Stereoselective Construction of the C_{18}–C_{32} Fragment of Swinholide A

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A stereoselective construction of the fully functionalized C_{18}–C_{32} fragment **3** of swinholide A **1** starting with building blocks **4** and **5** is described.

In the preceding communication[1] we outlined a highly convergent strategy for the total synthesis of swinholide A (**1**, Scheme 1) and a stereoselective construction of an appropriately functionalized C_3–C_{17} fragment **2** of the molecule (Scheme 1). Here, we report an enantioselective synthesis of the second required fragment **3** (C_{18}–C_{32})[2] *via* the intermediacy of key building blocks **4** and **5** defined by the disconnections shown in Scheme 1.

Scheme 2† summarizes the present construction of the C_{18}–C_{32} fragment, starting with L-rhamnose **12** and allyl alcohol **16**. Thus, peracetylation of L-rhamnose **12** (91%) followed by *C*-glycosidation[3] with allyl trimethylsilane in the presence of $BF_3{\cdot}Et_2O$ and TMSOTf, led exclusively, to the corresponding α-glycoside (81%), which was subsequently deacetylated completely with NaOMe and subjected to regioselective methylation[4] using Bu^n_2SnO and MeI in the presence of CsF, to afford compound **13** in 68% overall yield.

The conversion of **13** to iodide **14** required bis(xanthate) formation and subsequent Bu^n_3SnH reduction (51% overall),[5] followed by ozonolysis–reduction (72%) and halogenation[6] with I_2/Ph_3P/imidazole (75%). Enders alkylation[7] using iodide **14** and SAMP hydrazone **15**, followed by ozonolysis to remove the chiral auxiliary group, furnished ketone **4**‡ stereoselectively and in 90% overall yield.

Aldehyde **5** was synthesized in 46% overall yield from allyl alcohol **16** by the following sequence: **16** was benzylated and then ozonized to afford aldehyde **17**. Asymmetric crotylboration of **17** using (−)-β-methoxydiisopinocampheylborane under Brown's conditions[8] followed by benzylation and a second ozonolysis, furnished the targeted aldehyde **5**.‡

Coupling of the two carbonyl fragments **4** and **5** was accomplished *via* the chlorotitanium enolate of ketone **4**, leading to the expected *syn* aldol product[9] **19** in 63% yield. A samarium catalysed intramolecular Tishchenko–Evans reduction[10] of the hydroxy ketone **19** furnished, stereoselectively, the differentiated 1,3-*anti* diol (72%), which was silylated with TBSOTf to afford compound **20** (86%).

Finally, debenzylation of **20** *via* hydrogenolysis, followed by selective monotosylation and base treatment led to the desired epoxide **3**‡ in 65% overall yield. The described chemistry in this and the preceding communication[1] sets the stage for an eventual total synthesis of swinholide A **1** and related compounds.

