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A STEREOSELECTIVE SYNTHESIS OF THE C-15 TO C-20 SEGMENT OF RIFAMYCIN-S

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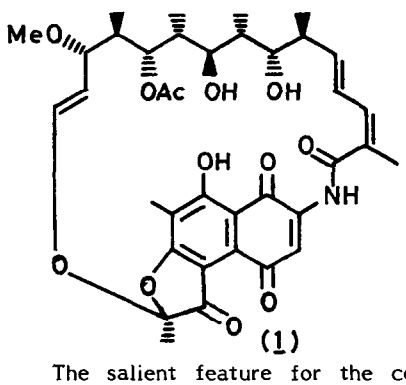
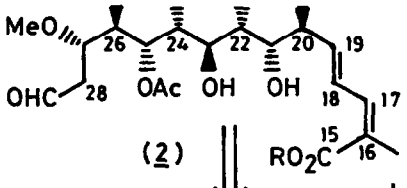
Abstract A convenient method has been described for the stereoselective construction of 5-substituted-2-methyl-2Z,4E-pentadienoic acid, present in the ansa bridge of rifamycin-S.

We have recently reported[1] a stereoselective synthesis of C-21 to C-27 fragment present in the ansa bridge of rifamycin-S (1)[2]. In continuation of our programme on the total synthesis of rifamycin-S, at some stage of our synthetic plan for the complete construction of the ansa chain 2, we require to introduce the 5-substituted-2-methyl-2Z,4E-pentadienoic acid (3; C-15 to C-20) in the correct stereochemical arrangement.

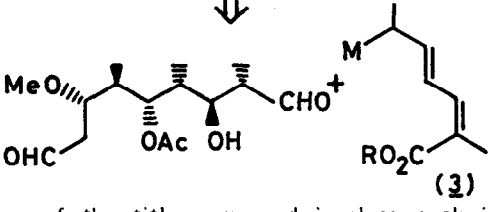
The stereoselective construction of (3) has been accomplished independently by Corey[3] and Masamune[2b] from cyclic intermediates and Kishi[2a] by making use of Wittig reaction. In this communication we present a new and stereoselective method for the construction of 5-substituted-2-methyl-2Z,4E-pentadienoic acid present in the ansa chain of rifamycin-S (Scheme-1).



(1)



(2)



(3)

The salient feature for the construction of the title compound involves exclusive formation of the cis olefin via deselenation of the cyclic intermediate 7. Thus ethyl 2-selenophenyl propionate[4] (4) was alkylated with substituted allyl chloride 5 in presence of LDA to give 6a in 75% yield. Its subsequent hydrolysis with aqueous 10% KoH afforded the corresponding acid, 6b. The acid 6b was subjected to iodolactonization[5] by using iodine, potassium iodide and 0.5 N $NaHCO_3$ to give the iodolactone, 7 in 60% yield. Treatment of 7 with hydrogen peroxide in THF containing a trace of AcOH at 0° effected oxidative elimination of the selenophenyl group to furnish the unsaturated lactone 8 as an exclusive product[6]. The cis-double bond in 8 would constitute the Z olefin of the target molecule.

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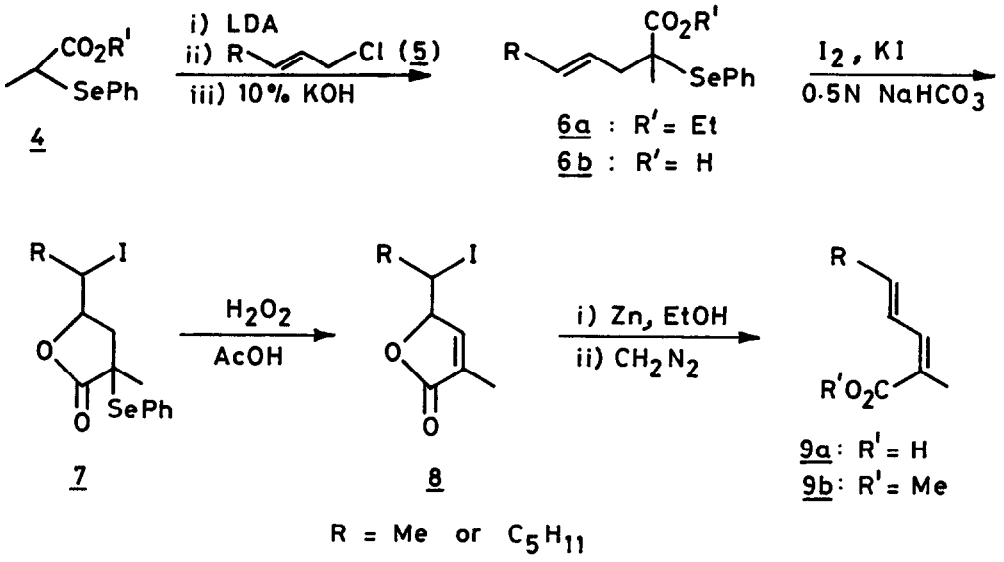
Scheme 1



Compound 8 was then treated with zinc in refluxing ethanol to afford the dienoic acid, 9a in 90% yield[7]. The E configuration of the newly formed olefin was based on ample evidences available in literature and also proved beyond doubt by ^{1}H-NMR spectrum which unequivably established the structure of the dienoic acid. The acid was then esterified with CH_2N_2 to give the methyl dienoate 9b.

The above methodology should be of value in a wide variety of synthetic approaches and is being extended for the construction of ansa chain 2 of rifamycin-S.

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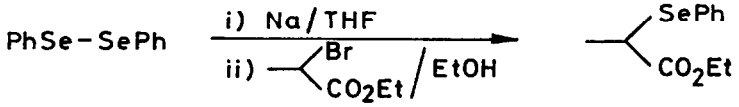
4. Preparation of Ethyl-2-selenophenyl propionate.



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