Toward a Total Synthesis of the Immunosuppressant Sanglifehrin A. Preparation of Two Relay Compounds by Degradation and Their Use in the Reassembly of the Natural Product

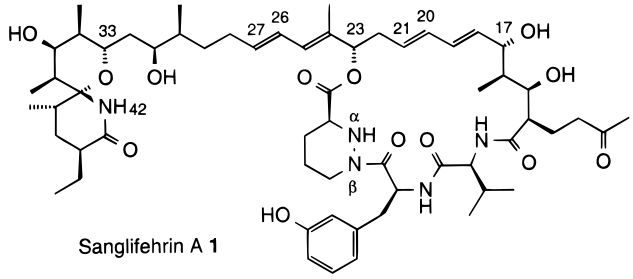
Rainer Metternich,* Donatienne Denni, Binh Thai, and Richard Sedrani*

Preclinical Research, Novartis Pharma AG, CH-4002, Basel, Switzerland

Received August 5, 1999

A potential relay route for the synthesis of the novel immunosuppressive agent sanglifehrin A (**1**) has been developed. Degradation of **1** by a sequence involving regioselective dihydroxylation of the C26,C27 double bond, followed by periodate cleavage of the resulting diol **4**, afforded lactol **2** and macrocyclic aldehyde **3**. Intramolecular ketal formation between the 1,3-diol and ketone functions present in **3** gave ketal−aldehyde **5**. Lactol **2** was converted into sulfone **14** in four steps. The fragments **5** and **14** were reassembled, using the Julia−Kocienski olefination procedure, to afford intermediate **15**, which was converted back to sanglifehrin A (**1**) after two deprotection steps.

The discovery of the immunosuppressive natural product cyclosporin A (CsA) revolutionized organ transplantation by dramatically increasing the survival of transplant recipients.[1] Since the introduction of this drug into clinical practice, the search for novel immunosuppressants has been pursued by many companies, resulting most notably in the discovery of the macrolides FK506[2] and rapamycin[3] as clinically useful drugs for the prevention of graft rejection. The macrocyclic undecapeptide CsA, like FK506 and rapamycin, is a so-called "dual-domain" inhibitor.[4] In the first step it binds to its intracellular binding protein, cyclophilin (CyP).[5] The CyP/CsA complex then associates with and inhibits the serine/threonine phosphatase calcineurin.[6] It is the formation of this ternary complex which is ultimately responsible for the inhibition of T-cell activation by CsA. Since the time when CyP was identified as a binding protein for CsA, various research groups have been searching for novel immunosuppressive CyP ligands. Screening of microbial fermentation extracts in a cyclophilin binding assay recently led to the discovery of a novel macrolide, sanglifehrin A (**1**), by researchers at Novartis.[7] This macrolide binds to cyclophilin with a 20-fold higher affinity than CsA.[7a,c] Moreover, **1** exhibits immunosuppressive activity.[7a,c] The activity profile in vitro is clearly distinct from that of other immunosuppressive drugs.



Sanglifehrin A **1**

These data indicate that **1** represents a novel type of immunosuppressive agent.

The structure of **1** is quite interesting. The compound consists of a 22-membered macrocycle, bearing in position 23 a nine-carbon chain terminated by a spirobicyclic moiety. The macrocyclic part of the molecule contains a tripeptide subunit consisting of valine and two rather unusual amino acids, piperazic acid and metatyrosine. Interestingly, the β-nitrogen of piperazic acid is involved in amide bond formation. This stands in contrast to other natural products containing this particular amino acid, in which usually the α-nitrogen is linked to a carbonyl.[8] One of the most remarkable features of the molecule, in structural terms, is certainly the highly substituted spirobicyclic oxaazaspiro[5.5]undecanone system (C33−N42). To the best of our knowledge, no other natural product described until now contains this substructure. The spirobicycle contains seven stereocenters, six of which are contiguous (C33−C38).

The immunosuppressive activity profile and the structural attractiveness of sanglifehrin A (**1**) led us to

* To whom correspondence should be addressed: (R.S.) phone, (+) 41 61 324 2609; fax, (+) 41 61 324 6735; e-mail, richard.sedrani@pharma.novartis.com. (R.M.) phone, (+) 41 61 696 6260; fax, (+) 41 61 696 6283, e-mail, rainer.metternich@pharma.novartis.com.

(1) Borel, J. F.; Baumann, G.; Chapman, I.; Donatsch, P.; Fahr, A.; Mueller, E. A.; Vigouret, J.-M. *Adv. Pharmacol. (San Diego)* **1996**, *35*, 115−246.

(2) Spencer, C. M.; Goa, K. L.; Gillis, J. C. *Drugs* **1997**, *54*, 925−975.

(3) Kahan, B. D. *Clin. Biochem.* **1998**, *31*, 341−344.

(4) Schreiber, S. L. *Science* **1991**, *251*, 283−287.

(5) Handschumacher, R. E.; Harding, M. W.; Rice, J.; Drugge, R. J.; Speicher, D. W. *Science* **1984**, *226*, 544−547.

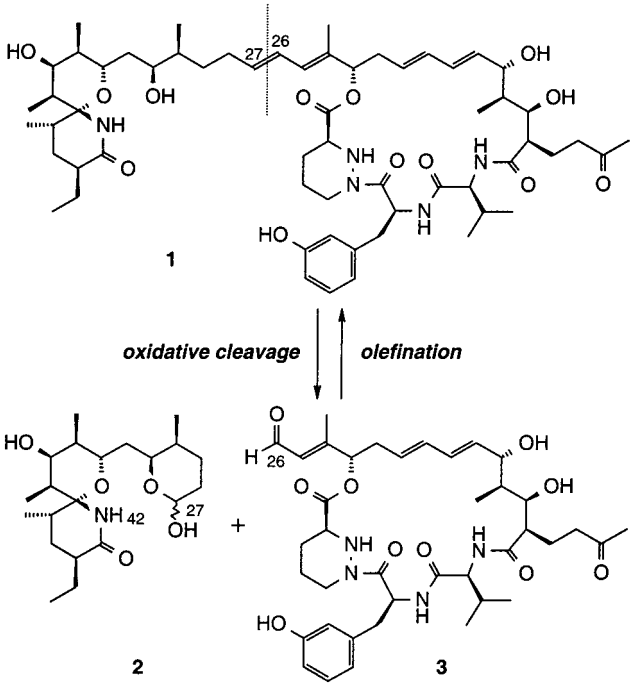
(6) Liu, J.; Farmer, J. D. Jr.; Lane, W. S.; Friedman, J.; Weissman, I.; Schreiber, S. L. *Cell* **1991**, *66*, 807−815.

(7) (a) Sanglier, J.-J.; Quesniaux, V.; Fehr, T.; Hofmann, H.; Mahnke, M.; Memmert, K.; Schuler, W.; Zenke, G.; Gschwind, L.; Maurer, C.; Schilling, W. *J. Antibiot.* **1999**, *52*, 466−473. (b) Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J.-J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474−479. (c) Fehr, T.; Oberer, L.; Quesniaux Ryffel, V.; Sanglier, J.-J.; Schuler, W.; Sedrani, R. PCT International Patent Application WO 97/02285-A1, 1997.

(8) Examples of macrocyclic natural products containing piperazic acid: (Antibiotic GE3) (a) Sakai, Y.; Yoshida, T.; Tsujita, T.; Ochiai, K.; Agatsuma, T.; Saitoh, Y.; Tanaka, F.; Akiyama, T.; Akinaga, S.; Mizukami, T. *J. Antibiot.* **1997**, *50*, 659−664. (b) Agatsuma, T.; Sakai, Y.; Mizukami, T.; Saitoh, Y. *J. Antibiot.* **1997**, *50*, 704−708. (Aurantimycins) (c) Graefe, U.; Schlegel, R.; Ritzau, M.; Ihn, W.; Dornberger, K.; Stengel, C.; Fleck, W. F.; Gutsche, W.; Haertl, A.; Paulus, E. F. *J. Antibiot.* **1995**, *48*, 119−125. (Verucopeptin) (d) Nishiyama, Y.; Sugawara, K.; Tomita, K.; Yamamoto, H.; Kamei, H.; Oki, T. *J. Antibiot.* **1993**, *46*, 921−927. (e) Sugawara, K.; Toda, S.; Moriyama, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1993**, *46*, 928−935. (Antibiotic A83586C) (f) Smitka, T. A.; Deeter, J. B.; Hunt, A. H.; Mertz, F. P.; Ellis, R. M.; Boeck, L. D.; Yao, R. C. *J. Antibiot.* **1988**, *41*, 726−733. (Azinothricin) (g) Maehr, H.; Liu, C. M.; Palleroni, N. J.; Smallheer, J.; Todaro, L.; Williams, T. H.; Blount, J. F. *J. Antibiot.* **1986**, *39*, 17−25.

