Total Synthesis of Sanglifehrin A**

K. C. Nicolaou,* Jinyou Xu, Fiona Murphy, Sofia Barluenga, Olivier Baudoin, Heng-xu Wei, David L. F. Gray, and Takashi Ohshima

Dedicated to Professor Richard A. Lerner on the occasion of his 60th birthday

Sanglifehrin A (**1**, Figure 1) is a newly discovered immunosuppressive agent whose molecular structure has been fully elucidated by spectroscopic and X-ray crystallographic techniques.[1, 2] This naturally occurring substance was isolated originally from *streptomyces* sp. A92-308110 found in soil samples collected at Dembo-Bridge (Malawi) by a group of scientists from Novartis and was found to exhibit impressive biological properties, including strong cyclophilin A binding (20-fold higher affinity than cyclosporin) and immunosuppressive activity (10-fold less potent than cyclosporin). Sanglifehrin's unprecedented molecular architecture is characterized by a [5.5] spirolactam system, a 22-membered macrocyclic ring with one ester and three amide bonds, and the two unusual amino acid residues piperazic acid and *meta*-tyrosine. Its novel structural features, seventeen stereogenic centers, and sensitive functionalities coupled with its important biological activity make sanglifehrin A (**1**) a prime target for total synthesis.[3, 4] Herein we wish to report the total synthesis of this unusual natural product in its enantiomerically pure form.

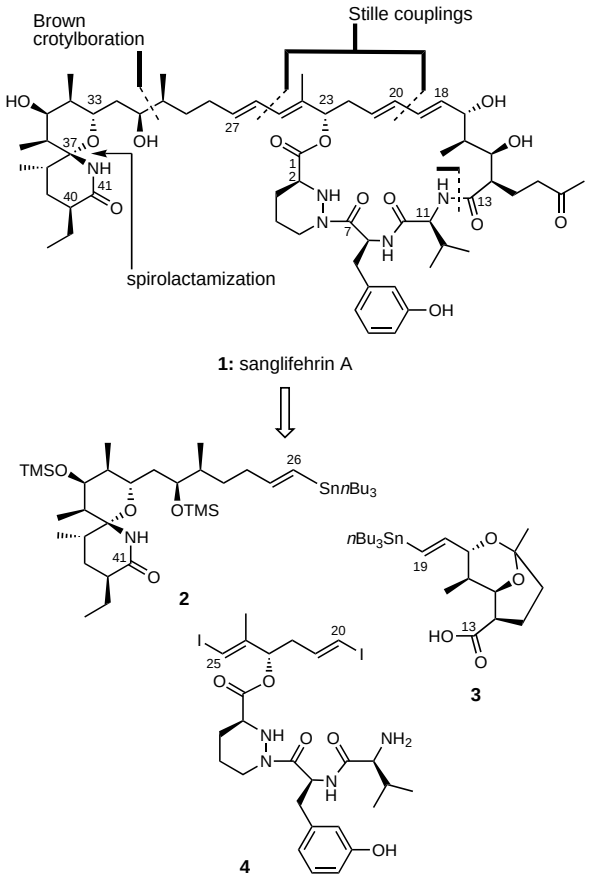

Figure 1. Retrosynthetic analysis of sanglifehrin A (**1**). TMS = trimethylsilyl.

Figure 1 depicts, in a retrosynthetic format, the overall strategy employed in the present total synthesis. Sanglifehrin A (**1**) was retrosynthetically disconnected at the indicated bonds, from which stannanes **2** and **3** and bis(vinyliodide) **4** were defined as key intermediates. Central to the success of this strategy were the two Stille cross-couplings indicated in Figure 1 and the expected differential reactivity between the two vinyl iodides within structure **4**. Specifically, it was anticipated that the C-20 iodide would react faster than the C-25 iodide, and thus allow for the proposed sequential construction of the macrocycle followed by the attachment of the spirolactam side chain. The successful execution of this strategy is described below.

The required spirolactam fragment **2** was synthesized from 3-pentanone (**5**) as summarized in Scheme 1. Thus, formation of the (*Z*)-boron enolate from **5** and (+)-diisopinocampheylboron triflate in the presence of $i\mathrm{Pr}_2\mathrm{NEt}$, followed by addition of methacrolein according to the protocol of Paterson et al.[5] furnished, after silylation with triethylsilyl chloride in the presence of imidazole, ketone **6**. Formation of the (*E*)-boron enolate from treatment of **6** with chlorodicyclohexylborane and triethylamine,[6] followed by addition of 3-benzyloxypropanal[7] and in situ lithium borohydride reduction[6c] of the resulting aldol product, afforded dihydroxy compound **7** as the major isomer in 72% overall yield. Exposure of **7** to dimethoxypropane in acetone in the presence of CSA (for abbreviations, see legends to schemes) resulted in the formation of hydroxy acetonide **8** (95% yield) in which the originally TES-protected hydroxyl group was now free. Reaction of **8** with propionic anhydride and triethylamine led smoothly to the desired Claisen rearrangement precursor **9** (98% yield) which upon conversion into its TBS-enol ether **10** (LDA, TBSCl, $-78\,^{\circ}\mathrm{C}$; then HMPA) and warming to $70\,^{\circ}\mathrm{C}$ furnished, after hydrolytic workup, carboxylic acid **11** in 84% overall yield. Regio- and stereoselective hydroboration of the olefin in **11** followed by oxidation (NMO/TPAP) led directly to a mixture of the corresponding δ-lactones (51% yield) in which diastereoisomer **12** was the major product (ca. 5:1 ratio). The opening of lactone **12** with $\mathrm{Me}_2\mathrm{AlNH}_2$[8] followed by hydrogenolysis of the benzyl ether led to hydroxyamide **13** in 90% yield. Subsequent oxidation of **13** with Dess–Martin periodinane in dichloromethane allowed the generation of aldehyde **14**, whose collapse to spirolactam **15** was

