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The Total Synthesis of Scytophycin C. Part 2: Synthesis of Scytophycin C from the Protected Seco Acid.

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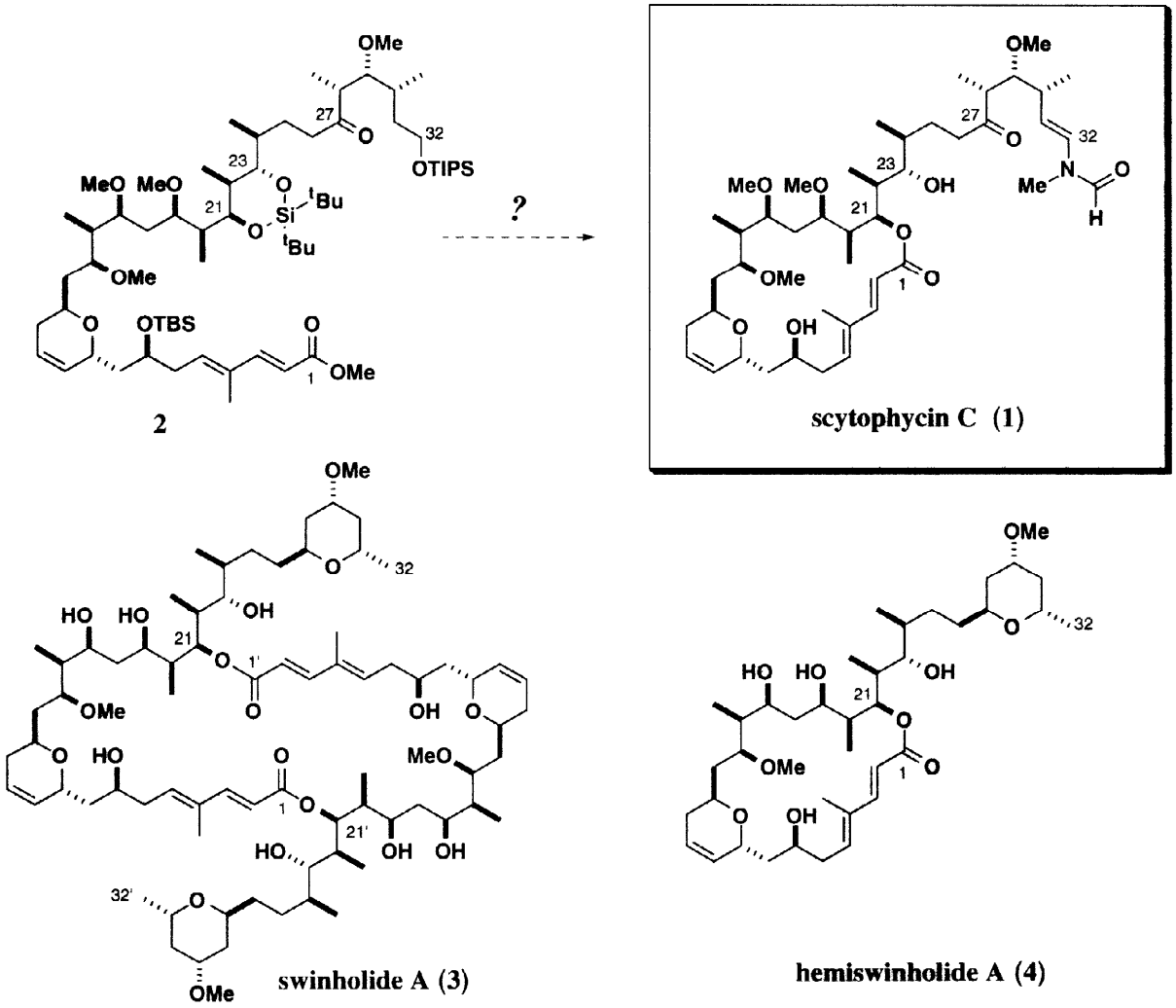
Abstract: Scytophycin C (**1**) was synthesised in 8 steps from the fully protected seco acid **2**. Key steps include: (*i*) a high yielding macrolactonisation reaction of **15** followed by regioselective isomerisation of the undesired, 24-membered macrolide, **18** → **16**; (*ii*) the chemoselective oxidation steps, **16** → **6** and **7** → **8**; (*iii*) the P_2O_5-promoted condensation of **8** with HN(Me)CHO to install the *N*-methyl vinylformamide moiety in **1**.



Scheme 1

In the preceding paper, we outlined our strategy for the total synthesis of the 22-membered macrolide, scytophycin C (**1**).[1] Following this strategy, a stereocontrolled synthesis of the advanced intermediate **2**

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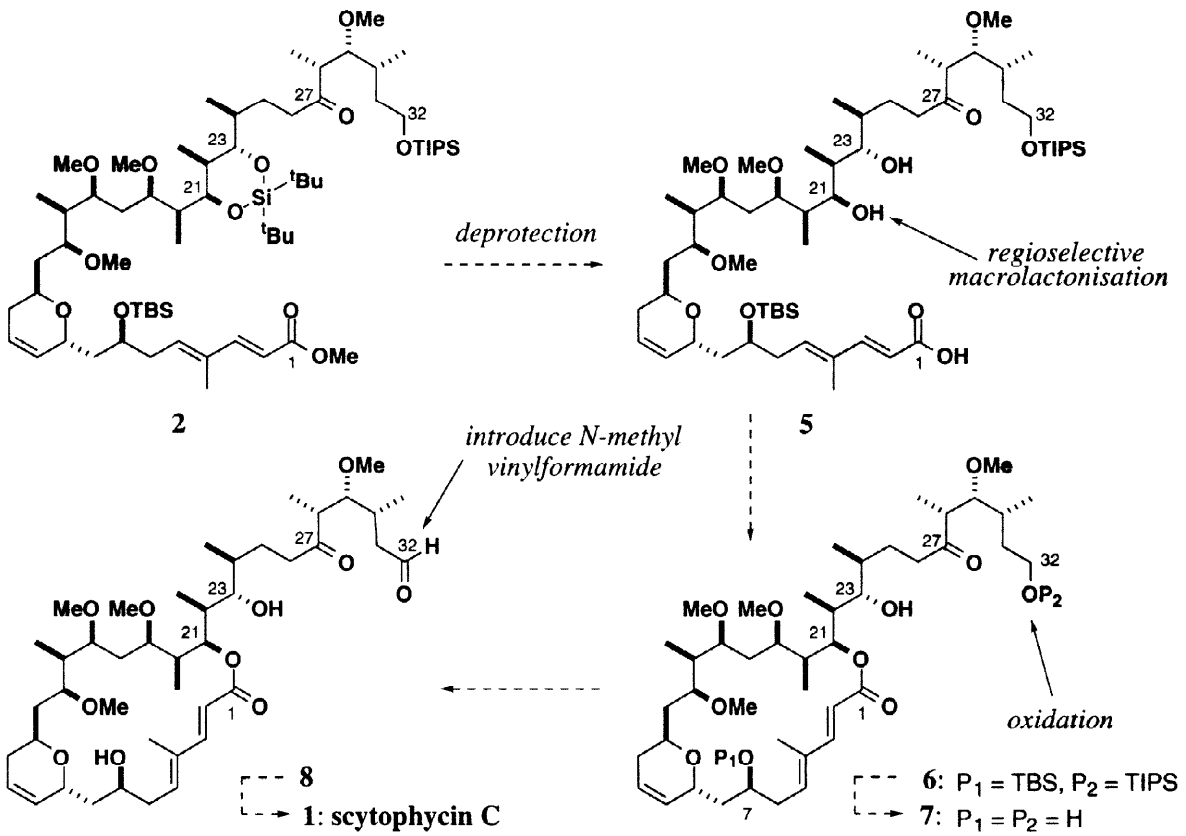
(**Scheme 1**), representing a fully protected seco acid incorporating all 15 stereogenic centres, was achieved in a direct and efficient manner. In this paper, we give full details of the further elaboration of **2** and completion of the first total synthesis of scytophycin C (**1**).[2] Notably, the crucial ring-closure step and final functional group adjustments proved much more challenging than that encountered in the late stages of our synthesis[3] of the related macrolides, swinholide A (**3**) and hemiswinholide A (**4**).