10.1021/jo9912395 CCC: $18.00 © 1999 American Chemical Society
Published on Web 12/01/1999

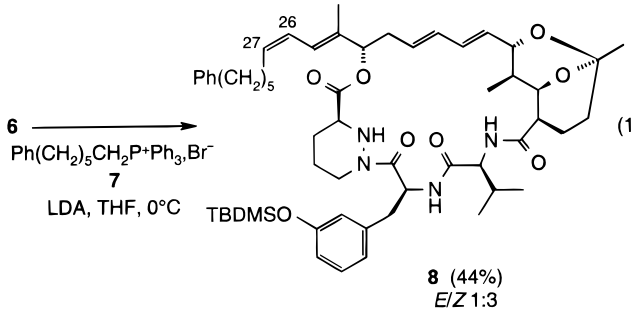
Scheme 1



contemplate a total synthesis of the natural product.[9,10] We were particularly interested in developing a relay synthesis of **1**,[11] in other words a synthesis in which the natural product is degraded to fragments which can be reassembled to the original molecule. In this paper, we report the successful implementation of this strategy, namely, the degradation of sanglifehrin A (**1**) into fragments **2** and **3** by oxidative cleavage of the C26,C27 double bond, and the subsequent coupling of derivatives of **2** and **3**, leading to the resynthesis of the natural product (Scheme 1).

For the oxidative cleavage of one of the exocyclic double bonds we envisaged a two-step procedure, involving regioselective dihydroxylation followed by cleavage of the resulting diol. Initial attempts using the Upjohn osmylation procedure[12] met with little success. Inseparable mixtures of various polyhydroxylated derivatives of **1** were obtained. We then envisaged using the Sharpless asymmetric dihydroxylation (AD) reaction. It has indeed been shown that with this protocol "mono"-dihydroxylation of polyenes, including conjugated ones, can be achieved.[13,14] We were pleased to find that treatment of **1** under modified AD conditions,[15] using $(DHQ)_2PHAL$ as a ligand (AD-mix-α), led to the desired 26(*S*),27(*S*)-dihydroxysanglifehrin A (**4**) in a remarkable 70% yield (Scheme 2).[16] This product was accompanied by approximately 10% of two diastereomeric 20,21,26,27-tetrahydroxysanglifehrins,[17] which were easily removed by column chromatography on silica gel. Interestingly, when the pseudoenantiomeric $(DHQD)_2PHAL$ ligand, corresponding to AD-mix-*β*, was used, the reaction was slower. After the 3 h typically required for complete conversion using AD-mix-α, significant amounts of starting material were still detected when AD-mix-*β* was employed. Longer reaction times resulted in the formation of large amounts of very polar material, and hence in lower yields of the isolated 26(*R*),27(*R*) diastereomer of **4**. Cleavage of the *C*26,*C*27-diol of **4** with sodium periodate proceeded cleanly to afford the lactol **2** and the aldehyde **3**, each in 87% yield, after chromatographic separation (Scheme 2). The 1,3-diol and ketone functions present in **3** were protected by acid-promoted intramolecular ketal formation, affording **5** in 92% yield (Scheme 2). Finally, the phenol in **5** was protected as the TBDMS ether **6**. Thus, an efficient two-step procedure allowed for the selective degradation of **1**. The resulting fragments **2** and **3**, or derivatives thereof, are of similar structural complexity and therefore represent very attractive subtargets for a convergent total synthesis of sanglifehrin A (**1**). To illustrate this point, we attempted the reconstruction of **1**.

We started investigating the olefination step required for the formation of the C26,C27 linkage using the aldehyde **6**. Preliminary experiments were conducted using the 6-phenylhexyl group as a model for the C27−N42 subunit of sanglifehrin A. Thus, deprotonation of the phosphonium salt **7** with LDA and reaction of the resulting phosphorane with aldehyde **6** led to the diene **8** in reasonable yield (eq 1). As could have been expected,



(1)

this nonstabilized Wittig reagent resulted in the prefer-

(9) For a report describing the synthesis of the tripeptide segment of sanglifehrin A, see: Bänteli, R.; Brun, I.; Hall, P.; Metternich, R. *Tetrahedron Lett.* **1999**, *40*, 2109−2112.

(10) For a synthesis of the sanglifehrin A macrocycle and a total synthesis of the natural product, see: (a) Nicolaou, K. C.; Ohshima, T.; Murphy, F.; Barluenga, S.; Xu, J.; Winssinger, N. *Chem. Commun.* **1999**, 809−810. (b) Nicolaou, K. C.; Xu, J.; Murphy, F.; Barluenga, S.; Baudoin, O.; Wei, H.; Gray, D.; Ohshima, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2447−2451.

(11) For elegant recent examples of relay syntheses of natural products, see: (Zaragozic acid A (squalestatin S1)) (a) Stoermer, D.; Caron, S.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9115−9125. (b) Stoermer, D.; Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1996**, *61*, 9126−9134. (Azadirachtin) (c) Denholm, A. A.; Jennens, L.; Ley, S. V.; Wood, A. *Tetrahedron* **1995**, *51*, 6591−6604.

(12) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973−1976.

(13) (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571. (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345−1376.

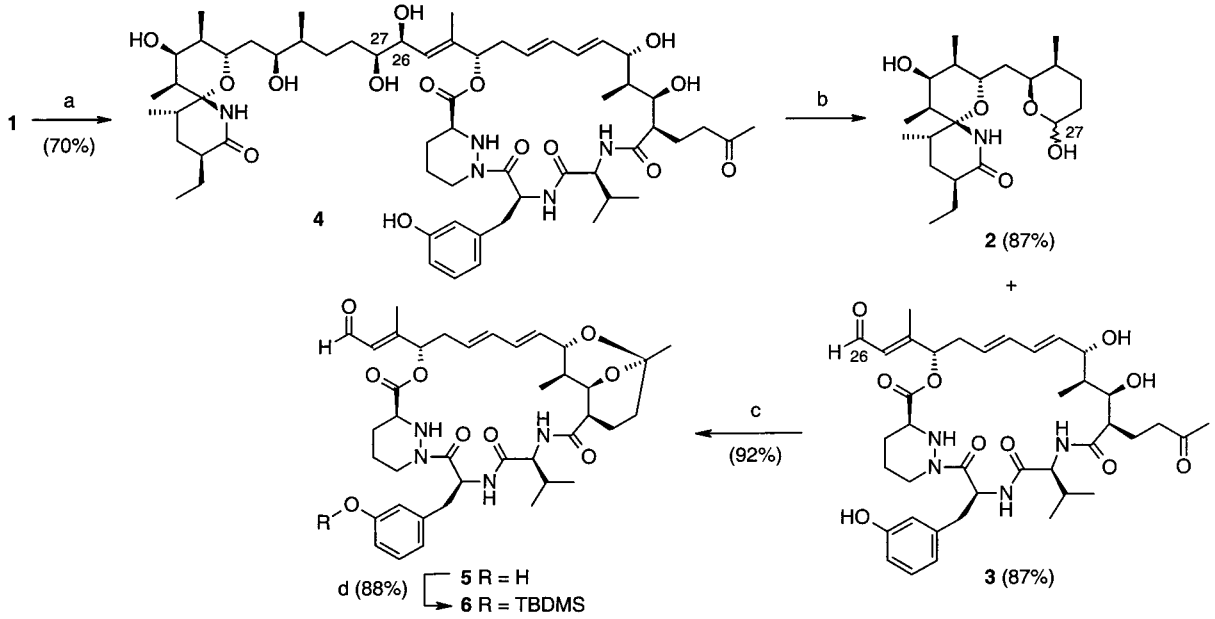
(14) For a recent application of the AD reaction to the complex, polyene-containing natural product rapamycin, see: Sedrani, R.; Thai, B.; France, J,; Cottens, S. *J. Org. Chem.* **1998**, *63*, 10069−10073.

