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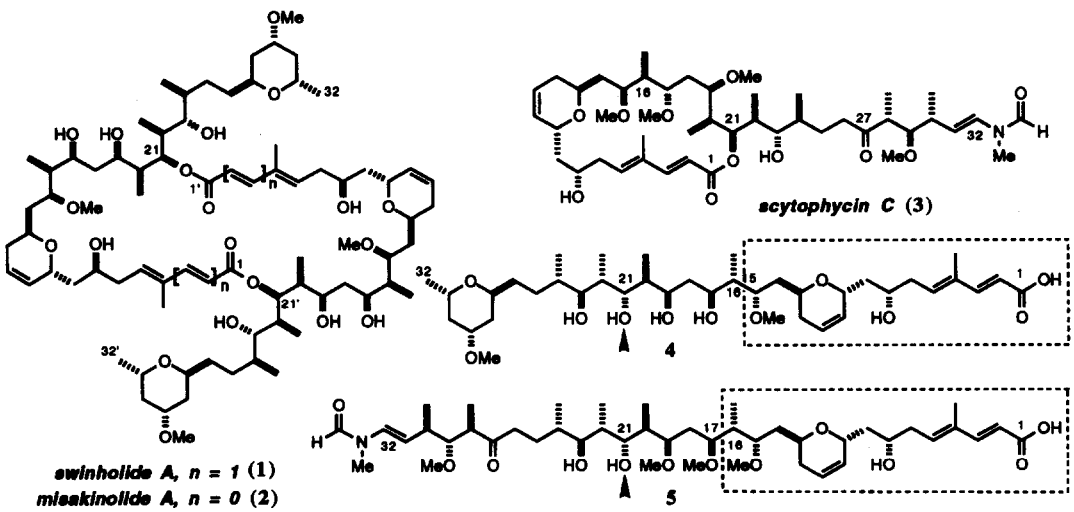
Studies in Marine Macrolide Synthesis: Asymmetric Synthesis of C_1–C_{15}/C_{16} Subunits of Swinholide A and Scytophycin C.

Ian Paterson* and Julian D. Smith

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK.

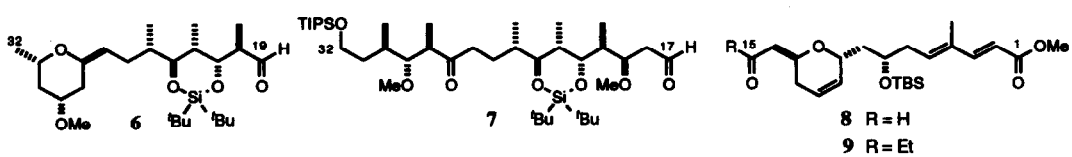
Abstract: The aldehyde **8**, a C_1–C_{15} subunit of swinholide A, was prepared in 10 steps (14.5% yield, 78% ds) by starting with the asymmetric aldol reaction, **15** + **17** → **18**. Conversion into the corresponding ethyl ketone **9** provides a C_1–C_{16} subunit of scytophycin C.

Swinholide A (**1**), isolated from the marine sponge *Theonella swinhoei*, is an unusual 44-membered dilactone having potent cytotoxic activity.[1] Other macrodiolides from *Theonella*[1,2] include misakinolide A[2a-c] (**2**) (≡ bistheonellide A[2b,d]), which lacks two of the swinholide double bonds and has a 40-membered macrocyclic ring. Scytophycin C (**3**) is a related 22-membered macrolide[3] obtained from the blue green alga *Scytonema pseudohofmanni*. As shown in **Scheme 1**, the swinholide A macrocycle is made up of two identical monomeric secoacid units **4** (≡ pre-swinholide A[4]), lactonised through the 21/21' hydroxyls as indicated, while that of scytophycin C corresponds to the secoacid **5**.

