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Synthetic Studies on Polypropionate Antibiotics Based on the Stereospecific Methylation of γ,δ-Epoxy Acrylates by Trimethylaluminum. A Highly Stereoselective Construction of the Eight Contiguous Chiral Centers of Ansa-chains of Rifamycins

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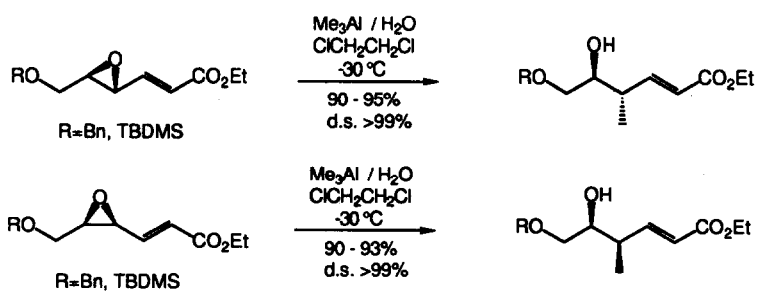
Abstract: A highly stereoselective construction of the eight contiguous chiral centers of ansa-chains of rifamycins has been accomplished by the iterative use of the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum which was recently developed by us. The present work demonstrates the synthetic potential of the method for the synthesis of polypropionate antibiotics including ansamycins and macrolides.

Rifamycins are representative ansamycin antibiotics[1] and structurally characterized by the aromatic core consisting of a naphthoquinone or naphthalene moiety and a long aliphatic bridge called "ansa-chain" spanned to the aromatic nucleus. Ansa-chains of these antibiotics are known to be biogenetically derived from several propionate units[2] and consist of characteristic sequences of alternating methyl- and hydroxyl-substituted carbons. Such structural features as well as their clinically important biological activities have elicited much attention from synthetic organic chemists[3] since the first total synthesis of rifamycin S by Kishi in 1980.[4]

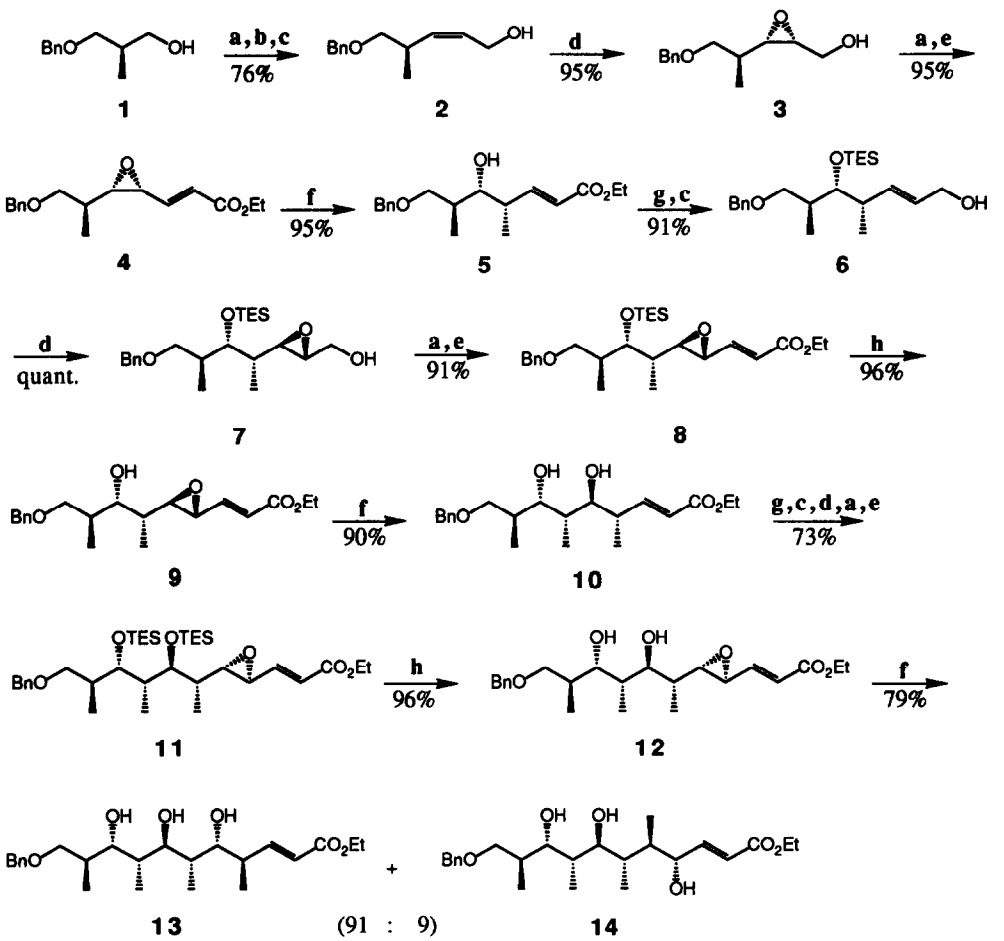
We recently developed the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum which can be applied iteratively for the construction of polypropionate chains (Scheme 1).[5] According to this methodology, anti compounds are produced from (*E*)-epoxy acrylates while syn compounds are produced from (*Z*)-epoxy acrylates, both stereospecifically (d.s.>99%) and in excellent yields. We report herein a highly stereoselective construction of the eight contiguous chiral centers of ansa-chains of rifamycins by the iterative use of the method in order to demonstrate the synthetic potential and validity of such methodology.[6]