(15) For a standard procedure, see: Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768−2771. In this study we added the individual components separately instead of using the premixed powder. Instead of potassium osmate, osmium tetraoxide solution was used. More importantly, the loads of osmium catalyst and phthalazine ligand were 15- and 6-fold higher, respectively, than those recommended in the published standard procedure (see the Experimental Section for more details).

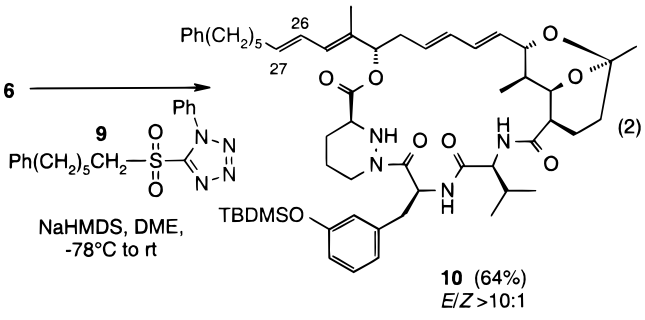
(16) The absolute configurations of the newly created stereocenters have not been unambiguously proven. Their assignment is based on the application of the Sharpless mnemonic device; see: Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278−1291.

(17) The diastereomers could be separated by HPLC. The regiochemical outcome of the tetrahydroxylation was thus determined on pure samples. No attempt was made to determine the configurations of the tetrols.

Scheme 2[a]

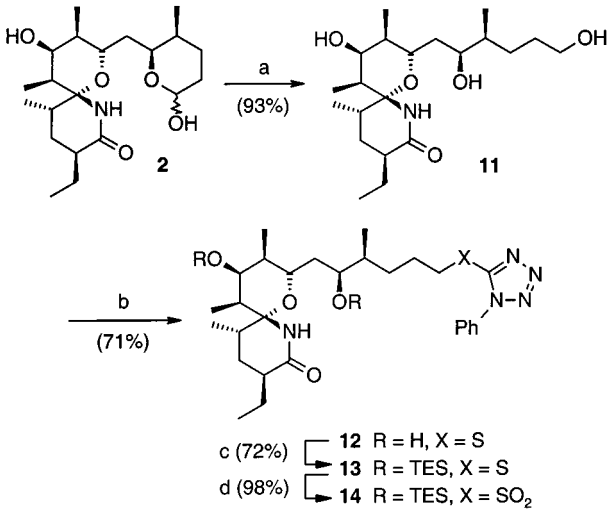


[a] Reagents and conditions: (a) 3 mol % OsO_4, 6 mol % $(DHQ)_2PHAL$, 3 equiv of $K_3Fe(CN)_6$, 3 equiv of K_2CO_3, 2 equiv of $CH_3SO_2NH_2$, 1:1 *t*-BuOH/H_2O, rt, 2 h; (b) 2 equiv of $NaIO_4$, 2:1 THF/H_2O, rt, 1 h; (c) HF·pyridine, CH_3CN, 0 °C, 1h; (d) 1.2 equiv of MTBSTFA, CH_3CN, 50 °C, 1.5 h.



ential formation of the undesired *Z* C26,C27 olefin.[18] While we were considering different approaches for the formation of the desired *E* double bond, a publication by Kocienski, describing a modification of the olefination procedure developed by Sylvestre Julia, appeared.[19] The original procedure consists of the one-pot formation of alkenes by addition of α-lithiated benzothiazol-2-yl sulfones to aldehydes.[20] This olefination reaction is operationally simpler than the 3−4-step variant reported earlier by Marc Julia,[21] but suffers from the fact that stereoselectivities are often low.[20b,c] Kocienski found that *E*/*Z* selectivities can be influenced by the nature of the heterocycle on the sulfone. Thus, replacement of the benzothiazol-2-yl group by a 1-phenyl-1*H*-tetrazol-5-yl moiety leads to *E* alkenes with high selectivities. Though the examples reported by Kocienski were limited to the coupling of aliphatic aldehydes and alkyl(1-phenyl-1*H*-tetrazol-5-yl) sulfones, we made an attempt using our substrate **6**. We were pleased to find that the reaction of metalated 6-phenylhexyl sulfone **9** with **6** resulted in the highly selective formation of the desired *E* C26,C27 olefin **10** in an acceptable yield (eq 2). Stimulated by this very encouraging result, we decided to use this methodology for the reconstruction of sanglifehrin A (**1**) from the fragments **2** and **3**.

Scheme 3[a]



[a] Reagents and conditions: (a) 3 equiv of $NaBH_4$, MeOH, 0 °C, 2 h; (b) 1.1 equiv of 1-phenyl-1*H*-tetrazole-5-thiol, 1.1 equiv of PPh_3, 1.1 equiv of DIAD, THF, 0 °C to rt, 30 h; (c) 2.2 equiv of TESOTf, 2.6 equiv of pyridine, 1:1 Et_2O/CH_3CN, −50 °C, 0.5 h; (d) 5 equiv of mCPBA, 10 equiv of $NaHCO_3$, CH_2Cl_2, rt, 12 h.

It was first necessary to prepare sulfone **14**. This was accomplished as shown in Scheme 3. Reduction of the lactol **2** to the corresponding diol **11** was achieved using sodium borohydride in methanol at 0 °C. The primary hydroxy group of **11** was converted selectively into the 1-phenyl-1*H*-tetrazol-5-yl thioether **12** under Mitsunobu conditions.[19] Protection of the two hydroxyl functions of

(18) For an extensive review of the Wittig reaction, see: Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927.

(19) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.

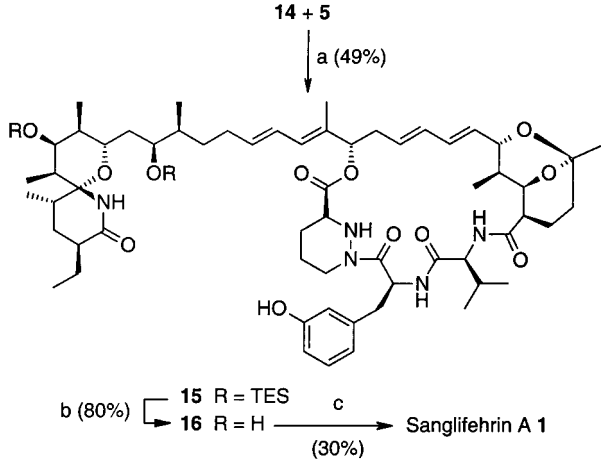
(20) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Tetrahedron Lett.* **1991**, *32*, 1175−1178. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336−357. (c) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856−878.

(21) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833−4836.

12 using TESOTf[22,23] led to the bissilyl ether **13**. Oxidation of **13** with 5 equiv of mCPBA in methylene chloride afforded sulfone **14**.[24] The overall yield for the four-step sequence leading from **2** to **14** was 47%.

With the aldehyde **5**, its silylated variant **6**, and the sulfone **14** in hand, we were in a position to investigate the reconstruction of sanglifehrin A (**1**). Initial attempts at coupling aldehyde **6** and sulfone **14** using the Julia−Kocienski olefination procedure were hampered by the fact that this particular sulfone quickly decomposed upon α-metalation with NaHMDS at low temperature. We therefore envisaged to carry out the reaction in a Barbier-type fashion, i.e., by adding the base to a mixture of the aldehyde **6** and the sulfone **14**. Unfortunately, this procedure only resulted in the recovery of starting materials.[25] Reasoning that the presence of rather bulky silyl protecting groups in both coupling partners might be retarding the reaction, we decided to attempt the coupling using aldehyde **5**, which lacks a protecting group on the phenol. In the event, deprotonation of the sulfone **14** using NaHMDS in DME at −78 °C in the presence of the unsaturated aldehyde **5**, followed by quenching of the reaction at −78 °C,[26] resulted in the formation of the *E*,*E* diene **15** as the only detectable product (Scheme 4).[28,29] The desired condensation product was accompanied by unreacted starting materials. Considering the complexity of the two fragments which are coupled, the 49% yield of **15** obtained after purification and the high *E* selectivity[30] are notable. It is worth mentioning that the use of 2 equiv of NaHMDS proved optimal for carrying out the olefination, despite the presence of one amino NH, three amidic NH's, and an unprotected phenol in the substrates. Having achieved the critical coupling step, further transformation of **15** into **1** was relatively straightforward. The removal of the two triethylsilyl protecting groups in **15** proceeded very efficiently.[31] Finally, acidic hydrolysis of the intramolecular ketal of **16** furnished sanglifehrin A (**1**) (Scheme 4).[32] The spectral and chromatographic characteristics of the hemisynthetic material were identical in all respects to those of an authentic sample of sanglifehrin A.[7b]

Scheme 4[a]



[a] Reagents and conditions: (a) 2 equiv of NaHMDS, DME, −78 °C, 8 h; (b) 5 equiv of Bu_4NF, THF, 0 °C to rt, 3 days; (c) 1 equiv of TsOH, 5 equiv of $B(OH)_3$, THF, rt, 5 h.

