Natural Products Synthesis

Stereocontrolled Total Synthesis of (+)-Streptazolin by a Palladium-Catalyzed Reductive Diyne Cyclization**

Barry M. Trost, Cheol K. Chung, and Anthony B. Pinkerton*

The palladium-catalyzed reductive diyne cyclization provides efficient access to dialkylidenecyclopentanes and -hexanes of defined geometry about the alkene.[1] Only one example of the synthetic utility of this atom-economic construction of dienes has recently been recorded with regard to a short synthesis of siccanin.[1b] To further demonstrate the efficiency of this approach, especially towards very sensitive 1,3-diene units, herein we describe the total synthesis of (+)-streptazolin, for which controlled generation of the delicate 1,3-diene constitutes a major challenge.

(+)-Streptazolin (**1**) is a lipophilic antibiotic, first isolated from cultures of *Streptomyces viridochromogenes* in 1981.[2] The tricyclic skeleton contains an internal urethane moiety, which is rarely found in natural products. Streptazolin exhibits only limited antimicrobial activities; however, structural variants such as 3,9-dihydrostreptazolin[2] and Diels–Alder adducts with naphthoquinones[3] show enhanced antimicrobial and cytotoxic activity. Owing to these biological properties as well as its interesting chemical structure, several studies have been reported aimed towards the synthesis of **1**[4–7] and related compounds.[8]

The first two reported syntheses of **1**[4,5] rely on Wittig reactions of a ketone to install the exocyclic ethylidene group which unfortunately gave a mixture of geometrical isomers and favored the undesired *E*-ethylidene stereoisomer. The third reported synthesis by Kibayashi and co-workers[6] utilizes an elegant enyne cycloisomerization[9] to construct the diene. This reaction, however, gave the 1,4-diene as the major product, which then had to be isomerized to the 1,3-diene by using an iron complex. A more recently reported synthesis[7] took advantage of another palladium-catalyzed reaction: an intramolecular reductive vinyl bromide–alkyne coupling reaction developed by Grigg.[10] This strategy, which required a number of functional-group modifications, suc-

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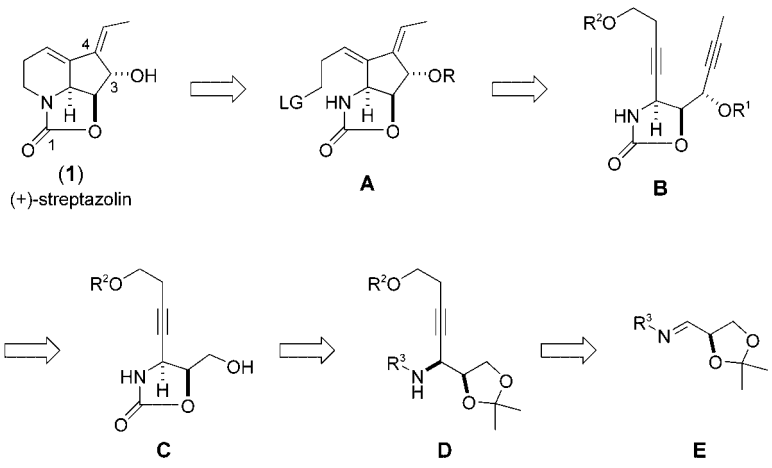
cessfully provided the desired 1,3-diene with the correct defined geometry.

Our goal was to provide a more efficient and atom-economical[11] approach to **1**, which is outlined in Scheme 1.



Scheme 1. Retrosynthetic analysis of (+)-streptazolin (**1**). LG = leaving group.

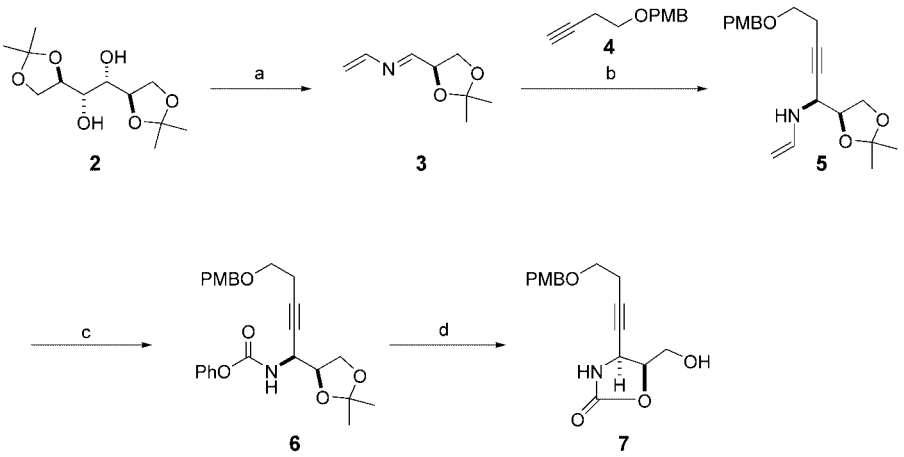
The target molecule **1** was envisioned to be obtained from the penultimate intermediate **A** through a cyclization of the oxazolidinone nitrogen center with an activated alcohol. The 1,3-diene **A** would come from the key palladium-catalyzed reductive diyne cyclization reaction of **B**, which itself results from the addition of an acetylide to an aldehyde derived from the alcohol **C**. The precursor of **C** would be a protected aminodiol **D**, which would come from the known imine derivative of D-glyceraldehyde acetonide **E**[12] in a series of straightforward steps.

