independent; $R1 = 0.0793$ ($I > 2\sigma(I)$), $wR2 = 0.1523$; $\mu = 0.332$ mm^{-1} (SADABS); full-matrix, least-squares on F^2.

[5] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163099 ($\mathbf{2}_2$-COT), CCDC-163100 (**4**), and CCDC-163101 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[9] **4**: triclinic; $P\bar{1}$; $a = 13.0793(5)$, $b = 13.1076(4)$, $c = 31.0368(11)$ Å, $\alpha = 86.89(1)$, $\beta = 89.21(1)$, $\gamma = 60.82(1)^\circ$; $V = 4638.2$ 3) Å^3; $Z = 2$, $H_{165}C_{80}O_6Si_6Nb_2$; $T = 173(2)$ K; $\lambda = 0.71073$; 20040 reflections, 12883 independent; $R1 = 0.0805$ ($I > 2\sigma(I)$), $wR2 = 0.1759$; $\mu = 0.368$ mm^{-1} (SADABS); full matrix, least squares on F^2.[5]

[10] $\mathbf{6}\cdot C_6H_6$: monoclinic, $P2_1/c$; $a = 24.6813(4)$, $b = 17.6046(3)$, $c = 25.4832(4)$ Å, $\beta = 116.96(1)^\circ$; $V = 9869.5(3)$ Å^3; $Z = 4$, $H_{171}C_{86}O_6Si_6Nb_2$; $T = 173(2)$ K; $\lambda = 0.71073$; 56059 reflections, 21816 independent; $R1 = 0.0864$ ($I > 2\sigma(I)$, 14073 reflections), $wR2 = 0.2119$; $\mu = 0.368$ mm^{-1} (SADABS); full-matrix, least-squares on F^2.[5]

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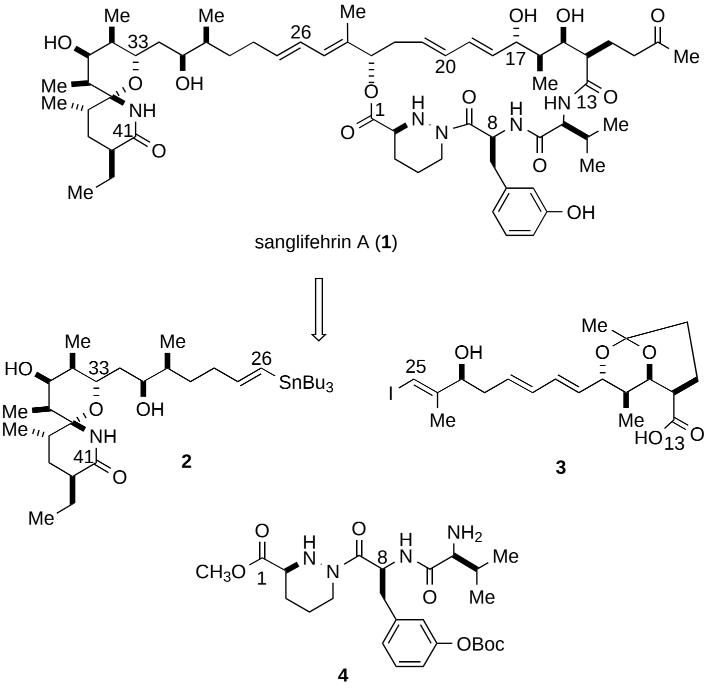
Enantioselective Total Synthesis of the Cyclophilin-Binding Immunosuppressive Agent Sanglifehrin A**

Maosheng Duan and Leo A. Paquette*

The sanglifehrins are structurally unusual Streptomyces metabolites discovered in a soil sample from Malawi.[1] The A factor **1** holds particular interest because of its strong cyclophilin-binding properties and remarkable capability to inhibit the proliferation of B and T cells. Since neither FK binding protein binding activity nor calcineurin-inhibiting capability is displayed, **1** exerts its powerful immunosupressive action in a manner quite different from that adopted by cyclosporin A, FK506, and rapamycin.[2, 3] The complex structural and stereochemical features associated with **1** and its congeners, ultimately corroborated by partial[4] and total synthesis,[5] have provided a bevy of challenging opportunities for de novo molecular assembly.

