Enantioselective Total Synthesis of Streptazolin. The Tandem Use of Iminium Ion–Vinylsilane Cyclizations and Intramolecular Acylations[1]

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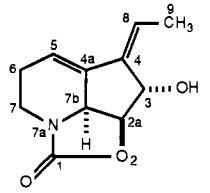
Abstract: The first enantioselective total syntheses of the natural antibiotic (+)-streptazolin (**1**) and its dihydro derivative **2** are described. Key steps are a stereoselective vinylsilane-terminated cyclization of a tartrate-derived *N*-acyliminium ion (**17** → **18**) and the intramolecular acylation of a vinyllithium intermediate (**21** → **22**).

The neutral lipophilic antibiotic streptazolin (**1**)[2] was recently isolated by Drautz and Zähner from cultures of *Streptomyces viridochromogenes*.[3] The isolation and purification of this antibiotic were markedly complicated by its propensity to polymerize upon concentration from organic solutions. Hydrogenation of streptazolin affords a stable dihydro product, whose crystalline acetate **2** was employed in much of the structural investigations.



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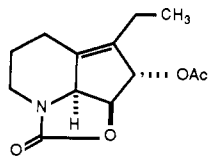

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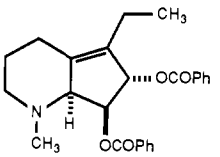
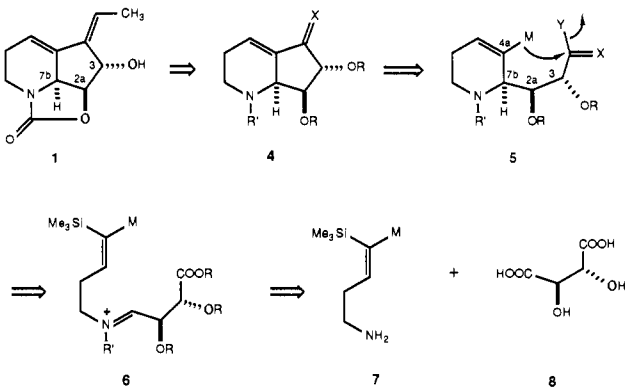


3

The structure of streptazolin, with the exception of the ethylidene stereochemistry, was established originally by classical chemical degradation and spectroscopic studies in Keller-Schlierlein's laboratory.[3] The absolute configuration of streptazolin was shown[3] to be 2a*S*,3*S*,7b*S* by application of the Nakanishi[4] dibenzoate chirality method to streptazolin degradation product **3**. The structure of dihydrostreptazolin acetate (**2**) was subsequently confirmed by crystallographic analysis.[5] Finally, Kozikowski and Park[6] showed that the stereochemistry of the ethylidene substituent was *Z* by ^{1}H NMR DNOE experiments. Preliminary pharmacological investigations show that dihydrostreptazolin exhibits limited antibacterial and antibiotic activity as well as effects on thymidine incorporation in mouse spleen lymphocytes.[3]

We were attracted to pursue the preparation of streptazolin by the unusual ring system[7] of this antibiotic and the belief that

Scheme I



chemistry recently developed in our laboratories for the regioselective synthesis of 1,2,5,6-tetrahydropyridines[1,8] would be particularly useful in this total-synthesis endeavor. During the course of our efforts to prepare optically active streptazolin, Kozikowski and Park[6] reported an excellent first total synthesis in this area, that of racemic streptazolin.

In this paper we detail the first total synthesis of natural (+)-streptazolin. The synthetic route is short and affords the target antibiotic in high enantiomeric purity. This synthesis, moreover, introduces a useful new sequence for controlled formation of bicyclic systems in which an iminium ion–vinylsilane cyclization is coupled with an intramolecular acylation.[1]

Results and Discussion

Synthetic Strategy and Preliminary Investigations. Our approach to the synthesis of (+)-streptazolin (see Scheme I) was based on two considerations: (1) the absolute chirality of L-tartaric acid (**8**) transcripts directly onto carbons 2a and 3 of the antibiotic target and (2) tetrahydropyridines can be readily prepared with regioselective incorporation of substituents at the vinylic carbons via iminium ion initiated cyclizations of vinylsilanes.[1,8] Since this substituent can be a heteroatom (e.g., Br, I, or $SiMe_3$),[8] a tetrahydropyridine intermediate **5** would be endowed with appropriate functionality for transformation to the key bicyclic pyrindine intermediate **4**. A variety of possibilities are available, in principle, for the substituents M, X, and Y of intermediate **5**. In our initial approach to streptazolin which is detailed here, we chose to form the cyclopentane ring by intramolecular acylation of a vinyllithium intermediate (M = Li, X = O). Recent investigations by Piers[9]

(1) For recent reviews of our studies of electrophilic cyclizations of vinylsilanes, see: Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857. Overman, L. E. *Lect. Hetrocycl. Chem.* **1985**, *8*, 59.