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1: Swinholide A

2: C_3–C_{17} Fragment

3: C_{18}–C_{32} Fragment

5: C_{18}–C_{21} Fragment

4: C_{22}–C_{32} Fragment

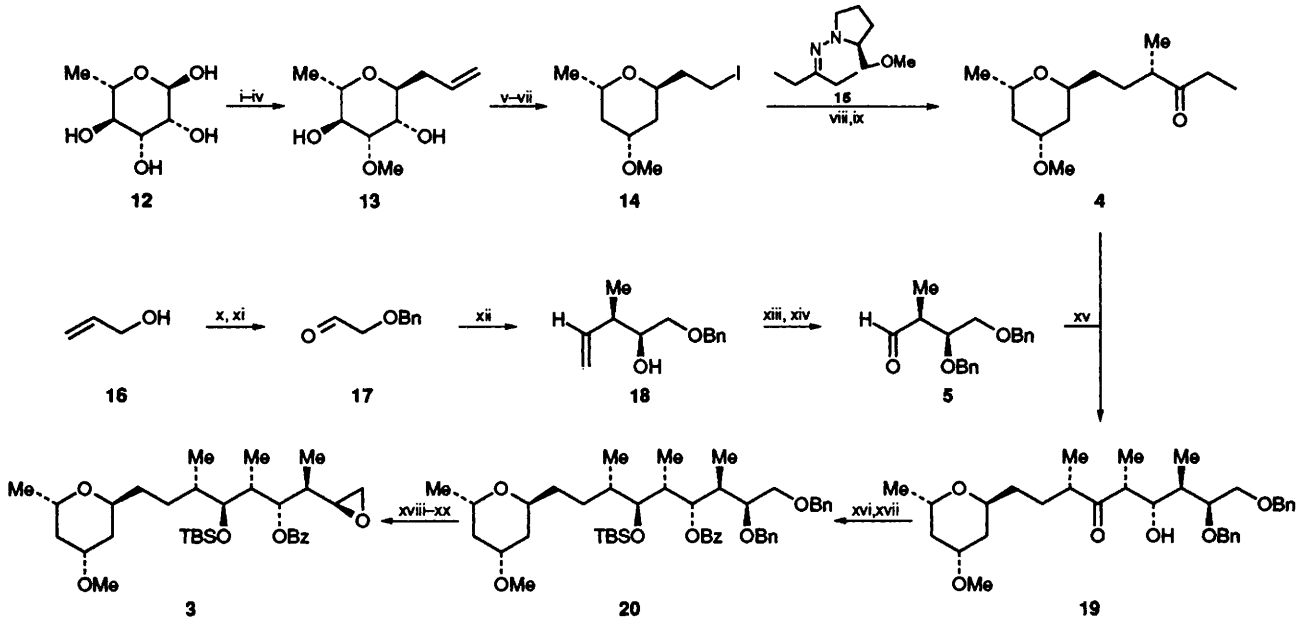
Scheme 1 Strategic bond disconnections and retrosynthetic analysis of swinholide A 1. Definition of requisite intermediates for a total synthesis of fragments **2** and **3**. TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl, PMB = *p*-methoxybenzyl.

Footnotes

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

‡ Selected data for compounds: **4**: Pale-yellow oil; R_f 0.61 (silica, 30% Et_2O in light petroleum); IR (neat) ν_{max}/cm^{-1}; 3401.1, 2940.4, 2810.4, 1708.2, 1454.2, 1371.5, 1277.0, 1253.4, 1194.3, 1152.9, 1105.7, 1028.9, 975.7, 840.3 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.95–3.92 (m, 1 H, H-27), 3.66–3.62 (m, 1 H, H-31), 3.48–3.44 (m, 1 H, H-29), 3.29 (s, 3 H, C-29-OCH_3), 2.60–2.50 (m, 1 H, H-24), 2.48–2.38 (m, 2 H, H-22), 1.95–1.91 (m, 1 H, H-30), 1.79–1.75 (m, 1 H, H-28), 1.67–1.58 (m, 2 H, H-25, H-26), 1.57–1.51 (m, 1 H, H-28), 1.46–1.39 (m, 1 H, H-25), 1.30–1.20 (m, 1 H, H-26), 1.17–1.16 (d, *J* 6.5 Hz, 3 H, H-32), 1.18–1.11 (m, 1 H, H-30), 1.06–1.04 (d, *J* 7.0 Hz, 3 H, C-24-CH_3), 1.03–1.00 (t, *J* 7.0 Hz, H-21); HRMS (FAB) Calcd. for $C_{14}H_{26}O_3Na$ (M + Na^+): 265.1780; found *m/z* 265.1790.

