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A tandem synthesis of polypropionate chains. Highly stereoselective construction of the C(13)–C(25) segment containing nine contiguous chiral centers of swinholides A–C based on the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminium

Hiroyuki Hayakawa and Masaaki Miyashita *

Division of Chemistry, Graduate School of Science, Hokkaido University, Hokkaido 060-0810, Japan

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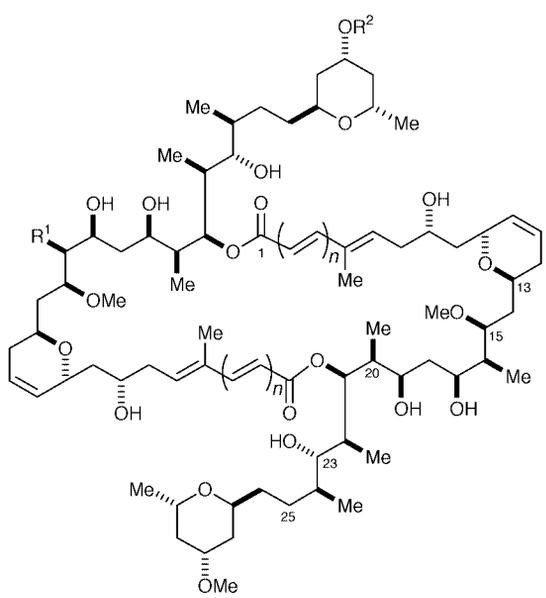
The highly stereoselective synthesis of the common C(13)–C(25) segment containing nine contiguous chiral centers of swinholides A–C and misakinolide A has been achieved by tandem methodology which involves the stereospecific methylation of γ,δ-epoxy acrylates with trimethylaluminium and the novel reductive cleavage of an epoxy aldehyde with an organoselenium reagent as key steps.

The marine natural products swinholides A (**1**), B (**2**) and C (**3**),



Swinholide A (**1**): $n = 1$, $R^1 = R^2 = Me$

Swinholide B (**2**): $n = 1$, $R^1 = H$, $R^2 = Me$

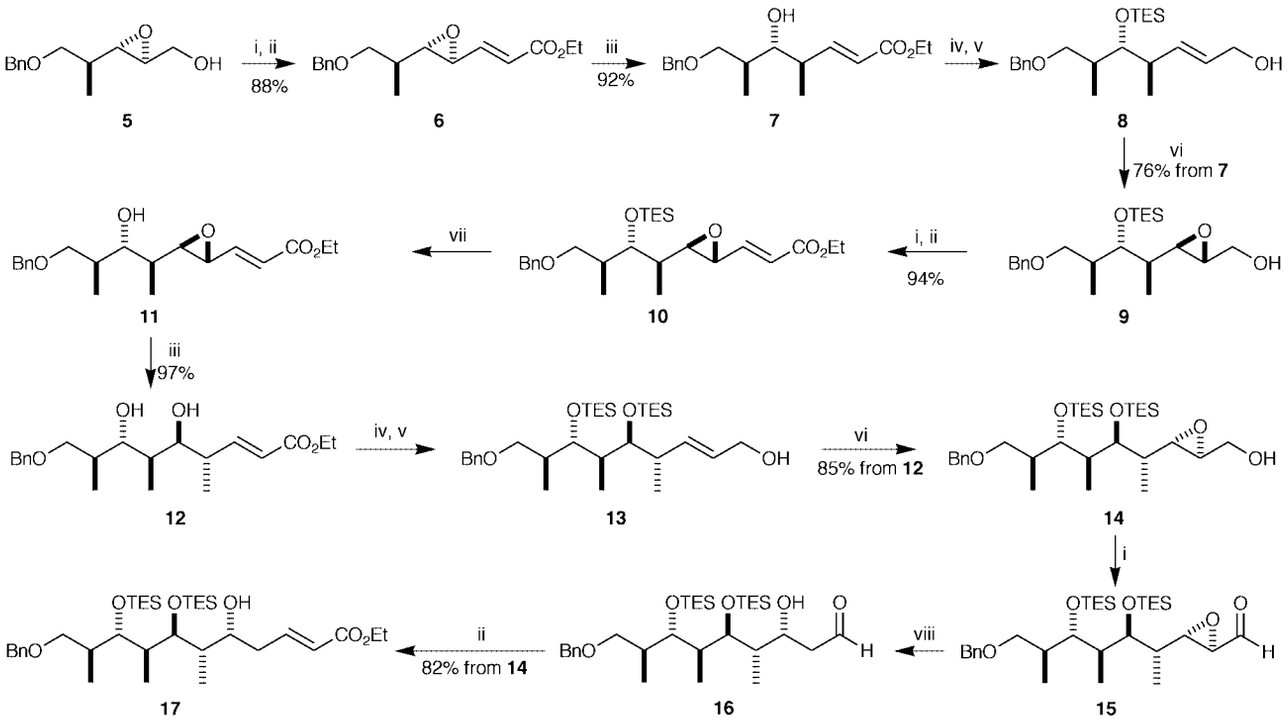
Swinholide C (**3**): $n = 1$, $R^1 = Me$, $R^2 = H$

