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A Convergent Three-Component Total Synthesis of the Powerful Immunosuppressant (−)-Sanglifehrin A

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Abstract: The potent immunosuppressive agent (−)-sanglifehrin A (**5**), initially discovered in a soil sample from Malawi, has been synthesized in a highly convergent and stereocontrolled manner. The enantioselective approach relies on initial construction of the iodovinyl carboxylic acid **14**, which is coupled to tripeptide **59** in advance of a key macrolactonization step that generates **61a**. An alternative protocol that involves the linkage of **14** to **46** for possible construction of the large ring failed due to an inability to bring about a corresponding macrolactamization maneuver. An efficient means for elaborating the C26−N42 spirolactam western sector of **5** is also detailed. This requisite fragment was assembled through the proper adaptation of consecutive aldol tactics for construction of the nine stereogenic centers, six of which are contiguous. The first aldol process consisted of the tin triflate-mediated reaction of the aldehyde derived from **72** with enantiopure ketone **73** to generate the syn C36−C37 relationship resident in **75**. Once the conversion of **75** to **78** had been completed, the attachment to ketone **66** was effected with (+)-DIPCl, thereby setting the C33−C34 relationship as anti. Once functional group modifications had given rise to **62**, spirolactamization was achieved to deliver predominantly **94**, thereby setting the stage for the acquisition of vinyl stannane **13** and its subsequent palladium-catalyzed Stille coupling to **61b**. Controlled acidic hydrolysis completed the synthesis of **5**. Other important features of the present route are addressed where relevant.

Introduction

The immune system is a multicellular ensemble designed to eliminate foreign entities from the body. The sophisticated response brought into play when such an event occurs involves the growth and proliferation of cells that recognize and ultimately reject the substance.[1−4] This phenomenon is triggered as the result of signal transduction, that process wherein extracellular molecules influence intracellular events.[5−8] In the past decade or so, several important signaling drugs have been discovered that become intimately involved in the orchestration of the immune response. These powerful biochemical tools exhibit specific cellular effects that allow dissection of the mechanisms of signal transduction at the molecular level, shed light on intracellular signaling pathways involved in T-cell activation, and make possible organ transplantation. The most prominent immunosuppressants are cyclosporin A (CsA, **1**),[9,10] FK506 (**2**),[11] and rapamycin (**3**).[12−18]A more recent newcomer is the marine sponge metabolite pateamine A (**4**).[19]

While **1**−**3** mediate their immunosuppressive properties through immunophilins, they do so in unique ways. Thus, **1** binds to cyclophilins, while **2** and **3** bind to protein receptors known as FKBPs.[20−27] Beyond this, calcineurin, the essential enzyme involved in intracellular signal transduction emanating

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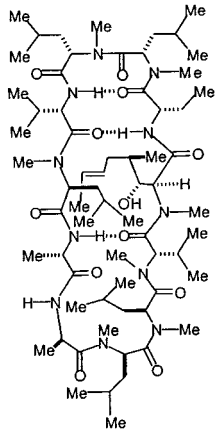
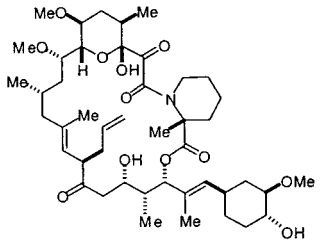
from the T-cell receptor, becomes bound to the cyclophylin-CsA and FKBP-FK506 complexes. In contrast, the FKBP-rapamycin complex inhibits FRAP, a kinase involved in interleukin-2 receptor-mediated T-cell proliferation.

Cyclosporin A, the fungal metabolite capable of blocking activation of the entire immune system, is widely used for the prevention of organ rejection in a variety of transplant surgeries. Acting as a prodrug, it becomes active following entry into the cytosol of T-cells and after formation of the cyclophilin-CsA complex with resultant specific inhibition of the phosphatase activity of calcineurin. Notwithstanding, **1** is not a perfect drug. CsA induces severe toxicity to the kidney and central nervous system, thereby preventing its use for the treatment of other immune disorders such as rheumatoid arthritis. Because calcineurin is responsible for both the immunosuppresive activity and the toxicity of CsA, the hope that new analogues of **1** may be less toxic is greatly diminished.



1



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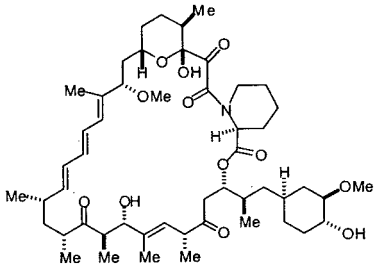

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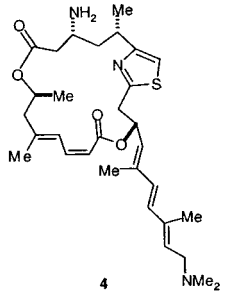

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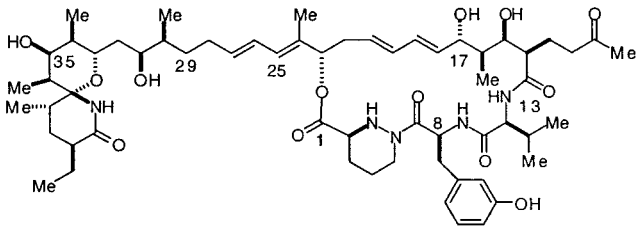
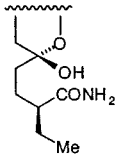
Novel immunosuppressants with different mechanisms of action are thus needed. From the standpoint of T-cell signal transduction, CsA has revealed only one of the many proteins that are involved in mediating the signaling events. New and different immunosuppressants may help to unravel new protein targets that play important roles in T-cell signal transduction. For these reasons, the recently disclosed sanglifehrins **5**−**9** represent a particularly exciting family of immunosuppressive natural products.

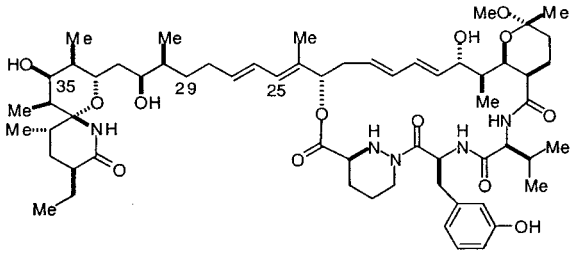


5, sanglifehrin A

6, sanglifehrin B : C35/C36 =

7, sanglifehrin E : C38/C42 =





8, sanglifehrin C

9, sanglifehrin D : C35/C36 =

Background

The sanglifehrins possess an entirely unprecedented type of structure having a macrocyclic lactone core containing the two uncommon amino acids (*S*)-3-carboxy-piperazine and (*S*)-*m*-tyrosine (*m*-hydroxyphenylalanine). Piperazic acids are not unknown, but they occur in the monamycins,[28,29] the antibiotic L- 156,602,[30−32] and the azinothricins[33−36] exclusively acylated at N2 rather than at N1. (*S*)-*m*-Tyrosine has found its widest use in medicinal chemistry, most particularly to probe metabolic pathways of the central nervous system.[37] In addition, a spirolactam subunit not previously encountered in another natural product holds a prominent position in the western sector.

The sanglifehrins were discovered by a team of Novartis scientists in the fermentation broths of *Streptomyces flaveolus* (A92-308110). Although early recognition was made of the presence of a 22-membered macrocyclic ring in combination with a [5.5]spirolactam subunit, endo- and exocyclic conjugated *E*,*E*-diene domains, and an unusual peptidic backbone,[38] a

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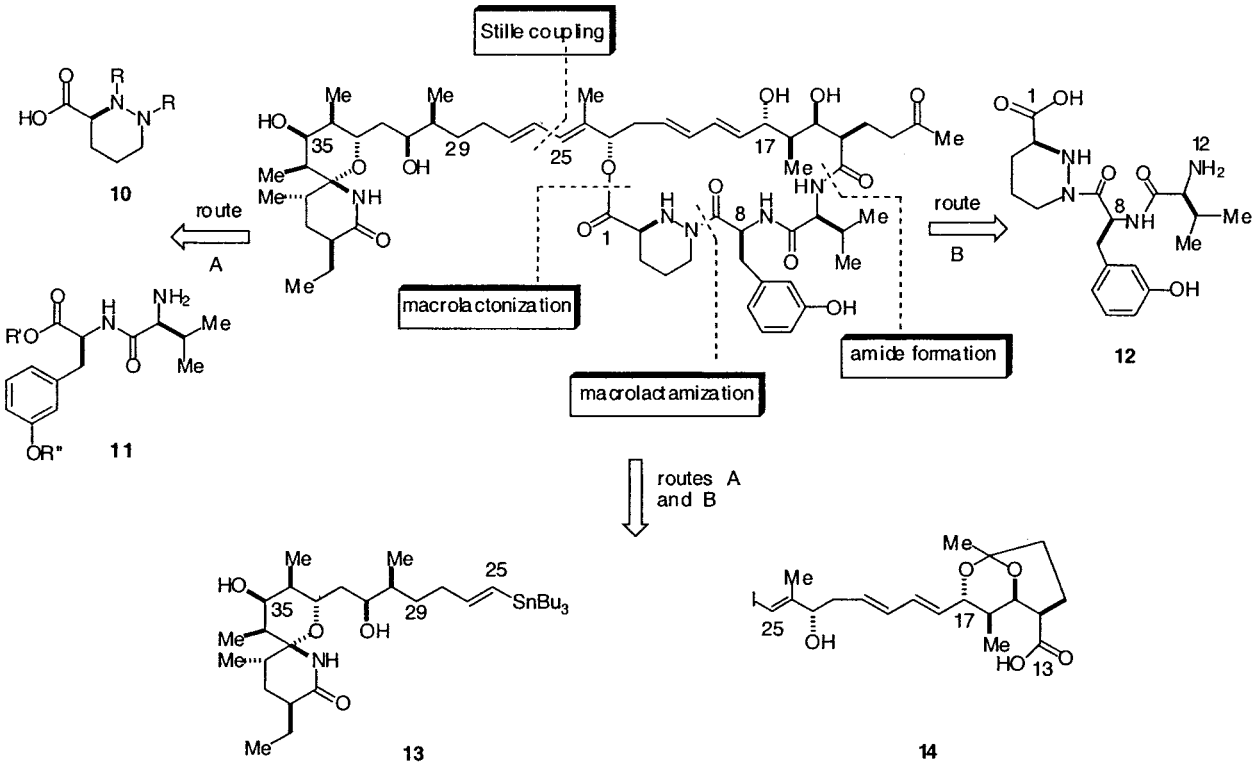

