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Total Synthesis of Scytophycin C. 2. Coupling Reaction of the C(1)–C(18) Segment and the C(19)–C(31) Segment, a Key Macrolactonization, and the Crucial Terminal Amidation Reaction

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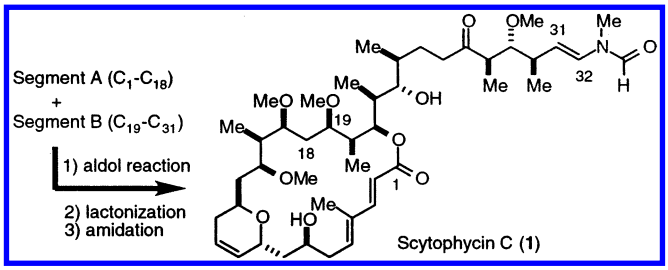
ABSTRACT



Stereoselective syntheses of the C(1)–C(18) segment (segment A) and the C(19)–C(31) segment (segment B) are described in the preceding paper. This paper reports the key coupling reaction of both segments, 22-membered lactonization, and the crucial terminal amidation reaction culminating in the total synthesis of scytophycin C.

Scytophycin C (**1**),[1a] isolated from the terrestrial blue-green alga *Scytonema pseudohofmanni*,[1] has been demonstrated to exhibit potent activity against a variety of human carcinoma cell lines including solid tumors.[1b,c,2,3]

From the significant antitumor activity of scytophycin C (**1**) and its scarce availability from natural sources, its supply by chemical synthesis has emerged as an urgent and important subject.[4−6] In the preceding paper,[15] we described the stereoselective syntheses of the C(1)−C(18) segment (segment A) including a dihydropyran ring and the C(19)−C(31) segment (segment B) having eight asymmetric centers by the use of new acyclic stereocontrol. We report in this paper the key coupling reaction of both segments, 22-