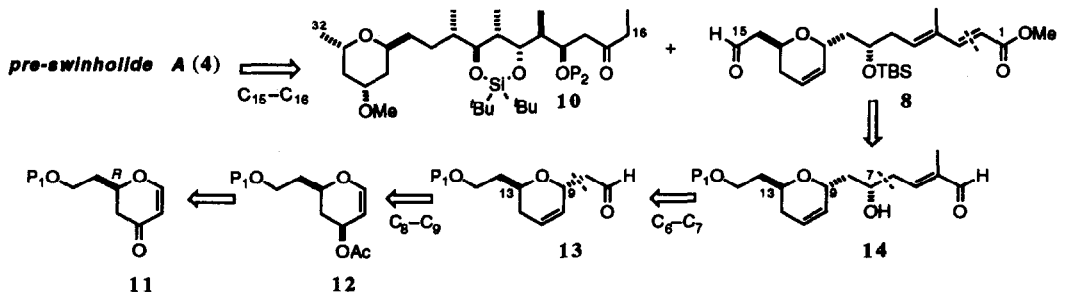


Scheme 1

As part of our efforts directed towards the total synthesis of these complex macrolides,[5] we have previously described the enantiocontrolled preparation of aldehydes **6**[5a] and **7**[5b], as C_{19}–C_{32} and C_{17}–C_{32} subunits of swinholide A (misakinolide A) and scytophycin C, respectively. We now report the asymmetric synthesis of the aldehyde **8** and the corresponding ethyl ketone **9**, as matching C_1–C_{15} and C_1–C_{16} subunits for swinholide A and scytophycin C.



Scheme 2 summarises our strategy for the synthesis of pre-swinholide A[4] (**4**), involving the stereocontrolled aldol coupling of the ethyl ketone **10** to the aldehyde **8** to form the C_{15}–C_{16} bond. We have already described[5a] an efficient asymmetric synthesis of **6**, which should serve as a precursor for **10**. Our approach[5b] to scytophycin C relies on a different aldol coupling at C_{16}–C_{17} between the ethyl ketone **9** and the aldehyde **7**. As outlined below, the aldehyde **8** should be available in enantiomerically correct form by starting with an asymmetric synthesis of the (*R*)-dihydropyrone **11**. A preliminary study,[5c] using racemic **11** with P_1 = Bn, demonstrated that the two-step sequence, **12** → **13** → **14**, worked well using silyl enol ether chemistry allowing efficient control of the relative stereochemistry at C_9 and C_7. However, in order to ensure efficient deprotection at C_{15} to give the alcohol precursor of **8**, it was subsequently found to be necessary to use P_1 = Bz (PhCO) rather than Bn.[6]