Figure 1. Retrosynthetic analysis of sanglifehrin A via two possible pathways.

defining X-ray crystallographic analysis was necessary to establish unequivocally the absolute configurations at C17, C38, and C40.[39] This accomplishment also confirmed in precise fashion the status of the four contiguous chiral centers spanning C14−C17. This level of challenging structural novelty is matched by the impressive immunosuppressant activity of sanglifehrin A (**5**), the most abundant factor produced by this microbial strain.[40] The high affinity of **5** for cyclophilin A and its capacity for inhibiting mitogen-induced B-cell proliferation without influencing T-cell receptor-mediated cytokine production are especially notable.[41] Consequently, **5** exerts its effect via a mode of action entirely different from that of CsA. Although the precise underlying mechanism remains unknown, hopes are high that our understanding of the immune response at the molecular level will be significantly enhanced as these matters become clarified.

The striking properties defined above have prompted significant interest in the targeted preparation of sanglifehrin A. A total synthesis was achieved by the Nicolaou research team in 1999,[42] a relay synthesis was concomitantly devised by Metternich et al.,[43] and stereoselective routes to significant fragments have been reported by the Novartis[44] and Paquette groups.[45] Macrolide analogues of **5** have also been accessed.[41] Herein we describe in full the design and execution of a convergent strategy for producing natural (−)-sanglifehrin A,[46] the flexibility of which can be expected to make rationally designed congeners available as extension is warranted.

Initial Retrosynthetic Analysis. The Macrolactamization/ Macrolactonization Distinction

In planning the synthesis of **5**, we focused our attention on two potentially complementary pathways, one involving assembly of the eastern sector by macrolactamization (route A), the other consisting of a macrolactonization protocol (route B, Figure 1). Both of these options call similarly for the construction and subsequent union of the vinyl stannane substituted spirolactam **13** and iodovinyl carboxylic acid **14**, and are distinguished only on the basis of whether dipeptide **11** or tripeptide **12** is generated early on. These considerations are distinctively different than the other routes examined previously, which are dependent on elaboration of the macrocyclic ring by C19−C20 bond construction via intramolecular palladium-mediated coupling[42] or ring closing olefin metathesis.[41,42c] Fragments **13** and **14** were designed such that the Stille process could ultimately be applied to craft the central C25−C26 bond of the exocyclic *E*,*E*-diene. In addition to primary concerns

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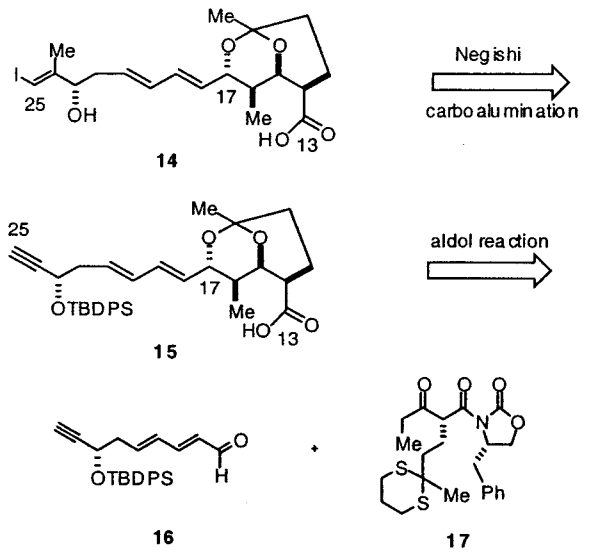


Figure 2. Retrosynthetic analysis of the C131−C25 sector.

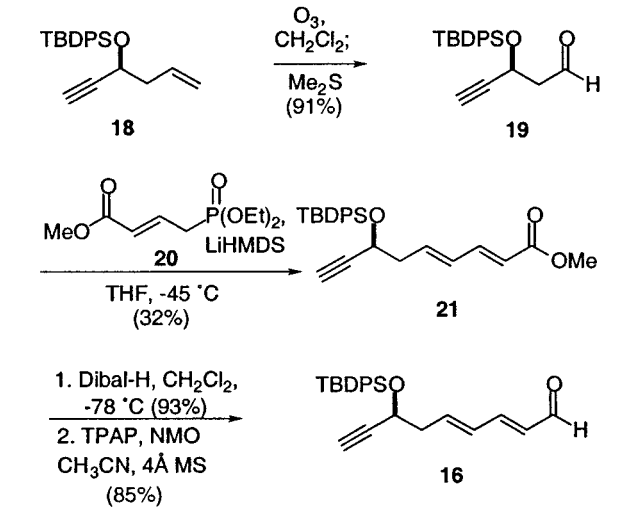
regarding incorporation of protected piperazic acid subunits such as **10** without racemization[47,48] and efficient union of the major subtargets, the plan called for paying strict attention to proper installation of the numerous stereocenters. The spans across C14−C17 and C30−C41 were clearly destined to be most challenging. The stereochemical course of the spirolactam ring closure also held interest and appeal.

Evaluation of an Alkyne Surrogate at the Chain Terminus of 14

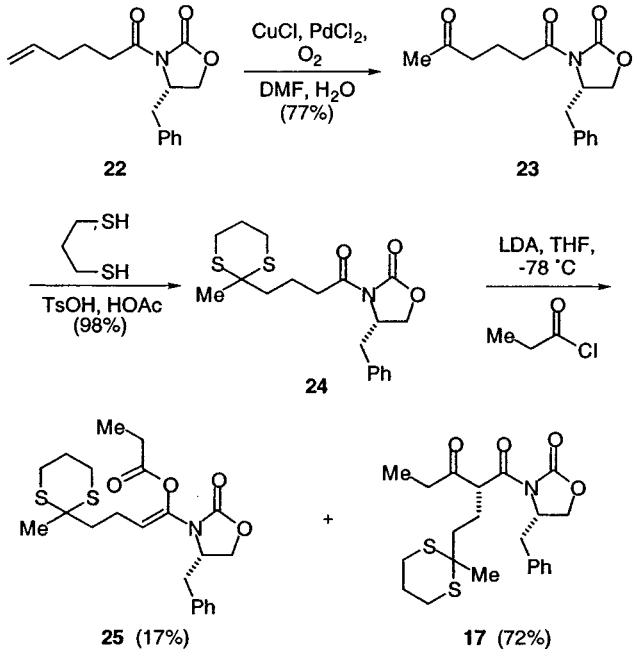
The initial thinking underlying incorporation of the sensitive vinyl iodide functionality into **14** was to delay matters until as late a stage as possible. Application of the Negishi carboalumination reaction to **15** seemed appropriate to the task at hand.[49] In this context, the zirconocene dichloride- or diiodide-promoted addition of trimethylaluminum to protected propargyl alcohol **15** would be expected to proceed in cis fashion and with high regioselectivity ultimately to deliver **14** after exposure to elemental iodine (Figure 2). To address the feasibility of this ploy, we elected to use a reagent-controlled aldol reaction between **16** and **17** as the means to reach **15**.

The preparation of **16** began with the ozonolytic conversion of readily available **18**[50] to aldehyde **19** (Scheme 1). Wittig−Horner chain homologation of **19** by reaction with methyl 4-(diethylphosphono)crotonate (**20**) in the presence of lithium hexamethyldisilazide[51,52] furnished principally the *E*,*E*-diene **21**. Removal of the other unwanted geometric isomers was easily accomplished chromatographically, thus setting the stage for reduction of the desired ester to the alcohol with diisobutylaluminum hydride and subsequent perruthenate oxidation. This two-step sequence routinely generated aldehyde **16** in very good yield.

Scheme 1



Scheme 2



Access to reaction partner **17** was realized in the manner shown in Scheme 2. Wacker oxidation of the enantiopure oxazolidinone **22**[53] led to regiospecific introduction of a ketone carbonyl group, which was subsequently converted into dithioketal **24** in conventional fashion. For installation of the propionyl substituent, the lithium enolate of **24** was allowed to react under conditions of kinetic control with the acid chloride. This process proceeded with high diastereoselectivity to deliver principally **17**. As anticipated from the prior observations of Evans,[54] the stereogenicity of the newly generated chiral center in **17** was not eroded during chromatographic purification as a consequence of low kinetic acidity presumably brought on by allylic strain effects.

