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Total Synthesis of Scytophycin C. 1. Stereoselective Syntheses of the C(1)–C(18) Segment and the C(19)–C(31) Segment

Ryoichi Nakamura, Keiji Tanino, and Masaaki Miyashita*

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

miyasita@sci.hokudai.ac.jp

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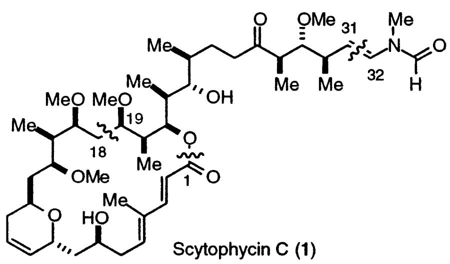
ABSTRACT



Scytophycin C (1)

Stereoselective total synthesis of scytophycin C, a marine 22-membered macrolide displaying potent activity against a variety of human carcinoma cell lines, has been reported in which the polypropionate structure bearing contiguous asymmetric centers was stereospecifically constructed by using new acyclic stereocontrol. This paper describes stereoselective syntheses of the C(1)–C(18) segment (Segment A) including a trans-disubstituted dihydropyran ring and the C(19)–C(31) segment (Segment B) having eight stereogenic centers.

The scytophycins, a novel series of polyoxygenated 22-membered macrolides isolated from the terrestrial blue-green alga *Scytonema pseudohofmanni*,[1] have demonstrated potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity.[1b,c,2] Among them, scytophycin C (**1**) isolated by Moore et al. in 1986[1a] has been demonstrated to exhibit significant activity against solid tumors in vitro.[3] The potent biological properties of scytophycin C, its scarce availability from natural sources, and its close structural resemblance to the marine natural product swinholide A have stimulated considerable interest in its synthesis.[4−10] So far, an elegant total synthesis of scytophycin C has been achieved by Paterson by the judicious use of stereoselective aldol reactions.[4,5] We report

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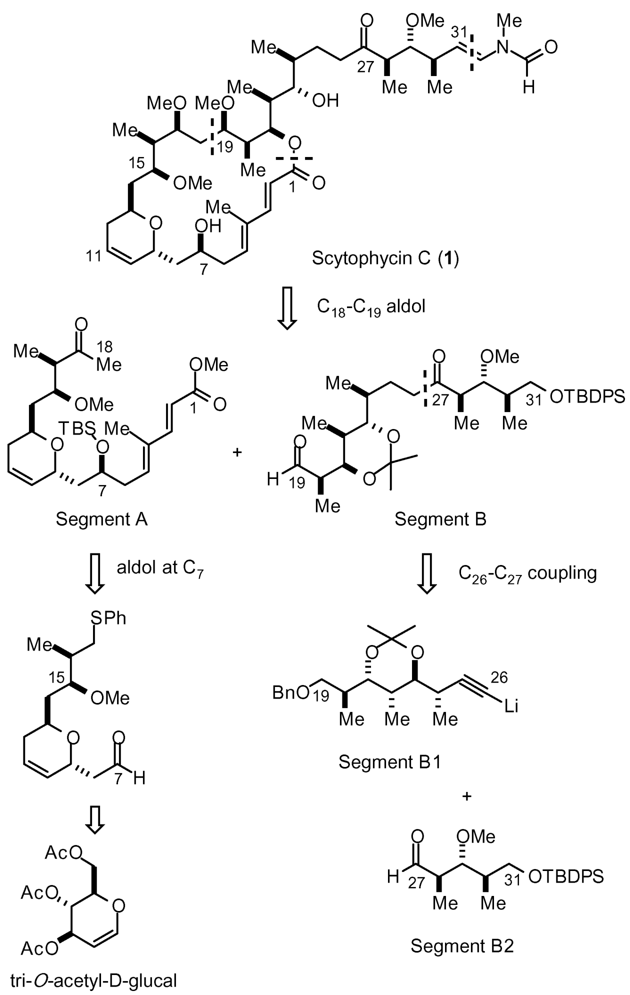
herein the stereoselective total synthesis of scytophycin C (**1**) based on new acyclic stereocontrol. The structure of scytophycin C is characterized by a 22-membered macrolide containing a dihydropyran ring bearing two trans-substituted side chains and a unique polypropionate-derived structure having a terminal *N*-methyl-*N*-vinylformamide moiety in which 15 asymmetric centers are included in total.

