Total Synthesis of Scytophycin C

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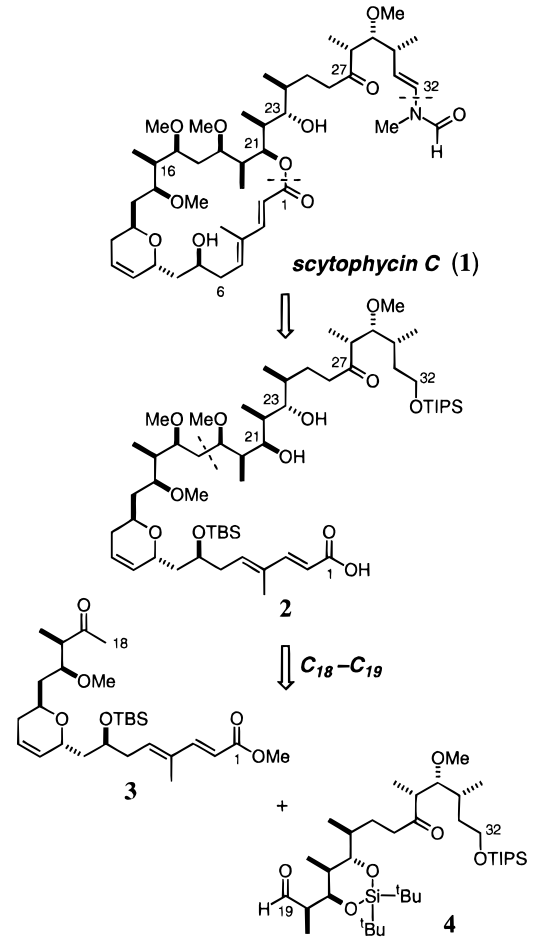
The scytophycins, isolated from the cultured terrestrial blue-green alga *Scytonema pseudohofmanni*, were first reported by Moore *et al.* in 1986.[1] Apart from scytophycin C (**1**), four related polyketide-derived[2] macrolides, scytophycins A, B, D, and E were also isolated.[3] Spectroscopic and X-ray crystallographic analysis (performed on an acid degradation product of scytophycin C[1]) indicated that the scytophycins are a novel series of polyoxygenated 22-membered macrolides, differing in substitution at C_6, C_{16}, and C_{27}, with a C_{21} side chain terminating in an *N*-methylvinylformamide group. They exhibit potent cytotoxicity against a variety of human carcinoma cell lines, as well as broad-spectrum antifungal activity. The scytophycins act as cytotoxic agents by microfilament depolymerization[4] and have been shown to circumvent P-glycoprotein-mediated multidrug resistance in tumor cells,[5] which gives them therapeutic potential for patients undergoing cancer chemotherapy. As part of our synthetic studies[6,7] toward these complex bioactive macrolides, we now report the first total synthesis of scytophycin C.

As outlined in Scheme 1, the complete carbon skeleton of scytophycin C (**1**) in the protected seco acid derivative **2** was anticipated to arise from an aldol-coupling process between the previously prepared C_1-C_{18} ketone **3**[6a,b] and the $C_{19}-C_{32}$ aldehyde **4**[6c] under Felkin−Anh control. As with our earlier synthesis of swinholide A,[8,9] we chose to forego differential hydroxyl protection at C_{21} and C_{23}. The known acid instability of scytophycin C[1] dictated that the final stages of the synthesis should be performed with caution. The introduction of the *N*-methyl vinylformamide group, which leads to slowly interconverting conformational isomers,[1] would necessarily be delayed until the end.

By using $BF_3{\cdot}OEt_2$ as the Lewis acid in CH_2Cl_2, the Mukaiyama aldol coupling[10] of the kinetic silyl enol ether derived from ketone **3** with aldehyde **4** gave a single adduct **5** in 84% yield (Scheme 2), where all but one of the 15 stereocenters of scytophycin C have been installed. Introduction of the remaining C_{17} stereocenter required chemo- and stereoselective reduction of the β-hydroxy ketone in **5** in the presence of the other ketone group at C_{27}. This was best achieved by using catecholborane,[11] where the C_{17} carbonyl group was activated by formation of a boron chelate followed by *in situ* reduction at −20 °C, giving the *syn* 1,3-diol **6** (85%) with 92% diastereoselectivity, without any competing attack at the C_{27} ketone. Methylation of diol **6** with MeOTf in the presence of 2,6-di-*tert*-butylpyridine[12] then led to **7** (82%), which represented a fully protected seco acid for scytophycin C.