Conveniently, **17** was cleanly transformed into its (*E*)-boron enolate on exposure to chlorodicyclohexylborane and ethyldimethylamine.[55] Introduction of aldehyde **16** resulted in conversion to the anti aldol **26** (Scheme 3). It is noteworthy that the

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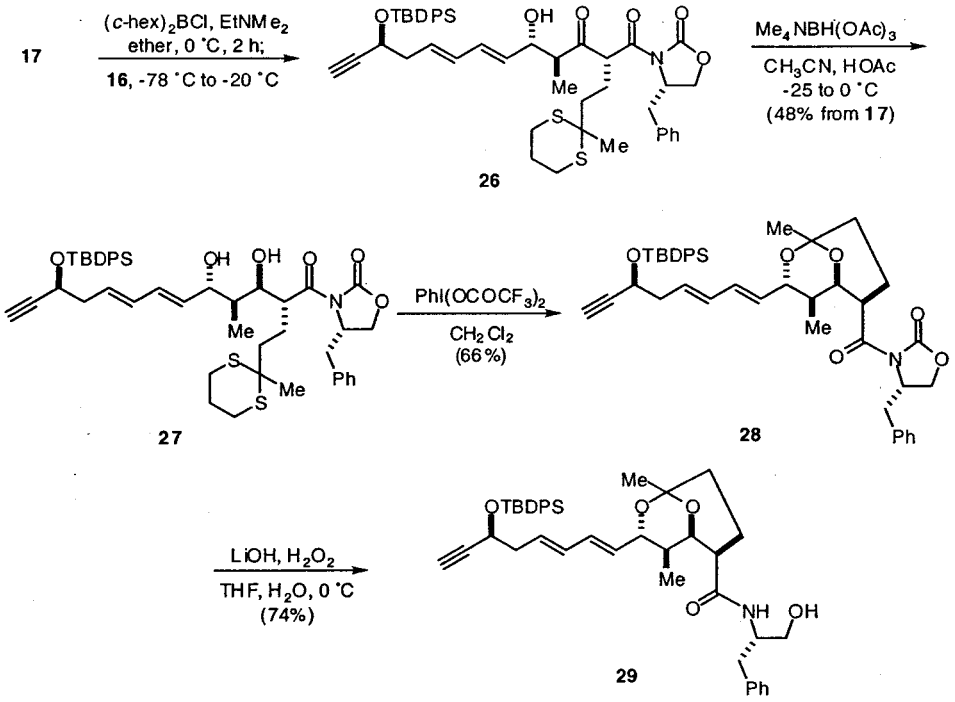
Scheme 3



efficiency of this key step was improved if the workup conditions defined by Paterson[56] were applied. The fourth contiguous stereogenic center was introduced as in **27** by direct reduction of **26** with tetramethylammonium triacetoxyborohydride.[57]

The dethioacetalization of **27** that was next planned met with irksome problems when a variety of carbonyl unmasking protocols were applied.[58] Ultimately, we found the use of phenyliodine(III) bis(trifluoroacetate)[59] to be highly preferred in this application, giving rise to **28** in 66% yield. Under these conditions, the intramolecular ketalization occurred spontaneously.

We next set about to effect the conversion of **28** into **15**, a goal that was unexpectedly thwarted by two unfavorable discoveries. Initially, the oxazolidinone exhibited substantial reluctance to undergo oxidative cleavage.[60] The efficiency with which **28** is transformed into **29** rather than the carboxylic acid could not be constructively diverted. Further, application of the classical carboalumination conditions to **28** as well as numerous variants thereof invariably proved too harsh for this substrate. The terminal acetylenic functionality could not be suitably modified even under conditions where steric congestion was abated by removal of the silyl protecting group. We also had occasion to consider an alternative synthetic tactic involving prior removal of the chiral auxiliary that had served us so well to this point. In the final analysis, these complications caused us to install the vinyl iodide unit from the very outset.

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(60) Evans, D. A.; Britton, T. C.; Ellman, J. H. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

The Second Generation Approach to 14

The readily availability of aldehyde **30**[61] enabled us to test the suitability of carrying a terminal vinyl iodide fragment through the necessary homologation process (Scheme 4). Coupling of **30** with the lithium salt of **20** proceeded uneventfully to install the dienyl ester functionality with a very acceptable 9:1 preference for the (*E*,*E*)-isomer **31**. Subsequent reduction to the primary carbinol with diisobutylaluminum hydride followed by oxidation with manganese dioxide proved to be relatively efficient operations. Beyond that, the coupling of **32** to the (*E*)-boron enolate of **17** and stereocontrolled hydride reduction proceeded in a manner very closely paralleling our earlier observations with the terminal alkyne. Once the dithioacetal group in **33** had been removed en route to **34**, we were particularly pleased to observe that reductive cleavage of the oxazolidinone ring in this advanced intermediate could be accomplished regioselectively on exposure to sodium borohydride in aqueous THF as the reaction medium.[62] Alternative recourse to the more customarily utilized lithium borohydride reagent in THF with methanol as a cosolvent resulted in deiodination and was therefore not serviceable. We could now attempt the two-stage oxidation of **35** to carboxylic acid **36**. As foreshadowed by successful model experiments, this transformation proceeded in notably efficient fashion (97%), as did unmasking of the free secondary hydroxyl to generate **14**. The discovery that all of the compounds depicted in Scheme 4 are relatively stable and readily handled was particularly satisfying.

Evaluation of the Macrolactamization Ring Closing Protocol (Route A)

As indicated earlier, we envisioned one possible option for proper elaboration of the complete C1−C25 sector of sanglifeh-

(61) Nicolaou, K. C.; King, N. P.; Finlay, M. V. R.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninokovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665−697.
(62) Prashad, M.; Har, P.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067−7070.

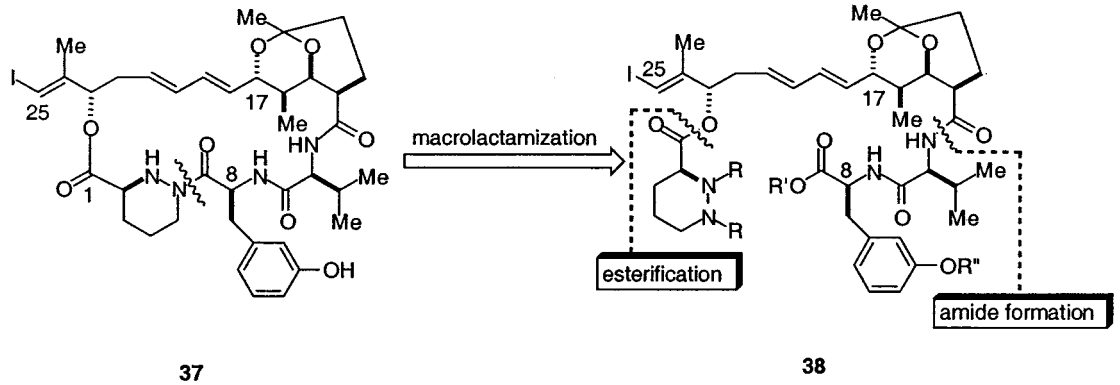
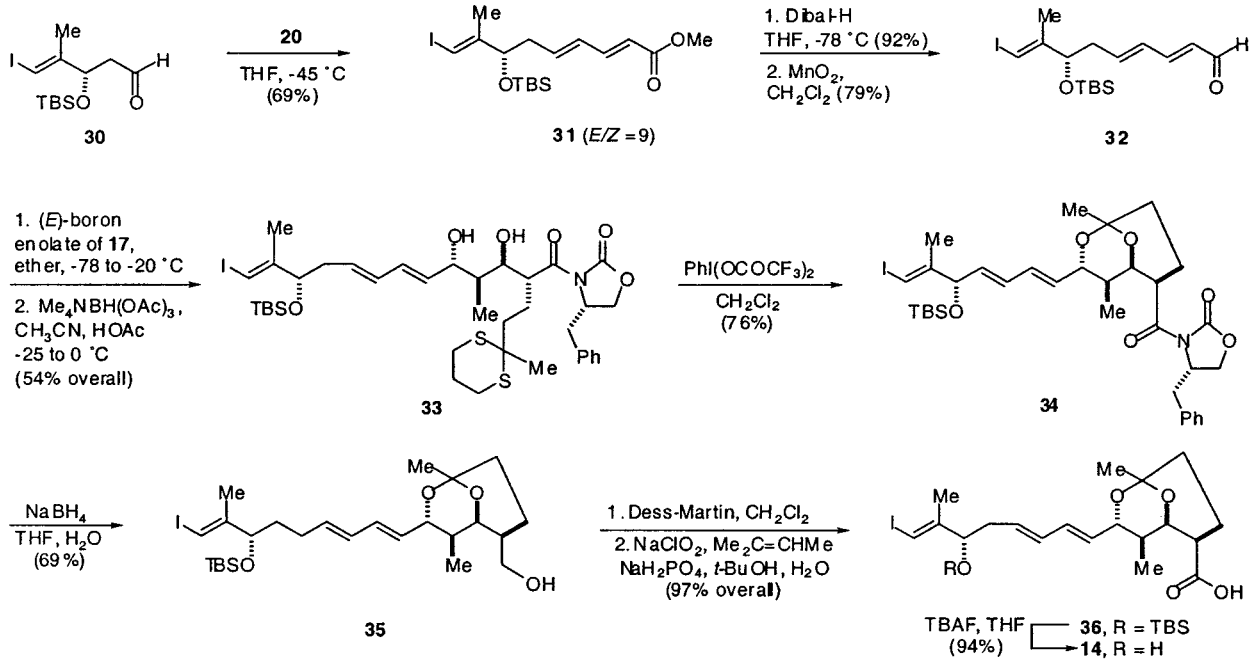


Figure 3. Retrosynthetic analysis of C1−C25 assembly by means of macrolactamization.

