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Synthesis of the tripeptide (C1–N12) and hydroxylated hexadecene (C26–C41) domains of sanglifehrin A and C

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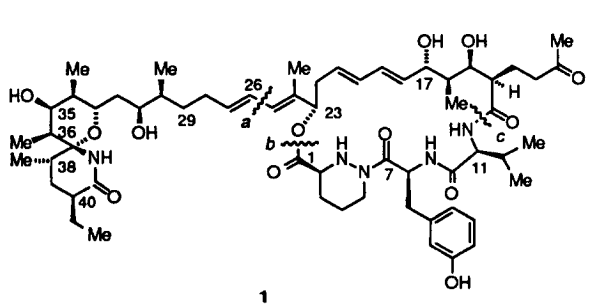
Abstract

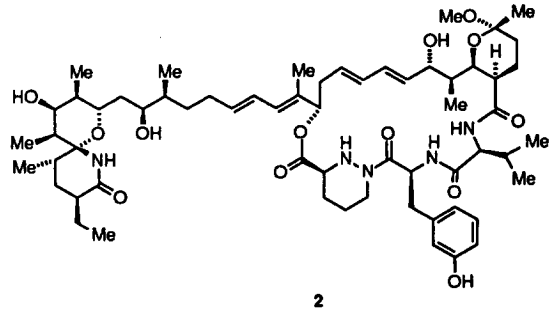
Fully enantio-controlled routes to two major segments of the newly discovered immunosuppressants sanglifehrin A and C are described.

Keywords: immunosuppressive compounds; peptide; stereocontrol; aldols; aminal.

A new class of powerful immunosuppressive agents has recently been isolated from culture broths of the Actinomycete strain identified as *Streptomyces flaveolus*.[1] Two of the more impressive members of this family, sanglifehrins A (**1**) and C (**2**), exhibit strong cyclophilin binding[2] and inhibit the proliferation of both B- and T-cells. Interestingly, **1** and **2** differ from cyclosporin A, FK506, and rapamycin by displaying neither FK binding protein binding activity nor calcineurin inhibiting capability. Their mode of action is therefore unusual and unparalleled. The extensive structural studies undertaken by the Novartis group have revealed the sanglifehrins to constitute a new type of macrocyclic lactone, the 22-membered ring of which incorporates piperazic, aliphatic, and aromatic amino acid components. The associated hemiaminal subunit is equally rich in stereochemical detail and uncommon functional group segments.



1



2

The disconnections possible for **1** and **2** are numerous. Through cleavage at the sites labelled as *a*, *b*, and *c* in **1**, the challenge of a total synthesis becomes focused on the individual construction and ultimate

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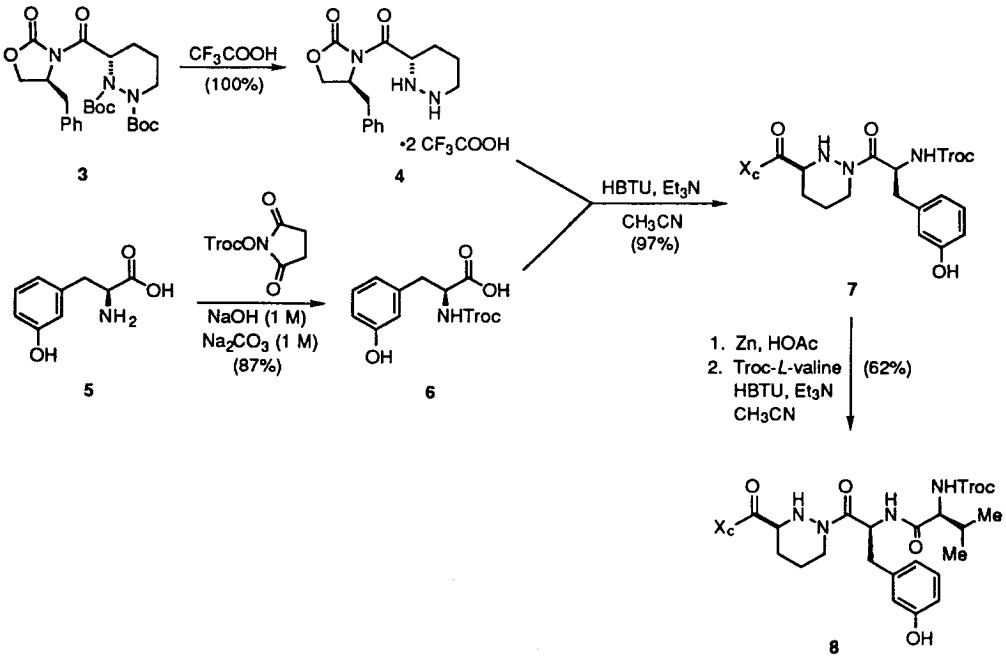
assembly of the tripeptide unit C1–N12, the hydroxylated hexadecene sector C26–C41, and the balance of the macrocyclic ring in the eastern sector. In the light of recent synthetic activity in this area,[3,4] we herein report on our successful acquisition of the first two of these building blocks.