(2) The *Chemical Abstracts* name is [2a*S*-(2aα,3α,4*Z*,7bα)]-4-ethylidene-2a,3,4,6,7,7b-hexahydro-3-hydroxy-1*H*-2-oxa-7a-azacyclopent-[*cd*]inden-1-one. This numbering system will be employed for streptazolin and all synthetic intermediates in the Results and Discussion section of this paper.

(3) Drautz, H.; Zähner, H.; Kupfer, E.; Keller-Schlierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752.

(4) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989.

(5) Karrer, A.; Dobler, M. *Helv. Chim. Acta* **1982**, *65*, 1432.

(6) Kozikowski, A. P.; Park, P. *J. Am. Chem. Soc.* **1985**, *107*, 1763. Park, P. Ph.D. Thesis, University of Pittsburgh, 1985.

(7) The hexahydropyrindine ring system (the bicyclic ring system containing carbons 3 and 6 of streptazolin) is not, to our knowledge, found in any other natural products.

(8) (a) Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993. (b) Flann, C.; Malone, T. C.; Overman, L. E., submitted for publication. (c) Overman, L. E.; Malone, T. C.; McCann, S. F. *Org. Synth.*, submitted.

(9) See, e.g.: Piers, E.; Friesen, R. W. *J. Org. Chem.* **1986**, *51*, 3405. Piers, E.; Tse, H. L. A. *Tetrahedron Lett.* **1984**, *25*, 3155.

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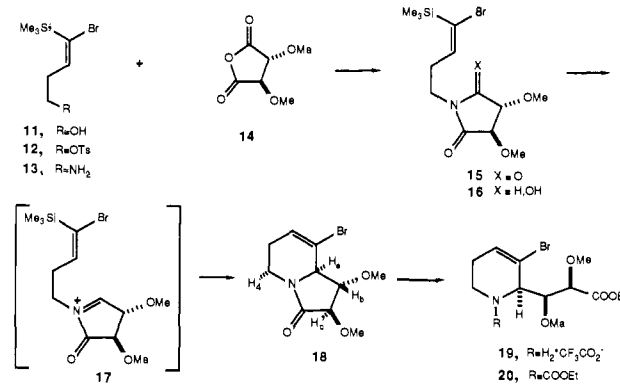
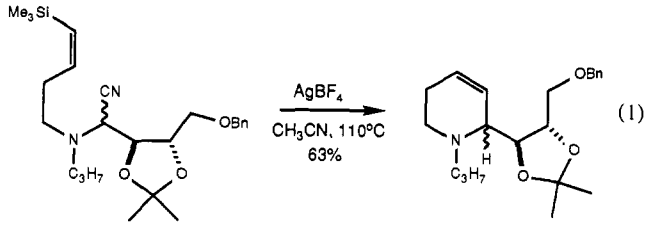
Scheme II



and earlier studies by Parham and others[10] provided the appropriate background for this choice.

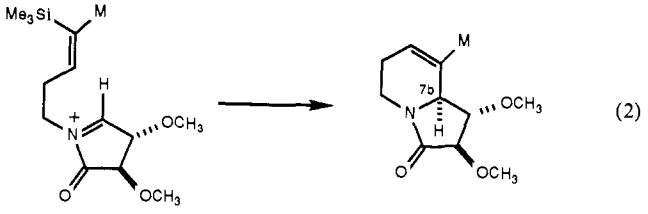
The initial stereochemical issue to address was the ability of the tartrate moiety to induce the proper chirality at C-7b in the first cyclization step. At the outset we felt that the lack of rigidity would compromise asymmetric induction in cyclizations of acyclic intermediates such as **6**. Nonetheless, we briefly examined the model cyclization shown in eq 1, since the amine[8] and aldehyde



