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Macrolide Analogues of the Novel Immunosuppressant Sanglifehrin: New Application of the Ring-Closing Metathesis Reaction**

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More than two decades ago, the discovery of cyclosporin A (CsA) allowed a spectacular progress in the field of organ transplantation.[1] Since then, the number of transplanted organs has grown continuously, and the search for novel immunosuppressants has been intensified.[2] Besides its important therapeutic use, CsA has also proven to be a powerful tool for dissecting signal transduction pathways at the molecular level.[3] It has been shown that the biological activity of CsA is mediated by an intracellular binding protein called cyclophilin (CyP). However, although CyP binding is required, it is not sufficient for the immunosuppressive activity of this drug. Full biological activity is obtained only once the CyP – CsA complex binds to and inhibits the serine/threonine phosphatase activity of calcineurin, thereby blocking the production of cytokines including interleukin-2.[4]

We wondered whether other ligands for cyclophilin might exist which would interfere with signaling pathways not involving calcineurin. The screening of microbial broth extracts for CyP-binding substances led to the isolation from *Streptomyces flaveolus* of a new class of compounds named sanglifehrins.[5a] Among the 20 different sanglifehrins isolated so far from this strain, sanglifehrin A (SFA, Figure 1) is the most abundant component. The affinity of SFA for cyclophilin is remarkably high ($IC_{50} = 2 – 4$ nM),[6] approximately 20-fold higher than that of CsA ($K_i = 82$ nM). Sanglifehrin A displays potent immunosuppressive activity in the mixed lymphocyte reaction ($IC_{50} = 170$ nM), an in vitro immune response assay.[5a] However, SFA does not affect T-cell receptor-mediated cytokine production, indicating a mode of action different from that of CsA. Moreover, in contrast to the T-cell-selective drug CsA, SFA inhibits mitogen-induced B-cell proliferation ($IC_{50} = 90$ nM). These data clearly indicate that the immunosuppressant SFA acts by a new mode of action. However, the details of the mechanism by which this compound exerts its immunosuppressive activity at the molecular level are unknown.

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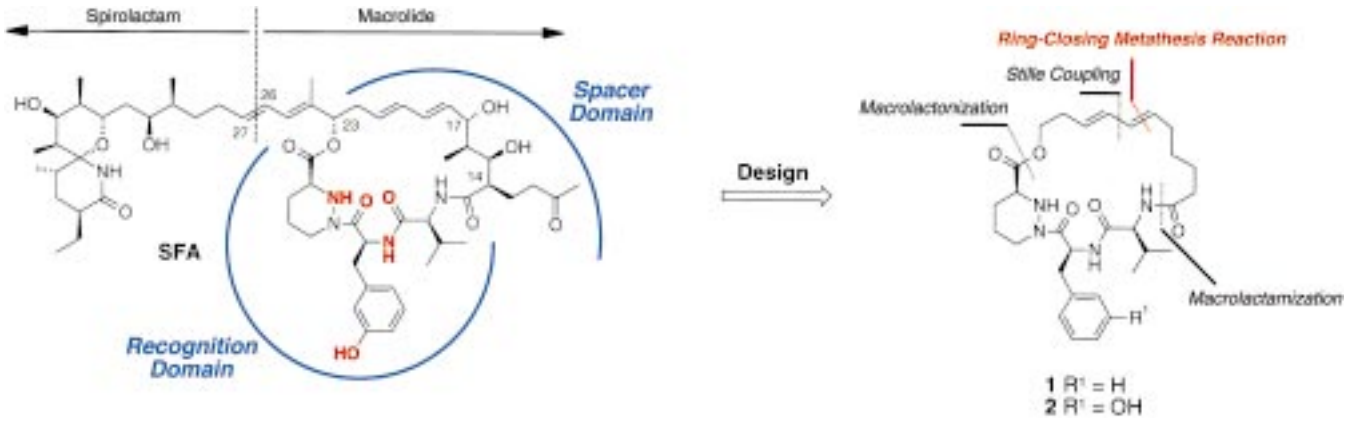

Figure 1. The structure of sanglifehrin A (SFA) and of the designed macrolides **1** and **2** (atoms forming hydrogen bonds to cyclophilin are shown in red). The possible macrocyclization strategies are also included.