Misakinolide A (**4**): $n = 0$, $R^1 = R^2 = Me$

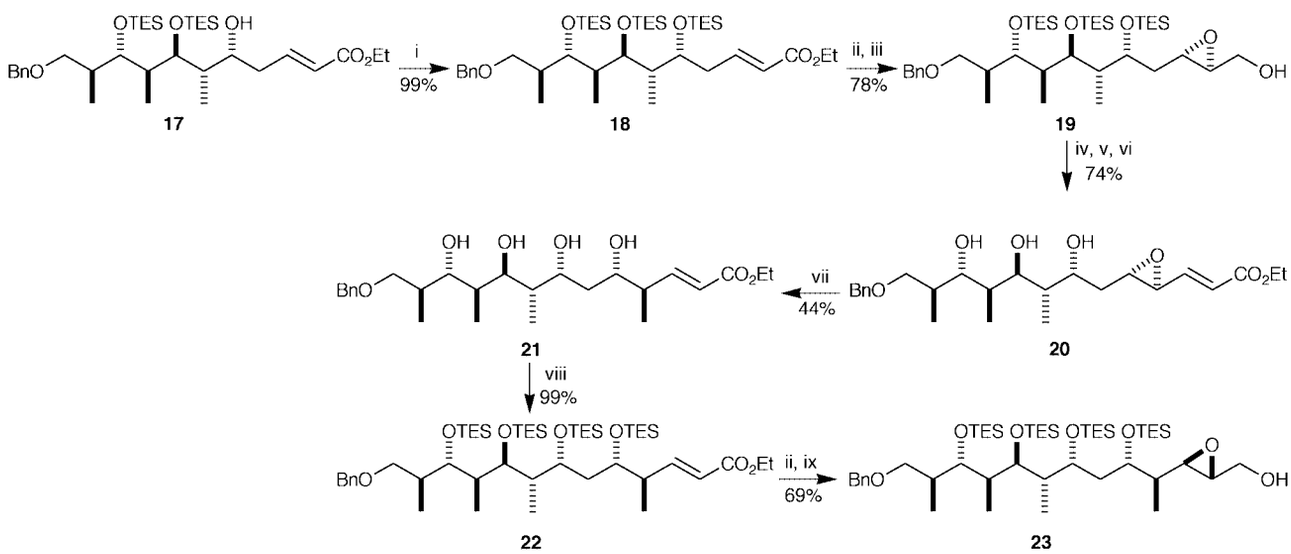
44-membered dimeric macrolides, isolated from the Okinawan marine sponge *Theonella swinhoei*,[1] and misakinolide A (**4**), a 40-membered dimeric lactone, isolated from another Okinawan marine sponge *Theonella*,[2] have been revealed to exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity.[1–3] The stereostructures of the monomeric units of swinholide A and misakinolide A are remarkably similar to one another and only the number of double bonds connected to a carboxy group is different. The structures of these families are characterized by the C_2-symmetrical dimeric macrolides in which two polypropionate-derived chains including a gigantic lactone ring are axially oriented on a tetrahydropyran ring. Their unique structures and potent anticancer activities have elicited much attention from synthetic organic chemists.[4,5] As part of our synthetic program toward the polypropionate-derived bioactive compounds possessing characteristic sequences of alternating methyl- and hydroxy-substituted carbons,[6] we set about asymmetric total synthesis of the swinholide family. We report here the highly stereoselective construction of the common C(13)–C(25) segment of swinholides A–C (**1**–**3**) and misakinolide A (**4**) containing nine contiguous chiral centers by the tandem methodology which involves the stereospecific methylation of γ,δ-epoxy acrylates with trimethylaluminium[7] and the novel reductive cleavage of an epoxy aldehyde with an organoselenium reagent as key steps.

The starting material **5**, a chiral α-epoxy alcohol easily available from (*S*)-3-benzyloxy-2-methylpropanol,[8] was subjected to Swern oxidation followed by Horner–Emmons reaction with triethyl phosphonoacetate to give the γ,δ-epoxy acrylate **6**† in 88% yield, Scheme 1. Upon treatment of **6** with excess trimethylaluminium in the presence of water in dichloromethane at −30 °C,[7] methylation took place at the γ-position with complete regio- and stereo-selectivity to afford the alcohol **7** as the sole product in 92% isolated yield. No isomeric products were formed. After protection of the hydroxy group of **7** with chlorotriethylsilane (TESCl), reduction of the ethyl ester with diisobutylaluminium hydride (DIBAL-H) gave the allylic alcohol **8**, which was subjected to epoxidation with MCPBA in dichloromethane to furnish the desired β-epoxy alcohol **9** as the sole product in 76% overall yield. As we have recently reported,[9] epoxidation of such a 4-methyl-5-(triethylsilyl)oxyallyl alcohol system with MCPBA in dichloromethane occurs highly stereoselectively from the opposite side of the C(5) triethylsilyloxy group regardless of the stereochemistry of an adjacent methyl group. The β-epoxy alcohol **9** thus obtained was transformed into the γ,δ-epoxy ester **10** by Swern oxidation followed by Horner–Emmons reaction in 94% yield. After removal of the triethylsilyl group of **10** with tetrabutylammonium fluoride (Bu_4NF) in THF, the resulting epoxy acrylate **11** was subjected again to the crucial methylation reaction. Thus, the treatment of **11** with excess trimethylaluminium in the presence of water at −30 °C produced the dihydroxy ester **12** having five contiguous chiral centers in 97% isolated yield. In this case too, the methylation reaction occurred in complete diastereoselectivity.