Recent synthetic efforts in this laboratory have resulted in the successful acquisition of certain subunits central to the construction of sanglifehrin A (**1**) in convergent and highly enantiocontrolled fashion.[6] Herein, we report useful refinements in these protocols as well as the successful conjoining of components **2**–**4** to arrive at **1** having all of its seventeen stereogenic centers properly installed.


sanglifehrin A (**1**)

2

3

4

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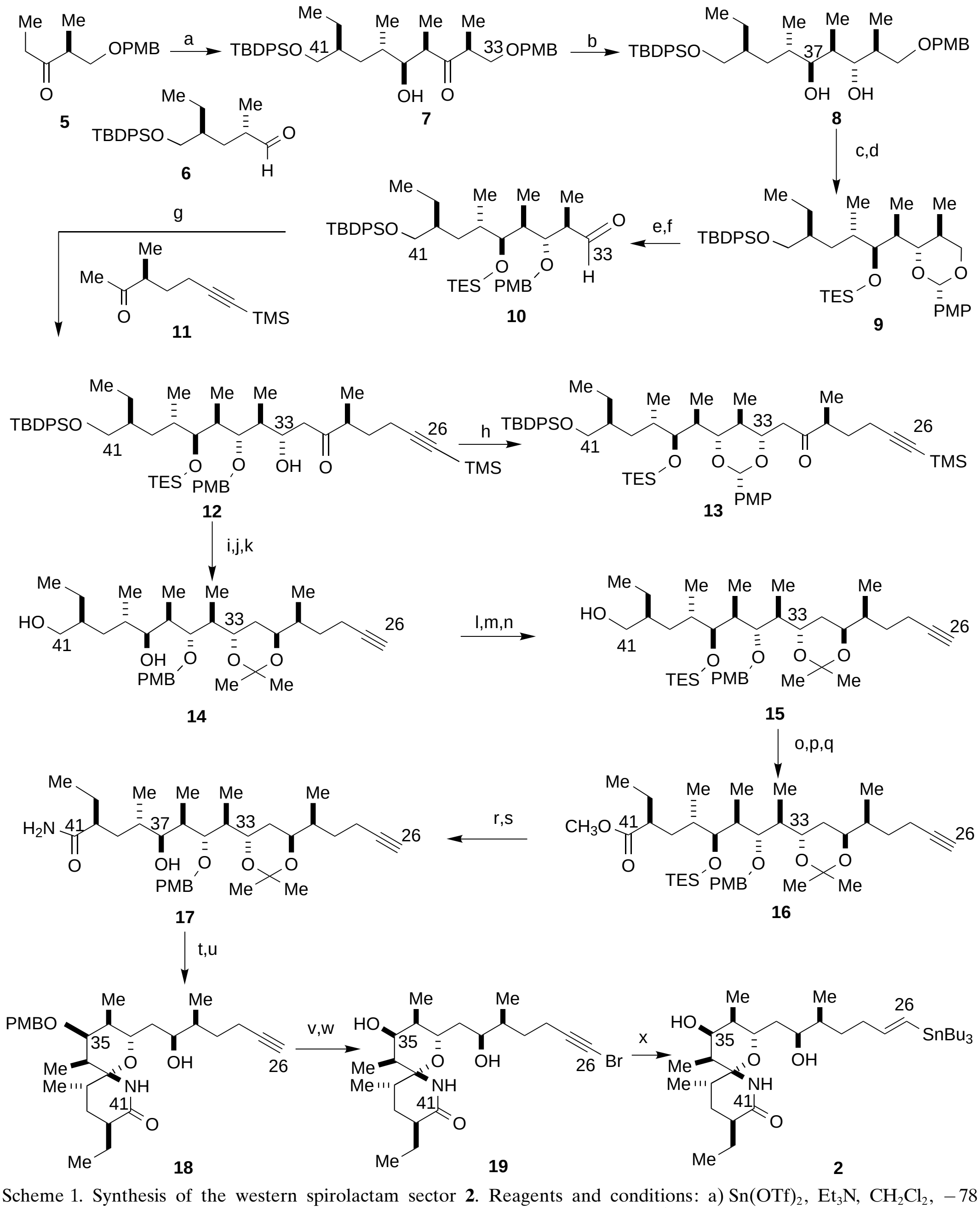
The key elements present in **1** are clearly a spirolactam fragment, a 22-membered macrolactone, an uncommon tripeptide array, and contiguous centers of chirality along C14–C17 as well as C33–C38. Retrosynthetically, **2** was expected to derive from a sequence of enantiocontrolled aldol condensations prior to more advanced backbone assembly (Scheme 1). To this end, we first focused on generation of the tin(II) enolate of *S*-**5**[7] and its condensation with the previously described aldehyde **6**[6a] under conditions of substrate control.[8] As expected, *Re*-face selectivity was exercised preferentially (*ds* 92:8) and **7** was thus generated. *anti*-Diol **8** was next obtained by hydroxy-directed reduction involving tetramethylammonium triacetoxyborohydride,[9] this step serving as a prelude to differentiation of the two OH groups by DDQ oxidation under kinetic control.[10] Selective O-silylation at C37 could then be accomplished as in **9**. The controlled



