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Synthetic Application of Acylnitroso Diels−Alder Derived Aminocyclopentenols: Total Synthesis of (+)-Streptazolin

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Concise total syntheses of (+)-streptazolin **1** and its more stable dihydro derivative **2** were accomplished via an intramolecular aldol condensation strategy starting from readily available aminocyclopentenol (−)-**7**. The synthetic sequence included reductive amination, stereoselective epoxidation, intramolecular aldol (and condensation) reaction, and Wittig reaction. The overall yield for dihydro derivative **2** from aminocyclopentenol (−)-**7** was about 7% for a total of 14 steps.

Introduction

Streptazolin (+)-**1** (Figure 1) was isolated from cultures of *Streptomyces viridochromogenes* for the first time in 1981 by Drautz and Zähner and later rediscovered by chemical screening of *Streptomyces luteogriseus*[1] and a high-producing strain of *Streptomyces*.[2] This lipophilic neutral tricyclic compound, which possesses an unusual ring system embodying an internal urethane unit and an exocyclic ethylidene side chain, has been shown to possess antibiotic and antifungal activities.[3] As reported, the isolation and purification of this antibiotic were markedly complicated by its propensity to polymerize upon concentration from organic solutions. However, hydrogenation of streptazolin affords a stable dihydro product, whose crystalline acetate **2** was employed in much of the structural investigations.[4] Puder et al.[5] recently reported the isolation of some co-secondary metabolites from *Streptomyces sp.* along with streptazolin, including 13-hydroxystreptazolin **3** and 5-*O*-(β-D-xylopyranosyl)streptazolin **4**, which have significant cytostatic activity against several human cancer cell lines. The unique structural features of **1**, as well as its promising biological activity profile, have thus far led to four total syntheses.[6−9] The first racemic total synthesis of **1** was reported by Kozikowski and Park.[6] Overman and Flann[7] completed an enantioselective synthesis of **1** starting from L-tartrate via a ring-closing reaction between the *N*-acyliminium cation and the vinylsilane species for construction of the azabicyclo[4.3.0] framework. Kibayashi and co-workers[8] also reported an enantioselective synthesis of **1** starting from L-tartrate by taking advantage of a palladium-mediated ring-closure reaction. In addition, a chiral auxiliary-mediated asymmetric synthesis of **1** was recently published by Comins and Huang.[9] As part of a project directed at synthetic applications of enantiopure versatile intermediate aminocyclopentenol (−)-**7** and its acetate derivative (−)-**8**,[10] we report herein a highly efficient chemoenzymatic asymmetric synthesis of (+)-streptazolin via an intramolecular aldol condensation strategy starting from aminocyclopentenols (−)-**7**.

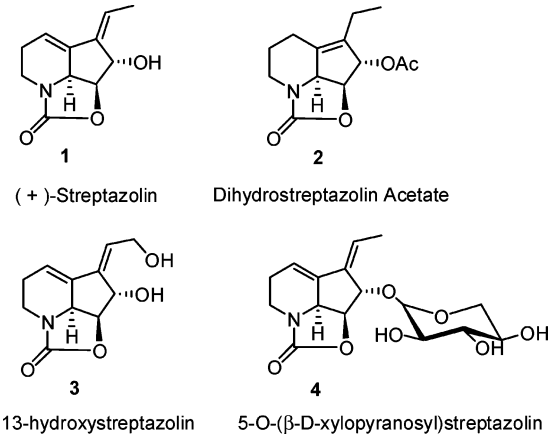

FIGURE 1. Structures of dihydrostreptazolinacetate, streptazolin, and co-secondary metabolites.

Results and Discussion

Our synthesis was based on a highly efficient and practical chemoenzymatic synthesis of enantiopure aminocyclopentenols developed in our group.[10,11] Cycloadduct

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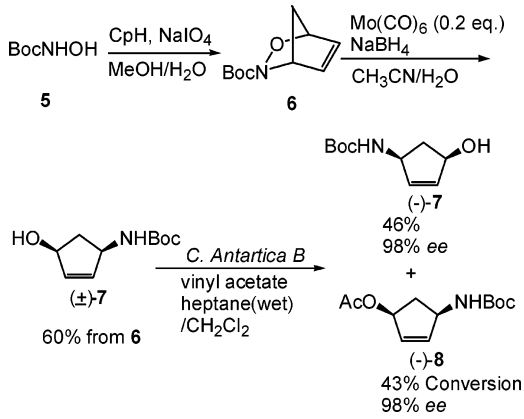
SCHEME 1