5: Pale-yellow oil; R_f 0.53 (silica, 15% Et_2O in light petroleum); IR (neat) ν_{max}/cm^{-1}; 3030.0, 2865.0, 2718.7, 1935.9, 1875.4, 1811.2, 1724.2, 1604.3, 1453.6, 738.0, 689.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 9.76 (s, 1 H, H-21), 7.41–7.30 (m, 10 H, ArH), 4.72–4.56



Scheme 2 Synthesis of C_{18}–C_{32} fragment **3**. *Reagents and conditions*: (i) Ac_2O (7.0 equiv.), Et_3N (8.0 equiv.), DMAP (0.2 equiv.), CH_2Cl_2 (0.4 mol dm^{-3}), 0 °C, 1 h, 91%; (ii) $CH_2{=}CH_2CH_2SiMe_3$ (2.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), TMSOTf (0.2 equiv.), CH_3CN (0.55 mol dm^{-3}), 0 °C, 3 h, 81%; (iii) NaOMe (0.1 equiv.), MeOH (0.5 mol dm^{-3}), 25 °C, 12 h, 100%; (iv) Bu^n_2SnO (1.2 equiv.), CH_3OH (0.25 mol dm^{-3}), reflux 4 h, concentrate, then CsF (1.2 equiv.), MeI (1.5 equiv.), DMF (0.2 mol dm^{-3}), 50 °C, 12 h, 68%; (v) NaH (3.0 equiv.), CS_2 (4.0 equiv.), MeI (3.4 equiv.), imidazole (0.02 equiv.), THF (0.2 mol dm^{-3}), 25 °C, 2 h, work-up, azeotrope, then add resultant bis-xanthate dropwise to Bu^n_3SnH (4.0 equiv.), AIBN (0.2 equiv.), toluene (0.4 mol dm^{-3}), 110 °C, 1 h, 51%; (vi) O_3, CH_2Cl_2 (0.05 mol dm^{-3}), MeOH (0.05 mol dm^{-3}) until blue, then $NaBH_4$ (2.5 equiv.), −78 °C, 72%; (vii) I_2 (3.0 equiv.), PPh_3 (3.0 equiv.), imidazole (3.0 equiv.), CH_2Cl_2 (0.25 mol dm^{-3}), 4 °C, 12 h, 75%; (viii) SAMP hydrazone **15** (1.5 equiv.), LDA (1.5 equiv.), Et_2O (0.5 mol dm^{-3}), −78 °C, 3 h, then cool −110 °C, iodide **14** (1.0 equiv.), −78 to 25 °C, 12 h, 93%; (ix) O_3, CH_2Cl_2 (0.1 mol dm^{-3}), till blue, −78 °C, 97%; (x) NaH (1.2 equiv.), benzylbromide (1.0 equiv.), TBAI (0.02 equiv.), imidazole (0.1 equiv.), THF (1.0 mol dm^{-3}), 0 °C, 4 h, 90%; (xi) O_3, CH_2Cl_2 (0.1 mol dm^{-3}), until blue, −78 °C, then Me_2S (3.0 equiv.), 84%; (xii) $KOBu^t$ (1.0 equiv.), cis-2-butene (2.0 equiv.), Bu^nLi (1.0 equiv.), THF (0.5 mol dm^{-3}), −78 to −55 °C then (−)-β-methoxy-diisopinocampheylborane (1.2 equiv.), $BF_3{\cdot}OEt_2$ (1.34 equiv.), aldehyde **17**, then −78 °C, 12 h, NaOH (1.84 equiv.), H_2O_2 (1.0 equiv.), −78 to 67 °C, 1 h reflux, 78%; (xiii) benzylbromide (2.0 equiv.), KH (2.0 equiv.), DMF (0.5 mol dm^{-3}), 0 °C, 1 h, 85%; (xiv) O_3, CH_2Cl_2 (0.05 mol dm^{-3}), until blue, −78 °C, then PPh_3 (2.2 equiv.), 92%; (xv) $TiCl_4$ (1.2 equiv.), ketone **4** (1.0 equiv.), CH_2Cl_2 (0.2 mol dm^{-3}), Et_3N (1.2 equiv.), aldehyde **5** (1.1 equiv.), −78 °C, 8 h, 63%; (xvi) benzaldehyde (5.0 equiv.), SmI_2 (0.3 equiv.), THF (0.22 mol dm^{-3}), −10 °C, 1 h, 72%; (xvii) TBSOTf (1.5 equiv.), lutidine (1.5 equiv.), CH_2Cl_2 (0.5 mol dm^{-3}), 25 °C, 15 min, 86%; (xviii) Pd/C 10% (0.5 equiv.), EtOH (0.25 mol dm^{-3}), H_2, 25 °C, 4 days, 84%; (xix) TsCl (1.1 equiv.), Et_3N (1.2 equiv.), DMAP (0.1 equiv.), CH_2Cl_2 (0.5 mol dm^{-3}), 0 °C, 1 h, 85%; (xx) K_2CO_3 (6.0 equiv.), MeOH (1.0 mol dm^{-3}), 0–25 °C, 4 h, 91%. Tf = CF_3SO_2; Ts = *p*-$MeC_6H_4SO_2$; CSA = camphorsulfonic acid; DIBAL = diisobutylaluminum hydride; SAMP = (*S*)-(−)-1-amino-2-methoxymethylpyrrolidine; TBAI = tetrabutylammoniumiodide.