Scheme 1. Synthesis of the western spirolactam sector **2**. Reagents and conditions: a) $Sn(OTf)_2$, Et_3N, CH_2Cl_2, −78 °C, then **6**, −78 °C, 5 h, 73 %; b) $Me_4NBH(OAc)_3$, HOAc, CH_3CN, −25 °C to 0 °C, overnight, 82 %; c) DDQ, 4-Å MS, CH_2Cl_2, 0 °C, 10 h, 85 %; d) Et_3SiCl, imidazole, DMF, 50 °C, 3 h, 99 %; e) *i*Bu_2AlH, THF, 0 °C, 1 h, 86 %; f) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 95 %; g) (+)-DIPCl, Et_3N, diethyl ether, 0 °C; then **11**, −78 °C to −20 °C, 36 h; 30 % H_2O_2, pH 7.0 buffer, MeOH, 0 °C, 48 %; h) DDQ, 4-Å MS, CH_2Cl_2, 0 °C to RT, 2 h, 65 %; i) $Me_4NBH(OAc)_3$, CH_3CN, HOAc, −25 to 0 °C, 91 %; j) 2,2-dimethoxypropane, acetone, PPTS, overnight, 97 %; k) $Bu_4N^+F^-$, THF, overnight, 100 %; l) pivaloyl chloride, pyr, DMAP, 20 °C, 1 h, 81 %; m) Et_3SiCl, imidazole, DMF, 50 °C, 3 h, 97 %; n) *i*Bu_2AlH, CH_2Cl_2, −78 °C, 2 h, 90 %; o) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 1 h; p) $NaClO_2$, NaH_2PO_4, $Me_2C{=}CHMe$, *t*BuOH, H_2O; q) CH_2N_2, EtOAc, 97 % for three steps; r) Me_2AlNH_2, CH_2Cl_2, 40 °C, 39 h, 71 %; s) $Bu_4N^+F^-$, THF, RT, 3 h, 97 %; t) Dess–Martin periodinane, CH_2Cl_2, 20 °C, 45 min, 98 %; u) camphorsulfonic acid, CH_2Cl_2, MeOH, 78 %; v) DDQ, CH_2Cl_2, H_2O, 4 h, 94 %; w) NBS, $AgNO_3$, acetone, 30 min, 97 %; x) $[Pd_2(dba)_3]\cdot CHCl_3$, Ph_3P, Bu_3SnH, THF, 10 min, RT, 70 %; DIPCl = *B*-chlorodiisopinocampheylborane; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PPTS = pyridinium *p*-toluenesulfonate; NBS = *N*-bromosuccinimide.

reduction of **9** with diisobutylaluminum hydride proceeded regioselectively[11] to deliver the primary alcohol and make possible the generation of aldehyde **10** by Swern oxidation. For installation of the C26 – C32 extension, **10** was coupled to **11** in a second asymmetric aldol reaction mediated by (+)-*B*-chlorodiisopinocampheylborane in the presence of triethylamine.[12] To confirm that the stereoinduction at C33 had indeed proceeded in the desired manner, **12** was oxidatively cyclized to the 1,3-dioxane **13**, ^{1}H NMR analysis of which unequivocally corroborated the equatorial projection of all four ring substituents as shown in Figure 1.

