A Convergent Approach to Swinholide A. Stereoselective Construction of the C_3–C_{17} Fragment of Swinholide A

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A strategy for a total synthesis of the cytotoxic dimeric macrolide swinholide A (**1**, Scheme 1) is outlined and a stereoselective construction of the suitably functionalized C_3–C_{17} fragment **4**, starting with building blocks **6**, **7**, **9** and **10** is described.

Swinholide A (**1**, Scheme 1) is a highly functionalized, 44-membered cytotoxic macrolide with an interesting biological profile.[1] Isolated from the marine sponge *Theonella swinhoei*[2] and fully characterized by NMR and X-ray crystallographic analyses,[3] this compound displays potent cytotoxic activity against L1210 (IC_{50} = 0.03 μg ml^{-1}) and KB(IC_{50} = 0.04 μg ml^{-1}) tumour cell lines. It has been proposed[1] that the high cytotoxicity may be related to swinholide's preference to assume a severely folded conformation (resembling a twisted saddle), with turns at the dihydropyran rings and the C_{21} and $C_{21'}$ atoms. Interestingly, the hydroxy acid monomer of swinholide A was recently isolated from marine sources as a natural product,[4] suggesting a possible biosynthetic pathway to swinholide through its monomer. Furthermore, misakinolide, a related compound, lacking the two disubstituted double bonds adjacent to the carbonyls C_1 and $C_{1'}$, has been found in the same sponge, revealing additional information about the occurrence and biosynthesis of these intriguing compounds.[5] In this communication, we outline a highly convergent strategy towards this target[6] (Scheme 1), and describe a stereoselective construction of the fully functionalized C_3–C_{17} fragment **4** (Scheme 2).

Scheme 1 depicts the strategic bond disconnections and retrosynthetic analysis of swinholide A **1**. Sequential disconnections at *a*, *a'*, *b* and *b'* (structures **1** and **2**) lead to the dimeric and monomeric structures **2** and **3**, respectively, with a ketophosphonate–aldehyde condensation[7] and an esterification[8] playing crucial roles in the synthetic strategy. Further disconnection at the C_{17}–C_{18} bond of **3** as indicated by *c*, reveals fragments **4** and **5** as potential key intermediates for the construction of **3**.[9] Fragment **4** can be further simplified by disconnections *d* and *e* yielding the lactol **8** and the silyl-enolethers **6** and **7**. Finally, disassembly of the six-membered ring as shown (disconnection *f*),[10] gives epoxide **9** and the sulfone orthoester **10** as potential starting points for the synthesis of **4**.

Scheme 2† summarizes the construction of **4** starting with (*S*)-dimethyl malate **11** which upon reduction with BH_3·Me_2S/$NaBH_4$ gave the corresponding 1,2-diol (92%).[11] Sequential silylation of this diol with TBDPSCl and TBSOTf (78% overall yield), followed by DIBAL reduction[12] (96%) furnished the bis-silyl ether aldehyde **12**. Asymmetric crotylboration of **12** using (+)-β-methoxydiisopinocampheylborane under Brown's conditions[13] (90%), followed by methylation (91%), led to the formation of compound **13** (>20:1 diastereoselectivity by ^{1}H NMR analysis). Ozonolysis of **13**, followed by reductive work-up and protection with *p*-methoxybenzyl trichloroacetimidate,[14] afforded the corresponding *p*-methoxybenzyl ether in 78% overall yield. Complete desilylation with excess TBAF and reprotection with TBDPSCl gave **14** (85%). Epoxide **9** was then obtained after mesylation of the secondary alcohol (97%), and exposure to anhydrous TBAF (91%).

The employment of Ghosez's methodology for the synthesis of α,β-unsaturated δ-lactones,[10] was instrumental in establishing the desired lactone **15**. Thus, the epoxide **9** was treated with the lithio-derivative of methyl-3-phenylsulfonyl orthopropionate **10** to afford, after acid hydrolysis and DBU-induced elimination, lactone **15**‡ in 92% overall yield (one pot, three steps). Subsequent DIBAL reduction of **15** led to lactol **8** (95%) and *C*-glycosidation of **8**, using $Bu^tMe_2SiOCH=CH_2$ **7**[15] and $ZnCl_2$, furnished aldehyde **16** in 65% yield (*ca.* 4:1 α:β isomeric ratio chromatographically separated).

