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Synthesis of the macrocyclic core of sanglifehrin A

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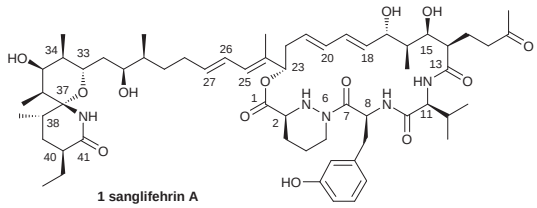
The synthesis of the macrocyclic core of sanglifehrin A, a newly discovered natural product, is described.

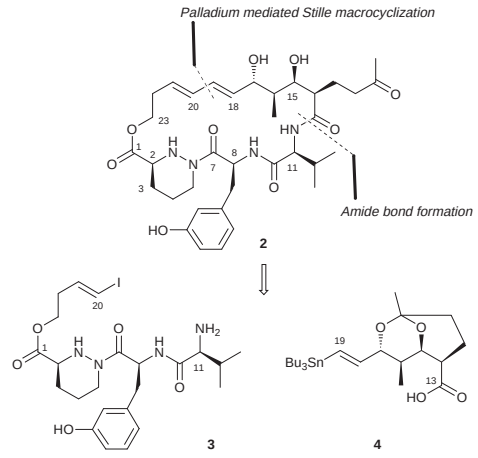
Sanglifehrin A[1] **1** is a newly discovered natural product with impressive biological properties, including cyclophilin binding,



immunosuppressive activity and inhibition of both B-cell and T-cell proliferation.[1] Isolated from the fermentation broths of an unidentified species of Actinomycetes by a team of scientists at Novartis, this substance possesses a novel molecular architecture whose main domains are a [5.5] spirolactam moiety and a 22-membered macrocycle featuring a number of novel functionalities. Here we report construction of the macrocyclic system of sanglifehrin A in which the diene segment at C23 has been judiciously replaced by a hydrogen substituent for the purpose of this model study (compound **2**, Scheme 1).

From the many disconnections one can envision for the construction of macrocycle **2**, we chose the strategy based on the intramolecular Stille coupling,[2] (Scheme 1). This approach requires the preparation of a precursor carrying the C21–C20 vinyl iodide and C18–C19 vinyl stannane functionalities for the cyclization process under the catalytic influence of palladium(0). Disconnection of the indicated NH–CO linkage led to building blocks **3** and **4**, which became our first subtargets.

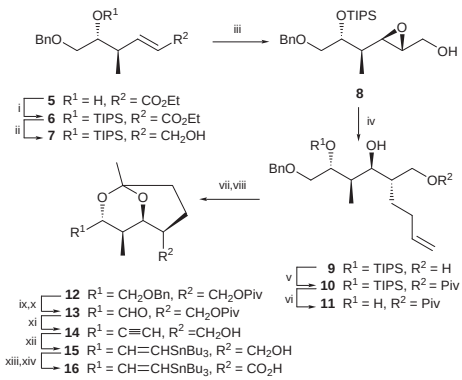
The synthesis of the C13–C19 vinyl stannane fragment **4** is summarized in Scheme 2. Thus, the α,β-unsaturated ester **5**[3] was converted to its TIPS ether **6** (95% yield) and thence reduced with DIBAL-H (87% yield) to afford allylic alcohol **7**. The MCPBA-mediated epoxidation of **7** proceeded stereoselectively to afford epoxide **8** in 100% yield (β:α epoxide ratio *ca.* 6:1). Regioselective epoxide opening[4] of **8** by



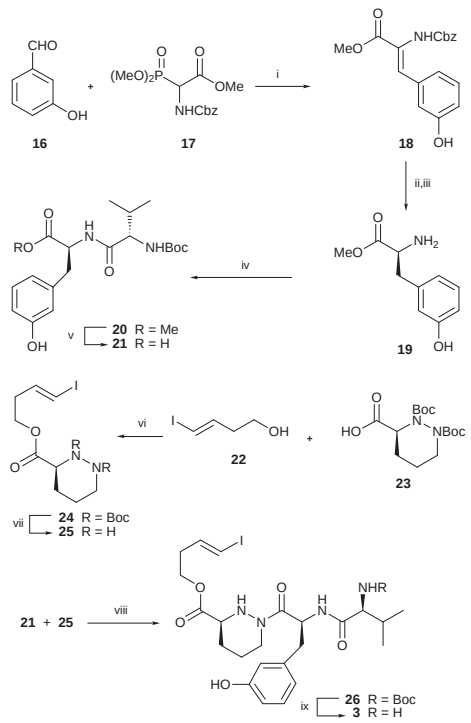
Scheme 1 Retrosynthetic analysis of sanglifehrin model system **2**.