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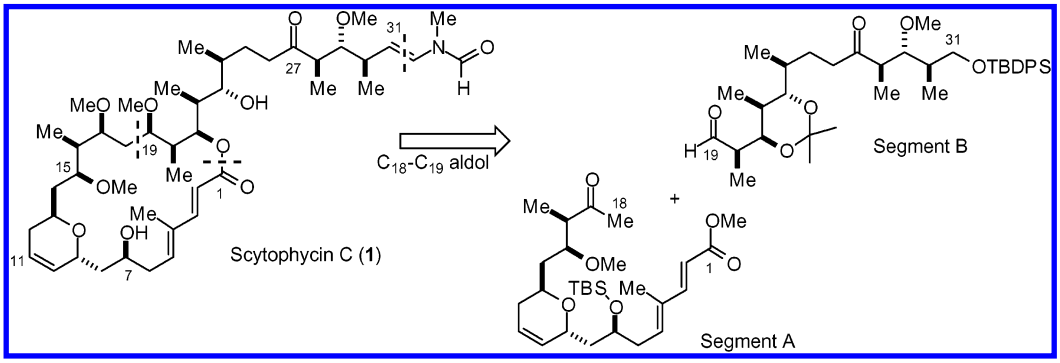
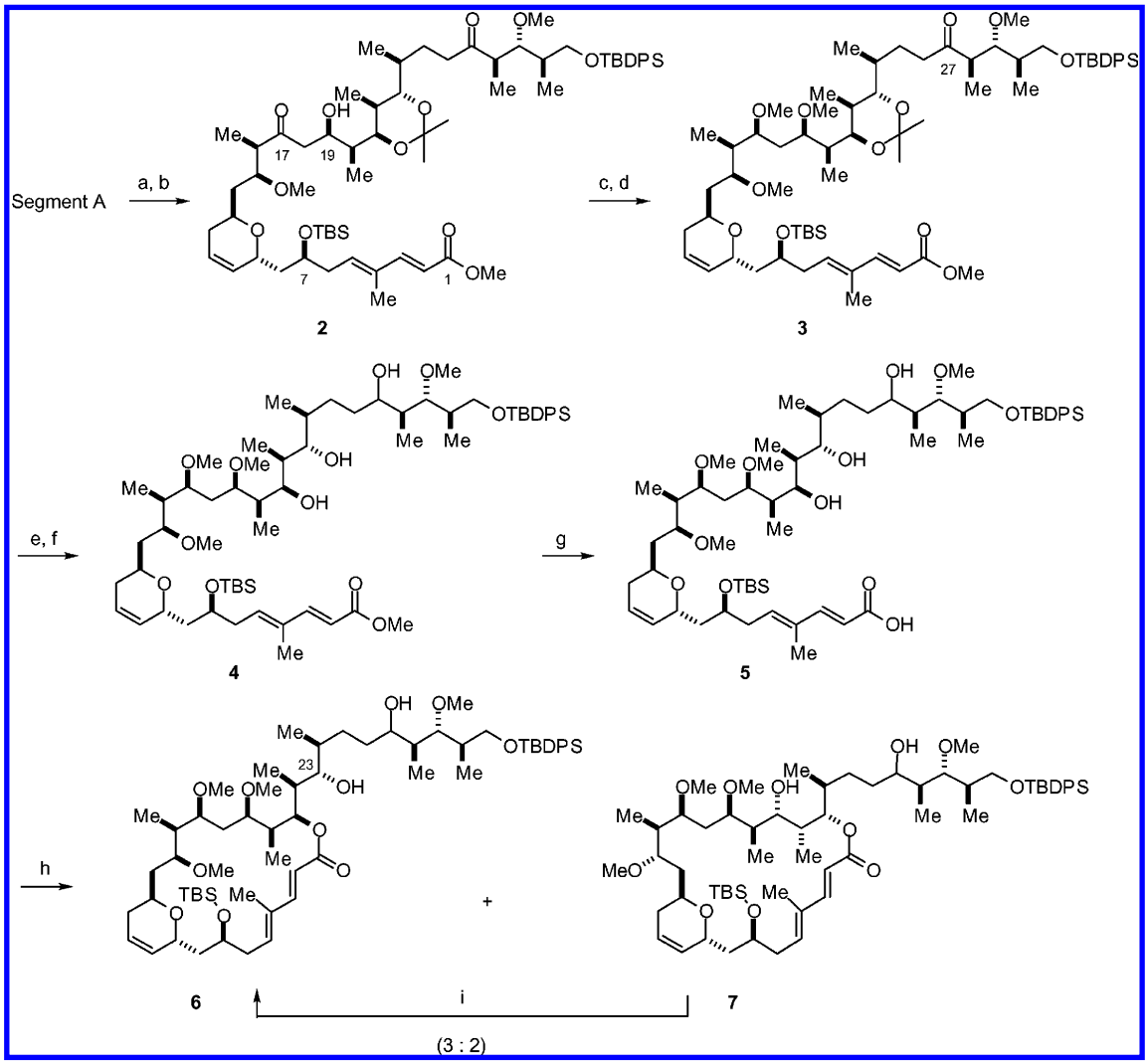
Scheme 1. Synthetic Strategy of Scytophycin C (1)



Scheme 2. Key Coupling Reaction of the Segments A and B and 22-Membered Lactonization[a]