Strategy for Completing the Total Synthesis of Scytophycin C



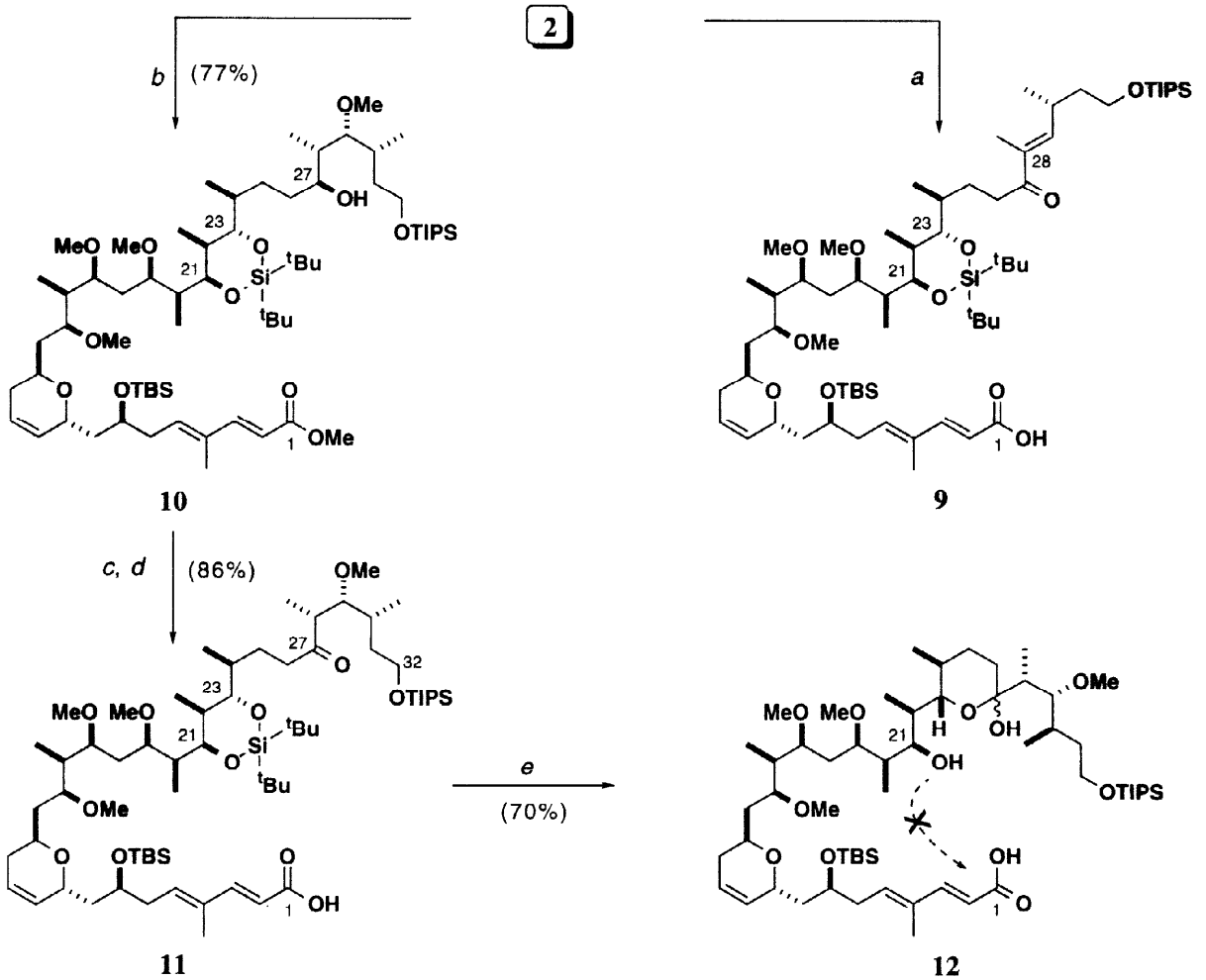
Scheme 2

Our initial plans for completing the total synthesis of scytophycin C (**1**) are summarised in **Scheme 2**. Ideally, the C_{27} ketone functionality of scytophycin C might be taken through the remainder of the synthesis without the need for further protecting group chemistry. We initially anticipated that such a substrate could be prepared by cleavage of the C_1 methyl ester and deprotection of the di-*tert*-butylsilylene group to release a 1,3-diol, as in **2** → **5**. Use of this cyclic silicon protecting group precluded selective deprotection of the C_{21} hydroxyl group and thus necessitated a regioselective macrolactonisation step. While the two secondary alcohols in **5** appear to have similar steric environments, by using the Yamaguchi macrolactonisation method[4] some selectivity for acylation at the C_{21} over the C_{23} hydroxyl, leading to the desired 22-membered macrolide **6**, was anticipated based on our total synthesis of hemiswinholide A (**4**).[3]

Following deprotection of **6** to give **7**, the macrolactone **8** might then be accessed by selective oxidation of the primary C_{32} alcohol in the presence of the two secondary alcohols at C_7 and C_{23}. The final step, *i.e.*

introduction of the *N*-methyl vinylformamide group, as in **8** → **1**, was anticipated to be particularly challenging as a result of the known acid sensitivity of the scytophycins.[5] However, it was hoped that mild, acid-catalysed, condensation of *N*-methyl formamide onto the aldehyde group in **8** would enable the completion of the total synthesis of scytophycin C (**1**).

Macrolactonisation Studies Leading to the Synthesis of Macrolide (16)

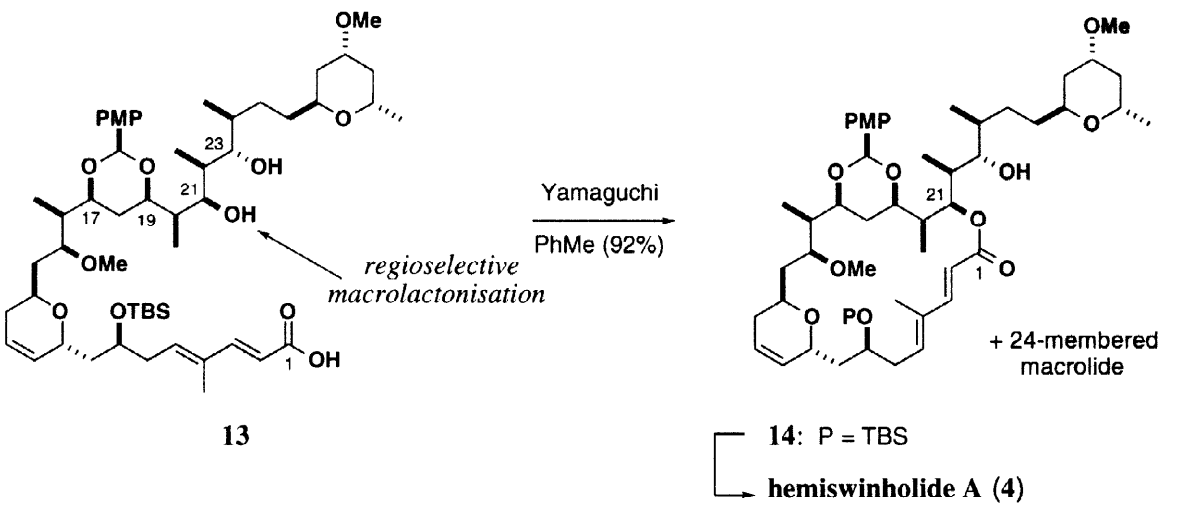


Scheme 3: (*a*) $Ba(OH)_2$, MeOH, 20 °C, 8 h; (*b*) $NaBH_4$, MeOH, −20 °C, 18 h; (*c*) TMSOK, Et_2O, 20 °C, 48 h; (*d*) Dess-Martin periodinane, CH_2Cl_2, 20 °C, 2 h; (*e*) HF•py, py, THF, 0 °C, 90 min.

Following this strategy, an investigation of the macrolactonisation reaction first required controlled hydrolysis of the methyl ester in **2** to generate the corresponding carboxylic acid (**Scheme 3**). Unfortunately, we were unable to achieve this apparently simple transformation without complications from the presence of the unprotected C_{27} ketone. Under standard basic conditions ($Ba(OH)_2$, MeOH), the enone **9** was obtained exclusively, resulting from elimination of MeOH across C_{28} and C_{29} (the product alkene stereochemistry was not determined). Screening of a wide range of basic and nucleophilic conditions (*e.g.* LiOH; LiOOH; LiI/pyridine;[6] TMSOK[7]) resulted in this same undesired carboxylic acid being isolated.

To overcome this problem, the C_{27} ketone was temporarily "protected" as the corresponding secondary alcohol during the ester hydrolysis reaction. Thus, the fully protected seco acid **2** was reduced with $NaBH_4$ (MeOH, –20 °C) to give the alcohol **10** as a single diastereomer in 77% yield (99% based on recovered starting material). The resulting stereochemistry at C_{27} was not determined and is assigned as shown based on the operation of Felkin-Anh selectivity. With the base-sensitive ketone group now removed, hydrolysis of the methyl ester proceeded cleanly using potassium trimethylsilanoate[7] (Et_2O, 20 °C). Reoxidation at C_{27} using the Dess-Martin periodinane[8] then generated the desired ketoacid **11** in 86% overall yield.

We now required selective deprotection of the silylene group in **11** in the presence of the TIPS and TBS groups to generate the required macrolactonisation substrate **5** (*cf.* **Scheme 2**). This was achieved smoothly using HF•pyridine (pyridine, THF).[9] However, the deprotected product was not isolated as the diol acid **5** but as the corresponding hemiacetal **12**, where the C_{23} hydroxyl had closed onto the ketone at C_{27}. Further cyclisation involving the free C_{21} hydroxyl to generate a bicyclic acetal from **12** was not observed. Notably, this tautomeric hemiacetal does not appear to form in the scytophycins, presumably due to the steric demands of the macrolide ring. For synthetic purposes, the alcohol at C_{23} had effectively been protected by forming the hemiacetal **12** and would presumably be unable to participate in the macrolactonisation reaction to generate the undesired, 24-membered macrolide. Thus, a completely regiocontrolled macrolactonisation appeared possible by selective acylation of the C_{21} hydroxyl group.



13

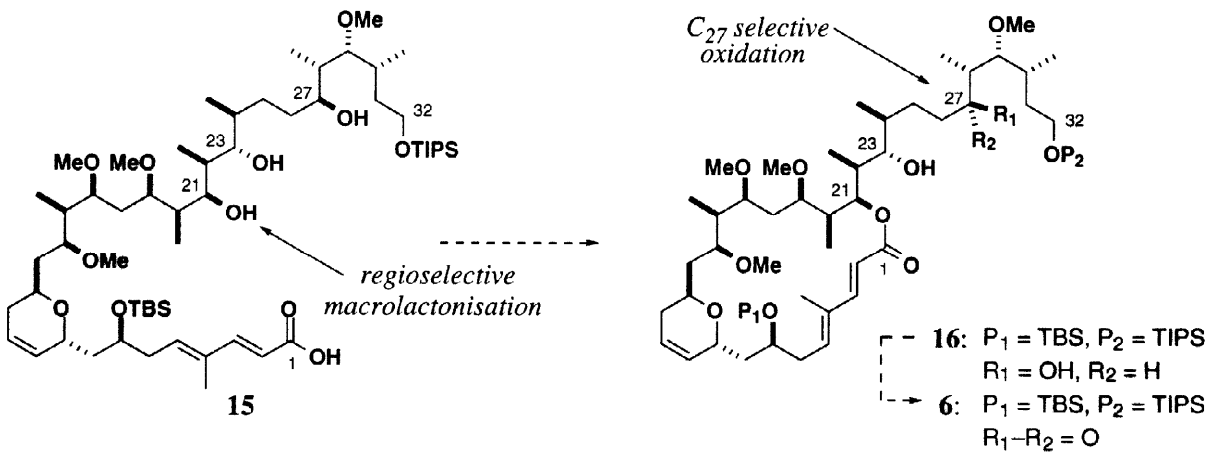
14: P = TBS

hemiswinholide A (4)

Scheme 4

Following the successful macrolactonisation protocol adopted earlier for the formation of the 22-membered ring in hemiswinholide A (**4**),[3] the seco acid **12** was subjected to cyclisation under Yamaguchi conditions[4] in toluene (2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N; 4-DMAP, 60 °C). Even under forcing conditions (further heating, large excess of reagent), no reaction was observed and the seco acid **12** was recovered in varying yield. In comparison, the corresponding macrolactonisation of seco acid **13**, *cf.* **Scheme 4**, proceeded without difficulty in excellent yield (92%) and a high level of regioselectivity (82 : 18) towards the 22-membered ring **14**, as required for hemiswinholide A (**4**), was achieved. To our dismay, formation of the hemiacetal in **12** apparently increased the steric hindrance around the C_{21} hydroxyl so much that it precluded intramolecular acylation. In the light of these disappointing results, we required a new strategy which would enable us to overcome the ketone-related problems of β-elimination and hemiacetal formation.

