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Asymmetric Synthesis of C-19 to C-27 Fragment of Rifamycin-S

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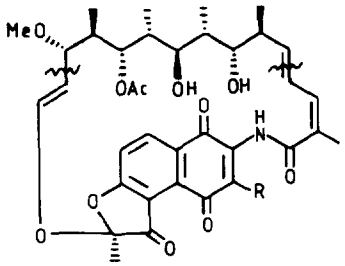
Abstract: *A highly stereoselective asymmetric synthesis of C-19 to C-27 fragment of Rifamycin-S consisting of 7 contiguous asymmetric centres is described involving Ipc_2BH as the chiral hydroborating reagent.*

Rifamycin-S (**1**),[1] belonging to ansamycin[2] class of medicinally important macrolide antibiotics having a 17-membered ansachain, was isolated from the fermentation broth of Norcardia mediteranei. Rifampacin (**2**), a derivative of **1**, is extensively used for TB[3] and has also shown antiviral and antileprosy[4] activity. The structure[5] and absolute stereochemistry[6] of **1** has been very well established and its profound biological activity has resulted in several formal[7] and one total synthesis[8] of **1**. In continuation of our studies[9] on the synthesis of this complex antibiotic, herein, we present the strategy for the construction of C-19 to C-27 segment **3** starting from bicyclic synthon **6**.



1, R = H **Rifamycin-S**

2, R = CH–N–N N–CH_3 **Rifampicin**

The ansa chain of **1** constitutes the C-15 to C-29 carbon framework, which encompasses a thermodynamically unfavourable E,Z-conjugate diene[10] (C-15 to C-19 segment) as well as eight contiguous asymmetric centres with alternating methyl and hydroxy groups. From the retrosynthetic studies of **3** (Scheme 1), it was reasoned that **3** could be easily made from **4** (C-19 to C-25 segment). The seven carbon framework **4** constituting five of the eight asymmetric centres, can be visualised in the folded form as shown in Scheme 1, which can be realised from **5**, that in turn could easily be made from the known bicyclic ketone **6** obtained by 4+2 cycloaddition of Furan and 2,4-dibromopentanone.[11] Thus, in the construction of **4** by using the bicyclic building block **6**, the inherent rigidity facilitates a) stereocontrolled functionalisation of the molecule and b) incorporation of the requisite chirality

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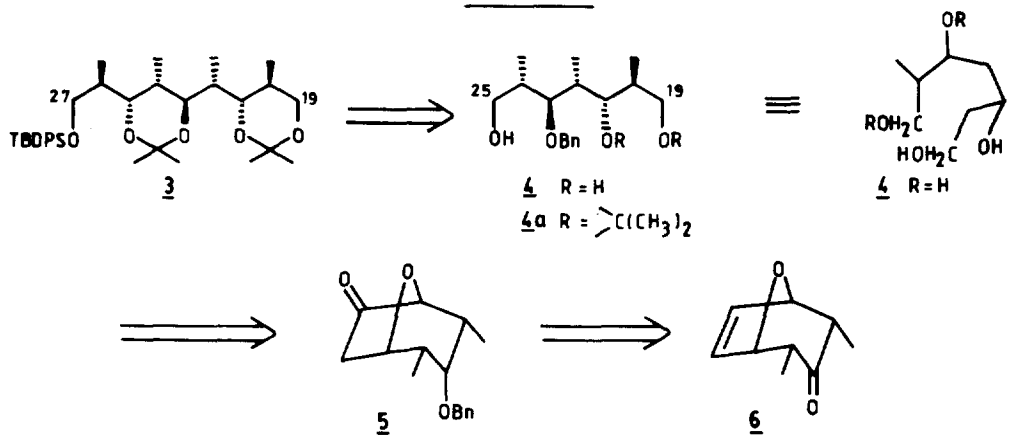
through an asymmetric hydroboration reaction. The C-1 to C-4 carbons in 6 can be correlated to C-25 to C-22 carbons of 4 respectively. The olefinic carbons at C-6 to C-7 help in the introduction of chirality.