Aldehyde **16** was then subjected to a Mukaiyama-type aldol reaction using vinylketene acetal **6**[16] and BF_3·Et_2O to afford hydroxy ester **17** in 99.5% yield (*ca.* 1.4:1 diastereoisomeric ratio at C-7, by ^{1}H NMR). Chromatographic separation of the two isomers and silylation at the C-7 hydroxy group of the major isomer **17** using TBSOTf, led to silyl ether **18** (89% yield). The stereochemistry in compounds **17** and **18** was based on ^{1}H and ^{13}C NMR comparisons with a similar intermediate reported by Paterson's group.[6c] Liberation[17] of the primary alcohol in **18**, with DDQ (76%), followed by Swern[18] oxidation (92%) and dithiane formation (85%), afforded **19**. Finally, the targeted intermediate **4**‡ was reached in two steps by reduction of **19** with DIBAL and silylation in 75% overall yield.

The following communication[19] describes the construction of the remaining requisite fragment **5** (C_{18}–C_{32}).

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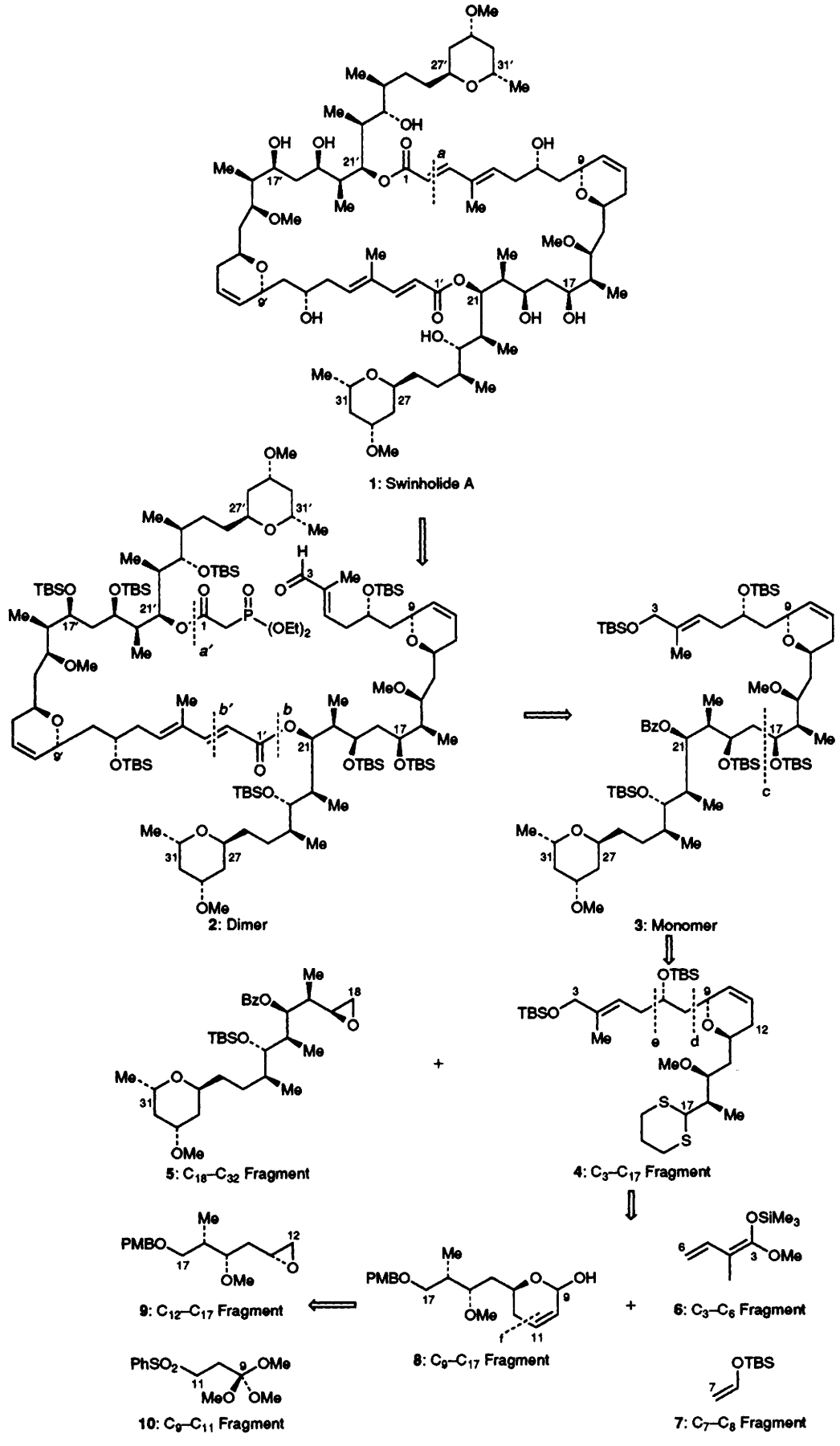
Footnotes