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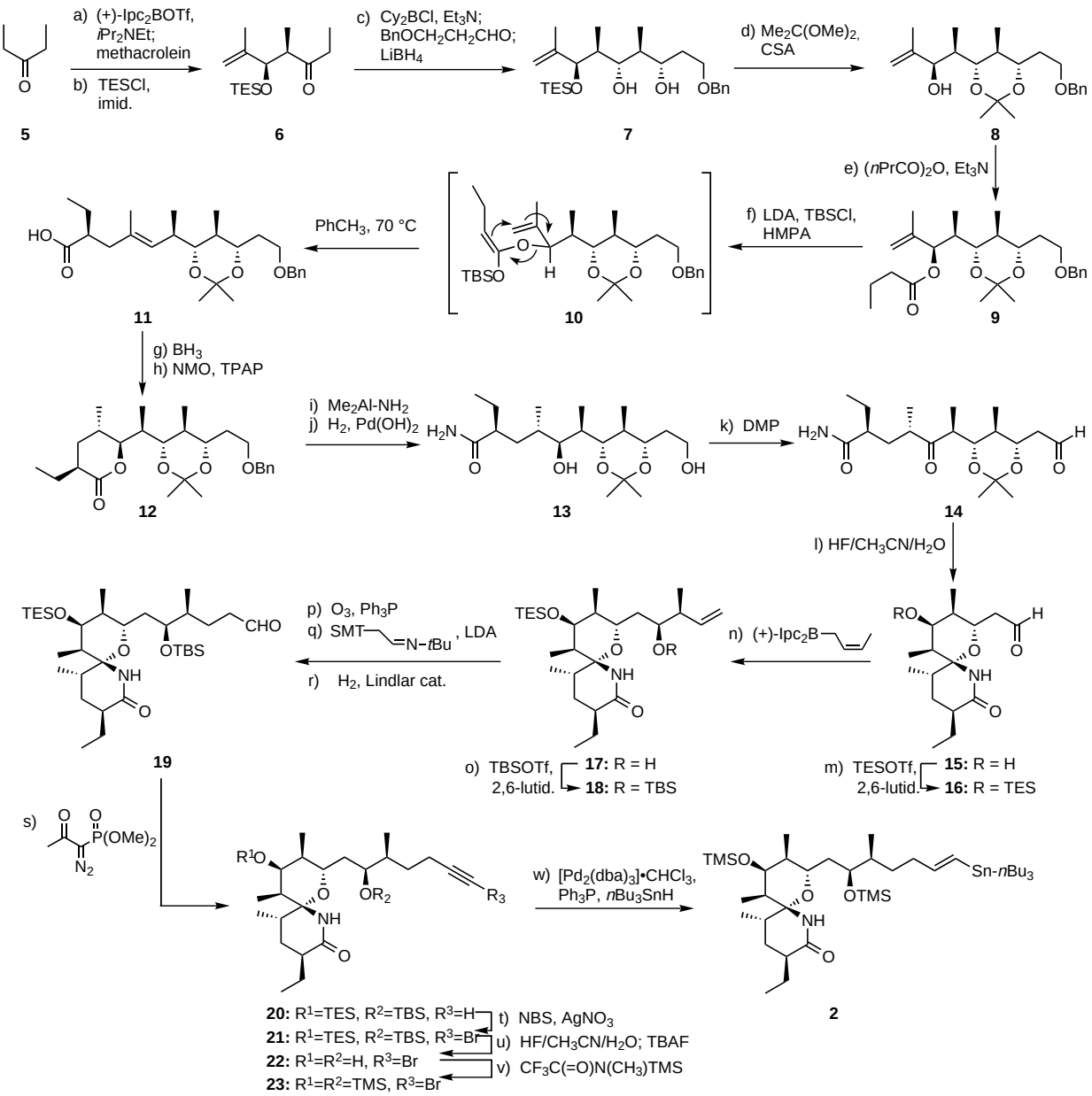