(1)

precursors of **9**[11] were available in our laboratories. Cyclization of **9** in the presence of $AgBF_4$ occurred, as anticipated, in a nearly stereorandom fashion to give **10** as a 45:55 mixture of diastereomers.[12]

We consequently turned to the use of the cyclic tartrate-derived cyclization initiator introduced by Speckamp and Wijnberg,[13] which, in the case at hand (see eq 2), would induce the proper

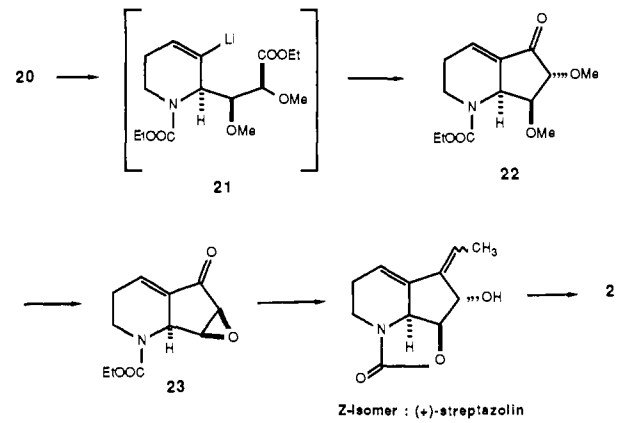


(2)

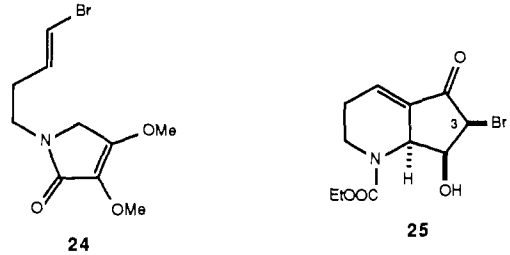
chirality at C-7b if stereoinduction was dominated by the proximal methoxy group. Although the earlier studies[13] of asymmetric induction using this initiator had given mixed results (varying from complete stereoinduction to no stereoinduction), it appeared from a consideration of molecular models that a bulky *Z*-trimethylsilyl group at the terminus of the alkene nucleophile would assist in obtaining the desired stereochemical result.

Total Synthesis of (+)-Streptazolin. The preparation of imide **15** (see Scheme II) began with bromo vinylsilane alcohol **11**, which is available[8b,c] in four steps and 60% overall yield from 3-butyn-1-ol. Conventional aminolysis of the tosylate derivative **12** provided amine **13** in 61% yield from **11**. The known[14] anhydride **14**

Scheme III



(available in three steps and ~50% yield from L-tartaric acid) was coupled with amine **13** following a conventional sequence[15] of first heating the two components to form the corresponding amide acid and subsequently dehydrating this intermediate with acetyl chloride to form the cyclic imide. In this way, imide **15** could be obtained in reproducible yields of ~90%.[16] Reduction[17] of **15** with an excess of $NaBH_4$ in methanol, followed by cyclization of the crude hydroxy amide **16** in refluxing trifluoroacetic acid afforded a single bicyclic product. Careful purification of this material by vacuum distillation and chromatography provided **18** in 74% yield. Since subsequent conversions of **18** were not highly sensitive to its purity, the volatile product obtained in 87% yield was typically employed. Attempted cyclization of **16** in formic acid or in mixtures of trifluoroacetic acid and acetonitrile afforded **18** in low yields only. The major product isolated in these reactions was the protodesilylated α,β-unsaturated lactam **24**. This intermediate would arise from **17** by deprotonation to the enamide, double-bond migration, and protodesilylation of the vinylsilane moiety.