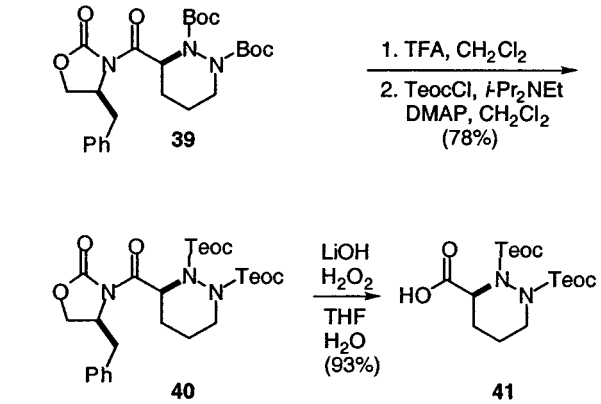
Scheme 4



rin A to involve a pivotal macrolactamization step. From the retrosynthetic perspective, the projected conversion of **38** into **37** demands judicious selection of the protecting groups defined as R, R′, and R″ (Figure 3). Similar considerations apply to the step involving appendage of the dipeptide fragment. These tactics are adequately precedented. Far more demanding of these protective groups was the need to remove them once **38** was accessed and to do so under conditions which were neither too basic nor overly acidic. These restrictions surfaced because of the sensitivity of the C1 carboxylate to alkaline hydrolysis, and of the proclivity of the acetal spanning C15 and C17 to acid-promoted cleavage.

With these considerations in mind, the 2-(trimethylsilyl)-ethoxycarbonyl (Teoc) protecting group[63] was installed on the piperazic acid nitrogen atoms as in Scheme 5. Because large supplies of the known **39**[64] were available to us, simple exchange of the Boc substituents proved to be highly expedient. Our expectations were that removal of the Teoc groups would not

Scheme 5



prove troublesome in view of their recognized usefulness in peptide chemistry[65] and in other settings involving highly functionalized, structurally complex intermediates.[66]

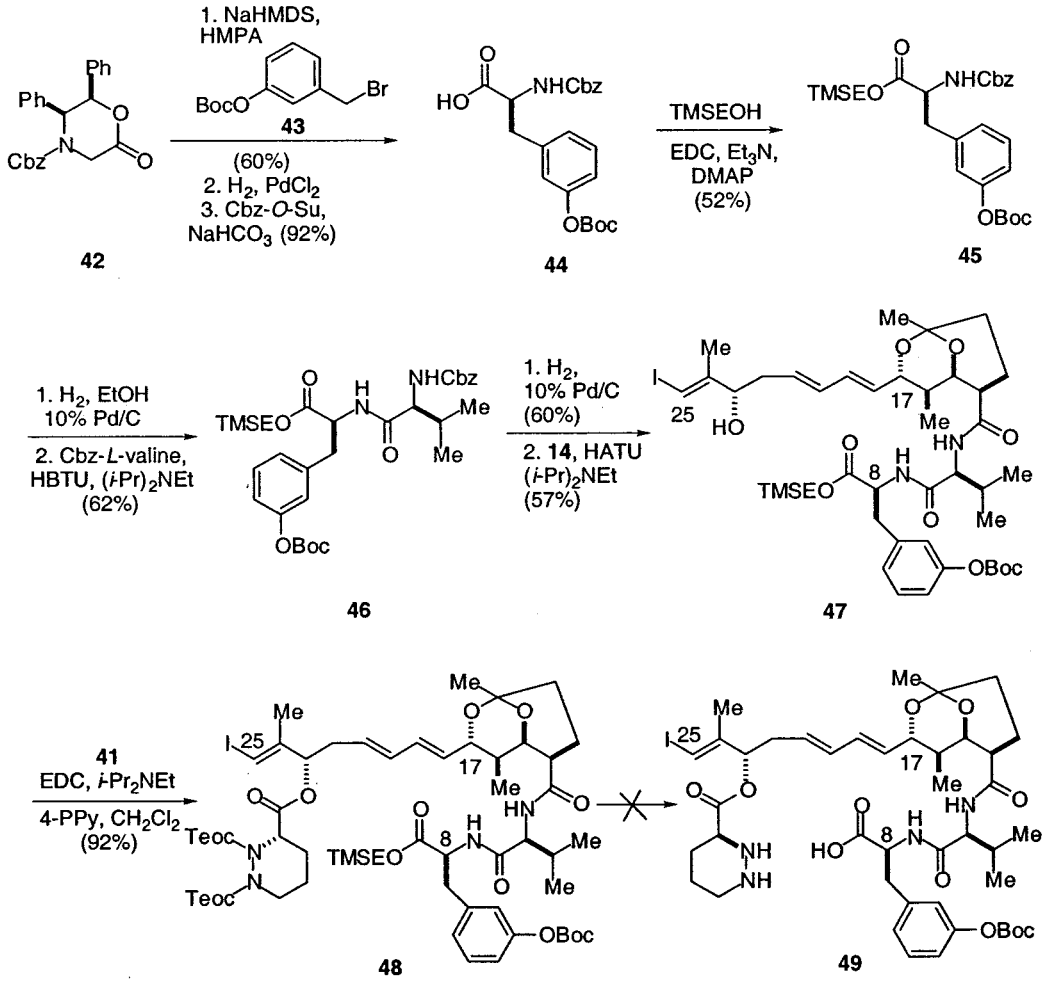
The second paradigm, guided by a desire to deprotect the carboxyl group concurrently with unmasking of the pair of

(63) (a) Carpino, L. A.; Tsao, J. H.; Ringsdorf, H.; Fell, E.; Hettrich, G. *J. Chem. Soc., Chem. Commun.* **1978**, 358−359. (b) Campbell, A. L.; Pilipauskas, D. R.; Khanna, I. K.; Rhodes, R. A. *Tetrahedron Lett.* **1987**, *28*, 2331−2334.

(64) The enantiomer of **39** has been reported earlier; consult ref 33.

(65) (a) Wünsch, E.; Moroder, L.; Keller, O. *Hoppe-Seyler's Z. Physiol. Chem.* **1981**, *362*, 1289−1292. (b) Rosowsky, A.; Wright, J. E. *J. Org. Chem.* **1983**, *48*, 1539−1541. (c) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346−349.

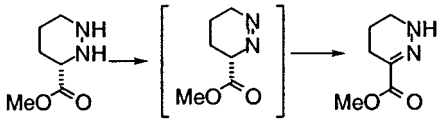
Scheme 6



amino nitrogens, led us to consider the esterification of **44** with trimethylsilylethanol (TMSEOH).[67] This option was exercised following the acquisition of the functionalized *m*-tyrosine **44** by a modification of the Bender and Williams method[37] involving the alkylation of commercially available oxazinone **42** (>98% ee) with *m*-(benzyloxy-carbonyl)benzyl bromide[68] (**43**, Scheme 6). These steps were followed by the hydrogenolysis of **45** over 10% Pd/C to free the NH_2 group, and subsequent peptidic coupling to Cbz-L-valine as promoted by *O*-benzotriazolyl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU).[69,70] This pair of reactions proceeded quite smoothly, giving rise to enantiopure **46** in 62% overall yield.

Reduction of intermediate **46** led to removal of the Cbz substituent, thereby allowing for linkage to **14**. Conditions designed for HATU[71] to provide the driving force for amide bond formation resulted in proper integration of the entire C13–C25 sector as in **47**. The reaction between **41** and **47** necessary to advance to **48** was most efficiently brought about in the presence of *N*-ethyl-*N*′-(3-(dimethylamino)propyl)-carbodiimide hydrochloride (EDC)[67] and 4-pyrrolidinopyridine (4-PPy).[72]

