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Highly diastereocontrolled synthesis of the C1–C25 domain of sanglifehrin A

Maosheng Duan and Leo A. Paquette *

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, USA

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Abstract

We report a diastereoselective synthesis of **2** containing the core structure of the entire eastern sector of sanglifehrin A. The route proceeds by directed chain extension of appropriate building blocks, their timely convergent amalgamation, and ultimate coupling to a preformed tripeptide subunit.

Keywords: immunosuppressive agents; aldol reaction; enol borinate; peptide coupling; vinyl iodide.

Scientists at Novartis Pharma reported in a 1997 patent application on the isolation of sanglifehrins A–D from cultures of *Streptomyces* sp. A92–308110.[1a] In a later disclosure, the characterization of additional members of this compound class was detailed.[1b] Although the absolute configurations at C17, C38 and C40 were self-contradicted several times in these documents, this issue was ultimately rectified by X-ray crystallography[2] and more recently verified by partial[3,4] and total synthesis.[5] As reflected in the structure of the A factor (**1**), the conformationally rigid 22-membered ring that is richly adorned with functionality is linked via a dienyl tether to a spiro aminal subunit. This combination of structural features causes **1** to exhibit a 20-fold higher binding affinity for cyclophilin A than cyclosporin, and otherwise to differ from known immunosuppressant agents by displaying neither FK binding protein affinity nor calcineurin inhibiting capability. These striking biological properties make **1** and analogs thereof very attractive synthetic targets. Here we define a convenient means for constructing the entire eastern sector that houses C1–C25 (see **2**).

* Corresponding author. Fax: 1-614-292-1685; e-mail: paquette.1@osu.edu (L. A. Paquette)

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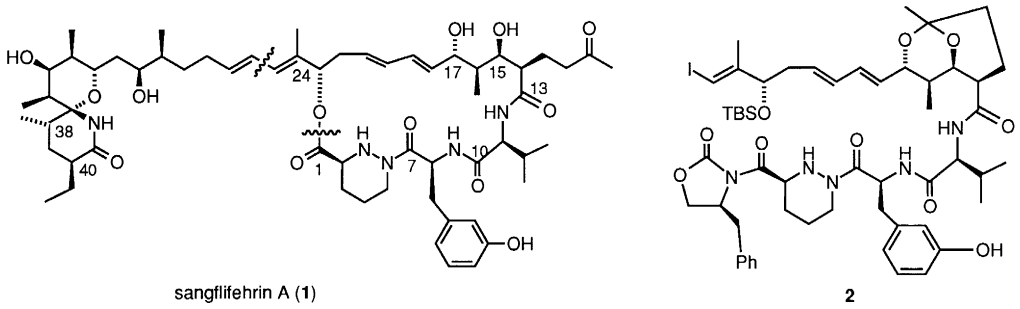
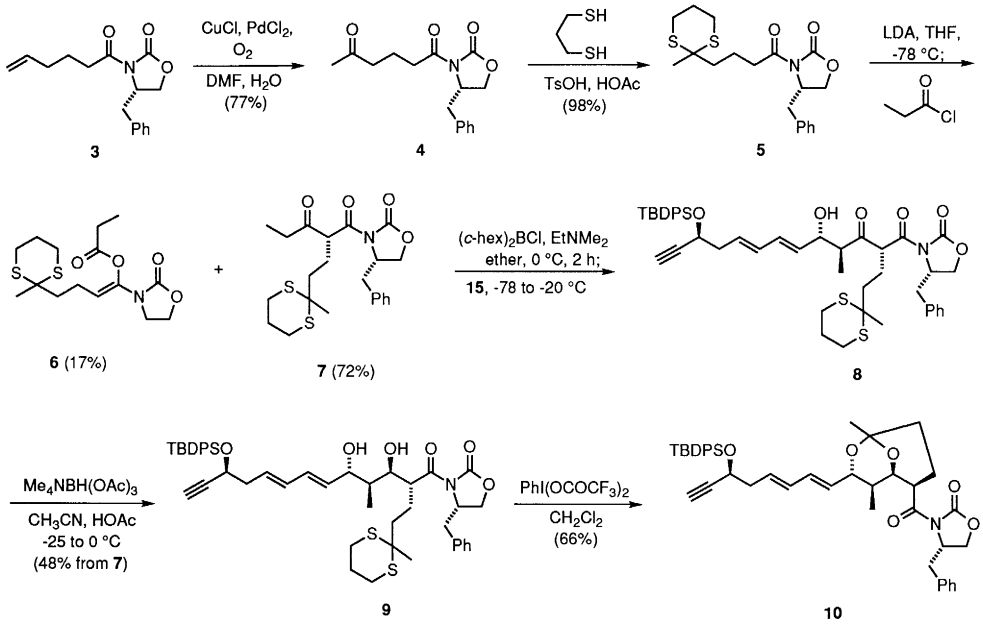


