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The Total Synthesis of Swinholide A. Part 4: Synthesis of Swinholide A and Isoswinholide A from the Protected Monomeric Seco Acid, Pre-Swinholide A.

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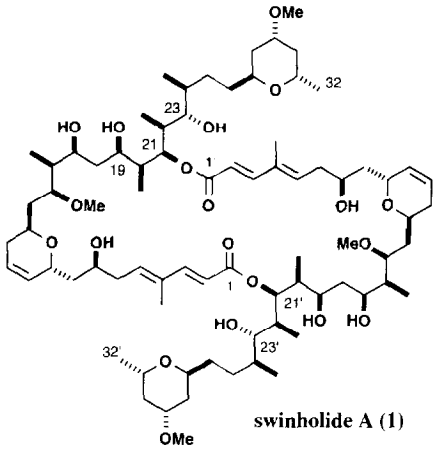
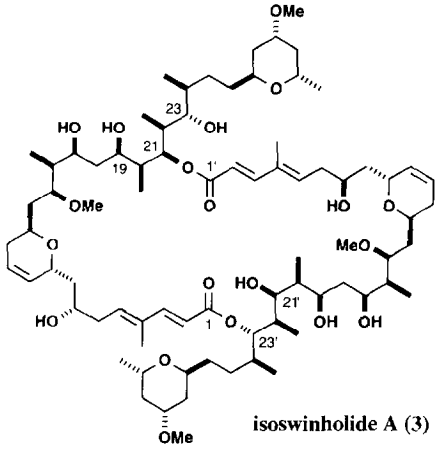
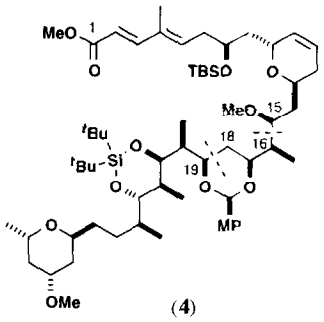
Abstract: Swinholide A and isoswinholide A were synthesised in 7 steps from the fully protected seco acid **4**. Key steps include: (*i*) bimolecular acylation, **7** + **10** → **12**, (*ii*) selective hydrolysis of the methyl ester, **16** → **17**, and (*iii*) regioselective macrolactonisation, **17** → **18**. The monomeric lactone analogues **2** and **5** were prepared by regioselective macrolactonisation of the seco acid **6**, where the ring size was controlled by variation of the reaction conditions.



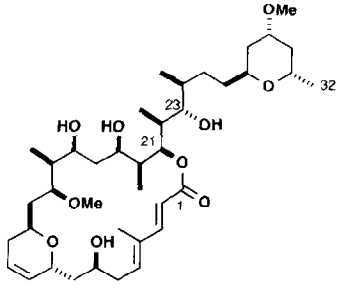
swinholide A (1)



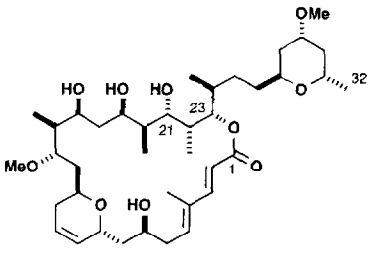
isoswinholide A (3)



(4)



hemiswinholide A (2)



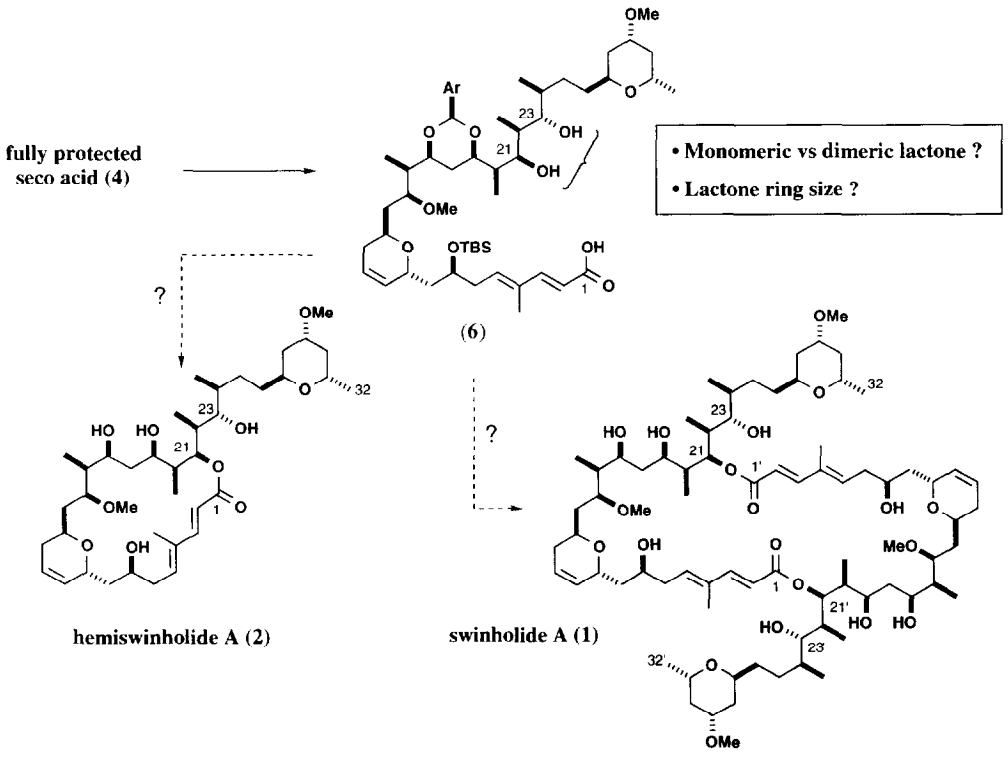
isohemiswinholide A (5)

Swinholide A (**1**) is a potent cytotoxic sponge metabolite, which was first isolated from *Theonella swinhoei* by Carmely and Kashman in 1985.[1a] The gross structure was originally misassigned as the monomeric macrolide **2**, the correct structure being later elucidated by Kitagawa *et al.*[1b-e] as the highly oxygenated macrodiolide **1**.

This symmetrical dimer ($C_{78}H_{132}O_{20}$ = 1388.93) is constructed in two halves from a complex polyketide seco acid, leading to an unusually large, 44-membered ring. From the structure-activity studies already carried out by the Kitagawa group,[1c-e,2] the symmetrical 44-membered ring appears to be essential for swinholide's cytotoxic potency, with isoswinholide A (**3**)[1f] and derivatives of the monomeric seco acid (pre-swinholide A[3]) showing significantly reduced activity. To date, there have been no studies reported on the mechanism of action, although there has been some speculation that their biological effect may involve some aspects of ionophoric activity.[4] Alternatively, the swinholides may possibly act as bifunctional alkylating agents through their two dienoate functions, which are able to crosslink the DNA of the cancerous cell.

In the preceding three papers,[5] we have outlined our synthetic approach to swinholide A and described an efficient route to **4**, a fully protected version of the monomeric seco acid pre-swinholide A. In this final paper of the series, we provide full details[6] of the completion of the first total synthesis of swinholide A, using an expedient macrolactonisation to generate the key 44-membered ring. In addition, we have prepared the unsymmetrical, ring-expanded isomer, isoswinholide A (**3**), and the monomeric 22- and 24-membered lactone analogues **2** and **5**, which we have named hemiswinholide A and isohemiswinholide A, respectively.

Strategy for Generating the Swinholide Macrocycle



Scheme 1

Our strategy for generating the symmetrical, 44-membered, ring system of swinholide A required a suitable endgame for the selective deprotection and controlled dimerisation of **4**. As already described,[5] this fully protected version of the monomeric seco acid, pre-swinholide A, was prepared by an aldol-mediated fragment coupling to construct the C_{15}–C_{16} bond or, more efficiently, the C_{18}–C_{19} bond. Earlier in the synthesis,[5a] we chose to simplify the synthetic route by installing a cyclic silicon protecting group for the C_{21} and C_{23} hydroxyls and forego the opportunity for selective protection, intending to differentiate these hydroxyls (which are in similar steric environments) later, on dimerisation and macrolactonisation. By adopting this bold strategy, we would be able to explore the ring-size preference in macrocyclisation, which might also enable access to isomeric swinholide analogues.

Synthesis of Hemiswinholide A and Isohemiswinholide A

As shown in **Scheme 1**, the formation of swinholide A from the monomeric unit **4** requires some means for the controlled introduction of the two lactone linkages at C_{21} and $C_{21'}$. We initially chose to investigate macrocyclisations of seco acid derivative **6**, Ar = *p*-MeO(C_6H_4), to give monomeric lactone analogues (with the potential for dimer formation). This would provide valuable information regarding the conditions required for generating the unusually large, 44-membered ring in swinholide A. Moreover, as we had elected earlier to protect the C_{21},C_{23} diol system using a cyclic di-*tert*-butylsilylene group, suitable conditions for selective acylation at the hydroxyl groups at C_{21} / $C_{21'}$ in preference to those at C_{23} / $C_{23'}$ needed to be found.

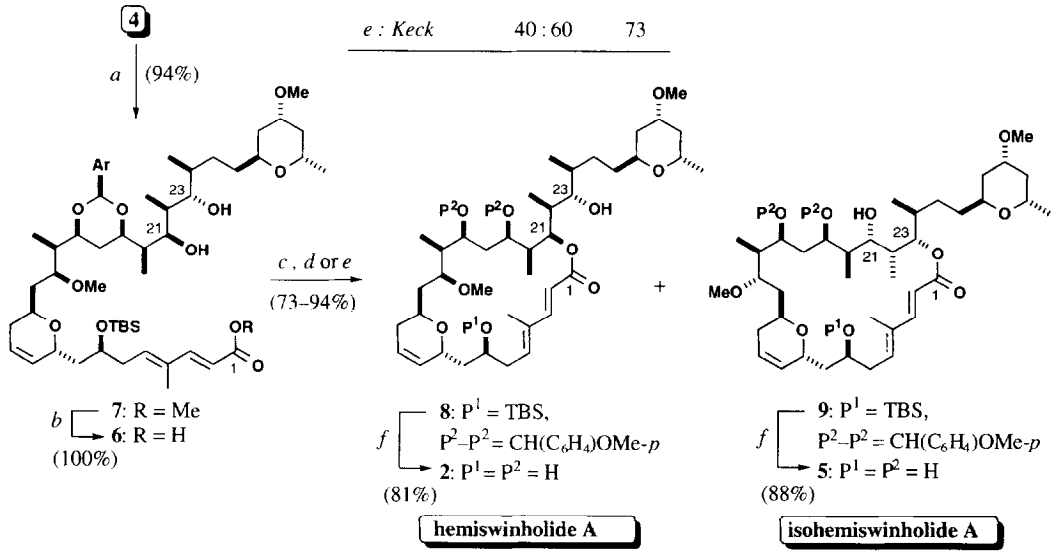
The silylene protecting group was first removed from **3** under standard conditions (HF•pyridine, pyridine, THF)[7] to give a 94% yield of diol **7** (**Scheme 2**). Methyl ester hydrolysis (NaOH, aq. THF) in **7** was rather slow at room temperature, but heating the reaction mixture to reflux (2 h) provided the desired seco acid **6** in quantitative yield. The macrolactonisation regioselectivity in **6** to give the monomeric lactones **8** and **9** was now explored. A remarkable dependence of acylation regioselectivity on reaction conditions was uncovered.

Initially, we opted to use the Yamaguchi macrolactonisation protocol[8,9] which had previously been used to good effect in our laboratory.[10] After formation of the mixed anhydride from **6** under standard conditions (2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe), slow addition to a hot solution of DMAP in toluene gave the two macrolides **8** and **9** in a combined yield of 92% following work up. The desired C_{21} acylated compound **8**, having a 22-membered ring, was the major product (**8** : **9** = 82 : 18) and could be obtained in 76% yield after HPLC separation.[11] No formation of larger rings (dimers, trimers, *etc.*) was observed under these conditions, as judged by HPLC analysis and FAB mass spectrometry of the crude reaction products. The efficient macrolactonisation suggests that **6** can readily access the required conformation for cyclisation to give the monomeric ring. This is attributed to the *trans*-substituted dihydropyran acting as a conformational anchor for the two sidechains bringing them close together in space.[5b] The conformational restriction imposed by the cyclic acetal protecting group attached to C_{17} and C_{19} may also be a contributory factor.