Due to the competing elimination of MeOH at C_{28}/C_{29} encountered in the hydrolysis of the methyl ester in **7**, it proved necessary to temporarily reduce the C_{27} ketone with $NaBH_4$.[13] Selective deprotection of the silylene group by brief treatment with HF·py was then followed by clean ester hydrolysis with $Ba(OH)_2$ in MeOH to afford acid **8** (70%). This seco acid has three possible modes of cyclization to generate 22-, 24-, or 28-membered macrolides. In practice, a modified[14] Yamaguchi macrolactonization[15] of **8** in PhMe (without recourse to high-

Scheme 1



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(13) The configuration shown at the temporary hydroxyl-bearing center at C_{27} in **9** assumes that Felkin−Anh selectivity is operating in the reduction.

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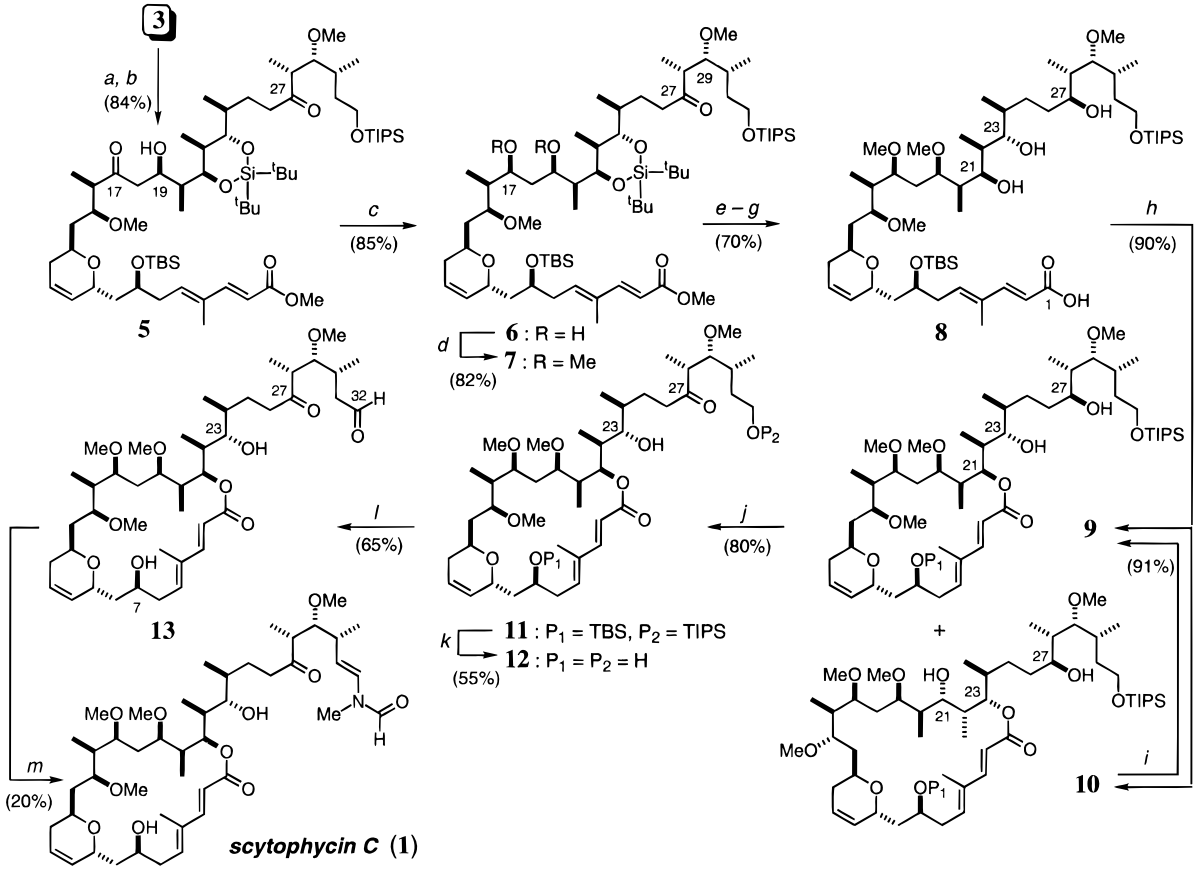
Scheme 2[a]