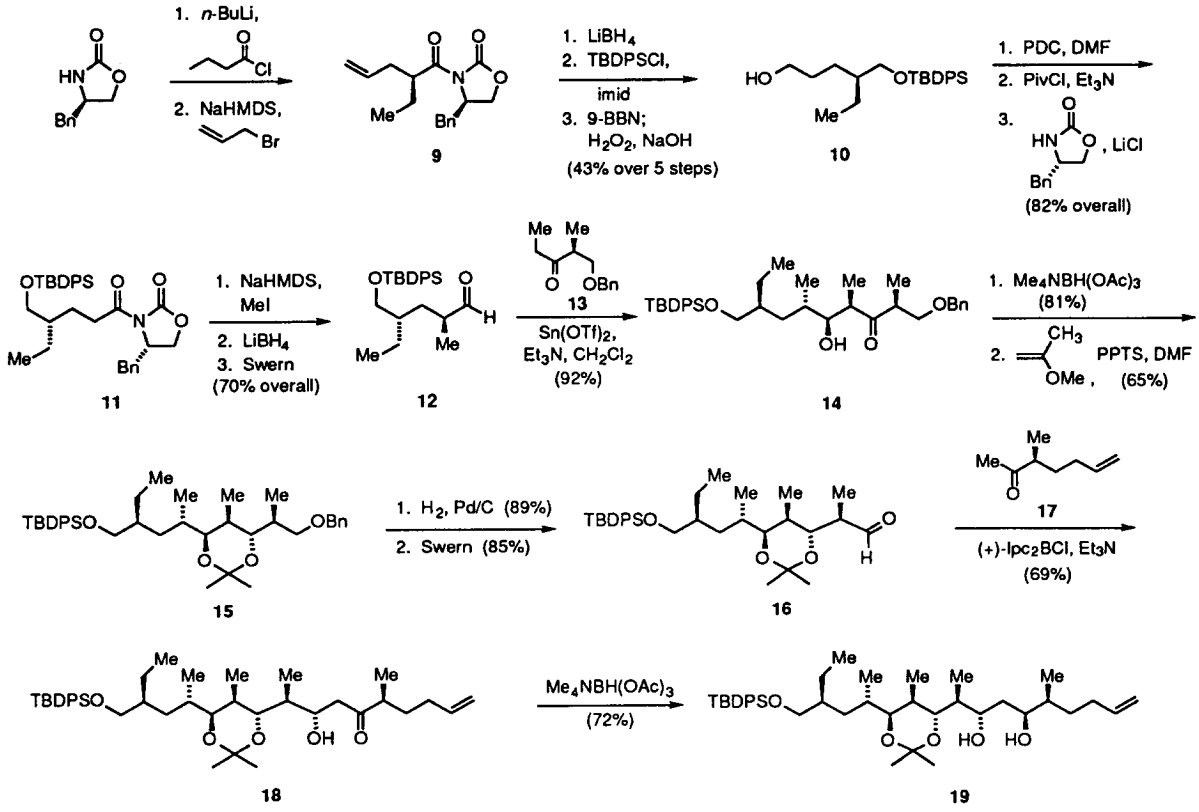
As indicated in Scheme 1, we have found it possible to accomplish the task of producing **8** in five efficient steps from known compounds. Thus, stirring **3**[5] in trifluoroacetic acid results in deprotection of the nitrogen atoms and formation of the bistrifluoroacetate salt **4**. The other component was synthesized by direct reaction of synthetic (*S*)-*m*-tyrosine (**5**)[6] with an activated Troc ester.[7] The realization that the phenolic hydroxyl in **6** requires no protection is noteworthy. *O*-Benzotriazol-1-yl-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (HBTU) proved to be a particularly effective agent in bringing about proper acylation of **4** at N1.[8] Reduction of **7** with zinc in acetic acid was followed by union of the carboxylic acid so liberated with Troc-L-valine. Our ultimate expectation for **8** is its expedient stepwise coupling of the northeastern subunit when it becomes available.