Unexpectedly, changing to Keck's conditions[12] (slow addition to DCC, DMAP, DMAP•HCl, $CHCl_3$) for macrolactonisation of **6** completely reversed the acylation regioselectivity. The C_{23} acylated product **9**, having a 24-membered ring, was now isolated in 89% yield along with only traces of the C_{21} acylated material **8** (5%). In this way, we could control the macrolactonisation regioselectivity to give either **8** or **9** as the major product. When the Keck protocol was carried out in toluene (the same solvent as in the Yamaguchi cyclisation), a 40 : 60

mixture of **8** and **9** was obtained (73% combined yield). Hence, the macrolactonisation selectivity is sensitive to reaction conditions including solvent polarity, which presumably contributes to altering the conformational preferences of the activated seco acid. This effect appears to be kinetic in origin and further studies are needed to understand its precise origins.

macrolactonisation conditions	**8** : **9**	yield (%)
c : *Yamaguchi*	82 : 18	92
d : *Keck*	5 : 95	94
e : *Keck*	40 : 60	73

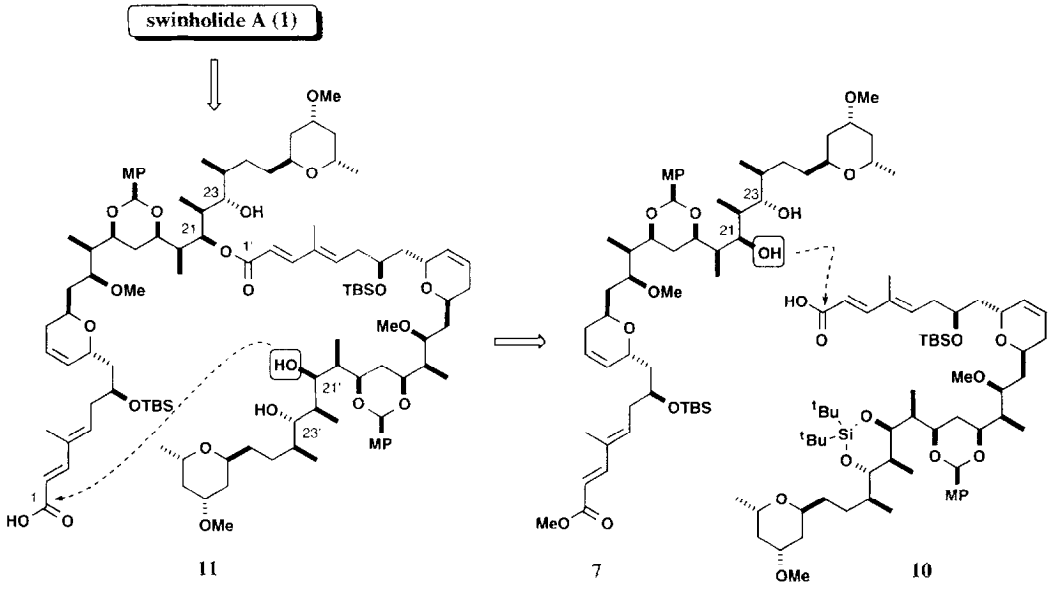


Scheme 2: (a) HF•py, py, THF, 20 °C, 20 min; (b) NaOH, MeOH, H_2O, 60 °C, 2 h; (c) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe, 20 °C, 2 h; add to DMAP, PhMe, 60 °C, 3 h; (d) add **6** over 16 h to DCC, DMAP, DMAP•HCl, $CHCl_3$, 60 °C; (e) add **6** over 16 h to DCC, DMAP, DMAP•HCl, PhMe, 60 °C; (f) HF, MeCN, 0 °C, 1 h.

Full deprotection of the separated macrolides **8** and **9** occurred using HF in acetonitrile (0 °C, 1 h) to give the C_{21} and C_{23} linked monomers **2** (81%) and **5** (89%), respectively. Notably, no lactone migration (C_{21} OH → C_{23} OH or *vice versa*) was observed, despite the known propensity of swinholide A to give acyl migration under acidic conditions.[1f,2] This is likely to be due to the relatively short reaction times employed. Recently, these same monomeric lactones have also been prepared by Kitagawa *et al.*[2] by non-selective macrolactonisation of pre-swinholide A (*i.e.*, using the unprotected seco acid), which was itself obtained by degradation of swinholide A. Hemiswinholide A (**2**), $[\alpha]_D^{20} = -43.1°$ (*c* 1.95, $CHCl_3$), which corresponds to the erroneous monomeric structure originally proposed by Carmely and Kashman,[1a] showed subtle differences in its ^1H and ^{13}C NMR spectra relative to that of the symmetrical dimer **1** (see **Tables 1** and **2** in the experimental section). As expected, its ring-expanded isomer isohemiswinholide A (**5**), $[\alpha]_D^{20} = -53.9°$ (*c* 1.4, $CHCl_3$), showed much more distinct differences in its ^1H and ^{13}C NMR spectra relative to swinholide A. Notably, the chemical shift of protons attached to C_{21} or C_{23} ($CDCl_3$) proved diagnostic for the site of acylation/ring size.[11]

Swinholide A Synthesis by Regioselective Dimerisation-Macrolactonisation

We now turned our attention to completing the synthesis of swinholide A itself. As outlined in the analysis in **Scheme 3**, we required conditions to effect *inter*molecular esterification between the two, differentially protected, monomeric units **7** and **10**, followed by regioselective macrolactonisation of a suitable dimeric seco acid **11** to close the 44-membered ring.

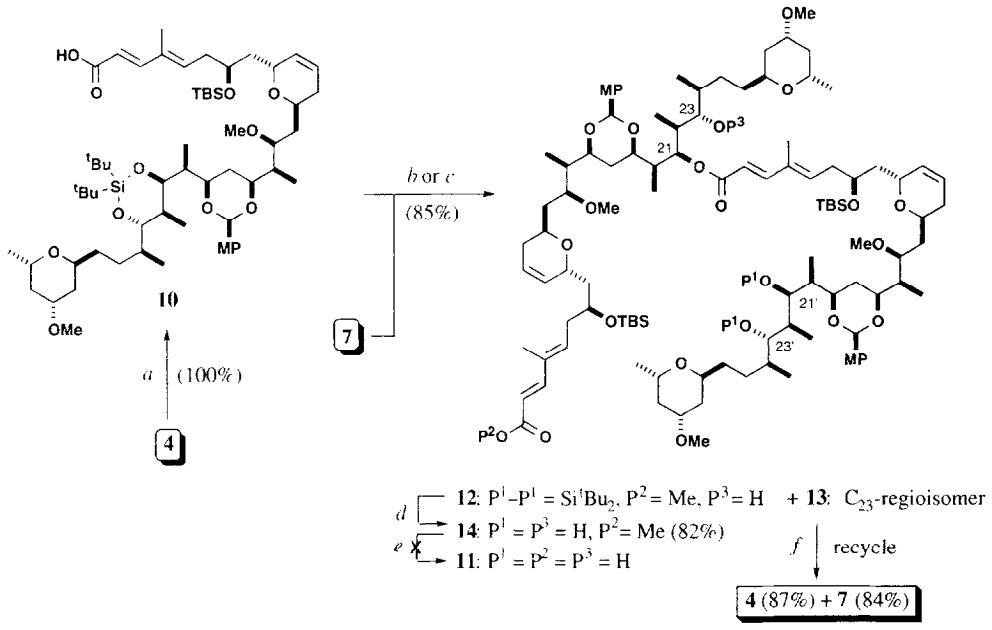


Scheme 3

With the diol **7** already in hand, the monomeric seco acid was next prepared by basic hydrolysis of **4**, giving **10** in essentially quantitative yield (**Scheme 4**). We initially investigated the bimolecular acylation of diol **7** by **10** under the Yamaguchi conditions used earlier to macrolactonise the monomeric seco acid **6**, which had favoured acylation at the C_{21} over the C_{23} hydroxyl. Thus activation of the carboxylic acid **10** by formation of a mixed anhydride with 2,4,6-trichlorobenzoyl chloride in PhMe, followed by addition of diol **7** (1.5 equiv.) and DMAP, gave a 64 : 36 mixture of the C_{21} and C_{23} coupled dimers[11] **12** and **13** in 85% combined yield, along with recovered unreacted diol. When this esterification was carried out using DCC in $CHCl_3$, the regioselectivity was reversed (**12** : **13** = *ca.* 33 : 67) and the yield was reduced (40%). The unwanted, C_{23}-acylated regioisomer **13** could be recycled by methanolysis using K_2CO_3 in MeOH to give back diol **7** (84%) and the fully protected methyl ester **4** (87%). Using the standard conditions, removal of the silylene protecting group from the correct regioisomer **12** proceeded uneventfully to give the $C_{21'}$,$C_{23'}$ diol **14** (82%).

Selective cleavage of the methyl ester in **14** to give the seco acid **11** was now required. Unfortunately, we were unable to achieve this apparently simple transformation under any conditions attempted. Basic conditions (*e.g.*, NaOH, LiOH, LiOOH, $Ba(OH)_2$) led primarily[13] to hydrolysis of the internal ester linkage between the two seco acid units in preference to attack at the terminal methyl ester. This produced mixtures, which contained substantial amounts of the monomeric seco acid **6**. This outcome is consistent with the methanolysis results for

13 and is attributed to a directing effect from the neighbouring free C_{23} hydroxyl group, which accelerates the rate of cleavage at the internal C_{21} ester linkage relative to that of the less hindered, terminal, methyl ester. We also investigated the use of nucleophilic ester cleavage methods (*e.g.*, LiI, pyridine;[14a] LiI, NaCN, DMF;[14b] NaHTe, DMF,[14c] NaSEt, DMF[14d]), but these tended to give complex mixtures due to deleterious side reactions with little, if any, of the desired acid **11** being formed.

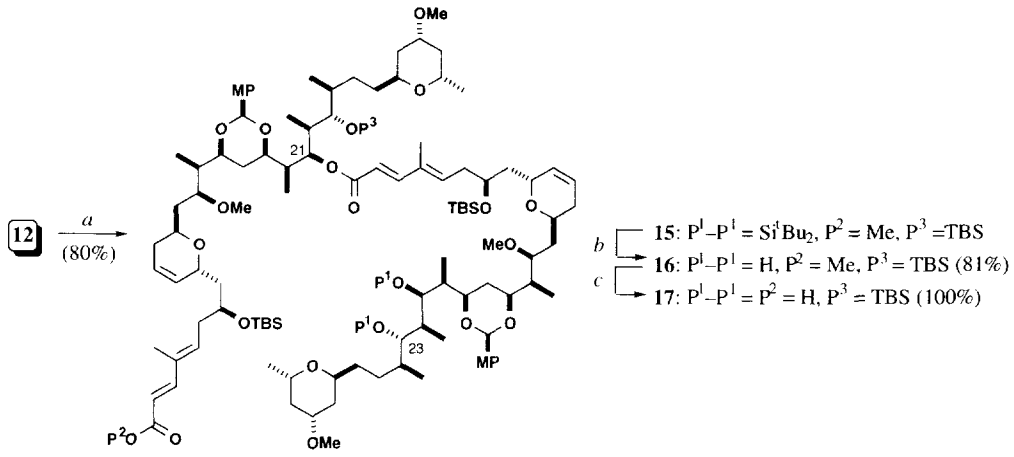


Scheme 4: (a) NaOH, MeOH, H_2O, 60 °C, 2 h; (b) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe, 20 °C, 1 h; **7**, DMAP, PhMe, 25 °C, 18 h; (c) DCC, DMAP, DMAP•HCl, $CHCl_3$, 25 °C, 18 h; (d) HF•pyridine, pyridine, THF, 20 °C, 20 min; (e) see text for conditions tried; (f) K_2CO_3, MeOH, 20 °C, 72 h.

As our initial approach had apparently been thwarted by the presence of the free hydroxyl at C_{23}, this was protected as its TBS ether prior to removal of the silylene group and cleavage of the methyl ester (**Scheme 5**). Although this hydroxyl was quite hindered, prolonged reaction (80 °C, 36 h) of **12** with a large excess of TBSCl (Et_3N, DMAP, DMF) was effective and gave an 80% yield of the C_{23} TBS ether **15**.[15] As before, removal of the silylene proceeded uneventfully to give the $C_{21'}$,$C_{23'}$ diol **16** in 81% yield. We were delighted to find that hydrolysis of the methyl ester occurred smoothly using $Ba(OH)_2$ to give the dimeric seco acid **17** in essentially quantitative yield, now without any interfering chain cleavage.

