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Stereoselective Total Synthesis of (+)-Streptazolin by Using a Temporary Silicon-Tethered RCM Strategy

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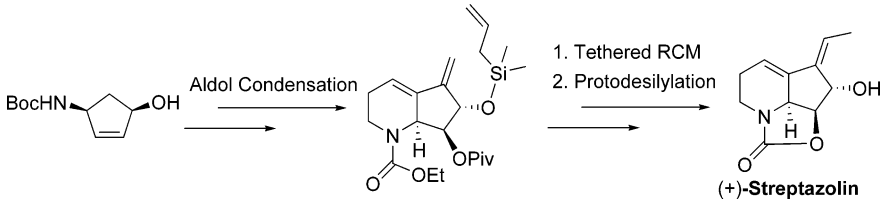

A stereoselective total synthesis of (+)-streptazolin **1** was accomplished starting from readily available aminocyclopentenol (−)-**7**. The synthetic sequence highlights an intramolecular aldol condensation strategy to construct the piperidine core and a silicon-tethered ring-closing metathesis strategy to install the *Z* exocyclic ethylidene side chain of streptazolin. Separate protodesilylation and Tamao oxidation of a common intermediate **32** afforded streptazolin and the precursor for 13-hydroxystreptazolin. The overall yield for (+)-streptazolin **1** from aminocyclopentenol (−)-**7** was 4.8% for a total of 16 steps.

Introduction:

Streptazolin (+)-**1** (Figure 1) was isolated from cultures of *Streptomyces viridochromogenes* for the first time in 1981 by Drautz and Zahner and later discovered by a chemical screening of *Streptomyces* luteogriseus[1] and a high-producing strain of *Streptomyces*.[2] This lipophilic neutral tricyclic compound, which possesses the structural feature of 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 (+)-streptazolin **1** were markedly complicated by its propensity to polymerize upon concentration from organic solutions. For this reason, 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 of co-secondary metabolites from *Streptomyces* sp. with streptazolin including 13-hydroxystreptazolin **3** and 5-*O*-(*β*-D-xylopyranosyl)streptazolin **4** which have shown significant cytostatic activity against several human cancer cell lines. The unique structural features of streptazolin as well as its promising biological activity profile have prompted several total syntheses.[6−8]

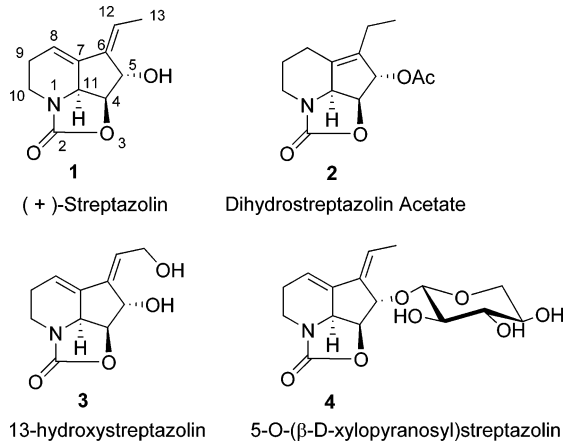

FIGURE 1. Structures of dihyrostreptazolin acetate, streptazolin, and cosecondary metabolites.

As part of a project directed at synthetic applications of acylnitroso Diels−Alder cycloadducts in our group, we devel-

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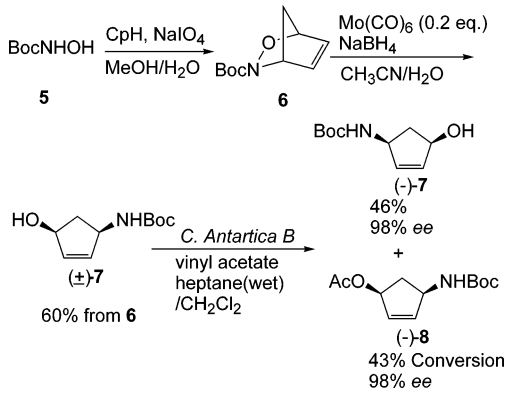
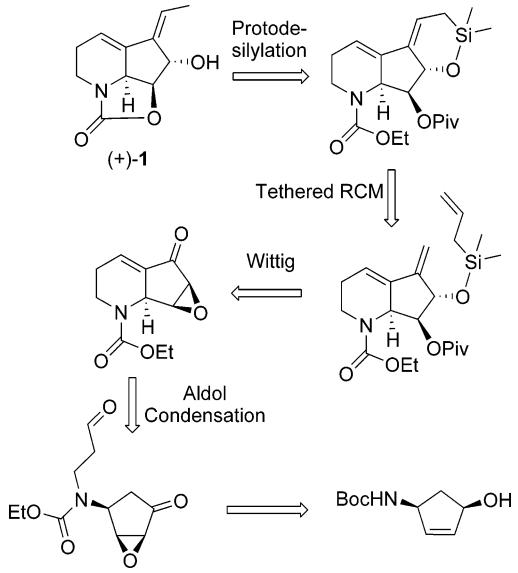
SCHEME 1



SCHEME 2. Second-Generation Retrosynthetic Analysis



oped a highly efficient and practical chemoenzymatic synthesis of enantiopure aminocyclopentenols (Scheme 1).[9,10] Starting from enantiopure versatile intermediate aminocyclopentenol (−)-**7**, we recently accomplished a total synthesis of (+)-streptazolin[11] by combining an intramolecular aldol condensation strategy and a Wittig olefination late-stage strategy developed earlier by Kozikowski and Overman.[6,7]

In both Kozikowski and Overman's syntheses,[6,7] however, the ethylidene side chain was introduced by the Wittig reaction of the cyclic ketone and led to streptazolin as a 1:2 mixture of the ethylidene stereoisomers with the incorrect *E* isomer predominating. The lack of stereoselectivity in the introduction of the ethylidene side chain by the Wittig reaction prompted us to propose a ring-closing metathesis/silicon-assisted intramolecular cross-coupling strategy to overcome this problem (Scheme 2). The use of tethered heteroatoms such as silicon, boron, or esters in ring-closing metathesis (RCM) reactions has been shown to be synthetically very effective in controlling the geometry of di- and trisubstituted alkenes.[12−14] We considered that this methodology could be applied to introduction of the *Z* ethylidene side chain of 13-hydroxystreptazolin and (+)-streptazolin. In this paper, we detail our efforts toward a highly stereoselective asymmetric synthesis of (+)-streptazolin based on a ring-closing metathesis/silicon-assisted intramolecular cross-coupling strategy and an intramolecular aldol condensation strategy starting from aminocyclopentenols (−)-**7**.

