

hydroxyl by conversion to a good leaving group¹²). With the imidazole an efficient noncatalyzed reaction occurs. This difference is explained by relative nitrenium ion stability.¹³ With the heterocyclic system, a resonance contributor **5b** can be written with all atoms satisfying the octet rule.

In conclusion we note that nitrenium ions are now generally accepted as important intermediates of the metabolism of aromatic amines,¹⁴ responsible for covalent binding to various biological nucleophiles. These same nucleophiles also interact with reduced nitroimidazoles.¹ The results of this study suggest that a mechanism involving an electrophilic intermediate is entirely plausible with this system also.

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Registry No. 1-HCl, 94944-71-5; *cis*-2-Cl, 94944-72-6; *trans*-2-Cl, 94944-73-7; *N*-methylguanidine hydrochloride, 21770-81-0; glyoxal, 107-22-2.

(12) See: Gassman, P. G.; Granrud, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1498-1499.

(13) Hartman, G. D.; Hartman, R. D. *Mutat. Res.* **1983**, *117*, 271-277.

(14) Miller, E. C. *Cancer Res.* **1978**, *38*, 1479-1496.

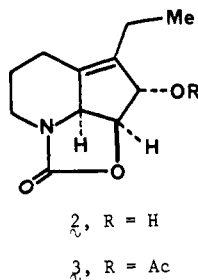
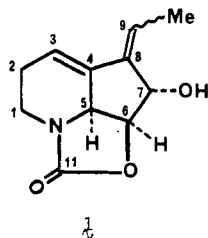
Total Synthesis of Streptazolin: An Application of the Aza Analogue of the Ferrier Rearrangement

Alan P. Kozikowski* and Pyeong-uk Park

University of Pittsburgh, Department of Chemistry
Pittsburgh, Pennsylvania 15260

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Streptazolin (**1**) is a lipophilic neutral compound first isolated by Drautz and Zähler in 1981 from cultures of *Streptomyces viridochromogenes*.¹ Due to the ease with which streptazolin



polymerizes in concentrated form, its purification and characterization were made additionally difficult. Its dihydro derivative **2** does, on the other hand, represent a stable compound. An X-ray structural analysis² as well as extensive NMR studies were carried out on the acetate derivative **3** of this dihydro material. 3,9-Dihydrostreptazolin has been found to exhibit marginal antibacterial and antifungal activity.¹

A total synthesis effort directed toward streptazolin is made particularly intriguing because of the necessity of generating this molecule in a manner that is suited to its interception and detection in dilute form. Starting from the allyl-substituted tetrahydropyridine **4**, prepared by a Ferrier-like reaction between allyltrimethylsilane and *N*-carboethoxy-4-hydroxy-1,2,3,4-tetrahydropyridine as described previously,³ the terminal double bond was

hydrated,⁴ the intermediate alcohol oxidized to aldehyde,⁵ and the oxime derivative **5** generated (Scheme I).

An INOC reaction of this oxime was then induced with sodium hypochlorite to provide the isoxazoline **6**.⁶ The N-O bond was cleaved by Raney nickel/acetic acid hydrogenolysis with maintenance of the *cis* ring fusion stereochemistry (*J* = 8.5 Hz)⁷ and the resulting β -hydroxy ketone transformed to α -bromo ketal **7** by exposure to bromine in ethylene glycol. The hydroxyl group was protected as its MOM ether,⁸ and dehydrobromination was brought about by DBU/Me₂SO treatment. Since attempts to epoxidize the double bond of the ketone derived from **8** failed, the carbonyl group of **9** was reduced to alcohol, and epoxidation with 3,5-dinitroperoxybenzoic acid⁹ was carried out. That the epoxidation reaction had occurred from the concave face of the *cis*-fused ring system (hydroxyl directed)¹⁰ was made apparent from the subsequent transformations.