One bold approach for advancing the synthesis further is shown in **Scheme 5**. As the reduction of the C_{27} ketone was dictated by the need to achieve trouble-free ester hydrolysis, we now proposed to postpone the re-oxidation at C_{27} until after the key macrolactonisation reaction. In this way, hemiacetal formation would be prevented with no increase in the number of synthetic steps. The disadvantages of such an approach were obvious. Firstly, the macrolactonisation reaction would now be even more challenging with *three free hydroxyl groups available for acylation* in the new substrate **15**, leading potentially to 22-, 24- and 28-membered rings. Secondly, reoxidation at C_{27}, as in **16** → **6**, might no longer be straightforward. Nevertheless, chemoselectivity over competing C_{23} oxidation might still be possible as a result of the different steric environments of the two secondary alcohols in **16**. Final completion of the synthesis of scytophycin C from **6** was envisaged to proceed as proposed in **Scheme 2**.

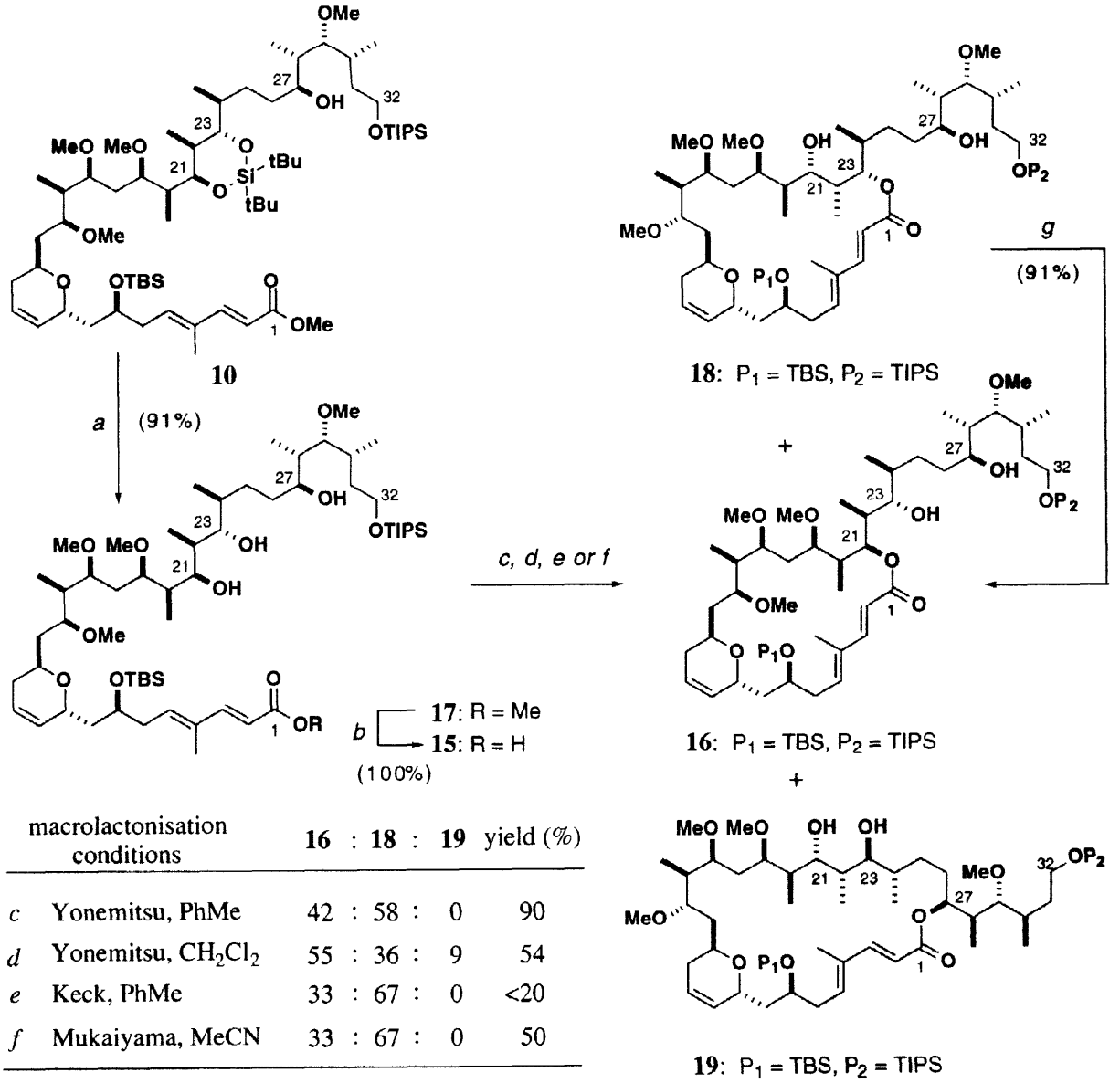


Scheme 5

The first two steps of this new route proved to be straightforward (**Scheme 6**). The triol acid **15** was prepared from **10** in 91% yield by silylene deprotection (HF•py, pyridine, THF) to give the triol **17** followed by ester hydrolysis ($Ba(OH)_2$, MeOH). The key macrolactonisation step was now investigated. Initially, we decided to employ modified Yamaguchi conditions as these had given remarkable selectivity in favour of the desired 22-membered over the isomeric 24-membered ring in our synthesis of hemiswinholide A (**4**), *cf.* **Scheme 4**. Treatment of the acid **15** under Yonemitsu's conditions,[10] using 2,4,6-trichlorobenzoyl chloride, Et_3N and 4-DMAP in toluene (20 °C, 8 h), resulted in an excellent yield (90%) of a 42 : 58 mixture of two macrocycles, **16** and **18**. Unfortunately, this mixture was slightly in favour of the 24-membered over the desired 22-membered ring. No acylation at C_{27} to form the 28-membered macrolide **19** was detected. Reaction in a more polar solvent (CH_2Cl_2) reversed this selectivity to now favour **16** (along with a small amount of an isomeric macrolide which was tentatively assigned as **19**); however, the yield (54%) was substantially lower. Other macrolactonisation procedures investigated (Keck,[11] Mukaiyama[12]) gave rise to poor selectivities and low yields. We were unable to attain the level of macrolactonisation regioselectivity achieved in the equivalent hemiswinholide reaction, *i.e.* **13** → **14** in **Scheme 4**, which benefits from the presence of a cyclic acetal protecting group across the equivalent C_{17} and C_{19} hydroxyls acting as an additional conformational anchor.

Under kinetic macrolactonisation conditions using the Yonemitsu procedure (without recourse to high dilution techniques), a high yield of the separable macrolactones **16** and **18** could be obtained. Presumably, the conformational preferences of the molecular backbone makes the participation of the hydroxyl at C_{27} in the

intramolecular esterification step less favoured than those at C_{21} and C_{23}. However, a method for recycling the 24-membered ring **18** was required to obtain sufficient stocks of **16** to complete the synthesis of scytophycin C. Titanium tetraisopropoxide is a mild reagent known to mediate transesterification reactions on complex, highly functionalised compounds.[13,14] Thus the undesired macrocycle **18** was treated with a 1M solution of $Ti(O^iPr)_4$ in CH_2Cl_2 (**Scheme 6**). After 48 h at ambient temperature, a 70 : 30 mixture of **16** and **18** was isolated in 91% yield. Thus under equilibrating conditions, the 24-membered ring **18** could be isomerised to the desired 22-membered ring **16** with excellent mass recovery. In contrast, attempts to carry out the macrolactonisation reaction directly on the methyl ester **17**, under thermodynamic conditions ($[Bu_2SnCl(OH)_2]_2$ $[Bu_2SnO]_2$, PhMe),[15] failed to give any detectable macrolide products.

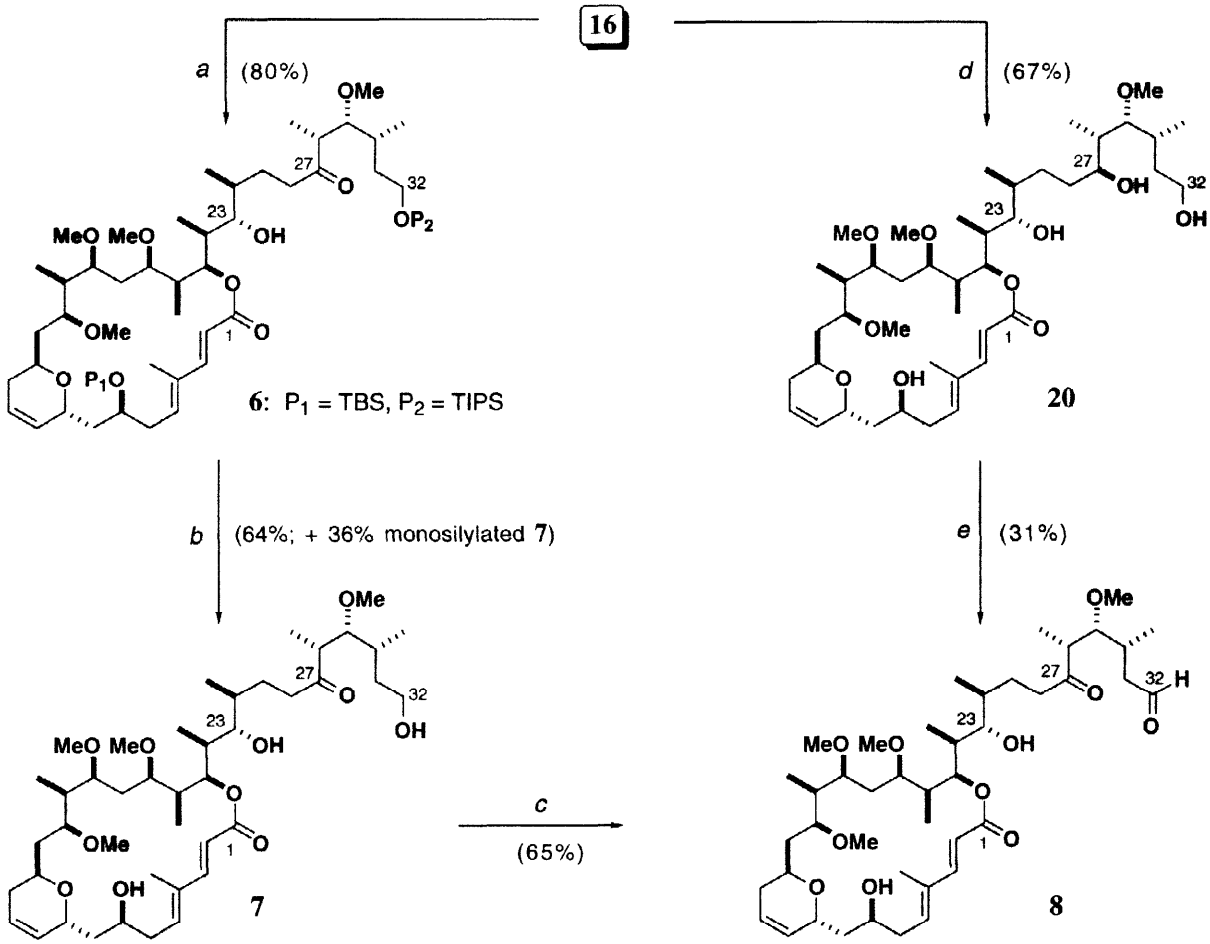


macrolactonisation conditions		16 : 18 : 19	yield (%)
c	Yonemitsu, PhMe	42 : 58 : 0	90
d	Yonemitsu, CH_2Cl_2	55 : 36 : 9	54
e	Keck, PhMe	33 : 67 : 0	<20
f	Mukaiyama, MeCN	33 : 67 : 0	50