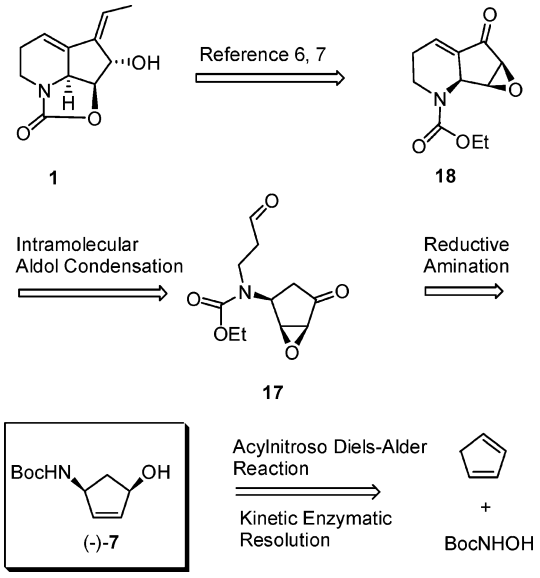


6 was obtained from hetero-Diels−Alder reaction of cyclopentediene with transient acylnitroso species derived from *in situ* oxidation of Boc-hydroxylamine. N−O bond reduction with substoichiometric $Mo(CO)_6$ afforded racemic *cis*-4-aminocyclopent-2-en-1-ol (±)-**7** in 60% yield in three steps. Kinetic resolution of racemic alcohol (+)-**7** was achieved by using commercially available immobilized *Candida antartica* B lipase. With this immobilized enzyme, the enantiopure acetate (−)-**8** and alcohol (−)-**7** were obtained in 43%, and 46% yield, respectively, with 98% ee after recrystallization. This protocol worked well on tens of grams scale and the resin-bound enzyme could be easily recovered and reused (Scheme 1).

With aminocyclopentenol (−)-**7** in hand, we envisioned that the piperidine core of streptazolin enone **18**, the final stage intermediate in both the Overman and Kozikowski syntheses, could be obtained from aldehyde ketone **17** via an intramolecular aldol condensation strategy. Epoxyketone **17** could be derived from the aminocyclopentenol (−)-**7** through the installation of an *N*-propanol moiety, epoxidation, and oxidation of the diol. With the epoxide enone **18**, the synthesis of (+)-streptazolin could be completed easily by the three-step sequence developed earlier by Kozikowski and Overman[6,7] (Scheme 2).

As shown in Scheme 3, our synthesis began with treatment of (−)-**7** with acetic anhydride and imidazole in methylene chloride to afford **9** in 96% yield. Allylic acetate **9** was converted to secondary amine **11** in 69% yield by a stepwise reductive amination procedure developed by Abdel-Magid.[12] This one-pot reductive amination reaction involved preformation of the imine, followed by *in situ* reduction with sodium borohydride. On the other hand, the common direct reductive amination procedure[12] was found to give significant amounts of dialkylated products. *N*-Alkylated amine **11** was then treated with ethyl chloroformate in 1:1 methylene chloride and pyridine to provide ethyl-carbonate protected amine **12** in 90% yield. Removal of the TBS group of **12** afforded alcohol **13** in 96% yield. Deprotection of acetate **13** gave diol **14** quantitatively, without formation of any potential cyclic carbamate byproduct. Treatment of allylic alcohol **14** with m-CPBA and $NaHCO_3$ in methylene chloride at room temperature induced stereoselective

SCHEME 2



epoxidation to produce epoxide **15** as a single diasteromer in 92% yield. The configuration of the epoxide was confirmed based on the comparison of spectroscopic data and specific rotation of enone **18** and our final synthetic dihydro acetate **2** to those reported in the literature.[4,7] The oxidation of epoxide diol **15** with Swern oxidation conditions provided the desired epoxy ketone **17** and simultaneously formed intramolecular aldol product **16** in a ~3:1 ratio in 82% total yield.

Since the major stereochemical issues were addressed by our very convenient synthetic route to epoxide ketone **17**, an efficient method for intramolecular aldol condensation was pursued. Initial studies showed that a series of common acidic and basic conditions failed to afford the intramolecular aldol condensation product, enone **18**.[13] Exposure to excess alumina (Al_2O_3) was reported to be a very mild method to obtain intramolecular aldol dehydration products[14a] and intramolecular aldol products.[14b] Therefore, epoxy ketone **17** was treated with excess alumina (30 equiv of Al_2O_3) in methylene chloride at room temperature for 8 h. The desired enone **18** and aldol product **16** were obtained cleanly in a combined 76% yield in a 8:5 ratio after simple filtration and chromatography (Scheme 4). Although the reaction could be pushed completely to enone **18** by adding more Al_2O_3 and using a longer reaction time (24 h), the yield dropped to around 50%. We also found that treatment of epoxy ketone **17** with L-proline in DMSO at room temperature provided enone **18** and aldol product **16** in a 1:1 ratio with a total yield of 60%. Aldol product **16** was then converted to enone **18** in 78% yield by a one-pot mesylation and base-induced dehydration reaction (Scheme 4).

With epoxy enone **18** in hand, the synthesis of (+)-streptazolin was first accomplished by the three-step

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(13) Conditions we investigated for intramolecular aldol condensation of compound **17** include acidic conditions (10 mol % of CSA, reflux in benzene for 4 h, compound **17** was recovered; 10 mol % of TsOH, reflux in benzene, compound **17** was recovered (reflux in toluene overnight resulted in decomposition)) and basic conditions (1 N NaOH, THF, decomposed; *t*-BuO K, *t*-BuOH/THF, decomposed).