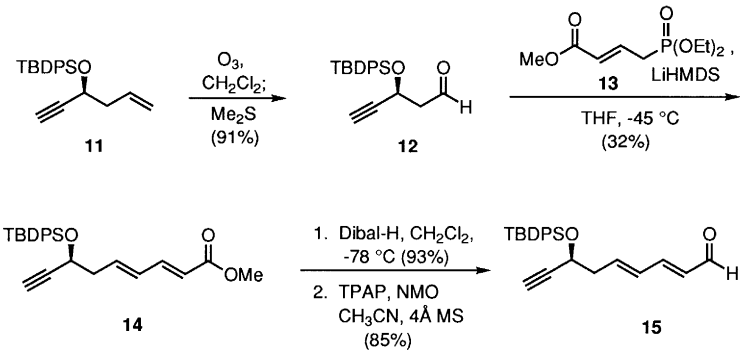
In a continuation of our synthetic plan,[3] which is to involve Stille coupling of the major molecular segments across C25 and C26 in the last step, the acetylenic diene acetal **10** was initially generated from the enantiopure oxazolidinone **3**[6] as summarized in Scheme 1. Thus, sequential Wacker oxidation and thioketal formation furnished **5** efficiently, thereby allowing for highly diastereoselective conversion to **7** by acylation of the lithium enolate with propionyl chloride. As anticipated from the prior observations of Evans,[7] the stereogenecity of **7** at the newly formed chiral center was not eroded during chromatographic purification due to the low kinetic acidity brought on by allylic strain effects.



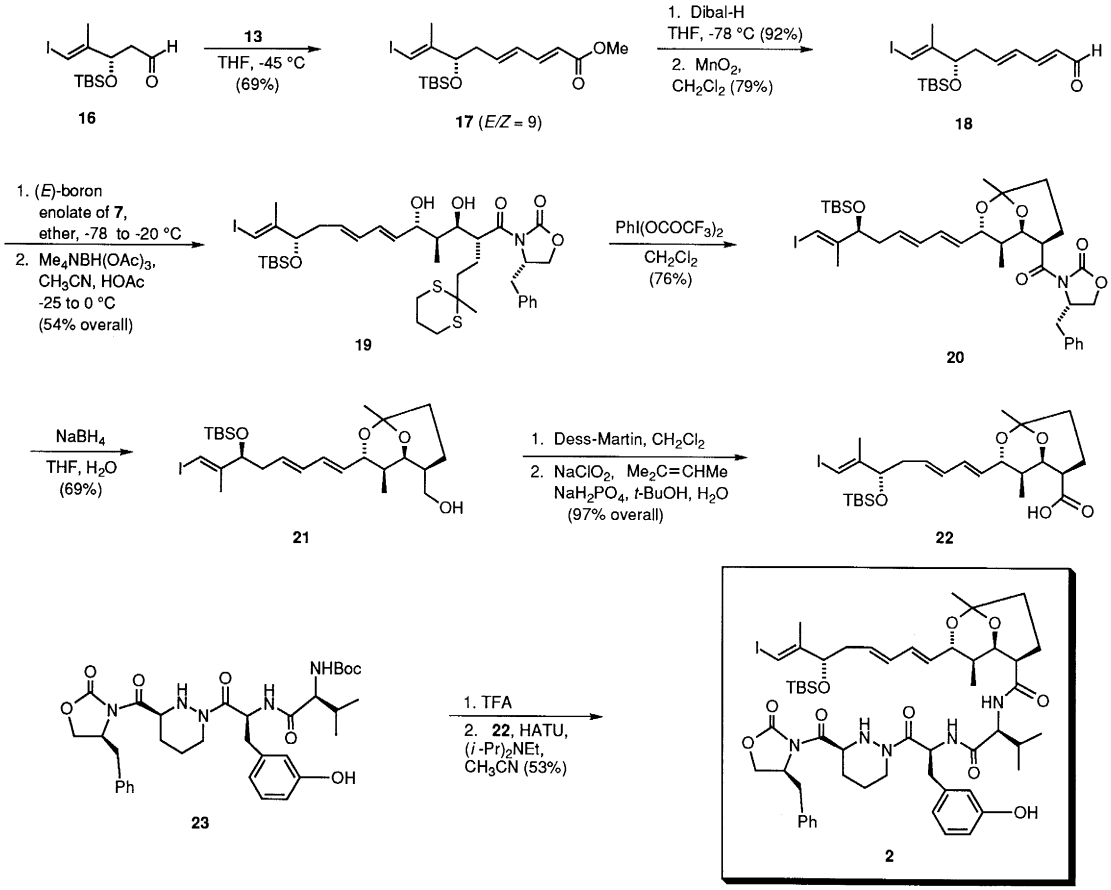
Scheme 1.