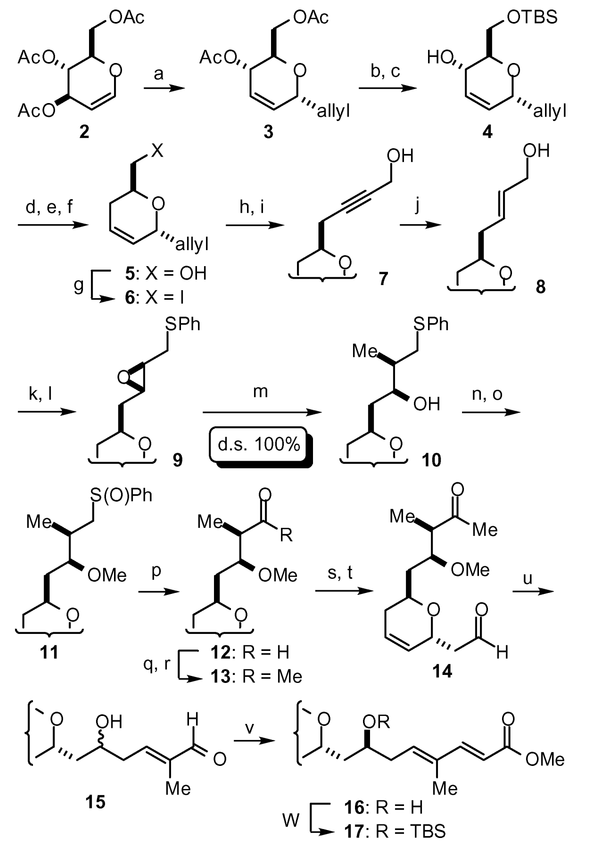
Our retrosynthesis of scytophycin C (**1**) is shown in Scheme 1. Namely, **1** was divided into the C(1)−C(18) segment (Segment A) and the C(19)−C(31) segment (Segment B), and both segments were designed to connect by an aldol reaction at the C18 and C19 positions under Felkin−Anh control similarly to the synthesis by Paterson.[4,5] Segment A, including a dihydropyran ring bearing trans-substituted side chains, would be assembled from commercially available tri-*O*-acetyl-D-glucal. On the other hand, segment B containing eight asymmetric centers was further divided into the C(19)−C(26) acetylenic segment (Segment B1) and the C(27)−C(31) aldehyde segment (Segment B2) by disconnecting the C(26)−C(27) bond. Due to the acid instability of scytophycin C,[1] the acid-labile *N*-methyl-*N*-vinylformamide moiety at the terminus was designed to be introduced at the final stage of the synthesis. At first, we describe the stereoselective syntheses of both segments A and B in this paper and then discuss the key coupling reaction of both segments and macrolactonization culminating in the total synthesis of scytophycin C (**1**) in the next paper.

Scheme 1. Synthetic Strategy of Scytophycin C (**1**)



Segment A containing the dihydropyran ring was efficiently and stereoselectively synthesized according to Scheme 2, which involves novel acyclic stereocontrol with double inversion of the configuration as the key step. Thus, allylation of tri-*O*-acetyl-D-glucal (**2**) with allyltrimethylsilane and TMSOTf[11] followed by removal of the acetyl groups

Scheme 2. Stereoselective Synthesis of Segment A[a]