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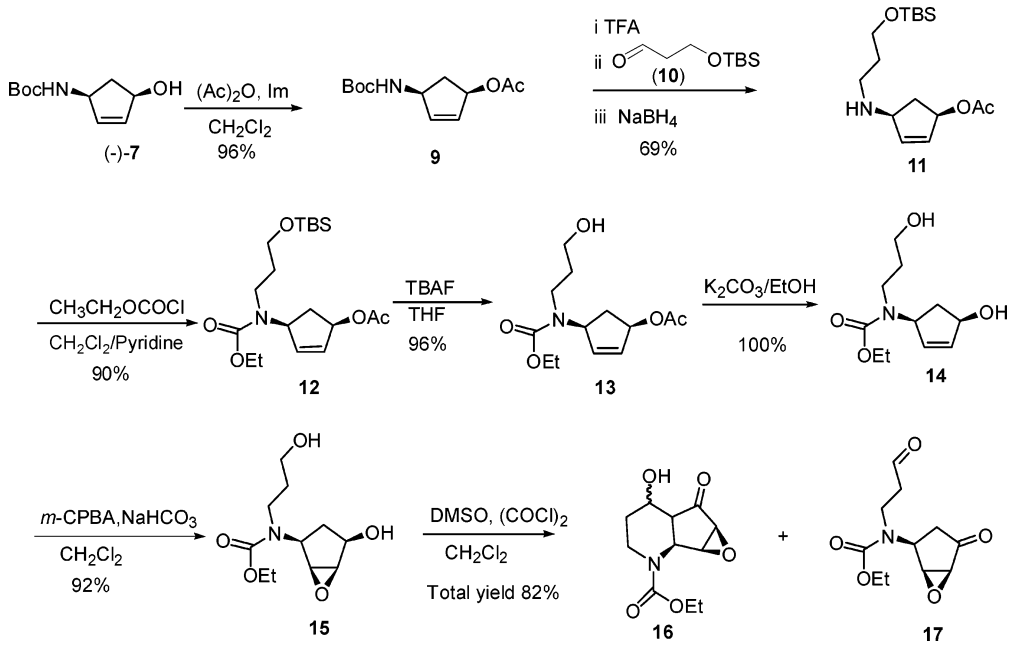
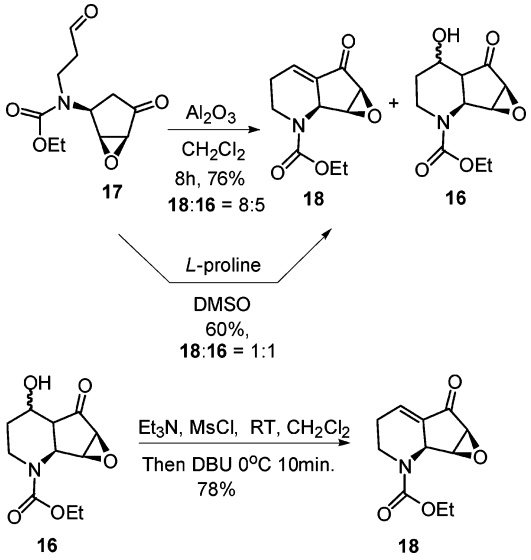
SCHEME 3



SCHEME 4



sequence developed earlier by Kozikowski and Overman[6,7] (Scheme 5). Thus, **18** was treated with ethylidenetriphenylphosphorane, and *n*-BuLi to provide **19** as a 1.5:1 *E*/*Z* mixture (literature 2:1) in 68% yield. The mixture then was treated 25% AcOH/NaOAc to provide a mixture of **20** and its *E*-ethylidene stereoisomer **21** in 70% total yield. Although we found that compounds **20** and **21** were hard to separate,[6b] a few milligrams (~5 mg) of a mixture of compounds **20** and **21** were separated by HPLC (30% EtOAc in hexanes) to provide ^{1}H NMR data for **20** and **21** as pure isomers, respectively. The mixture of compounds **20** and **21** was then treated with 5% NaOMe/MeOH to provide a mixture of (+)-streptazolin **1** and its *E*-ethylidene stereoisomer **22** in 71% total yield. Since it has been found that these materials partially decomposed upon isolation,[6,7] the enantiomeric purity of our product was ascertained after hydrogenation and acetylation to yield the stable crystalline dihydro acetate **2**. Compound **2** was confirmed by comparison of spectroscopic data and specific rotation to those reported in the literature for this natural product.[4]

