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STUDIES DIRECTED TOWARD THE TOTAL SYNTHESIS OF SCYTOPHYCIN C: SYNTHESIS OF THE C(1) - C(18) FRAGMENT OF SCYTOPHYCIN C

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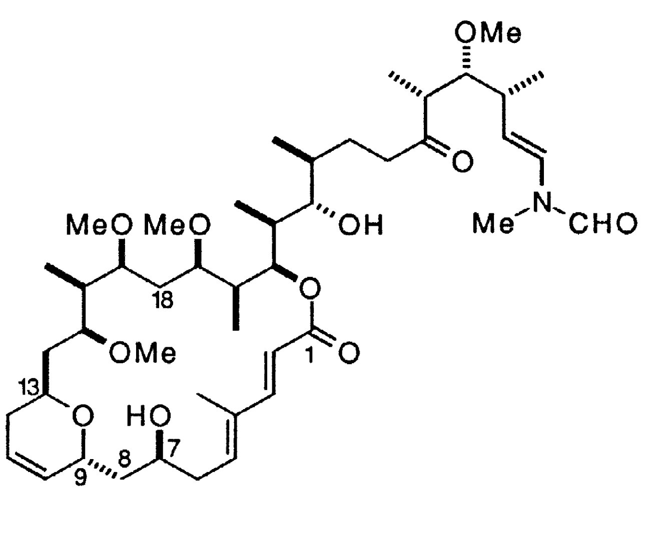
Abstract: The synthesis of the C(1) to C(18) fragment of Scytophycin C is described which features a highly stereoselective carbon Ferrier-type reaction in 3.0 M lithium perchlorate/ethyl acetate.

Scytophycin C(**1**), isolated from the terrestrial blue-green alga *Scytonema pseudohofmanni*, is a polyoxygenated twenty-two membered macrolide reported by Moore et. al. in 1986.[1] The potent cytotoxicity[2] associated with Scytophycin C[3] and the closely related complex polyketide macrodiolide Swinholide A,[4] has been responsible for the intense synthetic acitivity in this area. We detail below a synthesis of the C(1)-C(18) fragment **2** of Scytophycin C which features a highly stereoselective carbon Ferrier-type reaction in polar media between di-O-acetyl-4-deoxyglucal **3** and the *t*-butyldimethylsilyl enol ether of acetaldehyde (cf. Equation 1).



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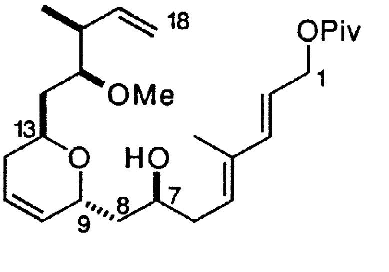

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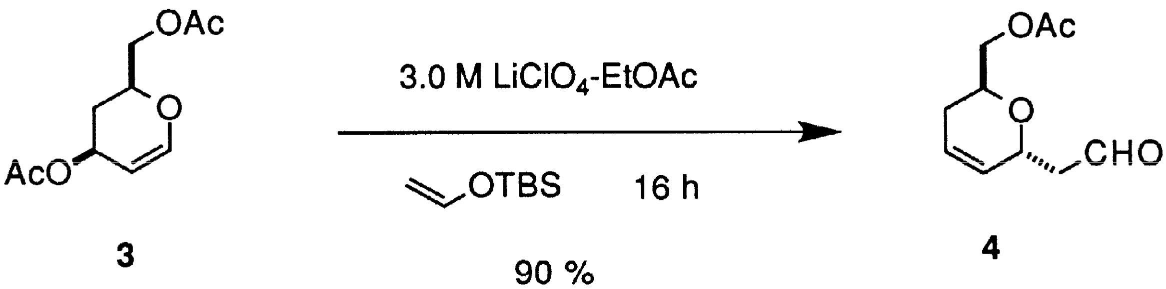

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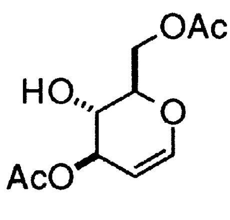
The diacetoxy-4-deoxyglucal **3** required for the Ferrier reaction was obtained from tri-O-acetyl-D-glucal. Cleavage (NaOMe, MeOH) of the acetates followed by selective acetylation (acetyl chloride, pyridine, methylene chloride) afforded (83% yield) the 4-hydroxydiacetylglucal **5**, mp 65 - 67 °C, which was deoxygenated[5] via the following two-step procedure. Treatment with phenylchlorothionoformate and 4-dimethylaminopyridine in acetonitrile gave the corresponding thionocarbonate which upon exposure to tributyltin hydride and AIBN in toluene at reflux provided (72 %) the desired deoxyglucal **3**, $[\alpha]_D^{25}$ -23.4 (c 1.59, $CHCl_3$)[lit.[6] $[\alpha]_D^{25}$ -25.0(c 1, $CHCl_3$)].