Scheme 1



(*R*)-3-Benzyloxy-2-methyl-1-propanol (**1**), starting material, was converted to cis allylic alcohol **2** by a three-step reaction sequence in 76% overall yield (Scheme 2): 1) Swern oxidation; 2) Horner-Emmons reaction using potassium hydride as base[7]; 3) reduction with DIBAH. Epoxidation of **2** with MCPBA in CH_2Cl_2 exclusively produced α-epoxide **3** in high yield as reported by Kishi.[4d] The α-epoxide **3** thus obtained was easily transformed into *cis*-γ,δ-epoxy acrylate **4** by the Swern oxidation followed by the Horner-Emmons reaction with triethyl phosphonoacetate in 95% overall yield. The reaction of **4** with $(CH_3)_3Al$, a crucial step, was carried out in 1,2-dichloroethane in the presence of water at -30 °C to give solely the syn compound **5** in 95% yield.[8] After protection of the hydroxyl group newly formed of **5** with chlorotriethylsilane, the resulting

Scheme 2

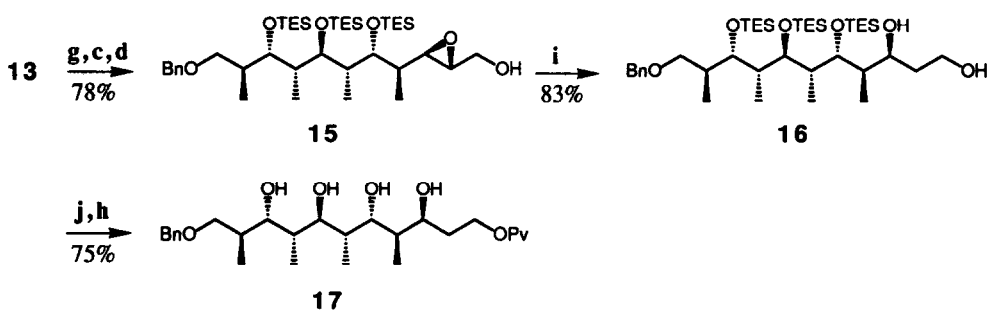


Reagents: **a.** $(COCl)_2$, DMSO, CH_2Cl_2, -70°C, then Et_3N; **b.** $(MeO)_2POCH_2CO_2Me$, KH, 18-crown-6, THF, 0 °C, then aldehyde at -78 °C, 77% for the 2 steps; **c.** DIBAH, toluene, -78 °C, 99%; **d.** MCPBA, CH_2Cl_2, 0 °C; **e.** $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, then aldehyde at -78 °C; **f.** $(CH_3)_3Al$ (10 equiv), H_2O (6 equiv), $ClCH_2CH_2Cl$, -30 °C; **g.** TESCl, ImH, DMAP, DMF, 40 °C; **h.** Bu_4NF, THF, 0 °C.