The stereostructure of **18** was initially assigned on mechanistic grounds (vide supra) and on the basis[13] of the 5.9-Hz coupling constant observed between the trans methine hydrogens H_a and H_b. Indolizidinone **18** also exhibits an unusually large[18] (1.2 Hz) five-bond coupling between the axial-oriented hydrogens H_c and H_d which flank the amide group. The stereochemistry at C-7b was ultimately defined by ring opening of **18** to provide the crystalline carbamate ester **20**, mp 65–66 °C, whose structure was confirmed by X-ray crystallography.[19] The conversion to this key intermediate was accomplished by O-alkylation of the amide with $Et_3O^+BF_4^-$, which was best carried out in the presence of

(10) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.
(11) Mukaiyama, T.; Suzuki, K.; Yamada, T. *Chem. Lett.* **1982**, 929.
(12) The imine analogue of **9** cyclized in the presence of 5 equiv of trifluoroacetic acid in refluxing acetonitrile (60%, 4 h) to give a 1.2:1 mixture of diastereomeric secondary amine products.
(13) (a) Speckamp, W. N.; Wijnberg, B. P. *Tetrahedron Lett.* **1980**, *21*, 1987. (b) Wijnberg, B. P. Ph.D. Thesis, University of Amsterdam, 1985.
(14) Felner, I.; Schenker, H. *Helv. Chim. Acta* **1970**, *53*, 754.
(15) See, e.g.: Lejczak, B.; Kafarski, P.; Soroka, M.; Mastalerz, P. *Synthesis* **1984**, 577.
(16) The one-step procedure of Speckamp and Wijnberg for preparing tartarimides proceeded in yields of <50%. The lack of success reported by Wijnberg[13b] in using the acetyl chloride procedure to prepare N-unsubstituted tartarimides probably derives from the low solubility of these substrates in acetyl chloride.
(17) Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.
(18) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: Oxford, 1969; p 3238. Chapman, O. L.; Hoganson, E. D. *J. Am. Chem. Soc.* **1964**, *86*, 498.
(19) The unweighted *R* value was 0.041.

0.3 equiv of 2,6-di-*tert*-butylpyridine. Hydrolysis of the resulting imidate salt in aqueous trifluoroacetic acid provided tetrahydropyridine salt **19**, which quickly relactamized to **18** in the presence of base. However, this amino ester could be trapped with an excess of ethyl chloroformate to provide the desired monocyclic intermediate **20** in 62% overall yield from **18**.

Cyclization of **20** to form the bicyclic pyrindine ring system proved easier than anticipated. Thus, simple treatment of **20** in THF at −78 °C with 1.2 equiv of *sec*-butyllithium provided bicyclic enone **22** in yields of 60–70% (see Scheme III). Reproducibility in this transformation required that the organolithium reagent be added slowly at −78 °C and that the reaction be quenched at this temperature with acetic acid. The success of this conversion is notable in light of the dense functionality of the vinyllithium intermediate **21**. To our knowledge, this conversion is one of few examples of the successful intramolecular acylation[10] of an organolithium intermediate with an ethyl ester.

In an attempt to cleave the methyl protecting groups, enone **22** was treated at 0 °C with 2.5 equiv of BBr_3. Quenching this reaction into a solution of $NaHCO_3$ in aqueous methanol at room temperature provided, to our surprise, the epoxy ketone **23**, mp 69–70 °C. The properties of this intermediate, with the exception of optical rotation and melting point,[20] were identical with those reported[6] for a racemic sample of this material. An intermediate in this transformation could be detected by TLC analysis immediately after the bicarbonate quench and was slowly converted to the epoxy ketone **23**. Unfortunately, attempts to isolate or characterize this material resulted in its decomposition. A possible candidate[21] for this intermediate is the β-hydroxy-α-bromo ketone **25**, which would need to epimerize at C-3 prior to cyclization to the observed epoxide product.

The synthesis of (+)-streptazolin was completed easily from epoxide **23** by the three-step sequence developed earlier by Kozikowski and Park.[6] Thus, **23** was treated sequentially with ethylidenetriphenylphosphorane, sodium acetate, and sodium methoxide to provide a 1:2 mixture of (+)-streptazolin and its *E*-ethylidene stereoisomer. Since we also found[3,6] that these materials partially decomposed upon isolation, the enantiomeric purity of our product was ascertained after hydrogenation and acetylation[3] to yield the stable crystalline dihydro acetate **2**. This five-step sequence provided (+)-dihydrostreptazolin acetate (**2**), mp 76–77 °C, in 24% overall yield. The optical rotation of our synthetic product at the sodium D line was +142°, which compared favorably with that reported[3] ($[\alpha]_D$ +143°) for the natural antibiotic derivative. Synthetic (+)-dihydrostreptazolin acetate was also indistinguishable from an authentic sample provided by Professor Keller-Schlierlein by mixture melting point and comparison of spectroscopic and chromatographic properties.

