Tandem synthesis of polypropionate chains–highly stereoselective synthesis of the ansa chain of streptovaricin U and protostreptovaricins based on stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminium

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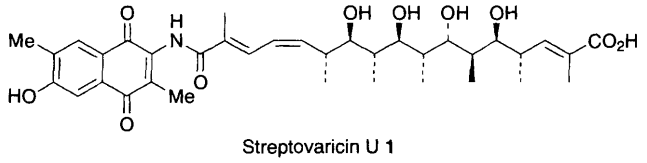
The highly stereoselective synthesis of the ansa chain segment 23 of streptovaricin U and protostreptovaricins (I and II) is achieved by stereospecific methylation of γ,δ-epoxy acrylates with trimethylaluminium.

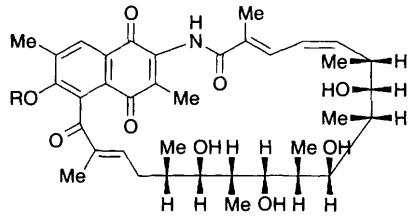
The streptovaricin family including protostreptovaricins and damavaricins are representative ansamycin antibiotics as well as rifamycins and are a clinically important class of antibiotics.[1] All the streptovaricin antibiotics consist of a unique naphthoquinone core and a polypropionate ansa chain composed of nine contiguous chiral centres.[1] Among them streptovaricin U **1** is a novel open-chain ansamycin and has inhibitory activity against RAUSCHER leukemia virus RNA-dependent DNA polymerase.[2] Unique structures and important biological activities of the streptovaricins have elicited considerable attention from synthetic chemists.[3]

Recently we developed a novel stereospecific methylation of γ,δ-epoxy acrylates with trimethylaluminium in the presence of water,[4] which provides a useful means for the synthesis of natural products.[5] We report here a tandem methodology for the synthesis of polypropionate chains based on the above methylation reaction involving the first and stereospecific synthesis of the ansa chain of streptovaricin U **1** and protostreptovaricins I **2** and II **3** having nine chiral centres.

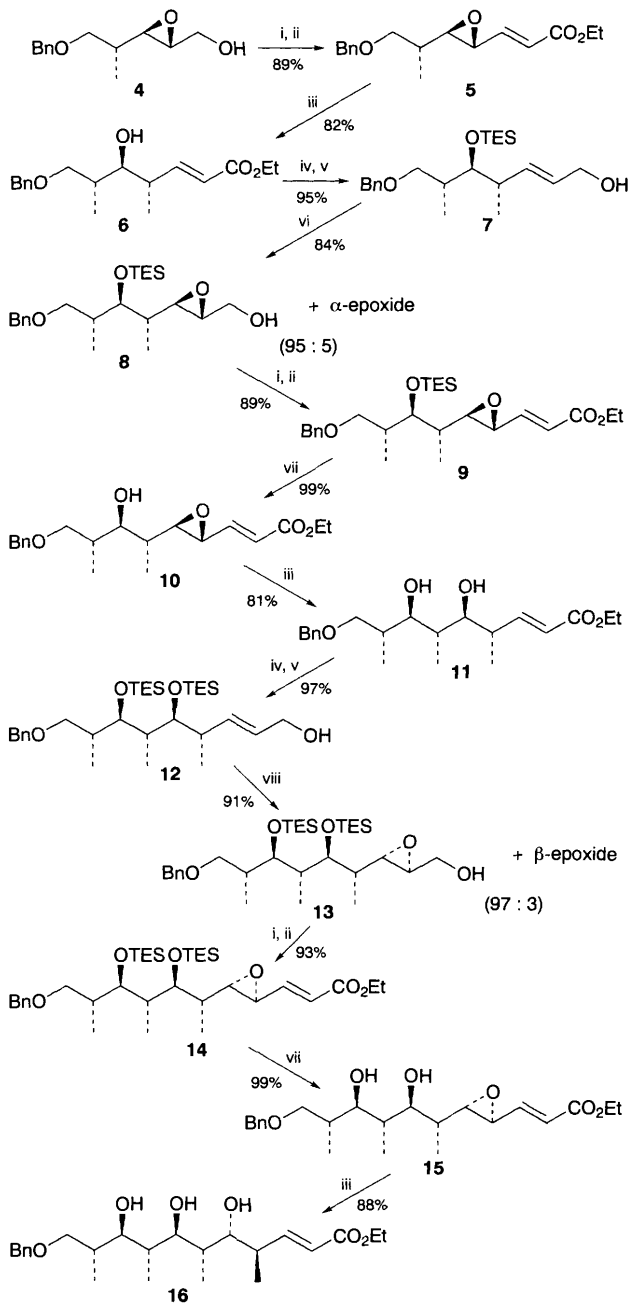
The starting material **4**, a chiral epoxy alcohol easily available from (*S*)-3-benzyloxy-2-methylpropanol,[6] was subjected to the Swern oxidation followed by the Horner–Emmons reaction with triethyl phosphonoacetate to give the γ,δ-epoxy acrylate **5**† in 89% yield, Scheme 1. Upon treatment of **5** with excess trimethylaluminium in the presence of water in 1,2-dichloroethane at −30 °C, methylation reaction took place at the γ-position with complete regio- and stereo-selectivity to afford the alcohol **6** as the sole product in 82% yield. No isomeric products were formed. After protection of the hydroxy group of