Herein we describe the design and the syntheses of the first synthetic analogues of the SFA macrolide which bind to cyclophilin. The simplified macrocycles **1** and **2** (Figure 1) were designed in order to study the relevance of the CyP–SFA interaction, which is important for a better understanding of the mechanism. We also disclose the first example of the construction of macrocyclic conjugated 1,3-dienes by the ring-closing metathesis (RCM) reaction.

The structure of SFA has been determined by spectroscopic analysis, and its stereochemistry has been confirmed by X-ray analysis of the Cyp–SFA complex.[5b, c] The sanglifehrins have a unique structure: A novel, highly substituted spirolactam system is linked to a 22-membered macrolide through a rigid, partially unsaturated alkyl chain. The macrolide contains a tripeptide unit composed of piperazic acid (according to IUPAC the acid should be called hexahydropyridazine-3-carboxylic acid), *meta*-tyrosine, and valine. (For a synthesis of the macrolide, see reference [18].) Interestingly, the peptidic backbone extends through the β-nitrogen atom of piperazic acid rather than its α-nitrogen atom. This feature, unique to the sanglifehrins, is a key element for optimal binding to cyclophilin.

Degradation studies on SFA and the X-ray crystallographic structure of SFA bound to cyclophilin provided the basis for the design of compounds **1** and **2**. Cleavage of SFA at the C_{26}–C_{27} double bond by a two-step procedure (Sharpless dihydroxylation, periodate oxidation) allowed selective removal of the complex spirolactam.[7] The resulting macrolide and SFA have comparable affinities for cyclophilin. Therefore, the whole side chain attached to the macrolide at C_{23} was not incorporated into the target compounds. As observed from the degradation studies, the X-ray crystal structure showed that the macrocycle alone is responsible for the binding to cyclophilin.

A detailed analysis of this structure suggested that the macrolide can be viewed as the combination of a recognition domain and a spacer domain (Figure 1). The recognition domain corresponds to the tripeptide, where all the functional groups forming hydrogen bonds with cyclophilin are located (shown in red). The spacer domain, which extends from C_{14} to C_{23}, combines a short polypropionate chain (C_{14}–C_{17}) and a conjugated (*E*,*E*)-diene. These two features might play a key role in locking the macrolide into the optimal conformation for binding to cyclophilin.

Having established the part of the macrolide which is important for binding, we chose, for our first-generation macrolide analogues an intact recognition domain, except that *meta*-tyrosine was replaced by phenylalanine in **1**. The difference in binding between **1** and **2** should reflect the strength of the phenol-mediated hydrogen bond. Several functionalities of the spacer region were removed, but the conjugated (*E*,*E*)-diene was conserved in order to provide the required conformational stability.

A retrosynthetic analysis showed that several routes can be considered for the construction of the macrocycles: macrolactonization, macrolactamization, Stille coupling, and RCM (Figure 1). The development of a new methodology based on the RCM reaction promised to be particularly attractive, because 1) the macrolides can be rapidly accessed in a convergent manner, 2) the strategy has potential for the creation of analogue libraries, and 3) the formation of simple macrocyclic olefins by RCM has already proven to be one of the most powerful techniques in organic synthesis.[8]

The syntheses of the macrocycles **1** and **2** are shown in Scheme 1. At first, two different tripeptide fragments had to be assembled. The synthesis of tripeptide fragment **5** began with the optically pure piperazic acid derivative **3**, which was obtained according to Hale et al. in multigram quantities.[9] On the other hand, the first step in the construction of tripeptide **11** involved the synthesis of benzyl-protected *meta*-tyrosine in a chiral form. The alkylation of the bis-lactim ether (Schöllkopf auxiliary) **8** with 3-benzyloxybenzyl bromide provided intermediate **9** with 89% diastereoselectivity.[10] The undesired isomer was readily separated by chromatography. With the two unnatural amino acids **3** and **9** in hand, the tripeptides **5** and **11** were assembled by using carbodiimide-based coupling procedures or activation of the acids by the mixed anhydride methodology. It is noteworthy that the coupling of **3** occurred selectively at the less hindered β-nitrogen atom.[11] At that stage, the correct choice of orthogonal protecting groups was critical for the further transformation of **11**. Therefore, the benzyl group was removed by hydrogenolysis in isopropyl alcohol and replaced by the TBDMS group to afford **12**. Use of a less hindered