Scheme 6: (a) HF•py, py, THF, 0 → 20 °C, 1 h; (b) $Ba(OH)_2$, MeOH, 20 °C, 18 h; (c) 2,4,6-(C_6H_2)COCl, Et_3N, 4-DMAP, PhMe, 20 °C, 18 h; (d) 2,4,6-(C_6H_2)COCl, Et_3N, 4-DMAP, CH_2Cl_2, 20 °C, 18 h; (e) DCC, 4-DMAP, 4-DMAP•HCl, PhMe, 60 °C, 16 h; (f) 2-chloro-*N*-methylpyridinium iodide, Et_3N, MeCN, 80 °C, 18 h; (g) $Ti(O^iPr)_4$, CH_2Cl_2, 20 °C, 48 h.

Completing the Total Synthesis of Scytophycin C (1)

While the free hydroxyl group at C_{27} did not participate in the macrolactonisation reaction, selective re-oxidation at this position over the C_{23} alcohol remained as a potential problem. As shown in **Scheme 7**, tetrapropylammonium perruthenate (TPAP)[16] was selected as a sterically demanding oxidant, where the proximity of the C_{23} hydroxyl to the macrolide ring was anticipated to interfere with the oxidation reaction at this position. In the event, treatment of **16** with 0.2 equivalents of TPAP (NMO, CH_2Cl_2, molecular sieves) for 1 h at room temperature gave the desired ketone **6** in 80% yield with no oxidation at C_{23} observed.

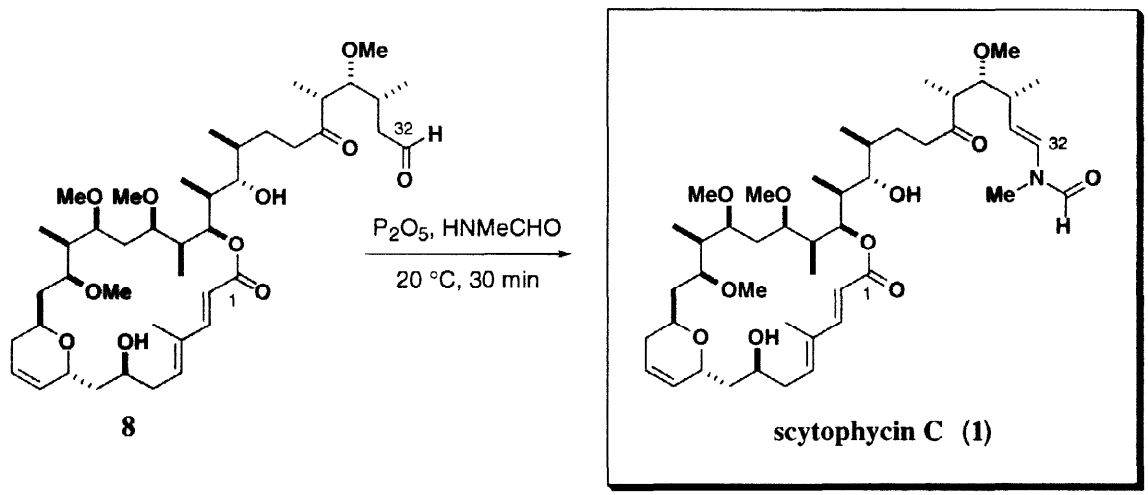


Scheme 7: (a) TPAP, NMO, CH_2Cl_2, 4Å mol sieves, 20 °C, 1 h; (b) HF•py, py, THF, 20 °C, 48 h; (c) TPAP, NMO, CH_2Cl_2, 4Å mol sieves, 0 °C, 30 min; (d) aq. HF, MeCN, 20 °C, 20 min; (e) TPAP, NMO, CH_2Cl_2, 4Å mol sieves, 20 °C, 2 h.

At this stage, we hoped to minimise further protecting group manipulations by carrying out a global deprotection. Treatment of **6** with HF•py (pyridine, THF) for 48 h resulted in a mixture of the desired triol **7** (64%) and monodeprotected intermediates (36%) which could be readily recycled. Attempts to improve the yield and rate of this reaction using HF or TBAF resulted in a complex mixture of products in both cases, including some eliminated material. We now required a further selective oxidation, this time of a primary alcohol in the presence of the secondary hydroxyl groups at C_7 and C_{23}. As TPAP had proved to be a mild and selective reagent in the oxidation of **16**, it was the obvious choice for this second oxidation. Thus triol **7** was treated with TPAP and NMO, in the presence of powdered molecular sieves, for 30 min at 0 °C. On work-up,

the required aldehyde **8** was isolated in 65% yield with no other oxidation products being detected. This same aldehyde **8** could also be prepared in just 2 steps from macrolactonisation product **18**. Global deprotection of **18** with HF in MeCN gave the tetrol **20** in 67% yield with no competing elimination being observed due to the absence of the ketone in this case. Oxidation of **20** using TPAP, as before, gave an unoptimised 31% yield of ketoaldehyde **8**. Hence, this shorter synthetic sequence gave a similar overall yield to that described above.

With the advanced intermediate **8** for scytophycin in hand, effort turned towards the challenging final step in the synthesis, *i.e.* the controlled introduction of the terminal *N*-methyl vinylformamide. Initially, the aldehyde **8** was treated with PPTS, *N*-methyl formamide and hydroquinone, at reflux in toluene, using a Dean-Stark apparatus, according to the conditions employed by Yamada *et al.* in their total synthesis of aplyronine A.[14] Unfortunately, none of the desired vinylformamide was observed. The known acid instability of scytophycin C is likely to be the problem here.[5]



Scheme 8

Other studies performed in our group had shown phosphorus pentoxide to be a promising reagent to achieve the condensation of *N*-methylformamide with aldehydes to give *N*-methyl vinylformamides.[17] However, the conditions which had proven to be high yielding in a model system (P_2O_5, HNMeCHO, CH_2Cl_2, sonication, 20 °C, 3 h) failed to give any scytophycin C in the reaction of the sensitive aldehyde substrate **8**. We, therefore, explored a wide range of conditions for this crucial final step in the synthesis. Ultimately, treatment of **8** with P_2O_5 in neat HNMeCHO at 20 °C for 30 min, followed by reverse phase HPLC purification, gave a modest 20% yield of the required *N*-methyl vinylformamide **1** (**Scheme 8**). This material exhibited ^1H and ^{13}C NMR, IR and MS data in accordance with the published values for natural scytophycin C.[5, 18]

Conclusions

The first total synthesis of the cytotoxic macrolide scytophycin C (**1**) has been completed. The key steps include: (*i*) the high yielding kinetic macrolactonisation, **15** → **16** + **18**; (*ii*) isomerisation under equilibrating conditions of the undesired macrolactone **18** to give **16**; (*iii*) selective oxidation reactions at C_{27} and C_{32}, as in **16** → **6** and **7** → **8** respectively, which minimised the need for protecting group manipulations at a late stage in the synthesis; (*iv*) the P_2O_5-promoted installation of the *N*-methyl vinylformamide moiety, **8** → **1**.

The entire synthesis of scytophycin C proceeds in a total of 41 steps (22 steps longest linear sequence) with an overall yield of 0.7%. The stereocontrolled construction of the protected seco acid **2** relied heavily on various types of asymmetric aldol reactions, which were used to form the C_6–C_7, C_{12}–C_{13}, C_{18}–C_{19} and C_{22}–C_{23} bonds. Notably, the regioselectivity of macrolactonisation was controlled without the need for differential hydroxyl protection by taking advantage of the thermodynamic preference for the smaller, 22-membered ring, **16**. The final step of the synthesis, *i.e.* **8** → **1**, proved to be especially challenging due to the acid-sensitivity of this system and improved methods are clearly needed for the introduction of such *N*-methyl vinylformamide units, as they occur in a variety of marine macrolide structures. With further work, this route should allow the preparation of a range of structural analogues of the scytophycins, enabling the mode of action and structure-activity relationships to be probed.

Experimental Section

For general experimental details, see the preceding paper.