In conclusion, we have been able to selectively and efficiently cleave sanglifehrin A (**1**) into the fragments **2** and **3**. These fragments could be used to investigate the endgame of a total synthesis of **1**. We have indeed demonstrated that subunits derived from **2** and **3**, namely, aldehyde **5** and sulfone **14**, can be reassembled to intermediate **15**, which after two deprotection steps affords sanglifehrin A (**1**). Application of the recently described Julia−Kocienski olefination procedure proved to be crucial for our approach. The results described herein make the aldehyde **5** and the sulfone **14** very attractive subtargets for a total synthesis of sanglifehrin A. Furthermore, each of these two subunits can be used for the synthesis of sanglifehrin analogues which could not be obtained by simple derivation of the natural product. For example, the replacement of the spirobicyclic system by simpler moieties can be envisaged, as is demonstrated by the reaction shown in eq 2. Alternatively, the sulfone **14** could be coupled with synthetic analogues of the sanglifehrin macrocycle. Work along

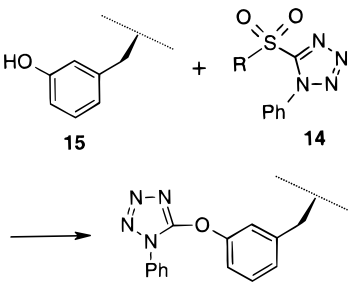
(22) Heathcock, C. H.; Young S. D.; Hagen J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095−2105.

(23) The use of triethylsilyl chloride led to selective monoprotection of the *C*31-hydroxyl.

(24) When smaller amounts of mCPBA were used, a mixture of sulfone and sulfoxide was obtained.

(25) The Barbier-type Julia−Kocienski olefination between **14** or related sulfones, bearing other hydroxyl protecting groups, and 3-phenylpropionaldehyde proceeded in acceptable yields.

(26) Allowing the reaction mixture to warm to room temperature, as recommended in ref 19, resulted in displacement of the alkylsulfonyl moiety of **14** by the sodium phenoxide of **15**, resulting in the formation of significant amounts of the *O*-(1-phenyl-1*H*-tetrazol-5-yl) derivative of **15**, as shown below.



For examples of the displacement of alkylsulfonyl moieties from alkyl tetrazolyl sulfones by alkoxides, see ref 27.

(27) (a) Gol'tsberg, M. A.; Koldobskii, G. I. *Zh. Org. Khim.* **1995**, *31*, 1726−1727. (b) Gol'tsberg, M. A.; Koldobskii, G. I. *Zh. Org. Khim.* **1996**, *32*, 1238−1245.

(28) In contrast to the lack of selectivity observed in their reactions with aliphatic aldehydes, α-lithiated benzothiazol-2-yl sulfones have been reported to give high *E* selectivities with α,*β*-unsaturated aldehydes. For examples in natural product syntheses, see: (a) Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996,** 652−666. (b) Bellingham, R.; Jarowicki, K.; Kocienski, P.; Martin, V. *Synthesis* **1996**, 285−296. In our case, however, the yield and selectivity were much lower when the benzothiazol-2-yl sulfone analogue of **14** was employed.

(29) Recent applications of the Julia−Kocienski olefination in natural product synthesis: Herboxidiene: (a) Blakemore, P. R.; Kocienski, P. J.; Morley, A.; Muir, K. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 955−968. Hennoxazole A: (b) Williams, D. R.; Brooks, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924−4925.

(30) Recently a case has been described in which the use of 1-phenyl-1*H*-tetrazol-5-yl sulfones resulted in low *E* selectivity or even in preferential formation of the *Z* alkene: Williams, D. R.; Clark, M. P. *Tetrahedron Lett.* **1999**, *40*, 2291−2294.

(31) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

(32) The acidic hydrolysis of the intramolecular ketal subunit of **16** to afford **1** stops at approximately 40−50% conversion. The yield given is for pure sanglifehrin A after HPLC purification. Despite extensive efforts, we were not able to improve this deprotection step. The addition of boric acid slightly increases conversions with respect to reactions performed in its absence. Furthermore, it allows side reactions which readily occur in aqueous acidic conditions and which are going to be reported elsewhere to be prevented. The beneficial effect of boric acid is presumably due to in situ trapping of the 1,3-diol function of **1** as the corresponding borate.

these lines, as well as efforts toward the total synthesis of sanglifehrin A (**1**), are currently underway in our laboratories and are going to be reported in due course.

Experimental Section

General Procedures. Dry THF, acetonitrile, methylene chloride, and diethyl ether (puriss., absolute, over molecular sieves) were purchased from Fluka in septum-capped bottles and were used as such. All reactions were performed under an atmosphere of argon. Sanglifehrin A was obtained from Novartis Pharma Research, Core Technology Area, Biomolecules Production, Basel, Switzerland. Osmium tetroxide (2.5 wt % solution in *tert*-butyl alcohol), $(DHQ)_2PHAL$, and $(DHQD)_2PHAL$ were purchased from Aldrich. Sodium bis(trimethylsilyl) amide was titrated with 2,6-di-*tert*-butyl-4-methylphenol in THF using fluorene as an indicator.[32] Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates or on precoated HPTLC silica gel 60 F254 plates with concentrating zone (Merck). HPLC analyses were performed at 40 °C using a Merck LiChroCART 125-4 cartridge packed with LiChrospher 100 RP-18 (5 μm). Gradients consisting of mixtures of solvent A (acetonitrile:water = 1:9) and solvent B (acetonitrile: water = 9:1) or of mixtures of acetonitrile and water were used. The flow rate was 1.5 mL/min. Detection was performed at 210 nm. Purification by flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Reversed phase HPLC purifications were performed at 25 °C using a Macherey-Nagel 250/10 Nucleosil 100-7 C_{18} column. The elution system consisted of 10:90−90:10 acetonitrile/water over 2.5 min, followed by 10:90−90:10 acetonitrile/water (linear gradient over 20 min) and finally 90:10 acetonitrile/water over 7.5 min. The flow rate was 10-12.5 mL/min. Detection was performed at 214 and 254 nm.