The alcohol was now reoxidized to ketone, and elimination of the MOM-protected β -alcohol was triggered by 1 N NaOH treatment. A standard Wittig reaction on the resulting enone **11** employing ethylidenetriphenylphosphorane (from the phosphonium bromide and *n*-BuLi) in ether (sealed tube, 65 °C) afforded a 2:1 mixture of the *E* olefin **12a** and the *Z* olefin **12b**. By using the phosphorane prepared from the corresponding iodide and conducting the reaction at room temperature, the *E/Z* ratio varied from 2/1 to 7/6.¹¹ Since the structures of these Wittig products could not be firmly established through chemical shift comparisons, NOE difference experiments were carried out.¹² The data acquired provided good support for the assignment of *E* stereochemistry to **12a** and *Z* stereochemistry to **12b**. On treating this *E/Z* mixture with sodium methoxide, ring opening of the epoxide at its allylically activated site occurred with concomitant intramolecular attack by the newly freed alkoxide anion on the neighboring urethane carbonyl group. The moderately stable *O*-methyl ether derivative **13** of streptazolin was so formed (2:1 *E/Z* mixture). To ensure the structure of this material, especially as regards the stereochemical relationships among carbon centers 5, 6, and 7, the synthetic material was hydrogenated over palladium on carbon to the tetrahydro derivative **14**. Authentic dihydrostreptazolin acetate, kindly provided by Professor Drautz, was converted to dihydrostreptazolin by methanolic ammonia treatment and this intermediate was *O*-methylated and hydrogenated to furnish **14**. The 300-MHz ¹H NMR spectrum of this "naturally derived" substance matched *precisely* that obtained for the synthetic material (Scheme II).

To prepare streptazolin itself, opening of the epoxide with an easily deprotectable hydroxyl derivative was required. Surprisingly, sodium acetate in acetic acid led in 71% yield to the hydroxy acetates **15** as an *E/Z* mixture. These poorly stable intermediates were separated by HPLC and then admixed individually with

(3) Kozikowski, A. P.; Park, P.-u. *J. Org. Chem.* **1984**, *49*, 1676. The use of silicon reagents for the functionalization of carbohydrates has proven quite popular: Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281. Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z.-b. *Tetrahedron Lett.* **1983**, *24*, 1563. Hosomi, A.; Sakata, Y.; Sakurai, H. *Tetrahedron Lett.* **1984**, *25*, 2383. Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. Williams, R. M.; Stewart, A. O. *Tetrahedron Lett.* **1983**, *24*, 2715. Dawe, R. D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1981**, 1180. Cupps, T. L.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **1982**, *47*, 5115. Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803. Sakurai, H.; Sasaki, K.; Hayashi, J.; Hosomi, A. *J. Org. Chem.* **1984**, *49*, 2808.

(4) Brown, H. C.; Liotta, R.; Scouten, C. G. *J. Am. Chem. Soc.* **1976**, *98*, 5297.

(5) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(6) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(7) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, 3123.

(8) Fujii, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

(9) Rastetter, W. H.; Richard, T. J.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