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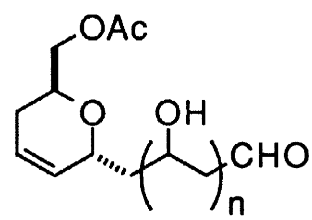

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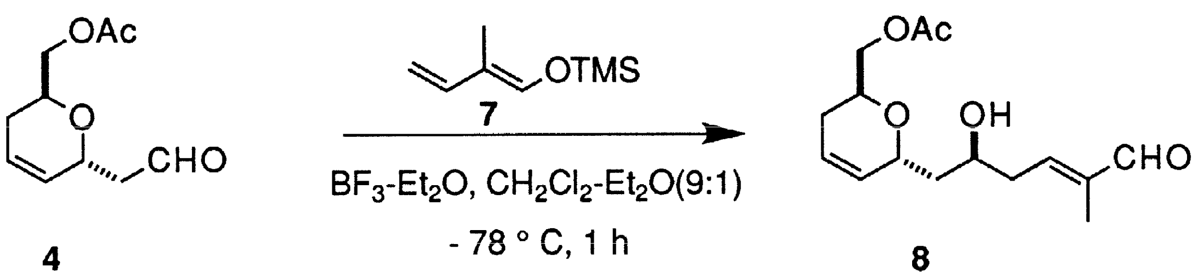
Generation of the C(8), C(9) carbon-carbon bond via a Ferrier-type reaction proved problematic, at first. For example, exposure of **3** to the *t*-butyldimethylsilyl enol ether of acetaldehyde in the presence of conventional Lewis acids (e.g. $MgBr_2$, $ZnCl_2$, $(i\text{-PrO})_2TiCl_2$) gave rise to substantial amounts of the oligomeric structure **6**. Equally disappointing was the use of 5.0 M lithium perchlorate in diethyl ether. In an effort to attenuate the polar nature of the reaction medium, 3.0 M lithium perchlorate in ethyl acetate[7] was employed which gave rise (after 16 h) to **4**, $[\alpha]_D^{25}$ -97.6 (c 0.87, $CHCl_3$), in 90 % yield as a single stereoisomer about C(9). Subjection of aldehyde **4** to a vinylogous Mukaiyama aldol reaction (-78 °C, BF_3•Et_2O, 1h) employing silyl dienol ether **7** afforded **8** as the major product in 64 % yield, along with 14 % of a diastereomer. Subsequent Horner-Emmons reaction (THF, -78 °C, 30 min; 0 °C, 2 h) generated the corresponding α,β-unsaturated ester in 90% yield. Protection (TIPSOTf, 2,6-lutidine, methylene chloride, 2 h) of the C(7) hydroxyl as a triisopropylsilyl ether and hydrolysis of the acetate group provided **9** (R = TIPS), $[\alpha]_D^{25}$ -70.5 (c 8.4, $CHCl_3$), in 77 % overall yield. The structure of **9** was confirmed by subjecting the highly crystalline diol **9** (R = H), mp 79 - 80 °C, to single-crystal x-ray analysis.



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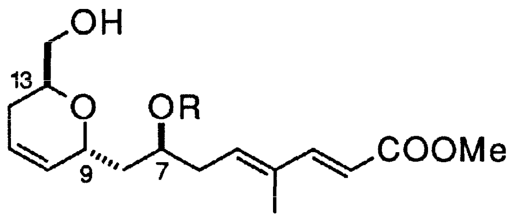

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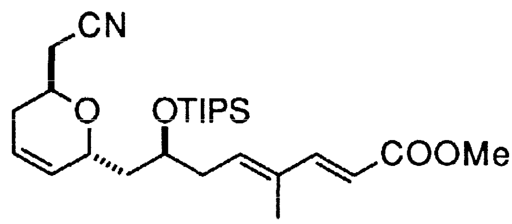

