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SYNTHESIS OF (±)-DESEPOXY-4,5-DIDEHYDROMETHYLENOMYCIN A

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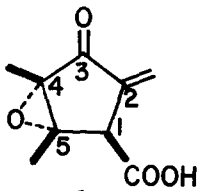
Summary: An efficient and regiochemically controlled synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A is reported.

Methylenomycins A 1[1] and B 2[2] are highly functionalized antibiotics produced by a streptomycete strain # 2416 (Streptomyces violaceoruber). Recently, a closely related and exceedingly labile cyclopentanoid antibiotic (+)-desepoxy-4,5-didehydromethylenomycin A 3 was isolated from the culture filtrate of the same strain.[3] Furthermore, this desepoxy compound was demonstrated to be a biosynthetic precursor of methylenomycin A,[3] thus assigning it the S-configuration.



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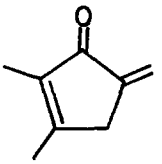

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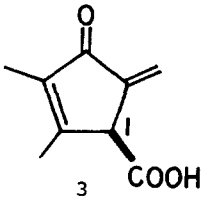

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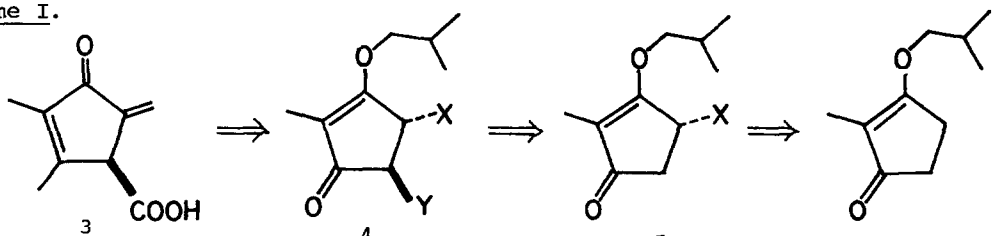
Herein we wish to report the synthesis of (±)-desepoxy-4,5-didehydromethylenomycin A 3. This synthesis presented considerable difficulty in establishing experimental conditions due to the instability of the final compound as well as some of the intermediates. Our strategy, based on retrosynthetic analysis (Scheme I), was to utilize our finding that 3-alkoxycyclopent-2-en-1-one (e.g., 6)

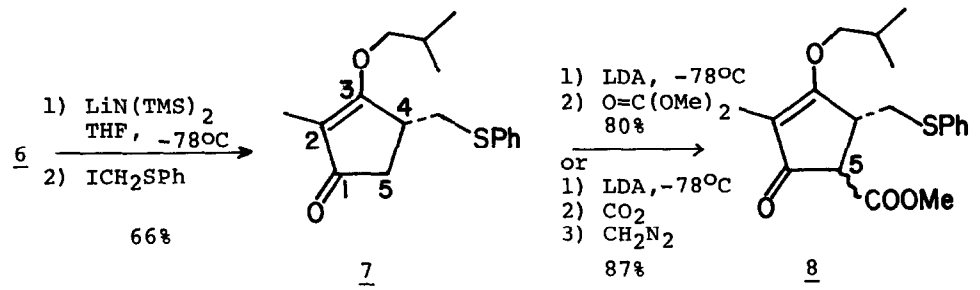
Scheme I.