The stage was now set for the unprecedented macrolactonisation to give the 44-membered ring of swinholide A (**Scheme 6**). The high degree of functionality and substitution in seco acid **17**, combined with the very large ring size and use of the $C_{21'}$,$C_{23'}$ diol, contributed to serious concern over the feasibility of achieving an efficient macrolactonisation to give the desired 44-membered ring. Nevertheless, submitting **17** to the optimum Yamaguchi conditions established earlier for **6**, gave a gratifying 84% yield of macrodiolides, as an 83 : 17 mixture in favour of the desired **18** (acylation at the $C_{21'}$ hydroxyl) over the larger ring in **19** (acylation at the $C_{23'}$ hydroxyl).[11] Remarkably, facile cyclisation occurred even at ambient temperature, without the need for

high dilution techniques, leading after 17 h to a 60% yield of macrodiolides in a similar ratio. These highly favourable results indicate that the activated seco acid can adopt a low energy conformation to bring the two reacting functional groups together, which must be assisted *inter alia* by the two *trans*-substituted dihydropyrans[5b] and the cyclic acetal protecting groups. Furthermore, as with the monomeric seco acid **6**, the ring-size selectivity for **17** proved sensitive to the macrolactonisation conditions employed and could be reversed by changing to the Keck DCC protocol.[12] Using the Keck conditions ($CHCl_3$) with **17** gave a 91 : 9 mixture of **19** and **18** (65%), where preferential formation of the 46-membered ring **19** corresponding to isoswinholide A now occurred.



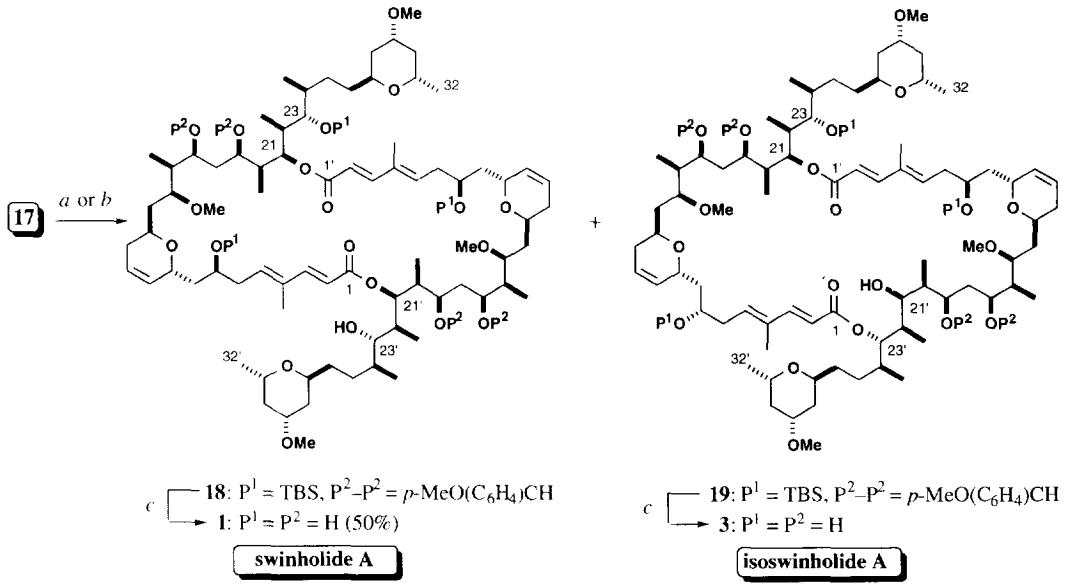
Scheme 5: (a) TBSCl, Et_3N, DMAP, DMF, 80 °C, 36 h; (b) HF•pyridine, pyridine, THF, 20 °C, 25 min; (c) $Ba(OH)_2$•$8H_2O$, MeOH, 20 °C, 4 d.

As the two isomeric macrodiolides were inseparable even by HPLC, we proceeded to deprotect the mixture rich in the desired isomer **18** which was obtained from the Yamaguchi macrolactonisation. Treatment of this macrodiolide mixture with aqueous hydrofluoric acid led to removal of all five protecting groups.[16] After purification by reverse phase HPLC, swinholide A (**1**) was obtained in 37% yield (50% allowing for unwanted **19** in the starting material), which was identical by ^1H NMR (500 MHz, $CDCl_3$), UV, IR and TLC to an authentic sample provided by Prof. Kitagawa. The synthetic swinholide A also had ^{13}C NMR data in agreement with an authentic spectrum and published values.[1b,d] The specific rotation of our synthetic material ($[\alpha]_D^{20}$ = –4.7° (*c* 0.32 $CHCl_3$)), did not match the literature value[1b,d] ($[\alpha]_D^{20}$ = +16.0° (*c* 1.3 $CHCl_3$)), and was closer to the value we obtained for a natural sample of swinholide A provided by Professor Kitagawa (authentic sample: $[\alpha]_D^{20}$ = –1.64° (*c* 0.07 $CHCl_3$)). This may be due to a non-linear dependence on concentration through aggregation behaviour or the presence of minor impurities such as metal ion contamination. However, the CD spectra of both natural and synthetic samples were found to be almost identical in the range 180–320 nm, thus indicating that we had, of course, made the correct enantiomer of the natural product.

In addition to obtaining swinholide A from this final deprotection, we also isolated 12% of isoswinholide A (**3**) derived from the 46-membered isomer **19** present in the starting material. Synthetic isoswinholide A was identical by ^1H NMR to that reported in the literature[1f] and also had a specific rotation, $[\alpha]_D^{20}$ = –44.5° (*c* 0.30,

$CHCl_3$), in good agreement with the literature value for naturally-derived material (lit[1f] $[\alpha]_D^{20} = -42.0°$ (*c* 0.51, $CHCl_3$)).

macrolactonisation conditions	**18** : **19**	yield (%)
a : *Yamaguchi*	83 : 17	84
b : *Keck*	9 : 91	65



Scheme 6: (a) 2,4,6-$Cl_3(C_6H_2)COCl$, Et_3N, PhMe, 20 °C, 2.5 h; add to DMAP, PhMe, 80 °C, 15 h; (b) add **17** over 16 h to DCC, DMAP, DMAP•HCl, $CHCl_3$, 60 °C; (c) HF, MeCN, 0 °C, 105 min.

Conclusions

The first total synthesis of swinholide A, a cytotoxic macrodiolide obtained from the marine sponge *Theonella swinhoei*, has been completed. The synthesis is based on the selective deprotection and regiocontrolled dimerisation of **4**, a fully protected version of the monomeric seco acid pre-swinholide A. Key features of the route include: (*i*) the regioselective acylation, **7** + **10** → **12**, (*ii*) the C_{23} hydroxyl protection, **12** → **15**, in order to prevent cleavage of the C_{21} ester linkage and (*iii*) regioselective macrolactonisation to generate the desired 44-membered ring, **17** → **18**. The monomeric lactone analogues **2** and **5** were prepared by regioselective macrolactonisation of the seco acid **6**, where the ring size was controlled by variation of the reaction conditions.

The entire synthesis of swinholide A proceeds in a total of 38 steps (28 steps longest linear sequence) with an overall yield of 0.4%. Of particular note, is the fact that the regioselectivity of macrolactonisation was controlled without the need for differential hydroxyl protection. The stereocontrolled construction of the monomeric unit **4**

relied heavily on various types of asymmetric aldol reactions, which were used to form the C_6–C_7, C_{12}–C_{13} and C_{22}–C_{23} bonds. Since this key intermediate has been prepared in gram quantities, significant amounts of swinholide A could be prepared by this sequence. This route should allow the preparation of other structural analogues of the swinholides, enabling the mode of action and structure-activity relationships to be probed in these fascinating molecules.

The exquisitely complex structures of bioactive marine macrolides, such as swinholide A, serve as an inspiration for the development of new methodology in organic synthesis, and as a challenging platform for testing the creativity of organic chemists.[17] It is important to stress that even more practical synthetic routes must be developed, if sufficient synthetic material is to be made available for clinical evaluation in cases where the natural supply is inadequate. This remains the key challenge for the future.

Experimental Section

For general experimental details, see the first paper in this series.[5a]

(*E*,*E*,7*S*)-Methyl-8-[(2*R*,6*S*)-6-{(2*S*,3*R*,4*S*,6*R*,7*R*,8*R*,9*S*,10*S*,11*S*)-2-methoxy-3,7,9,11-tetramethyl-8,10-dihydroxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-tridecan-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoate (7)

To a solution of the fully protected seco acid **4** (40.0 mg, 0.0361 mmol) in THF (0.8 ml) at room temperature was added pyridine (182 µl, 2.26 mmol), followed by HF•pyridine complex (56 µl). The reaction mixture was stirred for 15 min before being diluted with Et_2O (2 ml) and quenched with $NaHCO_3$ solution (2 ml, sat. aq.). The mixture was extracted with Et_2O (3 x 10 ml) and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Flash chromatography (1% MeOH/Et_2O) gave diol **7** as a colourless foam (32.1 mg, 0.0345 mmol, 94%): R_f = 0.36 (Et_2O); $[\alpha]_D^{20}$ = –46.7° (*c* 1.8, $CHCl_3$); IR (thin film) 3450 (m, br), 1717 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.35 (2H, d, *J* = 8.7 Hz, ArH), 7.30 (1H, d, *J* = 15.7 Hz, 3-CH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.90 (1H, dd, *J* = 7.3, 7.3 Hz, 5-CH), 5.77 (2H, m + d, *J* = 15.7 Hz, 2-CH, 11-CH), 5.61 (1H, dd, *J* = 10.4, 2.8 Hz, 10-CH), 5.46 (1H, s, O_2CHAr), 4.27 (1H, d, *J* = 9.4 Hz, 9-CH), 4.14 (1H, m, 19-CH), 4.08 (1H, d, *J* = 9.1 Hz, 21-CH), 3.97 (2H, m, 7-CH, 27-CH), 3.82 (1H, m, 17-CH), 3.79 (1H, m, 15-CH), 3.78 (3H, s, OMe), 3.74 (3H, s, OMe), 3.71 (1H, m, 31-CH), 3.58 (1H, m, 13-CH), 3.51 (1H, m, 29-CH), 3.36 (3H, s, OMe), 3.32 (3H, s, OMe), 3.27 (1H, m, 23-CH), 3.13 (1H, d, *J* = 6.9 Hz, OH), 2.24 (2H, m, 6-CH), 1.99 (1H, m, 22-CH), 1.95 (1H, m, 12-CH_a), 1.90 (1H, m, 14-CH_a), 1.86 (2H, m, 12-CH_b, 30-CH_a), 1.83 (1H, m, 26-CH_a), 1.77 (1H, m, 20-CH), 1.74 (1H, m, 16-CH), 1.72 (1H, m, 24-CH), 1.70 (3H, s, 4-CMe), 1.66 (1H, m, 18-CH_a), 1.58 (1H, m, 8-CH_a), 1.57 (2H, m, 28-CH), 1.55 (1H, m, 18-CH_b), 1.54 (1H, m, 26-CH_b), 1.53 (1H, m, 14-CH_b), 1.36 (1H, m, 8-CH_b), 1.30 (2H, m, 25-CH), 1.19 (3H, d, *J* = 6.2 Hz, 32-CMe), 1.17 (1H, m, 30-CH_b), 1.01 (3H, d, *J* = 7.0 Hz, 20-CMe), 0.90 (3H, d, *J* = 7.0 Hz, 24-CMe), 0.85 (6H, 2 x buried d, 16-CMe, 22-CMe), 0.84 (9H, s, ^{t}Bu), 0.01 (3H, s, SiMe), –0.06 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.0, 159.8, 149.7, 138.2, 134.0, 131.1, 130.3, 127.3, 123.6, 115.1, 113.5, 101.1, 80.5, 79.6, 78.7, 76.1, 73.2, 72.1, 71.7, 69.1, 67.9, 64.7, 64.3, 58.1, 55.2, 55.1, 51.4, 41.7, 40.6, 39.5, 38.6, 37.6, 37.4, 35.8, 34.7, 34.6, 31.0, 29.8, 29.0, 28.6, 25.8, 21.7, 18.0, 16.5, 12.4, 11.7, 10.5, 8.3, –4.4, –4.8; m/z (FAB, NOBA) 960 (100, $[M+H]^+$), 824 (70), 590 (100), 526 (35), 476 (45), 423 (45); HRMS (FAB, NOBA) Calcd for $C_{54}H_{91}O_{12}Si$ ($[M+H]^+$): 959.6279, found 959.6236.