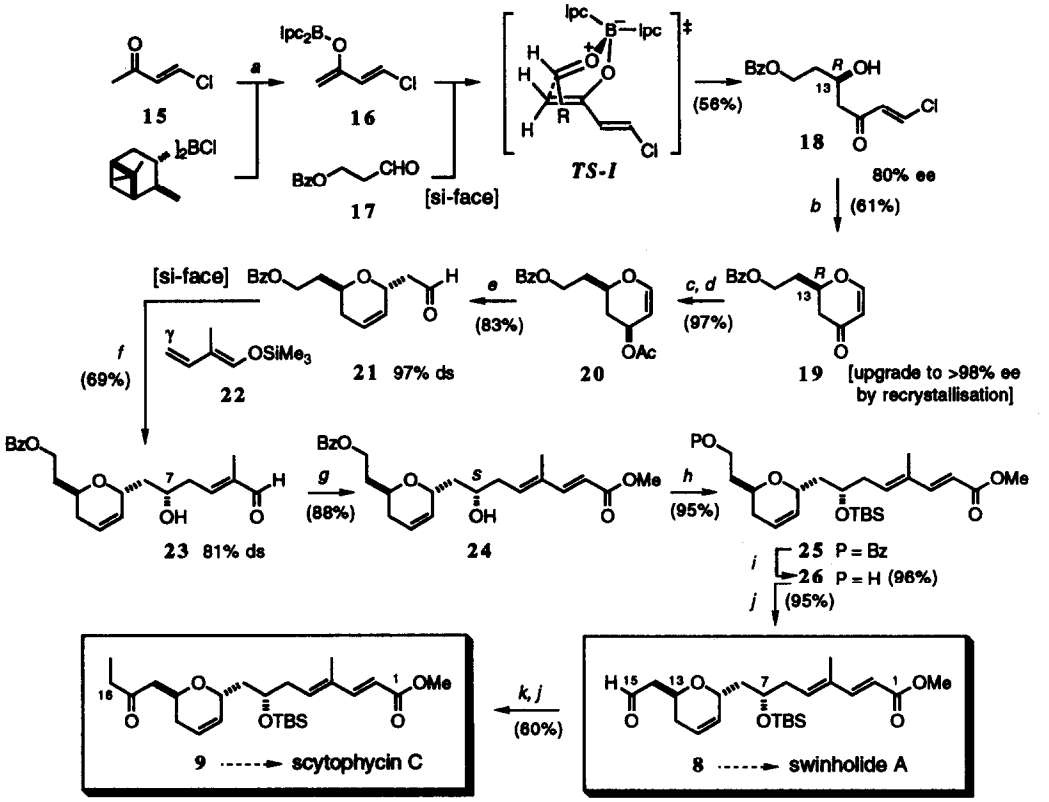
Scheme 2

The enantiocontrolled synthesis of the aldehyde **8** and its derived ethyl ketone **9**, starting from (*E*)-1-chloro-2-buten-3-one (**15**),[7] is shown in **Scheme 3** and outlined below. Enolisation[8] of **15** with (+)-Ipc_2BCl/$^iPr_2NEt$ (PhMe, 0 °C, 1 h) was followed by the addition of the aldehyde **17** to the derived enol borinate **16** (–78 °C, 3.5 h).[9] Subsequent warming of the reaction mixture (–20 °C, 18 h) gave, after mild oxidative workup, a 56% yield of the aldol product **18**[10] in 80% ee, $[\alpha]_D^{20}$ = –15.2° (*c* 2.6, $CHCl_3$). Higher yields of **18** (up to 77%) could be obtained by using shorter reaction times, or by carrying out the aldol reaction in Et_2O, but this led to a reduction in enantioselectivity (50–60% ee).[11] As with other asymmetric boron aldol reactions of methyl ketones,[12a] moderate levels of enantioselectivity are obtained, due to competition between twist-boat (cf. ***TS-I*** = preferred *si*-face attack) and chair transition structures.[12b] Under our standard conditions using Me_3SiOTf/$^iPr_2NEt$ in CH_2Cl_2,[8] cyclisation of **18** to the crystalline (*R*)-dihydropyrone **19** was then achieved in 61% yield. This key intermediate was readily obtained in *enantiomerically pure form*, $[\alpha]_D^{20}$ = +66.2° (*c* 2.9, $CHCl_3$), simply by recrystallisation from Et_2O/hexane (m.p. 62–63 °C).[13]

Using $NaBH_4$/$CeCl_3$,[14] reduction of **19** to the corresponding allylic alcohol, followed by acetylation, gave the acid-sensitive glycal **20**, $[\alpha]_D^{20}$ = –36.5° (*c* 3.1, $CHCl_3$), in 97% overall yield. A variant[5c] of the Ferrier rearrangement,[15] subsequently allowed the stereocontrolled introduction of the C_9 aldehydic side-chain with concomitant allylic transposition. Reaction of **20** with the *tert*-butyldimethylsilyl enol ether of acetaldehyde,[5c] in the presence of $Cl_2Ti(O^iPr)_2$ (2.2 equiv, PhMe, –42 °C, 0.5 h), gave an 83% yield of the aldehyde **21**, $[\alpha]_D^{20}$ = –17.5° (*c* 2.9, $CHCl_3$), with 97% ds. This has the correct oxidation level for chain-extension by an aldol addition. Introduction of the C_7 stereocentre in the desired sense relied on the γ-selective addition of the silyl dienol ether **22** to the *si*-face of the aldehyde **21**. This vinylogous Mukaiyama aldol reaction[5e] was best achieved by using BF_3•OEt_2 (2.2 equiv) as a mono-coordinating Lewis acid in CH_2Cl_2/Et_2O at –78 °C, *i.e.* without chelate participation from the dihydropyran oxygen. Under these conditions, an 81 : 19 ratio of epimeric alcohols was obtained in 85% yield. The major alcohol **23** (69% yield) was shown to have the correct (7*S*) configuration, together with the required (*E*)-enal terminus. Horner-Emmons olefination of **23** cleanly introduced the second (*E*)-double bond of the diene ester moiety to give **24** in 88% yield. At this point,