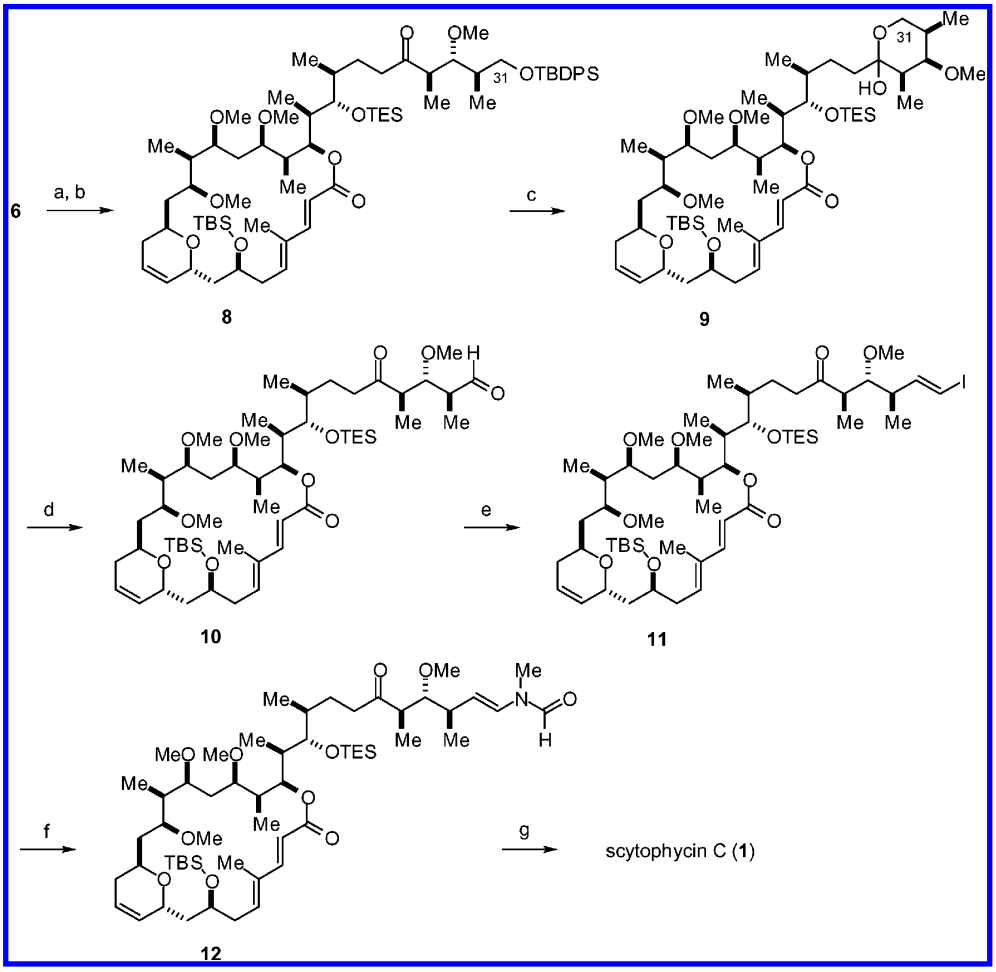


[a] Reagents and conditions: (a) LHMDS, TMSCl, Et_3N, THF, −78 °C; (b) segment B, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −78 °C, 82% in two steps; (c) catecholborane, THF, −78 to −20 °C, 77%; (d) MeOTf, 2,6-di-*tert*-butylpyridine, rt, 99%; (e) $NaBH_4$, MeOH, −20 to 0 °C; (f) $FeCl_3$−silica gel $CHCl_3$, rt, 77% in two steps; (g) $Ba(OH)_2$, MeOH, 40 °C, 93%; (h) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene, rt, 86%; (i) $Ti(O^iPr)_4$, CH_2Cl_2, rt, 96%.

membered macrolactonization, and the crucial construction of the terminal enamide moiety culminating in the total synthesis of scytophycin C (**1**) (Scheme 1).