Conclusion

This report details the first enantioselective total synthesis of the structurally unusual antibiotic (+)-streptazolin and its more stable dihydro derivative **2**. The total synthesis of (+)-dihydrostreptazolin acetate (**2**) was accomplished in a stereocontrolled fashion in ten total steps (involving six isolated and purified intermediates) from the readily available tartrate-derived anhydride **14**. The overall yield from anhydride **14** was 4.2%, while the yield from commercially available L-(+)-diethyl tartrate was 2.2%. Significantly, this synthesis exercise demonstrates a new highly controlled sequence for assembling unsaturated bicyclic systems in which the product of a vinylsilane-termination cyclization is employed to trigger a second cyclization reaction at a vinylic center. We anticipate that this strategy will find other applications in the area of complex-molecule total synthesis.

Experimental Section[23]

(*E*)-4-Bromo-4-(trimethylsilyl)-3-buten-1-yl *p*-Toluenesulfonate (12). A solution of **11**[8b] (6.67 g, 29.9 mmol), *p*-toluenesulfonyl chloride (6.56 g, 34.4 mmol), and dry pyridine (60 mL) was stirred at 0 °C until all the sulfonyl chloride had dissolved, and the resulting solution was kept at −20 °C for 24 h. The reaction mixture was then poured onto ice and extracted with Et_2O. The ether extracts were washed with cold $Cu(NO_3)_2$ solution until no color change was observed and further washed with H_2O, 1 M HCl, and brine. After drying ($MgSO_4$) concentration gave 9.4 g (83%) of **12** as a pale yellow solid. Recrystallization from petroleum ether (30–60 °C) gave analytically pure white crystals: mp 59–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 6.94 (d, *J* = 7.2 Hz, 2 H, Ar*H*), 6.17 (t, *J* = 7.1 Hz, CR_2=C*H*R), 3.85 (t, *J* = 7.2 Hz, CH_2OR), 2.40 (m, 5 H, ArCH_3 and CH_2CH_2OR), 0.33 (s, 9 H, $SiCH_3$); IR (KBr) 3029, 2971, 2858, 1609, 1355, 1178, 939, 850 cm^{-1}; MS (CI, isobutane) *m/z* 379 (MH^+), 377 (MH^+), 245, 207, 205, 135, 133, 110. Anal. Calcd for $C_{14}H_{21}BrO_3SSi$: C, 44.56; H, 5.57. Found: C, 44.63; H, 5.58.

(*E*)-4-Bromo-4-(trimethylsilyl)-3-buten-1-amine (13). A solution of **12** (9.40 g, 24.9 mmol) and dry THF (20 mL) was added to 20 mL of ammonia condensed in a Fisher-Porter pressure bottle at −70 °C. The bottle was closed and the temperature was allowed to rise to room temperature. *Caution*: A pressure of 130 psi develops in the pressure bottle. This solution was maintained at room temperature for 48 h and the pressure was vented slowly and the ammonia allowed to evaporate. The residue was diluted with CH_2Cl_2 (100 mL) and washed with 1 M NaOH. The basic washes were extracted with CH_2Cl_2, and the organic phases were combined, dried (K_2CO_3), and concentrated. The crude amine was purified by distillation (0.1 mm) to give 4.1 g (73%) of **13**: bp 51–53 °C (0.1 mm); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (t, *J* = 8.0 Hz, CR_2=C*H*R), 2.76 (t, *J* = 6.8 Hz, CH_2NH_2), 2.23 (q, *J* = 6.8 Hz, $CH_2CH_2NH_2$), 1.2 (bs, NH_2), 0.27 (s, 9 H, $SiCH_3$); IR (film) 3371, 2955, 1600, 1250, 842 cm^{-1}; MS (CI, isobutane) *m/z* 224 (MH^+), 142; high-resolution MS (EI, 70 eV) 205.9975 [206.0000 calcd for C_6H_{13}BrNSi (M − CH_3)].