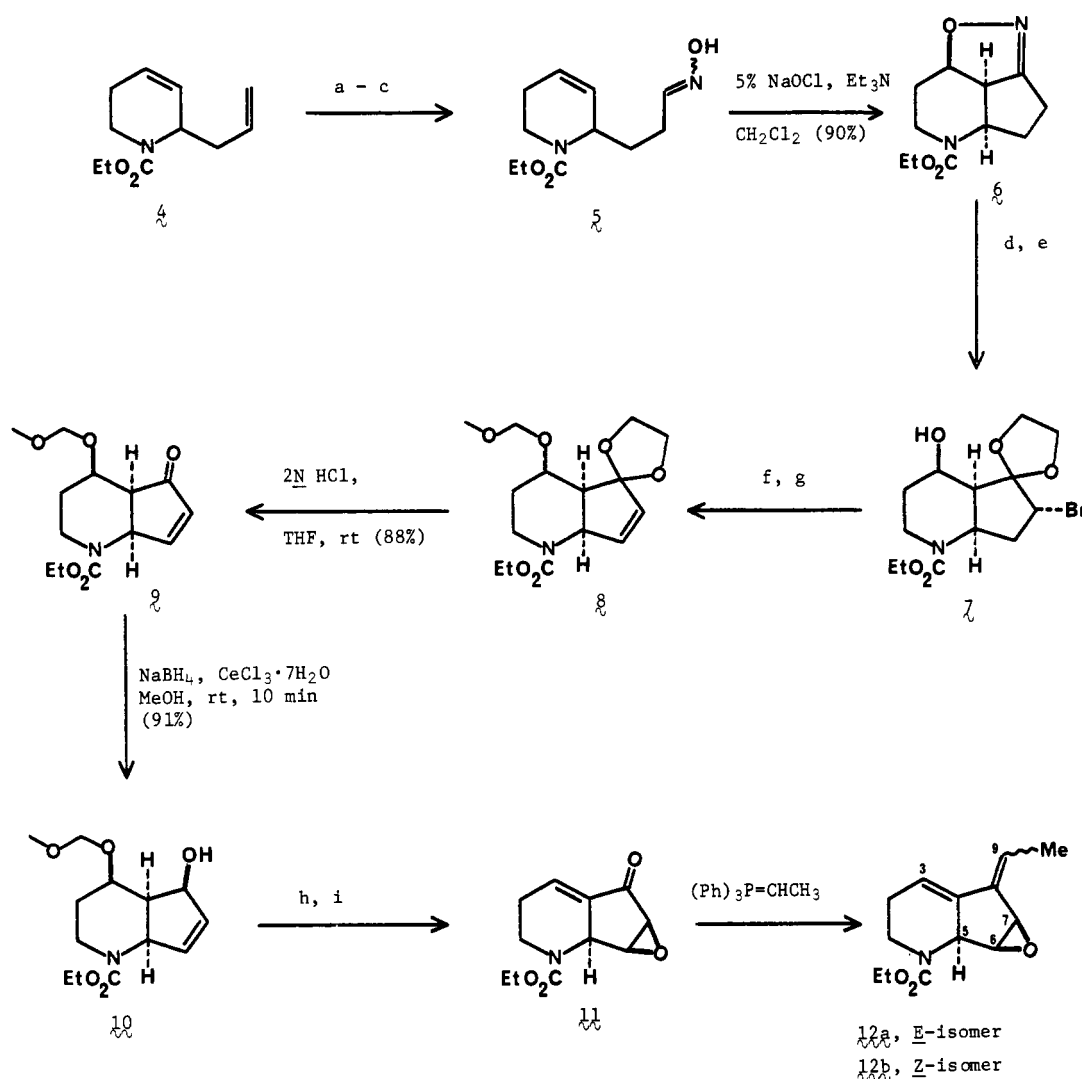
(10) Berti, G. *Top. Stereochem.* **1973**, *7*, 93.

(11) The use of salt-free Wittig conditions (Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 4260) led to a 10:1 mixture of the *E* and *Z* isomers. The stereochemical outcome of this reaction can be rationalized by Schlosser's "leeward approach" model: Schlosser, M.; Schaub, B. *J. Am. Chem. Soc.* **1982**, *104*, 5821.

(12) The NOE data are available as supplementary material.

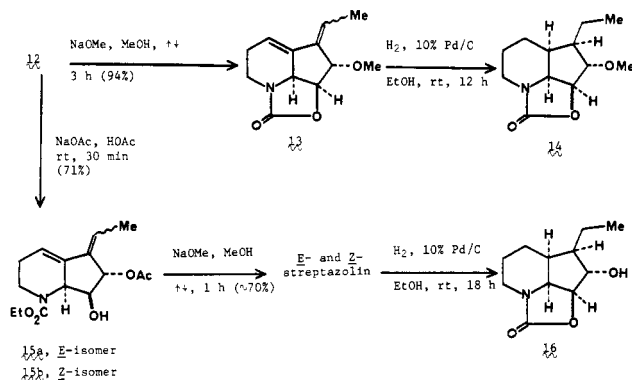
(1) Drautz, H.; Zähler, H.; Kupfer, E.; Keller-Schierlein, W. *Helv. Chim. Acta* **1981**, *64*, 1752. Professor W. Keller-Schierlein has informed us (private communication, Aug 24, 1984) that the *Z* configuration shown in their paper for streptazolin was drawn arbitrarily.

