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

A. P. Patron, P. K. Richter, M. J. Tomaszewski, R. A. Miller and K. C. Nicolaou*

Department of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093 USA
Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, California 92037 USA

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 silylenolethers **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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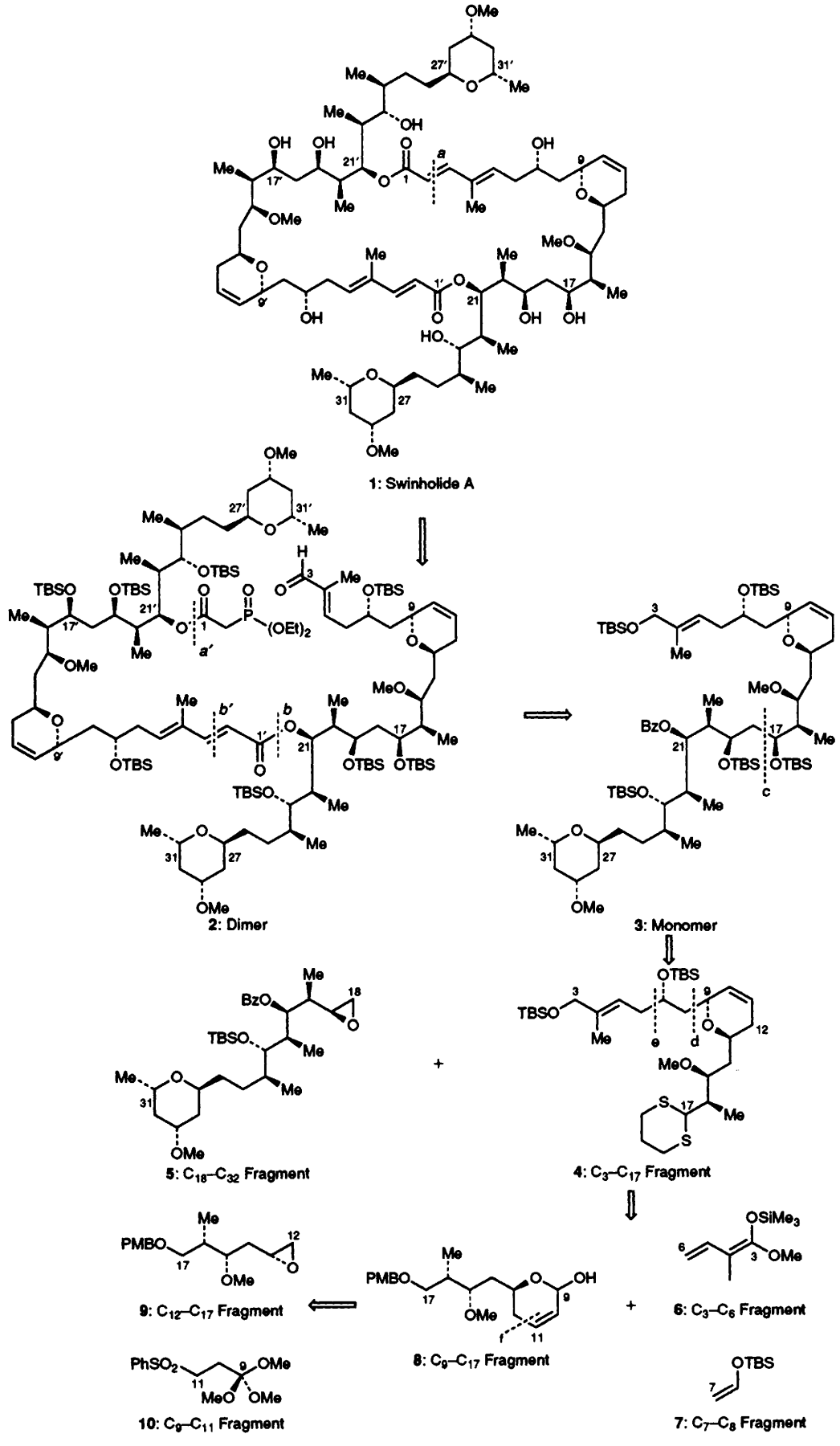
Footnotes

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

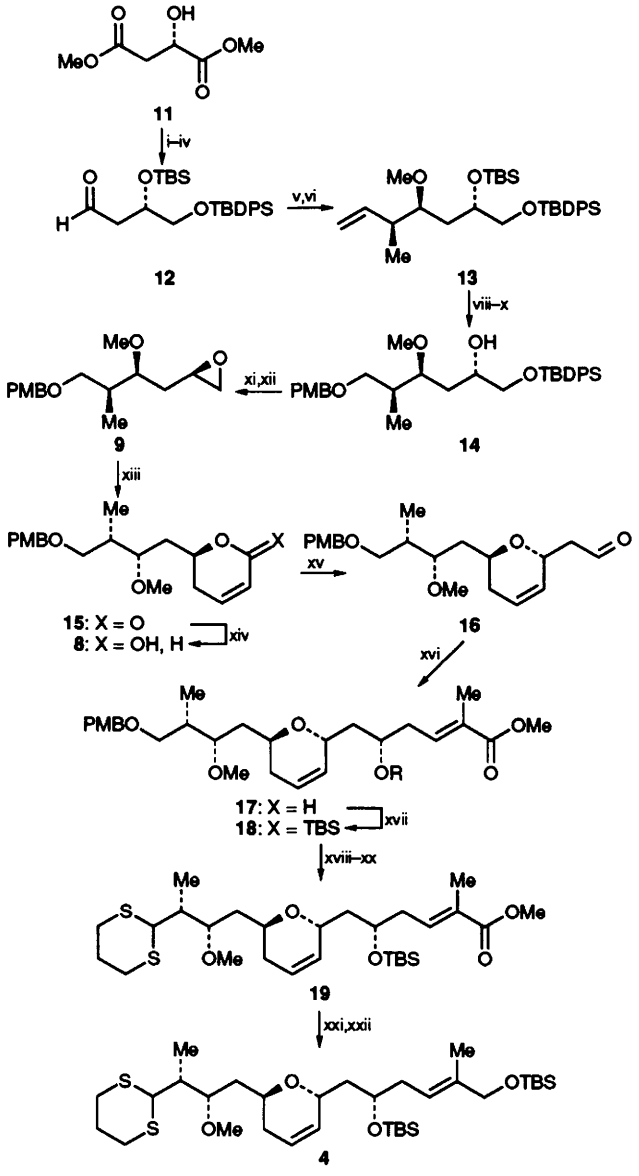
‡ *Selected data* for compounds:

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·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^nLi (1.0 equiv.), THF (0.5 mol dm^{-3}), −78 to −55 °C then (+)-β-methoxydiisopinocampheylborane (1.2 equiv.), BF_3·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^nLi (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.),

Footnotes (continued)
1.09–1.07 (d, *J* 6.8 Hz, 3 H, C-16-CH_3), 0.89 (s, 9 H, Bu^tSi), 0.88 (s, 9 H, Bu^tSi), 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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BF_3·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.

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