(3*R*,4*R*)-1-[(*E*)-4-Bromo-4-(trimethylsilyl)-3-butenyl]-3,4-dimethoxypyrrolidine-2,5-dione (15). A solution of amine **13** (2.94 g, 13.1 mmol), anhydride **14**[14] (2.1 g, 13.12 mmol), and CH_2Cl_2 (40 mL) was left at room temperature overnight. After concentration, the crude acid amide was resuspended in toluene (30 mL), and this mixture was warmed to 90 °C, at which time a clear solution was formed. Thionyl chloride was added (2.1 mL, 29 mmol), and the resulting solution was stirred for an additional 30 min at 90 °C and then concentrated. Flash chromatography (240/400-mesh silica gel, 4:1 hexane–Et_2O → 2:1 hexane–Et_2O) gave 4.24 g (89%) of **15** as a pale yellow oil: $[\alpha]_D$ + 127° (*c* 1.02, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.65 (t, *J* = 8.0 Hz, C*H*=C), 4.12 (s, C*H*OCH$_3$C*H*OCH$_3$), 3.70 (s, OCH_3), 3.55 (m, R_2NCH_2), 2.39 (q, *J* = 7.7 Hz, CH_2CH=C) 0.27 (s, $SiCH_3$); IR (film) 2954, 1721, 1396, 1348, 1252, 1088, 844 cm^{-1}; MS (CI, isobutane) *m/z* 366 (MH^+), 364 (MH^+), 284; high-resolution MS (EI, 70 eV) 363.0503 (363.0501 calcd for $C_{13}H_{22}BrNO_4Si$).

8-Bromo-1,2-dimethoxy-1,5,6,8a-tetrahydro-3(2*H*)-indolizinone (18). To a solution of imide **15** (1.77 g, 4.84 mmol) and methanol (50 mL) at 0 °C was added $NaBH_4$ (1.75 g, 48.4 mmol) in portions. The reaction was stirred at this temperature for an additional 15 min and then quenched by the addition of a saturated solution of $NaHCO_3$. The aqueous portion was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The crude hydroxy lactam **16** was dissolved immediately in trifluoroacetic acid (35 mL) and heated at reflux for 6 h. After cooling to room temperature, the solution was concentrated and then diluted with CH_2Cl_2, and the CH_2Cl_2 solution was washed with 1 M NaOH, dried ($MgSO_4$), and concentrated. Distillation of the residue (150 °C, 0.3 mm, bulb-to-bulb) gave 1.17 g (87%) of **18** as an amber oil of sufficient purity (~85%) for use in the next reaction.

An analytical sample of **18** was obtained by HPLC (silica gel, 2:1 hexane–EtOAc): $[\alpha]_D$ +198° (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3COCD_3) δ 6.21 (m, CH=C), 4.10 (dd, *J* = 13.1, 6.37 Hz, equatorial CH_2NCO), 4.04 (m, C=CBrC*H*), 3.97 (*J* = 1.3, 5.9 Hz, NCOC*H*OCH3), 3.61 (s, OCH_3), 3.58 (apparent t, *J* = 5.9 Hz, NCOCHOCH$_3$C*H*OCH$_3$), 3.47 (s, OCH_3), 2.87 (ddt, *J* = 1.2, 5.05, 12.70 Hz, axial CH_2NCO), 2.26 (m, 1 of CH_2CH=C), 2.16 (m, 1 of CH_2CH=C); IR (film) 2988, 2934, 1709, 1430, 1174, 841 cm^{-1}; MS (CI, isobutane) *m/z* 278 (MH^+), 276 (MH^+); high-resolution MS (EI,

(20) Racemic epoxide **23** is reported[6] to be an oil.

(21) Nucleophilic substitution reactions of leaving groups α to ketones is often faster than the corresponding reactions of methyl substrates.[22]

(22) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; Chapter 3. Bordwell, F. G.; Branner, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4545.

(23) General experimental procedures have been described.[24] ^{1}H NMR spectra at 300 and 500 MHz were determined with GE QE-300 and GN-500 spectrometers, respectively. Chemical shift assignments employ the numbering system implicit in the compound name.

(24) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745.

70 eV) 275.0136 (275.0157 calcd for $C_{10}H_{14}BrNO_3$).