Scheme - 1

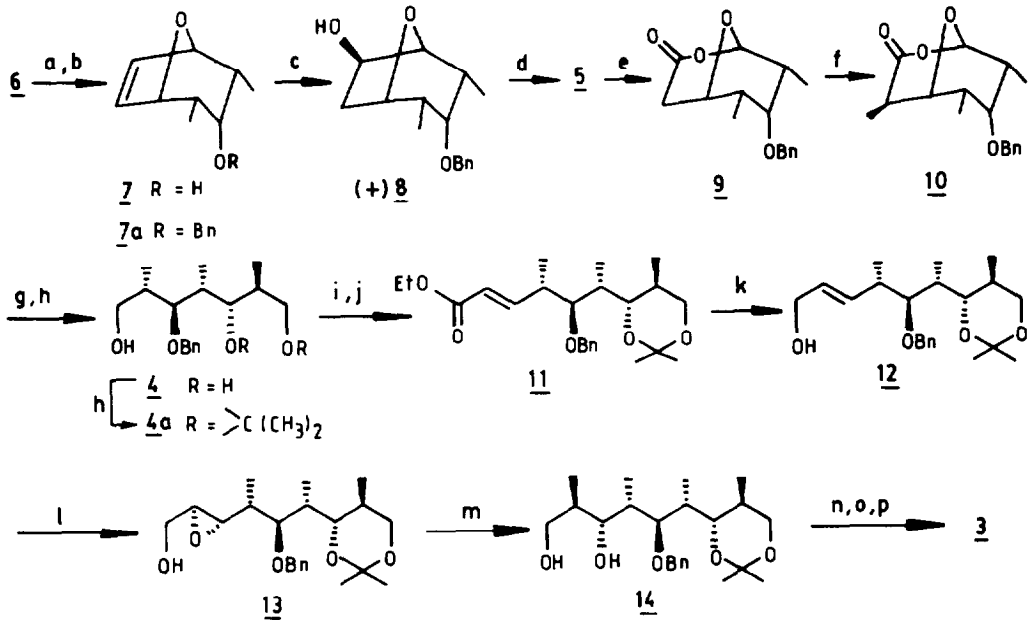


The bicyclic ketone 6 (8:1:1 unseparable isomeric mixture) on stereoselective reduction with DIBAL-H (Scheme 2) provided the endo-alcohol 7 after chromatographic purification which on subsequent reaction with benzylbromide (NaH,THF) was converted to the corresponding benzyl ether **7a**. The attempted incorporation of chirality on the functionalised bicyclic olefin **7a** through the asymmetric hydroboration[12] using (+) Ipc_2BH as the reagent met with failure in providing carbinol (+)**8**. However, finally the use of **7a** both as solvent as well as substrate effected the reaction smoothly and provided (+)**8** (96%) in high optical purity (100% ee)$[\alpha]_D$ +3.6 (c 6.63,$CHCl_3$) as determined from the ^1H NMR of (+)**8** as its MTPA ester. Similarly, the racemic alcohol (±)**8** (Scheme 3) obtained by hydroboration of **7a** with B_2H_6-THF complex, on esteri-fication with (-)camphanic acid chloride[13] followed by crystallisation and hydrolysis of the resulting ester **14a** gave (-)**8**, $[\alpha]_D$ -3.89° (c 5.9,$CHCl_3$).

Further functionalisation of chiral carbinol (+)**8** has been achieved in 3 steps. Thus, oxidation of (+)**8** with PCC in DCM afforded the ketone **5** in 95% yield. The crucial Baeyer-Villegar oxidation of **5** with a variety of reagents met with failure or gave the lactone **9** in very poor yields, while oxidation with selenium dioxide in combination with 90% H_2O_2[14] afforded **5** in 40% yield, $[\alpha]_D$ +46.2° (c 6.5,$CHCl_3$). Finally, alkylation of **5** with LDA-MeI furnished **10** thus completing the total functionalisation operation.