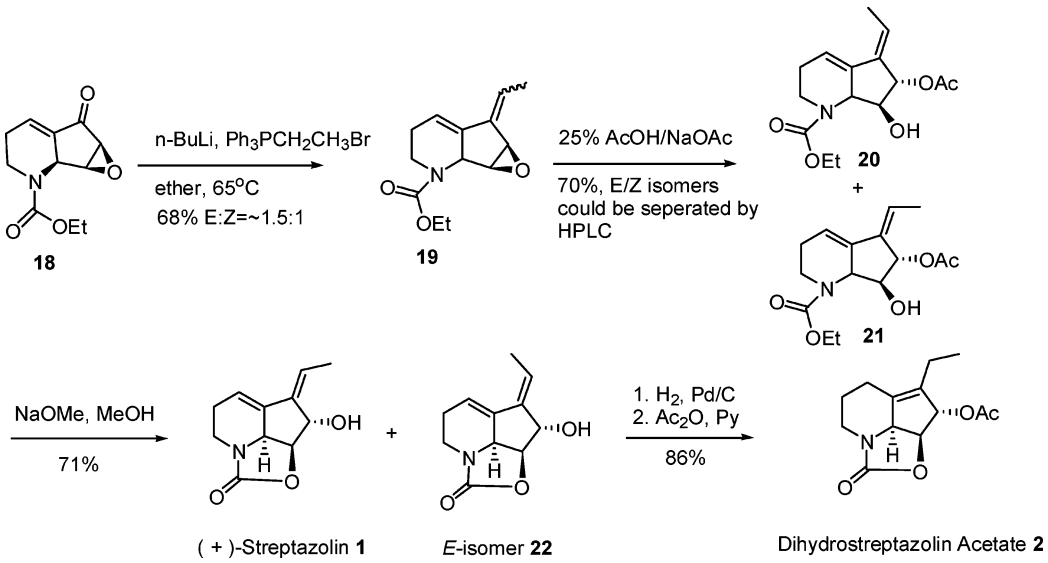
Conclusion

In summary, the highly efficient and enantioselective total synthesis of the structurally unusual antibiotic (+)-streptazolin **1** and its more stable dihydro derivative **2** was accomplished by using an intramolecular aldol condensation strategy based on the development of a concise, inexpensive chemoenzymatic synthesis of enantiopure aminocyclopentenols. The overall yield for dihydro derivative **2** from readily available aminocyclopentenol (−)-**7** was about 7% for a total of 14 steps. Significantly, this synthetic exercise demonstrates a new synthetic application for the versatile enantiopure aminocyclopentenol building block. Further investigation of stereoselective installation of the ethylidene side chain of (+)-streptazolin and total syntheses of streptazolin's co-secondary metabolites **3** and **4** are currently in progress. The results will be disclosed in due course.

Experimental Section

(1*R*,4*S*)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol (7) and (1*S*,4*R*)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol-1-*O*-acetate (8). Alcohol (±)-**7**[10a] (12.74 g, 63.94 mmol) was dissolved in CH_2Cl_2 (170 mL). Water saturated *n*-heptane (480 mL), then vinyl acetate (20 mL, 217 mmol) and immobilized *Candida antarctica* B lipase (1.7 g, Boerhinger Mannheim; c-*f*, c-*3*) were added. The mixture was shaken (with monitoring by TLC and ^{1}H NMR) for 2.3 h at a rate fast enough to ensure mixing of the heterogeneous reaction, then gravity filtered to remove the carrier-fixed enzyme. The carrier-fixed enzyme was recovered for later reuse. At this point, ^{1}H NMR analysis indicated that the reaction had reached ~43% conversion. The filtrate was concentrated under reduced pressure and chromatographed on silica (20−75% EtOAc in hexanes) to give alcohol (−)-**7** (7.09 g, 29.41 mmol) and acetate (−)-**8** (6.31 g, 26.20 mmol) as white solids. Alcohol (±)-**7**: yield 46% with 98% ee (after recrystallization from

SCHEME 5



hexanes/EtOAc at 0 °C, enantiomeric excess was determinated by ^{19}F NMR of its Mosher ester derivatives); $[\alpha]^{20}_D$ −69.0 (*c* 1.0, $CHCl_3$); physical properties and spectral data were identical with those of racemic (±)-**7**. Acetate **8**: yield 41% with 98% ee (after recrystallization from hexanes at room temperature, enantiomeric excess was determinated by ^{19}F NMR of its Mosher ester derivative); $[\alpha]^{20}_D$ −22.6 (*c* 0.4, $CHCl_3$); mp 56.5−58.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.37 (s, 9 H), 1.45 (dt, J = 13.5, 6.0 Hz, 1 H), 1.98 (s, 3 H), 2.68 (dt, J = 13.5, 7.5 Hz, 1 H), 4.38 (m, 1 H), 5.40 (m, 1 H), 5.81 (dt, J = 5.4, 2.1 Hz, 1 H), 5.90 (m, 1 H), 7.11 (d, J = 7.5 Hz, 1 H); ^{13}C NMR (300 MHz, DMSO-d_6) δ 20.8, 28.2, 37.6, 53.3, 77.1, 77.8, 130.9, 137.3, 154.9, 170.1; HRMS [MH$^+$] calcd for $C_{12}H_{20}NO_4$ 242.1392, found 242.1382.

(1*R*,4*S*)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol-1-*O*-acetate (9). To a solution of alcohol (−)-**7** (3.07 g, 15.41 mmol) in CH_2Cl_2 (10 mL) was added imidazole (1.68 g, 24.67 mmol) at room temperature. The reaction mixture was cooled to 0 °C, and then acetic anhydride (2.91 mL, 30.78 mmol) was added slowly. The resultant reaction mixture was stirred at room temperature overnight, then was diluted with CH_2Cl_2 (30 mL) and washed with 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave crude product. Flash chromatography (EtOAc:hexanes 1:3) afforded **9** (3.55 g, 14.73 mmol) as a white solid. Yield: 96%, 99% ee (after recrystallization from hexane); $[\alpha]^{20}_D$ +23.2 (*c* 1.0, $CHCl_3$); physical properties and spectral data are identical with those of the enantiomer **8**.