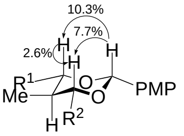
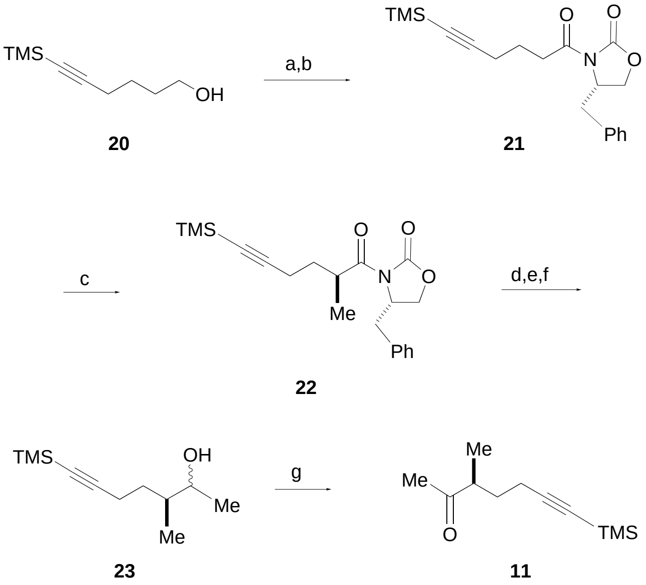


Figure 1. NOE interactions observed for **13** at 500 MHz in $CDCl_3$ solution.

Preparation of the required acetylenic ketone **11** was initiated by sequential oxidation of **20**[13] to the carboxylic acid level with pyridinium chlorochromate (PCC), generation of the mixed anhydride with pivaloyl chloride in the presence of triethylamine, and condensation with (*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one[14] (Scheme 2). Following highly enantioselective α-methylation of the enolate of **21**, the methyl ketone **11** was generated by conventional methods in an overall yield approximating 70 %.

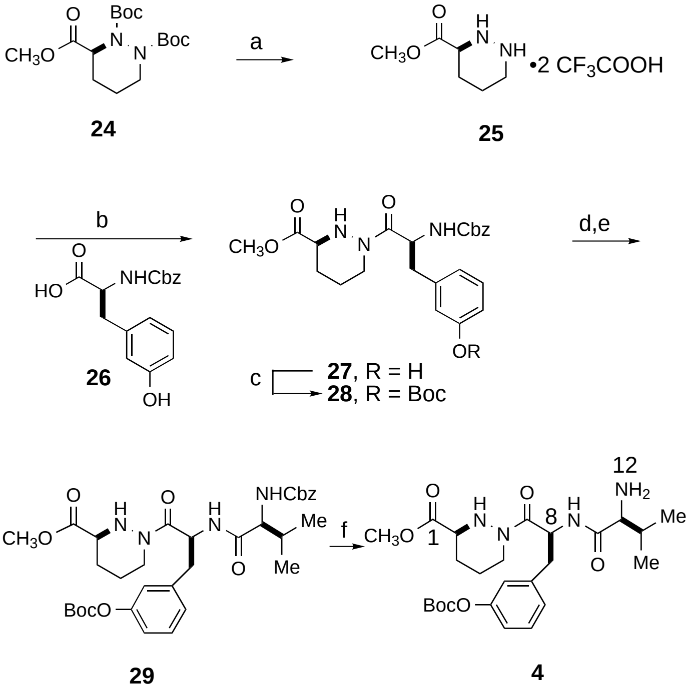


Scheme 2. Synthesis of ketone **11**. Reagents and conditions: a) PCC, DMF, 20 °C, 24 h, 72 %; b) $(CH_3)_3CCOCl$, Et_3N, THF, −40 °C to 0 °C, then LiCl, (*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one, 20 °C, overnight, 94 %; c) $NaN(SiMe_3)_2$, THF, −78 °C; CH_3I, −78 °C to −40 °C, 69 %; d) $LiBH_4$, diethyl ether, H_2O, 0 °C, 1 h, 74 %; e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 0 °C, 100 %; f) CH_3MgBr, diethyl ether, 20 °C, 92 %; g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; Et_3N, 0 °C, 94 %.

