Total synthesis of (+)-streptazolin

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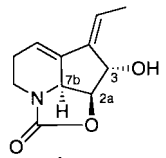
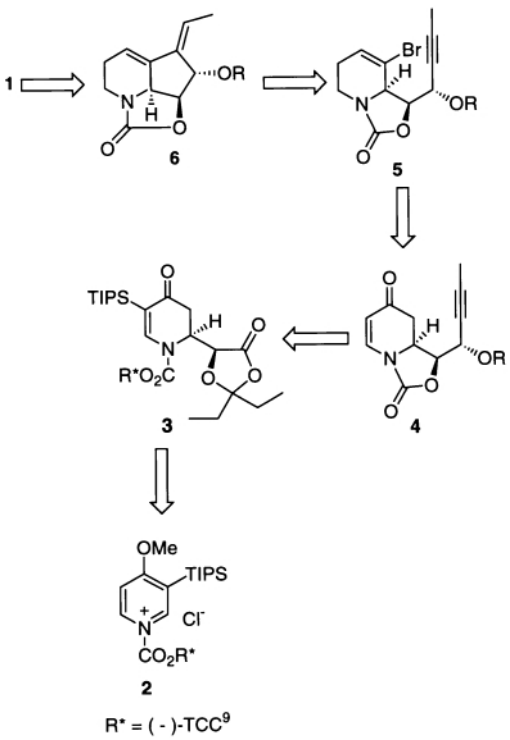
The first chiral auxiliary mediated asymmetric synthesis of (+)-streptazolin has been accomplished in 13 steps and with a high degree of stereocontrol.

Streptazolin **1** was first isolated from cultures of *Streptomyces viridochromogenes* by Drautz *et al.* in 1981.[1] Streptazolin and a derivative, 3,9-dihydrostreptazolin, were found to exhibit antibacterial and antifungal properties.[1,2] Some naphthoquinone Diels–Alder adducts of **1** have been reported to have



1
(+)-streptazolin

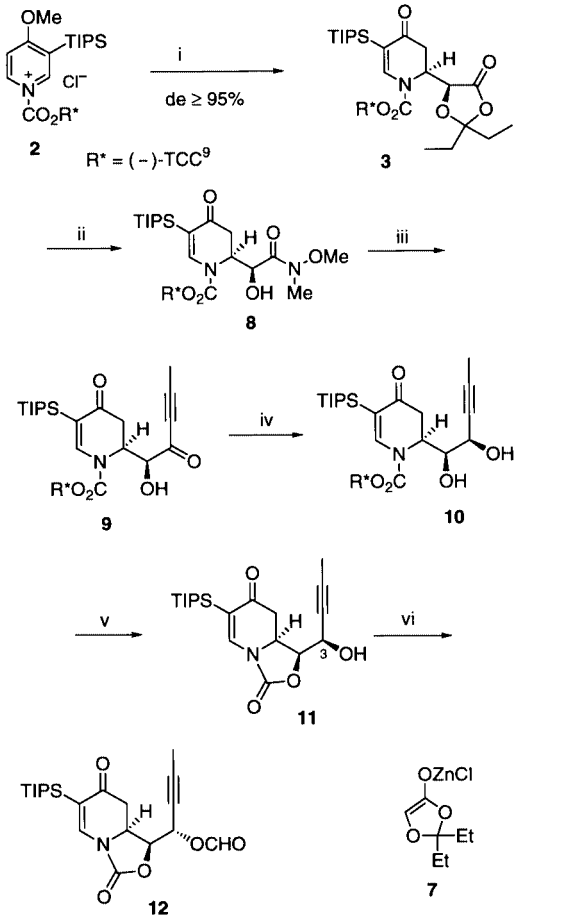
striking bactericidal, fungicidal and protozoacidal activities, as well as antitumor activity similar to adriamycin on leukemia L1210 cells.[3] The unique structure of the natural product, and its interesting biological activities, have stimulated synthetic efforts that resulted in three total syntheses. Kozikowski and Park[4] reported a racemic synthesis of **1**, and Flann and Overman[5] completed an enantioselective synthesis starting from L-tartaric acid. Recently, Kibayashi and coworkers[6] reported a total synthesis of (+)-streptazolin also starting from L-tartaric acid.