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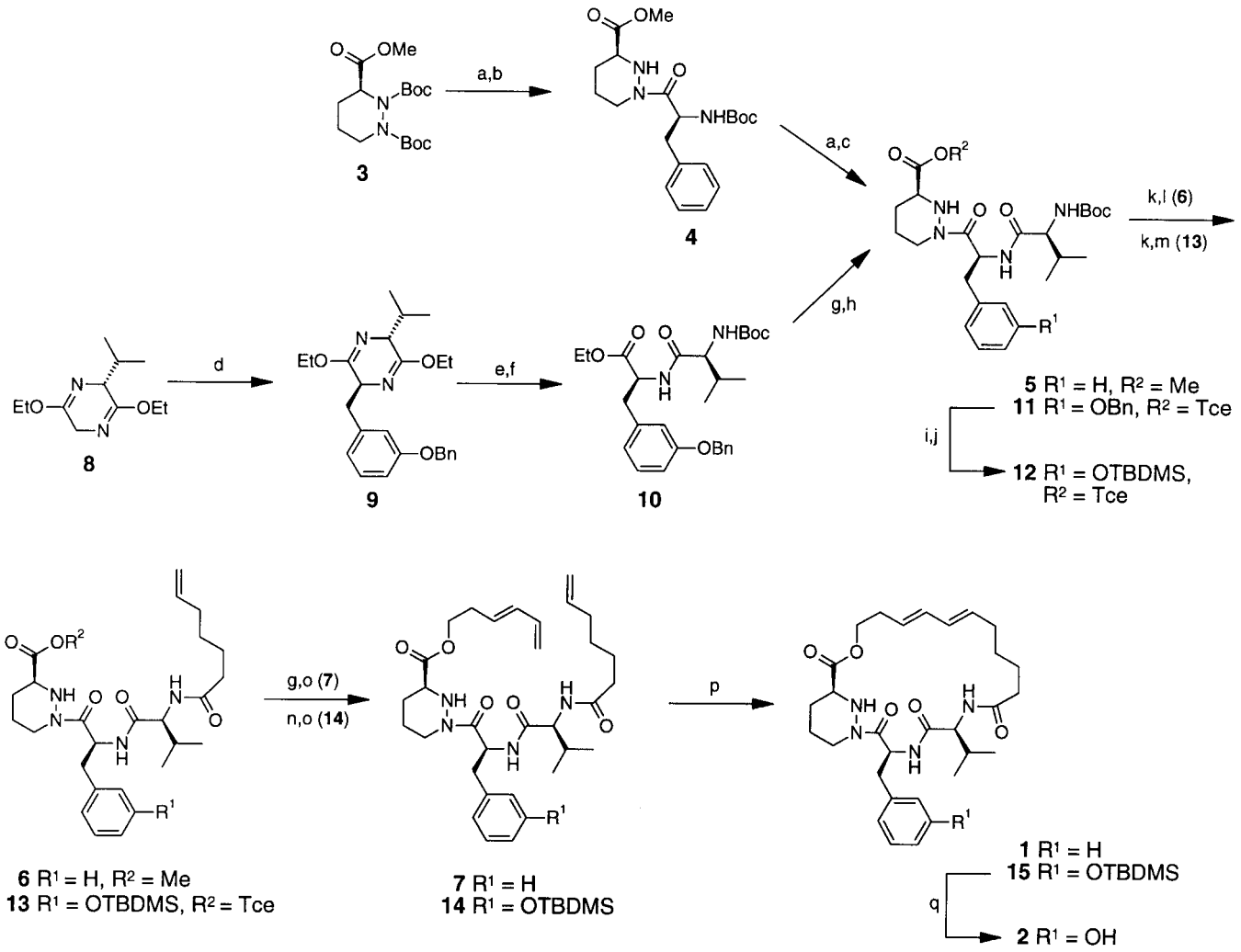