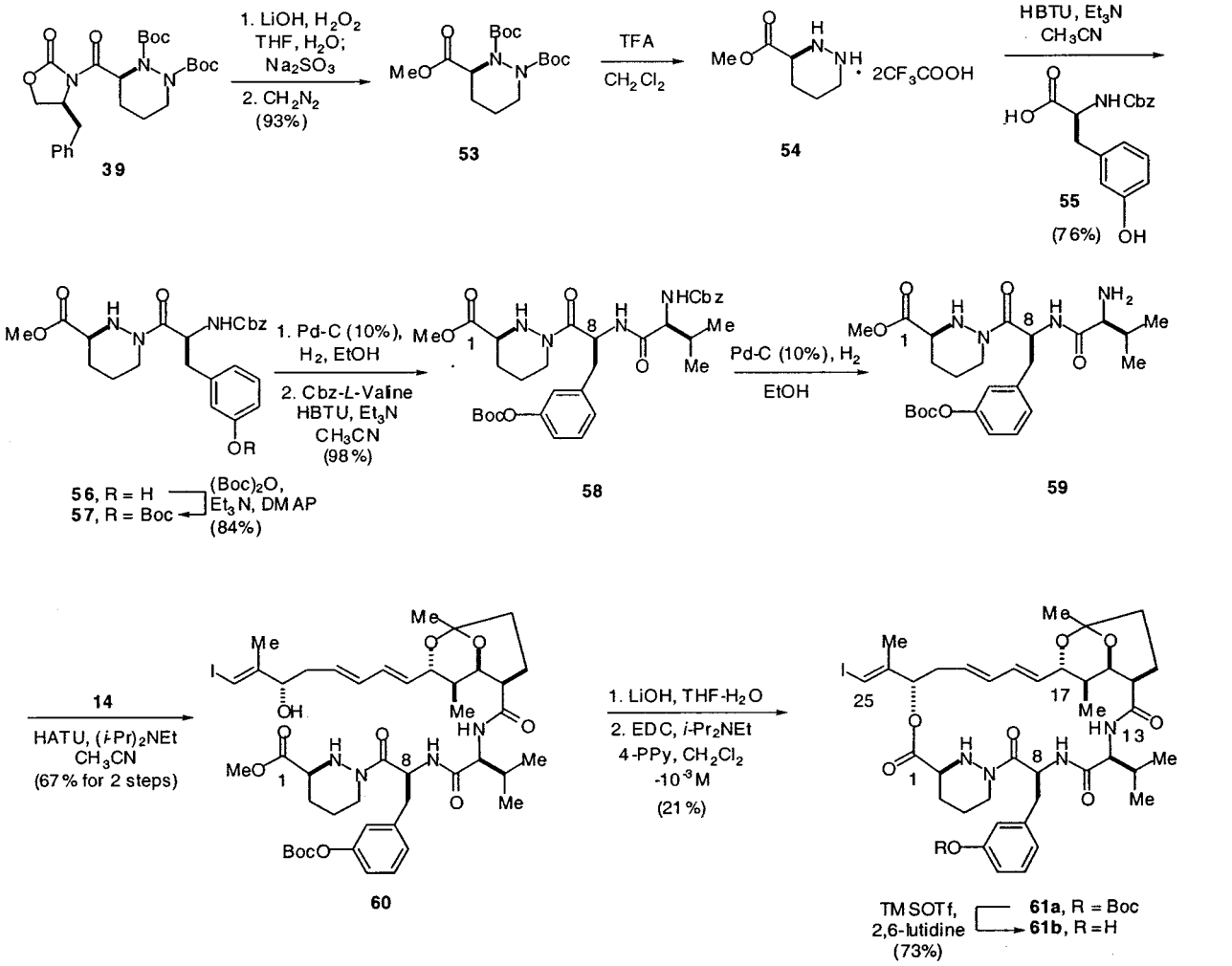
Scheme 7



At this juncture, removal of the Teoc and TMSE groups became our next goal. Unfortunately, many attempts to liberate **49** met with failure. All of the conditions screened (e.g., TBAF, TBAF/SiO_2, HF, HF·py, TASF, etc.) led to the formation of uncharacterizable products. To gain insight into the source of this complication, the methyl ester of piperazic acid was prepared and stored for several hours at room temperature. During this time, **50** (prepared under acidic conditions followed by neutralization of the salt) was transformed in part into the dehydro derivative **52** (perhaps via **51**) as clearly recognized by ^1H and ^{13}C NMR spectroscopy[73] (Scheme 7). Polymerization again materialized to a major extent. Careful examination of the literature revealed that N2-acylated piperazic acids experience ready oxidation under a wide variety of conditions.[47]

(66) For example: (a) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732–4734. (b) Roush, W. R.; Coffey, D. S.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 11331–11332.
(67) Bourne, G. T.; Howell, D. C.; Pritchard, M. C. *Tetrahedron* **1991**, *47*, 4763–4774.
(68) Obi, N.; Amada, J. Japanese Patent Appl. JP 98-126310.
(69) Dourtoglou, V.; Ziegler, J. C.; Gross, B. *Tetrahedron Lett.* **1978**, 1269–1272.
(70) Dourtoglou, V.; Gross, B.; Lambropoulou, Z. C. *Synthesis* **1984**, 572–574.
(71) *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate: Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397–4398.
(72) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, 2069–2076.
(73) ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (br s, 1H), 3.78 (s, 3H), 3.25–3.20 (m, 2H), 2.45 (t, J = 6.7 Hz, 2H), 1.90 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 132.1, 51.9, 41.7, 21.0, 17.4.

Scheme 8



Consequently, the inherent tendency of **49** and **50** to react in this manner was not surprising. The rapidity of this process, which was sufficient to deter effective direct macrolactamization, even under extremely mild conditions was, however, not anticipated.

Highly Diastereocontrolled Synthesis of the C1−C25 Domain via Macrolactonization (Route B)

With the demise of route A, the focus of our attention turned to the interesting macrolactonization option that required access to a tripeptide array patterned after **11**. The ready availability of **39**[33] allowed for its conversion via **53** to **54** on a multigram scale according to the Hale procedure (Scheme 8). HBTU proved to be a particularly effective agent in bringing about the acylation of **54** at N1 with the *m*-tyrosine **55**. The realization that the phenolic hydroxyl in **55** requires no protection during the amidation step is noteworthy. Conversion to Boc derivative **57** and hydrogenolysis were followed by union with Cbz-protected L-valine to give tripeptide **58**. Once the primary amino group had been unmasked as in **59**, the requisite coupling to **14** could be accomplished efficiently.

This short series of steps provided **60** in straightforward fashion. Our ultimate expectation of bringing about the chemoselective saponification of **60** at the methyl ester site and ring closure to deliver synthetic **61a** was indeed realized successfully with an overall efficiency closely paralleling the norm encountered for such large ring-forming steps.[74] That the structural assignment to this advanced intermediate is properly formulated follows most convincingly from its electrospray high-resolution mass spectrum, the clear delineation in the 500 MHz ^{1}H NMR spectrum of all the requisite resonances for its constituent protons, and a fully compatible ^{13}C NMR spectrum. The phenolic hydroxyl was unmasked with trimethylsilyl triflate and 2,6-lutidine in CH_2Cl_2 solution.

Elaboration of the C26−N42 Spirolactam Western Zone

Both disconnections envisioned at the outset (Figure 1) shared in common the need for **13** or a protected form thereof. The presence of an (*E*)-vinylstannane moiety and the high density of stereogenic centers (with 11 of the 16 framework carbons bearing stereochemical information) was certain to provide challenging complexities. The critical role of this precursor demanded the development of a route that would be amenable to the reliable throughput of material. The retrosynthetic prospects shown in Figure 4 are seen to be dependent on the independent preparation of enantiopure building blocks **64**, **65**, and **66**, and their proper amalgamation via stereocontrolled aldol

(74) Compare, for example: (a) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776−2778. (b) White, J. D.; Amedio, J. C. *J. Org. Chem.* **1989**, *54*, 736−738. (c) Parmee, E. R.; Steel, P. G.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1250−1252.

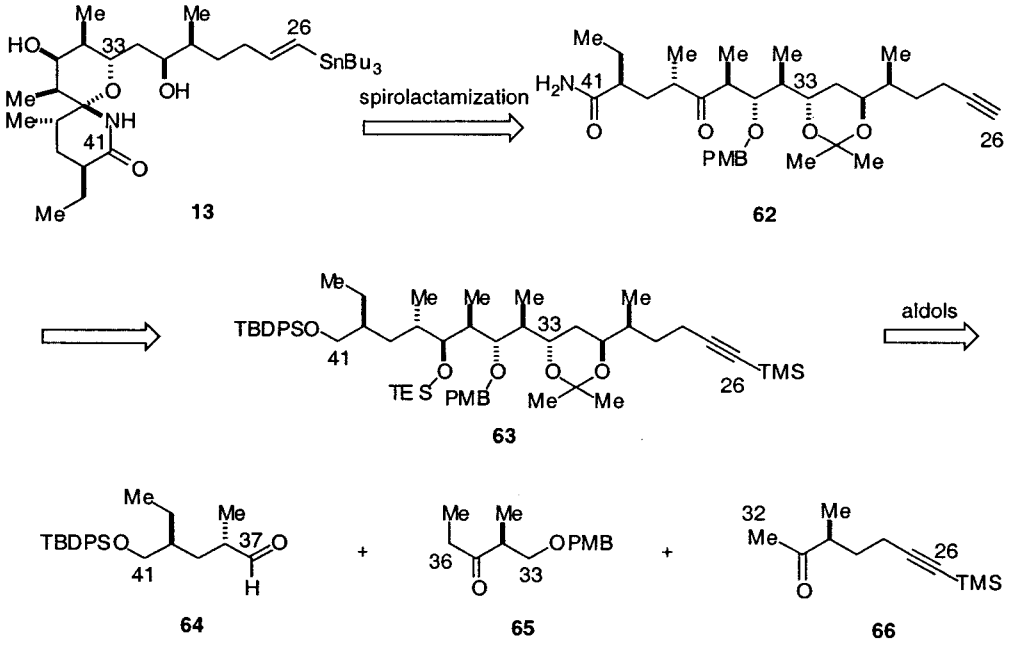
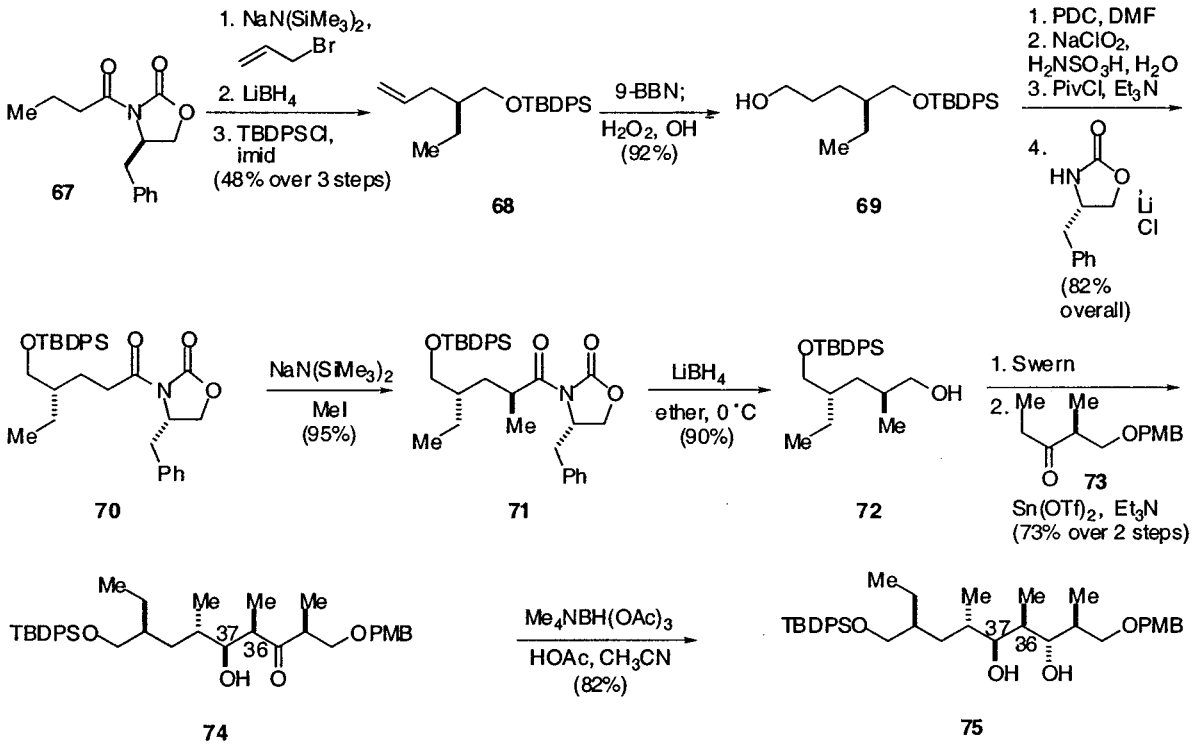


