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Towards the Synthesis of Swinholide A and Scytophycin C. A Highly Stereocontrolled Synthesis of (–)-Pre-Swinholide A.

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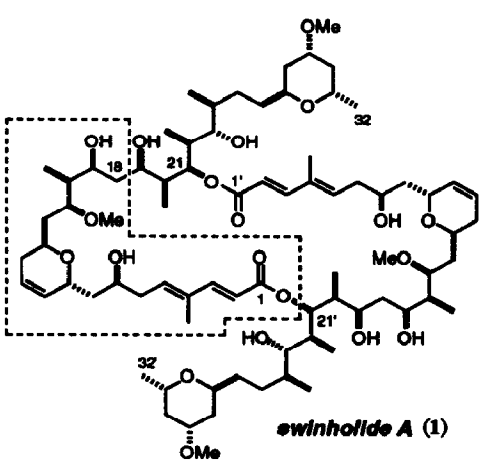
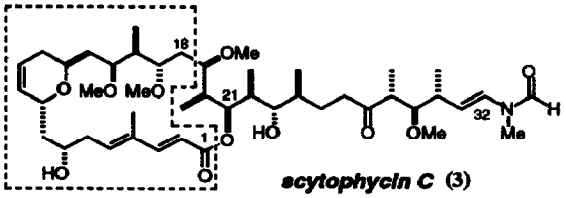
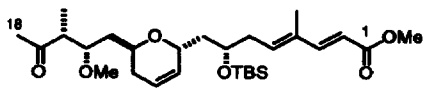
Abstract: The fully protected monomeric unit **19** of the marine macrodiolide, swinholide A (**1**), was obtained with >97% ds by a Mukaiyama aldol reaction between **16** and **5**, followed by a boron-mediated reduction to give the syn 1,3-diol **18**. Deprotection gave (–)-pre-swinholide A (**2**), the putative biosynthetic precursor of **1**.

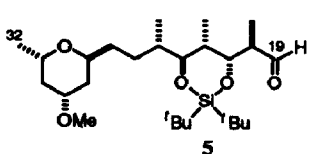
Swinholide A (**1**), first isolated[1a] in 1985 from the marine sponge *Theonella swinhoei*, is a 44-membered dimeric macrodiolide[1b-d] which displays potent cytotoxic activity against various human carcinoma cell lines. Swinholides B-G[1e,f] and a biosynthetic precursor, the monomeric acid pre-swinholide A (**2**),[1f,g] have also been isolated from *Theonella*. The related 22-membered macrolide scytophycin C (**3**),[2] produced by the terrestrial blue green alga *Scytonema pseudohofmanni*, has a close structural homology with the swinholides and also exhibits potent cytotoxic activity. The significant biological activity of these macrolides, combined with the scarcity of the natural supply, make swinholide A and scytophycin C important targets for total synthesis.[3,4]

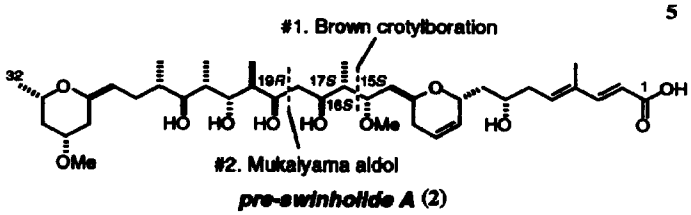
We now report (*i*) the synthesis of a common C_1–C_{18} methyl ketone **4** for swinholide A and scytophycin C using a Brown asymmetric crotylboration reaction, (*ii*) its stereocontrolled Mukaiyama aldol coupling with the C_{19}–C_{32} aldehyde **5**, and (*iii*) an efficient synthesis[4] of (–)-pre-swinholide A.