Results and Discussion

In this event, the advanced intermediate, enone **18**, was synthesized in nine steps and 32% total yield from aminocyclopentenol (−)-**7** by an improved synthetic sequence based on our previous work (Scheme 3).[11] Careful optimization of the previous reductive amination step revealed that the use of TBDPS- instead of TBS-protected aldehyde **10** and Na_2SO_4 instead of 4 Å molecular sieves as a drying agent improved both the yield (from 69% to 76%) and, most importantly, the reproducibility on large scale. An improved yield (86%) for the preparation of enone **18** was also realized by treatment of aldol product **16** with Et_3N, DMAP, and MsCl to induce the desired dehydration reaction.

With the advanced intermediate enone **18** in hand, the initial plan was to install a methylidene unit instead of ethylidene by a Wittig reaction. Hence, compound **18** was treated with an ylide premade from sodium hydride and methyltriphenylphosphonium bromide to provide diene **19** in 71% yield. Epoxide opening of **19** with 25% AcOH/NaOAc was followed by base (NaOMe/MeOH)-induced cyclization and deprotection to give rise to methylidene streptazolin **21** in 78% total yield for the two steps. At this point, commercially available allylchlorodimethylsilane was chosen as the silane tether for the ring-closing metathesis substrate. Compound **22** was obtained in 88% yield by the treatment of triethylamine, DMAP, and allylchlorodimethylsilane in methylene chloride. Further ring-closing metathesis, catalyzed by 5 mol % of Grubbs' II catalyst **24**, was found to proceed smoothly to furnish six-five-six ring fused diene **25** in quantitive yield. Further manipulation of **25** by treatment with different fluoride reagents (TBAF, HF−pyridine) was found to give rise to triene **26** via an elimination reaction, which was similar to a recently reported example (Scheme 4).[15]

Attempts to convert compound **25** to 13-hydroxystreptazolin **3** using Tamao oxidation conditions[16] ($KF/KHCO_3/H_2O_2$) led to decomposition. To explore alternatives, we used an allyoxydiphenylchlorosilane as a tethering reagent in the RCM reaction (Scheme 5). The advantage of this approach was that instead of incorporating a carbon silicon bond into the conjugated diene system, an oxygen silicon bond was used, with the anticipation that it would make the RCM product much more prone to further manipulation. Meanwhile, we also envisioned that the RCM

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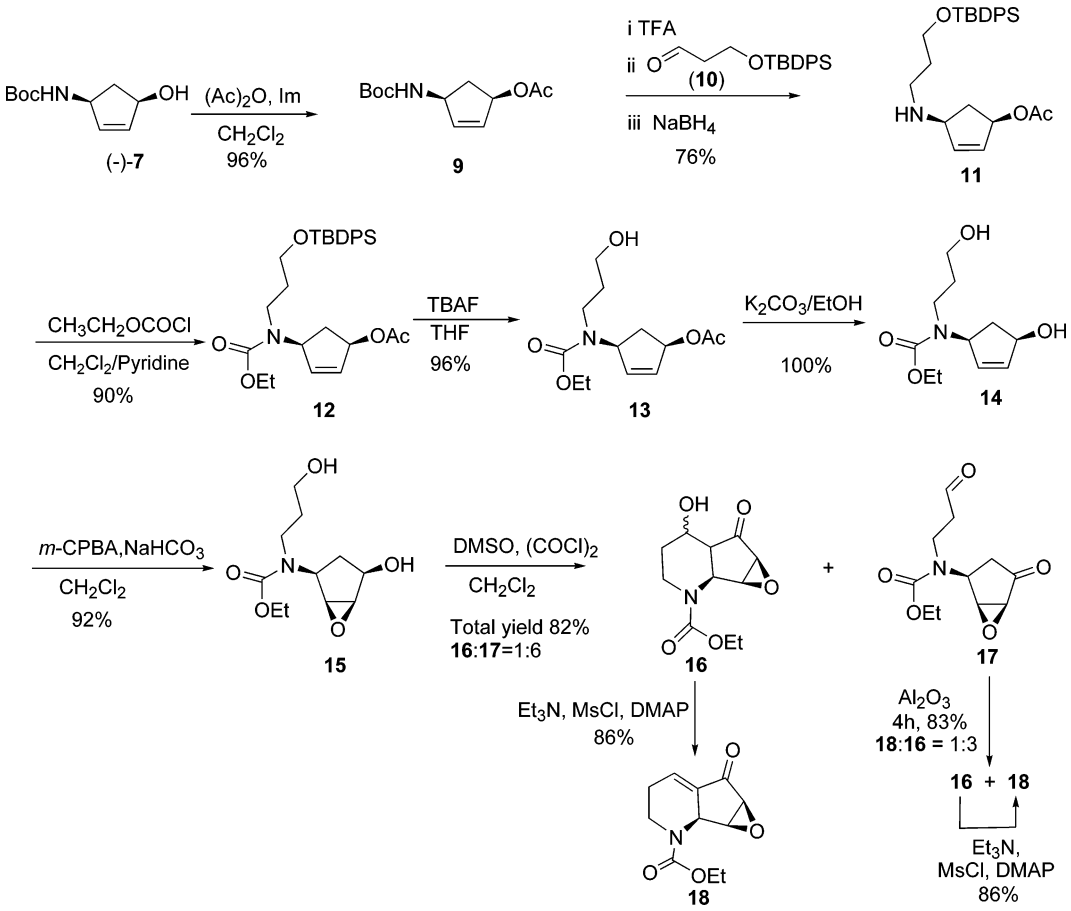
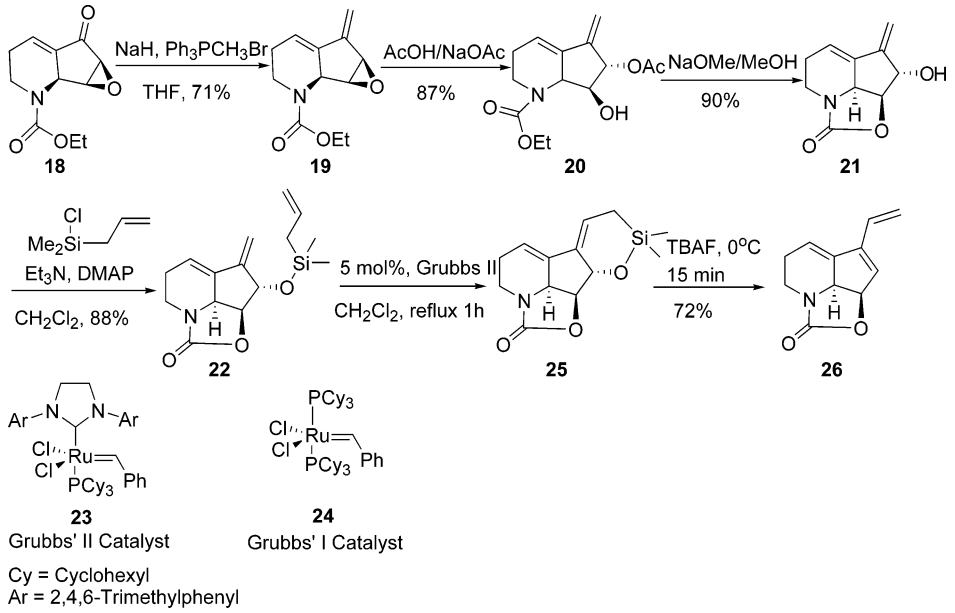
SCHEME 3