Figure 4. Retrosynthetic analysis of C26−N42 construction via multiple aldol tactics.

Scheme 9

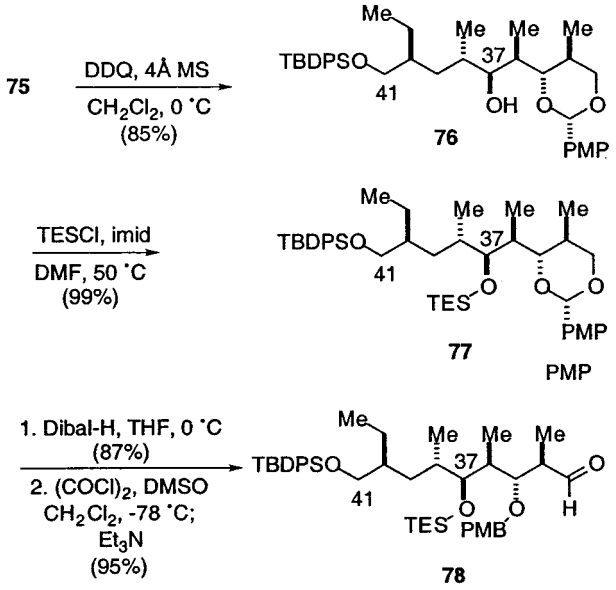


reactions. Our ultimate expectation for **62** was an intramolecular cyclization that would set the aminal configuration at C37 with high fidelity.

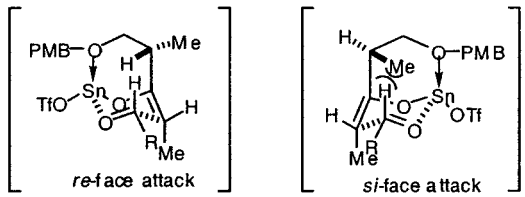
These considerations led us to consider the known[75,76] (*R*)-acyloxazolidinone **67** as a point of departure. By allylation of the enolate of **67**, it was possible to set the proper absolute configuration α to the external carbonyl[54] (Scheme 9). Subsequent conversion to the monoprotected 1,5-diol **69** was accomplished by sequential reductive cleavage of the chiral auxiliary with $LiBH_4$ in wet ether, transformation of the relatively volatile alcohol to its TBDPS ether, and hydroboration-oxidation with 9-BBN. Following two-step oxidation to the carboxylic acid, the latter was most efficaciously converted into **70** through adaptation of an activated anhydride protocol.[77,78] Following highly enantioselective methylation of the enolate anion of **70** to give **71**, the chiral auxiliary was reductively cleaved with lithium borohydride. This tactic allowed for the

(75) Göschke, R.; Cohen, N. C.; Wood, J. M.; Mailbaum, J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2735−2340.
(76) Thom, C.; Kocienski, P. *Synthesis* **1992**, 582−586.
(77) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775−7778.
(78) The formation of the *N*-pivaloyloxazolidinone as an insoluble byproduct was noted if the same reaction was carried out under the conditions described by Evans (Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453).

Scheme 10



generation of alcohol **72**, Swern oxidation of which smoothly generated a pivotal aldehyde whose role it was to enter into condensation with the tin(II) enolate of *S*-(**73**)[79,80]under substrate control.[81] In light of precedent, our expectation was that *re*-face selectivity as in **A** would be significantly favored over the *si*-face alternative **B** because of the differing nonbonded steric interactions operative in these transition states.

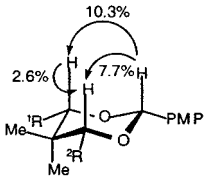


A **B**

The conditions shown, which required minimal screening to uncover, gave rise to **74** in 92% yield as a chromatographically separable 92:8 mixture of diastereomers. The stereochemical assignment to this syn aldol product follows from a complete COSY analysis performed on its OTBS/OBn analogue, in line with previous successes realized upon application of the *J*-based method to conformationally flexible systems ($J_{H36,H37}$ = 1.7 Hz).[82] Hydroxyl-directed reduction of **74** with tetramethylammonium triacetoxyborohydride[57] made available the anti diol **75**, the two hydroxyls in which were differentiated by DDQ oxidation under kinetic control[83] (Scheme 10).

With formation of the terminal *p*-methoxyphenyl (PMP) acetal,[76] we could now attempt protection of the remaining hydroxyl as its triethylsilyl ether and follow that by regioselective reductive cleavage of **77** with diisobutylaluminumhydride.[84] Careful Swern oxidation of the primary carbinol so formed led to aldehyde **78**.

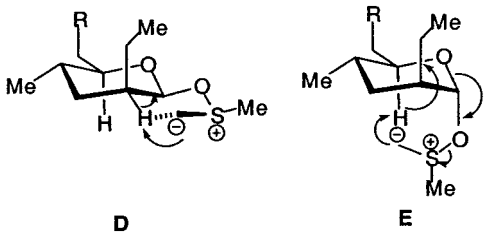
The seven-carbon extension of **78** in the direction of C26−C32 began with oxidation of **79** with pyridinium chlorochromate,[85] activation of the resulting carboxylic acid by coupling to pivaloyl chloride, and condensation of the mixed anhydride with (*S*)-4-(phenylmethyl)-1,3-oxazolidin-2-one (Scheme 11). The elaboration of **80** via its monomethylation product **81** to methyl ketone **66** provided no unforeseen difficulties and proceeded with high reaction efficiencies. The conjoining of **66** with **78** was mediated by a second asymmetric aldol reaction, this time involving the chiral Lewis-acidic (+)-*B*-chlorodiisopinocampheylborane (DIP chloride) in the presence of triethylamine. In view of the somewhat checkered history of this reagent,[86] we were compelled to verify the stereochemical outcome in **83**. To this end, we elected to transform **83** into **84**, and to analyze the resulting acetal **84** by NOE methods. As shown in **C**, it was quickly made apparent that all four groups positioned on the 1,3-dioxane ring were equatorially disposed. Consequently, the stereogenicity established at C33 was as programmed.



C

We could now attempt the directed triacetoxyborohydride reduction of **83** to give **84** in advance of incorporation of the resulting trans diol into an acetonide ring as in **85**. With this intermediate in hand, it proved an easy matter to rid the molecule of its three different silyl protecting groups in a single operation with TBAF in THF. Following this treatment, diol **86** emerged as a polar colorless oil in 92% yield.

We set as our next interim goal the keto amide **93**. It was hoped that **86** would initially be amenable to oxidative lactonization. Tetra-*n*-propylammonium perruthenate (TPAP) failed to give the desired product, resulting instead chiefly in decomposition. Therefore, attention was directed to Swern conditions. This protocol was less than optimal, giving rise to lactol **87**, a material highly sensitive to more advanced oxidative conversion to the lactone. In fact, attempts in this direction induced competitive elimination to afford **88** and fragmentation leading to **89**. Passage through transition states **D** and **E** is therefore implicated.

