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Synthesis of C_{19}-C_{27} Fragment of Ansa Chain Part of Rifamycin S

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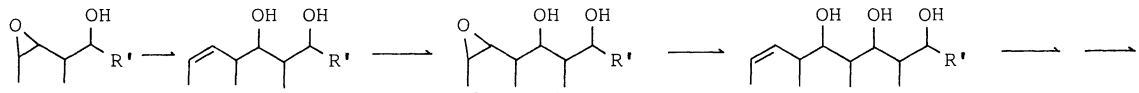
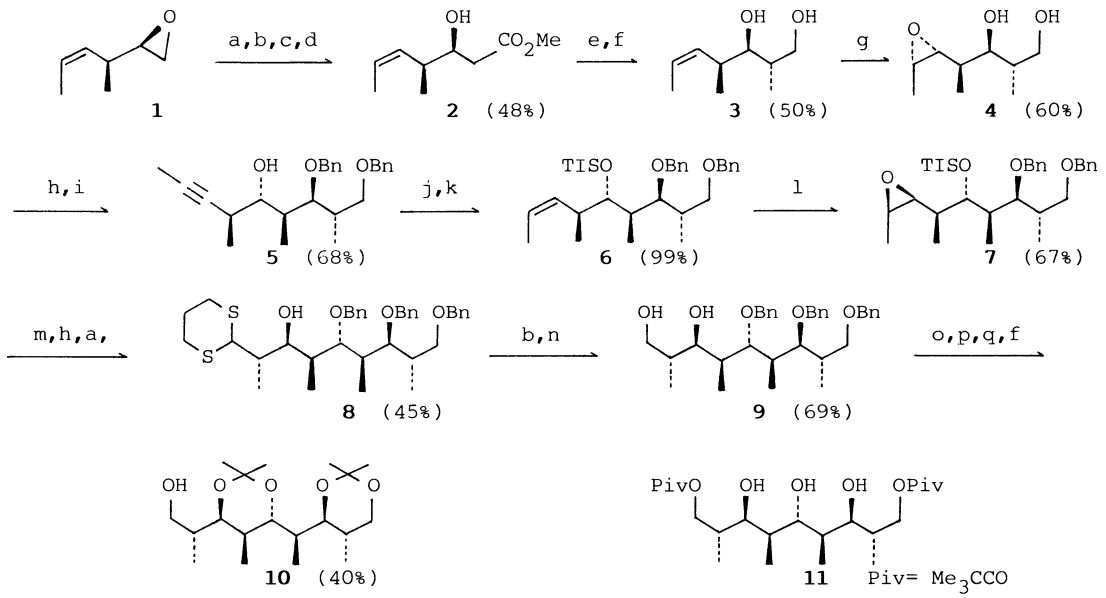
The C_{19}-C_{27} fragment of the ansa chain part of rifamycin S was stereoselectively synthesized from (4Z)-1,2-epoxy-3-methyl-4-hexene by reiterative use of stereoselective epoxidation of cis-homoallylic alcohol and regioselective opening of the resulting epoxy alcohol as key steps.

We recently reported a general methodology for the stereoselective construction of four consecutive asymmetric centers, where stereoselective epoxidation of β-methyl-cis-homoallylic alcohols and regioselective alkylation of the resulting epoxy alcohols, were used as key steps.[1] If a cis-vinyl anion or its synthetic equivalent is used in the alkylation steps of the above process, successive addition of two consecutive asymmetric centers will be realized as illustrated by scheme 1. We here describe the synthesis of the C_{19}-C_{27} fragment (**10**) of the ansa chain part of rifamycin S, carried out according to the above strategy. The intermediate bears seven consecutive asymmetric centers and has been prepared by Kishi et al. in the total synthesis of rifamycin S.[2]



Scheme 1.

The synthetic sequence is shown in Scheme 2. (4Z)-1,2-Epoxy-3-methyl-4-hexene (**1**)[1] readily derived from the product of stereoselective [2,3]Wittig rearrangement,[3] was successively subjected to dithianative epoxide ring opening to a dithio acetal,[4] alkylative desulfurization to an aldehyde, oxidation to a carboxylic acid,[5] and esterification to **2**. α-Methylation by Fráter's procedure[6] gave a mixture of an anti- and a syn-products (5:1). The anti-isomer separated by silica gel column was reduced to a diol (**3**). Mihelich's epoxidation[7] gave a mixture of an anti- (**4**) and a syn-epoxide (7:1). **4** was separated by column and after benzylation of hydroxyl groups, the epoxide group was cleaved by propynyllithium with the aid of $BF_3 \cdot OEt_2$[8] to give **5**. Partial hydrogenation followed by triisopropylsilyl(TIS) O-protection[9] gave **6** which was then epoxidized in a syn-fashion by the procedure reported previously[1] with $WO_5 \cdot HMPA$[10] to give **7** in a quite high selectivity over 30:1. The TIS O-protective group of **7** was replaced by a benzyl group and the resulting epoxy tribenzyl ether was treated with lithiated dithiane to give **8**. The dithioacetal group was converted into an aldehyde group which was reduced to give **9**. Here, **9** was debenzylated and then selectively dipivaloylated to give **11**, the meso-configuration of which was proved by ^1H and ^{13}C NMR.[11] The compound **9** was



a) 2-lithio-1,3-dithiane, THF, 0 °C b) MeI, $CaCO_3$, aq. MeCN c) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, t-BuOH-H_2O, -5 °C–rt d) CH_2N_2, Et_2O, rt e) LDA, MeI, THF-HMPA, -50–-20 °C f) LAH, THF, 0 °C g) $VO(acac)_2$, TBHP, CH_2Cl_2, -20 °C–rt h) $C_6H_5CH_2Br$, NaH, THF-DMF, 50 °C i) $MeC{\equiv}CLi$, $BF_3.Et_2O$, THF, -78–-20 °C j) H_2/Pd-$CaCO_3$, quinoline, C_6H_6, rt k) $(i\text{-}Pr)_3SiOTf$, 2,6-dimethylpyridine, CH_2Cl_2, rt l) WO_5.HMPA, CH_2Cl_2, rt m) n-Bu_4NF, THF, rt n) LAH, THF, -78–-20 °C o) Me_3CCOCl, DMAP, Et_3N, CH_2Cl_2, rt p) H_2/$Pd(OH)_2$-C and $PdCl_2$-C (1:1), MeOH, rt q) $(MeO)_2CMe_2$, camphorsulfonic acid, rt

Scheme 2.

then transformed into the desired Kishi's intermediate (**10**),[2] the C_{19}-C_{27} fragment of rifamycin S, by conventional manipulation of protective groups. The identity of **10** was confirmed by ^1H NMR comparison with the authentic datum.

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References

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