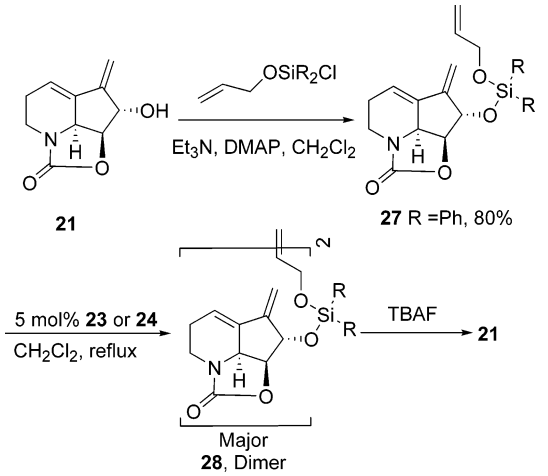


SCHEME 4



product of the bis-alkoxysilane could be a potential precursor for 13-hydroxystreptazolin. Toward this end, compound **21** was converted to allyoxydiphenylsilane **27** in 80% yield. Unfortunately, a series of attempts with different metathesis conditions and different substitutions in the allyoxysilane tether (R= Me or *i*-Pr in **27**) gave a mixture of *E*/*Z* intermolecular dimerization products (**28**, R = Ph**)** as the major products based on mass spectrometry and crude NMR data. None of the expected intramolecular seven-membered ring RCM silane was detected even when the reaction was performed at low concentration (2 mM) and with the use of less active Grubbs I catalyst **24**. When treated with TBAF, compound **28** was converted to methylidene streptazolin **21** smoothly in ∼60% yield, which also was consistent with the dimerization product as the major product.

SCHEME 5



In contrast to the RCM reaction of **22** which preceded very smoothly, a possible explanation for the failure of the RCM with **27** is that the required seven-membered ring transition state for the reaction of **27** is less ordered relative to the rigid six-membered ring transition state involved in the reaction of **22** (Figure 2).

At this point, we decided to focus on use of allylchlorodimethylsilane as a temporary silane tether for the ring-closing metathesis reaction and explore alternative synthetic sequences. Because of the rather labile character of streptazolin, presumably due to the fused ring system and the conjugated diene, we decided to explore the possibility of conducting ring-closing metathesis and protodesilylation before the formation of the cyclic urethane unit of streptazolin. Accordingly, compound **20** was treated with trimethylacetic anhydride in the presence of a catalytic amount of TMSOTf to furnish compound **29** in 80% yield. Removal of the acyl group of **29** followed by silylation with allylchlorodimethylsilane provided RCM substrate **30** in a total of 74% yield for two steps. We were delighted to find that the RCM reaction of **30** proceeded smoothly with 2 mol % of Grubbs II catalyst in CH_2Cl_2 to give RCM product **31** cleanly. With compound **31** in hand, we fortunately found that by treatment with KF and $KHCO_3$ compound **31** underwent a protodesilylation process to give compound **32** in 50% yield. To our knowledge, this is one of very few examples of protodesilylation of a conjugated and fused allylic silane system. On the other hand, diol **33** was obtained under Tamao oxidation conditions in 55% yield. Attempts to convert diol **33** to 13-hydroxystreptazolin **3** were unsuccessful.[17] Further removal of