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

Scheme I.^a Synthesis of a Streptazolin Precursor

^a (a) 9-BBN, THF, room temperature, 2 h; 3 N NaOH, 30% H₂O₂, 50 °C, 1 h (90%); (b) PCC, CH₂Cl₂, room temperature, 8 h (85%); (c) NH₂OH·HCl, py, room temperature, 10 h (96%); (d) H₂, W-2 Raney Ni, HOAc, 4:1 MeOH, H₂O, room temperature, 11–24 h (88%); (e) Br₂, HO(CH₂)₂OH, 30–40 °C, 3–6 h (75%); (f) H₂C(OMe)₂, P₂O₅, CHCl₃, room temperature, 8 h (92%); (g) DBU, Me₂SO, 120 °C, 12 h (91%); (h) 3,5-(NO₂)₂C₆H₃CO₂H, Na₂HPO₄, CH₂Cl₂, room temperature, 7 h (70%); (i) CrO₃·py₂, CH₂Cl₂, room temperature, 30 min (87%).

Scheme II. Completion of the Synthesis



methanolic sodium methoxide in order to effect both acetate cleavage and oxazolidinone formation. By keeping the reaction products in dilute form, ¹H NMR spectra (300 MHz) could be obtained for the (*E*)- and (*Z*)-streptazolins.¹³ The ¹H NMR of

(13) The approximate yield shown in Scheme II for the final step was obtained by quickly concentrating and weighing a dilute solution of streptazolin obtained as a homogeneous fraction from silica gel chromatography. The *E* isomer, in contrast to the *Z* isomer, shows a lower tendency toward polymerization.

(*Z*)-streptazolin matched nearly perfectly that (100 MHz) of streptazolin provided us by Professor Keller-Schierlein. Furthermore, the tetrahydro derivative 16 prepared by hydrogenation of synthetic streptazolin over palladium on charcoal was identical in its spectral properties with a sample prepared from authentic dihydrostreptazolin acetate.

In conclusion, we have shown that it is possible to constitute in the laboratory a substance that possesses marginal stability through the judicious selection of the culminating synthetic step. The aza analogue of the Ferrier rearrangement¹⁴ in combination with the INOC reaction thus provides an efficient means for crafting ring-fused pyridine structures. The synthesis serves additionally to elucidate the stereochemistry of the exocyclic olefin unit of streptazolin, a feature that was not assigned rigorously in the structure work cited above.¹

Acknowledgment. We are indebted to the National Institutes of Health and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their support of these investigations. We thank Professors Drautz and Keller-Schierlein for providing a sample of dihydrostreptazolin acetate and detailed spectra of streptazolin and its derivatives. We are most grateful to Dr. Prasanna K. Mishra of the Mellon Institute

(14) Ferrier, R. J. *J. Chem. Soc.* 1964, 5443.

for carrying out the NOE experiments on the NIH sponsored Bruker WH-600 NMR.