Scheme 1 Retrosynthetic analysis.

As part of a program directed at synthesizing alkaloids using enantiopure *N*-acyldihydropyridones as chiral building blocks,[7] we developed a strategy for the first chiral auxiliary mediated asymmetric synthesis of (+)-streptazolin. In addition to effectively installing the required stereocenters, the direct incorporation of the diene system of **1** in a regio- and stereo-controlled manner was given high priority. Metallo-enolate addition to chiral 1-acylpyridinium salts is a useful method for the enantioselective synthesis of 2-substituted piperidines containing functionality and stereocenters in the C-2 side chain[8] The piperidine core of streptazolin, with its highly functionalized cyclopentane apendage, seemed to be an attractive target for this recently developed methodology. We now report a concise and highly stereocontrolled asymmetric synthesis of **1**.

Our synthesis plan was based on the retrosynthetic analysis depicted in Scheme 1. The enantiopure *N*-acyldihydropyridone **3**, prepared from chiral pyridinium salt **2**, would be converted to bicyclic carbamate **4**. Through a bromination/reduction/elim-



Scheme 2 *Reagents and conditions*: i, **7** (3 equiv.), THF, −78 °C, 3 h, then 10% HCl, 76%; ii, MeONHMe–HCl, $AlMe_3$, CH_2Cl_2, 25 °C, 1 h, 95%; iii, prop-1-ynyllithium (2.5 equiv.), THF, −78 → −15 °C, 1 h, 84%; iv, $NaBH_4/CeCl_3$, MeOH, −50 °C, 95%; v, NaH (2.2 equiv.), THF, 25 °C, 6 h, 81%; vi, formic acid, DEAD, PPh_3, THF, 64%.

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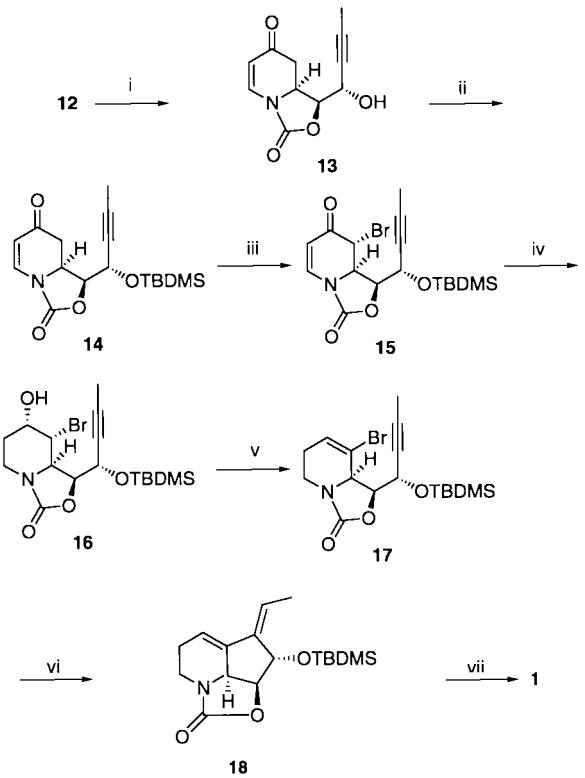
ination sequence, vinyl bromide **5** would be prepared from **4**. At this stage, an intramolecular palladium-catalyzed cyclization would be used to give streptazolin precursor **6**, which contains the diene in the proper position and with the required stereochemistry. Removal of the alcohol protecting group would provide **1**.