[a] Reagents and conditions: (a) allyltrimethylsilane, TMSOTf, MeCN, 0 °C, 98%; (b) K_2CO_3, MeOH, rt; (c) TBSCl, imidazole, DMF, 0 °C to rt, 76% yield for two steps; (d) MsCl, Et_3N, Me_3N−HCl, toluene, 0 °C; (e) $LiBEt_3H$, THF, 0 °C to rt; (f) TBAF, THF, rt, 84% yield for three steps; (g) $(PhO)_3P^+MeI^-$, DMF, rt, 89%; (h) propargyl tetrahydropyranyl ether, *n*BuLi, HMPA, THF, −40 to 60 °C; (i) PPTS, MeOH, 60 °C, 77% yield for two steps; (j) Red-Al, Et_2O, 0 °C to rt, 94%; (k) $Ti(O^iPr)_4$, L-(+)-DET, TBHP, 4 Å MS, CH_2Cl_2, −25 °C; (l) $(PhS)_2$, Bu_3P, pyridine, 0 °C, 76% yield for two steps; (m) Me_3Al, CH_2Cl_2, −30 °C; (n) NaH, MeI, DMF, 50 °C, 91% yield for two steps; (o) $NaIO_4$, aq MeOH, 0 °C to rt, 90%; (p) TFAA, 2,6-lutidine, $HgCl_2$, aq MeCN, 0 °C to rt; (q) MeLi, $CeCl_3$, THF, −78 °C; (r) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N, 69% yield for three steps; (s) OsO_4, NMO, aq acetone, rt; (t) $NaIO_4$, aq MeOH, 0 °C to rt, 67% yield for two steps; (u) 2-methyl-1-trimethylsilyloxy-1,3-butadiene, BF_3−Et_2O, Et_2O−CH_2Cl_2, −78 °C, 85% (7α/7β = 2:7); (v) trimethyl phosphonoacetate, *n*BuLi, THF, 0 °C, 92%; (w) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 83%.

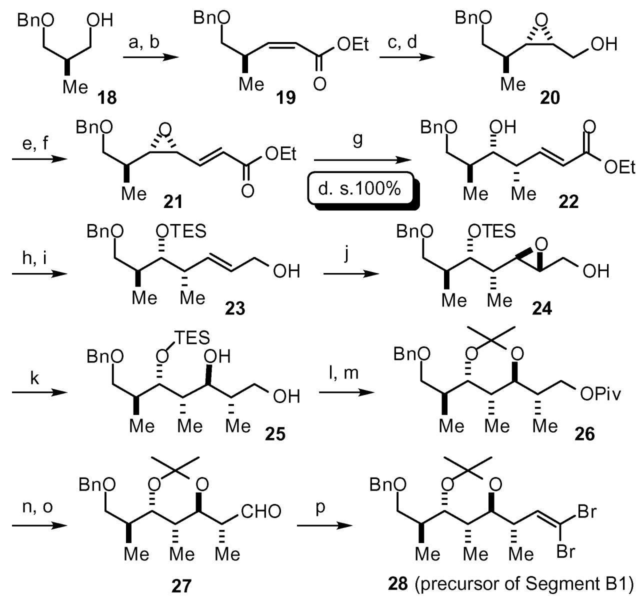
with K_2CO_3 and subsequent protection of the primary alcohol with TBSCl gave the alcohol **4** in 74% overall yield. The product was then converted to **5** in three steps: (1) mesylation by the Tanabe protocol;[12] (2) reduction with super hydride; and (3) removal of the TBS group with TBAF, in 84% yield. Conversion of the resulting alcohol **5** to the iodide **6** and subsequent coupling reaction with alkynyllithium followed by removal of the THP group with PPTS[13] afforded **7**, which in turn was reduced with Red-Al to give the (*E*)-allylic alcohol **8** in high yield. Upon treatment of **8** under the asymmetric epoxidation conditions,[14] the desired β-epoxy alcohol was obtained, which was subjected to sulfenylation with diphenyl disulfide[15] to furnish the β-epoxy sulfide **9** in 76% overall yield. The subsequent methylation reaction of **9** with double inversion of the configuration, a crucial step in the present synthesis, was successfully performed by using the methodology recently developed by Saigo[16] and us.[17] Namely, on treatment of **9** with trimethylaluminum, the methylation occurred stereospecifically via an episulfonium ion, giving rise to the syn compound **10** as a single product in 91% yield. After O-methylation of the hydroxyl group in **10**, the sulfide was oxidized to the corresponding sulfoxide **11**, which was submitted to the Pummerer reaction,[18] resulting in the formation of the aldehyde **12**. The aldehyde **12** was routinely transformed into the methyl ketone **13** by methylation followed by oxidation in 69% overall yield from **11**.