The key coupling reaction of the segments A and B was performed by the aldol reaction of the silyl enol ether derived from segment A and the aldehyde segment B by using

Scheme 3. Crucial Terminal Amidation Reaction and Completion of Total Synthesis of Scytophycin C[a]



[a] Reagents and conditions: (a) TPAP, NMO, MS4A, CH_2Cl_2, rt; (b) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 58% in two steps; (c) TBAF, AcOH, DMF, rt, 80%; (d) Dess−Martin periodinane, CH_2Cl_2, rt, 82%; (e) $CrCl_2$, CHI_3, THF, 0 °C, 69%; (f) *trans*-1,2-cyclohexanediamine, CuI, K_3PO_4, *N*-methylformamide, 1,4-dioxane, 60 °C, 85%; (g) HF−pyridine, pyridine, THF, rt, 66%.

conditions similar to those of Paterson[5] resulting in the formation of an almost single aldol **2** in 82% yield (Scheme 2). Then, the aldol **2** was treated with catecholborane to give the *syn*-diol exclusively,[5] which was treated with methyl trifluoromethanesulfonate to furnish the dimethyl ether **3** quantitatively. Subsequent reduction of the ketone moiety at the C27 position with $NaBH_4$ followed by removal of the acetonide with $FeCl_3$−silica gel produced the triol **4** in 77% yield. The reduction of the C27 ketone was critical to obtain the key *seco*-acid **5**, since the following hydrolysis of the ester with $Ba(OH)_2$ without reducing the C27 ketone moiety caused elimination of methanol to afford the C28−C29 unsaturated ketone. The stereochemistry of the newly introduced hydroxyl group at the C27 position was not determined at this stage.

Upon treatment of **4** with $Ba(OH)_2$ in MeOH, the key *seco*-acid **5** was obtained in 93% yield. The crucial macrolactonization of the *seco*-acid **5** was carried out by using the Yamaguchi conditions[7] resulting in the formation of a mixture of the 22- and 24-membered macrolides, **6** and **7**, in 34% and 52% yields, respectively. As was reported by Paterson,[5] on treatment of the 24-congener **7** with titanium tetraisopropoxide in CH_2Cl_2, a 3:2 equilibrium mixture of **6** and **7** was formed in 96% yield. By repeating this process twice, the desired 22-membered macrolide **6** was obtained in 75% combined yield.

Regioselective oxidation of the hydroxyl group at the C27 position with tetrapropylammonium perruthenate (TPAP) and subsequent protection of the remaining C23 hydroxyl group with TESOTf afforded the ketone **8** (Scheme 3). Upon treatment of **8** with TBAF in AcOH and DMF,[8] the terminal *tert*-butyldiphenylsilyl protective group was selectively removed giving rise to the lactol **9**, which was subjected to Dess−Martin oxidation[9] to provide the crucial keto aldehyde **10** in 82% yield.

The remaining task for the synthesis of scytophycin C (**1**) was the introduction of the terminal *N*-methyl-*N*-vinyl-

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formamide moiety. However, its assemblage was found to be extremely difficult since application of various Wittig- or Horner−Emmons-type reagents to **10** merely resulted in elimination of methanol and none of the desired product was obtained.[10] After many attempts, eventually we were able to overcome these difficulties by a two-step reaction process involving the Takai reaction leading to vinyl iodide[11] followed by Buchwald amidation reaction.[12] Namely, treatment of **10** with chromium(II) chloride and iodoform in THF afforded the desired (*E*)-vinyl iodide **11** in 69% yield without elimination of methanol which was then subjected to Buchwald amidation conditions recently reported[12] to give rise to the long-awaited enamide compound **12** in 85% yield. Finally, removal of the two silyl protective groups of **12** with HF−pyridine yielded scytophycin C (**1**) in 66% isolated yield. ^{1}H and ^{13}C spectral data of the synthetic compound were identical with those of the synthetic compound elaborated by Paterson.[5]

Thus, we have achieved the stereoselective total synthesis of scytophycin C (**1**) by the use of new types of acyclic stereocontrol.[13,14] The overall yield of **1** was 1.1% for the 36 steps based on the longest segment B sequence. The newly developed assemblage of the *N*-methylenamide moiety by the combination of a vinyliodide and the Buchwald amidation reaction should provide a powerful means for the synthesis of a variety of natural products having such functional group(s). Application of these methodologies to natural product synthesis is underway in our laboratory.

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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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