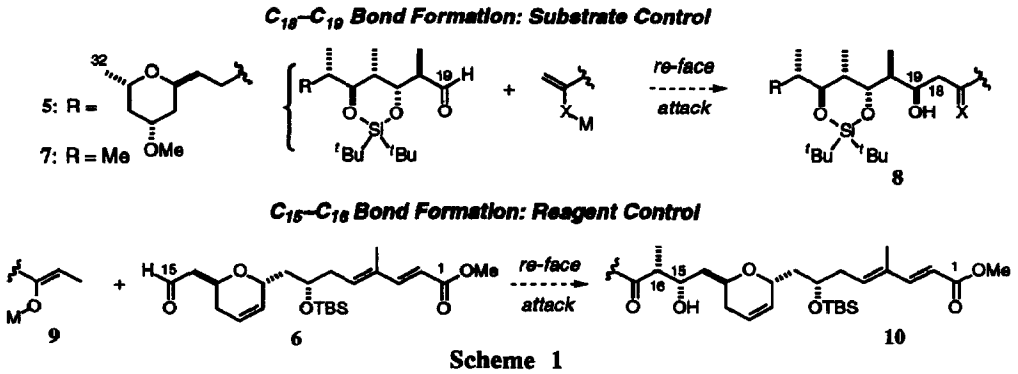








We have already reported the asymmetric synthesis of **5**[3b] and **6**[3c] as C_{19}–C_{32} and C_1–C_{15} subunits for swinholide A (**Scheme 1**). The sequential aldol coupling of these chiral aldehydes with a suitable butanone synthon, followed by C_{17} ketone reduction, was now required. This should give a protected version of **2**, correctly incorporating the (15*S*,16*S*,17*S*,19*R*)-stereocentres. For this purpose, the intrinsic diastereofacial preferences of aldehydes **6**[3c] and **7** with various enolate and allyl metal reagents were first determined.[3e] For C_{18}–C_{19} bond formation, Lewis acid-promoted additions of allylsilane or silyl enol ether nucleophiles to **7** predominantly occurred by desired *re*-face attack under substrate control to give **8** (>95% ds, X = CH_2 or O). For syn aldol coupling at C_{15}–C_{16}, however, the β-chiral aldehyde **6** showed an unexpectedly high preference for undesired *si*-face attack with simple boron enolates **9**. Hence, reagent control was necessary[3e] to enforce *re*-face attack on **6** to give **10**.