The preparation of the oxazolidinone core of streptazolin is outlined in Scheme 2. Commercially available D-mannitol diacetonide (**2**) was subjected to oxidative cleavage with periodate followed by imine formation with allylamine.[13] The imine **3** was obtained in sufficiently pure form to be used in the subsequent reaction without further purification and was, therefore, treated directly with the metal alkynylide derived from the alkyne **4**.[14] Although the use of alkynyl Grignard reagents resulted in poor diastereofacial selection (< 2:1) and that of alkynyllithium trifluoroborate[15] showed rather capricious selectivity (2:1 ~ 12:1), the use of alkynyllithium trimethylaluminate[16] gave the desired Felkin–Anh adduct **5** with high diastereoselectivity and in good yield (13:1, 69%).

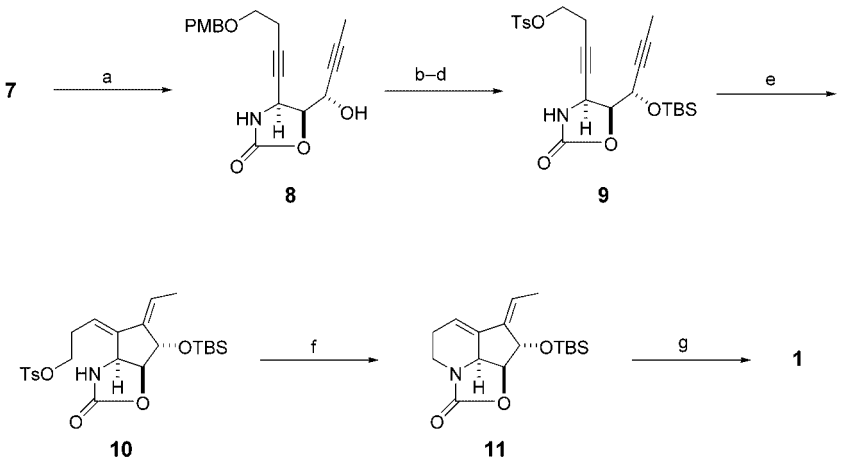
The protecting group of the amine (allyl group) needed to be removed at this stage because its cleavage would be problematic after the oxazolidinone was formed. The one-pot palladium-catalyzed removal of the allyl group[17] and formation of the carbamate gave **6** in nearly quantitative yield (Scheme 2). The carbamate **6** was, in turn, derivatized to the oxazolidinone compound **7** through sequential treatment with *p*-toluenesulfonic acid and potassium carbonate in methanol to give the oxazolidinone core in 88% yield after removal of the undesired diastereomer. These two sequences of one-pot procedures nicely circumvented the difficulty associated with the isolation of the polar compounds.

The alcohol **7** then needed to be oxidized to the corresponding aldehyde in the next step. Disappointingly, both Dess–Martin[18] and Moffatt–Swern[19] oxidation reactions were plagued with problems of epimerization and low yields after workup, presumably owing to the destabilization of the resultant aldehyde by the neighboring electronegative oxazolidinone group. The reaction mixture from the Moffatt–Swern oxidation reaction was treated directly with an excess amount of propynyl magnesium bromide in the presence of zinc chloride at low temperature to give a diastereomeric mixture (6:1) of the secondary alcohol **8** in 50% yield (Scheme 3).[20,8c] The two diastereomers were easily separated by flash chromatography after protection of the secondary alcohol as a silyl ether. The relative stereochemistry of the major diastereomer was unclear at this stage but was later confirmed (at the completion of the synthesis) to be the desired chelation-controlled product (Scheme 3). Interestingly, the use of an alkynyllithium–trimethylaluminate complex, which is known to favor Felkin–Anh addition, also gave the chelation-controlled product as the major diastereomer (≈4:1). This indicates that the Felkin–Anh mode of addition is unfavorable, even in the absence of a chelating metal species, owing to the steric hindrance by a neighboring substituent, which stretches along the trajectory of the incoming nucleophile (Scheme 4).