Scheme 1. Synthesis of spirolactam **2**. Reagents and conditions: a) (+)-Ipc$_2$BOTf (1.3 equiv), *i*Pr$_2$NEt (4.0 equiv), THF, $-78\,^{\circ}C$, 2 h; then methacrolein (5.0 equiv), 10 h; then 30% aq H_2O_2/MeOH/pH 7 buffer (1.3/5/1), $0\,^{\circ}C$, 3 h; b) TESCl (1.2 equiv), imidazole (1.8 equiv), CH_2Cl_2, $0\,^{\circ}C$, 2 h, 97% over two steps; c) Cy_2BCl (1.5 equiv), Et_3N (1.5 equiv), Et_2O, $0\,^{\circ}C$, 1.5 h; then $BnO(CH_2)_2CHO$ (2.0 equiv), $-78 \rightarrow -10\,^{\circ}C$, 4 h; then $LiBH_4$ (10 equiv), $-78 \rightarrow 25\,^{\circ}C$, 12 h; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (3/2), $25\,^{\circ}C$, 12 h, 72%; d) CSA (0.1 equiv), $Me_2C(OMe)_2$ (30 equiv), acetone, 72 h, 95%; e) (*n*PrCO)$_2$O (2.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 24 h, 98%; f) LDA (1.4 equiv), TBSCl (6.0 equiv), THF, $-78\,^{\circ}C$; then HMPA/THF (1/5), $-78 \rightarrow 0\,^{\circ}C$, 1 h; then toluene, $70\,^{\circ}C$, 2 h, 84%; g) $BH_3 \cdot THF$ (5.0 equiv), THF, $-20\,^{\circ}C$, 17 h; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (3/2), $25\,^{\circ}C$, 12 h; h) TPAP (0.01 equiv), NMO (6.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 8 h, 51% over two steps, **12**:diastereoisomer $\approx$5:1; i) Me_2Al-NH_2 (20 equiv), CH_2Cl_2, $25\,^{\circ}C$, 2 h; j) H_2, 10% $Pd(OH)_2$/C (cat.), EtOH, $25\,^{\circ}C$, 12 h, 90% over two steps; k) DMP (2.7 equiv), pyridine (4.0 equiv), CH_2Cl_2, $25\,^{\circ}C$, 30 min, 55%; l) $CH_3CN/HF/H_2O$ (20/1/1), $25\,^{\circ}C$, 36 h, 90%; m) TESOTf (2.0 equiv), 2,6-lutidine (2.5 equiv), CH_2Cl_2, $-40 \rightarrow 25\,^{\circ}C$, 88%; n) (*Z*)-crotyldiisopinocampheylborane (3.0 equiv), THF, $-78\,^{\circ}C$; then $NaBO_3 \cdot 4H_2O$ (15 equiv), THF/H_2O (3/2), $25\,^{\circ}C$, 12 h, 67%, **17**:β isomer $\approx$3:1; o) TBSOTf (2.0 equiv), 2,6-lutidine (2.0 equiv), CH_2Cl_2, $-40 \rightarrow 25\,^{\circ}C$, 88%; p) O_3, CH_2Cl_2, $-78\,^{\circ}C$; then Ph_3P (1.5 equiv), $-78 \rightarrow 25\,^{\circ}C$, 12 h, 92%; q) LDA (5.0 equiv), $TMSCH_2CH{=}NtBu$ (5.0 equiv), THF, $-78 \rightarrow -20\,^{\circ}C$, 2 h, 87%; r) H_2, Lindlar cat., MeOH, $25\,^{\circ}C$, 12 h, 93%; s) $CH_3C(=O)C(=N_2)P(=O)(OMe)_2$ (2.0 equiv), K_2CO_3 (2.5 equiv), MeOH, $25\,^{\circ}C$, 3.5 h, 94%; t) NBS (1.2 equiv), $AgNO_3$ (0.3 equiv), acetone, $25\,^{\circ}C$, 1 h, 93%; u) $CH_3CN/HF/H_2O$ (20/1/1), $25\,^{\circ}C$, 3 h; then TBAF (1.2 equiv), THF, $25\,^{\circ}C$, 15 min, 88%; v) $CF_3C(=O)N(CH_3)TMS$ (excess), $25\,^{\circ}C$, 1 h, 98%; w) $[Pd_2(dba)_3] \cdot CHCl_3$ (0.1 equiv), Ph_3P (0.8 equiv), nBu_3SnH (2.2 equiv), $25\,^{\circ}C$, 30 min, 70%; TES = triethylsilyl; Cy_2BCl = chlorodicyclohexylborane; CSA = camphorsulfonic acid; LDA = lithium diisopropylamide; HMPA = hexamethylphosphoramide; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine-*N*-oxide; DMP = Dess–Martin periodinane; TBS = *tert*-butyldimethylsilyl; NBS = *N*-bromosuccinimide; TBAF = tetra-*n*-butylammonium fluoride; TMS = trimethylsilyl; dba = dibenzylideneacetone.

achieved in 50% overall yield by exposure to aqueous HF in acetonitrile.

A TES group was installed in **15** (TESOTf, 2,6-lutidine, 88% yield) and the resulting aldehyde **16** was treated with Brown's *cis*-crotyl borane [(+)-Ipc$_2$B(*cis*-crotyl)][9] to afford a mixture of diastereomeric alcohols (ca. 3:1 ratio, 67% total yield) from which the major isomer **17** (Table 1) was chromatographically separated and then protected as a TBS

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Table 1. Selected physical properties of compounds **17**, **2**, **35**, and **37**.