C_{27} Alcohol (10) To a cooled (–20 °C), stirred solution of ketone **2** (190 mg, 0.160 mmol) in MeOH (10 ml) was added $NaBH_4$ (183 mg, 4.82 mmol) in one portion. The reaction mixture was warmed gradually, over 3 h, to 0 °C then stirred at this temperature for 1 h. The reaction was quenched with $NaHCO_3$ (10 ml, sat. aq.) and diluted with Et_2O (20 ml). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 25 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (30 → 50% Et_2O/hexane) gave some recovered **2** (43 mg, 23%) and product **10** as a colourless oil (146 mg, 77%); R_f 0.33 (40% Et_2O/hexane); $[\alpha]_D^{20}$ –46.8 (*c* 1.4, $CHCl_3$); IR (liquid film) 2937, 2863, 1722, 1623, 1463, 1387, 1256, 1091, 983 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.33 (1H, d, *J* = 15.7 Hz, 3-C<u>H</u>), 6.04 (1H, t, *J* = 6.8 Hz, 5-C<u>H</u>), 5.80-5.77 (2H, br d, *J* = 15.7 Hz, 2-C<u>H</u>, 11-C<u>H</u>), 5.64 (1H, d, *J* = 10.1 Hz, 10-C<u>H</u>) 4.33 (1H, d, *J* = 10.1 Hz, 9-C<u>H</u>), 4.20-4.10 (1H, m, 7-C<u>H</u>), 4.16 (1H, br d, *J* = 11.6 Hz, 21-C<u>H</u>), 4.05 (1H, d, *J* = 7.6 Hz, C<u>H</u>O), 3.79-3.75 (1H, m, 32-C<u>H</u>$_A$CH$_B$), 3.75 (3H, s, CO_2<u>Me</u>), 3.70-3.63 (3H, m, 32-CH$_A$C<u>H</u>$_B$, 23-C<u>H</u>, C<u>H</u>O), 3.60-3.53 (2H, m, 13-C<u>H</u>, C<u>H</u>O), 3.48 (3H, s, O<u>Me</u>), 3.44 (3H, s, O<u>Me</u>), 3.34 (3H, s, O<u>Me</u>), 3.30 (3H, s, O<u>Me</u>), 3.07 (1H, t, *J* = 7.9 Hz, C<u>H</u>O), 2.97 (1H, dd, *J* = 8.3, 2.4 Hz, C<u>H</u>O), 2.47-2.42 (1H, m, 6-C<u>H</u>$_A$CH$_B$), 2.42-2.35 (1H, m, 6-CH$_A$C<u>H</u>$_B$), 2.02-1.85 (3H, m, 3xC<u>H</u>), 2.02-1.95 (1H, m, 12-C<u>H</u>$_A$CH$_B$), 1.95-1.85 (1H, m, 12-CH$_A$C<u>H</u>$_B$), 1.75 (3H, s, 4-C<u>Me</u>), 1.76-1.70 (7H, m, 31-C<u>H</u>$_A$CH$_B$, 22-C<u>H</u>, 20-C<u>H</u>, 4xC<u>H</u>), 1.65-1.58 (3H, m, 8-C<u>H</u>$_A$CH$_B$, 2xC<u>H</u>), 1.43-1.40 (1H, m, 8-CH$_A$C<u>H</u>$_B$), 1.50-1.40 (2H, hidden m, 2xC<u>H</u>), 1.35-1.28 (2H, m, 31-CH$_A$C<u>H</u>$_B$, C<u>H</u>), 1.06 (18H, br s, (<u>Me</u>$_2$CH)$_3$Si), 1.05 (9H, s, ^{t}<u>Bu</u>), 1.02 (9H, s, ^{t}<u>Bu</u>), 1.04-1.02 (3H, hidden d, CH<u>Me</u>), 1.10-0.98 (3H, m, (Me$_2$C<u>H</u>)$_3$Si), 0.91 (3H, d, *J* = 7.2 Hz, CH<u>Me</u>), 0.89 (12H, s+hidden d, SiMe$_2$^{t}<u>Bu</u>, CH<u>Me</u>), 0.86 (3H, d, *J* = 7.2 Hz, CH<u>Me</u>), 0.83 (3H, d, *J* = 7.2 Hz, CH<u>Me</u>), 0.74 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>), 0.12 (3H, s, <u>Me</u>Si), 0.08 (3H, s, <u>Me</u>Si); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 167.9, 149.6, 137.9, 134.0, 130.4, 123.7, 115.3, 92.6, 83.9, 80.2, 76.7, 75.7, 74.4, 72.5, 69.1, 67.4, 63.9, 61.5, 61.0, 59.2, 56.5, 56.1, 51.4, 41.2, 40.8, 40.4, 39.7, 38.7, 37.3, 36.3, 34.8, 34.8, 33.8, 32.4, 32.3, 31.4, 31.2, 28.6, 27.6, 27.5, 25.9, 22.2 (2C), 21.7, 18.0, 17.6, 15.4, 14.2, 12.4, 12.0, 9.4, 8.4, -4.4, -4.8; m/z (+ve FAB, NOBA) 1234 (10, $[M + Na]^+$), 313 (40), 283 (100), 227 (80); HRMS (+ve FAB, NOBA) $[M + Na]^+$ found 1233.8848, $C_{67}H_{130}O_{12}Si_3Na$ requires 1233.8768.

Triol Ester (17) To a cooled (0 °C) solution of alcohol **10** (56 mg, 0.0472 mmol) in THF (3 ml) was added HF•py solution (1.0 ml of a stock solution of 2.1 g pyridinium hydrofluoride in 5.7 ml pyridine + 10 ml THF). The reaction mixture was stirred at room temperature for 1 h by which time TLC indicated complete

consumption of starting material. The reaction was quenched with $NaHCO_3$ (5 ml, sat. aq.) and diluted with EtOAc (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 ml). The combined organic extracts were washed with $CuSO_4$ (30 ml, sat. aq), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (30 → 50% EtOAc/hexane) gave **17** as a colourless oil (46 mg, 91%); R_f 0.52 (60% EtOAc/hexane); $[\alpha]_D^{20}$ –23.8 (*c* 2.0, $CHCl_3$); IR (liquid film) 3814, 2937, 2865, 1720, 1622, 1462, 1258, 1092, 983 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.34 (1H, d, *J* = 15.7 Hz, 3-CH), 6.04 (1H, br t, *J* = 7.0 Hz, 5-CH), 5.82-5.77 (1H, m, 11-CH), 5.80 (1H, d, *J* = 15.7 Hz, 2-CH), 5.64 (1H, dm, *J* = 10.5 Hz, 10-CH), 4.35-4.33 (1H, m, 9-CH), 4.33-4.27 (1H, br, OH), 4.18-4.13 (1H, m, 7-CH), 4.05 (1H, d, *J* = 10.5 Hz, OH), 3.80-3.75 (2H, m, 32-CH_ACH_B, CHO), 3.75 (3H, s, CO_2Me), 3.71-3.64 (2H, m, 32-CH_ACH_B, 15-CH), 3.58-3.55 (1H, m, CHO), 3.54-3.48 (1H, m, 13-CH), 3.40-3.35 (2H, m, 2xCHO), 3.49 (3H, s, OMe), 3.39 (3H, s, OMe), 3.35 (3H, s, OMe), 3.34 (3H, s, OMe), 3.23-3.18 (1H, m, CHO), 2.97 (1H, dd, *J* = 8.3, 2.8 Hz, CHO), 2.44-2.39 (2H, m, 6-CH_2), 2.08-2.02 (1H, m, CH), 2.02-1.92 (3H, m, 12-CH_2, 30-CH), 1.76 (3H, s, 4-CMe), 1.88-1.70 (6H, m, 14-CH_2, 31-CH_AH_B, 3xCH), 1.68-1.62 (4H, m, 8-CH_AH_B, 16-CH, 2xCH), 1.55-1.50 (2H, m, 2xCH), 1.44-1.38 (2H, m, 8-CH_AH_B, CH), 1.37-1.28 (2H, m, 31-CH_AH_B, CH), 1.06 (18H, br s, $(Me_2CH)_3Si$), 1.10-1.04 (3H, m, $(Me_2CH)_3Si$), 1.04 (3H, d, *J* = 7.1 Hz, CHMe), 1.02 (3H, d, *J* = 6.0 Hz, CHMe), 0.92 (3H, d, *J* = 7.1 Hz, CHMe), 0.89 (12H, s+hidden d, $SiMe_2{}^tBu$, CHMe), 0.86 (3H, d, *J* = 7.2 Hz, CHMe), 0.74 (3H, d, *J* = 7.0 Hz, CHMe), 0.13 (3H, s, MeSi), 0.09 (3H, s, MeSi); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 168.0, 149.6, 138.2, 133.9, 130.4, 123.8, 115.2, 92.8, 82.0, 80.8, 80.7, 80.2, 74.3, 72.6, 69.2, 69.1, 67.6, 64.0, 61.4, 61.0, 57.1 (2C), 51.4, 41.3, 40.5, 40.3, 37.5, 36.8, 36.4, 35.6, 34.6, 33.8, 32.9, 32.3, 31.3, 30.9, 30.7, 28.0, 25.9, 18.0, 17.6, 16.5, 14.2, 12.5, 12.1, 12.0, 10.7, 9.2, -4.3, -4.7; m/z (+ve FAB, NOBA) 1094 (100, $[M+Na]^+$), 1072 (20, $[M+H]^+$), 1063 (11), 1038 (7); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 1093.5497, $C_{59}H_{114}O_{12}Si_2Na$ requires 1093.7747.

Triol Acid (15) To a solution of ester **17** (96 mg, 0.897 mmol) in MeOH (5 ml) was added dry $Ba(OH)_2$ (1.0 g, 5.84 mmol). The reaction mixture was stirred at room temperature overnight by which time TLC indicated complete consumption of starting material. The reaction mixture was poured into NH_4Cl (50 ml, sat. aq.) and the aqueous layer acidified to pH 1 with 1 M HCl. The layers were separated and the aqueous extracted with EtOAc (4 x 50 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (5% MeOH/1% AcOH/CH_2Cl_2) gave **15** as a colourless oil (95 mg, 100%); R_f 0.20 (5% MeOH/1% AcOH/CH_2Cl_2); $[\alpha]_D^{20}$ –24.4 (*c* 1.8, $CHCl_3$); IR (liquid film) 3420, 2938, 1693, 1622, 1462, 1382, 1265, 1901, 983 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.38 (1H, d, *J* = 15.7 Hz, 3-CH), 6.06 (1H, br t, *J* = 7.3 Hz, 5-CH), 5.78 (1H, d, *J* = 15.7 Hz, 2-CH), 5.80-5.77 (1H, hidden m, 11-CH), 5.64 (1H, dm, *J* = 9.9 Hz, 10-CH), 4.39 (1H, d, *J* = 9.9 Hz, 9-CH), 4.15-4.08 (2H, br m, 7-CH, OH), 3.82 (1H, d, *J* = 10.3 Hz, OH), 3.80-3.75 (2H, m, 32-CH_AH_B, CHO), 3.71-3.66 (1H, m, CHO), 3.58-3.50 (1H, m, CHO), 3.49 (3H, s, OMe), 3.45-3.35 (2H, hidden m, 2xCHO), 3.40 (3H, s, OMe), 3.38 (3H, s, OMe), 3.35 (3H, s, OMe), 3.33-3.30 (1H, m, CHO), 3.28-3.27 (1H, m, CHO), 3.18-3.16 (1H, m, CHO), 2.99 (1H, dd, *J* = 8.5, 2.5 Hz, CHO), 2.50-2.43 (1H, m, 6-CH_AH_B), 2.40-2.32 (1H, m, 6-CH_AH_B), 2.10-1.95 (3H, m, 3xCH), 1.88-1.75 (7H, m, 7xCH), 1.76 (3H, s, 4-CMe), 1.70-1.53 (5H, m, 5xCH), 1.35-1.25 (5H, m, 5xCH), 1.06 (18H, br s, $(Me_2CH)_3Si$), 1.05-1.04 (3H, m, $(Me_2CH)_3Si$), 1.03 (3H, d, *J* = 7.1 Hz, CHMe), 1.00 (3H, d, *J* = 6.9 Hz, CHMe), 0.89 (9H, s, $SiMe_2{}^tBu$), 0.86 (3H, d, *J* = 6.5 Hz, CHMe), 0.84 (3H, d, *J* = 6.5 Hz, CHMe), 0.83 (3H, d, *J* = 6.9 Hz, CHMe), 0.79 (3H, d, *J* = 7.0 Hz, CHMe), 0.14 (3H, s, MeSi), 0.10 (3H, s, MeSi); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 170.5, 150.9, 138.8, 134.0, 130.4, 123.8, 115.3, 92.6, 82.2, 80.4, 80.2, 74.0, 72.1, 69.0 (2C), 67.8, 63.7, 61.4, 60.9, 57.4, 57.2, 56.9, 41.1, 41.0, 40.6, 38.3, 36.6, 36.0, 35.7, 34.9, 33.8, 32.1, 31.5 (2C), 30.5, 29.7, 27.1, 25.9, 18.0, 17.5, 16.8, 13.9, 12.4, 11.9, 12.0, 10.4, 9.2, -4.2, -4.7; m/z (+ve FAB, NOBA) 1080 (60, $[M+Na]^+$), 269 (40), 165 (30), 145 (63), 115 (100); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 1079.5523, $C_{58}H_{112}O_{12}Si_2Na$ requires 1079.7590.