Registry No. (\pm)-(E)-1, 95119-34-9; (\pm)-(Z)-1, 95119-35-0; (\pm)-2, 95119-36-1; (\pm)-3, 95119-37-2; (\pm)-4, 95019-32-2; (\pm)-5, 95019-33-3; (\pm)-6, 95019-34-4; (\pm)-7, 95019-35-5; (\pm)-8, 95019-36-6; (\pm)-9, 95019-37-7; (\pm)-10, 95019-38-8; (\pm)-11, 95019-39-9; (\pm)-(E)-12a, 95019-40-2; (\pm)-(E)-12b, 95119-38-3; (\pm)-(E)-13, 95019-41-3; (\pm)-(Z)-13, 95119-39-4; (\pm)-14, 95019-42-4; (\pm)-(E)-15a, 95019-43-5; (\pm)-(Z)-15b, 95119-40-7; (\pm)-16, 95019-48-0; $\text{CH}_3\text{CH}=\text{PPh}_3$, 1754-88-7; ethyl (\pm)-2-(3-hydroxypropyl)-5,6-dihydro-1(2H)-pyridine-carboxylate, 95019-44-6; ethyl (\pm)-2-(3-oxopropyl)-5,6-dihydro-1(2H)-pyridinecarboxylate, 95019-45-7; ethyl (\pm)-(4 α ,4 $\alpha\beta$,7 $\alpha\beta$)-4-hydroxy-5-oxooctahydro-1H-1-pyridinecarboxylate, 95044-88-5; ethyl (\pm)-(1 α ,1 $\beta\alpha$,5 β ,5 $\alpha\alpha$,6 β ,6 $\alpha\alpha$)-5-(methoxymethoxy)-6-hydroxyoctahydro-1aH-oxireno[4,5]cyclopenta[1,2-b]pyridine-2-carboxylate, 95019-46-8; ethyl (\pm)-(1 α ,1 $\beta\alpha$,5 β ,5 $\alpha\alpha$,6 $\alpha\alpha$)-5-(methoxymethoxy)-6-oxooctahydro-1aH-oxireno[4,5]cyclopenta[1,2-b]pyridine-2-carboxylate, 95019-47-9.

Supplementary Material Available: ^1H NMR, IR, and high-resolution mass spectral data on all compounds and results of the NOE difference experiments (8 pages). Ordering information is given on any current masthead page.

Charge-Transfer-Biradical Excited States: Relation to Anomalous Fluorescence. "Negative" S_1 - T_1 Splitting in Twisted Aminoborane

Vlasta Bonačić-Koutecký*¹ and Josef Michl²

Departments of Chemistry, Free University of Berlin
1000 Berlin 33, West Germany
University of Utah, Salt Lake City, Utah 84112

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We wish to report results of an ab initio calculation of the ground and excited states of aminoborane, H_2BNH_2 , as a function of twist angle. At orthogonality, T_1 lies a little above S_1 and both are of charge-transfer-biradical nature. We believe that the results are useful for the understanding of anomalous fluorescence of the so-called twisted internal charge-transfer type.

Low-lying electronic states of two-electron two-orbital (A,B) systems are profitably discussed in terms of the four configurations, ^1AB , $^1\text{A}^2$, $^1\text{B}^2$, and ^3AB .³ When A and B are orthogonal and A is at most moderately more electronegative than B, as in a twisted alkene, ^1AB and ^3AB represent the nearly degenerate S_0 and T_1 states, and $^1\text{A}^2$ with an admixture of $^1\text{B}^2$ represents the S_1 state (case I). If the electronegativity difference Δ increases sufficiently, $^1\text{A}^2$ becomes more stable than ^1AB and ^3AB . It then represents S_0 , while the latter two describe the still nearly degenerate S_1 and T_1 states (case II).⁴

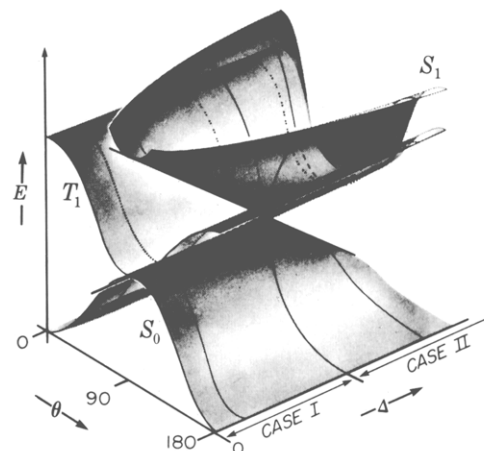


Figure 1. Schematic two-dimensional plot of S_0 , S_1 , and T_1 energies as function of the twist angle θ and electronegativity difference between two p orbitals at the termini of the double bond.

