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# A SYNTHESIS OF MOENOCINOL FROM ISOPRENOID PRECURSORS

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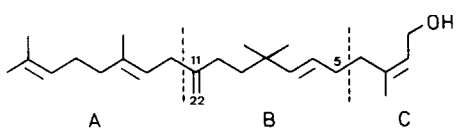
Abstract : The $C_{25}$ compound moenocinol (1) is synthesized starting from 7, geranyl chloride, and Moiseenkov's $C_5$ unit .

The antibiotic moenomycin A belongs to the most efficient inhibitors of the bacterial cell wall peptidoglycan biosynthesis [1,2]. Its structure consists of an oligosaccharide part linked to phosphoglycerate which in turn carries at the 2-position the moenocinol unit 1 [3]. On short acid hydrolysis moenocinol (1) is liberated from the rest of the molecule [1]. 1 is a $C_{25}$ compound. Three isoprene units can easily be identified whereas the central $C_{10}$ part ( C-5 through C-22 ) does not obey the isoprene rule in an obvious way. It has been speculated that not all of the carbon atoms of this central part of 1 are derived from mevalonate [4]. A number of syntheses of 1 has been published [4,5] but in neither of them any indication has been given of how the carbon skeleton might be formed in the course of the biosynthesis.

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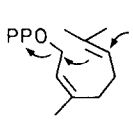


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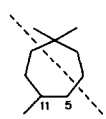


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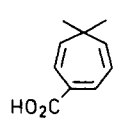


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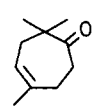


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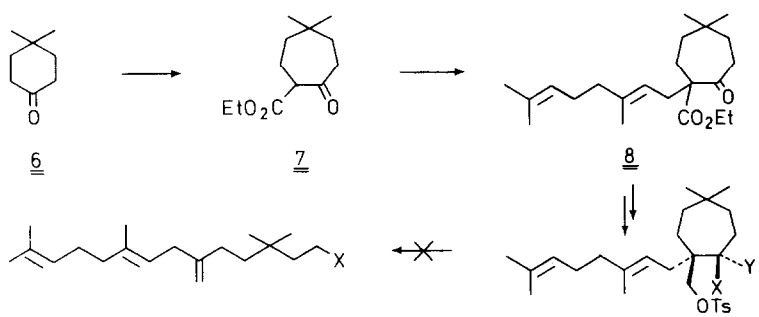
Disconnection of 1 at the C-4–C-5 and at the C-11–C-12 bonds gives two isoprenoid synthons ( A and C ). We realized that reconnection ( in the retrosynthetic sense ) of the B unit at C-5 and C-11 also leads to an isoprenoid synthon ( of type 3 ). Thujic acid (4) and kharahanaenon (5) have this carbon skeleton which is biogenetically formed by anti-Markovnikov cyclization of geranyl pyrophosphate ( see 2 ). This communication describes the first synthesis of moenocinol from purely isoprenoid precursors based on the retrosynthetic considerations described above.

Our starting material was ß-keto ester 7 which is readily obtained ( 94% yield ) from 6 [6] by triethyloxonium tetrafluoroborate-catalyzed reaction with ethyl diazoacetate [7]. Generation of the anion of 7 ( sodium in boiling toluene [8] ) followed by addition of geranyl chloride produced a 69% yield of 8, 11 and 12 were obtained from 8 by a) $LiAlH_4$ reduction, b) selective monotosylation, and c) column chromatography and pyridinium chlorochromate oxidation, respectively. It was planned to open the C-5–C-11 bond ( moenocinol numbering see 1 and 3 ) in 11 or 12 by Grob fragmentation which would have lead to the A-B part of 1 in a straightforward manner. Unfortunately, we were unable to find any experimental conditions to induce the desired fragmentation reactions to give 9 from 11 and 10 from 12, respectively. The results obtained in theses studies will be reported elsewhere.