† All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous material.

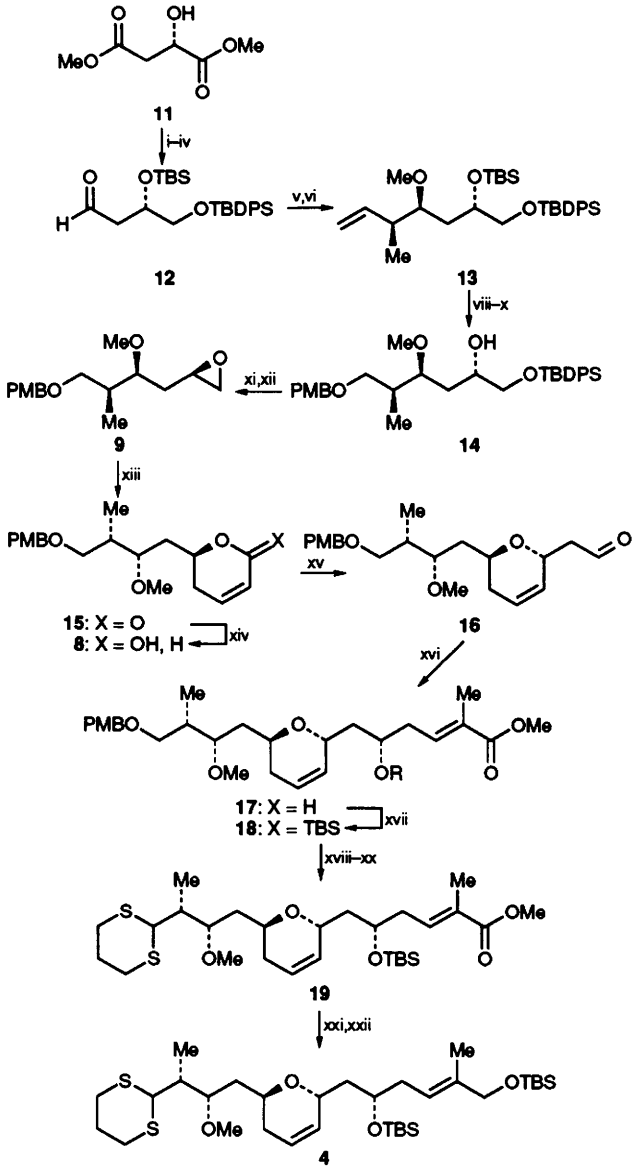
‡ *Selected data* for compounds:

15: Pale yellow oil: R_f 0.30 (silica, 70% Et_2O in light petroleum); IR (neat) ν_{max}/cm^{-1}; 2932.6, 1710.0, 1611.7, 1585.6, 1512.7, 1462.2, 1387.8, 1301.7, 1246.7, 1173.8, 1088.7, 1035.9, 960.4, 817.6, 755.6 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.25 (d, *J* 8.5 Hz, 2 H, Ar-H), 6.88–6.87 (d, *J* 8.5 Hz, 2 H, Ar-H), 6.87–6.85 (m, 1 H, H-11), 6.04–6.02 (d, *J* 10 Hz, 1 H, H-10), 4.56–4.50 (ddt, *J* 5.5, 5.0, 1.3 Hz, 1 H, H-13), 4.43 (s, 2 H, $ArCH_2$-O), 3.81 (s, 3 H, CH_3-OAr), 3.50–3.41 (m, 2 H, H-17), 3.34–3.29 (m, 1 H, H-15), 3.32 (s, 3H, C-15-OCH_3), 2.38–2.36 (m, 2 H, H-12), 2.07–2.00 (m, 1 H, H-16), 2.03–1.98 (m, 1 H, H-14), 1.80–1.76 (m, 1 H, H-14), 0.95–0.92 (d, *J* 6.5 Hz, 3 H, C-16-CH_3); HRMS (FAB) Calc. for $C_{19}H_{26}O_5Cs$ (M + Cs): 467.0835; found *m/z* 467.0842.