The ensuing convergent step required the availability of aldehyde **15**. To this end, easily accessible **11**[8] was subjected to ozonolysis and Wittig–Horner reaction with methyl 4-(diethylphosphono)crotonate as promoted by lithium hexamethyldisilazide (**13**, Scheme 2).[9,10] Chromatographic removal of the minor (2*E*,4*Z*) isomer gave rise to pure **14** (32%). Reduction of this ester with diisobutylaluminum hydride and perruthenate oxidation made available the required intermediate **15** in very good yield.

Formation of the (*E*)-boron enolate from treatment of **7** with chlorodicyclohexylborane and ethyldimethylamine[11] followed by the addition of **15** afforded the anti aldol **8**. Efficiency was improved if the workup conditions defined by Paterson[12] were implemented. Direct reduction of **8** with tetramethylammonium triacetoxyborohydride[13] served to complete elaboration of the four contiguous stereogenic centers and delivered **9** in 48% overall yield as the major product. Dethioacetalization of



Scheme 2.



Scheme 3.

9 with phenyliodine(III) bis(trifluoroacetate)[14] skirted troublesome problems encountered with other carbonyl unmasking protocols,[15] and emerged as the preferred route to **10** (66%). Our inability to carry **10** onward to **2** now surfaced from two directions: (a) the lack of a means to functionalize the terminal acetylenic functionality even under conditions where steric congestion was abated by removal of the silyl protecting group;[16] and (b) substantial reluctance on the part of the chiral auxiliary to undergo oxidative cleavage.[17] These complications caused us to install the vinyl iodide functionality from the very outset (Scheme 3).

The new approach began from the known aldehyde **16**,[18] which was homologated into **17** in the predescribed manner. Two-step reduction of **17** delivered **18** whose coupling to the (*E*)-boron enolate of **7** and stereocontrolled hydride reduction proceeded uneventfully as before. Once ketal **20** had been obtained by dethioacetalization, we were pleased to recognize that reduction with sodium borohydride in THF and water (3:1) as solvent[19,20] did indeed proceed regioselectively to furnish **21** in 69% yield. Two-step oxidation of this primary carbinol to carboxylic acid **22** was accomplished in notably efficient fashion (97%). In preparation for peptidic coupling, the previously synthesized **23**[3] was simultaneously freed of its Boc protecting group by stirring with trifluoroacetic acid. The final conjoining of **22** with unmasked **23**, accomplished with HATU[21] because of the hindered nature of the reacting components, gave rise to **2** in 53% overall yield.

The described chemistry not only opens up a possibly efficient entry to sanglifehrin A, but is expected to find useful application in analog synthesis.

Acknowledgements

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