The optically pure bicyclic segment **10** was subjected to reductive opening with $LiAlH_4$ and the resultant triol **4** was acetonated with dimethoxy propane-PTSA to provide **4a** which constitutes the synthesis of C-19 to C-25 segment of **1**. Alcohol **4a** on Swern oxidation and subsequent reaction with (carbethoxymethylene)triphenylphosphorane gave **11** (72%). Reduction of **11** with DIBAL-H in CH_2Cl_2 and Sharpless asymmetric epoxidation[15] of **12** with (+)DIPT furnished the epoxy alcohol **13**. Regioselective ring opening of **13** with Me_2CuLi gave the 1,3-diol moiety **14**, which

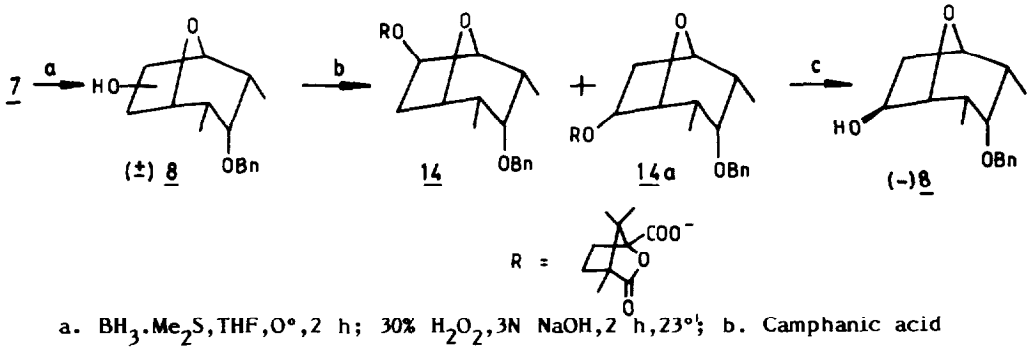
Scheme - 2



a. DIBAL-H,CH_2Cl_2,-10°C,1 h; b. NaH,BnBr,THF,65°,6 h; c. (-)Ipc_2BH,-20°, 24 h; 3NNaOH,30% H_2O_2,5 h; d. PCC,CH_2Cl_2,23°,3 h; e. 90% H_2O_2,SeO_2,tBuOH, Reflux,1 h; f. LDA,MeI,THF,-78°,3 h; g. LAH,THF,0°,4 h; h. 2,2-dimethoxy propane, PTSA,acetone,23°,12 h; i. $(COCl)_2$,DMSO,Et_3N,CH_2Cl_2,-75°,30 min; J. PPh_3=CHCOOEt,benzene,80°,6 h; k. DIBAL-H,CH_2Cl_2,-10°,30 min; l. +DET,TIP, TBHP,molecular sieves,CH_2Cl_2,-25°,48 h; m. Me_2CuLi,ether,-40°,5 h; n. TBDPSCl,imidazole,DMF,23°,5 h; o. 10%Pd-C,H_2,40 psi,EtOH,2 h; p. DMP, PPTS,CH_2Cl_2,2 h.

constitutes the C-19 to C-27 segment of 1. The structure of 14 was confirmed by converting it into a known Kishi's intermediate 3 by a simple sequence of reactions as

Scheme - 3



a. $BH_3.Me_2S$,THF,0°,2 h; 30% H_2O_2,3N NaOH,2 h,23°; b. Camphanic acid chloride,Pyr,0°,2 h; c. NaOH,THF:H_2O,1 h.

described.[9] Accordingly, diol **14** was subjected to selective protection of primary alcohol with TBDPSCl, which on subsequent hydrogenation followed by acetonation afforded **3**, having identical spectral data and optical rotation value as reported[16] earlier. $[\alpha]_D$ -3.25 (c 0.82, $CHCl_3$) lit. $[\alpha]_D$ -3.49 (c 1.52, $CHCl_3$)].

Thus, in conclusion it is pertinent to mention that the rigid bicyclic ketone or lactone moiety has been utilised as a key synthon for the construction of C-19 to C-27 fragment of Rifamycin-S and can be extended to the synthesis of similar class of compounds.[17,18]

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18. All compounds gave satisfactory spectral data and accurate HRMS.

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