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SYNTHESIS OF (±)-2β,20-EPOXY-12-METHOXYABIETA-8,11,13-TRIENE[1]

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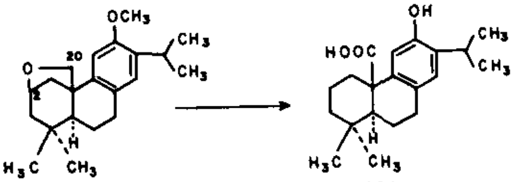
Abstract - The synthesis of the titled compound (1) and its conversion to pisiferic acid (2) are described.

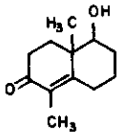
In the year 1982 Matsumoto and Usui[2] reported the synthesis of abieta-triene (1) and its transformation to pisiferic acid (2), a tricyclic diterpene which shows antimicrobial activities against all gram-positive bacteria tested.[3]



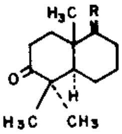
(1) (2)

As a part of our project directed towards the diterpene synthesis we have tried to design an alternative approach to this important precursor (1) and its conversion to pisiferic acid (2). The present communication describes the route developed to realize the desired objective. The important features of the present synthesis are (i) *easy availability of the starting material* and (ii) stereoselectivity concerning the steps of (12)→(13)→(14) involved.

The keto-alcohol (4)[4] prepared from the α,β-unsaturated ketone (3)[5] was chosen as starting material for our synthetic approach. Treatment of the keto alcohol (4) with dihydropyran containing p-toluenesulfonic acid yielded the oily pyranyl derivative (5) in 72% yield, m/z 210 ($M^+-C_5H_8O$) and ir (film) 1720 (C=O) cm^{-1}. Reduction of the C-3 carbonyl group of (4) with sodium borohydride yielded a mixture of alcohols whose tosyl derivatives on heating with lithium bromide, lithium carbonate and dimethyl formamide produced an oily olefin (6) in 52% yield, m/z 196 (M^+) and 178 (M^+-H_2O), ir (film) 3450 (OH) cm^{-1}, nmr (CCl_4): δ 5.62 and 5.78 (2H, olefinic protons). It is interesting to observe that dehydrosulfonation and hydrolysis of tetrahydropyranyl group were realized by a single experiment. The oily ketone (7) obtained by oxidation of the olefin (6) with Jones reagent[6] was formylated with ethyl formate to obtain (8) which was subjected to Robinson annulation reaction with methyl vinyl ketone prepared in situ following the procedure of Howell and Taylor.[7] The oily adduct without purification was cyclized by boiling with sodium methoxide in methanol to yield α,β-unsaturated ketone (9) (40%), m/z 244 (M^+) and ir (films) 1645 (C=O) cm^{-1}. Its nmr spectrum clearly indicated that the ketone (9) was a mixture of 8α and 8β-epimers. The signal δ 5.55-5.72 ppm indicate the presence of more than three protons and this can be accounted owing to the presence of the epimeric mixture of the ketone (9). As the compounds (1) and (2) were our synthetic goal it was considered unnecessary to separate the epimers of (9) because the aromatization of both the epimers would lead finally to the same product.

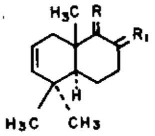


(3)