17: $R_f = 0.34$ (silica gel, ethyl acetate/hexane 1/3); $[\alpha]_D^{20} = -76.6^\circ$ ($CHCl_3$, $c = 1$); IR (film): $\tilde{\nu}_{max} = 3348, 2962, 1660, 1463, 1180, 1006, 740\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.83$ (s, 1H), 5.69 (ddd, $J = 17.2, 10.3, 8.1$ Hz, 1H), 5.06 (ddd, $J = 17.2, 1.8, 1.1$ Hz, 1H), 5.01 (ddd, $J = 10.3, 1.8, 0.5$ Hz, 1H), 4.08 (ddd, $J = 10.5, 6.0, 3.8$ Hz, 1H), 3.86 (t, $J = 2.3$ Hz, 1H), 3.62 (td, $J = 7.6, 2.9$ Hz, 1H), 3.24 (br s, 1H), 2.23 (m, 2H), 1.98 (m, 2H), 1.83 (m, 2H), 1.69 (m, 3H), 1.49 (m, 1H), 1.44 (m, 1H), 1.05 (d, $J = 6.7$ Hz, 3H), 1.00 (t, $J = 8.0$ Hz, 9H), 0.98 (d, $J = 5.9$ Hz, 3H), 0.95 (t, $J = 7.6$ Hz, 3H), 0.90 (d, $J = 6.2$ Hz, 3H), 0.83 (d, $J = 6.9$ Hz, 3H), 0.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 175.5, 140.9, 114.9, 88.3, 76.9, 71.9, 68.2, 44.1, 41.1, 39.6, 38.3, 35.0, 30.0, 28.3, 25.8, 16.1, 14.8, 14.3, 13.6, 12.1, 7.0, 5.3$; HR-MS (MALDI) calcd for $C_{26}H_{49}NaNO_4Si$ [M+Na$^+$]: 490.3328, found: 490.3334.

2: $R_f = 0.27$ (silica gel, diethyl ether/hexane 3/7); $[\alpha]_D^{20} = -53.9^\circ$ (CH_2Cl_2, $c = 0.67$); IR (film): $\tilde{\nu}_{max} = 3357, 2959, 2927, 1669, 1461, 1379, 1251, 1027, 841\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 7.73$ (s, 1H), 5.94 (dt, $J = 18.9, 5.8$ Hz, 1H), 5.86 (d, $J = 18.9$ Hz, 1H), 3.78 (t, $J = 1.8$ Hz, 1H), 3.76 (m, 1H), 3.73 (t, $J = 10.3$ Hz, 1H), 2.18 (m, 2H), 2.06 (m, 2H), 1.94 (m, 1H), 1.87 (m, 1H), 1.80 (m, 1H), 1.59 (m, 2H), 1.48 (m, 1H), 1.48 (quint, $J = 7.7$ Hz, 6H), 1.38 (m, 3H), 1.30 (sext, $J = 7.2$ Hz, 6H), 1.27 (m, 1H), 1.12 (m, 1H), 0.98 (t, $J = 7.7$ Hz, 3H), 0.95 (d, $J = 7.1$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 9H), 0.86 (d, $J = 6.7$ Hz, 3H), 0.85 (t, $J = 8.1$ Hz, 6H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.19 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 175.1, 149.8, 126.9, 86.9, 77.5, 73.3, 66.9, 41.7, 41.0, 38.9, 38.1, 37.9, 35.8, 31.4, 29.9, 29.1, 27.8, 27.3, 25.5, 15.1, 14.8, 14.7, 13.8, 13.7, 12.3, 9.3, 0.7, 0.6$; HR-MS (MALDI) calcd for $C_{37}H_{74}NO_4SiSn$ [$M - Si(CH_3)_3$+H+H$^+$]: 744.4409, found: 744.4396.

35: $R_f = 0.23$ (silica gel, ethyl acetate); $[\alpha]_D^{20} = +28.7^\circ$ (CH_2Cl_2, $c = 0.18$); IR (film): $\tilde{\nu}_{max} = 3314, 2926, 2361, 1654, 1636, 1508, 1381, 1226, 1123, 1050, 754\ cm^{-1}$; ^1H NMR (600 MHz, C_6D_6): $\delta = 9.59$ (m, 1H), 9.14 (m, 1H), 7.03 (dd, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 8.7$ Hz, 1H), 6.84 (d, $J = 9.7$ Hz, 1H), 6.79 (dd, $J = 14.8, 10.4$ Hz, 1H), 6.67 (d, $J = 7.0$ Hz, 1H), 6.57 (m, 1H), 6.11 (s, 1H), 6.01 (dd, $J = 15.3, 10.5$ Hz, 1H), 5.68 (m, 1H), 5.41 (dd, $J = 7.8$ Hz, 1H), 5.39 (m, 1H), 5.16 (m, 1H), 4.93 (dd, $J = 8.8$ Hz, 1H), 4.63 (m, 1H), 4.4 (br d, $J = 12.3$ Hz, 1H), 3.21 (dd, $J = 11.9$ Hz, 1H), 3.06 (d, $J = 12.3$ Hz, 1H), 2.88–2.85 (m, 2H), 2.34–2.24 (m, 3H), 2.11 (m, 1H), 1.95 (m, 1H), 1.81–1.70 (m, 2H), 1.62 (s, 3H), 1.60–1.28 (m, 3H), 1.45 (s, 3H), 1.18 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 6.6$ Hz, 3H), 1.02–0.92 (m, 3H), 0.82–0.73 (m, 2H), 0.68 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 172.9, 172.3, 170.8, 170.7, 157.6, 144.9, 136.5, 135.9, 131.6, 130.9, 130.8, 129.9, 121.0, 116.3, 114.0, 95.9, 80.7, 80.5, 76.2, 73.2, 58.6, 57.7, 47.3, 43.4, 41.5, 39.2, 35.7, 34.2, 30.8, 29.6, 29.2, 27.7, 26.8, 22.1, 20.3, 19.3, 17.9, 13.7$; HR-MS (MALDI) calcd for $C_{38}H_{51}INaN_4O_8$ [M+Na$^+$]: 841.2651, found: 841.2612.