(*E*,*E*,7*S*)-8-[(2*R*,6*S*)-6-{(2*S*,3*R*,4*S*,6*R*,7*R*,8*R*,9*S*,10*S*,11*S*)-2-methoxy-3,7,9,11-tetramethyl-8,10-dihydroxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*R*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-tridecan-1-yl}-5,6-dihydro-2*H*-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoic acid (6)

To a solution of diol **7** (49.0 mg, 0.0511 mmol) in MeOH (1 ml) was added sodium hydroxide (0.204 ml of a 2.5M aq. solution, 0.511 mmol) and the mixture heated to reflux for 2 h. The solution was cooled and acidified to pH3 with $KHSO_4$ solution (1M, aq.), extracted with EtOAc (4 x 8 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give the acid **6** as a colourless foam (48.2 mg,~100%); R_f = 0.60 (10% MeOH/89% CH_2Cl_2/1% AcOH); $[\alpha]_D^{20}$ = -51.8° (*c* 2.4, $CHCl_3$); IR (thin film) 3428 (m, br), 1688 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.34 (2H, d, *J* = 8.7 Hz, ArH), 7.34 (1H, d, *J* = 15.7 Hz, 3-CH), 6.83 (2H, d, *J* = 8.7 Hz, ArH), 5.91 (1H, dd, *J* = 7.3, 7.3 Hz, 5-CH), 5.75 (1H, d, *J* = 15.7 Hz, 2-CH), 5.74 (1H, m, 11-CH), 5.60 (1H, dd, *J* = 10.3, 2.9 Hz, 10-CH), 5.45 (1H, s, O_2CHAr), 4.28 (1H, br d, *J* = 9.4 Hz, 9-CH), 4.15 (1H, m, 19-CH), 4.10 (1H, d, *J* = 9.1 Hz, 21-CH), 4.00 (1H, m, 7-CH), 3.93 (1H, m, 27-CH), 3.82 (1H, m, 17-CH), 3.79 (1H, m, 15-CH), 3.77 (3H, s, OMe), 3.71 (1H, m, 31-CH), 3.53 (2H, m, 13-CH, 29-CH), 3.37 (3H, s, OMe), 3.32 (3H, s, OMe), 3.30 (1H, m, 23-CH), 2.24 (2H, m, 6-CH), 1.99 (1H, m, 22-CH), 1.93 (1H, m, 12-CH_a), 1.91 (1H, m, 14-CH_a), 1.87 (2H, m, 12-CH_b, 30-CH_a), 1.81 (1H, m, 26-CH_a), 1.79 (1H, m, 20-CH), 1.73 (1H, m, 16-CH), 1.71 (1H, m, 24-CH), 1.69 (3H, s, 4-CMe), 1.67 (1H, m, 18-CH_a), 1.57 (1H, m, 8-CH_a), 1.55 (2H, m, 28-CH), 1.54 (1H, m, 18-CH_b), 1.52 (1H, m, 26-CH_b), 1.51 (1H, m, 14-CH_b), 1.36 (1H, m, 8-CH_b), 1.30 (2H, m, 25-CH), 1.21 (3H, d, *J* = 6.3 Hz, 32-CMe), 1.17 (1H, m, 30-CH_b), 0.99 (3H, d, *J* = 7.0 Hz, 20-CMe), 0.90 (3H, d, *J* = 7.0 Hz, 24-CMe), 0.85 (6H, 2 x buried d, 16-CMe, 22-CMe), 0.84 (9H, s, ^{t}Bu), 0.01 (3H, s, SiMe), -0.09 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 171.4, 159.8, 151.3, 139.2, 134.0, 131.2, 130.3, 127.3, 123.7, 115.0, 113.6, 101.2, 80.4, 79.6, 78.8, 76.2, 73.2, 72.0, 71.6, 69.2, 68.0, 64.8, 64.2, 58.0, 55.2, 55.1, 41.6, 40.7, 39.5, 38.6, 37.6, 35.5, 34.8, 34.7, 31.1, 39.7, 29.6, 28.8, 28.3, 25.8, 21.7, 18.0, 16.5, 12.4, 11.7, 10.4, 8.3, -4.4, -4.6; m/z (FAB, NOBA) 946 (40, $[M+H]^+$), 810 (50), 696 (50), 664 (20), 648 (25), 576 (100); HRMS (FAB, NOBA) Calcd for $C_{53}H_{89}O_{12}Si$ ($[M+H]^+$): 945.6123, found 945.6103.

Selective formation of 22-membered lactone (8)

To a solution of seco acid **6** (24.8 mg, 0.0261 mmol) in dry toluene (1 ml) was added triethylamine (37.2 μl of 1M solution), followed by 2,4,6-trichlorobenzoyl chloride (32.5 μl of a 1M solution) and the resulting mixture was stirred at room temperature for 2 h to complete mixed anhydride formation. The reaction mixture was then diluted with more dry toluene (6.5 ml), before slow addition over 3 h (*via* syringe pump) to a solution of DMAP (30.3 mg, 0.248 mmol) in dry toluene (10 ml) at 50 °C. After 45 min, the solution was cooled and then evaporated *in vacuo*. Flash chromatography (50% EtOAc/hexane) provided a mixture of the two regioisomeric lactones, which were separated by HPLC to give the C_{21} acylated product **8** (18.7 mg, 76%) and the C_{23} acylated material **9** (4.0 mg, 16%).

8: R_f = 0.40 (50% EtOAc/hexane); t_R = 12.6 min (60% EtOAc/hexane); $[\alpha]_D^{20}$ = -29.3° (*c* 1.2, $CHCl_3$); IR (thin film) 3293 (m, br), 1682 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.54 (1H, d, *J* = 15.7 Hz, 3-CH), 7.43 (2H, d, *J* = 8.7 Hz, ArH), 6.88 (2H, d, *J* = 8.7 Hz, ArH), 5.73 (1H, m, 11-CH), 5.70 (1H, d, *J* = 15.7 Hz, 2-CH), 5.57 (1H, dt, *J* = 10.2, 2.2 Hz, 10-CH), 5.46 (1H, s, O_2CHAr), 5.23 (1H, dd, *J* = 7.3, 7.3 Hz, 5-CH), 5.08 (1H, d, *J* = 9.6 Hz, 21-CH), 4.29 (1H, d, *J* = 9.4 Hz, 9-CH), 4.01 (2H, m, CHO), 3.87 (1H, dt, *J* = 11.6, 2.2 Hz, CHO), 3.80 (2H, m, CHO), 3.78 (3H, s, OMe), 3.69 (2H, m, CHO), 3.53 (2H, m, CHO), 3.38 (3H, s, OMe), 3.32 (3H, s, OMe), 3.17 (1H, m, 23-CH), 3.11 (1H, d, *J* = 6.9 Hz, OH), 2.42 (1H, m, 6-CH_a), 2.21 (1H, q, J = 7.1 Hz, 6-CH_b), 2.0-1.0 (20H, m), 1.63 (3H, s, 4-CMe), 1.19 (3H, d, *J* = 6.2 Hz, 31-CMe), 1.04 (3H, d, *J* = 6.9 Hz, CHMe), 1.02 (3H, d, *J* = 6.9 Hz, CHMe), 0.92 (3H, d, *J* = 6.5 Hz, CHMe), 0.88 (9H, s, ^{t}Bu), 0.81 (3H, d, *J* = 7.0 Hz, CHMe), 0.10 (3H, s, SiMe), 0.09 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 169.5, 159.5, 150.8, 138.3, 133.8, 131.3, 130.6, 127.3, 123.8, 115.6,

113.5, 100.7, 80.8, 78.7, 76.3, 76.0, 73.3, 71.7, 69.9, 69.5, 64.5, 63.6, 57.1, 55.2, 55.1, 40.5, 40.4, 39.7, 38.8, 38.5, 36.6, 34.9, 33.3, 31.8, 29.7, 29.3, 29.0, 25.9, 24.3, 21.8, 18.0, 15.2, 12.1, 10.0, 8.7, –4.2, –4.9; m/z (FAB, NOBA) 927 (100, $[M+H]^+$), 824 (70), 590 (100), 526 (35), 476 (45), 423 (45); HRMS (FAB, NOBA) Calcd for $C_{53}H_{87}O_{11}Si$ ($[M+H]^+$): 927.6017, found 927.6067.

9: R_f = 0.35 (50% EtOAc/hexane); t_R = 15.1 min (60% EtOAc/hexane); $[\alpha]_D^{20}$ = –16.0° (*c* 2.0, $CHCl_3$); IR (thin film) 3493 (m, br), 1702 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.50 (1H, d, *J* = 15.6 Hz, 3-C<u>H</u>), 7.26 (2H, d, *J* = 8.7 Hz, Ar<u>H</u>), 6.79 (2H, d, *J* = 8.7 Hz, Ar<u>H</u>), 5.83 (1H, d, *J* = 15.6 Hz, 2-C<u>H</u>), 5.75 (2H, m, 5-C<u>H</u>, 11-C<u>H</u>), 5.69 (1H, dt, *J* = 10.2, 2.2 Hz, 10-C<u>H</u>), 5.40 (1H, s, $O_2C\underline{H}Ar$), 4.88 (1H, dd, *J* = 7.3, 6.5 Hz, 23-C<u>H</u>), 4.37 (1H, m, 9-C<u>H</u>), 4.00 (2H, m, C<u>H</u>O), 3.81 (2H, m, C<u>H</u>O), 3.77 (3H, s, O<u>Me</u>), 3.69 (2H, m, C<u>H</u>O), 3.52 (2H, m, C<u>H</u>O), 3.40 (1H, m, C<u>H</u>O), 3.32 (3H, s, O<u>Me</u>), 3.30 (3H, s, O<u>Me</u>), 2.33 (1H, m, 6-C$\underline{H}_a$), 2.30 (1H, m, 6-C$\underline{H}_b$), 2.0-1.0 (20H, m), 1.80 (3H, s, 4-C<u>Me</u>), 1.18 (3H, d, *J* = 6.2 Hz, 31-C<u>Me</u>), 0.95 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>), 0.92 (3H, d, *J* = 6.9 Hz, CH<u>Me</u>), 0.90 (6H, 2 x overlapping d, CH<u>Me</u>), 0.84 (9H, s, ^{t}Bu), 0.81 (3H, d, *J* = 7.0 Hz, CH<u>Me</u>), -0.06 (3H, s, Si<u>Me</u>), -0.12 (3H, s, Si<u>Me</u>); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 167.4, 159.9, 149.1, 136.4, 134.3, 130.8, 130.5, 127.5, 123.8, 116.9, 113.6, 102.0, 82.1, 79.6, 77.9, 76.0, 73.2, 72.0, 69.4, 64.0, 57.0, 55.3, 55.2, 40.8, 40.2, 39.7, 39.2, 38.8, 38.6, 36.8, 35.9, 35.0, 31.7, 29.7, 29.0, 28.7, 27.2, 25.9, 21.8, 18.0, 16.4, 13.4, 12.5, 11.7, 9.2, –4.6, –5.0; m/z (FAB, NOBA) 927 (35, $[M+H]^+$), 792 (70), 351 (40), 319 (40), 269 (100), 251 (60), 223 (100); HRMS (FAB, NOBA) Calcd for $C_{53}H_{87}O_{11}Si$ ($[M+H]^+$): 927.6017, found 927.6098.

Selective formation of 24-membered lactone (9)

A solution of the seco acid **6** (26.0 mg, 0.0275 mmol) in dry $CHCl_3$ was added by syringe pump over 16 h to a solution of DCC (17 mg, 0.0825 mmol), DMAP (16.8 mg, 0.1375 mmol) and DMAP•HCl (13.1 mg, 0.0825 mmol) in dry $CHCl_3$ at reflux. The reaction mixture was stirred at this temperatue for a further 1 h, before cooling and evaporating *in vacuo*. Flash chromatography (50% EtOAc/hexane) provided a mixture of the two regioisomeric lactones, which were separated by HPLC to give the C_{21} acylated product **8** (1.2 mg, 5%) and the C_{23} acylated material **9** (23.3 mg, 89%). These compounds had spectral data as reported above.