4: Pale yellow oil: R_f 0.21 (silica, 6% Et_2O in light petroleum); IR (neat) ν_{max}/cm^{-1}; 2927.1, 2854.8, 1723.6, 1676.8, 1461.8, 1360.4, 1252.1, 1187.5, 1073.1, 1005.5, 938.6, 836.5, 775.2, 699.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.77–5.73 (m, 1 H, 11-H), 5.65–5.53 (dt, *J* 10.5, 1.6 Hz, 1 H, H-10), 5.56–5.52 (dt, *J* 8, 1.2 Hz, 1 H, H-5), 4.35–4.32 (bd, *J* 10.5 Hz, 1 H, H-9), 4.21–4.19 (d, *J* 7.3 Hz, 1 H, H-17), 4.16–4.10 (m, 1 H, H-7), 4.03 (s, 2 H, H-3), 3.79–3.70 (dt, *J* 7.7, 5.2 Hz, 1 H, H-15), 3.56–3.50 (m, 1 H, H-13), 3.40 (s, 3 H, C-15-OCH_3), 2.92–2.79 (m, 4 H, CH_2S), 2.27–2.22 (m, 2 H, H-6), 2.11–2.06 (m, 1 H, $SCH_2CH_2CH_2S$), 2.04–1.95 (m, 1 H, H-12), 1.93–1.80 (m, 5 H, H-16, H-14, H-12, $SCH_2CH_2CH_2S$), 1.68–1.58 (m, 1 H, H-8), 1.60–1.59 (s, 3 H, C-4-CH_3), 1.43–1.33 (ddd, *J* 14.3, 10.5, 2.4 Hz, 1 H, H-8),



Scheme 1 Strategic bond disconnections and retrosynthetic analysis of swinholide A **1**. Definition of requisite intermediates for a total synthesis of fragments **4** and **5**. TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; PMB = *p*-methoxybenzyl.