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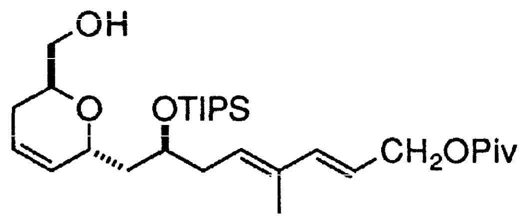
With the stereochemistry at C(7), C(9), and C(13) unambiguously established, attention was directed at appending carbon atoms C(15) - C(18) onto the C(1) - C(14) fragment **9** (R = TIPS). Toward this end, **9** (R = TIPS) was transformed in high yield into nitrile **10** by reaction of the triflate derived from **9** (R = TIPS) with potassium cyanide. Unfortunately, all attempts to selectively manipulate the cyano group in the presence of the C(1) carbomethoxy group met with failure. In order to circumvent these difficulties, **9** (R = TIPS) was transformed via a four-step sequence [1. TBSCl, imidazole, DMF, 1.5 h; 2. *i*-Bu_2AlH, THF, 0 °C, 30 min; 3. PivCl, pyr, CH_2Cl_2, 10 h; 4. 1 N HCl:THF(1:10), 20 h] into **11**, $[\alpha]_D^{25}$ -45.9 (c 0.96, $CHCl_3$), in 80 % overall yield. Once again, one carbon homologation via the derived nitrile was unsuccessful due to problems in the conversion of the nitrile into aldehyde **12**. However, alkylation[8] of the anion derived from deprotonation of N,N-diethylamino acetonitrile with lithium diisopropylamide in THF-HMPA at - 78 °C with the triflate prepared (Tf_2O, pyr, THF, 0 °C, 10 min) from **9** (R = TIPS) provided the sensitive aldehyde **12** in 65 % yield.



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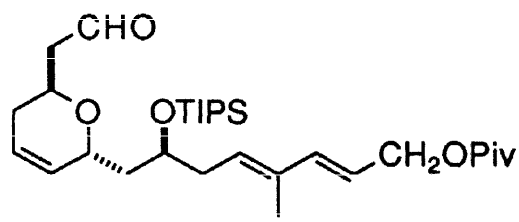

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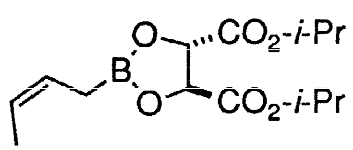
Treatment (4 Å mol sieves, toluene, - 78 °C, 3 h) of aldehyde **12** with Roush's (*S*,*S*)-diisopropyltartrate-Z-crotylboronate **13**[9] gave rise (55 %) to a 2:1 mixture of alcohol **14**, $[\alpha]_D^{25}$ -55.2 (c 1.8, $CHCl_3$), and the corresponding diastereomer. Methylation[MeOTf, 2,6-di-*t*-butylpyridine, rt(2h) to 70 °C(6 h)][10] of **14** afforded the C(1) - C(18) fragment **2**, $[\alpha]_D^{25}$ -45.9 (c 1.47, $CHCl_3$), of Scytophycin C.



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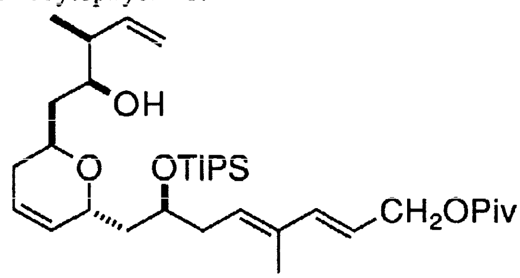

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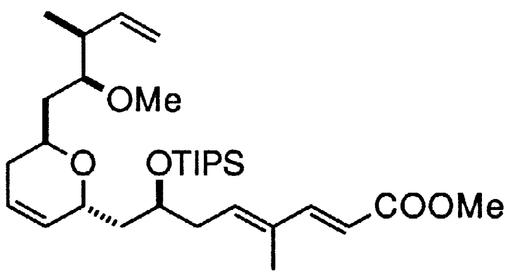
The structure of **2** was confirmed by conversion into **16,** which was prepared previously by Paterson in conjunction with a synthesis of Scytophycin C. Toward this end, the pivaloate group in **14** was cleaved by treatment with diisobutylaluminum hydride in THF giving rise (93 %) to the corresponding allylic alcohol which upon oxidation (MnO_2, MeOH, 20 h; KCN, 16 h) provided methyl ester **15** in 86 % yield. Exposure of **15** to tetra-*n*-butylammonium flouride in THF followed by treatment with *t*-butyldimethylsilyl triflate in methylene chloride containing 2,6-lutidine afforded **16**, $[\alpha]^{25}_{D}$ - 89.9 (c 0.3, $CHCl_3$)[lit.[11] $[\alpha]^{25}_{D}$ - 91.2 (c 1.7, $CHCl_3$)], which was identical in all respects with the spectral data reported in the literature by Paterson.[11]



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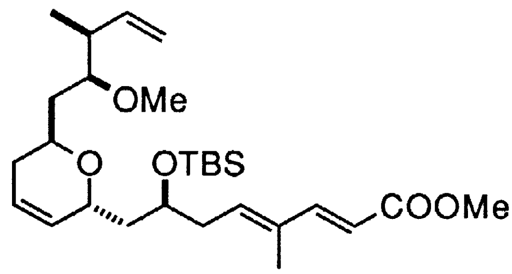

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