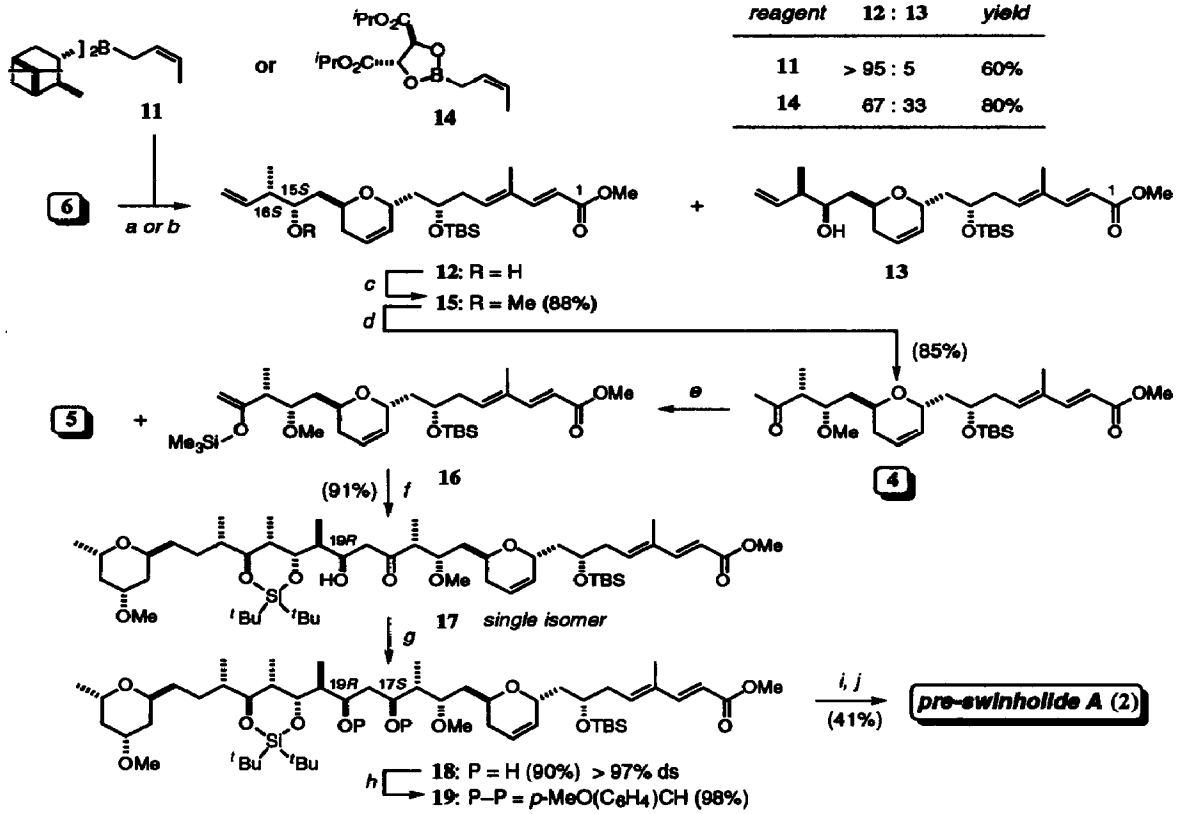
Scheme 1

These model coupling studies indicated the best way forward for the stereocontrolled synthesis of both swinholide A and scytophycin C. *Reagent*-controlled C_{15}–C_{16} bond formation with aldehyde **6**, using a masked "butanone thermodynamic enolate" equivalent, should be followed by *substrate*-controlled fragment coupling at C_{18}–C_{19} using a Mukaiyama aldol reaction.

As shown in **Scheme 2**, use of a chiral crotyl boron reagent allowed control in the formation of the C_{15}–C_{16} bond with aldehyde **6**, where subsequent Wacker oxidation of the terminal alkene gave the corresponding methyl ketone **4**.[5] The syn crotylboration of **6** was best performed using the Brown Ipc reagent **11**,[6] which gave alcohol **12** with >95% ds in 60% yield. The corresponding Roush tartrate reagent **14**,[7] when used in toluene (–90 → –25 °C), proved less selective in this mismatched situation, generating a 2 : 1 ratio of **12** and **13** in 80% yield. The (15*S*)-configuration assigned to the major alcohol **12** was established by ^{1}H NMR analysis of the diastereomeric (*R*)- and (*S*)-MTPA esters.[8] Reaction of **12** with methyl triflate (30 equiv) in 2,6-di-*tert*-butylpyridine then gave the corresponding methyl ether **15** in 88% yield. Under optimum conditions, the Wacker oxidation[9] proved highly selective for the terminal double bond in **15**. Pre-treatment of a mixture of palladium dichloride (20 mol%) and freshly prepared copper (I) chloride (2 equiv) in aqueous DMF with oxygen for 2 h, was followed by addition of **15**. Stirring was then maintained under an oxygen atmosphere at room temperature for 2 days. This gave a 66% yield of **4**, $[\alpha]_D^{20}$ = –73.2° (*c* 2.5, $CHCl_3$), and 22% recovered **15** (85% yield based on recovered starting material). Thus, methyl ketone **4**,[5] a C_1–C_{18} subunit for both swinholide A and scytophycin C, was obtained in just three steps from **6** with excellent control over the two new stereocentres.

The Mukaiyama aldol coupling of the two fragments **4** and **5** was performed under the conditions established from the model studies,[3e] which led to high levels of Felkin-Anh control. The silyl enol ether **16** was first prepared from **4** by kinetic enolisation with lithium hexamethyldisilazide (THF, –78 °C) and *in situ* trapping with trimethylsilyl chloride. After isolation using a pH 7 buffer/pentane work-up, **16** was used immediately without purification. Addition of boron trifluoride etherate (2 equiv) to a mixture of **5** and **16**

(CH_2Cl_2, –78 °C, 30 min) led to a clean aldol addition, providing the (19*R*)-adduct **17**, $[\alpha]_D^{20} = -65.3°$ (*c* 3.8, $CHCl_3$), as the sole product[10] in 91% yield. The introduction of the final stereocentre at C_{17} was achieved by a modified Narasaka-Prasad syn reduction of β-hydroxy ketone **17** *via* the pre-formed boron chelate.[11-14] The best conditions used lithium borohydride in THF/MeOH as the reducing agent.[11b,13] Treatment of **17** with di-*n*-butylmethoxyborane in THF/MeOH (5:1) at –78 °C was followed after 15 min by the addition of lithium borohydride in THF. Slow warming to –40 °C gave complete conversion, leading to isolation of the desired syn 1,3-diol **18** with >97% ds in 90% yield. Diol **18**, $[\alpha]_D^{20} = -65°$ (*c* 0.4, $CHCl_3$), was then protected as its *para*-methoxybenzylidene acetal **19**, $[\alpha]_D^{20} = -75.6°$ (*c* 3.4, $CHCl_3$), in 98% yield using *p*-$MeO(C_6H_4)CH(OMe)_2$ with catalytic CSA in CH_2Cl_2.