The dihydroxy ester **12** was transformed into the allylic alcohol **13** by the same sequence of reactions for **7** to **8**: protection of the hydroxy groups with TESCl followed by reduction with DIBAL-H. Subsequent epoxidation of **13** with MCPBA in dichloromethane gave a single α-epoxy alcohol **14**, as expected (*vide supra*),[9] in 85% overall yield from **12**. The epoxy alcohol **14** thus obtained was converted to the epoxy aldehyde **15** by Swern oxidation, which was submitted to the regioselective reductive cleavage of an epoxide, a crucial step in the present synthesis, in order to lead to the β-hydroxy aldehyde **16**. Although the reductive cleavage of an epoxide in the presence of an aldehyde seems very difficult, this key step was overcome by the organo-



Scheme 1 *Reagents and conditions*: i, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; ii, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, then aldehyde at 0 °C; iii, $(CH_3)_3Al$ (10 equiv.), H_2O (6 equiv.), CH_2Cl_2, −30 °C; iv, TESCl, ImH, DMAP, CH_2Cl_2; v, DIBAL-H, THF, 0 °C; vi, MCPBA, CH_2Cl_2, 0 °C; vii, Bu_4NF, THF; viii, $Na[PhSeB(OEt)_3]$, CH_3CO_2H, EtOH, 0 °C.



Scheme 2 *Reagents and conditions*: i, TESCl, ImH, DMAP, CH_2Cl_2; ii, DIBAL-H, THF, 0 °C; iii, $Ti(O^iPr)_4$, L-(+)-DET, TBHP, CH_2Cl_2, −23 °C; iv, $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N; v, $(EtO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, then aldehyde at 0 °C; vi, Bu_4NF, THF, 0 °C; vii, $(CH_3)_3Al$ (10 equiv.), H_2O (6 equiv.), CH_2Cl_2, −30 to 10 °C; viii, TESOTf, 2,6-lutidine, CH_2Cl_2; ix, MCPBA, CH_2Cl_2, 0 °C.

selenium-mediated reduction methodology recently developed by us.[10] Thus, the reductive cleavage of the epoxy aldehyde **15** by the use of sodium (phenylseleno)triethylborate[10] (3 equiv.) and acetic acid (3 equiv.) in ethanol occurred cleanly and regioselectively giving rise to the desired β-hydroxy aldehyde **16**, which was directly subjected to Horner–Emmons reaction with triethyl phosphonoacetate to afford the unsaturated ester **17** in 82% overall yield for the 3 steps. After protection of a hydroxy group in **17** with TESCl, Scheme 2, the resulting ester **18** was converted to the α-epoxy alcohol **19** by treatment with DIBAL-H followed by the Katsuki–Sharpless asymmetric epoxidation with L-(+)-diethyl tartrate (78% for the 3 steps). The α-epoxy alcohol **19** thus obtained was transformed into the γ,δ-epoxy acrylate **20** again by a similar three-step reaction sequence: 1) Swern oxidation; 2) Horner–Emmons reaction with triethyl phosphonoacetate; 3) removal of the TES group with Bu_4NF, in 74% overall yield. The resulting epoxy acrylate **20** was subjected to a third methylation with trimethylaluminium. The reaction took place again with complete diastereoselectivity to yield the trihydroxy ester **21** as the sole product, albeit in modest yield (44%, 60% yield based on the consumed substrate). In this way, the segment **21** having eight chiral centers was efficiently and straightforwardly synthesized by repeating three times the key methylation reaction with trimethylaluminium. Introduction of an asymmetric center at the C(13) position was accomplished as follows. Protection of the four hydroxy groups in **21** with triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-lutidine in dichloromethane resulted in the formation of a nearly quantitative yield of **22**, which was submitted to reduction with DIBAL-H followed by oxidation with MCPBA to give a single β-epoxy alcohol **23**, the target molecule, in 69% overall yield. In this case too, epoxidation with MCPBA occurred in complete diastereoselectivity same as for **8** and **13**.

In summary, a highly stereoselective synthesis of the common C(13)–C(25) segment containing nine contiguous chiral centers of swinholides (**1**–**3**) and misakinolide A (**4**) has been achieved by the tandem strategy which involves the stereospecific methylation of γ,δ-epoxy acrylates with trimethylaluminium and the regioselective reductive opening of an epoxy aldehyde as key steps. It should be noted that the construction of all the nine chiral centers in the target molecule **23** has been achieved with complete stereoselectivity in the present synthesis.

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Notes and references

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

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