Scheme 2 Synthesis of C_3–C_{17} fragment **4**. *Reagents and conditions*: i, $BH_3{\cdot}SMe_2$ (1.04 equiv.), −78 °C, 30 min then $NaBH_4$ (0.05 equiv.), THF (0.5 mol dm^{-3}), 0 °C, 4 h, 92%; ii, TBDPSCl (1.1 equiv.), Et_3N (2.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2 (0.2 mol dm^{-3}), 25 °C, 14 h, 91%; iii, TBSOTf (1.2 equiv.), 2,6-lutidine (1.75 equiv.), CH_2Cl_2 (0.25 mol dm^{-3}), 25 °C, 2 h, 86%; iv, DIBAL (1.1 equiv.), CH_2Cl_2 (0.1 mol dm^{-3}), quench MeOH (10.0 equiv.), −78 °C, 30 min, 96%; v, KOBu^t (1.0 equiv.), (*Z*)-but-2-ene (2.0 equiv.), Bu^{n}Li (1.0 equiv.), THF (0.5 mol dm^{-3}), −78 to −55 °C then (+)-β-methoxydiisopinocampheylborane (1.2 equiv.), $BF_3{\cdot}OEt_2$ (1.34 equiv.), aldehyde **12**, then −78 °C, 12 h, NaOH (1.8 equiv.), H_2O_2 (1.0 equiv.), −78 to 67 °C, 1 h reflux, 90%; vi, NaH (4.0 equiv.), MeI (10.0 equiv.), THF (0.15 mol dm^{-3}), 0 °C, 14 h, 91%; vii, O_3, till blue, then $NaBH_4$ (4.0 equiv.), CH_2Cl_2 (0.025 mol dm^{-3}), MeOH (0.025 mol dm^{-3}), −78 °C, 95%; viii, *p*-methoxybenzyl 2,2,2-trichloroacetimidate (4.0 equiv.), CSA (0.15 equiv.), CH_2Cl_2 (0.25 mol dm^{-3}), 25 °C, 14 h, 83%; ix, TBAF (2.2 equiv.), THF (0.1 mol dm^{-3}), 0 °C, 2 h, 100%; x, TBDPSCl (1.1 equiv.), Et_3N (2.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2 (0.2 mol dm^{-3}), 14 h, 85%; xi, MsCl (1.2 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2 (0.2 mol dm^{-3}), 0 °C, 1.5 h, 97%; xii, TBAF (3.0 equiv., anhydrous), THF (0.1 mol dm^{-3}), 25 °C, 10 h, 91%; xiii, 3-phenylsulfonyl-orthopropionate **10** (4.0 equiv.), DMPU (16.0 equiv.), THF (0.33 mol dm^{-3}), Bu^{n}Li (4.0 equiv.), epoxide **9** (1.0 equiv.), −78 to −20 °C then 0 °C, H_2SO_4 (30.0 equiv.), 30 min then workup, next resuspend CH_2Cl_2 (0.33 mol dm^{-3}), TsOH (0.38 equiv.), 48 h, then cool −10 °C, Et_3N (1.5 equiv.), DBU (4.0 equiv.), 2 h conc., 92%; xiv, DIBAL (1.25 equiv.), CH_2Cl_2 (0.05 mol dm^{-3}), −78 °C, 30 min, 95%; xv, $ZnCl_2$ (1.0 equiv.), $CH_2{=}CH_2OTBS$ (2.0 equiv.), CH_2Cl_2 (0.1 mol dm^{-3}), −20 °C, 15 min, 65%; xvi, 1-methoxy-1-trimethylsiloxy-2-methyl-1,3-butadiene **6** (2.06 equiv.), $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2/Et_2O, 9:1 (0.09 mol dm^{-3}), −78 °C, 1.4:1, 99.5%; xvii, 2,6-lutidine (4.0 equiv.), TBSOTf (2.0 equiv.), CH_2Cl_2 (0.01 mol dm^{-3}), −78 °C, 1 h, 89%; xviii, DDQ (2.0 equiv.), CH_2Cl_2/H_2O, 20:1 (0.018 mol dm^{-3}), 25 °C, 45 min, 76%; xix, $(COCl)_2$ (5.0 equiv.), Me_2SO (7.0 equiv.), CH_2Cl_2 (0.15 mol dm^{-3}), −78 °C, 20 min, then Et_3N (15.0 equiv.), −78 to 25 °C, 92%; xx, 1,3-propane-dithiol (5.0 equiv.), $TiCl_4$ (2.0 equiv.), CH_2Cl_2 (0.03 mol dm^{-3}), −78 °C, 1 h 85%; xxi, DIBAL (3.0 equiv.), THF (0.03 mol dm^{-3}), −78 °C, 2.5 h; xxii, 2,6-lutidine (4.0 equiv.), TBSOTf (2.0 equiv.), CH_2Cl_2 (0.033 mol dm^{-3}), −78 °C, 1 h, 75% two steps. Tf = CF_3SO_2; Ms = $MeSO_2$; CSA = camphorsulfonic acid; DMPU = 1,3-dimethyl-3,4,5-tetrahydro-2(1H)-pyrimidinone; DBU = 1.8-diazabicyclo[5.4.0]undec-7-ene; DIBAL = diisobutylaluminium hydride.

Footnotes (continued)
1.09–1.07 (d, *J* 6.8 Hz, 3 H, C-16-CH_3), 0.89 (s, 9 H, Bu^{t}Si), 0.88 (s, 9 H, Bu^{t}Si), 0.15 (s, 6 H, Me_2Si), 0.07 (s, 6 H, Me_2Si); HRMS (FAB) Calcd. for $C_{33}H_{64}O_4Si_2S_2Na$ (M + Na^+): 667.3682; found *m/z* 667.3680.

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