Scheme 2 (*a*) **11** (4 equiv), THF, –78 °C, 2 h; H_2O_2, pH7 buffer/MeOH; (*b*) **14** (4 equiv), PhMe, 4Å mol. sieves, –90 → –25 °C, 18 h; (*c*) MeOTf (30 equiv), 2,6-di-*tert*-butylpyridine, 65 °C, 2.5 h; (*d*) $PdCl_2$ (20 mol%), CuCl, O_2 (1 atm), 10:1 DMF/H_2O, 20 °C, 48 h; (*e*) $LiN(SiMe_3)_2$, Me_3SiCl, Et_3N, THF, –78 °C, 30 min; (*f*) $BF_3{\cdot}OEt_2$ (2 equiv), CH_2Cl_2, –78 °C, 30 min; (*g*) $^nBu_2BOMe$, 5:1 THF/MeOH, –78 °C, 15 min; $LiBH_4$, –78 → –40 °C, 3 h; H_2O_2, pH7 buffer/MeOH; (*h*) *p*-$MeO(C_6H_4)CH(OMe)_2$, CSA (5 mol%), CH_2Cl_2, 20 °C, 2 h; (*i*) 40% aq. HF, MeCN, 0 → 20 °C, 2 h; (*j*) NaOH, MeOH, H_2O, 20 °C, 5 h.

Compound **19** represents a fully protected derivative of the monomeric seco-acid of swinholide A. It was identical[5] in all respects to material previously prepared by a more elaborate and less selective coupling strategy, where the C_{15}–C_{16} and C_{18}–C_{19} bonds were formed in the reverse order.[4] Full deprotection can be achieved under the previously described conditions[4] to give (–)-pre-swinholide A, which has been successfully correlated with authentic material derived from swinholide A. Thus, **18** and **19** have the correct stereochemistry for the synthesis of swinholide A.

In summary, a highly efficient coupling strategy has been developed to provide useful quantities of an advanced intermediate **19** for swinholide A. The high level of stereocontrol (>92% ds from **6**) and convergency associated with the present synthesis are notable. Further studies towards completing the total synthesis of swinholide A and scytophycin C are now underway.

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5. All new compounds gave spectroscopic data in agreement with the assigned structures. **4** had ^{1}H NMR (assigned using COSY) δ (400 MHz, $CDCl_3$) 7.29 (1H, d, J = 15.7 Hz, H_3), 5.94 (1H, dd, J = 7.4, 7.4 Hz, H_5), 5.78 (1H, d, J = 15.7 Hz, H_2), 5.76 (1H, m, H_{11}), 5.62 (1H, m, H_{10}), 4.32 (1H, m, H_9), 4.05 (1H, m, H_7), 3.73 (3H, s, CO_2Me), 3.69 (1H, m, H_{15}), 3.56 (1H, m, H_{13}), 3.30 (3H, s, $C_{15}OMe$), 2.65 (1H, qd, J = 7.1, 4.4 Hz, H_{16}), 2.39 (2H, m, H_6), 2.18 (3H, s, Me_{18}), 1.95 (2H, m, H_{12}), 1.75 (3H, s, C_4Me), 1.73 (1H, m, H_{14A}), 1.64 (1H, ddd, J = 14.3, 10.6, 2.7 Hz, H_{8A}), 1.57 (1H, ddd, J = 14.5, 7.1, 4.9 Hz, H_{14B}), 1.38 (1H, ddd, J = 14.3, 9.9, 2.6 Hz, H_{8B}), 1.09 (3H, d, J = 7.1 Hz, $C_{16}Me$), 0.87 (9H, s, ^{t}Bu), 0.10 (3H, s, $SiMe_A$), 0.08 (3H, s, $SiMe_B$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 211.2, 167.9, 149.6, 137.8, 134.2, 130.2, 123.7, 115.4, 78.7, 69.3, 68.1, 63.9, 57.2, 51.4, 49.6, 40.6, 37.7, 36.8, 30.9, 29.5, 25.9, 18.1, 12.5, 11.0, –4.3, –4.7; HRMS (CI, NH_3) $(M+H)^+$ found 509.3299, $C_{28}H_{49}O_6Si$ requires 509.3298. Full spectroscopic data for **19** are reported in the supplementary material for ref 4.
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