Hemiswinholide A (2)

Hydrofluoric acid (0.2 ml, 48% aq.) was added to a stirred solution of the fully protected macrolide **8** (14.0 mg, 0.0151 mmol) in acetonitrile (1 ml) at 0 °C. After 1 h, the reaction mixture was quenched with $NaHCO_3$ (sat., aq.) and extracted with EtOAc (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product. Flash chromatography (7% MeOH/CH_2Cl_2) gave **2** as a colourless oil (8.5 mg, 81%): R_f = 0.30 (5% MeOH/ 94% CH_2Cl_2/1% AcOH); $[\alpha]_D^{20}$ = –43.1° (*c* 1.2, $CHCl_3$); IR (thin film) 3460 (m, br), 1683 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$), see **Table 1** at the end of the experimental section; ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.9, 150.0, 137.7, 134.8, 129.9, 124.6, 116.1, 80.0, 77.4, 77.2, 73.8, 71.6, 70.8, 70.7, 69.2, 65.5, 64.6, 56.8, 55.3, 41.8, 40.8, 40.0, 39.0, 38.8, 38.1, 37.5, 36.1, 35.0, 33.0, 31.2, 29.7, 29.2, 24.2, 21.8, 17.8, 12.4, 10.4, 9.9, 9.3; m/z (FAB, NOBA) 695.8 (100, $[MH]^+$), 307 (35), 289 (45), 267 (30), 223 (45); HRMS (FAB, NOBA) Calcd for $C_{39}H_{66}O_{10}$ (MH^+): 695.4734, found 695.4784. Copies of the ^1H and ^{13}C NMR spectra are provided with the supplementary material in ref. 6.

Isohemiswinholide A (5)

Hydrofluoric acid (0.2 ml, 48% aq.) was added to a stirred solution of the fully protected macrolide **9** (21.8 mg, 0.0235 mmol) in acetonitrile (1 ml) at 0 °C. After 1 h, the reaction mixture was quenched with $NaHCO_3$ (sat., aq.) and extracted with EtOAc (3 x 20 ml). The combined extracts were dried ($MgSO_4$) and eaporated *in vacuo* to give the crude product. Flash chromatography (7% MeOH/CH_2Cl_2) gave **5** as a colourless oil (14.3 mg, 88%): R_f = 0.28 (10% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ = –53.9° (*c* 1.4, $CHCl_3$); IR (thin film) 3420 (m, br), 1703 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.37 (1H, d, *J* = 15.6 Hz, 3-C<u>H</u>), 5.99 (1H, dd, *J* = 8.0, 8.0 Hz, 5-

CH), 5.85 (1H, d, *J* = 15.6 Hz, 2-CH), 5.78 (1H, br d, *J* = 10.3 Hz, 11-CH), 5.68 (1H, br d, *J* = 10.3 Hz, 10-CH), 4.95 (1H, dd, *J* = 9.9, 1.9 Hz, 23-CH), 4.42 (1H, br d, *J* = 9.4 Hz, 9-CH), 4.01 (1H, m, 7-CH), 3.97 (1H, m, 27-CH), 3.89 (1H, m, 19-CH), 3.80 (1H, br t, *J* = 7.9 Hz, 17-CH), 3.69 (2H, m, 15-CH, 31-CH), 3.61 (1H, m, 13-CH), 3.53 (1H, m, 21-CH), 3.51 (1H, m, 29-CH), 3.33 (3H, s, OMe), 3.32 (3H, s, OMe), 2.44 (2H, m, 6-CH_a, 6-CH_b), 2.06 (1H, m, 12-CH_a), 2.04 (1H, m, 20-CH), 1.99 (1H, m, 30-CH_a), 1.98 (1H, m, 12-CH_b), 1.88 (2H, m, 24-CH, 26-CH_a), 1.82 (3H, s, 4-CMe), 1.80 (3H, m, 14-CH_a, 22-CH, 28-CH_a), 1.76 (1H, m, 8-CH_a), 1.67 (1H, m, 16-CH), 1.63 (1H, m, 28-CH_b), 1.58 (1H, m, 14-CH_b), 1.55 (1H, m, 18-CH_a), 1.52 (1H, m, 25-CH_a), 1.48 (1H, m, 8-CH_b), 1.45 (1H, m, 8-CH_b), 1.30 (1H, m, 25-CH_b), 1.25 (1H, m, 26-CH_b), 1.22 (1H, m, 30-CH_b), 1.21 (3H, d, *J* = 6.6 Hz, 31-CMe), 0.94 (3H, d, *J* = 6.9 Hz, 24-CMe), 0.89 (3H, d, *J* = 6.8 Hz, 20-CMe), 0.88 (3H, d, *J* = 7.0 Hz, 22-CMe), 0.74 (3H, d, *J* = 7.2 Hz, 16-CMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.7, 150.3, 138.1, 134.8, 129.7, 123.9, 115.6, 79.1, 79.0, 78.1, 75.8, 73.3, 71.7, 71.4, 69.1, 68.4, 65.3, 64.8, 56.8, 55.3, 40.9, 40.2, 38.8, 38.4, 37.7, 36.5, 35.5, 35.1, 34.6, 33.0, 31.0, 29.5, 25.3, 21.7, 17.0, 14.0, 12.5, 10.5, 8.9; m/z (FAB, NOBA) 718 (85, $[MNa]^+$), 695.8 (100, $[MH]^+$), 307 (90), 289 (60), 223 (80); HRMS (FAB, NOBA) Calcd for $C_{39}H_{66}O_{10}$ (MH^+): 695.4734, found 695.4714.

(*E*,*E*,7*S*)-8-[(2*R*,6*S*)-6-{2*S*3*R*,4*S*,6*R*,7*S*,8*S*,9*S*,10*S*,11*S*)-8,10-di-*tert*-butylsilylenedioxy-2-methoxy-4,6-((*R*)-*para*-methoxybenzylidenedioxy)-13-((2*S*,4*S*,6*S*)-2-methyl-4-methoxytetrahydropyran-6-yl)-3,7,9,11-tetramethyltridecan-1-yl}-5,6-dihydro-2H-pyran-2-yl]-7-*tert*-butyldimethylsilyloxy-4-methylocta-2,4-dienoic acid (10)

To a solution of ester **4** (39.0 mg, 0.0355 mmol) in MeOH (1.5 ml) was added sodium hydroxide (0.284 ml of a 2.5*M* aq. solution, 0.709 mmol) and the mixture heated to 60 °C for 2 h. The solution was cooled and acidified to pH3 with $KHSO_4$ solution (1*M*, aq.), extracted with EtOAc (3 x 20 ml), dried ($MgSO_4$) and evaporated *in vacuo* to give the acid **10** as a colourless foam (38.5 mg,~100%); R_f = 0.33 (5% MeOH/94% CH_2Cl_2/1% AcOH); $[\alpha]_D^{20}$ = –72.5° (*c* 1.38, $CHCl_3$); IR (thin film) 3500-3000 (br), 1687 cm^{-1}; ^1H NMR δ (400 MHz, C_6D_6) 7.80 (2H, d, *J* = 8.6 Hz, ArH), 7.76 (1H, d, *J* = 15.7 Hz, 3-CH), 6.99 (2H, d, *J* = 8.6 Hz, ArH), 6.60 (1H, m, 5-CH), 5.96 (1H, d, *J* = 15.7 Hz, 2-CH), 5.86 (1H, s, $ArCHO_2$), 5.68 (1H, m, 11-CH), 5.59 (1H, dm, *J* = 10.1 Hz, 10-CH), 4.79 (1H, d, *J* = 10.1 Hz, 19-CH), 4.56 (2H, m, 9-CH, 21-CH), 4.16 (4H, m, 7-CH, 17-CH, 15-CH, 27-CH), 3.76 (1H, dd, *J* = 5.0, 1.8 Hz, 23-CH), 3.57 (2H, m, 31-CH, 13-CH), 3.42 (3H, s, OMe), 3.40 (3H, s, OMe), 3.37 (1H, m, 29-CH), 3.19 (3H, s, OMe), 2.40-1.00 (22H, m), 1.58 (3H, s, 4-CMe), 1.26 (3H, d, 31-CMe), 1.25 (9H, s, *t*-Bu), 1.22 (9H, s, *t*-Bu), 1.20 (3H, d, *J* = 7.2 Hz, 22-CMe), 1.06 (3H, d, *J* = 6.9 Hz, 20-CMe), 0.98 (9H, s, *t*-Bu), 1.01 (3H, d, *J* = 6.3 Hz, 16-CMe), 0.90 (3H, d, *J* = 6.9 Hz, 24-CMe), 0.20 (3H, s, SiMe), -0.03 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, C_6D_6) 171.4, 160.3, 151.4, 139.7, 134.2, 132.3, 130.6, 128.5, 124.2, 115.9, 113.9, 101.5, 84.2, 79.1, 75.6, 75.0, 73.5, 72.9, 71.8, 69.4, 68.4, 65.1, 64.1, 57.5, 54.9, 54.7, 41.6 (2C), 41.4, 39.8, 39.0, 38.5, 37.1, 36.5, 35.4, 33.1, 31.8, 30.1, 29.2, 28.8, 28.2, 27.0, 26.2, 22.4, 22.0, 21.9, 18.2, 16.4, 14.0, 12.2, 9.7, 8.6, –3.9, –4.6; m/z (+FAB, NOBA) 1085 ($[MH]^+$); HRMS Calcd for $C_{61}H_{105}O_{12}Si_2$ ($[MH]^+$): 1085.7144, found: 1085.7182.

Bimolecular esterification to give 12 and 13

To a solution of fully protected acid **10** (106.2 mg, 0.0978 mmol) in dry toluene (1.5 ml) was added Et_3N (11.2 mg, 0.110 mmol), followed by 2,4,6-trichlorobenzoyl chloride (25.7 mg, 0.105 mmol), and the mixture stirred at room temperature until mixed anhydride formation was complete by TLC (~1 h). A solution of diol **7** (130 mg, 0.136 mmol) and DMAP (14 mg, 0.110 mmol) in dry toluene (1.5 ml) was then added and the mixture stirred at room temperature overnight. The reaction mixture was then quenched by addition of $NaHCO_3$ (sat., aq., 40 ml), followed by extraction with Et_2O (4 x 30 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* to give the crude product. Flash chromatography (gradient elution 70% Et_2O/hexane → Et_2O → 5% MeOH/Et_2O) then gave a mixture of the two acylation regioisomers **12** and **13**, along with

recovered diol **7** (35 mg). The two regioisomers were then separated by preparative TLC to give **12** (106.5 mg, 54%) and **13** (62.3 mg, 31%).