3 4 5 6

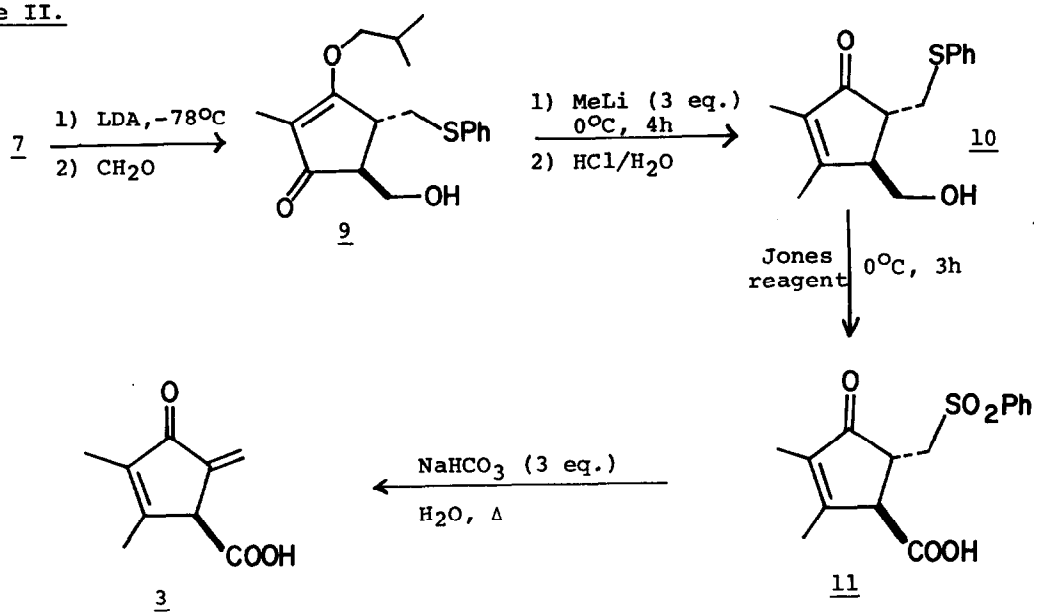
can be regioselectively alkylated successively by employing two different lithium bases, lithium diisopropylamide (LDA) and lithium bis(trimethylsilyl)amide ($LiN(TMS)_2$).[4] This should provide the key intermediate 4 where X and Y are appropriate precursors of exomethylene and carboxylic acid groups, respectively.

The enol ether-sulfide 7 was prepared regioselectively by treating the enol ether 6 first with $LiN(TMS)_2$ at -78°C then with thiophenylmethyl iodide. The initial approach was to directly introduce the carboxyl group at C-5 on the enol ether 7 and further, to convert the enol ether system to the enone. The introduction of the carbomethoxyl group did not present any problem involving the regioselectively generated anion at C-5 with LDA at -78°C.[5] The only exception was that the carboxylic acid produced by CO_2-quenching of the anion at C-5 was found to be exceedingly labile at room temperature, decarboxylating gradually to the starting enol ether 7. Therefore, the free acid was immediately esterified with diazomethane. Unfortunately, any attempt to generate the enone system from the enol ether-ester 8 utilizing either a methyl Grignard reagent or methyllithium solely resulted in deprotonation at C-5, even with excess reagents.



In order to circumvent the problem of enolate formation during the generation of the enone moiety, a hydroxymethyl group was introduced at C-5 on the enol ether 7. The hydroxymethyl group could then be oxidized to a carboxyl group after the enone system had been constructed. Thus, treatment of the enol ether 7 first with 1.1 equivalents of LDA then with distilled formaldehyde provided the hydroxymethyl product 9 in 82% yield. Treatment of this product with excess methyllithium followed by work-up with dilute acid afforded the enone 10, which was subsequently oxidized with excess Jones reagent to the carboxylic acid-sulfone 11 (75% yield from 9). The phenylsulfonyl group gradually eliminates at room temperature upon standing, but for efficient elimination the sulfone 11 was dissolved in water containing sodium bicarbonate. The solution was then heated to gentle reflux for 20 min, cooled, and acidified with dilute

Scheme II.



hydrochloric acid to pH 2. Extraction with ethyl acetate and evaporation of the solvent to dryness under reduced pressure below 15°C provided pure (±)-desepoxy-4,5-didehydromethylenomycin A 3 as a coloress oil in 80 % yield or 32.5% overall yield from the readily available enol ether 6.[6] The spectral data (ir, uv, and ^{1}H-nmr) of the synthetic material were identical to those reported by Hornemann and Hopwood[3] for the natural compound.[7]

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References and Notes

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