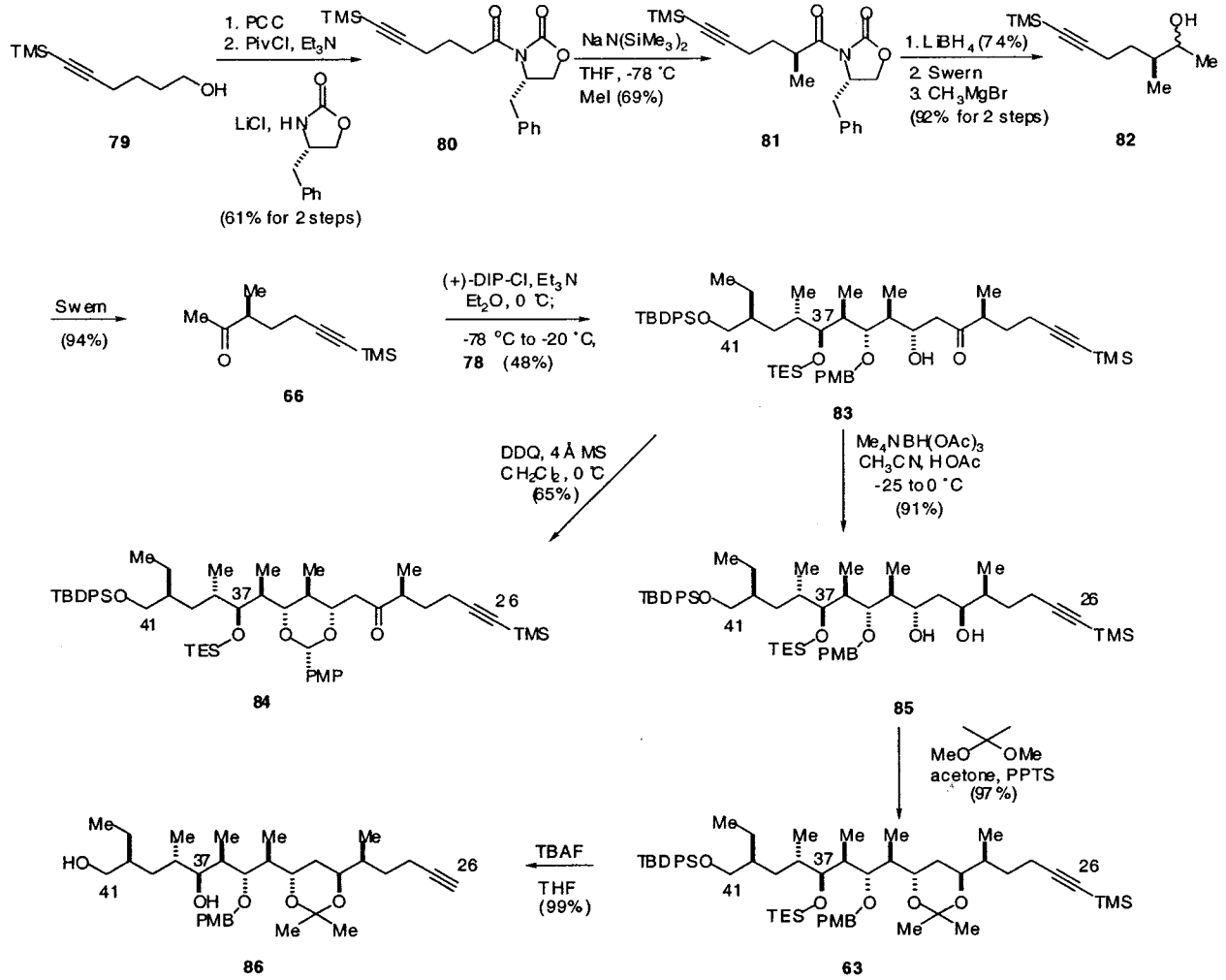


D **E**

Fortunately, an alternative approach involving differential protection and unmasking of the two hydroxyl groups was

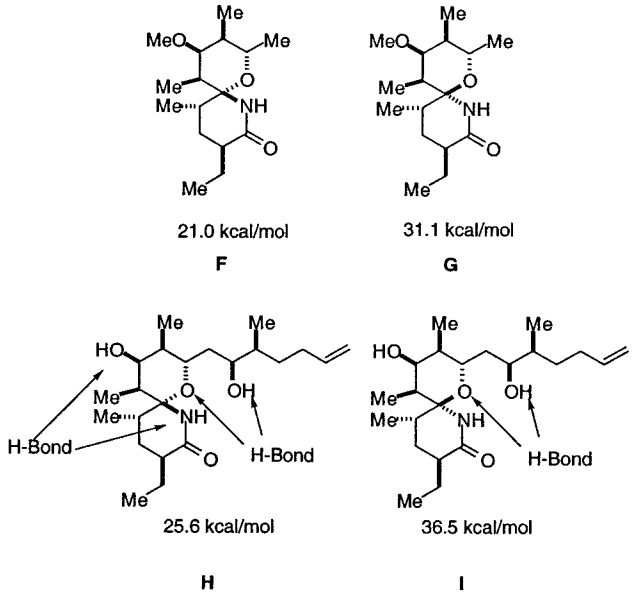
(79) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315−3319.
(80) In the present study, **73** was prepared by conversion of commercially available (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate into its Weinreb amide, followed by protection of the free hydroxyl as its PMB ether by reaction with the 2,2,2-trichloroacetimidate under catalysis by triflic acid [Paterson, I.; Nowak, T. *Tetrahedron Lett.* **1996**, *37*, 8243−8246]. The subsequent addition of ethylmagnesium bromide furnished **73** in 91% yield.
(81) (a) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233−4236. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287−11314.
(82) Murata, M.; Matsuoka, S.; Matsumori, N.; Paul, G. K.; Tachibana, K. *J. Am. Chem. Soc.* **1999**, *121*, 870−871.
(83) Oikawa, Y.; Nishi, T.; Yonemitsu, O. *Tetrahedron Lett.* **1983**, *24*, 4037−4040.

Scheme 11



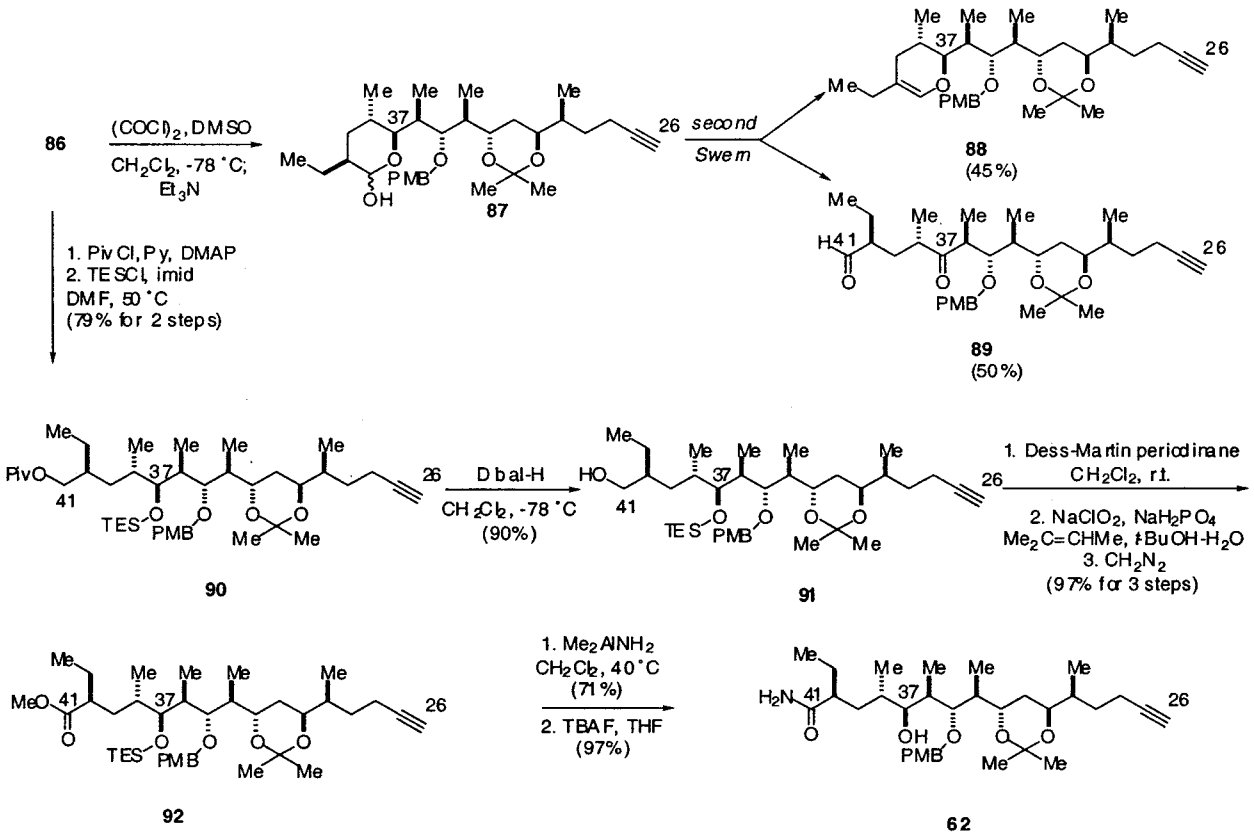
feasible. From among many available options, the decision was made to advance to the primary pivalate having triethylsilyl bonded to the secondary carbinol as in **90** (Scheme 12). This maneuver allowed for selective liberation of the OH group at C41 by Dibal-H reduction and its conventional three-stage conversion to the methyl ester **92**. The amide moiety was introduced by the treatment of **92** with freshly prepared dimethylaluminum amide in CH_2Cl_2 at the reflux temperature.[87] Subsequently, we took recourse to TBAF deprotection at C37 and oxidation of **62** at that site to provide **93** with exceptional efficiency (Scheme 13).