(4) R = OH, H

(5) R = OThP, H

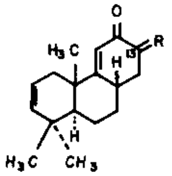


(6) R = OH, H, R_1 = H, H

(7) R = O, R_1 = H, H

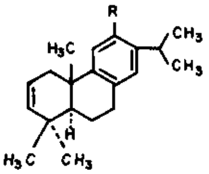
(8) R = O, R_1 = CHOH

Next phase of our studies consisted in the introduction of the isopropyl group at C-13 position of the ketone (9) and to accomplish this objective it was treated with diethyl carbonate in presence of sodium hydride to yield the β-ketoester (10) which on treatment with methyllithium in ether produced an alcoholic material as was evidenced by its spectroscopic data. Attempted dehydration of the resulting material by treatment with 1% hydrochloric acid in refluxing methanol led to the formation of a mixture products whose spectral data (ir and nmr) indicated the formation of phenolic compound which was contaminated by difficultly separable byproducts. In order to circumvent the problem the product mixture in acetone was methylated with dimethyl sulfate and anhydrous potassium carbonate. The resulting product on chromatographic purification on silica gel afforded a compound which was identified as olefinic methyl ether (12) on the basis of spectral evidences m/z 298 (M^+), nmr (CCl_4): δ 0.98 (3H,s), 1.08 (3H,s), 1.21-1.26 (9H,s) (4,4,10,14-CH_3), 3.75 (3H,s,OCH_3), 5.52-5.54 (m, 2H, vinyl protons), 6.62 (1H,s) and 6.72 (1H,s) (aromatic protons). The formation of (12) strongly confirmed the formation of olefinic phenol (11) during acid-catalyzed dehydration experiment. There is no doubt that the reaction of keto ester (10) with methyllithium followed by acid hydrolysis proceeded with concomitant dehydration, migration of the double bond yielding the dienone which underwent aromatization to furnish the phenol (11). Attention was next focused on the hydroxylation of (12) to obtain (14) which would be required for the preparation of 2β,20-epoxy-12-methoxyabieta-triene (1) and this proved to be one of the most difficult part of the present synthesis. After numerous attempts to effect this transformation the success was finally achieved by employing the hydroboration-oxidation reaction[8] which yielded the alcohol (13) (30%). The latter events confirm the position of the hydroxyl group. The nmr spectrum of the alcohol (13) was confusing and thus the configurational assignment of the C-2 proton of the alcohol (13) could not be ascertained on the basis of its half-width ($W_{1/2}$) value.[9] Oxidation of the alcohol (13) with Jones reagent[6] followed by reduction of the resulting ketone with lithium aluminium hydride in tetrahydrofuran afforded the β-isomer of the oily alcohol (14)[10] (63%), m/z 316 (M^+) and 298 (M^+-H_2O), ir (film) 3460 (OH) cm^{-1}, nmr (CCl_4): δ 3.86 (m, 1H, $W_{1/2}$ = 16 Hz, 2-H). Irradiation[15,16] of a mixture of lead tetraacetate and alcohol (14) in benzene with 250 W tungsten lamp yielded the target molecule (1) in 50% yield whose identity was established by comparison of ir, nmr, tlc behavior and melting points with an authentic specimen.[2]



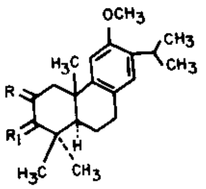
(9) R = H,H

(10) R = $COOCH_3$, H



(11) R = OH

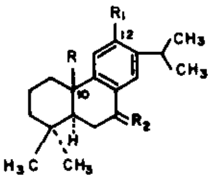
(12) R = OCH_3



(13) R = ∼OH, H , R_1 = H,H

(14) R = <OH ..H , R_1 = H,H

(15) R = <OH ..H , R_1 = <..Br H



(16) R = CH_2OH , R_1 = OH, R_2 = H,H

(17) R = $COOCH_3$, R_1 = OCH_3 , R_2 = O

(18) R = $COOCH_3$, R_1 = OCH_3, R_2 = H,H

With the synthesis of the abieta-triene (1) achieved, we turned our attention to the crucial phase of our work, the synthesis of pisiferic acid. The objective was accomplished efficiently by the route 1→16→17→18 in acceptable yield. All the intermediates were isolated and purified.

The abieta-triene (1) on being heated with zinc, zinc iodide and acetic acid[17] underwent cleavage of 2β,20-epoxy ring and demethylation yielding pisiferol (16) in 69% yield whose spectral data (ir and nmr) and melting point were identical with one reported.[2] In order to achieve the oxidation of C-10 alcoholic group to C-10 carboxyl group it was considered necessary to protect the 12-hydroxyl group of (16) and the methyl ether was chosen as suitable derivative. Pisiferol (16) in acetone was methylated with dimethyl sulfate and potassium carbonate. The resulting material was oxidized[18] and then esterified with diazomethane. The product obtained (43%) was characterized as ketoester (17) whose identity was confirmed by comparison of its melting point (mp. 167-168°C) which exhibited no depression in melting point with authentic specimen[2] (mp. 168.5-169°C). Its ir spectra was indistinguishable from the ir spectra of authentic specimen.

Reduction of ketoester (17) with sodium borohydride in methanol at 0°C afforded an alcoholic material, whose tosyl derivative on heating with sodium iodide and zinc dust in dimethoxyethane[19] yielded the ester (18) (82%) and its identity was confirmed by comparison of its ir, and melting points with the published data.[2] The transformation of ester (18) to pisiferic acid (2) was realized by two methods. The first procedure which consisted in treatment of ester (18) with anhydrous aluminium bromide and ethanethiol[20] afforded excellent yield of pisiferic acid (2). The second method which involved heating the ester (18) with quinoline and acetic acid[21] followed by demethylation[22] with boron tribromide yielded the pisiferic acid (2) in moderate yield. The identity of pisiferic acid (2) was confirmed by comparison of spectral properties (ir and nmr), melting points and tlc behavior with an authentic specimen of pisiferic acid.[2,23,24]

ACKNOWLEDGEMENTS

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16. Irradiation of a cyclohexane solution of the alcohol (14) with a tungsten lamp in presence of lead tetraacetate and iodine led to the formation of the

compound (1) in poor yield. A large amount of iodocyclohexane and other unidentified products were formed.

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18. A number of oxidizing agents were tried to realize the transformation $CH_2OH \rightarrow CHO \rightarrow COOH$ but most of them were unrewarding. There is no doubt that the primary alcoholic group situated in angular position requiered more drastic conditions for its transformation to carboxyl group. Therefore oxidation of the alcohol (16) was attempted with Jones reagent at room temperature (2 hr).

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