CH_2=$CHCH_2CH_2MgBr$[5] in the presence of CuI furnished diol **9** (80% yield), whose selective protection as a pivaloate ester proceeded smoothly (95% yield) to afford monopivaloate **10**. Desilylation of **10** with TBAF provided **11** (81% yield) which was subjected to Wacker oxidation[6] and internal ketalization to furnish **12** in 88% overall yield *via* the corresponding dihydroxy ketone. Sequential hydrogenolysis of the benzyl ether group from **12**, tetrapropylammonium perruthenate (TPAP)–NMO[7] oxidation of the resulting alcohol (83% for two steps), and reaction with $(MeCO)C(=N_2)PO(OMe)_2$[8] in the presence of K_2CO_3 led to terminal alkyne **14** (98%) *via* aldehyde **13**. Regio- and stereoselective addition of Bu_3SnH to acetylenic compound **14** proceeded in the presence of catalytic amounts of $PdCl_2(PhCN)_2$, P(*o*-Tol)$_3$ and Pr^i_2NEt to afford vinyl stannane **15** in 79% yield (regioselectivity > 20:1). The latter (**15**) was oxidised in high yield to carboxylic acid **4** by sequential treatment with TPAP–NMO and $NaClO_2$ (NaH_2PO_4, 2-methylbut-2-ene) and was judged to be of sufficient purity after work-up to be used as such in the subsequent coupling with amide **3**.

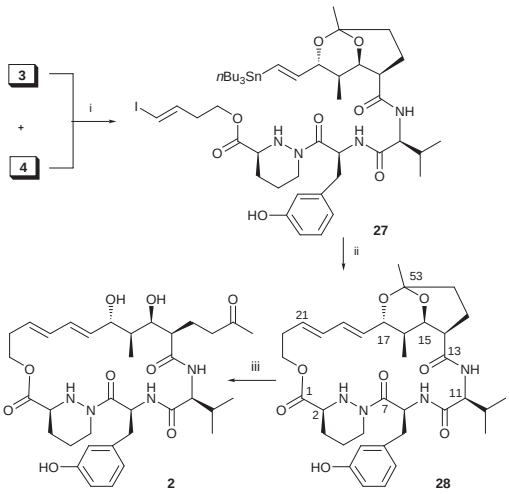
The second required fragment, compound **3**, was synthesized according to Scheme 3. Thus, coupling of *m*-hydroxybenzaldehyde **16** with phosphonate **17**[9] in the presence of DBU proceeded smoothly to afford olefinic product **18** in geometrically pure form (90% yield). The asymmetric hydrogenation of **18** was carried out in the presence of [SS-Et-DuP-Rh]$^+$TfO$^-$ catalyst[10] and was followed by hydrogenolysis of the Cbz group