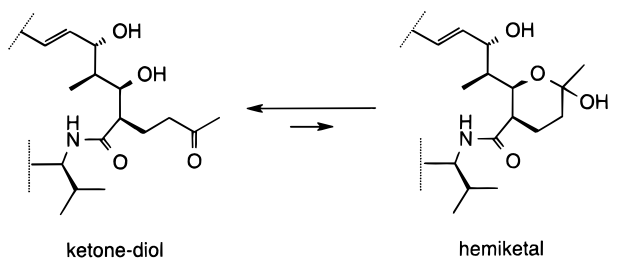
26(*S*),27(*S*)-Dihydroxysanglifehrin A (4). To a stirred solution of 21.80 g (20.00 mmol) of sanglifehrin A, 0.934 g (1.20 mmol) of $(DHQ)_2PHAL$, 7.5 mL (0.60 mmol) of a 2.5 wt % solution of osmium tetroxide in *tert*-butyl alcohol, and 3.80 g (39.95 mmol) of methanesulfonamide in 100 mL of *tert*-butyl alcohol were added, at room temperature, a solution of 19.70 g (59.84 mmol) of potassium ferricyanide and 8.30 g (60.06 mmol) of potassium carbonate in 100 mL of water, resulting in a brown emulsion. After 2 h a solution of 30.00 g (238.10 mmol) of sodium sulfite was added, and stirring was continued for 10 min. The resulting mixture was extracted with three portions of ethyl acetate. The organic solution was washed with four portions of saturated brine. After the combined aqueous layers were extracted with an additional portion of ethyl acetate, the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (85:15 methyl *tert*-butyl ether/methanol) to afford 15.65 g (70%) of **4** as an amorphous white solid. This material was 95.3% pure by HPLC analysis (80:20−0:100 solvent A/solvent B, linear gradient over 20 min, t_R 7.3 min): $[\alpha]^{20}_D = -34.1$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3387, 1714, 1644 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6)[34] δ 9.24 (s, 1H), 8.14 (d, J = 6.4 Hz, 1H), 7.89 (s, 1H), 7.52 (d, J = 9 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.58 (m, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.49 (s, 1H), 6.14 (dd, J = 10.7, 14.9 Hz, 1H), 6.02 (dd, J = 10.7, 14.9 Hz, 1H), 5.58 (m, 4H), 5.33 (m, 2H), 5.19 (m, 1H), 4.76 (d, J = 4.9 Hz, 1H), 4.58 (d, J = 4.3 Hz, 1H), 4.46 (d, J = 11.5 Hz, 1H), 4.32 (d, J = 4.5 Hz, 1H), 4.18 (m, 1H), 4.07 (t, J = 8.9 Hz, 1H), 3.96 (d, J = 5.6 Hz, 1H), 3.93 (m, 2H), 3.81 (m, 1H), 3.69 (t, J = 9.8 Hz, 1H), 3.55 (m, 1H), 3.43 (m, 1H), 3.18 (m, 1H), 2.83−2.33 (m, 7H), 2.11−1.72 (m, 9H), 2.05 (s, 3H), 1.64 (s, 3H), 1.63−1.18 (m, 16H), 0.89 (m, 6H), 0.82 (m, 12H), 0.72 (d, J = 6.4 Hz, 3H), 0.59 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6)[34] δ 208.4, 175.0, 174.4, 172.2, 171.1, 170.5, 157.7, 138.6, 135.2, 135.1, 134.7, 131.5, 130.9, 130.3, 130.1, 128.3, 120.4, 117.0, 113.6, 87.1, 77.2, 74.7, 74.6, 73.6, 71.6, 70.9, 70.8, 66.8, 58.1, 57.8, 51.7, 40.9, 40.7, 37.9, 37.5, 36.7, 30.4, 30.2, 29.0, 28.7, 27.7, 25.8, 22.8, 19.7, 18.8, 15.2, 14.8, 14.5, 13.7, 13.4, 12.3, 11.3; R_f 0.43 (85:15 methyl *tert*-butyl ether/methanol, HPTLC plate); HRMS calcd for $C_{60}H_{93}N_5NaO_{15}$ $[M + Na]^+$ requires 1146.6566, found 1146.6558.

Oxidative Cleavage of the Diol 4 to the Lactol 2 and the Macrocyclic Aldehyde 3. To a solution of 7.42 g (6.60 mmol) of diol **4** in 75 mL of a 2:1 mixture of THF and water was added 2.82 g (13.18 mmol) of sodium periodate. The resulting mixture was stirred at room temperature for 1 h, and saturated aqueous sodium bicarbonate was added. This mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed with one portion of water and two portions of saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (95:5−90:10 methyl *tert*-butyl ether/methanol) to afford 2.19 g (87%) of lactol **2** and 4.24 g (87%) of the aldehyde **3** as white amorphous solids. Purities, as determined by HPLC analysis, were 98.6% for **2** (20:80−100:0 acetonitrile/water, linear gradient over 20 min, t_R 11.7 min) and 97.4% for **3** (20:80−100:0 acetonitrile/water, linear gradient over 20 min, t_R 5.1 min).

Data for 2: $[\alpha]^{20}_D = -91.0$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3301, 1618, 1469 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (∼1:1 mixture of anomers) δ 7.92 and 7.91 (2s, 1H), 5.98 (d, J = 6.4 Hz, 0.5H), 5.63 (d, J = 5.5 Hz, 0.5H), 5.61 (d, J = 5.3 Hz, 0.5H), 5.42 (d, J = 4.3 Hz, 0.5H), 4.96 (s, 0.5H), 4.38 (m, 0.5H), 4.09 (m, 0.5H), 3.67(m, 1H), 3.58 (m, 1.5H), 2.16−1.86 (m, 3H), 1.81−1.13 (m, 12H), 0.99−0.73 (m, 15H); ^{13}C NMR (125 MHz, DMSO-d_6) (∼1:1 mixture of anomers) δ 175.1, 175.2, 96.9, 90.3, 87.5, 87.4, 74.6, 73.6, 67.8, 66.8, 66.5, 41.0, 40.9, 40.8, 40.7, 37.5,

(33) Brown, C. A. *Synthesis* **1974**, 427−428.

(34) Sanglifehrin A (**1**) and derivatives containing the macrocyclic subunit exist as an approximately 4:1:1 mixture of isomers in solution in DMSO-d_6. One of the isomers probably arises from the ketone−diol:hemiketal equilibrium shown below.



Evidence for this equilibrium is provided by the presence of a minor signal at approximately 95 ppm in the ^{13}C spectra of these compounds. The third isomer is presumably an amide bond rotamer. Only the signals corresponding to the major isomer are listed.

37.4, 36.6, 35.8, 31.2, 30.6, 30.4, 30.1, 29.0, 28.8, 28.3, 26.4, 26.0, 25.9, 25.5, 15.1, 14.5, 14.4, 13.3, 12.4, 0.12.3, 12.2, 12.1; R_f 0.62 (95:5 methyl *tert*-butyl ether/methanol, HPTLC plate); HRMS calcd for $C_{21}H_{37}NNaO_5$ $[M + Na]^+$ requires 406.2569, found 406.2567. Anal. Calcd for $C_{21}H_{37}NO_5$: C, 65.77; H, 9.72; N, 3.65. Found: C, 65.56; H, 9.78; N, 3.62.

Data for 3: $[\alpha]^{20}_D = +10.4$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3369, 1740, 1715, 1641 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6)[34] δ 9.98 (d, $J = 7.9$ Hz, 1H), 9.26 (s, 1H), 8.17 (d, $J = 7.0$ Hz, 1H), 7.52 (d, $J = 9.0$ Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 6.58 (m, 2H), 6.51 (s, 1H), 6.16 (dd, $J = 10.7$, 14.8 Hz, 1H), 6.08 (dd, $J = 10.7$, 14.8 Hz, 1H), 5.87 (d, $J = 7.7$ Hz, 1H), 5.60 (m, 2H), 5.39 (m, 2H), 5.32 (dd, $J = 1.6$, 9.0 Hz, 1H), 4.78 (d, $J = 4.7$ Hz, 1H), 4.62 (d, $J = 12.0$ Hz, 1H), 4.19 (m, 1H), 4.09 (t, $J = 8.7$ Hz, 1H), 3.97 (m, 1H), 3.79 (m, 1H), 2.77−2.33 (m, 7H), 2.16 (s, 3H), 2.14 (m, 1H), 2.05 (s, 3H), 1.87 (m, 1H), 1.75 (m, 3H), 1.61 (m, 2H), 1.35 (m, 3H), 0.80 (d, $J = 6.8$ Hz, 6H), 0.61 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6)[34] δ 208.4, 192.5, 174.8, 172.3, 170.8, 170.5, 160.2, 157.7, 138.8, 135.2, 132.3, 130.4, 130.2, 128.6, 125.5, 120.5, 117.0, 113.6, 75.8, 74.6, 72.0, 58.2, 57.7, 51.7, 49.2, 43.8, 40.9, 40.8, 38.9, 36.0, 30.6, 30.4, 27.6, 26.2, 22.8, 19.7, 18.8, 14.5, 14.3, 11.2; R_f 0.66 (90:10 methyl *tert*-butyl ether/methanol, HPTLC plate); HRMS calcd for $C_{39}H_{54}N_4NaO_{10}$ $[M + Na]^+$ requires 761.3737, found 761.3740.