(2*R*)-3-Bromo-1-(carboethoxy)-2-[(1*S*,2*R*)-2-(carboethoxy)-1,2-dimethoxyethyl]-1,2,5,6-tetrahydropyridine (20). To a solution of **18** (1.87 g, 6.79 mmol) and CH_2Cl_2 (10 mL) was added triethyloxonium tetrafluoroborate (1.93 g, 10 mmol) and 2,6-di-*tert*-butylpyridine (460 μL, 2.0 mmol), and the resulting solution was stirred at room temperature for 6 h. The reaction was then concentrated and the residue redissolved in CH_3CN (20 mL). This solution was cooled to 0 °C and 30% aqueous trifluoroacetic acid (2 mL) was added slowly with stirring. The cooling bath was then removed and after 10 min the reaction was concentrated and the residue was azeotropically dried by concentration with 2–10-mL portions of dry benzene. The resulting amine salt **19** was dissolved in CH_2Cl_2 (15 mL), the mixture was cooled to 0 °C, and ethyl chloroformate (2.3 mL, 19.7 mmol) was added. Triethylamine (3.3 mL, 23.7 mmol) was then added slowly to the stirring reaction mixture and after 30 min the reaction was quenched by pouring into a mixture of 1 M HCl and CH_2Cl_2. The organic portion was washed sequentially with 1 M HCl (3×) and 1 M NaOH, dried ($MgSO_4$), and concentrated. Chromatography (240/400-mesh silica gel, 2:1 hexane–ethyl acetate) gave 1.6 g (62%) of **20** as an amber solid. Recrystallization from hexane gave analytically pure **20** as white fluffy crystals: mp 65–66 °C; $[\alpha]_D$ −141° (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, toluene, 85 °C) δ 5.90 (m, CH=C), 5.18 (m, C-2 H), 4.3–3.9 (m, 7 H), 3.40 (s, OCH_3), 3.33 (s, OCH_3), 2.95 (m, axial C-6 H), 2.1–1.9 (m, 1 of C-5 H), 1.0–1.5 (m, 1 of C-5 H), 1.1–1.0 (m, 6 H, CH_2CH_3); IR (KBr) 2966, 2955, 2835, 1752, 1706, 1445, 1107, 755 cm^{-1}; MS (CI, isobutane) *m/z* 396 (MH^+), 394 (MH^+); high-resolution MS (EI, 70 eV) 393.0777 (393.0787 calcd for $C_{15}H_{24}BrNO_6$). Anal. Calcd for $C_{15}H_{24}BrNO_6$: C, 45.68; H, 6.09; N, 3.55. Found: C, 45.78; H, 6.18; N, 3.52.

(1*S*,8*R*,9*S*)-2-(Carboethoxy)-8,9-dimethoxy-2-azabicyclo[4.3.0]non-5-en-7-one (22). Carbamate **20** (103 mg, 0.26 mmol) was dissolved in dry benzene (5 mL), and the mixture was concentrated to azeotropically dry the sample. This process was repeated three times and then dry THF (3 mL) was added and the resulting solution was cooled to −78 °C and rapidly stirred. A hexane solution of *sec*-BuLi (0.22 mL of a 1.4 M solution, 0.31 mmol) then was added *slowly* (one drop per second). After an additional 30 min at −78 °C, the stirred reaction was quenched by adding glacial acetic acid (0.2 mL) and the cooling bath was removed. Aqueous 3 M HCl (0.5 mL) then was added, the reaction mixture was allowed to warm to room temperature where it was poured into CH_2Cl_2, and the aqueous phase was separated. The organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated. Chromatography (200/400-mesh silica gel, 3:2 hexane–Et_2O) gave 44 mg (66%) of chromatographically pure enone **22** as a yellow oil: $[\alpha]_D$ −80.0° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, toluene 85 °C) δ 6.72 (m, CH=CCO), 4.80 (bs, NC*H*R), 4.20–3.95 (m, 4 H), 3.32 (s, 1 H), 3.30 (s, OCH_3), 3.05 (s, OCH_3), 2.15–2.05 (m, axial CH_2NCO_2R), 1.7–1.6 (m, $CH_2CH{=}CR_2$), 1.05 (t, J = 7.0 Hz, CH_2CH_3); IR (film) 2952, 2904, 2831, 1731, 1705, 1660, 1449, 1103, 771 cm^{-1}; MS (CI, isobutane) *m/z* 270 (MH^+), 238; high-resolution MS (EI, 70 eV) 269.1269 (269.1263 calcd for $C_{13}H_{19}NO_5$).