Macrolides (16) and (18) To a solution of acid **15** (10.5 mg, 9.9 μmol) in toluene (2 ml) was added Et_3N (7 μl, 50 μmol), 2,4,6-trichlorobenzoylchloride (110 μl, 0.1 M solution in toluene, 11 μmol) and 4-DMAP (20 μl, 0.1 M solution in toluene, 2 μmol). The resulting cloudy solution was stirred at room temperature for 18 h then poured into $NaHCO_3$ (10 ml, sat. aq.). The aqueous layer was extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (30% EtOAc/hexane) gave a mixture of **16** and **18** (42 : 58 ratio) (9.3 mg, 90%), which were separated by normal phase HPLC (40% EtOAc/hexane).

C_{21} macrocycle **16**: R_f 0.23 (30% EtOAc/hexane); t_R 19 min (40% EtOAc/hexane); $[\alpha]_D^{20}$ −12.7 (*c* 0.45, $CHCl_3$); IR (liquid film) 3497, 2924, 1689, 1462, 1377, 1264, 1092 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.52 (1H, d, *J* = 15.8 Hz, 3-C<u>H</u>), 5.95 (1H, t, *J* = 7.6 Hz, 5-C<u>H</u>), 5.81-5.78 (1H, m, 11-C<u>H</u>), 5.76 (1H, d, *J* = 15.8 Hz, 2-C<u>H</u>), 5.63 (1H, dm, *J* = 10.1 Hz, 10-C<u>H</u>), 5.17 (1H, d, *J* = 10.1 Hz, 21-C<u>H</u>), 4.43 (1H, d, *J* = 10.1 Hz, 9-C<u>H</u>), 4.13 (1H, d, *J* = 4.6 Hz, O<u>H</u>), 4.16-4.01 (1H, m, 7-C<u>H</u>), 3.80-3.75 (1H, m, 32-C<u>H</u>$_A$H$_B$), 3.70-3.65 (2H, m, 32-CH$_A$<u>H</u>$_B$, C<u>H</u>O), 3.63-3.58 (1H, m, C<u>H</u>O), 3.52-3.48 (1H, m, 19-C<u>H</u>), 3.48 (3H, s, O<u>Me</u>), 3.40-3.35 (1H, m, 17-C<u>H</u>), 3.36 (3H, s, O<u>Me</u>), 3.25 (3H, s, O<u>Me</u>), 3.20 (3H, s, O<u>Me</u>), 3.21-3.17 (1H, m, C<u>H</u>O), 3.07-3.03 (1H, m, C<u>H</u>O), 2.97 (1H, dd, *J* = 8.2, 2.7 Hz, 23-C<u>H</u>), 2.47-2.44 (2H, m, 6-C<u>H</u>$_2$), 2.00-1.92 (3H, m, 26-C<u>H</u>$_A$H$_B$, 14-C<u>H</u>$_A$H$_B$, C<u>H</u>), 1.90-1.70 (7H, m, 12-C<u>H</u>$_2$, 24-C<u>H</u>, 26-CH$_A$<u>H</u>$_B$, 31-C<u>H</u>$_A$H$_B$, 18-C<u>H</u>$_2$), 1.70-1.60 (4H, m, 14-CH$_A$<u>H</u>$_B$, 8-C<u>H</u>$_A$H$_B$, 2xC<u>H</u>), 1.79 (3H, s, 4-C<u>Me</u>), 1.55-1.50 (2H, m, 16-C<u>H</u>, C<u>H</u>), 1.35-1.22 (4H, m, 31-CH$_A$<u>H</u>$_B$, 8-CH$_A$C<u>H</u>$_B$, 2xC<u>H</u>), 1.06 (18H, s, (<u>Me</u>$_2$CH)$_3$Si), 1.10-1.04 (3H, m, (Me$_2$C<u>H</u>)$_3$Si), 1.04 (3H, d, *J* = 6.8 Hz, CH<u>Me</u>), 1.02 (3H, d, *J* = 6.7 Hz, CH<u>Me</u>), 0.89 (9H, s, SiMe$_2$<u>^{t}Bu</u>), 0.95-0.85 (6H, m, 2xCH<u>Me</u>), 0.83 (3H, d, *J* = 6.7 Hz, CH<u>Me</u>), 0.82 (3H, d, *J* = 7.0 Hz, CH<u>Me</u>), 0.11 (3H, s, <u>Me</u>Si), 0.10 (3H, s, <u>Me</u>Si); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 169.3, 150.6, 138.2, 134.4, 130.5, 124.1, 115.6, 92.9, 79.0, 77.2, 76.5, 76.4, 75.9, 73.9, 69.2, 69.1, 64.8, 61.5, 60.9, 58.8, 56.6, 53.8, 41.1, 40.9, 40.8, 40.2, 38.8, 38.0, 37.5, 33.9, 33.7, 32.8, 32.3, 31.8, 31.5, 26.9, 25.8, 23.1, 19.1, 18.0, 17.5, 14.4, 12.2, 11.9, 9.1, 8.9, 8.7, -4.4, -4.8; m/z (+ve FAB, NOBA) 1062 (40, $[M+Na]^+$), 1040 (80, $[M+H]^+$), 510 (50), 497 (50), 428 (60), 399 (60), 269 (100); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 1061.7545, $C_{58}H_{110}O_{11}Si_2Na$ requires 1061.7484.

C_{23} macrocycle **18**: R_f 0.30 (30% EtOAc/hexane); t_R 16 min (40% EtOAc/hexane); $[\alpha]_D^{20}$ −3.0 (*c* 0.44, $CHCl_3$); IR (liquid film) 3503, 2925, 1709, 1462, 1378, 1248, 1086, 978 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.08 (1H, d, *J* = 15.8 Hz, 3-C<u>H</u>), 5.85 (1H, d, *J* = 15.8 Hz, 2-C<u>H</u>), 5.81-5.78 (1H, m, 11-C<u>H</u>), 5.74 (1H, br t, *J* = 6.1 Hz, 5-C<u>H</u>), 5.67 (1H, dm, *J* = 10.2 Hz, 10-C<u>H</u>), 5.00 (1H, dd, *J* = 9.8, 1.9 Hz, 23-C<u>H</u>), 4.47 (1H, d, *J* = 10.2 Hz, 9-C<u>H</u>), 4.08-4.04 (1H, m, 7-C<u>H</u>), 3.96 (1H, d, *J* = 9.0 Hz, O<u>H</u>), 3.88 (1H, d, *J* = 9.4 Hz, O<u>H</u>), 3.80-3.75 (1H, m, 32-C<u>H</u>$_A$H$_B$), 3.70-3.60 (3H, m, 32-CH$_A$<u>H</u>$_B$, 2xC<u>H</u>O), 3.48-3.42 (1H, m, 19-C<u>H</u>), 3.49 (3H, s, O<u>Me</u>), 3.40 (3H, s, O<u>Me</u>), 3.40-3.32 (1H, m, 17-C<u>H</u>), 3.32 (3H, O<u>Me</u>), 3.25-3.23 (1H, m, C<u>H</u>O), 3.22 (3H, s, O<u>Me</u>), 3.05-3.01 (1H, m, C<u>H</u>O), 2.97 (1H, dd, *J* = 8.3, 2.6 Hz, C<u>H</u>O), 2.54 (1H, dm, *J* = 12.3 Hz, 6-C<u>H</u>$_A$H$_B$), 2.32-2.26 (1H, m, 6-CH$_A$<u>H</u>$_B$), 2.17-2.10 (1H, m, C<u>H</u>), 2.00-1.90 (2H, m, 18-C<u>H</u>$_A$H$_B$, C<u>H</u>), 1.90-1.70 (7H, m, 31-C<u>H</u>$_A$H$_B$, 12-C<u>H</u>$_2$, 8-C<u>H</u>$_A$H$_B$, 18-CH$_A$<u>H</u>$_B$, 2xC<u>H</u>), 1.70-1.60 (4H, m, 4xC<u>H</u>), 1.77 (3H, s, 4-C<u>Me</u>), 1.55-1.45 (2H, m, 8-CH$_A$<u>H</u>$_B$, C<u>H</u>), 1.35-1.20 (4H, m, 4xC<u>H</u>), 1.05 (18H, s, (<u>Me</u>$_2$CH)$_3$Si), 1.10-1.04 (3H, m, (Me$_2$C<u>H</u>)$_3$Si), 1.03 (3H, d, *J* = 7.2 Hz, CH<u>Me</u>), 1.06-1.03 (3H, hidden d, CH<u>Me</u>), 0.89 (9H, s, SiMe$_2$<u>^{t}Bu</u>), 0.93 (3H, d, *J* = 6.8 Hz, CH<u>Me</u>), 0.92-0.90 (3H, hidden d, CH<u>Me</u>), 0.82 (3H, d, *J* = 7.1 Hz, CH<u>Me</u>), 0.80 (3H, d, *J* = 7.2 Hz, CH<u>Me</u>), 0.15 (3H, s, <u>Me</u>Si), 0.14 (3H, s, <u>Me</u>Si); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 167.5, 146.1, 135.3, 133.9, 130.8, 123.9, 118.0, 93.3, 86.5, 80.1, 79.0, 75.7, 74.3, 70.5, 69.4, 67.8, 64.0, 61.4, 61.1, 57.4, 56.9, 55.8, 42.1, 41.4, 40.7, 39.8, 35.9 (2C), 35.2, 35.0, 33.9, 32.3, 31.9, 31.7, 29.7, 26.0, 25.4, 21.1, 18.0, 17.6, 17.2, 14.6, 14.0, 12.7, 12.0, 9.8, 8.9, -4.4, -4.7; m/z (+ve FAB, NOBA) 1062 (80, $[M+Na]^+$), 1039 (40, $[M+H]^+$), 269 (100); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found: 1061.7463, $C_{58}H_{110}O_{11}Si_2Na$ requires 1061.7484.

