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Synthesis of Streptolydigin, a Potent Bacterial RNA Polymerase Inhibitor

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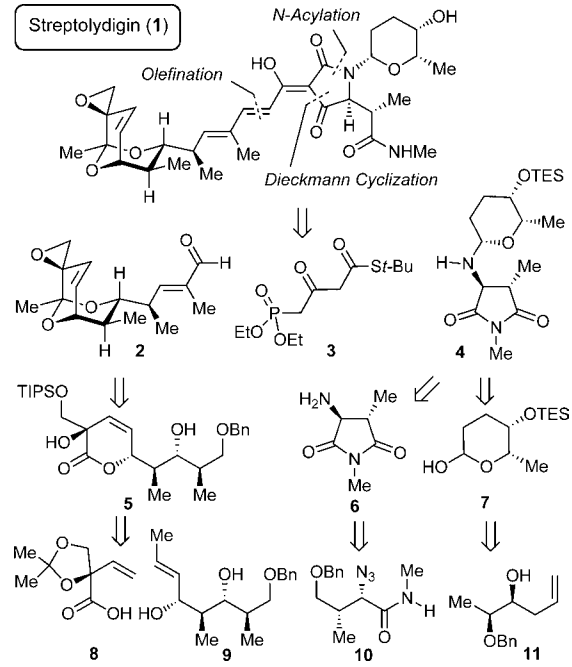
Abstract: Streptolydigin is a highly potent, broad-spectrum antibiotic produced by *Streptomyces lydicus*, which inhibits bacterial RNA polymerase. We describe the first synthesis of streptolydigin, which was assembled in a highly convergent and fully stereocontrolled fashion with a longest linear sequence of 24 steps starting from commercially available precursors. The assembly process entailed preparation of fully elaborated streptolic and ydiginic subunits of the natural product, followed by a highly efficient union in a three-step one-pot procedure, which included Dieckmann cyclization with a concomitant imide opening, Horner−Wadsworth−Emmons olefination, and desilylation.

In 1956, researchers from Upjohn described the isolation and broad-spectrum antibiotic activity of streptolydigin (**1**).[1] This natural product acts as a potent inhibitor of bacterial RNA polymerase (RNAP) by preventing the nucleotide triphosphate insertion step.[2,3] The biochemical mechanism of RNAP inhibition by streptolydigin is distinct from that of clinically used rifamycin antibiotics that are particularly important for treatment of tuberculosis.[4] The different mode of interaction of streptolydigin and rifamycins with RNAP results in essentially no cross-resistance[5] and is noteworthy in considering possible applications. The structure of streptolydigin was determined by the Rinehart group.[6] This seminal effort revealed the complex molecular architecture of the natural product, which is comprised of an epoxide-containing bicyclic ketal connected by a polyene spacer to a glycosylated, highly functionalized acyl tetramic acid (Scheme 1). Compared to other structurally related natural products, including tirandalydigin and tirandamycins,[7] streptolydigin has the most complex structure and highest antibacterial activity within this class of antibiotics.[8] While several syntheses of tirandamycins[9] and a protected form of tirandalydigin[10] have been reported, the solution of the streptolydigin synthetic problem has not been described despite the preparation of two separate degradation subunits known as streptolic and ydiginic acids.[11,10] In this communication, we present the first synthesis of streptolydigin, which was assembled with a longest linear sequence of 24 steps starting from commercially available precursors.

The initial disconnection of streptolydigin (**1**) was designed to unite three advanced fragments, including bicyclic aldehyde **2**, diethylphosphono-3-oxobutanthioate **3**,[12] and *N*-glycosyl imide **4** (Scheme 1). The assembly process would entail N-acylation of **4** with **3**, Dieckmann cyclization with a concomitant imide opening, which followed the pioneering work of Rinehart,[13] and Horner−Wadsworth−Emmons olefination, which was particularly successful during the assembly of tirandomycins.[9] The main challenge was to ensure that our assembly process would be compatible with the highly labile terminal epoxide moiety of

Scheme 1



aldehyde **2**. The bicyclic framework of **2** would be constructed from lactone **5**, which in turn would arise from esterification of acid **8** with diol **9**, followed by ring-closing metathesis. Imide **6** and protected rhodinose **7** would derive from acyclic precursors **10** and **11**, respectively.

The assembly process began with the preparation of unsaturated acid **8** (Scheme 2). Catalytic asymmetric dihydroxylation[14] of benzyl enoate **12**[15] proceeded in 92% ee. Acetalization of the resulting triol occurred chemoselectively at the primary and tertiary alcohols enabling the conversion of the remaining secondary alcohol into the corresponding triflate. Subsequent elimination with DBU and final saponification furnished carboxylic acid **8**. Preparation of diol **9** began with a diastereoselective aldol reaction of crotonaldehyde **13** with titanium enolate derived from benzyloxyketone **14**,[16] followed by the Evans−Tishchenko reduction[17] and saponification of the resulting acetate. Chemoselective acylation of diol **9** with acid **8** proceeded successfully using DCC and DMAP to give ester **15**. Removal of the acetonide and silyl protection of the primary alcohol afforded the diene, which underwent the ring-closing metathesis upon exposure to the Hoveyda−Grubbs catalyst **16**.[18] Lactone **5** was next converted into the Weinreb amide, which was treated with methyllithium and subjected to acid-mediated intramolecular ketalization to give the only expected bicyclic acetal **17**. Reductive cleavage of the benzyl ether, followed by oxidation and olefination, furnished ester **18**, which was subjected to DIBAL reduction, silylation of the resulting primary alcohol,