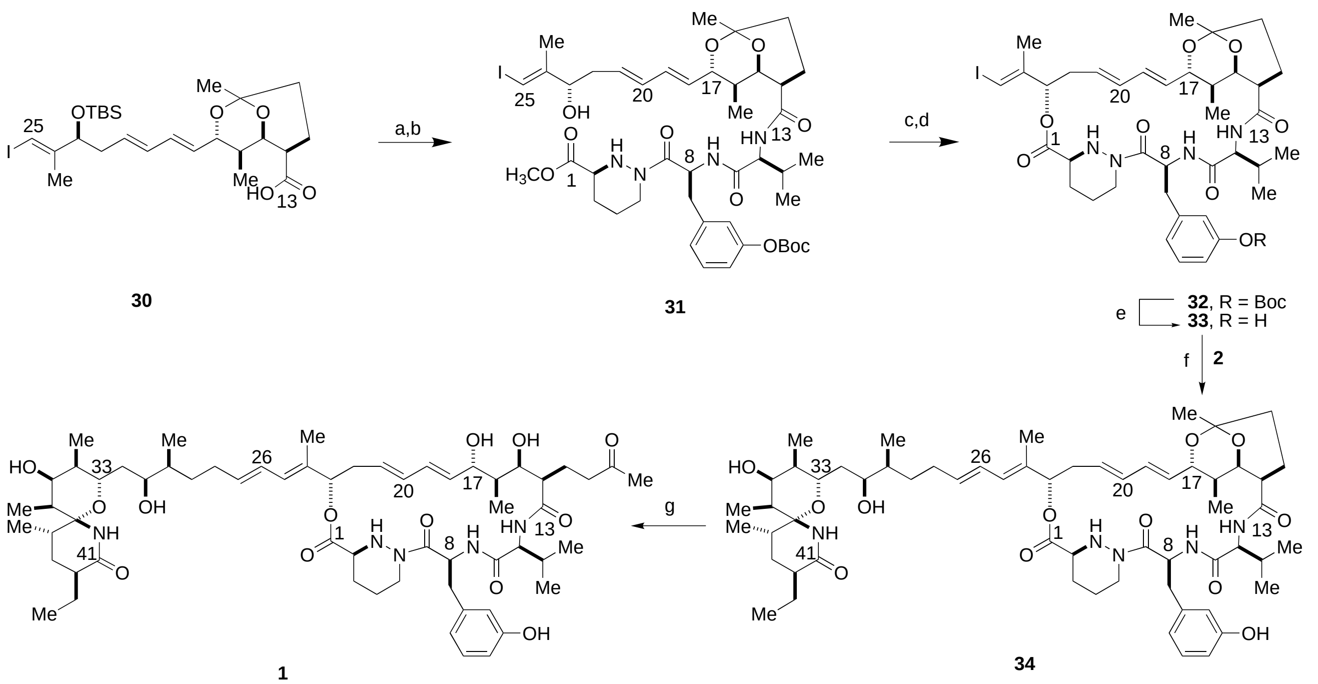
At this juncture, it was becoming increasingly clear that **12** might well serve as a suitable precursor of spirolactam **3**. We could now attempt directed triacetoxyborohydride reduction in advance of suitable incorporation of the resulting *trans*-1,3-diol array into an acetonide ring. With this maneuver accomplished, it proved an easy matter to rid the molecule of its three different silyl protecting groups in a single operation upon exposure to tetrabutylammonium fluoride (TBAF) in THF. Gratifyingly, **14** was isolated in 92 % yield. Significantly, the secondary hydroxy group in **14** could be selectively protected as in **15**, thereby facilitating arrival at methyl ester **16**.

The carboxamide structural motif was next introduced by treatment of **16** with freshly prepared dimethylaluminum amide in CH_2Cl_2 at the reflux temperature.[15] Subsequent removal of the triethylsilyl (TES) protecting group in the presence of fluoride ion, oxidation of the C37 hydroxy group with the Dess – Martin periodinane reagent,[16] and acid-catalyzed ring closure gave rise predominantly to the [5.5]spirolactam **18** with exceptional efficiency (78 %; diastereomeric ratio 8:1). The two-step conversion of **18** to **19** proved uneventful, thereby setting the stage for conversion to the (*E*)-vinylstannane **2**.