Considerable thought and computational assessment were devoted to our evaluation of the possible stereochemical course of the acid-catalyzed ring closure of **93** with generation of a [5.5]spirolactam system. It will be recognized that all but two carbons of the simplified structures **F** and **G** are stereogenic centers. The Monte Carlo conformational searching method was applied to **F** and **G** at the MM3 force field level. Each conformational search was allowed 1000 iterations to find the global minimum. The latter were further minimized using the full-matrix Newton−Raphson method to more accurately determine the associated relative steric energy values. Under these conditions, diastereomer **F**, which corresponds in stereochemical detail to the western sector of sanglifehrin A, was found to be 10 kcal/mol more stable than **G**. The more expanded structures **H** and **I**, which likewise differ only in the configuration at the

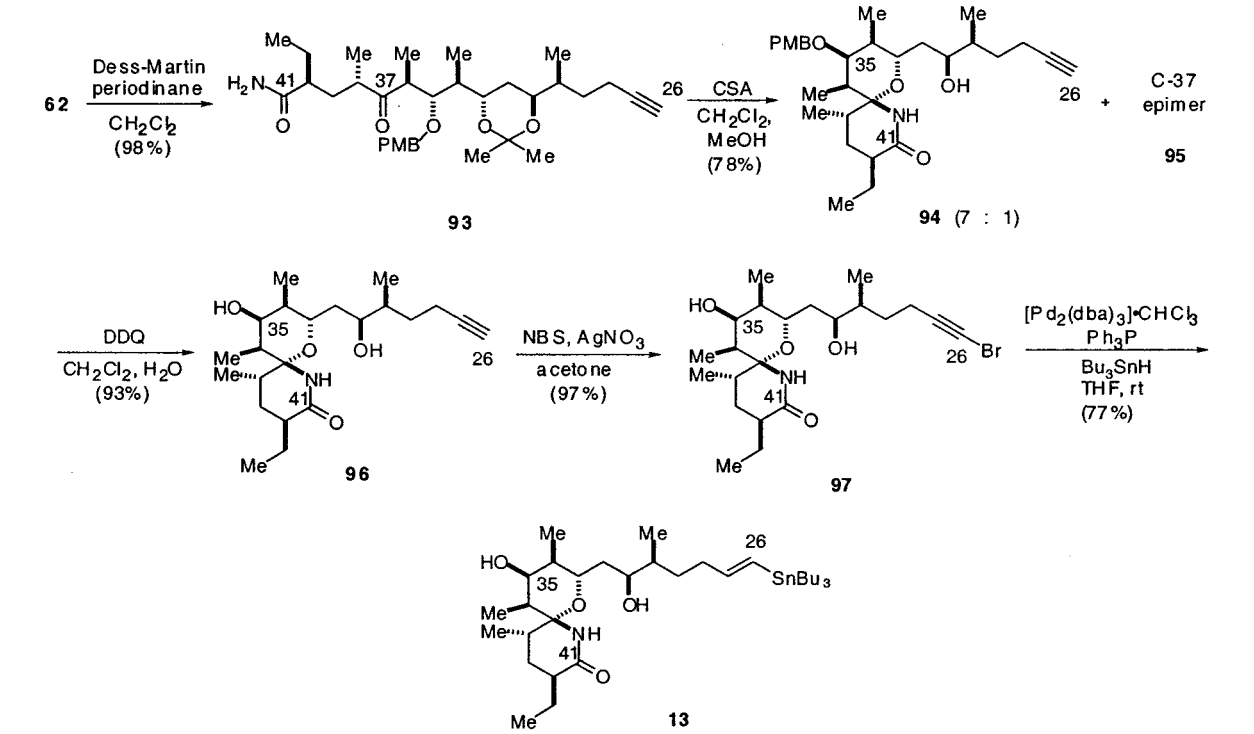


(84) Curtis, N. R.; Holmes, A. B.; Looney, M. G. *Tetrahedron Lett.* **1992**, *33*, 671−674.
(85) Spencer, R. W.; Tam, T. F.; Thomas, E.; Robinson, V. J.; Krantz, A. *J. Am. Chem. Soc.* **1986**, *108*, 5589−5597.
(86) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663−4684.
(87) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174.

Scheme 12



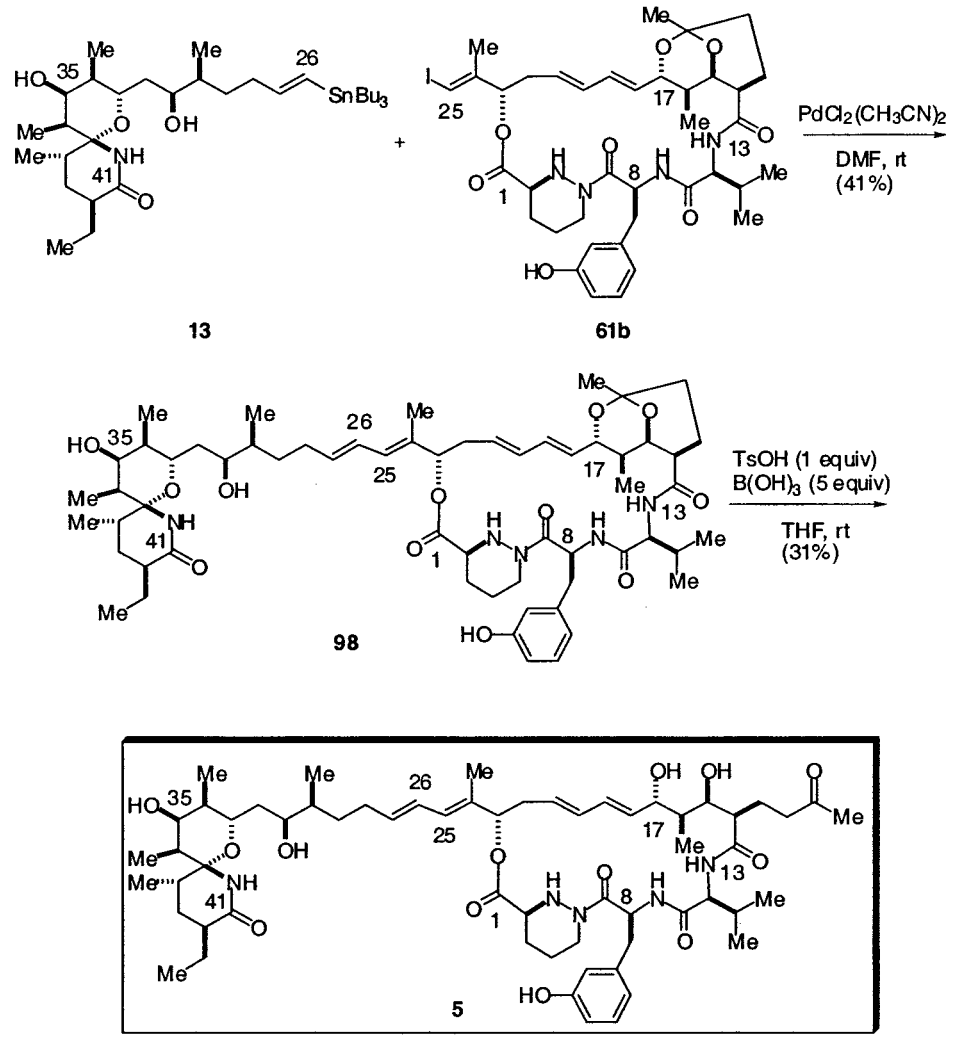
Scheme 13



spirocenter, were also examined to allow hydrogen bonding to play its usual role in guiding thermodynamic stability. Relevantly, **H** is also favored, a position likely solidified to a yet greater extent by the second intramolecular hydrogen bond it is capable of forming.

On this basis, we had little doubt that the acid-catalyzed spirolactamization of **93** would proceed to deliver predominantly **94** to gain the stabilization provided by the anomeric effects. Indeed, **94** was isolated alongside its epimer C37 **95** in a 7:1 ratio following the treatment of **93** with camphorsulfonic acid.

Scheme 14



The further elaboration of **96** and subsequently **97** proved straightforward, thereby setting the stage for conversion to the (*E*)-vinyl stannane **13**. The conditions preferred for this key step involved preliminary conversion to bromoalkyne **97** by treatment of **96** with *N*-bromosuccinimide in the presence of silver nitrate,[88] followed by exposure to tri-*n*-butylstannane, triphenylphosphine, and $[Pd_2(dba)_3]\cdot CHCl_3$ in THF solution according to the Guibé protocol.[89]

Arrival at the Target

With the availability of both **13** and **61b**, attention quickly turned to their palladium-catalyzed coupling. Earlier studies by our group that had targeted the synthesis of polycavernoside A[90] and analogues thereof[91] had demonstrated the feasibility of conjoining complex, highly functionalized subunits with $PdCl_2(CH_3CN)_2$ in DMF at room temperature. The adaptation of these conditions in the present context resulted in smooth operation of the Stille reaction to deliver sanglifehrin acetal **98** (Scheme 14). Ultimately, the difficult acidic hydrolysis of **98** to arrive at the title compound **5** was carried out in the presence of *p*-toluenesulfonic acid (1 equiv) and boric acid (5 equiv) as previously reported by a Novartis team.[43] Except for the slightly lower optical rotation of our synthetic sample ($[\alpha]^{22}_D$ −26.9 (*c* 0.06, CH_3OH)) relative to that given for natural sanglifehrin A ($[\alpha]^{20}_D$ −67.3 (*c* 0.99, CH_3OH)),[39] the spectroscopic and chromatographic properties of **5** duplicated those exhibited by the authentic substance.

To recapitulate, the total synthesis of (−)-sanglifehrin A has been completed in 64 steps using a variety of bond construction methods that have proven to be reliably stereocontrolled. The involvement of a terminal iodovinyl group from the outset to the penultimate stage of global construction is particularly noteworthy. The methodologies used for much of the structural assembly underscore the utility of chiral enolate based aldol reactions of different type, the applicability of chelate-controlled hydride delivery for the installation of anti 1,3-diol arrangements in complex settings, and the meritorious nature of proper functional group deployment. Last, the reliability of the large-ring macrolactonization maneuver is seen to facilitate subunit assembly and subsequent coupling, and as such warrant consideration in the manner in which analogues of this class of natural products are accessed.

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Supporting Information Available: Complete experimental procedures and spectral data for all compounds generated in the course of the investigation reported here, including copies of the ^{1}H NMR spectra of **13**, **14**, **61b**, and natural and synthetic **5** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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