37: $R_f = 0.19$ (silica gel, diethyl ether/methanol 95/5); HPLC (RP-18 column, acetonitrile/H_2O 7/3, 1.5 mL min^{-1}) $R_t = 5.4$ min; $[\alpha]_D^{20} = +18.3^\circ$ (CH_2Cl_2, $c = 0.12$); IR (film): $\tilde{\nu}_{max} = 3299, 2929, 1729, 1638, 1459, 1377, 1261, 1164, 1048, 797\ cm^{-1}$; ^1H NMR (600 MHz, $CDCl_3$): $\delta = 8.08$ (s, 1H), 7.13 (t, $J = 7.9$ Hz, 1H), 6.76 (d, $J = 7.9$ Hz, 1H), 6.73 (d, $J = 9.2$ Hz, 1H), 6.69 (s, 1H), 6.59 (d, $J = 7.4$ Hz, 1H), 6.46 (dd, $J = 14.7, 10.5$ Hz, 1H), 6.22 (m, 2H), 6.10 (m, 1H), 6.00 (d, $J = 10.5$ Hz, 1H), 5.71 (m, 2H), 5.43 (d, $J = 11.4$ Hz, 1H), 5.30 (dd, $J = 15.2, 10.6$ Hz, 1H), 4.77 (t, $J = 9.7$ Hz, 1H), 4.65 (m, 1H), 4.55 (d, $J = 12.7$ Hz, 1H), 4.47 (t, $J = 4.8$ Hz, 1H), 4.10 (m, 1H), 3.81 (s, 1H), 3.76 (m, 1H), 3.60 (d, $J = 11.9$ Hz, 1H), 3.26 (m, 1H), 3.20 (m, 1H), 3.04 (s, 1H), 2.89 (m, 1H), 2.68 (dd, $J = 12.1, 4.6$ Hz, 1H), 2.60–2.56 (m, 4H), 2.24–2.20 (m, 3H), 2.13–2.02 (m, 5H), 1.90 (m, 2H), 1.84 (m, 1H), 1.75 (s, 3H), 1.76–1.72 (m, 3H), 1.64–1.49 (m, 6H), 1.38 (s, 3H), 1.43–1.36 (m, 2H), 1.24 (m, 2H), 1.05 (d, $J = 7.0$ Hz, 3H), 1.00 (m, 6H), 0.95 (m, 12H), 0.66 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 176.9, 172.8, 172.3, 170.9, 170.8, 157.5, 136.7, 136.5, 136.1, 132.2, 132.0, 131.2, 130.9, 129.6, 129.5, 127.1, 125.6, 121.2, 116.4, 114.1, 95.9, 80.7, 77.9, 74.7, 73.3, 71.4, 68.4, 58.9, 57.8, 53.4, 47.7, 43.5, 42.0, 41.2, 39.1, 38.8, 38.1, 37.7, 35.8, 34.7, 34.2, 32.2, 31.0, 30.7, 29.9, 29.7, 29.3, 28.1, 27.2, 25.8, 23.2, 22.4, 19.4, 18.0, 14.9, 14.5, 13.8, 13.6, 13.0, 12.9$; HR-MS (MALDI) calcd for $C_{60}H_{89}NaN_5O_{12}$ [M+Na$^+$]: 1094.6405, found: 1094.6439.

ether (TBSOTf, 2,6-lutidine, 90% yield) to give **18**. The expected *syn* stereochemistry of the major isomer of this crotylboration was confirmed by X-ray crystallographic analysis of a subsequent intermediate (see Figure 2). Cleavage of the terminal olefin in **18** with ozone/Ph_3P led to the corresponding aldehyde (92%) which reacted with $TMSCH_2CH{=}NtBu$/LDA under Corey conditions[10] (87% yield) to afford, after chemoselective hydrogenation of the resulting double bond in the presence of Lindlar catalyst[11] (93% yield), the homologated aldehyde **19**. Compound **19** was converted into acetylene **20** in 94% yield by reaction with $[CH_3COC(=N_2)P(=O)(OMe)_2]$.[12]

At this juncture, the crystalline bis-TBS derivative **24** was prepared from the acetylene **20** by selective removal of the TES group with TBAF and resilylation with TBSOTf/2,6-lutidine (95% yield from **20**). X-ray crystallographic analysis of **24** (see ORTEP drawing, Figure 2)[13] revealed the stereochemical structure of this spirolactam fragment and confirmed the outcome of the crotylboration reaction described above (**16** → **17**).