(1*R*,4*S*)-4-[*N*-(*tert*-Butyldimethylsilanyloxy)propylamino]-2-cyclopenten-1-ol-1-*O*-acetate (11). To a solution of acetate **9** (2.6 g, 10.79 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (6 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h. TLC showed all starting material was consumed. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with 10% Na_2CO_3 solution (30 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were dried over $MgSO_4$ (it is important that the pH value of the aqueous layer should be >10, if not, more 10% Na_2CO_3 should be added to adjust pH). Filtration and concentration under reduced pressure gave the crude amine product (1.43 g) as a light yellow oil. The residue was dissolved in dry CH_2Cl_2 (10 mL). To this solution was added aldehyde **10**[15] (2.02 g, 10.79 mmol) in CH_2Cl_2 (10 mL) at 0 °C under Ar atmosphere, slowly. The mixture was stirred at room temperature for 6 h, then 4 Å molecular sieves (200 mg) were added. The reaction mixture was stirred for another 15 min at room temperature. $NaBH_4$ (0.6 g, 16 mmol) was added to the reaction mixture, followed by MeOH (10 mL) immediately. The reaction mixture was stirred for 10 min and quenched with saturated $NaHCO_3$ solution. The product was extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 extract was washed with saturated aqueous NaCl and dried over $MgSO_4$. The solvent was evaporated to give the crude product as a nearly colorless oil, which was purified by flash chromatography (MeOH:CH_2Cl_2 1:15) to provide amine **11** (2.33 g, 7.45 mmol) as a colorless oil. Yield 69%; $[\alpha]^{20}_D$ −74 (*c* 2.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.85 (s, 9 H), 1.46 (dt, J = 14.4, 4.5 Hz, 1 H), 1.67 (app q, J = 6.3 Hz, 2 H), 2.00 (s, 3 H), 2.70 (m, 3 H), 3.66 (t, J = 6.0 Hz, 4 H), 5.51 (m, 1 H), 5.84 (dt, J = 5.4, 1.8 Hz, 1 H), 6.07 (dt, J = 5.4, 1.8 Hz, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.2, 18.4, 21.4, 26.0, 33.3, 38.2, 45.1, 61.8, 62.5, 78.0, 130.9, 138.6, 170.9; HRMS [MH$^+$] calcd for $C_{16}H_{32}NO_3Si$ 314.2151, found 314.2142.

(1*R*,4*S*)-4-[*N*-(Carboethoxy)-*N*-(*tert*-butyldimethylsilanyloxy)propylamino]-2-cyclopenten-1-ol-1-*O*-acetate (12). To a solution of amine **11** (2.3 g, 7.34 mmol) in CH_2Cl_2/pyridine (3:1, 20 mL) was added ethyl chloroformate (1.14 mL, 11.74 mmol) slowly at 0 °C under Ar atmosphere. The resultant reaction mixture was stirred at room temperature overnight. Then the reaction mixture was diluted with CH_2Cl_2 (30 mL) and was quenched with saturated NH_4Cl solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated to provide the crude product as a light yellow oil that was purified by flash chromatography (hexanes:EtOAc 5:1) to afford **12** (2.54 g, 6.61 mmol) as a colorless oil. Yield 90%; $[\alpha]^{20}_D$ +15.9 (*c* 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.86 (s, 9 H), 1.24 (t, J = 6.9 Hz, 3 H), 1.55 (dt, J = 14.4, 5.1 Hz, 1 H), 1.68 (m, 1 H), 1.78 (m, 1 H), 2.02 (s, 3 H), 2.77 (dt, J = 14.4, 8.1 Hz, 1 H), 3.06 (m, 1 H), 3.16 (m, 1 H), 3.59 (t, J = 6.2 Hz, 2 H), 4.12 (q, J = 6.9 Hz, 2 H), 5.19 (m, 1 H), 5.51 (m, 1 H), 5.91 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ −5.2, 14.8, 18.4, 21.2, 26.1, 33.7, 36.3, 40.8, 60.2, 61.2, 61.3, 77.4, 132.7, 136.5, 156.5, 170.6; HRMS [MH$^+$] calcd for $C_{19}H_{36}NO_5Si$ 386.2363, found 386.2338.

(1*R*,4*S*)-4-[*N*-(Carboethoxy)-*N*-(propanolamino)]-2-cyclopenten-1-ol-1-*O*-acetate (13). To a solution of **12** (2.40 g, 6.23 mmol) in THF (10 mL) was added TBAF (1.0 M in THF, 6.86 mL, 6.86 mmol) slowly at 0 °C under Ar atmosphere. The resulting reaction mixture was stirred at room temperature

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for 1.5 h. The solvent was removed under reduced pressure. Flash chromatography (hexanes:EtOAc 1:3 to EtOAc 100%) provided alcohol **13** (1.62 g, 5.98 mmol) as a colorless oil. Yield 96%; $[\alpha]^{20}_D$ −2 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 6.9 Hz, 3 H), 1.55 (dt, J = 14.4, 4.8 Hz, 1 H), 1.67 (m, 2 H), 2.01 (s, 3 H), 2.76 (dt, J = 14.4, 8.4 Hz, 1 H), 3.16 (m, br, 2 H), 3.35 (m, br, 1 H), 3.55 (t, J = 5.6 Hz, 2 H), 4.11 (q, J = 6.9 Hz, 2 H), 4.98 (m, br, 1 H), 5.48 (m, 1 H), 5.91 (m, 2 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.7, 21.0, 33.5, 36.2, 40.0, 59.7, 60.2, 61.7, 77.2, 132.7, 136.1, 157.1, 170.5; HRMS [MH^+] calcd for $C_{13}H_{22}NO_5$ 272.1498, found 272.1494.

