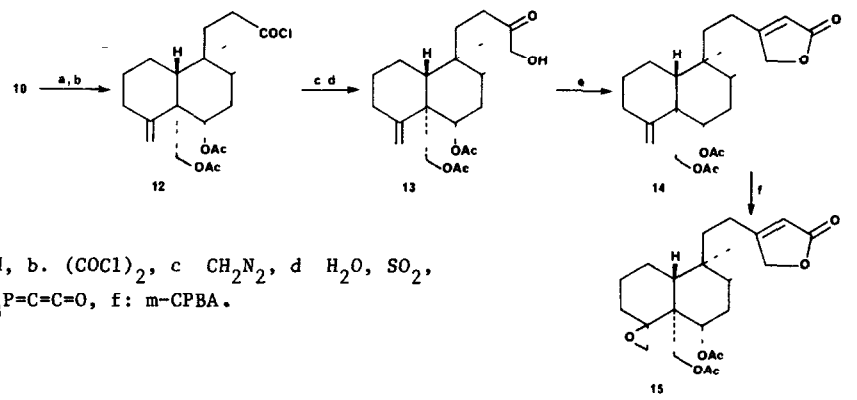
a Jones' reagent, b: CH_2N_2, c CrO_3, AcOH; d: H_2Pd/C, e $LiH(tBuo)_3Al$; f· H_3O^+; g: Py, Ac_2O, DAP.

Treatment of the acetate 7 with pyridine hydrochloride in refluxing acetic anhydride[11] gave the chlorodiacetate 9 in high yield Dehydrohalogenation of this compound with DBN in refluxing xylene afforded the carboxylic acid 10 (m.p. 165-166°C) in relatively low yield (40%) On reaction of 7 with pyridine hydrobromide the olefin 11 was obtained in 66% yield next to some starting material (30%), thus avoiding the troublesome DBN reaction.



a PyHCl, Ac_2O, Δ, b DBN, δ, c. PyHBr, Ac_2O, Δ; d: OH^-, H_2O, MeOH, e: Py, Ac_2O, DAP, f H_2O, Py

Hydrolysis followed by reacetylation gave 10 This carboxylic acid was converted into its potassium salt and reacted with oxalyl chloride to give the acid chloride 12 Reaction of this compound with diazomethane followed by hydrolysis of the intermediate diazoketone gave the hydroxy ketone 13[12]. The overall yield of these conversions (*i.e.* 10 → 13) was 73% Treatment of 13 with triphenylphosphoranylidene ketene gave the butenolide 14 (m.p. 165-167°C) in 92% yield[13]

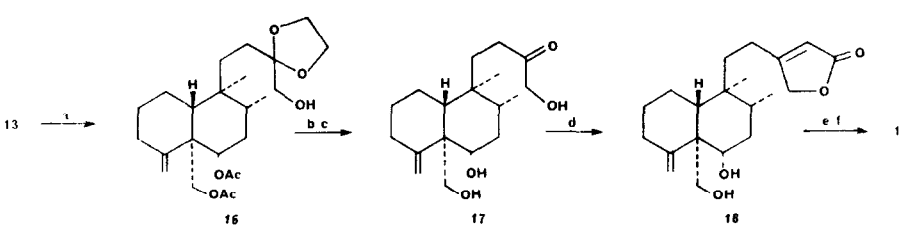


a KOH, b. $(COCl)_2$, c CH_2N_2, d H_2O, SO_2,
e: $Ph_3P{=}C{=}C{=}O$, f: m-CPBA.

In our previous paper we reported the epoxidation of the 9β-methyl analogue of 14[9]. In that reaction both epimeric spiro epoxides were formed using *m*-chloroperbenzoic acid It was expected that in the present case again both isomers would be formed, thus leading to 15 and ajugarin I Epoxidation of 14 with *m*-chloroperbenzoic acid in ether however afforded the epoxide 15 (m p 170-171°C) as sole product.

Alternatively the stereospecific epoxidation reaction using V^{5+} and *t*-butylhydroperoxide could be used to bring about the right stereochemistry at C-4[14] Prior to this the acetates in 14 have to be hydrolysed. Unfortunately both acid and base catalysed hydrolysis of 14 gave rise to the formation of numerous products The butenolide proved unstable under basic conditions, while acidic conditions caused rearrangement of the olefinic bond

Attempts to protect the butenolide in 14 were unsuccesful and therefore we tried to circumvent the problem by performing the acetate hydrolysis in an earlier stage of the synthesis



a: MED, TsOH, b OH^-, H_2O, c H_3O^+, d $Ph_3P{=}C{=}C{=}O$, e V^{5+}, *t*-BuOOH, f AC_2O, Py, DAP

Base catalysed hydrolysis of the hydroxy ketone 13 was unsuccessful as well since a Favorskii rearrangement occurred[15] Acid catalysed hydrolysis was expected to give the same complications

as in the case of 14 The ketone 13 was therefore protected as the ethylene ketal 16 and the acetates were reduced with lithium aluminium hydride to give, after hydrolysis, the triol 17. Treatment of this product with triphenylphosphoranylidene ketene[13] was expected to give the butenolide 18 since steric factors would probably favour reaction at the hydroxyl of the side chain. However, only a very small amount of impure material could be obtained after extensive chromatography. This product was further reacted with V^{5+} and *t*-butylhydroperoxyde and then acetylated. The ^{1}H-NMR spectrum of this compound revealed the presence of a small amount of ajugarin I. Improvement of this procedure is currently under investigation.

References and Notes

* This and subsequent products are pairs of enantiomers All intermediates had Mass, NMR and IR spectra in accord with their expected structures. ^{13}C-NMR spectra of compounds 7, 14 and 15 will be published in Organic Magnetic Resonance, 1982. Compounds 12, 13, 17 and 18 were obtained as oils. All other compounds were crystalline and showed correct elemental analysis

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