Regioselective osmylation of the terminal vinyl group in **13** and subsequent oxidation with periodate produced the aldehyde **14**, which was subjected to the Mukaiyama aldol reaction with 2-methyl-1-trimethylsilyloxy-1,3-butadiene in the presence of BF_3-etherate[4] to give a 7:2 mixture of epimeric alcohols in 85% combined yield. After separation of the mixture by silica gel chromatography, the major product was readily converted to segment A (**17**) by the Horner−Wadsworth−Emmons reaction with trimethyl phosphonoacetate followed by protection of the hydroxyl group with TBSOTf in high overall yield. ^{1}H and ^{13}C NMR spectra of the segment A were identical with those of the synthetic compound elaborated by Paterson et al. by a different synthetic strategy.[5] The overall yield of segment A was 6.5% for the 23 steps.

On the other hand, segment B1 containing five contiguous chiral centers was stereoselectively synthesized according to Scheme 3.

Namely, (*R*)-3-benzyloxy-2-methylpropanol (**18**) was subjected to Swern oxidation followed by the Horner−Emmons

Scheme 3. Stereoselective Synthesis of Segment B1[a]



[a] Reagents and conditions: (a) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N; (b) di-*o*-tolyl ethoxycarbonyl-methyl phosphate, NaH, THF, −78 °C, 91% yield for two steps; (c) DIBAH, THF, 0 °C; (d) *m*-CPBA, CH_2Cl_2, 0 °C, 74% yield for two steps; (e) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N; (f) triethyl phosphonoacetate, NaH, THF, 0 °C, 89% yield for two steps; (g) $(CH_3)_3Al$ (10 equiv), CH_2Cl_2, −30 °C, then H_2O (6 equiv), −30 °C, 2 h, 92%; (h) TESCl, DMAP, imidazole, CH_2Cl_2, rt; (i) DIBAH, THF, 0 °C, 85% yield for two steps; (j) *m*-CPBA, CH_2Cl_2, 0 °C, 97%; (k) Me_2CuLi, ether, −40 to 0 °C; (l) *t*-BuCOCl, pyridine, CH_2Cl_2 0 °C to rt; (m) 2,2-dimethoxypropane, CSA, DMF, 94% yield for three steps; (n) DIBAH, CH_2Cl_2, −78 °C; (o) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N; (p) Ph_3P, CBr_4, pyridine, CH_2Cl_2, 0 °C, 84% yield for three steps.

reaction with Ando's reagent[19] to afford the (*Z*)-unsaturated ester **19** in 91% yield. After reduction of the ester **19** with DIBAH, the resulting (*Z*)-allylic alcohol was oxidized with *m*CPBA to give the single α-epoxy alcohol **20** in 74% yield,[20] which was again subjected to Swern oxidation followed by the Horner−Wadsworth−Emmons reaction with triethyl phosphonoacetate to furnish the γ,δ-epoxy unsaturated ester **21** in high yield. A key methylation reaction of **21** was performed by using our original $(CH_3)_3Al-H_2O$ system[21,22] wherein the methylation occurred stereospecifically at the γ-position with inversion of the configuration, giving rise to the syn compound **22** as the sole product in 92% yield. The product was readily converted to the allylic alcohol **23** by protection of the hydroxyl group with TESCl followed by reduction with DIBAH. Upon treatment of **23** with *m*CPBA, the single β-epoxy alcohol **24** was obtained nearly quantitatively. As we have already reported, epoxidation of