Scheme 1. a) Trifluoroacetic acid, CH_2Cl_2 (100%); b) L-Boc-Phe-OH, EDC, HOBT, NMM, CH_2Cl_2 (66%); c) L-Boc-Val-OH, EDC, HOBT, NMM, CH_2Cl_2 (71%); d) BuLi, THF, $-78\,^{\circ}C$, 3-benzyloxybenzyl bromide (69%); e) HCl 0.5N, CH_3CN (70%); f) L-Boc-Val-OH, NMM, isobutyl chloroformate ($ClC(O)OiBu$), THF (70%); g) LiOH, H_2O/THF 1:4 (100%); h) trichloroethyl piperazate, NMM, isobutyl chloroformate, THF (62%); i) H_2, Pd/C, *i*PrOH (96%); j) TBDMSCl, imidazole, DMF (99%); k) TMSOTf, CH_2Cl_2 (97%); l) 6-heptenoic acid, EDC, HOBT, NMM, CH_2Cl_2 (95%); m) 6-heptenoic acid, NMM, isobutyl chloroformate, THF (70%); n) Zn, NH_4OAc 1.0N, THF (90%); o) DEAD, PPh_3, 3,5-hexadiene-1-ol, THF (64% (**7**); 82% (**14**)); p) [$(PCy_3)_2$-Cl_2-Ru=CHPh], CH_2Cl_2, 40 °C (57% (**1**); 47% (**15**)); q) Bu_4NF, THF (75%). Bn = benzyl, Boc = *tert*-butoxycarbonyl, DEAD = diethylazodicarboxylate, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, HOBt = 1-hydroxy-1*H*-benzotriazole, NMM = *N*-methylmorpholine, OTf = trifluoromethanesulfonate, TBDMS = *tert*-butyldimethylsilyl, Tce = trichloroethyl, TMS = trimethylsilyl.

alcohol during cleavage of the benzylic bond resulted in partial transesterification of the trichloroethyl ester. Nevertheless, the Tce group was selected, because it could be removed under very mild conditions even in the presence of the TBDMS protecting group.[12]

Deprotection of the Boc group with TMSOTf in CH_2Cl_2 followed by coupling of the resulting amines to 6-heptenoic acid afforded **6** and **13**. Methyl ester hydrolysis of **6** or selective deprotection of the trichloroethyl ester group of **13** with zinc provided the corresponding acids, which were esterified with 3,5-hexadiene-1-ol under Mitsunobu conditions.[13] The precursors **7** and **14** for the RCM reaction were thus obtained in good overall yield (28% from **3** and 11% from **8**). The diene moiety had to be introduced at this late stage of the synthesis, because partial isomerization of the double bonds occurred under the acidic Boc-cleavage conditions.

The ruthenium-based catalyst first described by Grubbs et al.[8a] was used for the critical macrocyclization step. The best yields of the macrocycles were obtained in CH_2Cl_2 under reflux and at dilute concentrations (<5 mM). Under these conditions, the desired products **1** and **15** were obtained selectively in 57% and 47% yield, respectively, after purification by HPLC. At higher concentrations, dimerization became an important side reaction, and in other solvents (benzene, toluene) the yields were lower. The configuration of the newly formed conjugated diene was assessed by ^1H NMR spectroscopy to be *E*,*E* in both cases.[14] The (*E*,*Z*)-diene was present as a minor component (<5%), but we could not detect any product resulting from metathesis of the internal diene double bond. The macrocyclization also proceeded in the presence of the free phenol, but at a slower rate. Removal of the silyl protecting group from **15** provided the final product **2**. The affinity of the macrolides **1** and **2** for

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cyclophilin was assessed in a competitive ELISA format.[6] They were found to bind with IC_{50} values of 7.3 and 5.7 μM, respectively. Several uncyclized tripeptide intermediates did not show any activity when tested in the same assay.

The synthesis of **1** and **2** is based on the RCM reaction, which has already proven to be one of the most powerful techniques for the construction of macrocyclic natural products in solution[15] or on solid support,[16] but whose use so far has been limited to the formation of simple olefins. However, various macrocyclic, biologically relevant, natural products embody conjugated 1,3-dienes.[17] For the first time, macrocycles containing a cyclic 1,3-diene moiety have been synthesized in good yields by a metathesis reaction, as exemplified by **1** and **2**. As this methodology is extendable to the creation of analogue libraries, it should be of interest for organic synthesis in general and natural product synthesis and medicinal chemistry in particular.

Compounds **1** and **2** are the first synthetic analogues of the macrocyclic core of sanglifehrin A which bind to cyclophilin. Indeed, all the open-chain tripeptides tested so far are inactive in the CyP-binding assay. The reduced affinity of **1** and **2** for cyclophilin compared to sanglifehrin A is a clear indication that the conformation of these first-generation macrolides is not yet optimal. In other words, the results suggest that the conjugated diene is not sufficient to lock the macrocycle into the ideal three-dimensional conformation. Therefore, future work will include the preparation of a library of macrolides based on the chemistry developed herein and taking into account other functional features of the sanglifehrins.

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