(1*R*,4*S*)-4-[*N*-(Carboethoxy)-*N*-(propanolamino)]-2-cyclopenten-1-ol (14). To a solution of alcohol **13** (1.43 g, 5.27 mmol) in ethanol (10 mL) was added K_2CO_3 (800 mg, 5.79 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 3 h. TLC analysis (100% EtOAc) showed that starting material was consumed. EtOH was removed under reduced pressure then CH_2Cl_2 (30 mL) was added to redissolve the residue followed by NH_4Cl (saturated, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated to provide diol **14** (1.21 g, 5.27 mmol) as a colorless oil. Yield 100%; $[\alpha]^{20}_D$ −67.4 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, CD_3OD) δ 1.27 (t, J = 6.9 Hz, 3 H), 1.46 (dt, J = 13.8, 5.7 Hz, 1 H), 1.80 (m, 2 H), 2.72 (dt, J = 13.8, 8.1 Hz, 1 H), 3.24 (m, 1 H), 3.60 (m, br, 1 H), 3.56 (t, J = 6.3 Hz, 2 H), 4.14 (q, J = 6.9 Hz, 2 H), 4.66 (m, br, 1 H), 5.02 (m, br, 1 H), 5.80 (m, 1 H), 5.97 (m, 1 H); ^{13}C NMR (300 MHz, CD_3OD) δ 15.1, 34.52 (br), 39.9 (br), 41.6, 60.9, 61.7, 62.8, 75.5, 134.2, 138.2, 158.3; HRMS [MH^+] calcd for $C_{11}H_{20}NO_4$ 230.1392, found 230.1404.

(1*R*,2*R*,3*S*,4*S*)-4-[*N*-(Carboethoxy)-*N*-(propanolamino)]-2,3-epoxycyclopentan-1-ol (15). To a solution of diol **14** (1.21 g, 5.27 mmol) in CH_2Cl_2 (10 mL) was added $NaHCO_3$ (531 mg, 6.32 mmol) and *m*-CPBA (77%, 1.3 g, 5.79 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature overnight. TLC analysis showed that all of the starting material was consumed. Then the reaction mixture was diluted with CH_2Cl_2 (30 mL) and quenched with saturated Na_2SO_3 solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (20 mL), and CH_2Cl_2 (2 × 30 mL) was used to extract the aqueous layer. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc 100% to CH_3OH:CH_2Cl_2 1:15) to provide epoxide **15** (1.19 g, 4.85 mmol) as a colorless oil. Yield 92%; $[\alpha]^{20}_D$ −3.4 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, CD_3OD) δ 1.27 (t, J = 6.9 Hz, 3 H), 1.33 (m, overlapping, 1 H), 1.86 (apparent q, J = 6.9 Hz, 2 H), 1.97 (dt, J = 12.3, 7.5 Hz, 1 H), 3.40−3.50 (m, 4 H), 3.60 (t, J = 6.3 Hz, 2 H), 4.14 (m, 3 H), 4.45 (m, br, 1 H); ^{13}C NMR (300 MHz, CD_3OD) δ 15.1, 29.5, 34.4, 41.8, 55.6, 57.1, 57.4, 61.0, 62.9, 70.9; HRMS [MH^+] calcd for $C_{11}H_{20}NO_5$ 246.1341, found 246.1338.

(2*S*,3*S*,4*S*)-4-[*N*-(Carboethoxy)-*N*-(propanalamino)]-2,3-epoxycyclopentan-1-ol (17) and (1*S*,8*S*,9*S*)-2-(Carboethoxy)-8,9-epoxy-2-azabicyclo[4.3.0]non-5-ol-7-one (16). To a solution of oxalyl chloride (0.76 mL, 8.68 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added DMSO (1.85 mL, 26.05 mmol) dropwise. The mixture was stirred at −78 °C for 15 min. To this solution was then added diol **15** (710 mg, 2.90 mmol) in CH_2Cl_2 (6 mL). The reaction mixture was maintained at −78 °C for 40 min, after which triethylamine (4.04 mL, 28.95 mmol) was added dropwise. This resulting mixture was stirred at −78 °C for 30 min then warmed to room temperature. CH_2Cl_2 (30 mL) and H_2O (20 mL) were poured into the reaction mixture and CH_2Cl_2 (3 × 40 mL) was used to extract the aqueous layer. The combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc:hexanes 1:1) to provide aldehyde **17** (430 mg, 1.78 mmol, R_f 0.32, EtOAc:hexanes 1:1) as a colorless oil and aldol product **16** (145 mg, 0.60 mmol, R_f 0.25, EtOAc:hexanes 1:1). The total combined yield for **16** and **17** was 82%. Spectral data for **17**: $[\alpha]^{20}_D$ −15.1 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, 56 °C, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 2.34 (dd, J = 8.4, 3.6 Hz, 2 H), 2.89 (td, J = 6.9, 1.2 Hz, 2 H), 3.46 (d, J = 2.4 Hz, 1 H), 3.66 (m, 1 H), 3.79 (m, 1 H), 3.96 (s, br, 1 H), 4.18 (q, J = 7.2 Hz, 2 H), 4.96 (m, br, 1 H), 9.83 (app. s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.7, 34.0, 37.4, 44.6, 51.6, 55.1, 58.2, 69.2, 156.2, 200.2, 203.8; HRMS [MH^+] calcd for $C_{11}H_{16}NO_5$ 242.1028, found 242.1033. Spectral data for **16** (as a mixture of diastereomers): ^1H NMR (500 MHz, $CDCl_3$) δ 1.31 (t, J = 7.0 Hz, 3 H), 1.93−1.99 (m, 1 H), 2.18−2.34 (m, 1 H), 2.62 (s, br, 1 H), 3.10 (3.03) (td, J = 13.0, 2 Hz, 1 H), 3.49 (d, J = 2.5 Hz, 1 H), 3.96−4.04 (m, 2 H), 4.11−4.27 (m, br, 3 H), 4.89 (4.78) (d, J = 9.5, 1 H); HRMS [MH^+] calcd for $C_{11}H_{15}NO_5$ 242.1028, found 242.1026.