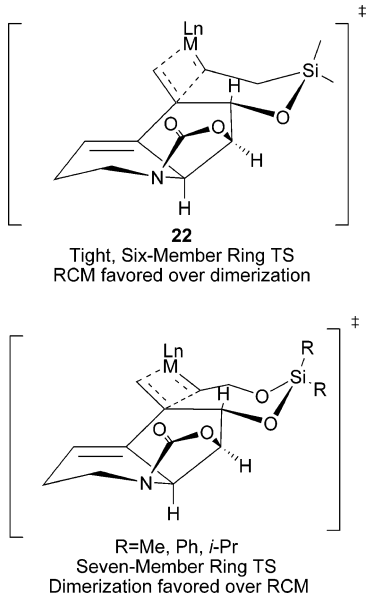


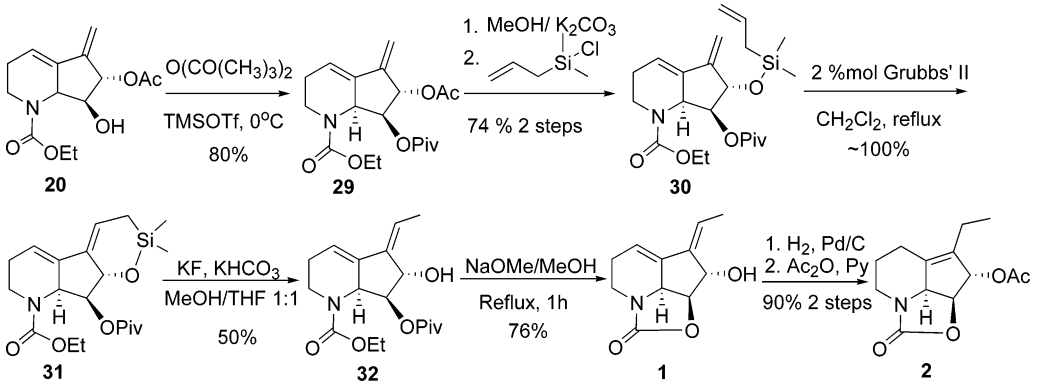
FIGURE 2. Proposed six-membered and seven-membered ring transition states of RCM reactions.

the pivaloate group and cyclization of **32** were achieved by refluxing it in 5% NaOMe in MeOH to provide Streptazolin **1** in ~76% yield. Since we also found that these materials partially decomposed upon isolation,[6,7] the crude spectroscopic data were compared to those reported in the literature[8] to confirm the structure of **1**. To further prove the structure, our synthetic streptazolin was converted to the stable crystalline dihydro acetate **2** after hydrogenation and acetylation. Compound **2** was confirmed by comparison of spectroscopic data and specific rotation to those reported in the literature for this natural product (Scheme 6).

Conclusion

In conclusion, the total synthesis of (+)-streptazolin **1** was accomplished using an intramolercular aldol condensation and temporary silicon-tethered RCM strategy in 16 steps and 4.8% total yield starting from readily available aminocyclopentenol (−)-**7**. Our synthesis features a silicon-tethered RCM to set the *Z* geometry of the ethylidene side chain and a novel protodesilylation reaction of cyclic allylsilane. This synthesis also highlights the versatile synthetic applications of aminocyclopentenol building blocks developed in this laboratory.[11] Meanwhile, a series of analogues of natural streptazolin were

SCHEME 6



prepared, and further synthetic investigations of novel streptazolin Diels−Alder derivatives and the evaluations of their biological activities are currently in progress.

Experimental Section:

(1*R*,4*S*)-4-[*N*-(*tert*-Butyldiphenylsilanyloxy)propylamino]-2-cyclopenten-1-ol 1-*O*-Acetate (11). Modified reductive amination procedure:[11] To a solution of acetate **9**[9b] (5.0 g, 20.75 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (5 mL) at room temperature. The reaction mixture was stirred at room temperature, until TLC showed that all starting material was consumed (~2 h). The reaction mixture was diluted with CH_2Cl_2 (40 mL) and was washed with 10% Na_2CO_3 solution (40 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. (It is important that pH value of aqueous layer should be >10, if not, 1 NaOH aqueous solution should be added to adjust the pH.) Filtration and concentration under reduced pressure gave the crude amine product (2.75 g) as a light yellow oil. The residue was dissolved in dry CH_2Cl_2 (15 mL). To this solution was added anhydrous Na_2SO_4 (3.0 g, 21.12 mmol), followed by aldehyde **10**[18] (6.48 g, 20.75 mmol) in CH_2Cl_2 (10 mL) at −20 °C under Ar atmosphere, slowly. The mixture was stirred at −20 °C for 12 h. The reaction mixture was warmed to room temperature and then stirred for another 0.5 h at room temperature. $NaBH_4$ (1.15 g, 30.77 mmol) was added to the reaction mixture, followed by MeOH (15 mL) immediately. The reaction mixture was stirred for 20 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** (6.90 g, 15.77 mmol) as a colorless oil: yield 76%; $[\alpha]^{20}_D$ = −96 (c = 1.0, CH_3OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9 H), 1.53 (td, J = 4.7,14.1 Hz, 1 H), 1.78 (m, 3 H), 2.03 (s, 3 H), 2.77 (m, 3 H), 3.73 (m, 3 H), 5.57 (m, 1 H), 5.90 (td, J = 1.59, 5.52 Hz, 1 H), 5.90 (m, 1 H), 7.40 (m, 6 H), 7.68 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 21.4, 27.0, 33.1, 38.1, 44.9, 62.5, 62.6, 78.0, 127.8, 129.8, 131.1, 135.7, 133.9, 138.4, 170.9; HRMS [FAB, MH^+] calcd for $C_{26}H_{36}NO_3Si$ 438.2426, found 438.2425.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-8,9-epoxy-2-azabicyclo[4.3.0]non-5-en-7-one (18). Modified procedure for dehydration of aldol product **16**: To a solution of aldol product **16** (600 mg, 2.49 mmol) in CH_2Cl_2 (5 mL) were added DMAP (61 mg, 0.50 mmol) and triethylamine (900 μL, 6.48 mmol) followed by MsCl (306 μL, 3.98 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature under Ar atmosphere for 2 h. TLC analysis showed that all of the aldol product **16** was converted to enone **18**. 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 Na_2SO_4 and filtered. The solvent was evaporated to provide the crude product as a light yellow oil which was purified by flash chromatography (EtOAc/hexanes 3: 1) to give enone **18** (474 mg, 2.14 mmol, 86%) as a colorless oil. All of the spectral data and physical properties are identical to our previously reported data.[11]