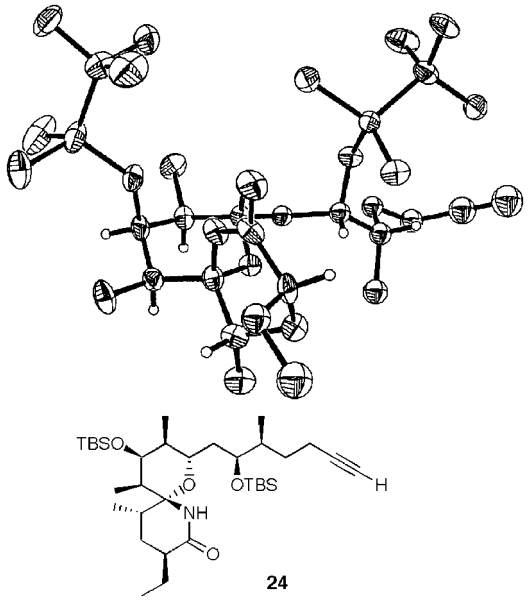

Figure 2. X-ray crystal structure of **24**.

Substitution of the acetylenic hydrogen atom in **20** with bromine took place smoothly when **20** was exposed to NBS/$AgNO_3$ (93% yield).[14] Difficulties with the final removal of the silyl ethers forced us to exchange them at this stage with the more labile TMS groups. Interestingly, it was found that while HF/MeCN/H_2O (25 °C) removed the TBS group selectively, TBAF in THF at room temperature cleaved only the TES group from **21**, which led, after resilylation of intermediate **22**, to the desired bis-TMS derivative **23**. Finally, palladium-catalyzed regio- and stereocontrolled (> 95% *E* isomer) hydrostannylation[15] of bromoacetylene **23** with nBu$_3$SnH furnished the vinyltin fragment **2** in 70% yield.

The synthesis of fragment **4** is shown in Scheme 2. Thus, the readily available iodo aldehyde **25**[16] was treated with CHI_3/$CrCl_2$[17] to furnish the (*E*,*E*)-bis(vinyl iodide) **26** as the major component (57% yield), along with the *E*,*Z* isomer (5%) (chromatographically separated). The TBS group in **26** was then removed under the influence of TBAF in THF to afford hydroxy compound **27** (88% yield). Coupling of **27** with

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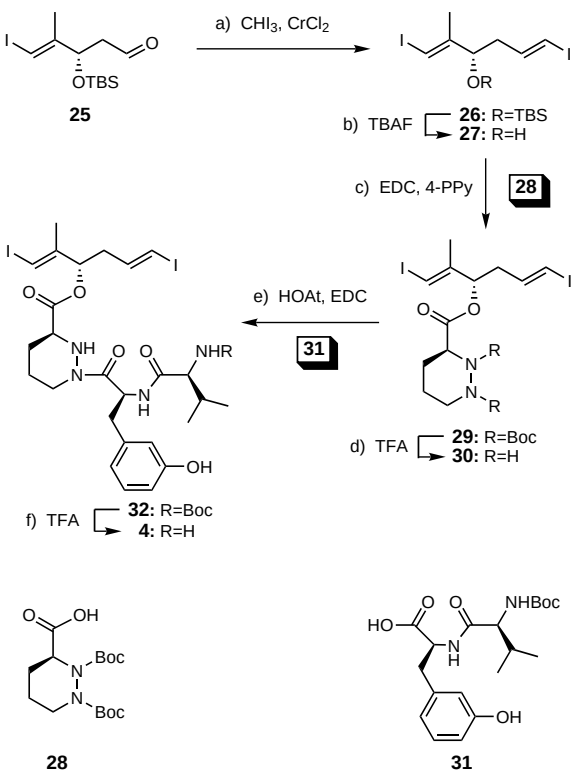
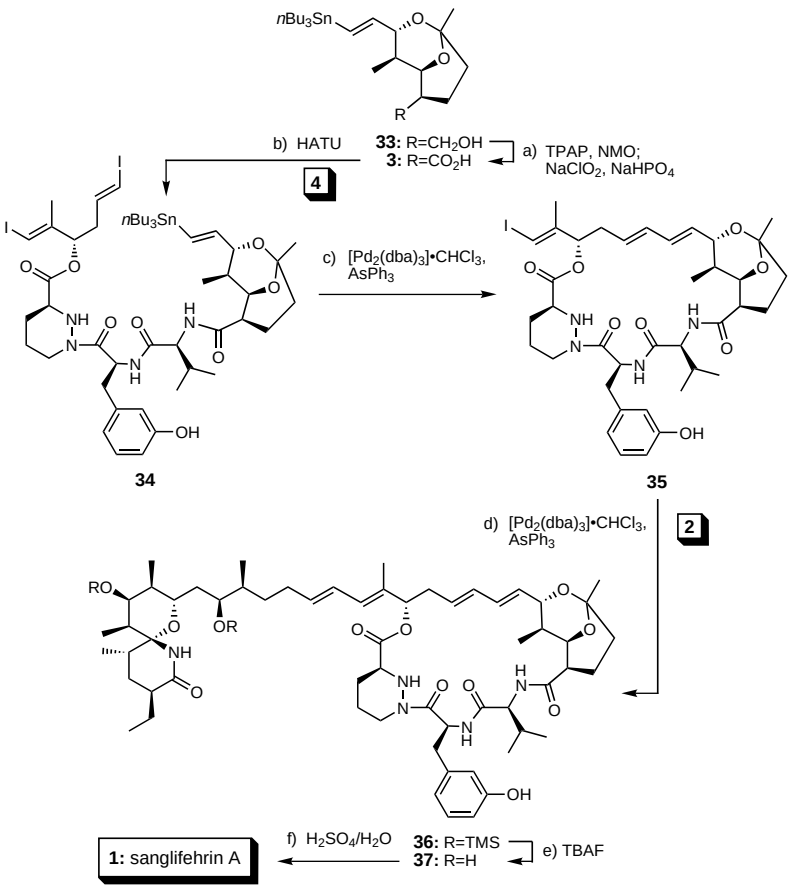