(1*S*,8*S*,9*S*)-2-(Carboethoxy)-8,9-epoxy-2-azabicyclo[4.3.0]-non-5-en-7-one (18). From aldehyde 17, alumina method: A solution of aldehyde **17** (110 mg, 0.46 mmol) in CH_2Cl_2 (5 mL) was treated with activated alumina (1.5 g, MCIB, 80−200 mesh, ALCOA, type F-20) and the resulting reaction mixture was stirred at room temperature under an Ar atmosphere for 8 h. The mixture was then filtered and the solid retained and washed with 60 mL of 9:1 CH_2Cl_2:MeOH solvent. The solvent was evaporated and the crude product was purified by flash chromatography (EtOAc hexanes 3:1) to provide enone **18** (48 mg, 0.21 mmol) as a colorless oil and aldol product **16** (32 mg, 0.13 mmol) as a colorless oil. Total yield 76%. **From aldehyde 17, L-proline method:** To a solution of aldehyde **17** (60 mg, 0.25 mmol) in DMSO (3 mL) was added L-proline (14 mg, 0.12 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature under Ar atmosphere for 10 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (EtOAc:hexanes 3:1) to provide enone **18** (17 mg, 0.075 mmol) as a colorless oil and aldol product **16** (18 mg, 0.075 mmol) as a colorless oil. Total yield 60%. **From aldol product 16:** To a solution of aldol product **16** (200 mg, 0.83 mmol) in CH_2Cl_2 (6 mL) was added triethylamine (300 μL, 2.16 mmol) followed by MsCl (160 μL, 2.08 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature under Ar atmosphere for 2 h and then cooled to 0 °C. DBU (70 μL, 0.50 mmol) was added slowly. The resulting reaction mixture was stirred for 10 min at 0 °C. Saturated NH_4Cl solution (15 mL) was added to quench the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$ and filtered. The solvent was evaporated to provide the crude product as a light yellow oil that was purified by flash chromatography (EtOAc:hexanes 3:1) to give enone **18** (144 mg, 0.65 mmol) as a colorless oil. Yield 78%; $[\alpha]^{20}_D$ −421 (*c* 0.1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.0 Hz, 3 H), 2.28−2.15 (m, 1 H), 2.42−2.52 (m, 1 H), 2.89 (td, J = 12.0, 2.7 Hz, 1 H), 3.48 (d, J = 3.0 Hz, 1 H), 4.11 (m, br, 1 H), 4.25 (q, J = 7.0 Hz, 2 H), 4.38 (m, br, 1 H),4.54 (s, 1 H), 7.07 (dt, J = 7.5, 3.0 Hz, 1 H); ^{13}C NMR 500 MHz, $CDCl_3$) δ 14.9, 25.7, 40.5, 53.9, 54.1, 55.7, 62.1, 133.4, 138.5, 156.0, 193.9; HRMS [MH^+] calcd for $C_{11}H_{14}NO_4$ 224.0923, found 224.0932.

(1*S*,8*S*,9*S*)-2-(Carboethoxy)-7-(*Z*/*E*)-8,9-epoxy-2-azabicyclo[4.3.0]non-5-ene (19). To a stirred suspension of powdered ethyltriphenylphosphonium bromide (372 mg, 1.00 mmol) in 5 mL of anhydrous ether at room temperature in a sealed tube was added 1.6 N *n*-butyllithium (625 μL, 1.00 mmol) in hexanes. After 30 min, a solution of the enone **18** (112 mg, 0.50 mmol) in 1 mL of ether was added to the yellow ylide solution. The mixture was heated at 65 °C for 4 h, cooled to room temperature, and quenched with water (5 mL). The mixture was extracted with ether (4 × 20 mL). The combined organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with 25% ethyl

acetate−hexanes afforded **19** (80 mg 0.34 mmol), an inseparable 1/1.5 mixture of *Z*/*E* isomers, as a colorless oil. Yield 68%. The following spectral data were obtained for the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3 H), 1.91 (1.92) (d, J = 6.9 Hz, 3 H), 2.24 (m, 2 H), 2.84 (td, J = 11.0, 4.4 Hz, 1 H), 3.63 (3.93) (d, J = 3.3 Hz, 1 H), 4.16−3.98 (m, 2 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.31 (s, br, 1 H), 5.89 (6.05) (qt, J = 7.2 Hz, 1 H), 6.30 (6.24) (dt, J = 6.9, 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.9 (15.2), 25.5 (25.0), 40.3 (40.8), 51.5, 56.4 (55.7), 57.3 (57.0), 61.6, 121.4 (122.4), 124.2 (128.1), 132.3, 135.0 (135.4), 156.1 (156.2); HRMS [MH$^+$] calcd for $C_{13}H_{18}NO_3$ 236.1287, found 236.1291.