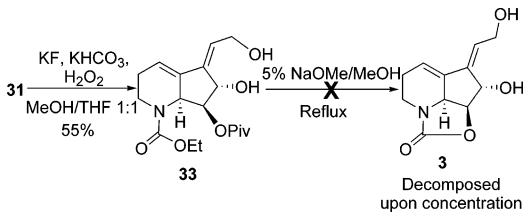
(1*S*,8*S*,9*S*)-2-(Carbethoxy)-8,9-epoxy-2-azabicyclo[4.3.0]-5,7-diene (19). A solution of methyltriphenylphosphonium bromide (346 mg, 0.97 mmol)/NaH (60%, 38.6 mg, 0.97 mmol) in dry THF (2 mL) in a flame-dried flask was stirred for 2 h at room temperature. Epoxy ketone **18** (180 mg, 0.81 mmol) in dry THF (2 mL) was added at 0 °C. The reaction mixture was warmed to room temperature over 1 h. After the mixture was stirred for another 0.5 h at room temperature, the reaction was quenched with saturated NH_4Cl aqueous solution (6 mL). The mixture was extracted with ether (4 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography (hexanes/AcOEt 5:1) yielded **19** (128 mg, 0.58 mmol, 71%) as a colorless oil: $[\alpha]^{20}_D$ = −221.1 (c = 0.6, $CHCl_3$); IR (thin film) 2982, 1698, 1412, 1244, 1117, 889 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3 H), 2.08−2.15 (m, 1 H), 2.24−2.30 (m, 1 H), 2.84 (dt, J = 2.5, 10 Hz, 1H), 3.69 (d, J = 3 Hz, 1 H), 4.06 (m, br, 1 H), 4.19−4.32 (m, 4 H), 5.26 (s, 1 H), 5.45 (s, 1 H), 6.38 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.9, 25.1, 40.6, 55.2, 56.8, 57.1, 61.7, 109.2, 125.3, 134.1, 143.1, 156.2; HRMS [FAB, MH^+] calcd for $C_{12}H_{16}NO_3$ 222.1130, found 222.1128.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-8-*O*-acetyl-9-hydroxy-2-azabicyclo-[4.3.0]-5,7-diene (20). To a solution of epoxide **19** (53 mg, 0.24 mmol) and sodium acetate (99%, 250 mg, 3.06 mmol) was added acetic acid (3 mL) at room temperature. The reaction mixture was heated to 65 °C for 2 h in an oil bath and then cooled to room temperature. Acetic acid was removed under reduced pressure. Saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (30 mL) were poured into the white solid residue. The aqueous layer was extracted with ether CH_2Cl_2 (2 × 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 50% EtOAc−hexanes afforded **20** (60 mg, 0.21 mmol, 89%): $[\alpha]^{20}_D$ = −119.1 (c = 0.6, $CHCl_3$); IR (thin film) 3401, 2919, 1736, 1678, 1420, 1370, 1227, 1112, 887 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (t, J = 7.5 Hz, 3 H), 2.07 (s, 3 H), 2.14−2.22 (m, 1 H), 2.27−2.33 (m, 1 H), 2.61 (d, J = 3 Hz, 1 H), 2.98 (s, br, 1 H), 4.07 (m, br, 1 H), 4.16−4.23 (m, 2 H), 4.40−4.43 (m, 2 H), 5.37 (s, 1 H), 5.38 (s, 1 H), 5.70 (s, 1 H), 6.44 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.8, 21.4, 24.9, 41.1, 58.8, 61.8, 74.1, 78.0, 112.7, 121.2, 136.3, 142.2, 156.2, 170.5; HRMS [FAB, MH^+] calcd for $C_{14}H_{20}NO_5$ 282.1341, found 282.1346.

12-Dihydrostreptazolin (21). A solution of **20** (60 mg, 0.21 mmol) in 3 mL of 2.5% 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. Flash chromatography of the residue on silica gel with 50% EtOAc−hexanes afforded **21** (37 mg, 0.19 mmol, 90%) as a colorless oil: $[\alpha]^{20}_D$ = +64.0 (c = 0.4, $CHCl_3$); IR (thin film) 3425, 2919, 1723, 1385, 1201, 1030, 764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.10 (d, J = 7.5 Hz, 1 H), 2.19−2.30 (m, 1 H), 2.50−2.62 (m, 1 H), 3.37−3.59 (m, 2 H), 4.30 (overlap d, br, J = 12.5, 1 H), 4.68 (s, br, 1 H), 4.75 (dd, J = 12.5, 0.5 Hz, 1 H), 5.31 (s, 1 H), 5.70 (s, 1 H), 6.19 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.0, 39.5, 58.5, 77.7, 81.7, 110.6, 122.6, 141.9, 147.2, 159.0; HRMS [FAB, MH^+] calcd for $C_{10}H_{12}NO_3$ 194.0817, found 194.0813.