Scheme 2 *Reagents and conditons:* i, TIPSC (2 equiv.), imidazole (3 equiv.), DMF, 60 °C, 24 h, 95%; ii, DIBAL-H (3 equiv.), CH_2Cl_2, −78 °C, 2 H, 87%; iii MCPBA (1.5 equiv.), CH_2Cl_2 −25 °C, 100%, β:α epoxide ratio *ca.* 6:1; iv, H_2C=$CHCH_2CH_2MgBr$ (5 equiv.), CuI (1 equiv.) Et_2O–THF (1:1), −40 → −20 °C, 18 h, 80%; v, PivCl (25 equiv.), pyridine (50 equiv.), 25 °C, 24 h, 95%; vi, TBAF (2 equiv.), THF, 25 °C, 1 h, 81%; vii, $PdCl_2$ (0.1 equiv.), benzoquinone (1.5 equiv.), DMF–H_2O (7:1), 25 °C, 3 h; viii, TsOH·H_2O (0.05 equiv.), benzene, reflux, 88% for two steps; ix, H_2, 10% Pd/C (0.1 equiv.), EtOH, 25 °C, 1 h; x, TPAP (0.05 equiv.), NMO (3 equiv.), 4 Å MS, CH_2Cl_2, 25 °C, 20 min, 83% for two steps; xi, $MeCOC(=N_2)PO(OMe)_2$ (5.0 equiv.), K_2CO_3 (5 equiv.), MeOH, 0 → 25 °C, 13 h; then K_2CO_3 (5 equiv.), 25 °C, 24 h, 98%; xii, Bu^n_3SnH (4 equiv.), $PdCl_2(PhCN)_2$ (0.3 equiv.), P(*o*-Tol)$_3$ (0.6 equiv.), Pr^i_2NEt (4.0 equiv.), CH_2Cl_2 −20 °C, 1 h, 79%; xiii, TPAP (0.05 equiv.), NMO (3.0 equiv.), 4 Å MS, CH_2Cl_2, 25 °C, 15 min; xiv, $NaClO_2$ (6.0 equiv.), NaH_2PO_4 (2. equiv.), 2-methybut-2-ene (10 equiv.), THF–Bu^tOH–H_2O (1:5:1), 25 °C, 15 min.



Scheme 3 *Reagents and conditions:* i, DBU (2 equiv.), CH_2Cl_2, 25 °C, 2 h, 90%; ii, [(*S*,*S*)-Et-DuP-Rh]$^+$TfO$^-$ (0.7 mol%), 60 psi, 96 h, 98% ee, 90%; iii, H_2, 10% Pd/C, MeOH, 25 °C, 12 h, 96%; iv EDC (3 equiv.), HOAt (3 equiv.), CH_2Cl_2, 0 → 25 °C, 3 h, 78%; v, LiOH (2 equiv.), THF–H_2O (3 : 1), 0 → 25 °C, 1.5 h, 89%; vi, EDC (2 equiv.), 4-pyrolidinopyridine (0.1 equiv.), Pr$^i_2$NEt (1 equiv.), CH_2Cl_2, 0 → 25 °C, 80%; vii, TFA–CH_2Cl_2 (1 : 1), 0 → 25 °C, 2 h, viii, HOAt (1 equiv.), Pr$^i_2$NEt (3 equiv.), EDC (1.2 equiv.), CH_2Cl_2, 0 → 25 °C, 3.5 h, 66% for two steps; ix, TFA–CH_2Cl_2 (1 : 1), 0 → 25 °C, 2 h.



Scheme 4 *Reagents and conditions:* i, HATU (1 equiv.) Pr$^i_2$NEt (4 equiv.) DMF, 0 → 25 °C, 10 h, 51% over three steps from **15**; ii, $Pd_2(dba)_3$·$CHCl_3$ (0.15 equiv.), $AsPh_3$ (0.6 equiv.), Pr$^i_2$NEt (10 equiv.), DMF, 25 °C, 3 h, 40%; iii, 0.8 M H_2SO_4, THF–H_2O (4 : 1), 25 °C, 10 h.

(H_2, 10% Pd/C), furnishing amino acid derivative **19** in 98% *ee* and 96% yield. Coupling of **19** with the Boc derivative of valine, facilitated by 1-(3-dimethylaminopropyl)-3-ethylcarbodümide hydrochloride (EDC) and 1-hydroxy-7-azabenzotriazole (HOAt)[11] gave peptide **20** in 78% yield. The next step involved mild hydrolysis of the methyl ester group of **20** (LiOH, THF : H_2O) to afford the carboxylic acid **21** (89% yield), whose coupling with piperazic acid derivative **25** (EDC, HOAt) led to product **26** (66% yield from **25**). Compound **25** was prepared by coupling of fragments **22**[12] and **23**[13] (80% yield), followed by TFA-induced removal of the Boc groups. Liberation of the amino group from **26** furnished segment **3** in high yield which was used directly in the coupling with acid **4**.