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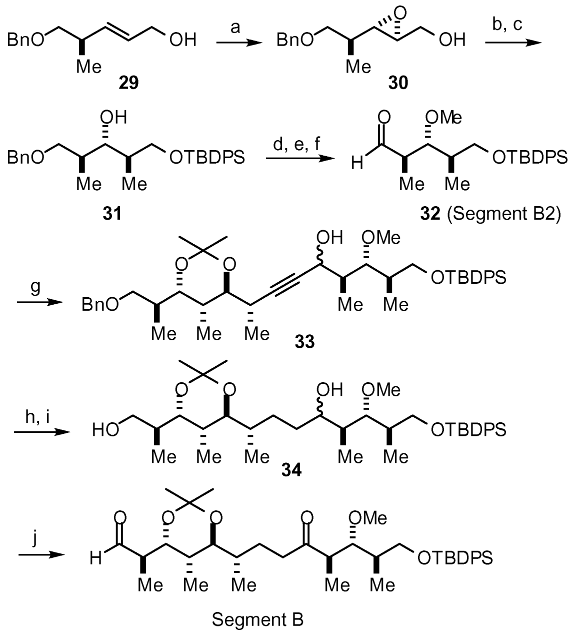
Scheme 4. Stereoselective Synthesis of Segment B[a]



[a] Reagents and conditions: (a) $Ti(O^iPr)_4$, L-(+)-DET, TBHP, 4 Å MS, CH_2Cl_2, −25 °C, 78%; (b) Me_2CuLi, ether, −45 °C, 85%; (c) TBDPSCl, imidazole, DMAP, CH_2Cl_2, rt; (d) NaH, MeI, TBAI, THF, 60 °C; (e) $AlCl_3$, *m*-xylene, CH_2Cl_2, −40 to −20 °C, 88% yield for three steps; (f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N, 85%; (g) **28**, *n*BuLi, THF, −10 to 0 °C, 87%; (h) Pt/Al_2O_3, H_2, 5 atm, AcOEt, 76%; (i) LDBB, THF, −45 °C, 90%; (j) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N, 97%.

such a 5-silyloxyallyl alcohol system with *m*CPBA exclusively occurs from the opposite side of the bulky TES group, regardless of the stereochemistry of an adjacent methyl group.[23] On treatment of the epoxy alcohol **24** with dimethylcupurate, the 1,3-diol **25** having five contiguous chiral centers was obtained quantitatively. Then, **25** was transformed into the acetonide **26** in two steps: (1) protection of the primary alcohol as a pivalate and (2) acetonide formation in 94% overall yield from **24**. After removal of the pivaloyl group in **26** with DIBAH, the resulting primary alcohol was transformed into dibromoolefin **28** through aldehyde **27** in 84% yield. Thus, the precursor of segment B1 containing five consecutive stereogenic centers was highly stereoselectively synthesized, actually without formation of any stereoisomers. The overall yield of segment B1 was 36% for the 18 steps.

Segment B2 having three contiguous chiral centers was also constructed by a similar reaction sequence involving an epoxide-opening reaction of **30** with dimethylcupurate[20] and subsequent manipulations (Scheme 4) in 32% overall yield for the 11 steps. The key coupling reaction of segment B1, which was generated quantatively from the dibromomethylene **28**, with segment B2 occurred cleanly and efficiently at −30 °C, giving rise to the desired adduct **33** in 87% isolated yield. The product was then converted to segment B by a three-step reaction sequence: (1) hydrogenation of the triple bond, (2) removal of the benzyl group with LDBB,[24] and (3) Swern oxidation. Thus, segment B having eight stereogenic centers was synthesized in a highly stereoselective manner. The overall yield of segment B was 21% for the 22 steps based on the longest linear sequence.

Thus, we have established the highly stereoselective synthesis of segments A and B required for the synthesis of scytophycin C (**1**). We will discuss the key coupling reaction of both segments, subsequent macrolactonization, and the crucial construction of the terminus *N*-methyl-*N*-vinylformamide moiety culminating in the total synthesis of scytophycin C (**1**), which will be described a following paper.

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Supporting Information Available: Experimental details and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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