5-*O*-(*o*-Allyldimethylsilyl)-12-dihydrostreptazolin (22). To a solution of **21** (21 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) were added a catalytic amount of DMAP (1−2 mg) and triethylamine (0.19 mL) at room temperature, followed by addition of allyldimethylsilyl

(17) Removal of the pivolayl group and cyclization of **33** by refluxing in 5% NaOMe in MeOH was tried in an attempt to afford 13-hydroxystreptazolin **3**. Unfortunately, compound **3** was found to be unstable upon concentration from organic solutions. This instability of **3** was also observed by Puder et al.[5] Further studies to solve this problem are currently in progress.



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chloride (0.08 mL, 0.55 mmol) at 0 °C. The mixture was allowed to warm to room temperature and was stirred at room temperature for 15 min. The solvent was removed under reduced pressure to give a white solid residue. Et_2O (30 mL) was added, and then the mixture was filtered. Flash chromatography of the residue on silica gel with hexanes/EtOAc (4: 1) afforded **22** (28 mg, 0.086 mmol, 88%): $[\alpha]^{20}_D = +161.3$ ($c = 0.2$, $CHCl_3$); IR (thin film) 2924, 1763, 1630, 1380, 1255, 1038, 882, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 6H), 1.71 (d, $J = 8$ Hz, 2 H),2.20−2.27 (m, 1 H), 2.50−2.57 (m, 1 H), 3.39−3.55 (m, 2 H), 4.26 (d, br, $J = 8$, 1 H), 4.68 (d, $J = 2$, 1 H), 4.65 (dd, $J = 8$, 1.5 Hz, 1 H), 4.94 (m, 1H), 4.97 (m, 1H), 5.15 (s, 1 H), 5.48 (s, 1 H), 5.76−5.85 (m, 1H), 6.12 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −1.85, −1.83, 23.0, 24.6, 39.4, 57.9, 78.8, 82.4, 110.0, 114.7, 121.9, 133.4, 141.4, 146.6, 158.7; HRMS [FAB, MH^+] calcd for $C_{15}H_{22}NO_3Si$ 292.1369, found 292.1370.

Silylstreptazolin (25). To a solution of **22** (25 mg, 0.086 mmol) in CH_2Cl_2 (6 mL) was added Grubbs II catalyst **23** (4 mg, ∼5 mol %), and the reaction mixture was heated to reflux under Ar. After 1 h, the reaction mixture was cooled to room temperature and concentrated to dryness under vacuum. Examination of the crude reaction mixture by ^1H NMR indicated complete consumption of **22** with clean and quantitative formation of the tethered diene. The crude reaction mixture was filtered through a pad of silica gel quickly (compound **25** was found to decompose on silica TLC over 10 min at room temperature) with hexanes/EtOAc (1:1) to afford **25** (22.6 mg, 0.086 mmol) as light yellow oil: $[\alpha]^{20}_D = +282.0$ ($c = 0.3$, $CHCl_3$); IR (thin film) 3351, 2924, 2853, 1760, 1644, 1380, 1252, 1043, 835, 768 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.12 (s, 3H), 0.25 (s, 3H), 1.38 (d, overlap, $J = 17$ Hz, 1 H), 1.58 (dd, $J = 17$ Hz, 8.5 Hz, 1 H), 2.18−2.24 (m, 1 H), 2.46−2.53 (m, 1 H), 3.36−3.41 (m, 1 H), 3.53 (dt, $J = 12.5$, 7.5 Hz, 1 H), 4.24 (d, br, $J = 8.5$ Hz, 1 H), 4.59 (s, 1 H), 4.79 (dd, $J = 8$, 1 Hz, 1 H), 5.90 (m, 1H), 6.18 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −0.38, −0.34, 14.2, 22.8, 39.2, 57.8, 78.6, 82.4, 119.3, 121.7, 140.7, 141.2, 158.6; HRMS [FAB, MH^+] calcd for $C_{13}H_8NO_3Si$ 264.1056, found 264.1037.

Triene (26). To a solution of **25** (11.3 mg, 0.043 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 45 μL, 0.045 mmol) slowly at 0 °C under Ar atmosphere. The resulting reaction mixture was stirred at 0 °C for 15 min. TLC showed that all starting material was consumed. The solvent was removed under reduced pressure. Flash chromatography with hexanes/EtOAc (2:1) provided triene **26** (6 mg, 0.031 mmol, 72%) as a colorless oil: $[\alpha]^{20}_D = +20.0$ ($c = 0.03$, $CHCl_3$); IR (thin film) 2924, 2852, 1753, 1389, 1216, 1039, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.36 (m, 1 H), 2.49 (dtd, $J = 2.52$, 6.88, 16.27 Hz, 1 H), 3.47 (m, 1H), 3.57 (m, 1 H), 4.40 (d, $J = 7.18$ Hz, 1 H), 5.22 (dd, $J = 2.47$, 7.38 Hz, 1 H), 5.46 (dd, $J = 1.16$, 11.10 Hz, 1 H), 5.75 (dd, $J = 0.87$, 17.71 Hz, 1 H), 6.16 (m, 1 H), 6.07 (d, $J = 1.98$ Hz, 1 H), 6.47 (dd, $J = 11.09$, 17.83 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 42.6, 59.0, 77.4, 120.2, 121.1, 129.0, 129.2, 145.1, 146.9, 156.6; HRMS [FAB, MH^+] calcd for $C_{11}H_{12}NO_2$ 190.0868, found 190.0870.