Isomerisation of **18** to **16** To a solution of the C_{23} macrocycle **18** (10.9 mg, 0.0105 mmol) in CH_2Cl_2 (1 ml) was added $Ti(O^iPr)_4$ (1.0 ml, 1.0 M solution in CH_2Cl_2, 1.0 mmol)). The reaction mixture was stirred at room

temperature for 72 h then poured into HCl (5 ml, 1 M). The layers were separated and the organic layer was washed with $NaHCO_3$ (5 ml, sat. aq.). The aqueous layers were back extracted with EtOAc (3 x 5 ml) and the combined organic extracts dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (30% EtOAc/hexane) gave a mixture containing **16** and **18** in a 2.3 : 1 ratio (46 mg, 91%) which was submitted to HPLC purification as described above.

Reoxidised Macrocycle (6) To a solution of the alcohol **16** (18.4 mg, 0.0177 mmol) in CH_2Cl_2 (4 ml) was added a spatula load of dried 4 Å powdered molecular sieves, followed by NMO (0.249 ml, 0.5 M solution in CH_2Cl_2, 0.125 mmol) and TPAP (0.52 ml, 0.1 M solution in CH_2Cl_2, 5.2 mmol). The reaction mixture was stirred at room temperature for 2 h then loaded directly onto a flash chromatography column (eluting with 10 → 30% EtOAc/hexane), which gave **6** as a colourless oil (14.7 mg, 80%); R_f 0.55 (30% EtOAc/hexane); $[\alpha]_D^{20}$ –4.7 (*c* 0.45, $CHCl_3$); IR (liquid film) 2923, 1693, 1691, 1461, 1376, 1264, 1092 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.52 (1H, d, *J* = 15.3 Hz, 3-C<u>H</u>), 5.96 (1H, t, *J* = 7.6 Hz, 5-C<u>H</u>), 5.81-5.77 (1H, m, 11-C<u>H</u>), 5.76 (1H, d, *J* = 15.3 Hz, 2-C<u>H</u>), 5.63 (1H, dm, *J* = 10.0 Hz, 10-C<u>H</u>), 5.16 (1H, d, *J* = 9.9 Hz, 21-C<u>H</u>), 4.43 (1H, br d, *J* = 10.0 Hz, 9-C<u>H</u>), 4.19 (1H, d, *J* = 4.6 Hz, 23-O<u>H</u>), 4.04-4.02 (1H, m, 7-C<u>H</u>), 3.79-3.76 (1H, m, 32-C<u>H</u>$_A$H$_B$), 3.68 (1H, td, *J* = 9.0, 5.6 Hz, 32-CH$_A$<u>H</u>$_B$), 3.62 (1H, d, *J* = 8.6 Hz, C<u>H</u>O), 3.53 (1H, br t, *J* = 5.6 Hz, C<u>H</u>O), 3.54-3.45 (1H, m, C<u>H</u>O), 3.40-3.33 (1H, m, C<u>H</u>O), 3.37 (3H, s, O<u>Me</u>), 3.30 (3H, s, O<u>Me</u>), 3.33-3.28 (1H, m, 29-C<u>H</u>), 3.25 (3H, s, O<u>Me</u>), 3.21 (3H, s, O<u>Me</u>), 3.06-3.02 (1H, m, 23-C<u>H</u>), 2.85-2.82 (1H, m, 28-C<u>H</u>), 2.63 (1H, ddd, *J* = 17.9, 8.5, 5.1 Hz, 26-C<u>H</u>$_A$H$_B$), 2.51-2.43 (3H, m, 26-CH$_A$<u>H</u>$_B$, 6-C<u>H</u>$_2$), 2.20-1.85 (4H, m, 20-C<u>H</u>, 22-C<u>H</u>, 24-C<u>H</u>, C<u>H</u>), 1.79 (3H, s, 4-C<u>Me</u>), 1.85-1.65 (7H, m, 12-C<u>H</u>$_2$, 25-C<u>H</u>$_A$H$_B$, 31-C<u>H</u>$_A$H$_B$, 8-C<u>H</u>$_A$H$_B$, 2xC<u>H</u>), 1.50-1.20 (6H, m, 25-CH$_A$<u>H</u>$_B$, 31-CH$_A$<u>H</u>$_B$, 8-CH$_A$<u>H</u>$_B$, 3xC<u>H</u>), 1.06 (18H, s, (<u>Me</u>$_2$CH)$_3$Si), 1.10-1.04 (3H, m, (Me$_2$C<u>H</u>)$_3$Si), 1.01 (6H, br d, *J* = 7.0 Hz, 2xCH<u>Me</u>), 0.95 (3H, d, *J* = 7.0 Hz, CH<u>Me</u>), 0.89 (12H, s + hidden d, SiMe$_2$<u>^{t}Bu</u> + CH<u>Me</u>), 0.84 (3H, d, *J* = 6.8 Hz, CH<u>Me</u>), 0.83 (3H, d, *J* = 7.0 Hz, CH<u>Me</u>), 0.12 (3H, s, <u>Me</u>Si), 0.11 (3H, s, <u>Me</u>Si); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 214.9, 169.3, 150.7, 138.3, 134.4, 130.5, 124.0, 115.5, 88.4, 79.0, 77.2, 76.5, 76.4, 75.7, 69.5, 69.1, 64.8, 61.3, 60.8, 58.8, 56.7, 53.8, 48.4, 41.7, 41.1, 40.8, 40.2, 38.8, 38.0, 37.5, 33.3, 33.0, 32.9, 31.8, 30.9, 29.7, 25.8, 21.8, 18.0, 17.8, 17.1, 13.6, 12.2, 12.0, 9.0, 8.8, 8.7, -4.4, -4.8; m/z (+ve FAB, NOBA) 1059 (30, $[M+Na]^+$), 1020 (90), 419 (60), 307 (90), 269 (100); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 1059.7321, $C_{58}H_{108}O_{11}Si_2Na$ requires 1059.7328.

Deprotected Macrocycle (7) To a solution of macrocycle **6** (38.6 mg, 0.0134 mmol) in THF (2 ml) was added HF•py solution (4.0 ml of a stock solution of 2.1 g pyridinium hydrofluoride in 5.7 ml pyridine + 10 ml THF). The reaction mixture was stirred at room temperature for 24 h before a further aliquot of HF•py (3 ml) was added. After stirring at room temperature for 24 h, the reaction mixture was cooled to 0 °C, quenched with $NaHCO_3$ (10 ml, sat. aq.) and extracted with EtOAc (10 ml). The layers were separated and the aqueous layer was extracted with EtOAc (4 x 20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Preparative TLC (EtOAc) gave **7** as a colourless oil (18.2 mg, 64%), as well as a mixture of monodeprotected products (12.2 mg, ~36%); R_f 0.24 (EtOAc); $[\alpha]_D^{20}$ –23.0 (*c* 0.29, $CHCl_3$); IR (liquid film) 3444, 2934, 1680, 1458, 1376 1266, 1087 cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.53 (1H, d, *J* = 15.8 Hz, 3-C<u>H</u>), 5.95 (1H, t, *J* = 9.1 Hz, 5-C<u>H</u>), 5.84-5.81 (1H, m, 11-C<u>H</u>), 5.77 (1H, d, *J* = 15.8 Hz, 2-C<u>H</u>), 5.65 (1H, dm, *J* = 10.1 Hz, 10-C<u>H</u>), 5.18 (1H, d, *J* = 10.2 Hz, 21-C<u>H</u>), 4.55 (1H, dm, *J* = 10.1 Hz, 9-C<u>H</u>), 4.14 (1H, d, *J* = 4.7 Hz, 23-O<u>H</u>), 4.10-4.05 (1H, m, 7-C<u>H</u>), 3.77-3.72 (1H, m, 32-C<u>H</u>$_A$H$_B$), 3.60 (1H, dm, *J* = 8.4 Hz, 15-C<u>H</u>), 3.60-3.56 (1H, m, 32-CH$_A$<u>H</u>$_B$), 3.46-3.42 (1H, m, 19-C<u>H</u>), 3.36-3.32 (2H, hidden m, 17-C<u>H</u>, 29-C<u>H</u>), 3.36 (3H, s, O<u>Me</u>), 3.35 (3H, s, O<u>Me</u>), 3.22-3.19 (1H, hidden m, 13-C<u>H</u>), 3.22 (6H, s, 2xO<u>Me</u>), 3.05-3.01 (1H, m, 23-C<u>H</u>), 2.96-2.90 (1H, m, 28-C<u>H</u>), 2.63-2.60 (1H, m, 26-C<u>H</u>$_A$H$_B$), 2.58-2.45 (3H, m, 26-CH$_A$<u>H</u>$_B$, 6-C<u>H</u>$_2$), 2.05-1.85 (5H, m, 22-C<u>H</u>, 20-C<u>H</u>, 30-C<u>H</u>, 12-C<u>H</u>$_2$), 1.79 (3H, s, 4-C<u>Me</u>), 1.80-1.73 (4H, m, 25-C<u>H</u>$_A$H$_B$, 18C<u>H</u>$_2$, 8-C<u>H</u>$_A$H$_B$), 1.70-1.60 (6H, m, 16-C<u>H</u>, 31-C<u>H</u>$_2$, 24-C<u>H</u>, 14-C<u>H</u>$_2$),

1.40-1.45 (1H, m, 25-CH_AH_B), 1.25-1.30 (1H, m, 8-CH_AH_B), 1.04 (3H, d, J = 7.0 Hz, 30-CHMe), 1.01 (3H, d, J = 6.8 Hz, 24-CHMe), 0.95 (3H, d, J = 7.0 Hz, 28-CHMe), 0.92 (3H, d, J = 7.0 Hz, 20-CHMe), 0.83 (3H, d, J = 6.8 Hz, 16-CHMe), 0.82 (3H, d, J = 6.9 Hz, 22-CHMe); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 214.5, 169.3, 150.4, 137.5, 134.7, 130.1, 124.5, 115.7, 87.7, 78.7, 76.7, 76.5, 75.8, 70.0, 66.7, 65.8, 65.4, 61.1, 59.3, 58.6, 56.8, 53.4, 48.4, 41.7, 40.5, 40.3, 38.5, 37.8, 37.4, 33.0 (2C), 32.5, 32.0, 31.8, 21.8, 17.8, 16.8, 15.3, 13.6, 12.2, 9.0, 8.9, 8.6; m/z (+ve FAB, NOBA) 789 (10, $[M+Na]^+$), 750 (80), 718 (30), 391 (60), 307 (100); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 789.5132, $C_{43}H_{74}O_{11}Na$ requires 789.5129.