Scheme 2. Synthesis of fragment **4**. Reagents and conditions: a) CHI_3 (2.0 equiv), $CrCl_2$ (6.0 equiv), dioxane/THF (9/1), $-5 \rightarrow 25\,^{\circ}C$, 12 h, 57%; b) TBAF (1.2 equiv), THF, $0 \rightarrow 25\,^{\circ}C$, 15 min, 88%; c) **28** (2.0 equiv), EDC (2.0 equiv), 4-PPy (0.1 equiv), iPr$_2$NEt (1.0 equiv), CH_2Cl_2, $0 \rightarrow 25\,^{\circ}C$, 64%; d) TFA/$CH_2Cl_2$ (1/1), $0 \rightarrow 25\,^{\circ}C$, 2 h; e) **31** (1.0 equiv), HOAt (1.0 equiv), iPr$_2$NEt (3.0 equiv), EDC (1.2 equiv), CH_2Cl_2, $0 \rightarrow 25\,^{\circ}C$, 3 h, 66% over two steps; f) TFA/CH_2Cl_2 (1/9), $0 \rightarrow 25\,^{\circ}C$, 4 h; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; 4-PPy = 4-pyrrolidinopyridine; TFA = trifluoroacetic acid; HOAt = 1-hydroxy-7-azabenzotriazole; Boc = *tert*-butyloxycarbonyl.

protected amino acid **28**[18] (EDC, 4-PPy, iPr$_2$NEt) led to ester **29** (64% yield) from which both Boc groups were removed by treatment with TFA in dichloromethane leading to piperazino derivative **30**. Dipeptide **31**[4] was then selectively attached onto the less hindered NH group of **30** by the action of EDC/HOAt/iPr$_2$NEt[19] to furnish the coupling product **32** (66% yield for two steps). Finally, TFA-induced deprotection of **32** led to fragment **4** in high yield, which was used directly in the coupling with carboxylic acid **3**.

The coupling of fragments **2**–**4** and the final stages of the total synthesis of sanglifehrin A (**1**) are presented in Scheme 3. Thus, formation of an amide bond between amine **4** and carboxylic acid **3** (freshly generated from alcohol **33**)[4] was effected by HATU/iPrNEt[19] furnishing cyclization precursor **34** (45% yield from **33**). Ring closure of **34** took place regioselectively in a dilute solution of DMF (0.01 mM) in the presence of $[Pd_2(dba)_3] \cdot CHCl_3$/$AsPh_3$[20] at ambient temperature to give rise to the desired macrocycle **35** in 40% yield through an intramolecular Stille coupling reaction. A second Stille reaction, this time carried out intermolecularly between vinyl stannane **2** and vinyl iodide **35** ($[Pd_2(dba)_3] \cdot CHCl_3$/$AsPh_3$, DMF, 35 °C) led to the formation of compound **36**, which represents a protected form of the target molecule. Compound **36** was then desilylated with TBAF (4.0 equiv, THF, 25 °C, 2 h) to give acetal **37** after purification by HPLC (40% yield for two steps) and subsequently sanglifehrin A (**1**) itself upon treatment with H_2SO_4/H_2O (50% conversion)[21] as already described by the Novartis group.[1] Synthetic sanglifehrin A (**1**) and acetal **37** were identical with authentic samples by the usual spectroscopic and chromatographic analyses.[21]

A shorter route to sanglifehrin acetal **37** was developed from aldehyde **15** which utilized the dihydroxystannane **43** (Scheme 4) as the spirolactam fragment. Thus **15** was coupled with (+)-Ipc$_2$B(*cis*-crotyl) to afford **38** as the major product (ca. 7:3 ratio of diastereoisomers, 67% total yield), which after isolation was converted into its bis-TBS derivative **39** (TBSOTf/2,6-lutidine, 92% yield). Processing of **39** as described above for **18** led smoothly to acetylene **24**, which was then desilylated, brominated, and hydrostannylated as described in



Scheme 3. Total synthesis of sanglifehrin (**1**). Reagents and conditions: a) see ref. [4]; b) **4** (1.0 equiv), HATU (1.0 equiv), iPr$_2$NEt (4.0 equiv), DMF, $0 \rightarrow 25\,^{\circ}C$, 12 h, 45% from **33**; c) $[Pd_2(dba)_3] \cdot CHCl_3$ (0.1 equiv), $AsPh_3$ (0.2 equiv), iPr$_2$NEt (10 equiv), DMF, 25 °C, 72 h, 40%; d) **2** (1.0 equiv), **35** (1.08 equiv), $[Pd_2(dba)_3] \cdot CHCl_3$ (0.1 equiv), $AsPh_3$ (0.8 equiv), iPr$_2$NEt (10 equiv), DMF, 35 °C, 10 h; e) TBAF (4.0 equiv), THF, 25 °C, 40% over two steps; f) 2 N H_2SO_4 (2.0 equiv), THF/H_2O (4/1), 25 °C, 7 h, 50% conversion (by HPLC); HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.