5-*O*-(*o*-Allyloxydiphenylylsilyl)-12-dihydrostreptazolin (27). To a solution of dichlorodiphenylsilane (0.163 mL, 0.78 mmol) in CH_2Cl_2 (2 mL) was added a catalytic amount of DMAP (1−2 mg) and triethylamine (0.22 mL), followed by the syringe-pump addition of the allylic alcohol (68 mg, 1.17 mmol) in CH_2Cl_2 (1 mL) over 1 h at 0 °C under an atmosphere of argon. The mixture was allowed to warm to room temperature and was stirred at room temperature for 3 h. This mixture was cooled to 0 °C, and then compound **21** (15 mg, 0.078 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred at room temperature for 15 min. The solvent was removed under reduced pressure to give a white solid residue. Et_2O (30 mL) was added, and then the mixture was filtered. Flash chromatography of the residue on silica gel with hexanes/EtOAc (15:1 to 9:1) afforded **27** (26.8 mg, 0.062 mmol, 80%): ^1H NMR (500 MHz, $CDCl_3$) δ 2.21 (m, 1 H), 2.51 (m, 1 H), 3.38 (ddd, $J = 4.08$, 8.49, 12.46 Hz, 1 H), 3.49 (td, $J = 7.63$, 12.57 Hz, 1 H), 4.26 (app d, $J = 7.48$ Hz, 1 H), 4.35 (td, $J = 1.74$, 4.68 Hz, 2 H), 4.79 (app d, $J = 7.48$ Hz, 1 H), 4.87 (s, 1 H), 5.14−5.17 (m, 1 H), 5.34−5.39 (m, 1 H), 5.49 (s, 1 H), 5.96 (tdd, $J = 4.68$, 10.42, 17.10 Hz, 1 H), 6.12 (m, 1 H), 7.38−7.49 (m, 6 H), 7.67−7.73 (m, 4 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 22.9, 39.5, 58.4, 64.4, 78.3, 81.9, 110.9, 115.2, 121.8, 128.2, 128.3, 130.7, 130.9, 131.0, 131.8, 131.9, 134.5, 135.1, 135.2, 136.3, 141.8, 146.0, 159.0; HRMS [FAB, MH^+] calcd for $C_{25}H_{26}NO_4Si$ 432.1631, found 432.1636.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-8-*O*-acetyl-9-*O*-trimethylacetyl-2-azabicyclo[4.3.0]-5,7-diene (29). To a solution of **20** (40 mg, 0.14 mmol) in CH_2Cl_2 (1.5 mL) was added trimethylacetic anhydride (40 mg, 0.21 mmol) at 0 °C, followed by addition of TMSOTf (20 μL, 1 M in CH_2Cl_2) slowly. The reaction mixture was stirred at 0 °C for 30 min. TLC showed that all starting material was consumed. Saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (20 mL) were poured into the reaction mixture. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography of the residue on silica gel with hexanes/EtOAc (6:1) afforded **29** (40 mg, 0.11 mmol, 80%) as a colorless oil: $[\alpha]^{20}_D = -65.9$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2925, 2853, 1733, 1704, 1423, 1150, 771 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 1.12 (1.19 rotamer) (s, 9H), 1.28 (t, $J = 7.10$ Hz, 3 H), 2.09 (s, 3 H), 2.14−2.39 (m, 2 H), 2.77 (br, m, 1 H), 4.12−4.17 (m, 4H), 4.56 (app q, $J = 3.78$, 3.83 Hz, 1 H), 5.34 (br, s, 2 H), 5.39 (d, $J = 4.40$ Hz, 1 H), 5.70 (s, 1 H), 6.53 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD, 50 °C) δ 15.0, 21.0, 25.7, 27.6, 27.8, 40.0, 41.8, 57.7, 63.1, 77.1, 112.7, 122.3, 137.2, 143.8, 157.5, 171.6, 178.8; HRMS [FAB, MH^+] calcd for $C_{19}H_{28}NO_6$ 366.1917, found 366.1920.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-8-*O*-allyldimethylsilyl-9-*O*-trimethylacetyl-2-azabicyclo[4.3.0]-5,7-diene (30). To a solution of alcohol **29** (40 mg, 0.11 mmol) in methanol (3 mL) was added K_2CO_3 (15 mg, 0.11 mmol) at room temperature. The resulting reaction mixture was stirred at room temperature for 1 h. TLC analysis showed that starting material was consumed. MeOH was removed under reduced pressure, and then CH_2Cl_2 (20 mL) was added to redissolve the residue, followed by saturated aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4 and filtered. The solvent was evaporated to provide a light yellow oil residue. To a solution of this crude residue (∼36 mg) in CH_2Cl_2 (4 mL) was added a catalytic amount of DMAP (1−2 mg) and triethylamine (0.07 mL) at room temperature, followed by addition of allyldimethylsilyl chloride (25 mg, 0.34 mmol) at 0 °C. The mixture warmed to room temperature and was stirred at room temperature for 0.5 h. The solvent was removed under reduced pressure to give a white solid residue. Et_2O (30 mL) was added, and then the mixture was filtered. The filtrate was concentrated. Flash chromatography of the residue on silica gel with hexanes/EtOAc (7:1) afforded **30** (34 mg, 0.082 mmol, 74% for two steps): $[\alpha]^{20}_D = -128.6$ ($c = 0.7$, $CHCl_3$); IR (thin film) 2924, 1734, 1706, 1678, 1636, 1152, 771 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.22 (0.15, rotamer) (br s, 6 H), 1.11 (s, 9 H), 1.25−1.28 (m, 3 H), 1.71 (d, $J = 7.95$ Hz, 2 H), 2.17−2.28 (m, 2 H), 2.73 (br, m, 1 H), 4.15−4.22 (m, 4 H), 4.65 (br, s, 1 H), 4.89 (dd, $J = 13.50$, 24.11 Hz, 2 H), 5.11 (s, 1 H), 5.15 (br, s, 1 H), (5.58 (br, s, 1 H), 5.81 (dt, $J = 8.48$, 17.48, 17.30 Hz, 1 H), 6.40 (m, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ −1.7, −1.6, 14.8, 24.8, 27.3, 29.9, 39.0, 40.3, 56.1, 61.7, 75.7, 77.9, 109.7, 114.1, 120.4, 133.9, 136.?2, 145.5, 156.0, 178.0; HRMS [FAB, MH^+] $C_{22}H_{36}NO_5Si$ 422.2363, found 422.2366.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-7-cyclo-8-*O*-allyldimethylsilyl-9-*O*-trimethylacetyl-2-azabicyclo[4.3.0]-5,7-diene (31). To a solution of **30** (34 mg, 0.081 mmol) in CH_2Cl_2 (6 mL) was added Grubbs II catalyst **23** (1.5 mg, ∼2 mol %), and the reaction mixture was heated to reflux under Argon. After 1 h, the reaction was cooled to room temperature and concentrated to dryness under vacuum.