C_{32} Aldehyde (8) To a cooled (0 °C) solution of **7** (15.5 mg, 20.3 μmol) was added a spatula load of dried 4 Å powdered molecular sieves followed by NMO (1.4 ml, 0.1 M solution in CH_2Cl_2, 102 μmol) and TPAP (81 μl, 0.05 M solution in CH_2Cl_2, 4.1 μmol). The green solution was stirred at this temperature for 30 min then loaded directly onto a flash chromatography column which was eluted with EtOAc. Preparative TLC (EtOAc) gave **8** (10.1 mg, 65%) as a colourless oil; R_f 0.70 (EtOAc); $[\alpha]_D^{20}$ −13.6 (*c* 0.22, $CHCl_3$); IR (liquid film) 3418, 2973, 1679, 1650, 1266, 1087 cm^{-1}; ^{1}H NMR δ ($CDCl_3$, 500 MHz) 9.75 (1H, br s, CHO), 7.54 (1H, d, J = 15.8 Hz, 3-CH), 5.97-5.92 (1H, m, 5-CH), 5.84-5.81 (1H, m, 11-CH), 5.77 (1H, d, J = 15.8 Hz, 2-CH), 5.66 (1H, dm, J = 10.2 Hz, 10-CH), 5.18 (1H, d, J = 9.9 Hz, 21-CH), 4.55 (1H, dm, J = 10.2 Hz, 9-CH), 4.16 (1H, d, J = 4.4 Hz, 23-OH), 4.10-4.07 (1H, m, 7-CH), 3.61 (1H, d, J = 8.4 Hz, 15-CH), 3.48-3.45 (1H, m, 19-CH), 3.36 (3H, s, OMe), 3.30 (3H, s, OMe), 3.35-3.20 (3H, hidden m, 29-CH, 17-CH, 13-CH), 3.22 (3H, s, OMe), 3.21 (3H, s, OMe), 3.05-3.02 (1H, m, 23-CH), 2.76-2.70 (1H, m, 28-CH), 2.63 (1H, ddd, J = 17.6, 8.3, 5.2 Hz, 26-CH_ACH_B), 2.60-2.50 (2H, m, 6-CH_2), 2.52-2.45 (2H, m, 26-CH_ACH_B, 31-CH_ACH_B), 2.30-2.26 (2H, m, 31-CH_ACH_B, 30-CH), 2.05-1.85 (4H, m, 22-CH, 20-CH, 12-CH_2), 1.80 (3H, s, 4-CMe), 1.80-1.60 (8H, m, 25-CH_ACH_B, 8-CH_ACH_B, 18-CH_2, 16-CH, 24-CH, 14-CH_2), 1.48-1.40 (1H, m, 25-CH_ACH_B), 1.27-1.22 (1H, m, 8-CH_ACH_B), 1.04 (6H, d, J = 7.1 Hz, 30-CHMe, 28-CHMe), 1.01 (3H, d, J = 6.4 Hz, 24-CHMe), 0.91 (3H, d, J = 7.0 Hz, 20-CHMe), 0.83 (3H, d, J = 6.7 Hz, 22-CHMe), 0.82 (3H, d, J = 6.9 Hz, 16-CHMe); ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 213.7, 201.9, 169.3, 150.5, 137.5, 134.7, 130.1, 124.5, 115.7, 87.4, 78.6, 76.7, 76.4, 75.7, 70.0, 68.7, 66.6, 60.6, 60.4, 58.6, 56.8, 48.7, 46.1, 41.1, 40.5, 40.3, 40.2, 38.5, 37.8, 37.4, 32.9, 32.4, 31.8, 30.9, 21.9, 18.2, 17.8, 14.2, 13.2, 12.2, 9.0, 8.8, 8.8; m/z (+ve FAB, NOBA) 788 (100, $[M + Na]^+$), 766 (10, $[M + H]^+$), 482 (10), 460 (20); HRMS (+ve FAB, NOBA) $[M+Na]^+$ found 787.5008, $C_{43}H_{72}O_{11}Na$ requires 787.4972.

Scytophycin C (1) To a solution of aldehyde **8** (5.0 mg, 6.5 mmol) in *N*-methylformamide (1 ml) was added P_2O_5 (~4 mg) and the resulting yellow solution was stirred at room temperature for 30 min. The reaction mixture was quenched with $NaHCO_3$ (5 ml, sat. aq.) and the aqueous layer extracted with EtOAc (4 x 10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was loaded onto a short column of reverse phase silica (Mitsubishi Kasei Corporation MCI GEL CHP20P (70-150μ)), eluting with 50% → 80% → 100% MeOH/H_2O. Further purification by reverse phase HPLC (80% MeOH/H_2O) gave **1** as a colourless oil (1.0 mg, 20%); R_f 0.43 (1:1:1 EtOAc:hexane:acetone); t_R 19 min (80% MeOH/H_2O); IR (liquid film) 3420, 1642, 1110 cm^{-1}; ^{1}H NMR δ (CD_3COCD_3), 500 MHz) see **Table 1**; ^{13}C NMR δ (CD_3COCD_3, 500 MHz, HMQC) see **Table 2**; m/z (+ve FAB, NOBA) 828 (10, $[M+Na]^+$), 805 (25, $[M+H]^+$), 788 (30, $[M - H_2O + H]^+$, 789 (100), 730 (90); HRMS (+ve FAB, NOBA) $[M]^+$ found 805.5389, $C_{45}H_{75}NO_{11}$ requires 805.5340.

Table 1: ^{1}H NMR Data in CD_3COCD_3 for scytophycin C (**1**)

Assignment	δ_H[a]	Mult	*J* Hz	δ_H[b] (Lit[5])	Mult[c]	*J* Hz
2	5.77	d	15.7	5.78	d	15.8
3	7.61	d	15.8	7.61	d	15.8
Me on 4	1.82	s		1.82	br s	
5	6.04	m		6.03	br d d	9.3, 4.3
6	2.47	m		2.46	m	
7	4.03	br t m		4.02	br t d	10.2, 3.1
8	1.26	m		1.28	d d d	14.7, 10.2, 1.8
8'	1.74	m		1.77	d d d	14.7, 9.8, 1.2
9	4.53	m		4.53	br d	9.8
10	5.68	br d	10.1	5.67	d d t	10.4, 2.9, 1.8
11	5.77	m		5.77	d t d	10.4, 4.0, 1.6
12	1.90	m		1.89	m	
13	3.34	m		3.34	m	
14	1.68	m		1.68	-	
14'	1.63	m		1.63	d d d	14.5, 8.4, 3.1
15	3.63	d m	8.0	3.62	dd	7.4, 3.1
MeO on15	3.30	s		3.30	s	
16	1.67	m		1.68	-	
Me on 16	0.80	d	7.0	0.80	d	-
17	3.26	d m	11.9	3.26	dd	11.4, 4.0
MeO on 17	3.24	s		3.23	s	
18	1.75	m		1.73	d d d	13.6, 9.7, 4.0
18'	1.85	m		1.83	d d d	13.6, 11.4, 4.0
19	3.48	m		3.47	d d d	9.7, 4.0, 1.0
MeO on 19	3.17	s		3.17	s	
20	2.00	m		2.04	m	
Me on 20	0.91	d	6.8	0.89	d	7.0
21	5.17	d	9.5	5.16	br d	10.3
22	2.00	m		2.00	m	
Me on 22	0.85	d	6.8	0.84	d	6.8
23	3.02	d m	9.7	3.00	dd	9.7, 2.0
24	1.68	m		1.67	m	
Me on 24	0.98	d	6.7	0.97	d	6.7
25	1.36	m		1.38	m	
25'	1.77	m		1.76	m	
26	2.53	m		2.55	m	
28	2.78	m		2.77	d q	9.5, 7.0
Me on 28	0.91	d	6.8	0.90	d	7.0
29	3.27	m		3.27	dd	9.5, 2.2
MeO on 29	3.29	s		3.29	s	
30	2.45	m		2.44	m	
Me on 30	1.14	d	7.0	1.13	d	7.0
31	5.11	dd	14.1, 9.2	5.12	dd	14.1, 9.2
31[d]	5.17	dd	14.9, 8.5	5.17	dd	14.8, 9.0
32	6.77	d	14.2	6.77	d	14.1
32[d]	7.10	d	14.6	7.09	d	14.8
Me on N	2.98	s		2.97	s	
Me on N[d]	3.09	s		3.09	s	
NCHO	8.35	s		8.34	s	
NCHO[d]	8.10	s		8.09	s	

[a]Measured at 500 MHz. Assignments were determined by COSY experiment. [b]Measured at 300 MHz. [c]Coupling constants given for scytophycin B. [d]Signals for minor conformer.

Table 2: ^{13}C NMR Data in CD_3COCD_3 for scytophycin C (**1**)

Assignment	δ_C[a]	δ_C[b] (Lit[5])
1	-	169.38
2	115.0	115.71
3	-	151.33
4	-	134.69
Me on 4	11.3	12.09
5	138.0	139.73
6	41.4	41.92
7	69.0	68.54
8	40.8	41.19
9	70.2	70.76
10	131.3	131.48
11	124.3	124.48
12	31.2	32.19
13	66.2	65.75
14	32.0	32.61
15	77.2	79.79
MeO on 15	55.8	56.46
16	39.5	40.93
Me on 16	8.0	9.25
17	-	76.32
MeO on 17	53.0	53.55
18	-	27.31
19	77.2	77.93
MeO on 19	57.5	58.03
20	40.0	40.29
Me on 20	8.6	9.05
21	76.0	76.56
22	39.0	38.45
Me on 22	8.2	8.79
23	77.0	77.18
24	33.2	33.69
Me on 24	17.3	18.13
25	-	22.55
26	40.0	39.17
27	-	213.84
28	49.0	49.33
Me on 28	12.7	13.47
29	87.4	88.11
MeO on 29	60.8	60.96
30	-	38.03
30[c]	38.3	38.18
Me on 30	18.7	19.45
31	111.2	110.97
31[c]	113.0	113.05
32	129.8	129.98
32[c]	124.9	125.46
Me on N	26.5	27.03
Me on N[c]	32.0	32.85
CHO	-	162.71
CHO[c]	-	161.62

[a]Values obtained by HMQC experiment. [b]Measured at 300 MHz. [c]Signals for minor conformer.

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