On the tripeptide front, modifications to our original route[6a] were made to improve efficiency in the required penultimate deprotection step. To this end, the known bis-Boc protected piperazic acid methyl ester **24**[4a] was converted to salt **25** by reaction with trifluoroacetic acid in CH_2Cl_2 at room temperature (Scheme 3). Direct acylation of **25** at its less hindered nitrogen atom with the derivatized (*S*)-*m*-tyrosine **26**[17] was most effectively accomplished by using HBTU and triethylamine in acetonitrile.[18] Following optimization of the step **27**→**28**, it proved convenient to effect hydrogenolytic removal of the Cbz group in preparation for smooth incorporation of the Cbz-L-valine fragment. Catalytic reduc-



Scheme 3. Synthesis of the tripeptide domain **4**. Reagents and conditons: a) CF_3COOH, CH_2Cl_2, RT, 3 h; b) **26**, HBTU, Et_3N (3.1 equiv), CH_3CN, 2 h, RT, 76 % over two steps; c) $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2, RT, 84 %; d) H_2, 10 % Pd/C, C_2H_5OH; e) Cbz-L-valine, HBTU, Et_3N (1 equiv), CH_3CN, 20 °C, 1.5 h, 98 % over two steps; f) H_2, 10 % Pd/C, C_2H_5OH, 98 %; DMAP = 4-dimethylaminopyridine; Cbz = benzyloxycarbonyl; HBTU = *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; $(Boc)_2O$ = di-*tert*-butyl dicarbonate.



Scheme 4. Completion of the synthesis of **1**. Reagents and conditons: a) tetra-*n*-butylammonium fluoride, THF, 0 °C to RT, 94 %; b) **4**, HATU, *i*Pr_2NEt, CH_3CN, 0 °C to RT, 5 h, 67 %; c) LiOH, THF, H_2O, 0 °C, 1 h, 100 %; d) EDC, *i*Pr_2NEt, 4-PPy, CH_2Cl_2, 10^{-3} M, 0 °C to RT, overnight, 21 %; e) Me_3SiOTf, 2,6-lutidine, CH_2Cl_2, 20 °C, 1.5 h, 73 %; f) $[PdCl_2(CH_3CN)_2]$, DMF, RT, 6 h, 40 %; g) *p*-toluenesulfonic acid (1 equiv), boric acid (5 equiv), THF, RT, 10 h, 30 %; HATU = *O*-(7-azabenzotriazol-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate; 4-PPy = 4-pyrrolidinopyridine; EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

tion of **29**, obtained in this manner without observable epimerization, furnished the targeted **4** and set in motion the final stages of the total synthesis.

The previously reported carboxylic acid **30**[6b] served as the third subunit. Following its desilylation, tripeptide **4** was regioselectively attached at C13 by the action of HATU and Hünig's base,[19] thereby furnishing **31** (Scheme 4). With **31** in hand, its methyl ester was chemoselectively saponified with lithium hydroxide in aqueous THF under conditions known not to induce possible loss of enantiomeric homogeneity.[4a] Exposure of the hydroxy acid so formed to EDC/*i*Pr_2NEt/4-PPy in CH_2Cl_2 at high dilution (~10^{-3} M) then furnished **32** in 21 % yield. At this point, the time had arrived to unmask the phenolic hydroxyl. After some trial and error, the capability of trimethylsilyl triflate and 2,6-lutidine in CH_2Cl_2[20] to deliver **33** was recognized.

We could now attempt the critical Stille coupling intended to merge the two large fragments while establishing the exocyclic *E*,*E* cumulated diene chromophore.[21] As foreshadowed by the success realized in our recent synthesis of polycavernoside A,[22] the use of $[PdCl_2(CH_3CN)_2]$ in DMF at room temperature afforded the sanglifehrin acetal **34** (40 %). Finally, the acidic hydrolysis of **34** with one equivalent of *p*-toluenesulfonic acid and five equivalents of boric acid as recommended by Metternich and co-workers[4b, 23] furnished **1**, the spectral and chromatographic properties of which duplicated those exhibited by the authentic natural substance.