Ketal−Aldehyde 5. To a stirred, cooled (0 °C) solution of 2.96 g (2 mmol) of **3** in 25 mL of acetonitrile was added 2.5 mL of HF−pyridine complex. The yellow solution was stirred at 0 °C for 1 h. The reaction was quenched with saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with three portions of ethyl acetate. The combined organic layers were washed once with saturated aqueous sodium bicarbonate and twice with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (95:5 methyl *tert*-butyl ether/methanol) to afford **5** (2.66 g, 92%) as a white amorphous solid. The purity of the compound was 96.1% according to HPLC analysis (30:70−70:30 acetonitrile/water, linear gradient over 15 min, t_R 4.2 min): $[\alpha]^{20}_D = +128.0$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3385, 1670, 1511, 1161 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz)[35] δ 9.96 (d, $J = 7.7$ Hz, 1H), 9.22 (s, 1H), 8.44 (d, $J = 7.5$ Hz, 1H), 6.92 (t, $J = 7.7$ Hz, 1H), 6.70 (d, $J = 9.2$ Hz, 1H), 6.54 (d, $J = 7.0$ Hz, 1H), 6.48 (m, 2H), 6.15 (dd, $J = 10.6$, 15.0 Hz, 1H), 6.04 (dd, $J = 10.6$, 15.2 Hz, 1H), 5.87 (d, $J = 4$ Hz, 1H), 5.66 (dt, $J = 6.5$, 15.2 Hz, 1H), 5.54 (dd, $J = 7.5$, 15.4 Hz, 1H), 5.35 (dd, $J = 3.1$, 9.4 Hz, 1H), 5.20 (dd $J = 7.9$, 15.2 Hz, 1H), 4.92 (d, $J = 12.2$ Hz, 1H), 4.55 (dd, $J = 8.1$, 10.9 Hz, 1H), 4.25 (m, 2H), 4.19 (t, $J = 4.7$ Hz, 1H), 2.87 (m, 1H), 2.76 (m, 1H), 2.65 (m, 2H), 2.55 (m, 2H), 2.35 (m, 1H), 2.25 (m, 1H), 2.14 (s, 3H), 2.03 (m, 2H), 1.91 (m, 2H), 1.80 (m, 1H), 1.66 (m, 1H), 1.47 (m, 2H), 1.32 (m, 1H), 1.19 (s, 3H), 0.85 (d, $J = 6.6$ Hz, 3H), 0.76 (d, $J = 6.6$ Hz, 3H), 0.37 (d, $J = 7.5$ Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz)[35] δ 192.5, 172.3, 170.9, 170.6, 159.7, 157.6, 138.7, 134.8, 131.2, 130.9, 130.5, 129.9, 125.7, 120.0, 117.0, 113.5, 95.7, 80.1, 75.7, 73.2, 59.0, 56.8, 49.3, 44.0, 40.9, 38.9, 38.6, 35.1, 34.2, 31.2, 29.5, 27.0, 23.0, 22.8, 19.8, 18.2, 14.4, 12.3; R_f 0.51 (95:5 methyl *tert*-butyl ether/methanol, HPTLC plate); HRMS calcd for $C_{39}H_{52}N_4NaO_9$ (M + Na) requires 743.3632, found 743.3634.

TBDMS-Protected Ketal−aldehyde 6. A solution of 1.35 g (1.87 mmol) of **5** and 0.52 mL (2.25 mmol) of MTBSTFA in 15 mL of dry acetonitrile was heated to 50 °C for 1.5 h. After the solution was cooled to cool to room temperature, saturated aqueous sodium bicarbonate was added. The resulting mixture was extracted three times with ethyl acetate. The combined organic layers were washed twice with saturated brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (95:5 methyl *tert*-butyl ether/methanol) to afford **6** (1.37 g, 88%) as a white amorphous solid. The purity of the compound was 94.5% according to HPLC analysis (50:50−0:100 solvent A/solvent B, linear gradient over 20 min, t_R 9.8 min): $[\alpha]^{20}_D = +11.7$ (*c* 1.0, CH_2Cl_2); IR (KBr) 3326, 1682, 1512, 841 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz)[35] δ 9.95 (d, $J = 7.7$ Hz, 1H), 8.45 (d, $J = 7.3$ Hz, 1H), 7.00 (t, $J = 7.9$ Hz, 1H), 6.70 (m, 2H), 6.61 (d, $J = 8.1$ Hz, 1H), 6.58 (s, 1H), 6.13 (dd, $J = 10.5$, 15.2 Hz, 1H), 6.02 (dd, $J = 10.6$, 15.3 Hz, 1H), 5.87 (d, $J = 7.7$ Hz, 1H), 5.68 (dt, $J = 6.4$, 15.2 Hz, 1H), 5.54 (dd, $J = 7.5$, 15.0 Hz, 1H), 5.32 (dd, $J = 3.3$, 9.3 Hz, 1H), 5.17 (dd, $J = 7.7$, 15.2 Hz, 1H), 5.04 (d, $J = 12.0$ Hz, 1H), 4.55 (dd, $J = 7.9$, 11.1 Hz, 1H), 4.24 (m, 2H), 4.17 (t, $J = 4.7$ Hz, 1H), 2.85 (m, 2H), 2.67 (m, 3H), 2.48 (m, 2H), 2.33 (m, 1H), 2.12 (s, 3H), 1.96 (m, 3H), 1.81 (m, 2H), 1.69 (m, 1H), 1.52 (m, 2H), 1.33 (m, 1H), 1.19 (s, 3H), 0.93 (s, 9H), 0.86 (d, $J = 6.6$ Hz, 3H), 0.75 (d, $J = 6.8$ Hz, 3H), 0.30 (d, $J = 7.5$ Hz, 3H), 0.16 (s, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz)[35] δ 192.3, 172.2, 170.8, 170.7, 170.4, 159.6, 155.3, 139.3, 134.6, 131.0, 130.9, 130.5, 129.9, 125.7, 122.4, 121.5, 117.6, 95.7, 80.2, 75.8, 73.2, 60.2, 59.3, 56.7, 49.5, 44.0, 39.0, 38.1, 35.0, 34.2, 31.3, 29.5, 26.9, 26.0, 23.0, 22.9, 21.2, 19.8, 18.3, 18.0, 14.5, 14.4, 12.2, −4.1, −4.2; R_f 0.59 (95:5 methyl *tert*-butyl ether/methanol, HPTLC plate); HRMS calcd for $C_{45}H_{66}N_4NaO_9Si$ (M + Na) requires 857.4497, found 857.4496.

Triol 11. To a stirred, cooled (0 °C) solution of 100 mg (0.26 mmol) of lactol **2** in 2 mL of methanol was added a solution of 30 mg (0.78 mmol) of sodium borohydride in 1 mL of methanol. The reaction mixture was stirred at 0 °C for 2 h and quenched with a saturated aqueous ammonium chloride solution and water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The crude product was purified by crystallization in *n*-hexane to afford 93.2 mg (93%) of **11** as white crystals. The purity of the compound was 95.3% according to HPLC analysis (10:90−50:50 acetonitrile/water, linear gradient over 4 min, and then 50:50−100:0 acetonitrile/water, linear gradient over 6 min, t_R 5.6 min): $[\alpha]^{20}_D = -84.0$ (*c* 0.5, acetone); mp 42.2−43.2 °C; IR (KBr) 3305, 1647, 1165, 1067 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.91 (s, 1H), 5.59 (d, $J = 4.9$ Hz, 1H), 4.32 (t, $J = 5.1$ Hz, 1H), 3.99 (d, $J = 5.5$ Hz, 1H), 3.71 (t, $J = 9.8$ Hz, 1H), 3.58 (m, 1H), 3.50 (m, 1H), 3.36 (m, 2H), 2.07 (m, 1H), 1.93 (m, 2H), 1.75 (m, 1H), 1.64 (m, 1H), 1.56−1.36 (m, 8H), 1.25 (m, 1H), 1.03 (m, 1H), 0.91 (m, 6H), 0.85 (m, 6H), 0.78 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.3, 87.1, 73.6, 70.3, 66.9, 61.7, 40.90, 40.76, 39.12, 37.94, 37.49, 30.97, 30.45, 29.34, 28.68, 25.77, 15.16, 14.88, 14.55, 13.41, 12.36; HRMS calcd for $C_{21}H_{39}NNaO_5$ (M + Na) requires 408.2726, found 408.2727. Anal. Calcd for

(35) Derivatives such as **16**, containing the intramolecular ketal substructure, exist as an approximately 10:1 mixture of isomers in solution in DMSO-d_6. Only the signals corresponding to the major isomer are listed.