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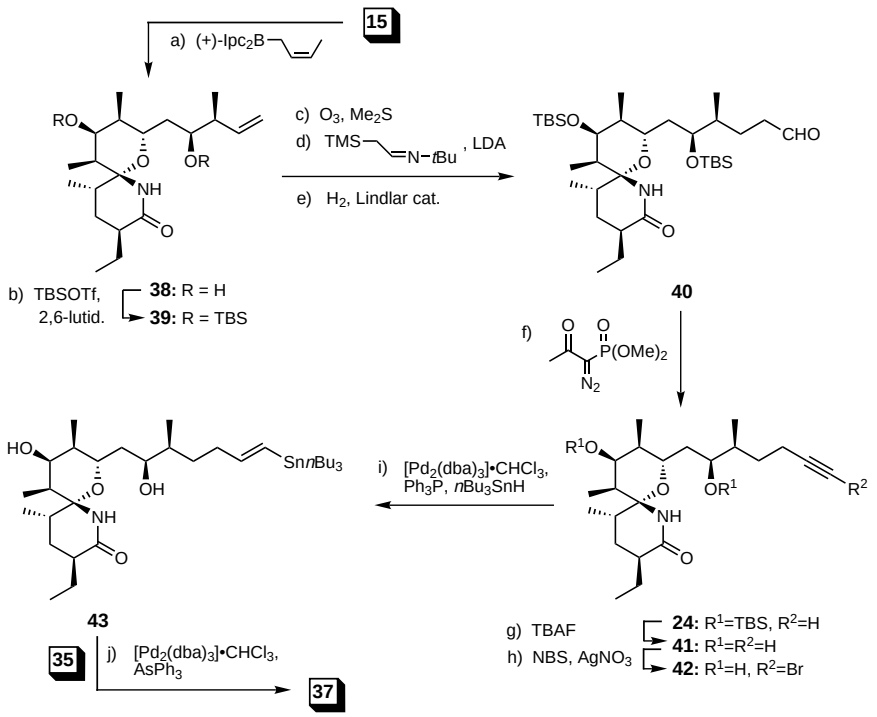

Scheme 4. Synthesis of sanglifehrin acetal **37**. Reagents and conditions: a) (*Z*)-crotyldiisopinocampheylborane (5.0 equiv), THF, $-78\,^{\circ}C$, 2 h; then $-78 \rightarrow 25\,^{\circ}C$, 1 h; then $NaBO_3 \cdot 4H_2O$, THF/H_2O (3/2), 25 °C, 12 h, 67 %, **38**:β isomer $\approx$7:3; b) TBSOTf (2.4 equiv), 2,6-lutidine (3.6 equiv), CH_2Cl_2, $-10 \rightarrow 25\,^{\circ}C$, 4 h, 92 %; c) O_3, Me_2S (100 equiv), CH_2Cl_2, $-78 \rightarrow 25\,^{\circ}C$, 45 h, 61 %; d) LDA (3.0 equiv), $TMSCH_2CH{=}NtBu$ (3.0 equiv), THF, $-78 \rightarrow 0\,^{\circ}C$, 2.5 h, 68 %; e) H_2, Lindlar cat., MeOH, 25 °C, 14 h, 92 %; f) $CH_3C(=O)C(=N_2)P(=O)(OMe)_2$ (2.0 equiv), K_2CO_3 (2.5 equiv), MeOH, $0 \rightarrow 25\,^{\circ}C$, 10 h, 98 %; g) TBAF (8.0 equiv), THF, 45 °C, 48 h, 87 %; h) NBS (1.2 equiv), $AgNO_3$ (0.3 equiv), acetone, 25 °C, 30 min, 69 %; i) $[Pd_2(dba)_3] \cdot CHCl_3$ (0.1 equiv), Ph_3P (0.8 equiv), nBu_3SnH (2.2 equiv), 25 °C, 30 min, 70 %; j) **43** (2.0 equiv), **35** (1.0 equiv), $[Pd_2(dba)_3] \cdot CHCl_3$ (0.1 equiv), $AsPh_3$ (0.8 equiv), iPr_2NEt (10 equiv), DMF, 40 °C, 5 h, 45 %.

Scheme 1, to furnish dihydroxystannane **43** via intermediates **41** and **42**. Finally, palladium-catalyzed coupling ($[Pd_2(dba)_3] \cdot CHCl_3/AsPh_3$, 45 % yield) of **43** with **35** led directly to sanglifehrin acetal (**37**).

The described chemistry demonstrates the power of the Stille coupling reaction in the construction of complex molecules, particularly those containing unsaturated and sensitive macrocycles and chains such as the sanglifehrins. Applications of the gained knowledge to solid-phase chemistry and combinatorial library construction should facilitate further evaluation of these newly isolated natural products with regard to their chemistry, biology, and medicine.

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[21] HPLC (RP-18 column, acetonitrile/H_2O 1/1, 1.5 mL min^{-1}) $R_t = 24.0$ (**1**), 36.0 min (**37**).
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