Examination of the crude reaction mixture by ^{1}H NMR indicated complete consumption of **30** with clean and quantitative formation of the tethered diene **31**. The crude reaction mixture was filtered through a pad of silica gel quickly (compound **31** was found to decompose on silica TLC over 5 min at room temperature) with hexanes/EtOAc (1:1) to afford **31** (30 mg, 0.076 mmol, 94%) as a light yellow oil: $[\alpha]^{20}_D = -36.2$ ($c = 0.5$, $CHCl_3$); IR (thin film) 2925, 2653, 1733, 1705, 1463, 1283, 1151, 1056, 834 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.10 (s, 3 H), 0.25 (s, 3 H), 1.16 (s, 9 H), 1.27 (app dd, $J = 5.31$, 8.55 Hz, 3 H), 1.37−1.43 (br, m, 1H), 1.60 (app dd, $J = 8.82$, 15.97 Hz, 1 H), 2.19 (br, m, 2 H), 2.77 (m, 1 H), 4.12−4.25 (m, 4 H), 4.40 (m, 1 H), 5.37 (d, $J = 5.37$ Hz, 1 H), 6.10 (m, 1 H), 6.20 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.660, 156.254, 136.785, 134.863, 122.606, 115.510, 78.113, 71.681, 61.462, 55.968, 40.471, 38.428, 29.356, 26.173, 24.000, 19.391, 13.586, −3.852, −3.895; HRMS [FAB, MH$^+$] calcd for $C_{20}H_{32}NO_5Si$ 394.2050, found 394.2041.

(1*S*,8*S*,9*S*)-2-(Carbethoxy)-7-(*Z*)-8-*O*-hydroxy-9-*O*-trimethylacetyl-2-azabicyclo[4.3.0]-5,7-diene (32). To a solution of compound **31** (30 mg, 0.076 mmol) in MeOH/THF (1.5 mL/1.5 mL) at 0 °C were added $KHCO_3$ (33 mg, 0.33 mmol) and KF (19 mg, 0.33 mmol). The resulting reaction mixture was allowed to warm to room temperature over 0.5 h and then stirred at room temperature for 2 h. TLC indicated complete consumption of the starting material, and the reaction mixture was poured into water and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated. Flash chromatography of the residue on silica gel with hexanes/EtOAc (1:1) afforded compound **32** (12.8 mg, 0.038 mmol, 50%) as a colorless oil: $[\alpha]^{20}_D = -132.7$ ($c = 0.06$, CH_2Cl_2); IR (thin film) 2960, 2926, 2854, 1734, 1706, 1426, 1283, 1153, 1055, 771 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13 (s, 9H), 1.28 (t, $J = 7.0$ Hz, 3 H), 1.87 (d, $J = 7.0$ Hz, 3 H), 2.20 (s, br, 2H), 2.22 (s, br, OH), 4.15−4.23 (m, 4 H), 4.50−4.64 (m, 2H), 5.26 (s, 1 H), 6.14−6.23 (m, 2 H); HRMS [FAB, MH$^+$] calcd for $C_{18}H_{28}NO_5$ 338.1967, found 338.1965.

(+)-Steptazolin (1). A solution of **32** (12.8 mg, 0.038 mmol) in 1.5 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 EtOAc (4 × 5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide (+)-steptazolin **1** (6 mg, 0.030 mmol, ∼76%) as a colorless oil (since we also found that streptazolin partially decomposed when concentrated and purified by chromatography on silica gel, the mixture was immediately diluted with deuterated chloroform to provide crude NMR data): $[\alpha]^{20}_D = +21.8$ ($c = 0.5$, $CHCl_3$); IR (thin film) 3420, 2956, 2924, 1734, 1380, 1201, 1038 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.91 (d, $J = 7.5$ Hz, 3 H), 2.15−2.24 (m, 1 H), 2.51 (dtd, $J = 17.5$, 7.0, 3.5 2 Hz, 1 H) 3.37−3.45 (m, 2 H), 4.28−4.30 (overlap d, br, $J = 7.5$, 1 H), 4.74 (d, $J = 7$ Hz, 1 H), 4.88 (s, br, 1 H), 6.04 (m, 1 H), 6.16 (q, $J = 7.5$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.1, 23.0, 40.1, 59.3, 74.6, 81.7, 119.0, 123.9, 139.1, 143.0, 159.1; HRMS [FAB, MH$^+$] calcd for $C_{11}H_{14}NO_3$ 208.0974, found 208.0972.

(+)-Dihydrostreptazolin Acetate (2). To a solution of **1** (6 mg, 0.030 mmol) in ethanol (1.5 mL) was added 10 wt % Pd on activated carbon (6 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 1.2 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 5 mg of chromatographically pure dihydrostreptazolin. To a solution of this material in CH_2Cl_2 (1 mL) was added Ac_2O (0.012 mL, 0.30 mmol) and pyridine (0.05 mL, 0.60 mmol) at room temperature. The resulting reaction mixture was stirred for 15 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 (86% for two steps) of dihydrostreptazolin acetate **2** (6.8 mg, 0.27 mmol, 90% for two steps) as a white crystalline solid. All of the spectral data and physical properties are identical to our previous reported data[11] and the original literature.[4]

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of new compounds **11**, **19**−**27**, **29**−**31**, **1**, and **2**. ^{1}H NMR of compound **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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