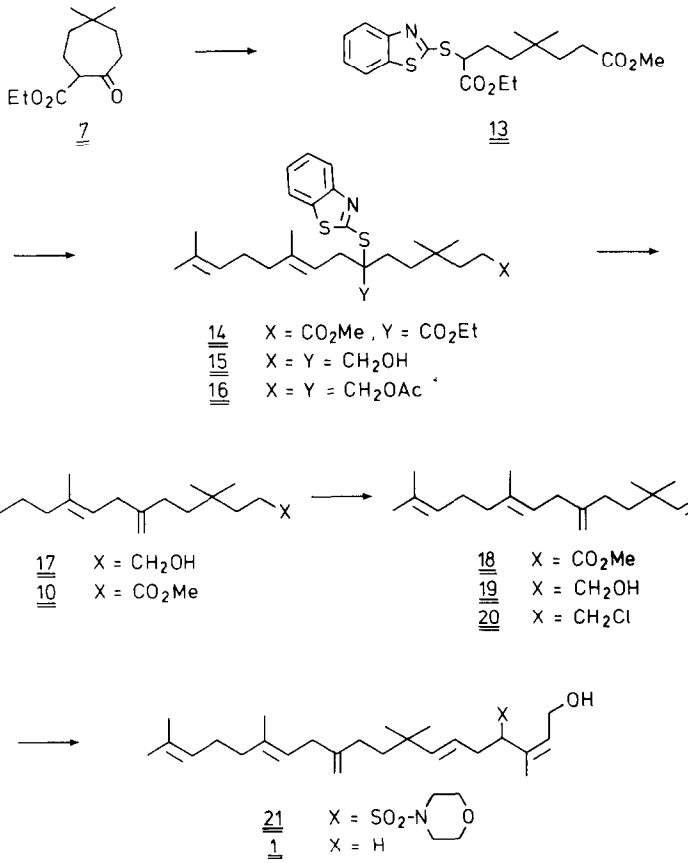

6 7 8

9 X = CHO
10 X = $CO_2Me$

11 X = H, Y = OH
12 X, Y = O

In an alternative approach, 7 was treated with 2-(morpholinothio-)benzothiazol [9] in methanol ( 8h reflux, 14h at 60°C ) to give 13 ( 77% ) by sulfenylating ß-keto ester cleavage [10]. Formation of the more stabilized ester enolate from 13 ( sodium hydride in DMF ) and alkylation with geranyl chloride furnished 14 in 85% yield. In order to introduce the 11(22) double bond the following sequence of reactions was performed : a) $LiAlH_4$ reduction of 14 to give 15 ( 76% ), b) acetylation to furnish 16 ( 93% ), c) reductive elimination [11] with lithium in liquid ammonia to give 17 after ester hydrolysis in 76% yield. Conversion of 17 into 20 was accom-

plished in the following manner : a) oxidation of 17 with pyridinium chlorochromate followed by Ag(I) oxidation of the resulting aldehyde and ester formation ( diazomethane ) gave 10 ( 88% overall yield), b) ester enolate formation ( LDA ) and reaction with phenylselenyl bromide [12] furnished the corresponding $\alpha$-phenylselenyl ester from which 18 was formed in 44% overall yield by phenylselenoxide syn elimination ( 30% $H_2O_2$ in $CH_2Cl_2$/pyridine, $0^oC \rightarrow$ room temperature ), c) DiBAH reduction of 18 ( 4h at $-78^oC$ in toluene ) led to 19 ( 44% ), and d) treatment of 19 with triphenylphosphine/$CCl_4$ ( 90h at reflux ) [13] gave 20. When 20 was reacted in THF-HMPT solution with the dilithium salt of the isoprenoid hydroxy sulfonamide recently introduced by Moiseenkov et al. [14] 21 was obtained in 16% yield ( based on 19 ). Finally, reductive desulfonylation was performed as described by Moiseenkov [15] to yield 1 identical with an authentic sample.



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