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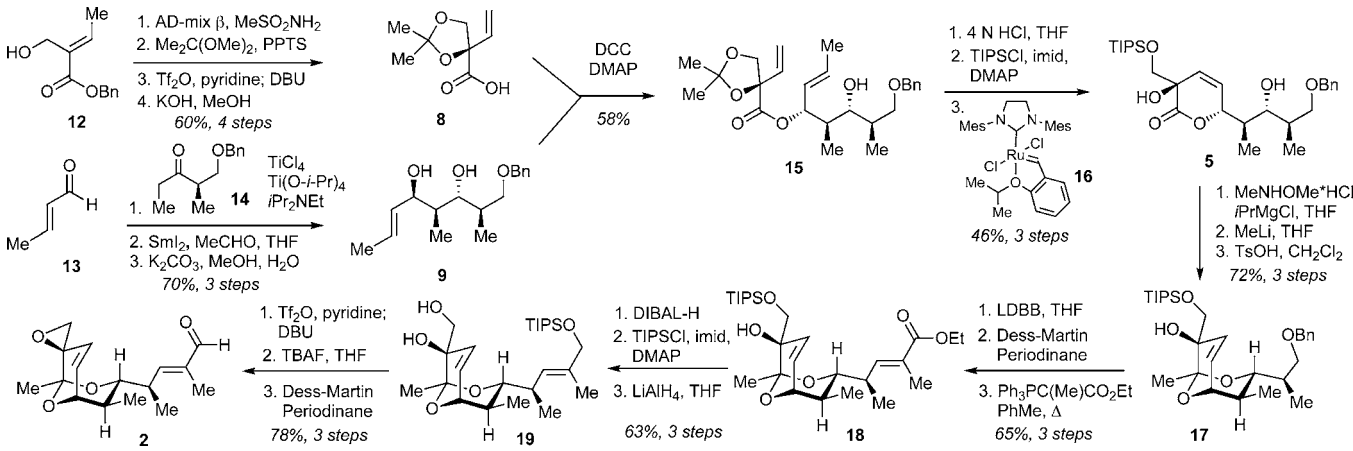
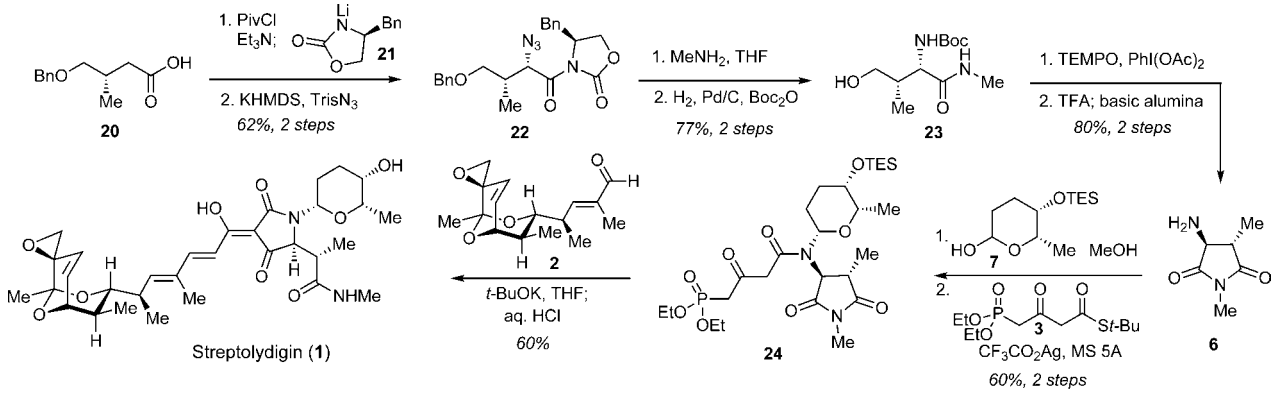
Scheme 2



Scheme 3



and chemoselective TIPS deprotection using $LiAlH_4$. Treatment of diol **19** with Tf_2O and pyridine, followed by DBU, induced efficient epoxide formation. Subsequent fluoride-mediated desilylation and Dess−Martin oxidation afforded aldehyde **2**.

Preparation of aspartimide **6** began with conversion of acid **20**[19] to the corresponding *N*-acyloxazolidinone, followed by diastereoselective azide transfer (Scheme 3).[20] Treatment of the resulting imide **22** with methylamine and hydrogenation in the presence of Boc_2O gave alcohol **23**, which underwent TEMPO-catalyzed oxidative cyclization and Boc-deprotection with TFA to afford the required primary amine **6**.

The end-game of the synthesis entailed diastereoselective N-glycosylation of imide **6** with rhodinose **7**,[21] followed by Ag-promoted N-acylation with thioate **3** to give phosphonate **24**.[12] Despite the reported preparation of a similar synthetic intermediate, which was converted to the tetramic acid fragment by the Boeckman group, no further elaboration has been described to date.[11a] After substantial effort, we found that treatment of the phosphonate **24** with *t*-BuOK (3 equiv), followed by the addition of aldehyde **2** and mild acidic workup, directly produced (−)-streptolydigin (**1**) as a result of sequential Dieckmann cyclization with concomitant imide opening, Horner−Wadsworth−Emmons olefination, and desilylation. Synthetic streptolydigin proved identical to the authentic sample of the natural product.[22] The ability to access this complex natural product in a fully synthetic manner sets the stage for the evaluation of the structure−activity relationship of streptolydigin for which only limited data are currently available[23] en route to potent and simplified synthetic antibiotics.

Supporting Information Available: Complete ref 3b and experimental details. This information is available free of charge via the Internet at http://pubs.acs.org.

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