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CANNABIS XXII[1]. SYNTHESIS OF SPIRO-COMPOUNDS

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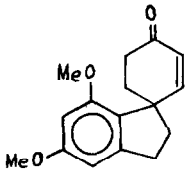
Summary: O-methyl-cannabispirenone has been synthesized by two new methods applying spiroannelation on 5,7-dimethoxyindan-1-aldehyde. An alternative high yield synthesis of the latter has been elaborated.

We wish to report on the synthesis of O-methyl-cannabispirenone 1, selected by us as the key intermediate in the synthesis of natural Cannabis spirans. Using aldehyde 4 two new efficient methods for 1 based on spiro-annelation have been elaborated. A very recent preliminary communication on related synthetic approach[2] prompts us to publish our own findings in this field.

To obtain compound 4, we succeeded as the first in applying the Wittig enol ether synthesis on the known 5,7-dimethoxyindan-1-one[3] 2. Treatment of indanone 2 with methoxymethylenetriphenylphosphorane (5 equiv.) yielded the enol ether 3 in 72% yield, only the E-isomer being formed. The hydrolysis of the enol ether to 4 was rather capricious due to the instability of the aldehyde in acidic media. As Crombie et al.[2] report frustrating attempts of the Wittig approach, we describe here the experimental details that seem to be of crucial importance.



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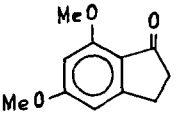

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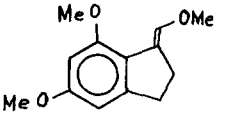

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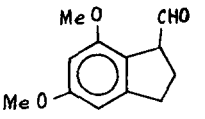

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To a stirred, cooled (waterbath of 20°) suspension of methoxymethyltriphenylphosphonium chloride (68,4 g) in dioxane (560 ml), potassium tert. butoxide (22,4 g) was added in one portion (slightly exothermic reaction). After 90 min. 5,7-dimethoxyindan-1-one (7,6 g) was added in one portion to the red solution. The mixture was stirred for 1 hr at 20°, then heated under reflux for 3 hr. The mixture was cooled, diluted with water (560 ml), extracted with diethyl ether, the organic extracts were washed twice

with water, dried, concentrated and the crude product was distilled, b.p. 170-180°/1mm. Crystallization from methanol provided the pure E-isomer 3 as white crystals (6,3 g, 72%), m.p. 95-96°.

The enol ether was hydrolyzed as follows. A mixture of p-toluenesulphonic acid (175 mg), water (12 ml), dioxane (60 ml) and 3 (1 g) was heated under reflux for 16 hr. The cooled mixture was diluted with water (60 ml), extracted with diethyl ether, the extracts were washed with water, dried and concentrated. This yielded the pure aldehyde 4 as a yellow viscous oil (0,9 g, 96%).

In the spiroannelation step involving a Michael addition followed by an aldol condensation, we treated equimolar amounts of aldehyde 4 and methyl vinyl ketone in ether with 0,4 equiv. of KOH solved in the minimal amount of 95% etOH (2 hr. 0°, 20 hr 20°). Heating the concentrated mixture under reflux for three hr in the tenfold volume of a mixture of KOH, H_2O and MeOH (1:9:10) afforded after work-up 75% of the expected O-methyl-cannabispirenone 1[4], m.p. 97-99° from ether (lit.[2] m.p. 94-96° from ether-hexane). As Crombie et al. obtained only poor yields in this step, our result represents a significant improvement. The main reason hereof is without doubt the application of a different catalyst.

As the possibility of a different spiroannelation procedure using a cycloalkane-aldehyde enamine has been noted[5], we also succesfully explored the spiroannelation of 4 using a Michael-type addition reaction of the piperidine enamine of 4 to methyl vinyl ketone, followed by hydrolysis and aldol cyclization. The desired spiran 1 was thus obtained in a fully satisfying yield. Use of an optically active amine like (S) (+)-2-(1-pyrrolidinomethyl)pyrrolidine[6] offers the possibility of an asymetric synthesis of cannabispirenones and its investigation is now in progress.

Since the final trivial transformations of 1 into natural cannabispirans have already been performed[2], our present synthesis of 1 facilitates and improves the synthesis of all the known cannabispirans.

References and notes

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