unsaturated ester was reduced to allylic alcohol **6** with DIBAH. Subsequent epoxidation of **6** with MCPBA cleanly and exclusively produced β-epoxide **7** in nearly quantitative yield.[8,9] This result unambiguously shows that the epoxidation of **6** occurred highly stereoselectively from the opposite side of the bulky triethylsilyl (TES) group, i. e., from the β-side, hence the TES group is ideally suited for both protection of the hydroxyl group and stereocontrol of subsequent epoxidation. The epoxy alcohol **7** was again transformed into *trans*-γ,δ-epoxy acrylate **8** by the Swern oxidation followed by the Horner-Emmons reaction with triethyl phosphonoacetate in 91% overall yield. Contrary to our expectations, however, the second application of the trimethylaluminum reaction to **8** resulted in a complex mixture. This result is probably due to the lack of chelation between an aluminum atom and two ether oxygen atoms of the epoxide and the silyl ether which plays the crucial role in trimethylaluminum reactions,[5] owing to the steric bulkiness of the TES group. Indeed, the same reaction of the hydroxy congener **9**, derived from **8** by desilylation, with $(CH_3)_3Al$ in the presence of water gave the desired product **10** with 98% diastereoselectivity[8] in 90% yield. Thus the five chiral centers were stereoselectively assembled by repeating the trimethylaluminum reaction.

In order to construct the remaining chiral centers, the dihydroxy ester **10** was again converted to γ,δ-epoxy acrylate **11** by a similar five-step reaction sequence in 73% overall yield: 1) Protection of two hydroxyl groups with TESCl; 2) reduction with DIBAH ; 3) epoxidation of the resulting allylic alcohol with MCPBA; 4) Swern oxidation; 5) Horner-Emmons reaction. Upon epoxidation of the intermediary allylic alcohol with MCPBA α-epoxide was stereoselectively produced in 79% yield (*vide supra*).[8,9] After desilylation of **11** with Bu_4NF in THF, the resulting dihydroxy epoxy ester **12** was conducted with $(CH_3)_3Al$ in 1,2-dichloroethane in the presence of water at -30 °C to give a 91 : 9 mixture of **13** having seven chiral centers and its regioisomer **14** in 79% yield. The eighth chiral center, last one, was stereoselectively assembled by using a similar reaction sequence (Scheme 3). Thus the three hydroxyl groups of **13** was protected with TESCl and subsequent reduction of the unsaturated ester with DIBAH led to allylic alcohol which was oxidized with MCPBA in CH_2Cl_2 to afford exclusively β-epoxy alcohol **15**[8,9] in 78% overall yield from **13**. Regioselective ring

Scheme 3



Reagents: **i.** $NaBH_3CN$, $BF_3{\cdot}OEt_2$, THF, r. t.; **j.** $(CH_3)_3CCOCl$, DMAP, py.

opening of the epoxide **15** was accomplished with $NaBH_3CN$ in THF in the presence of $BF_3{\cdot}Et_2O$[10] resulting in the formation of **16** in 83% yield. After protection of the primary hydroxyl group of **16** with pivaloyl chloride, three TES groups were desilylated with Bu_4NF giving the target molecule **17** bearing eight contiguous chiral centers in 75% yield. Thus a highly stereoselective construction of the eight contiguous chiral centers of

ansa-chains of rifamycins has been accomplished by the iterative use of the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum. The overall yield of **17** was 11% starting from the known *cis*-allylic alcohol **2**.

The present work demonstrates the synthetic potential of the methodology for the synthesis of polypropionate antibiotics and further extensions to other antibiotics are in progress in our laboratory.

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7) The corresponding (*E*)-unsaturated ester was accompanied in 11% yield.

8) The diastereoselectivity of the product or non-formation of other stereoisomers was determined by ^{1}H-NMR (400 or 500 MHz) spectrum.

9) Stereochemistry of the epoxide was unequivocally established by comparison with the authentic epoxide prepared from the allylic alcohol by the Katsuki-Sharpless asymmetric epoxidation using D-(-)- or L-(+)-tartrate.

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