12: R_f = 0.40 (80% Et_2O/hexane); $[\alpha]_D^{20}$ = −102.2° (*c* 3.6, $CHCl_3$); IR (thin film) 3496 (m, br), 1719 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.38 (2H, d, *J* = 8.7 Hz, ArH), 7.35 (2H, d, *J* = 8.9 Hz, ArH), 7.34 (1H, d, *J* = 15.7 Hz, 3-CH), 7.29 (1H, d, *J* = 15.7 Hz, 3'-CH), 6.83 (4H, d, *J* = 8.8 Hz, ArH), 5.99 (1H, t, *J* = 7.2 Hz, 5-CH), 5.93 (1H, t, *J* = 8.0 Hz, 5'-CH), 5.79 (1H, d, *J* = 15.7 Hz, 2-CH), 5.76 (2H, m, 11-CH, 11'-CH), 5.75 (1H, d, *J* = 15.7 Hz, 2'-CH), 5.60 (2H, m, 10-CH, 10'-CH), 5.52 (1H, br d, *J* = 9.6 Hz, 21-CH), 5.43 (1H, s, $ArCHO_2$), 5.34 (1H, s, $ArCHO_2$), 4.40 (1H, br d, *J* = 10.7 Hz, 9-CH), 4.25 (2H, m, 9'-CH, CHO), 4.13 (1H, dd, *J* = 10.0, 2.5 Hz, CHO), 3.98 (3H, m, CHO), 3.9-3.7 (10H, m, CHO), 3.765 (3H, s, OMe), 3.761 (3H, s, OMe), 3.73 (3H, s, OMe), 3.60 (1H, br t, J = 6.6 Hz, CHO), 3.53 (2H, m, CHO), 3.39 (3H, s, OMe), 3.35 (3H, s, OMe), 3.32 (3H, s, OMe), 3.31 (3H, s, OMe), 2.98 (1H, m, CHO), 2.3-1.0 (40H, m, 16 x CH_2 and 8 x CH), 1.73 (3H, s, 4-CMe or 4'-CMe), 1.69 (3H, s, 4-CMe or 4'-CMe), 1.18 (6H, m, 2 x CHMe), 1.04 (9H, s, ^{t}Bu), 0.99 (9H, m, 3 x CHMe), 0.94 (9H, s, ^{t}Bu), 0.88 (9H, m, 3 x CHMe), 0.83 (9H, s, ^{t}Bu), 0.82 (9H, s, ^{t}Bu), 0.011 (3H,s, SiMe), 0.005 (3H, s, SiMe), -0.05 (3H, s, SiMe), -0.09 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.8, 167.9, 159.5, 159.4, 150.9, 149.7, 149.0, 138.1, 134.0, 131.9, 131.5, 130.4, 130.3, 127.5, 127.2, 123.7, 123.6, 115.2, 114.6, 113.4, 113.2, 100.5, 100.1, 83.4, 78.4, 78.0, 77.2, 76.1, 75.8, 75.7, 75.6, 74.3, 74.1, 73.3, 73.2, 72.5, 72.0, 71.5, 69.3, 69.1, 68.0, 67.8, 64.6, 64.5, 58.3, 55.23, 55.17, 55.13, 51.4, 42.1, 41.1, 40.9, 40.7, 39.3, 38.9, 38.8, 37.6, 37.3, 37.3, 35.5, 35.0, 34.8, 32.9, 32.6, 30.9, 30.8, 29.7, 29.2, 28.5, 28.1, 27.8, 25.9, 24.1, 22.1, 21.9, 21.8, 21.7, 18.0, 17.97, 17.91, 15.8, 13.8, 12.5, 12.4, 10.3, 9.4, 9.0, 8.38, 8.36, -4.40, -4.44, -4.8; m/z (FIB, NOBA) 2048 $[M+Na]^+$.

13: R_f = 0.35 (80% Et_2O/hexane); $[\alpha]_D^{20}$ = −78.3° (*c* 3.6, $CHCl_3$); IR (thin film) 3494 (m, br), 1720 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.35 (1H, d, *J* = 15.5 Hz, 3-CH), 7.34 (2H, d, *J* = 8.7 Hz, ArH), 7.29 (1H, d, *J* = 15.7 Hz, 3'-CH), 7.28 (2H, d, *J* = 8.9 Hz, ArH), 6.83 (2H, d, *J* = 8.8 Hz, ArH), 6.73 (2H, d, *J* = 8.8 Hz, ArH), 5.99 (1H, t, *J* = 7.4 Hz, 5-CH), 5.92 (1H, t, *J* = 7.0 Hz, 5'-CH), 5.79 (1H, d, *J* = 15.5 Hz, 2-CH), 5.76 (2H, m, 11-CH, 11'-CH), 5.75 (1H, d, *J* = 15.7 Hz, 2'-CH), 5.60 (2H, m, 10-CH, 10'-CH), 5.46 (1H, s, $ArCHO_2$), 5.43 (1H, s, $ArCHO_2$), 4.94 (1H, dd, *J* = 9.1, 3.3 Hz, 23-CH), 4.40 (1H, br d, *J* = 10.5 Hz, 9-CH), 4.31 (1H, m, 9'-CH), 4.25 (1H, m, CHO), 4.13 (1H, dd, *J* = 10.1, 2.3 Hz, CHO), 3.98 (3H, m, CHO), 3.9-3.5 (13H, m, CHO), 3.76 (3H, s, OMe), 3.73 (3H, s, OMe), 3.71 (3H, s, OMe), 3.38 (3H, s, OMe), 3.36 (3H, s, OMe), 3.33 (3H, s, OMe), 3.31 (3H, s, OMe), 3.16 (1H, d, *J* = 3.7 Hz, CHO), 2.3-1.0 (40H, m, 16 x CH_2 and 8 x CH), 1.73 (3H, s, 4-CMe or 4'-CMe), 1.69 (3H, s, 4-CMe or 4'-CMe), 1.19 (6H, m, 2 x CHMe), 1.05 (9H, s, ^{t}Bu), 1.01 (3H, d, *J* = 7.1 Hz, CHMe), 0.95 (9H, s, ^{t}Bu), 0.9-0.8 (21H, m, 7 x CHMe), 0.83 (9H, s, ^{t}Bu), 0.82 (9H, s, ^{t}Bu), 0.03 (3H, s, SiMe), 0.01 (3H, s, SiMe), -0.06 (3H, s, SiMe), -0.07 (3H,s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 169.1, 168.0, 159.5, 159.4, 150.8, 149.8, 138.9, 138.2, 134.02, 133.96, 131.9, 130.39, 130.33, 127.5, 127.1, 123.7, 123.6, 115.1, 114.7, 113.2, 100.5, 100.0, 83.3, 80.1, 78.5, 78.3, 76.1, 76.0, 75.7, 74.2, 73.3, 72.6, 71.9, 71.2, 69.3, 69.2, 69.1, 67.9, 67.8, 64.7, 64.6, 64.5, 58.3, 55.28, 55.24, 55.13, 55.06, 51.4, 42.2, 42.0, 41.09, 40.7, 40.3, 39.3, 38.9, 38.4, 37.9, 37.3, 37.2, 35.7, 35.5, 35.0, 34.8, 32.8, 32.6, 30.9, 30.8, 29.7, 29.1, 28.5, 28.2, 27.8, 25.9, 25.5, 22.1, 21.9, 21.74, 21.72, 18.0, 16.9, 15.8, 13.8, 12.5, 12.4, 10.0, 9.4, 8.43, 8.40, 8.3, -4.4, -4.5, -4.8 (2C); m/z (FIB, NOBA) 2048 $[M+Na]^+$.

C_{23}-*tert*-Butyldimethylsilyl ether (15)

To a mixture of the hydroxyester **12** (35.6 mg, 17.6 μmol) and DMAP (53.8 mg, 0.44 mmol) in DMF (0.6 ml) at room temperature was added a mixture of TBSCl/Et_3N (1:1 wt/wt, 590 μl, *ca* 3.52 mmol), followed by Et_3N (245 μl, 1.76 mmol), and the resulting mixture was stirred at 80 °C for 30 h. After cooling, the mixture was diluted with EtOAc (15 ml) and washed with $NaHCO_3$ solution (7 ml, sat. aq.). The aqueous layer was re-extracted with EtOAc (2 x 10 ml) and the combined organic extracts washed successively with H_2O (5 ml) and

brine (5 ml), dried ($MgSO_4$), and concentrated *in vacuo*. The crude material was purified by preparative thin-layer chromatography (eluting with 80% Et_2O/hexane) to give the fully protected compound **15** as a colourless glass (29.7 mg, 80%); $R_f = 0.60$ (80% EtOAc/hexane); $[\alpha]_D^{20} = -94.4°$ (*c* 1.97, $CHCl_3$); IR (liquid film) 1716 (s) cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.35 (2H, d, *J* = 8.7 Hz, ArH), 7.29 (1H, d, *J* = 15.6 Hz, 3-CH or 3'-CH), 7.28 (1H, d, *J* = 15.6 Hz, 3-CH or 3'-CH), 6.63 (2H, d, *J* = 8.7 Hz, ArH), 6.62 (2H, d, *J* = 8.7 Hz, ArH), 5.96-5.88 (2H, overlapping dd, 5-CH and 5'-CH), 5.79-5.73 (2H, overlapping m, 11-CH and 11'-CH), 5.77 (1H, d, *J* = 15.6 Hz, 2-CH or 2'-CH), 5.75 (1H, d, *J* = 15.6 Hz, 2-CH or 2'-CH), 5.60 (2H, overlapping br d, *J* = 9.1 Hz, 10-CH and 10'-CH), 5.43 (1H, s, ArCH), 5.38-5.35 (1H, buried d, 21-CH), 5.35 (1H, s, ArCH), 4.40 (1H, br d, *J* = 10.4 Hz, CHO), 4.25 (2H, overlapping br d, *J* = 7.6 Hz, CHO), 4.13 (1H, br d, *J* = 8.7 Hz, CHO), 4.04-3.90 (4H, overlapping m, CHO), 3.83 (4H, overlapping br dd, *J* = 13.7, 5.6 Hz, CHO), 3.79-3.66 (2H, overlapping m, CHO), 3.77 (3H, s, OMe), 3.76 (3H, s, OMe), 3.73 (3H, s, OMe), 3.66-3.58 (3H, overlapping m, CHO), 3.58-3.42 (4H, overlapping m, CHO), 3.39 (3H, s, OMe), 3.36 (3H, s, OMe), 3.32 (3H, s, OMe), 3.31 (3H, s, OMe), 2.41-2.12 and 2.03-1.09 (5H and 39H respectively, overlapping m, 18 x CH_2 and 8 x CH), 1.71 (3H, s, 4-CMe or 4'-CMe), 1.69 (3H, s, 4-CMe or 4'-CMe), 1.16 (6H, overlapping d, *J* = 6.0 Hz, 2 x CHMe), 1.09-0.70 (18H, d, 6 x CHMe), 1.04 (9H, s, ^{t}Bu), 1.01 (3H, d, *J* = 7.2 Hz, CHMe), 0.98 (3H, d, *J* = 7.0 Hz, CHMe), 0.95 (9H, s, ^{t}Bu), 0.85 (9H, s, ^{t}Bu), 0.83 (9H, s, ^{t}Bu), 0.82 (9H, s, ^{t}Bu), 0.12 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.05 (3H, s, SiMe), 0.00 (3H, s, SiMe), –0.06 (3H, s, SiMe), –0.09 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.0, 166.8, 159.5, 159.4, 149.8, 149.3, 138.2, 137.7, 134.0, 133.9, 131.9, 131.7, 130.4, 127.5, 127.4, 123.63, 123.61, 116.0, 115.1, 113.23, 113.18, 100.5, 100.1, 83.3, 79.1, 78.4, 78.0, 76.1, 75.7, 75.5, 74.6, 74.2, 73.3, 72.6, 72.2, 71.9, 69.3, 69.1, 68.0, 67.8, 64.6, 64.5, 64.4, 58.33, 58.30, 55.23, 55.16, 55.14, 51.4, 42.1, 41.1, 40.8, 40.7, 40.4, 39.6, 39.3, 38.94, 38.93, 37.7, 37.3, 37.1, 36.2, 35.5, 34.9, 34.8, 33.0, 32.6, 30.9, 30.8, 29.8, 28.5, 28.1, 27.8, 26.7, 26.4, 25.87, 25.86, 25.6, 22.1, 21.9, 21.8, 21.7, 18.7, 18.01, 17.98, 17.0, 15.8, 13.8, 12.5, 12.4, 10.9, 10.7, 9.4, 8.39, 8.35, –3.1, –3.6, –4.37, –4.41, –4.43, -4.8; m/z (+ve FIB, NOBA matrix) $C_{121}H_{206}O_{23}Si_4$ (M^+) requires 2139, found 2141 ($[M+2H]^+$), 2164 ($[M+Na+2H]^+$).