The 1-acylpyridinium salt **2**[9] was treated with zinc enolate **7**[8] to afford dihydropyridone **3** in 76% yield (Scheme 2).† Conversion of **3** to Weinreb's amide **8** proceeded in excellent yield using standard conditions.[8,10] Addition of propynyllithium[11] (2.5 equiv.) to **8** provided ketone **9**, which was reduced under Luche conditions to afford diol **10** (> 95% de) in high yield.[12] The presence of the bulky C-5 TIPS group allowed the previous three steps to be carried out without serious side reactions at the enone functionality. Treatment of **10** with sodium hydride (2.2 equiv.) effected cyclization to give bicyclic carbamate **11** with concomitant release of the chiral auxiliary, (−)-TCC[13] (93% recovery). The C-3 secondary alcohol in **11** has the wrong stereochemistry for the natural product. This stereogenic center was inverted using the Mitsunobu reaction to provide formate ester **12**. The key intermediate **14** was prepared in good yield from **12** in three steps by removing the TIPS group through protodesilylation using formic acid, cleaving the formate ester with refluxing methanol, and reprotecting the hydroxyl as its TBDMS ether (Scheme 3). At this stage, conversion of dihydropyridone **14** to vinyl bromide **17** was needed. Bromination of the lithium enolate of **14** with NBS gave exclusively the desired *trans*-bromide **15**. Reduction of the enone moiety with K-Selectride (2 equiv.) provided the *cis*-bromohydrin **16** *via* a one-pot reaction.[14] After considerable effort, conditions were found to convert **16** into vinyl bromide **17**. This was carried out by first forming the corresponding triflate and then effecting a regioselective anti-elimination *in situ* with DBU to afford a good yield of **17** as the only vinyl bromide isolated.[15] This intermediate contains three contiguous stereocenters with the correct configuration for the natural product, and the alkyne and vinyl bromide are properly positioned for a palladium-catalyzed cyclization. Subjection of **17** to Grigg's conditions[16] effected ring closure to give the desired diene **18**. Cleavage of the silyl protecting group with fluoride provided the labile natural (+)-streptazolin **1** in near quantitative yield. Our synthetic **1** exhibited spectral data in agreement with reported data for authentic material.[6] The optical rotation, $[\alpha]_D^{22}$ = + 20.6 (*c* = 0.15, $CHCl_3$), is also in agreement with the literature value, $[\alpha]_D^{23}$ = + 22 (*c* = 2.8, $CHCl_3$).[6]



Scheme 3 *Reagents and conditions*: i, formic acid, reflux, 2 h, then MeOH, reflux, 3 d, 88%; ii, TBDMSCl, imidazole, DMF, 83%; iii, LiHMDS (1.1 equiv.), THF, −78 → −40 °C, NBS (1.1 equiv.), 84%; iv, K-Selectride (2 equiv.), THF, −78 °C, 30 min., 58%; v, Tf_2O (1.1 equiv.), CH_2Cl_2, pyridine (5 equiv.), 25 °C, 4 h, then DBU (5 equiv.), 25 °C, 10 h, 79%; vi, $Pd(OAc)_2$/TPP (cat.), sodium formate, THF, 130 °C (sealed tube), 20 h, 50%; vii, TBAF, THF, 0 °C, 30 min., 95%.

In summary, the first chiral auxiliary mediated asymmetric synthesis of (+)-streptazolin **1** has been accomplished in 13 steps and with a high degree of stereocontrol. The piperidine ring and two of the required stereocenters were introduced in one step using a metallo-enolate addition to chiral pyridinium salt **2**. Other key features are the use of a TIPS group to protect an enone moiety, and the regio- and stereo-specific construction of the diene system using a palladium-catalyzed vinyl bromide/alkyne cyclization.

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Notes and references

† Satisfactory IR, ^1H and ^{13}C NMR, HRMS or microanalyses were obtained for all compounds described.

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