we confirmed the C_7 configuration as (*S*) by ^1H NMR analysis[16a] of the Mosher ester[16b,c] derivatives of **24**. Next, the 7–OH was protected as its TBS ether **25**, $[\alpha]_D^{20} = -45.0°$ (*c* 2.9, $CHCl_3$), which was followed by the efficient cleavage of the benzoate ester by transesterification, to give a 91% yield of **26**, $[\alpha]_D^{20} = -81.6°$ (*c* 1.5, $CHCl_3$). Dess-Martin oxidation[17] of **26** then gave the aldehyde **8**[10] (95%), $[\alpha]_D^{20} = -83.3°$ (*c* 1.7, $CHCl_3$), as required for swinholide A.

Conversion of **8** into the ethyl ketone **9**[10] required for scytophycin C could be achieved in 60% yield (unoptimised) by the addition of EtMgBr to give a 1 : 1 mixture of C_{15} secondary alcohols, followed by Dess-Martin oxidation.[17]



Scheme 3 (*a*) (+)-$(Ipc)_2BCl$, $^iPr_2NEt$, PhMe, 0 °C, 1 h; **17**, –78 → –20 °C, 21.5 h; H_2O_2, MeOH, pH-7 buffer; (*b*) 1.05 equiv Me_3SiOTf, 0.8 equiv $^iPr_2NEt$, CH_2Cl_2, –78 → 20 °C, 2.5 h; (*c*) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, –78°C, 2 h; (*d*) Ac_2O, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 18 h; (*e*) $H_2C{=}CHOTBS$, 2.2 equiv $Cl_2Ti(O^iPr)_2$, PhMe, –42 °C, 0.5 h; (*f*) **22**, 2.2 equiv $BF_3{\cdot}OEt_2$, 9:1 CH_2Cl_2/Et_2O, –78 °C, 1 h; (*g*) $(MeO)_2P(O)CH_2CO_2Me$, ^{n}BuLi, THF, 0 → 20 °C, 3 h; (*h*) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 20 min; (*i*) K_2CO_3, MeOH, 20 °C, 5.5 h; (*j*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 0.5–1.5 h; (*k*) EtMgBr, Et_2O, –78 → 0°C, 20 min.

In summary, the C_1–C_{15} subunit **8** of swinholide A has been efficiently prepared in *enantiomerically pure form* in ten steps (14.5% yield, 78% ds) from **15**. This aldehyde has also been converted in two further steps into the C_1–C_{16} subunit **9** of scytophycin C. In this synthesis, the introduction of the C_{13} stereocentre relies on the reagent-controlled boron aldol reaction, **15** + **17** → **18**, while the remaining two stereocentres are set up by the sequence, **20** → **21** → **23**, using substrate-induced control. Further studies directed towards the total synthesis of swinholide A and scytophycin C are underway.