(m, 4 H, $PhCH_2$), 4.08–4.05 (ddd, *J* 10.0, 5.0, 2.5 Hz, 1 H, H-19), 3.69–3.67 (dd, *J* 10.0, 5.0 Hz, 1 H, H-18), 3.62–3.59 (dd, *J* 10.0, 5.0 Hz, 1 H, H-18), 2.73–2.71 (dq, *J* 7.0, 2.5 Hz, 1 H, H-20), 1.16–1.15 (d, *J* 7.0 Hz, 3 H, C-20-CH_3); HRMS (FAB) Calcd. for $C_{19}H_{22}O_3Na$ (M + Na^+): 321.1467; found *m/z* 321.1477.

3: Pale-yellow oil; R_f 0.60 (silica, 30% Et_2O in light petroleum); IR (neat) ν_{max}/cm^{-1}; 2929.6, 2856.1, 1718.7, 1601.9, 1451.0, 1381.1, 1313.5, 1272.0, 1176.1, 1153.8, 1108.4, 1026.6, 973.7, 913.4, 835.9, 775.1, 711.1 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03–8.01 (dd, *J* 8.5, 1.5 Hz, 2 H, ArH), 7.59–7.56 (m, 1 H, ArH), 7.48–7.42 (m, 2 H, ArH), 5.44–5.40 (dd, *J* 11.5, 2 Hz, 1 H, H-21), 3.95–3.89 (m, 1 H, H-27), 3.66–3.56 (m, 1 H, H-31), 3.52–3.44 (m, 2 H, H-23, H-29), 3.31 (s, 3 H, C-29-OCH_3), 2.86–2.82 (ddd, *J* 10.55, 4.8, 3.4 Hz, 1 H, H-19), 2.59–2.57 (dd, *J* 6.25, 4.8 Hz, 1 H, H-18), 2.43–2.41 (dd, *J* 6.25, 3.4 Hz, 1 H, H-18), 2.15–2.01 (m, 1 H, H-22), 1.98–1.91 (m, 1 H, H-30), 1.85–1.75 (m, 1 H, H-26), 1.79–1.72 (m, 1 H, H-28), 1.68–1.60 (m, 1 H, H-24), 1.58–1.49 (m, 2 H, H-20, H-28), 1.43–1.37 (m, 1 H, H-26), 1.30–1.22 (m, 2 H, H-25), 1.17–1.07 (m, 10 H, H-30, H-20, H-22, H-24), 0.946–0.932 (d, *J* 7.0 Hz, H-32), 0.904–0.874 (m, 9 H, C-23-TBS-Bu^t-CH_3), 0.13–0.05 (m, 6 H, C-23-TBS-CH_3); HRMS (FAB) Calcd. for $C_{32}H_{54}O_6SiCs$ (M + Cs^+): 695.2744; found *m/z* 695.2740.

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