Streptovaricin U **1**



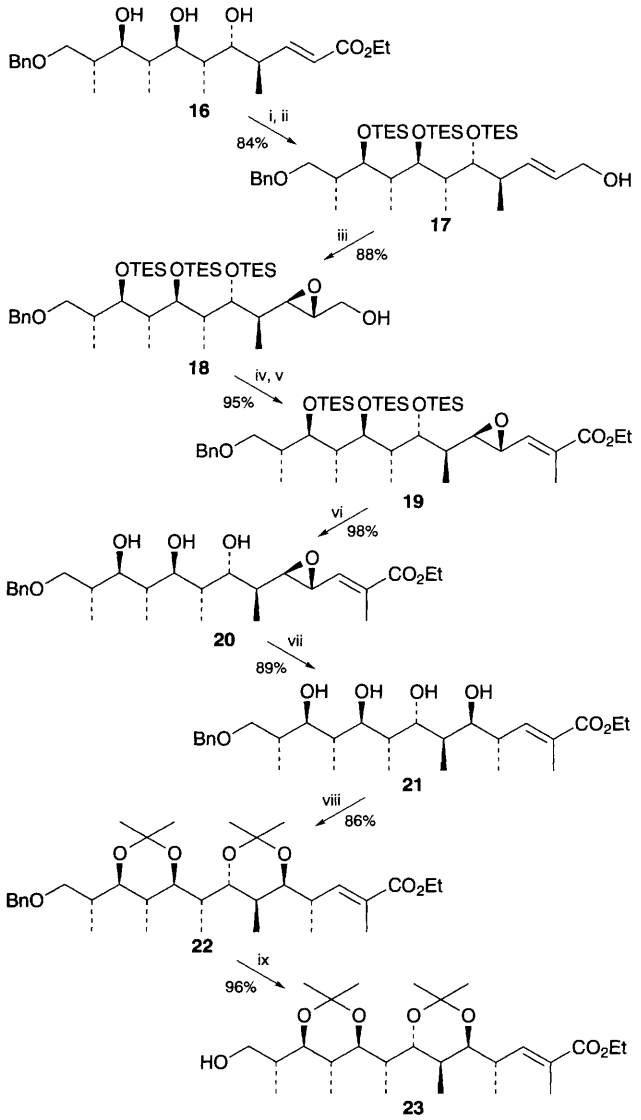
Protostreptovaricin I **2** R = H
Protostreptovaricin II **3** R = Me



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, Me_2SO, CH_2Cl_2, −70 °C, then Et_3N; ii, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, then aldehyde at −78 °C; iii, Me_3Al (10 equiv.), H_2O (6 equiv.), $ClCH_2CH_2Cl$, −30 °C; iv, TESCl, imidazole, DMAP, CH_2Cl_2; v, DIBAL-H, toluene, −78 °C; vi, $Ti(OPr^i)_4$, D-(−)-DET, Me_3COOH, CH_2Cl_2, −23 °C; vii, Bu_4NF, THF, 0 °C; viii, MCPBA, CH_2Cl_2, −10 °C