Union of fragments **3** and **4** proceeded smoothly in the presence of *o*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexofluorophosphate (HATU),[11] furnishing the cyclisation precursor **27** (51% over three steps from **15** *vs*. 58% over two steps from **3**), whose cyclisation was realized upon exposure to $Pd_2(dba)_3$ and $AsPh_3$[14] in DMF at room temperature affording compound **28**† (40% yield). Acidic rupture of the internal ketal **3** furnished the sanglifehrin model system **2** as part of a three component mixture presumably due to the formation of two diastereomeric six-membered ring lactols[1a] [HMRS (FAB) calc. for $C_{35}H_{50}N_4O_9$ (M+Cs): 803.2632, found 803.2606].

The described chemistry demonstrates the feasibility of an intramolecular Stille coupling approach to sanglifehrin's macrocyclic skeleton and paves the way for a total synthesis of this novel natural product. A solid phase version of this strategy may also be envisioned, as can the application of the developed technology to combinatorial sanglifehrin libraries for biological screening.

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Notes and references

† *Selected data* for **28**: R_f = 0.30 (silica, EtOAc-hexane, 1 : 1) $[\alpha]_D^{23}$ +45 (*c* 0.35, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3332, 2919, 1713, 1660, 1644, 1530, 1454, 1351, 1126, 2093, 1044; δ_H(600 MHz, $CDCl_3$, sanglifehrin numbering) 7.53 (brs, 1 H, 9), 7.07 (t, *J* 7.5, 1 H, ArH), 6.78–6.71 (m, 1 H, ArH), 6.74 (d, *J* 7.5, 1 H, ArH), 6.69 (s, 1 H, ArOH), 6.62 (d, *J* 7.5, 1 H, ArH), 6.47 (brd, *J* 9.2, 1H, 12), 6.34 (dd, *J* 15.2, 10.4, 1 H, 19), 6.17 (dd, *J* 15.1, 10.4 , 1 H, 20), 5.87 (ddd, *J* 15.1, 7.5, 7.0, 1 H, 21), 5.63–5.58 (m, 1 H, 8), 5.22 (dd, *J* 15.2, 7.8, 1 H, 18), 4.66 (dd, *J* 10.7, 7.8, 1 H, 17), 4.51–4.46 (m, 2 H, 5 and 11), 4.42 (m, 1 H, 15), 4.22 (m, 1 H, 23), 4.16 (m, 1 H, 23'), 3.57 (td, *J* 11.9, 3.0, 1 H, 2), 3.16–3.12 (m, 1 H, 14), 2.74 (m, 2 H, 58), 2.57 (brd, *J* 11.9, 1 H, NH), 2.53–2.46 (m, 5 H, 5', 22 and 51), 2.17 (dd, *J* 13.8, 5.7, 1 H, 52), 2.05–1.98 (m, 3 H, 3, 16 and 55), 1.93–1.87 (m, 1 H, 52'), 1.83 (brd, *J* 12.8, 1 H, 4), 1.69 (m, 1 H, 4'), 1.35 (s, 3 H, 54), 1.31 (m, 1 H, 3'), 1.03 (d, *J* 6.7, 3 H, 56 or 57), 0.96 (d, *J* 6.7, 3 H, 56 or 57), 0.37 (d, *J* 7.3, 3 H, 50); δ_c (150 MHz, $CDCl_3$) 172.8 (CO), 172.0 (CO), 170.8 (CO), 170.5 (CO), 156.8 (C), 137.2 (CH), 136.1 (C), 132.2 (CH), 130.4 (CH), 129.7 (CH), 128.7 (CH), 121.3 (CH), 116.0 (CH), 114.6 (CH), 95.8 (C), 81.0 (CH), 73.2 (CH), 65.2 (CH_2), 58.5 (CH), 58.1 (CH), 50.0 (CH), 43.8 (CH), 41.8 (CH_2), 38.7 (CH), 34.0 (CH_2), 30.8 (CH_3), 29.7 (CH_2), 29.3 (CH_2), 29.0 (CH_2), 27.8 (CH), 27.2 (CH_2), 22.8 (CH_2), 19.3 (CH_3), 18.5 (CH_3), 13.7 (CH_3); HRMS (FAB) calc. for $C_{35}H_{48}NaN_4O_8$ (M+Na$^+$): 675.3370, found 675.3356.

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