$C_{21'}$,$C_{23'}$ diol (16)

To a solution of the fully protected ester **15** (41.4 mg, 19.4 μmol) in THF (0.8 ml) at room temperature was added pyridine (91 μl, 1.13 mmol), followed by HF•pyridine complex (28 μl). A further 0.5 ml of THF was added to the reaction mixture, which was stirred for 25 min before being quenched with $NaHCO_3$ solution (6 ml, sat. aq.). The mixture was then extracted wih EtOAc (15 + 3 x 10 ml) and the combined organic extracts washed with brine (6 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was purified by preparative thin-layer chromatography (eluting with 5% MeOH/CH_2Cl_2) to give the $C_{21'}$,$C_{23'}$ diol **16** as a colourless glass (31.4 mg, 81%): $R_f = 0.40$ (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20} = -75.6°$ (*c* 2.01, $CHCl_3$); IR (liquid film) 3462, 1714 cm^{-1}; ^1H NMR δ (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 8.7 Hz, ArH), 7.35 (2H, d, *J* = 8.8 Hz, ArH), 7.28 (1H, d, *J* = 15.8 Hz, 3-CH or 3'-CH), 7.27 (1H, d, *J* = 15.8 Hz, 3-CH or 3'-CH), 6.65 (2H, d, *J* = 8.7 Hz, ArH), 6.61 (2H, d, *J* = 8.8 Hz, ArH), 5.95-5.85 (2H, overlapping dd, 5-CH and 5'-CH), 5.79-5.73 (2H, buried m, 11-CH and 11'-CH), 5.77 (1H, d, *J* = 15.8 Hz, 2-CH or 2'-CH), 5.74 (1H, d, *J* = 15.8 Hz, 2-CH or 2'-CH), 5.60 (2H, overlapping br d, *J* = 10.4 Hz, 10-CH and 10'-CH), 5.45 (1H, s, ArCH), 5.37 (1H, d, *J* = 9.1 Hz, 21-CH), 5.34 (1H, s, ArCH), 4.30-4.20 (3H, m, CHO or OH), 4.19-4.10 (1H, m, CHO or OH), 4.10 (1H, d, *J* = 7.2 Hz, CHO or OH), 4.07 (1H, br d, *J* = 8.2 Hz, CHO or OH), 4.02-3.48 (13H, overlapping m, CHO or OH), 3.76 (9H, s, 3 x OMe), 3.72 (3H, s, OMe), 3.45 (1H, br d, *J* = 6.3 Hz, CHO or OH), 3.39-3.19 (2H, overlapping m, CHO or OH), 3.35 (6H, s, 2 x OMe), 3.31 (3H, s, OMe), 3.11 (1H, br d, *J* = 6.9 Hz, CHO or OH), 2.38-2.12, 2.01-1.86, 1.86-1.45, 1.45-1.34 and 1.34-1.28 (6H, 2H, 30H, 4H and 2H respectively, overlapping m, 18 x CH_2 and 8 x CH), 1.71 (3H, s, 4-CMe or 4'-CMe), 1.69 (3H, s, 4-CMe or 4'-CMe), 1.18 (6H, overlapping d, *J* = 6.3 Hz, 2 x CHMe), 1.16 (6H, overlapping d, *J* =

6.3 Hz, 2 x CHMe), 0.99 (3H, d, J = 7.6 Hz, CHMe), 0.98 (3H, d, J = 7.6 Hz, CHMe), 0.90 (6H, overlapping d, J = 6.8 Hz, 2 x CHMe), 0.89 (6H, overlapping d, J = 6.8 Hz, 2 x CHMe), 0.85 (9H, s, ^{t}Bu), 0.83 (9H, s, ^{t}Bu), 0.82 (9H, s, ^{t}Bu), 0.12 (3H, s, SiMe), 0.04 (3H, s, SiMe), 0.01 (3H, s, SiMe), –0.02 (3H, s, SiMe), –0.04 (3H, s, SiMe), –0.10 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, $CDCl_3$) 168.0, 166.8, 159.8, 159.4, 149.8, 149.3, 138.2, 137.6, 134.1, 133.9, 131.7, 131.2, 130.38, 130.37 127.4, 127.3, 123.6, 123.5, 116.0, 115.1, 113.6, 113.2, 101.0, 100.1, 80.6, 79.6, 79.1, 78.7, 78.0, 76.2, 75.7, 75.5, 74.6, 73.3, 73.2, 72.2, 72.1, 71.7, 69.3, 69.0, 68.0, 67.9, 64.7, 64.6, 64.5, 64.4, 58.33, 58.30, 55.3, 55.2, 55.1, 51.4, 42.1, 42.0, 40.8, 40.7, 40.4, 39.6, 39.5, 38.9, 38.6, 37.8, 37.7, 37.30, 37.26, 36.2, 35.8, 34.8, 34.74, 34.71, 33.0, 30.9, 30.7, 29.82, 29.77, 29.0, 28.7, 26.7, 26.4, 25.9, 25.7, 21.8, 21.7, 18.7, 18.00, 17.97, 17.0, 16.6, 14.2, 12.5, 12.4, 11.7, 10.8, 10.6, 10.5, 8.4, 8.3, –3.2, –4.3, –4.39, –4.41, –4.7, –4.8; m/z (+ve FIB, NOBA matrix) $C_{113}H_{190}O_{23}Si_3$ (M^+) requires 1999, found 2000 ($[M+H]^+$), 2023 ($[M+Na+H]^+$).

Dimeric seco acid (17)

A mixture of the $C_{21'}$,$C_{23'}$ diol **16** (27.7 mg, 13.9 μmol) and barium hydroxide octahydrate (powdered, 1.75 g, 5.56 mmol) in MeOH (2 ml) was stirred at room temperature for 97 h. The heavy white suspension was diluted with brine (3 ml) and acidified with 1 *M* HCl to give a clear solution of pH 3-4. This aqueous solution was extracted with EtOAc (2 x 25 + 2 x 10 ml) and the combined organic extracts washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the seco acid **17** as a colourless glass (27.7 mg, 100%). The product **17** was judged to be pure by TLC and ^{1}H NMR (400 MHz, $CDCl_3$) and was used in the macrolactonization reaction without any further purification: R_f = 0.24 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{20}$ = –73.7° (*c* 0.76, $CHCl_3$); IR (liquid film) 3442 (br), 1710 (s) cm^{-1}; ^{1}H NMR δ (400 MHz, C_6D_6) 7.81 (2H, d, J = 8.6 Hz, ArH), 7.62 (2H, d, J = 8.7 Hz, ArH), 7.84-7.78 (1H, buried d, 3-CH or 3'-CH), 7.70 (1H, d, J = 15.6 Hz, 3-CH or 3'-CH), 7.02 (2H, d, J = 8.6 Hz, ArH), 6.88 (2H, d, J = 8.7 Hz, ArH), 6.18 (1H, d, J = 15.6 Hz, 2-CH or 2'-CH), 6.05 (1H, br dd, 5-CH or 5'-CH), 6.00 (1H, d, J = 15.6 Hz, 2-CH or 2'-CH), 5.94 (1H, br dd, J = 7.5, 7.5 Hz, 5-CH or 5'-CH), 5.87 (1H, d, J = 8.9 Hz, 21-CH), 5.72-5.62 (2H, overlapping m, 11-CH and 11'-CH), 5.69 (1H, s, ArCH), 5.62-5.52 (2H, overlapping dd, 10-CH and 10'-CH), 5.61 (1H, s, ArCH), 4.65-4.55 (2H, overlapping m, CHO or OH), 4.41 (1H, br d, J = 10.1 Hz, CHO or OH), 4.35-4.25 (1H, br m, CHO or OH), 4.25-3.89 (9H, overlapping m, CHO or OH), 3.82 (1H, br d, J = 6.9 Hz, CHO or OH), 3.70-3.53 (4H, overlapping m, CHO or OH), 3.50-3.30 (4H, buried m, CHO or OH), 3.45 (3H, s,OMe), 3.44 (3H, s, OMe), 3.42 (3H, s, OMe), 3.38 (3H, s, OMe), 3.21-3.14 (1H, buried m or dd, CHO or OH), 3.20 (3H, s, OMe), 3.18 (3H, s, OMe), 2.50-2.40, 2.40-2.20, 2.20-2.08, 2.08-1.50 and 1.50-1.32 (1H, 3H, 2H, 35H and 3H respectively, overlapping m, 18 x CH_2 and 8 x CH), 1.72 (3H, s, 4-CMe or 4'-CMe), 1.59 (3H, s, 4-CMe or 4'-CMe), 1.32-1.20 (15H, overlapping d, 5 x CHMe), 1.20-1.07 (3H, buried d, CHMe), 1.14 (9H, s, ^{t}Bu), 1.07-0.95 (6H, buried d, 2 x CHMe), 1.00 (9H, s, ^{t}Bu), 0.99 (9H, s, ^{t}Bu), 0.93 (3H, d, J = 7.1 Hz, CHMe), 0.90 (3H, d, J = 6.7 Hz, CHMe), 0.50 (3H, s, SiMe), 0.35 (3H, s, SiMe), 0.22 (3H, s, SiMe), 0.20 (3H, s, SiMe), 0.07 (3H, s, SiMe), 0.05 (3H, s, SiMe); ^{13}C NMR δ (100.6 MHz, C_6D_6) 170.2, 167.1, 160.4, 160.2, 150.8, 149.9, 138.7, 138.4, 134.51, 134.46, 132.4, 132.1, 130.7, 128.6, 128.3, 127.3, 124.2, 124.0, 116.8, 116.2, 114.0, 113.8, 101.6, 101.1, 81.0, 80.0, 78.9, 78.7, 76.3, 75.9, 75.8, 75.1, 73.6, 73.5, 71.9, 71.4, 71.3, 69.5, 69.4, 68.5, 68.4, 65.1, 64.7, 64.5, 64.3, 57.9, 55.01, 55.00, 54.8, 42.3, 42.1, 41.1, 40.9, 40.5, 40.0, 39.1, 38.7, 38.2, 38.1, 38.0, 36.4, 36.1, 35.6, 35.4, 35.2, 33.6, 31.71, 31.66, 31.5, 30.1, 29.4, 29.2, 27.5, 27.0, 26.9, 26.14, 26.12, 22.0, 21.9, 19.1, 18.3, 17.4, 17.0, 12.6, 12.4, 11.4, 11.3, 11.2, 11.0, 8.84, 8.77, –2.6, –3.95, –4.04, –4.1, –4.5, –4.6; m/z (+ve FIB, NOBA matrix) $C_{112}H_{188}O_{23}Si_3$ (M^+) requires 1985, found 1986 ($[M+H]^+$), 2008 ($[M+Na]^+$).

Macrodiolides 18 and 19 using the Yamaguchi Method

To a stirred solution of the seco acid **17** (15.2 mg, 7.66 μmol) in PhMe (1 ml) at room temperature was added Et_3N (0.5 *M* in PhMe, 94 μl, 47 μmol) and 2,4,6-trichlorobenzoyl chloride (78 μl, 39 μmol, 0.5 *M* in PhMe).

A further 188 µl (94 µmol) of Et_3N and 156 µl (78 µmol) of 2,4,6-trichlorobenzoyl chloride were added after 1 h. The reaction mixture was stirred for a total of 2.5 h. This solution was diluted with PhMe (2 ml) and added to a refluxing solution of DMAP in PhMe (4 ml) at 80 °C over 2 h *via* syringe pump. The anhydride flask was washed with PhMe (1 ml) and the washings added to the mixture over 20 min. The reaction was then heated under reflux for a total of 15 h. After cooling, the white suspension was diluted with $NaHCO_3$ solution (4 ml, sat. aq.) and stirred until the solution became clear. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 4 ml). The combined organic extracts were washed with brine (8 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product mixture was purified by preparative thin-layer chromatography (eluting with 5% MeOH/CH_2Cl_2) to give the macrodiolides **18** and **19** (12.7 mg, 84%) as a colourless oil (R_f = 0.48). Analysis of the ^1H NMR spectrum indicated an 83 : 17 mixture of **18** and **19**. This mixture was submitted to the subsequent deprotection reaction without any separation.

Swinholide A (1) and Isoswinholide A (3)

To a solution of the mixture of protected compounds **18** and **19** (83 : 17, 9.5 mg, 4.83 µmol) at 0 °C in CH_3CN (0.5 ml) was added HF (0.2 ml, 40% aq.) and the resulting solution was stirred for 105 min. The reaction mixture was quenched with $NaHCO_3$ solution (8 ml, sat. aq.) to destroy excess HF and extracted with EtOAc (4 x 6 ml). The combined organic extracts were washed with brine (6 ml), dried ($MgSO_4$) and evaporated *in vacuo*. The crude product mixture was purified by preparative reverse phase HPLC (95% MeOH/H_2O) to give swinholide A (**1**) (2.5 mg, 37%) and isoswinholide A (**3**) (0.8 mg, 12%), both as colourless oils.