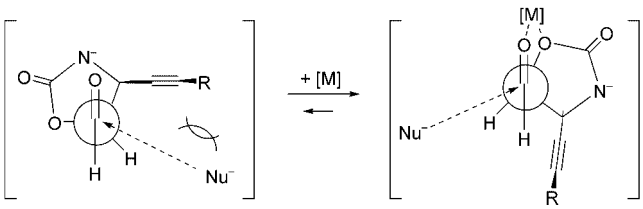
Deprotection of the PMB ether in **8**, followed by tosylation of the resultant primary alcohol, gave the diyne **9**, which set the stage for the crucial palladium-catalyzed reductive cyclization reaction (Scheme 3). Compound **9** was subjected to our standard



Scheme 2. Stereoselective construction of oxazolidinone core of **1**. Reagents and conditions: a) $NaIO_4$, H_2O, 0 °C; allylamine, 1,2-dichloroethane, 0 °C → RT, 95%; b) **4**, *n*BuLi, Me_3Al, toluene, −78 °C, then **3**, −78 °C → RT, 69%, d.r. = 13:1; c) $[Pd(dba)_2]$, dppb, 2-thiosalicylic acid, THF, 60 °C, then PhOCOCl, aqueous $NaHCO_3$, room temperature, 99%, d.r. = 13:1; d) *p*-TsOH, methanol, then K_2CO_3 (solid), room temperature, 88%. PMB = *p*-methoxybenzyl, dba = dibenzylideneacetone, dppb = 1,4-bis(diphenylphosphanyl)butane, Ts = *p*-toluenesulfonyl.



Scheme 3. Total synthesis of (+)-streptazolin. Reagents and conditions: a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, then $ZnCl_2$, −78 °C, propynyl magnesium bromide, THF, −78 °C→RT, 50%, d.r. = 6:1; b) TBSCl, imidazole, CH_2Cl_2, room temperature, 75% (+13% C3 epimer); c) DDQ, aqueous CH_2Cl_2, 0 °C→RT, 93%; d) *p*-TsCl, pyridine, 0 °C→RT, 75%; e) $[Pd_2(dba)_3{\cdot}CHCl_3]$, HCO_2H, Et_3SiH, toluene, room temperature, 64%; f) NaH, THF, 0 °C→RT, 84%; g) TBAF, THF, 0 °C, 99%. DMSO = dimethylsulfoxide, TBSCl = *tert*-butyldimethylsilyl chloride, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBAF = tetra-*n*-butylammonium fluoride.



Scheme 4. Proposed explanation for the stereoselectivity.

"ligandless" reductive cyclization conditions ($[Pd_2(dba)_3{\cdot}CHCl_3]$ 2.5%, HCO_2H, Et_3SiH, toluene, 80 °C) to provide the desired diene **10** in 61% yield. The nature of the primary alcohol group had a dramatic impact on the efficiency of the process. The reductive cyclization of the free alcohol or the mesylate, instead of the tosylate, yielded the corresponding diene products in only 15 and 41%, respectively. Lowering the reaction temperature to 23 °C gave a slightly higher yield of **10** (64%) along with some unconverted starting material **9** (7%).

Finally, an intramolecular cyclization through nucleophilic displacement of the tosylate **10** to form the third ring of the structure was required. The cyclization reaction took place smoothly in the presence of sodium hydride, and treatment of the resulting tricyclic compound **11** with TBAF gave the natural product (+)-streptazolin in near-quantitative yield. The spectroscopic data of the product prepared herein were indistinguishable from those reported in the literature,[6] and the specific rotation, $[\alpha]_D^{24} = +18.43$ ($c = 0.16$, $CHCl_3$), was also in good agreement ($[\alpha]_D^{23} = +22$ ($c = 2.8$, $CHCl_3$)).[2]

In conclusion, the total synthesis of (+)-streptazolin was performed in 11 steps starting from D-mannitol diacetonide. Our synthesis features a palladium-catalyzed reductive cyclization reaction of a diyne as the key step. The diyne precursor was constructed stereoselectively from the sequential additions of alkynylides to a chiral imine and aldehyde. The current strategy is atom economical and efficiently addresses the problems associated with the location and geometry of the double bonds. This synthesis also highlights the utility of the palladium-catalyzed cycloreduction reaction in the construction of complex and labile molecules.

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