6 with chlorotriethylsilane (TESCl), reduction of the ethyl ester with diisobutylaluminium hydride (DIBAL-H) gave the allylic alcohol **7** in 95% yield from the 2 steps. The Katsuki–Sharpless asymmetric epoxidation[7] of the resulting allylic alcohol with D-(−)-diethyl tartrate furnished a 95 : 5 mixture of the desired β-epoxy alcohol **8** and its α-isomer in 84% combined yield. Since these epoxides could not be separated by silica gel chromatography, the mixture was directly submitted to Swern oxidation followed by Horner–Emmons reaction with triethyl phosphonoacetate to give the γ,δ-epoxy unsaturated ester **9** in 89% yield.‡ After removal of the triethylsilyl group of **9** with tetrabutylammonium fluoride in THF (99%), the corresponding epoxy alcohol **10** was subjected again to the crucial methylation reaction.§ Thus the treatment of **10** with excess trimethylaluminium in the presence of water at −30 °C produced the dihydroxy ester **11** having five contiguous chiral centres in 81% isolated yield. In this case too, the methylation reaction occurred in very high diastereoselectivity (> 99%).

The dihydroxy ester **11** was transformed into the allylic alcohol **12** by the same sequence of reactions for **6** to **7**: protection of the hydroxy groups with TESCl followed by reduction with DIBAL-H (97% for the 2 steps). Subsequent



Scheme 2 *Reagents and conditions*: i, TESCl, Imidazole, DMAP, CH_2Cl_2; ii, DIBAL-H, toluene, −78 °C; iii, MCPBA, CH_2Cl_2, −10 °C; iv, $(COCl)_2$, Me_2SO, CH_2Cl_2, −70 °C, then Et_3N; v, $Ph_3P{=}C(Me)CO_2Et$, THF; vi, Bu_4NF, THF, 0 °C; vii, Me_3Al (10 equiv.), H_2O (6 equiv.), CH_2Cl_2, −45 °C; viii, $Me_2C(OMe)_2$, PPTS, CH_2Cl_2; ix, H_2, Pd–$BaSO_4$, EtOH

treatment of **12** with MCPBA in dichloromethane gave a 97 : 3 mixture of the desired α-epoxy alcohol **13** and its β-isomer in 91% yield. The epoxide mixture was directly submitted to the Swern oxidation followed by the Horner–Emmons reaction with triethyl phosphonoacetate to afford the γ,δ-epoxy unsaturated ester **14** in 93% yield.‡ After removal of the triethylsilyl group of **14** with tetrabutylammonium fluoride (99%), the resulting epoxy diol **15** was subjected to a third methylation with trimethylaluminium. The reaction took place with complete diastereoselectivity to yield the trihydroxy ester **16** as the sole product in 88% yield. In this way, the segment **16** having seven chiral centres was efficiently and straightforwardly synthesized by repeating three times the key methylation reaction with trimethylaluminium.

Introduction of the remaining two chiral centres was accomplished as follows, Scheme 2. The trihydroxy ester **16** was converted to the allylic alcohol **17** by a two-step reaction sequence: (1) protection of the hydroxy groups with TESCl and (2) reduction with DIBAL-H (84% yield for the 2 steps). In turn the allylic alcohol **17** was oxidized with MCPBA to give a single β-epoxy alcohol **18** in 88% yield, which was transformed into the corresponding γ,δ-epoxy unsaturated ester **19** by Swern oxidation and subsequent Wittig reaction with (carbethoxyethylidene)triphenylphosphorane in 95% yield. After removal of the triethylsilyl groups of **19** with tetrabutylammonium fluoride (98%), the resulting epoxy triol **20** was subjected to a fourth methylation with trimethylaluminium. The key methylation reaction was carried out at −45 °C in dichloromethane to furnish the desired product **21** in 89% isolated yield along with other diastereoisomers. Compound **21** was then transformed intthe bis-acetal **22**. Finally, the benzyl protecting group of **22** was removed by hydrogenolysis over Lindlar catalyst to cleanly provide the target molecule **23**, $[\alpha]_D^{22}$ + 6.8 (*c* 0.56, $CHCl_3$), having nine chiral centres in 96% yield.

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Footnotes

† All new compounds had satisfactory spectra (^1H and ^{13}C NMR, IR) and elemental analyses.

‡ At this stage, the major product was cleanly separated from the minor one by silica gel column chromatography.

§ Reaction of the triethylsilyl compound itself with trimethylaluminium was very sluggish and resulted in a complex mixture.

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