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6. Controlled debenzylation of **25**, P = Bn, was unsuccessful under a wide range of conditions, or gave an unacceptably low yield (*e.g.* 30% yield of **26** using DDQ).
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9. The aldehyde **17** was prepared from 1,3-propanediol by (*i*) $(PhCO)_2O$, pyridine; (*ii*) Dess-Martin periodinane, CH_2Cl_2. It is unstable to chromatography and best used immediately after the oxidation step. To avoid the use of the Dess-Martin periodinane reagent on a large scale, we have also developed an alternative sequence starting from 3-buten-1-ol: (*i*) $(PhCO)_2O$, pyridine; (*ii*) OsO_4, NMO, Me_2CO; (*iii*) $NaIO_4$.
10. All new compounds gave spectroscopic data in agreement with the assigned structures. **8** had ^1H NMR δ (400MHz, $CDCl_3$) 9.78 (1H, dd, *J* = 2.4, 1.4 Hz, CHO), 7.33 (1H, d, *J* = 15.7 Hz, 3-CH), 5.96 (1H, br dd, *J* = 7.4, 7.4 Hz, 5-CH), 5.82–5.73 (2H, m, 2-CH and 11-CH), 5.64 (1H, dm, *J* = 10.3 Hz, 10-CH), 4.30 (1H, br d, *J* = 10.8 Hz, 9-CH), 4.14–4.07 (1H, m, 13-CH), 4.01–3.92 (1H, m, 7-CH), 3.73 (3H, s, CO_2Me), 2.63 (1H, ddd, *J* = 16.5, 8.6, 2.4 Hz, 14-CH_A), 2.49 (1H, ddd, *J* = 16.5, 3.9, 1.4 Hz, 14-CH_B), 2.43–2.33 (2H, m, 6-CH_2), 2.04-1.95 (2H, m, 12-CH_2), 1.77 (3H, s, 4-CMe), 1.69 (1H, ddd, *J* = 14.4, 10.8, 2.2 Hz, 8-CH_A), 1.39 (1H, ddd, *J* = 14.4, 10.0, 2.6 Hz, 8-CH_B), 0.86 (9H, s, CMe_3), 0.03 (6H, s, $SiMe_2$); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 200.9, 168.0, 149.6, 137.7, 134.3, 130.3, 123.2, 115.4, 69.2, 67.8, 62.5, 51.5, 49.0, 40.3, 37.6, 30.2, 25.8, 18.0, 12.4,–4.4, -4.8; HRMS (CI, NH_3) $(M+H)^+$ found 423.2567, $C_{23}H_{39}O_5Si$ requires 423.2567. **9** had ^1H NMR δ ($CDCl_3$, 400MHz) 7.34 (1H, d, *J* = 15.6 Hz, 3-CH), 6.02 (1H, br dd, *J* = 7.3, 7.3 Hz, 5-CH), 5.79 (1H, d, *J* = 15.6 Hz, 2-CH), 5.78–5.71 (1H, m, 11-CH), 5.62 (1H, dm, *J* = 10.3 Hz, 10-CH), 4.26 (1H, br d, *J* = 10.9 Hz, 9-CH), 4.11–4.04 (1H, m, 13-CH), 3.99–3.93 (1H, m, 7-CH), 3.73 (3H, s, CO_2Me), 2.68 (1H, dd, *J* = 15.7, 8.9 Hz, 14-CH_A), 2.46 (2H, q, *J* = 7.3 Hz, 15-CH_2), 2.41–2.33 (3H, m, 6-CH_2 and 14-CH_B), 2.03–1.90 (2H, m, 12-CH_2), 1.77 (3H, s, 4-CMe), 1.68 (1H, ddd, *J* = 14.4, 11.0, 2.2 Hz, 8-CH_A), 1.34 (1H, ddd, *J* = 14.4, 10.1, 2.4 Hz, 8-CH_B), 1.04 (3H, t, *J* = 7.3 Hz, 15-CH_2Me), 0.86 (9H, s, CMe_3), 0.024 (3H, s, SiMe), 0.018 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 209.5, 168.1, 149.9, 138.2, 134.1, 130.3, 123.4, 115.2, 69.3, 67.6, 63.6, 514, 47.8, 40.2, 37.6 (2 carbons), 30.3, 25.9, 18.0, 12.4, 7.6, -4.4, -4.8; HRMS (CI, NH_3) $(M+H)^+$ found 451.2880, $C_{25}H_{43}O_5Si$ requires 451.2880.
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