$C_{21}H_{39}NO_5$ C, 65.42; H, 10.20; N, 3.63. Found: C, 65.22; H, 10.32; N, 3.66.

Sulfide 12. To a stirred, cooled (0 °C) solution of 102.10 mg (0.57 mmol) of 1-phenyl-1*H*-tetrazole-5-thiol and 150.27 mg (0.57 mmol) of triphenylphosphine in 5 mL of THF was added via cannula a solution of 200.8 mg (0.52 mmol) of **11** in 2 mL of THF. Then, 0.11 mL (0.57 mmol) of diisopropyl azodicarboxylate was added dropwise over 10 min. The resulting mixture was allowed to warm to room temperature and stirred for 30 h. The solvents were removed under reduced pressure, and the crude product was purified by HPLC, using the elution system described in the General Procedures, to afford 201.5 mg (71%) of **12** (t_R 18.8 min) as a white solid. The purity of the compound was 97.4% according to HPLC analysis (10:90−100:00 acetonitrile/water, linear gradient over 5 min, and then acetonitrile over 2 min, t_R 5.6 min): $[\alpha]^{20}_D$ = −16.0 (*c* 1.0, acetone); IR (KBr) 3288, 1500, 1645, 1500, 761, 695 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.90 (s, 1H), 7.66 (s, 5H), 5.61 (s, 1H), 4.10 (d, J = 5.5 Hz, 1H), 3.70 (t, J = 10 Hz, 1H), 3.57 (m, 1H), 3.50 (m, 1H), 3.32 (m, 2H), 2.03 (m, 1H), 1.90 (m, 2H), 1.73 (m, 3H), 1.62−1.20 (m, 9H), 0.92−0.77 (m, 15H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.3, 154.9, 133.6, 131.0, 130.4, 125.0, 87.1, 73.6, 70.0, 66.9, 40.9, 40.8, 39.5, 38.7, 37.5, 33.5, 31.9, 30.4, 28.7, 27.2, 25.8, 15.1, 14.7, 14.5, 13.4, 12.3; R_f 0.33 (98:2 methyl *tert*-butyl ether/methanol); HRMS calcd $C_{28}H_{43}N_5NaO_4S$ (M + Na) requires 568.2933, found 568.2931. Anal. Calcd for $C_{28}H_{43}N_5O_4S$ C, 61.62; H, 7.94; N, 12.83. Found: C, 61.27; H, 7.98; N, 12.69.

Bissilylated Sulfide 13. To a mixture of 1.03 mL of ether and 0.74 mL of acetonitrile at −20 °C were added 0.098 mL (1.22 mmol) of pyridine and 0.233 mL (1.032 mmol) of triethylsilyl trifluoromethanesulfonate. This mixture was cooled to −50 °C, and a solution of 256 mg (0.469 mmol) of **12** in 0.2 mL of acetonitrile was added. Stirring at −50 °C was continued for 30 min, and the reaction was quenched with saturated aqueous sodium bicarbonate. This mixture was diluted with hexane, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. The solvents were removed under reduced pressure, and the crude product was purified by chromatography on silica gel (80:20 hexane/ethyl acetate) to afford 261 mg (72%) of **13** as a colorless oil. The purity of the compound was 96.6% according to HPLC analysis (70:30−100:00 acetonitrile/water, linear gradient over 10 min, and then acetonitrile over 16 min, t_R 13.1 min): $[\alpha]^{20}_D$ = −62.0 (*c* 1.0, acetone); IR (film) 3352, 1667, 1069, 1007 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.66 (m, 5H), 7.56 (s, 1H), 3.86 (s, 1H), 3.74 (d, J = 7.4 Hz, 1H), 3.64 (t, J = 10.3 Hz, 1H), 3.36 (m, 2H), 1.94 (m, 3H), 1.83 (m, 2H), 1.64 (m, 3H), 1.45 (m, 5H), 1.28 (m, 1H), 1.10 (m, 1H), 0.98 (t, J = 7.9 Hz, 9H), 0.92−0.81 (m, 21H), 0.78 (d, J = 6.9 Hz, 3H), 0.66 (m, 6H), 0.48 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.7, 154.8, 133.5, 131.0, 130.4, 124.9, 86.9, 77.4, 72.9, 66.6, 41.6, 40.9, 40.5, 37.8, 37.6, 33.5, 30.1, 29.9, 28.3, 27.6, 25.6, 15.4, 15.1, 14.8, 13.8, 12.6, 7.3, 5.3, 5.2; R_f 0.45 (80:20 hexane/ethyl acetate); HRMS calcd $C_{40}H_{71}N_5NaO_4SSi_2$ (M + Na) requires 796.4663, found 796.4651. Anal. Calcd for $C_{40}H_{71}N_5O_4SSi_2$ C, 62.05; H, 9.24; N, 9.05. Found: C, 61.97; H, 9.10; N, 8.91.

Sulfone 14. To a solution of 249.0 mg (0.32 mmol) of **13** in 4 mL of dichloromethane was added 270.2 g (3.2 mmol) of sodium bicarbonate followed by a solution of 277.5 mg (1.6 mmol) of mCPBA in 2 mL of dichloromethane. The reaction mixture was stirred at room temperature for 14 h and quenched by addition of saturated aqueous sodium bicarbonate and saturated aqueous sodium thiosulfate. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (70:30 hexane/ethyl acetate) to afford 252.8 mg (98%) of **14** as a colorless oil. The purity of the compound was 100% according to HPLC analysis (70:30−100:00 acetonitrile/water, linear gradient over 10 min, and then acetonitrile over 6 min, t_R 11.0 min): $[\alpha]^{20}_D$ = −43.0 (*c* 1.0, acetone); IR (film) 3351, 1347, 1154 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.71 (m, 5H), 7.57 (s, 1H), 3.87 (s, 1H), 3.77 (m, 3H), 3.64 (t, J = 10.2 Hz, 1H), 1.93 (m, 3H), 1.84 (m, 2H), 1.67 (m, 3H), 1.44 (m, 5H), 1.27 (m, 1H), 1.10 (m, 1H), 0.99 (t, J = 7.9 Hz, 9H), 0.88 (m, 21H), 0.76 (d, J = 6.6 Hz, 3H), 0.66 (m, 6H), 0.50 (m, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.7, 153.9, 133.4, 132.0, 129.9, 126.7, 86.9, 77.4, 72.9, 66.5, 56.1, 41.6, 40.9, 40.7, 37.8, 37.4, 29.9, 29.7, 28.3, 25.6, 20.6, 15.4, 15.1, 14.8, 13.8, 12.6, 7.3, 7.2, 5.3, 5.2; R_f 0.62 (70:30 hexane/ethyl acetate); HRMS calcd $C_{40}H_{71}N_5NaO_6SSi_2$ (M + Na) requires 828.4561, found 828.4564.