Swinholide A (**1**): R_f = 0.22 (5% MeOH/CH_2Cl_2); t_R = 18.5 min (95% MeOH/H_2O); CD 280 nm (max., MeOH), Δε –5.6 (0.72 mM) (authentic sample: 280 nm (max., MeOH), Δε –5.1 (0.43 mM)), lit[2] 280 nm (max., MeOH), Δε –5.0; [α]\s(20. D) = –4.69° (*c* 0.32 $CHCl_3$) (authentic sample: –1.64° (*c* 0.07 $CHCl_3$)), lit[1b,d] $[\alpha]_D^{20}$ = +16.0° (*c* 1.3 $CHCl_3$); IR ($CHCl_3$) 3443 (m, br), 1683 (s), 1617 (s) cm^{-1}, lit[1b,d] ($CHCl_3$) 3440, 1675, 1615 cm^{-1}; UV 270 nm (MeOH), lit[1b,d] 270 nm (MeOH); ^1H NMR δ ($CDCl_3$, 500 MHz) see **Table 2** at the end of the experimental section; ^{13}C NMR δ ($CDCl_3$, 100.6 MHz) 170.0, 153.2, 142.3, 134.3, 129.9, 123.3, 113.3, 76.1, 75.2, 74.5, 73.9, 73.3, 71.4 (2C), 66.7, 65.9, 65.8, 64.7, 57.5, 55.3, 41.4, 41.1, 41.0, 38.7, 38.6, 37.8, 37.5, 34.9, 34.0, 33.3, 30.0, 29.4, 24.0, 21.8, 17.8, 12.3, 9.5, 9.3, 9.2; HRMS (+ve FAB, NOBA matrix) $[M+H]^+$ $C_{78}H_{133}O_{20}$ requires 1389.9389, found 1389.9447. Copies of the ^1H and ^{13}C NMR spectra are provided with the supplementary material in ref. 6.

Isoswinholide A (**3**): R_f = 0.48 (10% MeOH/CH_2Cl_2); t_R = 20.5 min (95% MeOH/H_2O); $[\alpha]_D^{20}$ = –44.5° (*c* 0.30, $CHCl_3$), lit[1f] $[\alpha]_D^{20}$ = –42.0° (*c* 0.51, $CHCl_3$); IR ($CHCl_3$) 3442 (m, br), 1684 (s), 1616 (s) cm^{-1}; ^1H NMR δ ($CDCl_3$, 500 MHz) 7.44 (1H, d, *J* = 15.6 Hz, 3'-C<u>H</u>), 7.40 (1H, d, *J* = 15.8 Hz, 3-C<u>H</u>), 6.10 (2H, br dd, *J* = 6.1 Hz, 5-C<u>H</u> and 5'-C<u>H</u>), 5.90-5.75 (2H, m, 11-C<u>H</u> and 11'-C<u>H</u>), 5.85, (1H, d, *J* = 15.6 Hz, 2'-C<u>H</u>), 5.83 (1H, d, *J* = 15.6 Hz, 2-C<u>H</u>), 5.70-5.60 (2H, m, 10-C<u>H</u> and 10'-C<u>H</u>), 5.34 (1H, d, *J* = 10.6 Hz, 21-C<u>H</u>), 4.95-4.85 (1H, br dd, 23'-C<u>H</u>), 4.60-4.40 (2H, m, 9-C<u>H</u> and 9'-C<u>H</u>), 4.24 (1H, br d, *J* = 10.0 Hz, 19'-C<u>H</u>), 4.10 (1H, m, 7-C<u>H</u>), 4.05-3.90 (3H, buried m, 7'-C<u>H</u>, 27-C<u>H</u> and 27'-C<u>H</u>), 3.90-3.60 (9H, overlapping m, 13-C<u>H</u>, 13'-C<u>H</u>, 15-C<u>H</u>, 15'-C<u>H</u>, 17-C<u>H</u>, 17'-C<u>H</u>, 19-C<u>H</u>, 31-C<u>H</u> and 31'-C<u>H</u>), 3.60-3.44 (3H, overlapping m, 21'-C<u>H</u>, 29-C<u>H</u> and 29'-C<u>H</u>), 3.37 (3H, s, 15-O<u>Me</u>), 3.35 (3H, s, 15'-O<u>Me</u>), 3.34 (6H, s, 29-O<u>Me</u> and 29'-O<u>Me</u>), 3.07 (1H, br d, 23-C<u>H</u>), 2.50-2.22 (4H, overlapping m, 6-C<u>H</u>$_2$ and 6'-C<u>H</u>$_2$), 2.22-1.10 (40H, overlapping m, 8-C<u>H</u>$_2$, 8'-C<u>H</u>$_2$, 12-C<u>H</u>$_2$, 12'-C<u>H</u>$_2$, 14-C<u>H</u>$_2$, 14'-C<u>H</u>$_2$, 16-C<u>H</u>, 16'-C<u>H</u>, 18-C<u>H</u>$_2$, 18'-C<u>H</u>$_2$, 20-C<u>H</u>, 20'-C<u>H</u>, 22-C<u>H</u>, 22'-C<u>H</u>, 24-C<u>H</u>, 24'-C<u>H</u>, 25-C<u>H</u>$_2$, 25'-C<u>H</u>$_2$, 26-C<u>H</u>$_2$, 26'-C<u>H</u>$_2$, 28-C<u>H</u>$_2$, 28'-C<u>H</u>$_2$, 30-C<u>H</u>$_2$, 30-C<u>H</u>$_2$), 1.84 (3H, s, 4'-C<u>Me</u>), 1.81 (3H, s, 4-C<u>Me</u>), 1.19 (6H, d, *J* = 6.0 Hz, 31-C<u>Me</u> and 31'-C<u>Me</u>), 0.99 (3H, d, *J* = 6.5 Hz, 24-C<u>Me</u>), 0.92 (3H, d, *J* = 6.7 Hz, 24'-C<u>Me</u>), 0.90-0.88 (6H, d, 20-C<u>Me</u> and 22'-C<u>Me</u>), 0.86 (3H, d, *J* = 6.7 Hz, 22-C<u>Me</u>), 0.80 (9H, d, *J* = 6.7 Hz, 16-C<u>Me</u>, 16'-C<u>Me</u> and 20'-C<u>Me</u>); HRMS (+ve FAB, NOBA matrix) $[M+H]^+$ $C_{78}H_{133}O_{20}$ requires 1389.9389, found 1389.9392.

Table 1: ^{1}H NMR Data[a] in $CDCl_3$ for Hemiswinholide A (**2**)[b]

Atom	δ_H	Mult	J Hz	δ_H (lit[c])	Mult	J Hz (lit)
1	-	-	-	-	-	-
2	5.78	d	15.5	5.80	d	15.5
3	7.35	d	15.5	7.38	d	15.5
4	-	-	-	-	-	-
4-Me	1.79	s	-	1.81	s	-
5	5.87	dd	8.6, 8.3	5.89	dd	8.5, 8.5
6	2.50	m	-	2.50	m	-
	2.50	m	-	2.50	m	-
7	3.99	m	-	4.01	m	-
8	1.73	m	-	1.75	m	-
	1.25	m	-	1.30	m	-
9	4.44	br d	10.1	4.47	br d	10.0
10	5.67	br d	10.1	5.67	br d	10.0
11	5.80	m	-	5.82	m	-
12	2.00	m	-	2.02	m	-
	1.92	m	-	1.95	m	-
13	3.38	m	-	3.40	m	-
14	1.80	m	-	1.82	m	-
	1.58	m	-	1.60	m	-
15	3.45	m	-	3.50	m	-
15-OMe	3.35	s	-	3.37	s	-
16	1.67	m	-	1.70	m	-
16-Me	0.78	d	7.0	0.81	d	7.0
17	3.68	m	-	3.70	m	-
18	1.70	m	-	1.70	m	-
	1.60	m	-	1.60	m	-
19	3.86	br t	5.1	3.89	m	-
20	2.00	m	10.3, 7.2	2.02	m	-
20-Me	0.89	d	7.0	0.93	d	7.0
21	5.21	br d	9.1	5.24	dd	10.5, 1.5
22	1.92	m	-	1.95	m	-
22-Me	0.84	d	6.9	0.87	d	7.0
23	3.38	m	-	3.36	dd	9.5, 2.0
24	1.67	m	-	1.70	m	-
24-Me	0.99	d	6.7	1.02	d	7.0
25	1.37	m	-	1.44	m	-
	1.27	m	-	1.30	m	-
26	1.99	m	-	2.02	m	-
	1.22	m	-	1.25	m	-
27	3.97	m	-	3.99	m	-
28	1.79	m	-	1.82	m	-
	1.57	m	-	1.60	m	-
29	3.53	m	-	3.55	dddd	12, 10, 4.5, 4.5
29-OMe	3.32	s	-	3.35	s	-
30	1.99	m	-	2.02	m	-
	1.14	m	-	1.17	m	-
31	3.68	m	-	3.72	m	10.2, 2.9, 6.4
31-Me	1.18	d	6.2	1.20	d	6.5

[a]Measured at 400 MHz. Assignments were determined by COSY experiments.

[b]Copies of the spectra are provided with the supplementary material in ref. 6.

[c]Measured at 500 MHz, taken from ref. 2.

Table 2: ^{1}H NMR Data[a] in $CDCl_3$ for Swinholide A (**1**)[b]

Atom	δ_H	Mult	*J* Hz	δ_H (lit[c])	Mult	*J* Hz (lit)
1	-	-	-	-	-	-
2	5.79	d	15.6	5.79	d	15.8
3	7.59	d	15.6	7.58	d	15.8
4	-	-	-	-	-	-
4-Me	1.81	s	-	1.83	s	-
5	6.08	dd	9.3, 5.0	6.08	dd	9.6, 5.3
6	2.46	ddd	14.5, 9.5, 9.5	2.46	ddd	14.7, 9.6, 9.6
	2.17	br dd	14.5, 4.1	2.18	br d	14.7
7	4.14	m	-	4.14	br dd	9.7, 9.6
8	1.63	m	-	1.63	m	-
	1.58	m	-	1.58	m	-
9	4.52	br d	8.4	4.51	br d	8.9
10	5.70	br dd	10.0, 2.0	5.69	br dd	10.4, 1.8
11	5.77	br dd	10.0, 2.2	5.78	br d	10.4
12	2.29	br d	17.5	2.27	br d	16.1
	1.82	m	-	1.82	m	-
13	3.89	dd	10.9, 4.2	3.86	m	-
14	2.14	ddd	14.3, 10.5, 4.2	2.14	ddd	14.0, 10.7, 4.0
	1.45	ddd	14.3, 10.5, 3.8	1.46	ddd	14.0, 10.7, 3.4
15	4.01	m	-	4.01	m	-
15-OMe	3.36	s	-	3.35	s	-
16	1.68	m	-	1.68	m	-
16-Me	0.81	d	7.0	0.81	d	7.0
17	3.83	dd	9.3, 9.3	3.83	dd	9.8, 9.8
18	1.69	m	-	1.69	m	-
	1.62	m	-	1.62	m	-
19	4.00	m	-	3.98	m	-
20	1.75	dq	10.3, 7.2	1.75	dq	10.5, 7.0
20-Me	0.98	d	7.4	0.97	d	7.0
21	5.36	d	10.7	5.36	d	10.6
22	1.95	m	-	1.95	m	-
22-Me	0.84	d	7.0	0.84	d	7.0
23	3.13	d	9.4	3.12	d	9.5
24	1.65	m	-	1.65	m	-
24-Me	1.00	d	7.3	0.99	d	6.7
25	1.38	m		1.38	m	-
	1.27	m	-	1.27	m	-
26	1.90	m	-	1.90	m	-
	1.30	m	-	1.30	m	-
27	4.02	m	-	4.02	m	-
28	1.82	m	-	1.82	m	-
	1.60	m	-	1.60	m	-
29	3.53	m	-	3.53	dddd	10, 10, 5.5, 5.5
29-OMe	3.34	s	-	3.33	s	-
30	1.96	m	-	1.96	m	-
	1.18	m	-	1.18	ddd	12.5, 10.4, 10.2
31	3.68	m	-	3.69	ddq	10.2, 2.9, 6.4
31-Me	1.20	d	6.2	1.20	d	6.4

[a]Measured at 500 MHz. Assignments were determined by COSY experiments.

[b]Copies of the spectra are provided with the supplementary material in ref. 6.

[c]Measured at 500 MHz, taken from ref. 1d.

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