(1*S*,8*S*,9*S*)-2-(Carboethoxy)-7-(*E*)-8-*O*-acetyl-9-hydroxy-2-azabicyclo[4.3.0]non-5-ene (20) and (1*S*,8*S*,9*S*)-2-(Carboethoxy)-7-(*Z*)-8-*O*-acetyl-9-hydroxy-2-azabicyclo[4.3.0]non-5-ene (21). To a solution of the epoxides **19** (72 mg, 0.31 mmol) and sodium acetate (99%, 250 mg, 3.06 mmol) was added acetic acid (3 mL). After 45 min at room temperature, the acetic acid was removed under reduced pressure. The mixture was treated with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ether (4 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with 33% EtOAc−hexanes afforded a 1:1.5 mixture of **20** and **21** (64 mg, 0.217 mmol, 70%) as a colorless oil. Some of the isomers (∼5 mg) were separated by HPLC (Waters Model 590, Perp Nova-pak HR Silica, 3.9 × 300 mm column; 20% EtOAc−hexanes; 3 mL/min). ^{1}H NMR spectral data were obtained for the separated isomers, but mass spectral data were obtained from the mixture. Compound **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2 Hz, 3 H), 1.96 (d, J = 7.5 Hz, 3 H), 2.08 (s, 3 H), 2.29 (m, br, 2 H), 3.01 (m, 1 H), 4.18−4.07 (m, 1 H), 4.20 (q, J = 6.9 Hz, 2 H), 4.42 (s, br, 2 H), 5.32 (s, 1 H), 6.05 (q, J = 7.2 Hz, 1 H), 6.39 (s, br, 1 H). Compound **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2, 3 H), 1.96 (d, J = 7.2, 3 H), 2.08 (s, 3 H), 2.29 (m, br, 2 H), 3.01 (m, 1 H), 4.12−4.06 (m, 1 H), 4.22 and 4.21 (two q, J = 6.9 Hz, 2 H), 5.32 (s, 1 H), 4.42 (s, br, 2 H), 6.05 (q, J = 7.5 Hz, 1 H), 6.40 (s, br, 1 H); HRMS [MH$^+$] calcd for $C_{15}H_{22}NO_5$ 296.1498, found 296.1484.

Streptazolin 1 and Its *E*-Isomer 22. A solution of mixture of **20** and **21** (20 mg, 0.07 mmol) in 2 mL of 5% NaOMe/MeOH was heated to reflux for 1 h, and the methanol was removed under reduced pressure. The mixture was diluted with water and extracted with ethyl acetate (4 × 5 mL). The organic extracts were dried over anhydrous potassium carbonate, filtered, and concentrated to provide a mixture of **1** and **22** (10 mg, yield ∼70%) as a colorless oil (since we also found that streptazolin decomposed when concentrated, the mixture was immediately diluted with deuterated chloroform to provide crude NMR data). ^{1}H NMR (500 MHz, CDC_{l3}, **1** (**22**)) δ 1.91 (d, J = 7.5 Hz, 3 H), 2.15−2.24 (2.26−2.33) (m, 1 H), 2.51 (2.56) (dtd, J = 17.5, 7.0, 3.5 2 Hz, 1 H), 3.37−3.45 (3.45−3.51) (m, 2 H), 4.28−4.30 (4.26−4.28) (overlap d, br, J = 7.5 Hz, 1 H), 4.74 (4.7) (d, J = 7 Hz, 1 H), 4.88 (4.58) (s, br, 1 H), 6.04 (6.10) (m, 1 H), 6.16 (6.95) (q, J = 7.5 Hz, 1 H); ^{13}C NMR (125 MHz, CDC_{l3}) δ 15.1 (15.5), 23.0 (23.4), 40.1 (39.4), 59.3 (58.5), 74.6 (78.2), 81.7 (81.8), 119.0 (124.9), 123.9 (126.0), 139.1 (138.8), 143.0 (140.6), 159.1; HRMS [MH$^+$] calcd for $C_{11}H_{14}NO_3$ 208.0974, found 208.0972.

Dihydrostreptazolin Acetate (+)-2. To a solution of a mixture of **1** and **22** (∼10 mg) in ethanol (2 mL) was added 10 wt % of Pd on activated carbon (10 mg) at room temperature. The resultant reaction mixture was purged with H_2 three times and then stirred at room temperature under H_2 for 1.5 h. TLC was used to monitor the reaction carefully. The reaction mixture was filtered through a pad of Celite and washed with MeOH (15 mL). The solvent was removed under reduced pressure. Flash chromatography (EtOAc:hexanes 2:3) gave 7.0 mg of chromatographically pure dihydrostreptazolin. To a solution of this material in CH_2Cl_2 (2 mL) was added Ac_2O (0.05 mL, l.2 mmol) and pyridine (0.1 mL, l.2 mmol) at room temperature. The resulting reaction mixture was stirred for 16 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified by silica gel flash chromatography (hexanes:EtOAc 2:3) to provide 7.6 mg (86% for two steps) of dihydrostreptazolin acetate **2** as a white crystalline solid. Mp 75−77 °C (lit.[3,7] mp 76−77 °C); $[\alpha]^{20}_D$ +143 (*c* 0.2, $CHCl_3$) (lit.[3] $[\alpha]^{20}_D$ +143); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3 H), 1.44 (ttd, apparent qt, J = 13.2, 4.8 Hz, 1 H), 1.80−1.83 (m, 1H), 2.02−2.09 (m, 1 H), 2.08 (s, 3 H), 2.12−2.22 (m, 2 H), 2.70 (br d, J = 13.8 Hz, 1 H), 3.09 (dt, J = 13.2, 3.6 Hz, 1 H), 3.88 (dd, J = 14.4, 4.8 Hz, 1 H), 4.41 (d, J = 6.0 Hz, 1 H), 4.63 (d, J = 6.0 Hz, 1 H), 5.64 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.0, 19.0, 21.2, 24.7, 27.1, 42.7, 64.8, 78.0, 83.1, 134.0, 140.0, 157.0, 170.3; HRMS [MH$^+$] calcd for $C_{13}H_{18}NO_4$ 252.1236, found 252.1240.

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Supporting Information Available: NMR spectra for compounds **11**−**22**, **1**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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