Scheme 1.

On the second front, the oxazolidinone **9** constitutes the point of departure toward **19** (Scheme 2). The proper absolute configuration α to the carbonyl group was set by introducing the allyl substituent after appropriate acylation.[9] Transformation of **9** into the monoprotected 1,5-diol **10** was accomplished by sequential reductive cleavage of the chiral auxiliary with $LiBH_4$ in wet ether, conversion of the relatively volatile alcohol to its TBDPS ether, and hydroboration–oxidation with 9-BBN. The overall efficiency for the initial five steps was 43%. Oxidation of **10** with PDC in DMF led to the carboxylic acid, which most efficaciously afforded **11** through adaptation of an activated anhydride protocol.[10,11] Subsequent to the highly enantioselective methylation of **11**, aldehyde **12** was smoothly generated by conventional methods (70% overall).

In the expectation that the tin(II) enolate of (*S*)-**13** would engage in substrate control during its condensation with **12**,[12] recourse was made to Paterson's conditions and **14** was isolated in 92% yield. The stereochemical assignment to this *syn* aldol follows from a complete COSY analysis performed on its OTBS analog, in line with previous successes realized upon application of the *J*-based method



Scheme 2.

to conformationally flexible systems ($J_{H36,H37}$=1.7 Hz).[13] The high-level π-facial selectivity realized in the **12**→**14** conversion was matched during the ensuing reduction of **14** with tetramethylammonium triacetoxyborohydride.[14] After acetonide **15** had been elaborated, the primary alcohol was generated by hydrogenolysis, thus setting the stage for oxidation to aldehyde **16**.

With this intermediate in hand, we opted to evaluate the extent of 1,3-asymmetric induction capable of being realized via an enol borinate of **17**.[15] Use of (+)-(Ipc)$_2$BCl for this purpose[16,17] resulted in complete regiocontrol of the enolization process and high stereoselectivity for a matched reaction. The elevated *si*-face selectivity of **16** for **17** undoubtedly rests in large part on the steric demands and chirality of the boron reagent and aldehyde.[18] Subsequent reduction of **18** with triacetoxyborohydride proved to be a convenient means for setting the ninth stereogenic center, thereby furnishing the differentially protected polyol target **19**.

The body of chemistry developed herein has therefore allowed the preparation of two major components of **1** and **2**. In the case of **19**, it remains to explore construction of the [5.5] spirolactam moiety in a chemoselective manner. Plans to engage the terminal double bond directly in a Heck coupling reaction[19] are also contemplated and are under active investigation in these laboratories.

Acknowledgements

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