[a] Key: (a) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, −78 °C, 30 min; (b) **4**, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 0.5 h; (c) catecholborane, THF, −20 → 20 °C, 24 h; (d) MeOTf, 2,6-di-*tert*-butylpyridine, 20 °C, 18 h; (e) $NaBH_4$, MeOH, −20 → 0 °C, 4 h; (f) HF·py, py, THF, 0 → 20 °C, 1 h; (g) $Ba(OH)_2$, MeOH, 20 °C, 18 h. (h) Et_3N, 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, 20 °C, 18 h; (i) $Ti(O^iPr)_4$, CH_2Cl_2, 20 °C, 3 days; (j) TPAP, NMO, 4 Å molecular sieve powder, CH_2Cl_2, 20 °C, 2 h; (k) HF·py, py, THF, 0 → 20 °C, 48 h; (l) TPAP, NMO, 4 Å molecular sieve powder, CH_2Cl_2, 0 °C, 30 min; (m) P_2O_5, HNMeCHO, 20 °C, 0.5 h.

dilution techniques) proceeded in 90% yield to generate a 42:58 mixture of the 22-membered macrolide **9** and the isomeric 24-membered macrolide **10**. No 28-membered macrolide was detected. We attribute this to the conformational preferences of the molecular backbone, which makes the participation of the hydroxyl at C_{27} in the cyclization less favored than those at C_{21} and C_{23}. While other macrolactonization methods, as well as variation of the solvent polarity, were explored,[9] this modified Yamaguchi procedure was found to be optimum as it gave the highest yield of macrolides.[16] The 24-membered macrolide **10** could be easily equilibrated in favor of the required 22-membered macrolide **9** by transesterification with $Ti(O^iPr)_4$ in CH_2Cl_2.[17,18] This gave a separable 70:30 mixture of **9** and **10** in 91% yield.

It was now necessary to selectively manipulate the side-chain functionality at C_{27} and C_{32} in **9** to reach scytophycin C. First, selective oxidation of the more accessible hydroxyl at C_{27} over that at C_{23} was achieved by TPAP oxidation.[19] This gave ketone **11** (80%), which was then deprotected by extended treatment with HF·py to provide the triol **12**, along with a mixture of the monodeprotected intermediates (30%) that could be readily recycled. A second selective oxidation using TPAP was then achieved to give the aldehyde **13** with the hydroxyls at C_7 and C_{23} surviving unscathed. The final step, condensation of *N*-methylformamide with the C_{32} aldehyde carbonyl group in the presence of the C_{27} ketone in **13**, proved to be highly challenging due to the acid sensitivity of this system. After considerable effort, we employed P_2O_5 in HNMeCHO[20] followed after workup by reversed-phase HPLC purification. This gave (−)-scytophycin C (**1**) (20%), which exhibited ^1H and ^{13}C NMR, IR, and MS data in accordance with the published values.[21] This synthetic route should be amenable to the generation of novel scytophycin analogues.

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Supporting Information Available: Experimental procedures and complete spectroscopic data for all compounds (14 pages).

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(16) In contrast, the corresponding secoacid **2** (*cf.* Scheme 1), where the ketone was reintroduced at C_{27}, completely failed to give any macrolides under the normal Yamaguchi conditions. This is due to hemiacetal formation with the 23-OH, which presumably sterically blocks the 21-OH from acylation.

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(21) Unfortunately, an authentic sample of scytophycin C was not available from the Hawaii group (Dr. G. M. L. Patterson) for direct comparison.