(1*S*,8*S*,9*S*)-2-(Carboethoxy)-8,9-epoxy-2-azabicyclo[4.3.0]non-5-en-7-one (23). Enone **22** (111 mg, 0.41 mmol) was dissolved in CH_2Cl_2 (1 mL), and the resulting solution was cooled with stirring to 0 °C, at which time boron tribromide (1 mL of a 1.0 M solution, 1.0 mmol) was added. After 1 h at 0 °C the reaction mixture was added via a plastic syringe to a rapidly stirring solution of saturated aqueous sodium bicarbonate (20 mL). The syringe and reaction flask were rinsed with methanol, and these washes were added to the flask containing the quenched reaction mixture. The ice bath was removed and methanol was added until the CH_2Cl_2 phase had dissolved. Stirring was continued until TLC analysis of the reaction mixture (~20 min later) showed that an initially formed intermediate had been converted into epoxy ketone **23**. This mixture was filtered and the filtrate was extracted with CH_2Cl_2. The combined organic phases were washed with saturated $NaHCO_3$ solution and brine and were dried (K_2CO_3). Filtration and concentration of the filtrate gave 84 mg of crude **23**. Chromatographic purification (200/400-mesh silica gel, CH_2Cl_2) provided 51 mg (56%) of chromatographically pure **23** as a colorless oil. Recrystallization from hexane gave white needles: mp 69–70 °C; $[\alpha]_D$ −413° (*c* 0.4, $CHCl_3$). Spectroscopic properties of **23** were identical with those reported by Kozikowski and Park.[6]

(+)-5,8-Dihydrostreptazolin 3-Acetate (2). Epoxy enone **23** (33 mg, 0.15 mmol) was converted to a 1:2 mixture[25] of (+)-streptazolin (**1**) and its *E*-ethylidene isomer by sequential treatment with $Ph_3P{=}CHCH_3$ (ether, 65 °C), 25% NaOAc/HOAc (23 °C), and 5% NaOMe/MeOH (23 °C) following the procedure described by Kozikowski and Park.[6] Since we also found that streptazolin polymerized readily when concentrated, in this run the ethyl acetate solution of crude **1** and its ethylidene stereoisomer was diluted with EtOH and directly hydrogenated at atmospheric pressure (15 mg of 10% Pd on carbon catalyst, 23 °C). Purification by flash chromatography (200/400-mesh silica gel, 2:3 hexane–EtOAc) gave 7.5 mg of chromatographically pure 5,8-dihydrostreptazolin. A CH_2Cl_2 (1.0 mL) solution of this material was acetylated[3] with Ac_2O (0.05 mL, 1.2 mmol) and pyridine (0.1 mL, 1.2 mmol) at 23 °C for 12 h. Concentration and purification of the residue on silica gel (2:3 hexane–EtOAc) gave 9 mg (24% from **23**) of dihydrostreptazolin acetate **2** as a white crystalline solid, $[\alpha]_D$ +139° (*c* 0.3, $CHCl_3$). Recrystallization from hexane–EtOAc gave pure **2** as colorless crystals: mp 76–77 °C (lit.[3] mp 76–77 °C); $[\alpha]_D$ +142° (c 0.2, $CHCl_3$). Spectral (300-MHz ^1H NMR, FT-IR, and mass spectra) and chromatographic properties of this material were indistinguishable[3] from those of an authentic sample of (+)-dihydrostreptazolin acetate.

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Registry No. 1, 80152-07-4; **1** (*E* isomer), 109958-09-0; **2**, 80152-10-9; **2** (deacetyl), 80152-09-6; **9**-(*S*), 109908-59-0; **9**-(*R*), 109958-10-3; **10**-(*S*), 109908-60-3; **10**-(*R*), 109958-11-4; **11**, 87682-78-8; **12**, 109927-28-8; **13**, 109908-49-8; **14**, 28008-17-5; **15**, 109908-51-2; **15** (acid amide), 109908-50-1; **16**, 109927-29-9; **18**, 109908-52-3; **19**, 109908-56-7; **20**, 109908-57-8; **22**, 109908-58-9; **23**, 110012-02-7; 3-bromo-2-(1,2-dimethoxy-3-ethoxy-3-oxopropyl)-1-(1-ethoxyethylidenyl)pyridinium tetrafluoroborate, 109908-54-5; ethylidine triphenylphosphorane, 1754-88-7.

(25) Capillary GC analysis using a 15-m SE-30 column.