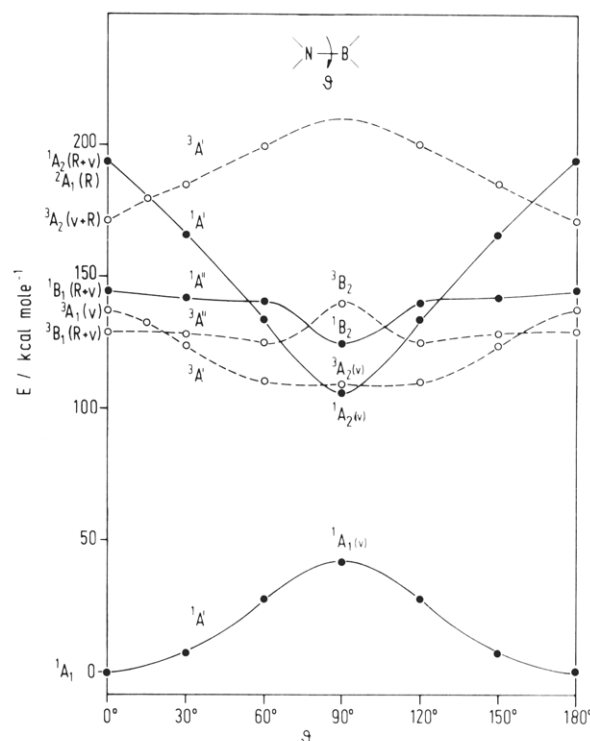
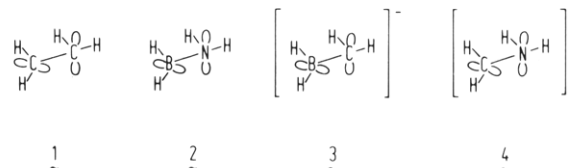


Figure 2. Energies of lowest singlet and triplet states of aminoborane as a function of twist angle θ around the B-N bond, obtained from the large scale MRD-CI treatments. Extrapolated energies for $T \rightarrow 0$ are plotted.

Three important situations are of interest: (i) ^1AB and ^3AB are nonpolar and $^1\text{A}^2$ zwitterionic (1), (ii) ^1AB and ^3AB are



zwitterionic and $^1\text{A}^2$ nonpolar (2), (iii) none of the three configurations involve charge separation (3, 4). Since charge separation requires energy, situation i usually corresponds to case I and situation ii to case II, while situation iii lies at the border line between cases I and II, with S_0 , S_1 , and T_1 all nearly degenerate.⁴

S_1 and T_1 surfaces should have a minimum at an orthogonal geometry which is particularly unfavorable for S_0 . Figure 1 plots the S_0 , S_1 , and T_1 energies as a function of the electronegativity difference Δ and the relative twist angle θ of two p orbitals located at the termini of a bond.

(1) Free University of Berlin, Berlin.

(2) University of Utah, Salt Lake City.

(3) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92. Michl, J. *Mol. Photochem.* **1972**, *4*, 257.

(4) (a) Bonačić-Koutecký, V.; Köhler, J.; Michl, J. *Chem. Phys. Lett.* **1984**, *104*, 440. (b) In the first approximation (3×3 CI, $K_{AB} = 0$), the change from case I to case II occurs when the difference of the AO energies $\epsilon_B - \epsilon_A$ equals the Coulomb integral difference $J_{AA} - J_{AB}$. The existence of case I and case II situations, separated by a region of near or exact touching between the S_0 and S_1 surfaces, is not limited to twisted double bonds but is found more generally for molecules that can reach biradicaloid geometries, such as those capable of undergoing a ground-state forbidden pericyclic process. These considerations lead to prediction of the effect of polar perturbations on the shape of the S_1 surface and on the S_0 - S_1 separation. The consequences for photochemical reactivity, in particular substituent effects and regiochemistry, will be reported elsewhere.