31,35-Bissilylated Sanglifehrin A Ketal (15). To a mixture of 510.3 mg (0.63 mmol) of **14** and 456.2 mg (0.63 mmol) of **5** in 5 mL of ethylene glycol dimethyl ether at −78 °C was added slowly 2.53 mL (1.27 mmol) of a 0.5 M solution of sodium bis(trimethylsilyl)amide in toluene. The reaction mixture was stirred at −78 °C for 8 h, quenched with saturated aqueous sodium bicarbonate, and diluted with water. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography on silica gel (gradient 100% methyl *tert*-butyl ether to 95:5 methyl *tert*-butyl ether/methanol) to afford 308.9 mg (49%) of **15** as a white amorphous solid. The purity of the compound was 96.8% according to HPLC analysis (70:30−100:00 acetonitrile/water, linear gradient over 4 min, and then acetonitrile over 21min, t_R 11.9 min): $[\alpha]^{20}_D$ = −35.0 (*c* 2.0, acetone); IR (KBr) 3352, 1736, 1648, 1506, 990 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz)[35] δ 9.23 (s, 1H), 8.48 (d, J = 9.0 Hz, 1H), 7.57 (s, 1H), 6.96 (t, J = 6.3 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.49 (m, 2H), 6.19 (m, 2H), 6.03 (m, 2H), 5.95 (m, 3H), 5.29 (d, J = 11.0 Hz, 1H), 5.20 (dd, J = 7.6, 14.8 Hz, 1H), 4.82 (d, J = 11. 0 Hz, 1H), 4.58 (dd, J = 8.4, 9.2 Hz, 1H), 4.23 (m, 3H), 3.86 (s, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 2.90 (m, 1H), 2.72 (m, 2H), 2.56 (m, 3H), 2.35 (m, 1H), 2.19 (m, 2H), 1.92 (m, 10H), 1.70 (s, 3H), 1.67 (m, 2H), 1.47 (m, 8H), 1.21 (s, 3H), 1.20 (m, 3H), 1.01−0.71 (m, 39H), 0.66 (m, 6H), 0.50 (m, 6H), 0.40 (d, J = 8.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 173.7, 172.3, 170.9, 170.6, 157.6, 138.6, 136.3, 134.9, 132.1, 130.4, 130.3, 130.2, 130.0, 129.8, 126.6, 126.1, 120.0, 117.0, 113.5, 95.6, 86.9, 80.0, 77.5, 73.2, 73.0, 66.6, 59.2, 56.9, 49.2, 44.0, 41.6, 40.9, 40.8, 39.2, 38.9, 38.8, 37.8, 37.6, 35.8, 34.2, 31.2, 31.0, 30.9, 29.9, 29.5, 28.3, 27.0, 25.6, 23.0, 22.8, 19.8, 18.2, 15.3, 15.1, 14.8, 13.8, 13.1, 12.6, 12.4, 7.3, 5.3, 5.2, 5.1; R_f 0.40 (98:2 methyl *tert*-butyl ether/methanol); HRMS calcd $C_{72}H_{117}N_5NaO_{12}Si_2$ (M + Na) requires 1322.8135, found 1322.8125.

Sanglifehrin A Ketal (16). To a solution of 155.5 mg (0.12 mmol) of **15** in 2 mL of tetrahydrofuran at 0 °C was added 0.6 mL (0.6 mmol) of a 1 M solution of TBAF in THF. The resulting solution was stirred at room temperature for 3 days. After evaporation of the solvent under reduced pressure, the residue was diluted with ethyl acetate and acidified to pH 1. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and filtered, and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel to afford 102.7 mg (80%) of **16** as a white amorphous solid. The purity of the compound was 93.8% according to HPLC analysis (10:90−100:00 acetonitrile/water, linear gradient over 20 min, t_R 13.5 min): $[\alpha]^{20}_D = -27.0$ (*c* 1.0, acetone); IR (KBr) 3500, 3422, 1735, 1648, 985 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz)[35] δ 9.24 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 7.91 (s, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 6.73 (d, *J* = 9.0 Hz, 1H), 6.57 (d, *J* = 8.2 Hz, 1H), 6.50 (m, 2H), 6.22 (dd, *J* = 11.5, 14.7 Hz, 1H), 6.16 (dd, *J* = 11.9, 14.5 Hz, 1H), 6.03 (m, 2H), 5.65 (m, 4H), 5.28 (dd, *J* = 3.0, 10.2 Hz, 1H), 5.20 (dd, *J* = 7.8, 15.1 Hz, 1H), 4.82 (d, *J* = 12.1 Hz, 1H), 4.69 (m, 1H), 4.24 (m, 3H), 4.07 (d, *J* = 5.5 Hz, 1H), 3.71 (t, *J* = 10. 0 Hz, 1H), 3.58 (m, 1H), 3.53 (m, 1H), 2.90 (m, 1H), 2.77 (m, 1H), 2.68 (m, 1H), 2.51 (m, 3H), 2.37 (m, 1H), 2.25−1.92 (m, 10H), 1.75 (m, 2H), 1.70 (s, 3H), 1.65 (m, 2H), 1.57−1.25 (m, 10H), 1.21 (s, 3H), 1.14 (m, 1H), 0.93−0.77 (m, 21H), 0.40 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 174.3, 172.3, 171.0, 170.9, 170.6, 157.6, 138.7, 136.6, 134.9, 132.8, 132.1, 130.4, 130.3, 130.0, 126.7, 125.9, 120.0, 117.0, 113.5, 95.6, 87.1, 80.1, 77.5, 73.6, 73.2, 69.9, 66.9, 59.2, 56.9, 49.2, 44.1, 40.9, 40.8, 40.5, 38.9, 38.8, 38.6, 38.0, 37.5, 35.7, 34.2, 32.7, 31.2, 30.6, 30.5, 29.5, 28.7, 27.1, 25.8, 23.0, 22.8, 19.8, 18.2, 15.2, 14.7, 14.5, 13.4, 13.2, 12.4; R_f 0.43 (94:6 methyl *tert*-butyl ether/methanol); HRMS calcd $C_{60}H_{89}NaN_5O_{12}$ (M + Na) requires 1094.64091 found 1094.63969.

Sanglifehrin A (1). To a solution of 206.3 mg (0.19 mmol) of **16** in 1 mL of THF were added 36.6 mg (0.19 mmol) of TsOH and 59.47 mg (0.96 mmol) of boric acid. The reaction mixture was stirred at room temperature for 5 h and quenched with a saturated aqueous sodium bicarbonate solution. The mixture was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude product was purified by preparative HPLC, using the conditions described in the General Procedures, to afford 62.2 mg (30%) of sanglifehrin A (**1**) (t_R 22.8 min) along with 42.9 mg (20%) of recovered **16** (t_R 24.1 min). The purity of the compound was 97.5% according to HPLC analysis (10:90−100:00 acetonitrile/water, linear gradient over 8 min, and then acetonitrile over 2 min, t_R 7.2 min). Hemisynthetic sanglifehrin A (**1**) exhibited the following characteristics: ^1H NMR (DMSO-d_6, 400 MHz)[34] δ 9.28 (s, 1H), 8.16 (d, *J* = 6.5 Hz, 1H), 7.91 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.08 (t, *J* = 7.7 Hz, 1H), 6.61 (d, *J* = 7. 0 Hz, 1H), 6.58 (d, *J* = 7.2 Hz, 1H), 6.52 (s, 1H), 6.11 (m, 4H), 5.65 (m, 3H), 5.61 (d, *J* = 4.5 Hz, 1H), 5.50 (m, 1H), 5.38 (m, 1H), 5.25 (d, *J* = 9.4 Hz, 1H), 4.80 (d, *J* = 3.5 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.19 (m, 1H), 4.12 (m, 1H), 4.06 (d, *J* = 5.1 Hz, 1H), 3.92 (m, 1H), 3.83 (m, 1H), 3.71 (t, *J* = 9.58 Hz, 1H), 3.58 (m, 1H), 3.53 (m, 1H), 2.78−2.23 (m, 7H), 2.10 (m, 4H), 2.07 (s, 3H), 1.93 (m, 4H), 1.78−1.13 (m, 17H), 1.71 (s, 3H), 0.93−0.79 (m, 21H), 0.62 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz)[34] δ 208.4, 174.9, 174.3, 172.2, 171.1, 170.5, 157.7, 138.7, 136.5, 134.7, 133.2, 131.6, 130.8, 130.2, 130.0, 126.4, 125.9, 120.4, 117.0, 113.6, 87.1, 77.5, 74.6, 73.6, 71.8, 69.9, 66.9, 58.2, 57.8, 51.7, 49.2, 40.9, 40.8, 38.9, 38.7, 38.1, 37.5, 36.6, 32.8, 30.6, 30.5, 30.4, 30.3, 28.7, 27.7, 25.8, 22.8, 19.7, −17.9, 15.2, 14.6, 14.5, 13.4, 13.2, 12.4, 11.4; HRMS calcd $C_{60}H_{91}N_5NaO_{13}$ (M + Na) requires 1112.65148, found 1112.64975.

Acknowledgment. We thank Drs. Sylvain Cottens, Jürgen Wagner, Mark Burlingame, and Rolf Bänteli for their contributions to this paper. We thank Lukas Oberer and Julien France for their assistance with NMR analyses, and Charles Quiquerez for the mass spectra.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **2**−**6**, **11**−**16**, hemisynthetic sanglifehrin A (**1**), and an authentic sample of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO9912395