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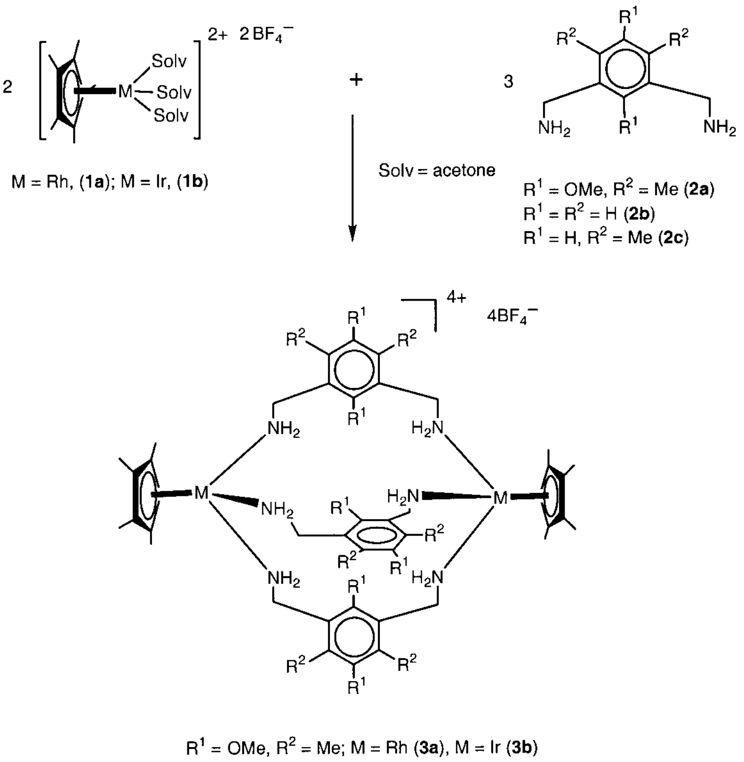
[23] The comments offered in footnote [32] of reference [4b] apply equally well to the present circumstances.

Rational Design and X-ray Molecular Structure of the First Irido-Cryptand and Encapsulation of a Tetrafluoroborate Anion[**]

Hani Amouri,[*] Marie Noelle Rager, Florence Cagnol, and Jacqueline Vaissermann

In memory of John A. Osborn

Supramolecular systems obtained by assembling molecular subunits through noncovalent interactions have been the focus of recent intense investigations.[1] In the last decade there has been a blossoming in the preparation of inorganic and organometallic macrocycles which have shown particular promise in the supramolecular chemistry of host–guest interactions.[2] Cryptands, which are the most fascinating macrobicyclic systems, possess intramolecular cavities that are available for the encapsulation of ionic guests.[3] In a spectacular demonstration by Lehn and co-workers a bis(tren) chelate receptor was used to encapsulate fluoride anions.[4] Recently Bowman-James and co-workers have elegantly shown that a bicyclic polyammonium receptor can encapsulate two nitrate anions.[5] Although the chemistry of organic cryptands is steadily expanding, less is known about metallocryptands.[6] Herein we report a rational high-yield (70–85%) strategy for preparing organometallic cryptands that is based on iridium coordination chemistry (Scheme 1) and demonstrate their properties as anion hosts. Although the coordination chemistry of cations is well developed, the chemistry of anion encapsulation is still in its infancy:[7] only one example of a metallo-helicate encapsulating a PF_6^- ion has been described by Steel and co-workers and two supramolecular tetrahedron complexes encapsulating a BF_4^- ion have been reported by the groups of Huttner, and Ward and McCleverty.[8] To our knowledge no metallo-cryptate that encapsulates a polyfluoroanion has so far been reported.



Scheme 1. General synthetic strategy for metallocryptands.

The novelty of our work is the use of $[Cp^*M(Solv)_3][BF_4]_2$ ($Cp^* = C_5(CH_3)_5$, M = Rh, Ir, Solv = acetone) (**1a**, **b**) complexes[9] as "tripod connectors". These compounds possess piano-stool structures in which the η^5-Cp* ligand remains firmly attached, whereas three weakly bound acetone molecules occupy the three legs of the tripod. In this work we have used diamines that were designed to coordinate to two different tripod connectors rather than to chelate to a single metal center. We sought the spontaneous and cooperative self-assembly of metallocryptands by combining two metal fragments and three diamines (Scheme 1).

To demonstrate the viability of our strategy we prepared the bidentate ligand 1,3-bis(aminomethyl)-2,5-dimethoxy-4,6-dimethylbenzene (**2a**). Significantly, treatment of three equivalents of the diamine **2a** with two equivalents of tripod connectors **1a** or **1b**, prepared in situ, affords in one-pot reactions the rhodium and iridium cryptands $[(Cp^*M)_2(\mathbf{2a})_3][BF_4]_4$ (**3a** and **3b**), respectively, in 77–85% yield. The ^1H and ^{13}C NMR data recorded in CD_3CN are consistent with the proposed formulas. Most remarkably, the resonances ascribed to the protons of the amino groups appear at very different fields: at $\delta = 5.12$ (td, $J = 11.5$, 4.4 Hz, 1H) and at $\delta = 1.41$ (br t, 1H) for **3a** and at $\delta = 5.91$ (td, $J =$

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