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Conversion of δ -(sulfonyl)amino- α -epoxy Ketones to Bicyclic Ketopyrroles via Intramolecular Conjugate-addition to Azoene Intermediates. Synthesis of the Bicyclic Ketopyrrole Core of the 1-Azafulvene Roseophilin.¹

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Abstract: Reaction of δ -(sulfonyl)amino- α -epoxy ketones with dimethylhydrazine results in cyclization to pyrrolidine-fused β -hydroxy dimethylhydrazones. Hydrolysis, mesylation, and elimination affords dihydropyrroles which can be converted to sulfonyl-protected ketopyrroles via oxidation with NIS; alternatively, treatment with DBU affords N-H bearing ketopyrroles. Copyright © 1996 Elsevier Science Ltd

Roseophilin **5** is a topographically interesting ansa-bridged 1-azafulvene which exhibits submicromolar cytotoxicity against several human cancer cell lines.² The recent publication of the synthesis and reactions of the roseophilin heterobiaryl moiety³ prompted us to report a new annulation method for construction of bicyclic ketopyrroles. Although there are a number of procedures employing Friedel-Crafts chemistry for the construction of pyrrole-fused cycloalkanones,⁴ we felt that application of our recently published method of β -substituted enone synthesis⁵ might provide efficient access to the requisite fused pyrroles (Scheme 1).



As expected, synthesis of δ -(sulfonyl)amino enones $7a^5$ and 7b was a straightforward prospect. Epoxidation⁶ followed by treatment with tosylhydrazine in ether⁷ afforded the stereochemically homogeneous⁸ anti α -epoxytosylhydrazones **9a** and **9b** in high overall yield. At this stage we treated **9b** with K₂CO₃ which afforded **13b** in 96% yield via the intermediacy of azoene **11b** (Scheme 2). Subsequent hydrolysis of hydrazone **13b** with NBS⁹ gave the corresponding ketone **15b**. Hydrazone **9a** was unreactive even under more forcing conditions.¹⁰ The difference in reactivity between **9a** and **9b** is consistent with the calculated¹¹ superior overlap between the imine π -systems (**9a** NCCO dihedral =137°; **9b** NCCO dihedral = 103°) as well as the smaller energy requirement to attain the ideal 90° dihedral angle for fragmenting the oxirane ring (**9a** = 3.6 kcal/mol vs **9b** = 0.2 kcal/mol). Heating **9a** in DMF in the presence of excess NaH afforded bicyclic pyrrolidine **17a**, presumably via the intermediacy of the diazo compound (not shown) followed by cyclization of vinyldiazonium ion **16a**.¹²

Since Gründemann has shown that reaction of acyclic α -epoxy ketones with phenylhydrazine affords γ -hydroxy azoenes,¹³ we reasoned that the more basic hydrazine lone pair of intermediate **10a** might facilitate opening of the oxirane. Thus the epoxy ketone **8a** was treated with phenylhydrazine in ether in the presence of a catalytic amount of camphorsulfonic acid (CSA) for 10 h at 25 °C to afford the bicyclic hydrazone **14a** (syn:anti \approx 1:3) in high yield via intermediate **12a**.¹⁴ Efforts to hydrolyze **14a** were not satisfactory, giving only ~30% yield of the ketone **15a** by reaction with BF₃•OEt₂ (Scheme 2).¹⁵

Scheme 2



We next investigated the use of N,N-dimethylhydrazine.¹⁶ Treatment of the ketone **8a** with excess N,N-dimethylhydrazine at -40 °C in EtOAc in the presence of propionic acid or CSA as catalyst directly afforded the desired bicyclic hydrazone **20a**, presumably via zwitterionic intermediate **19a** (Scheme 3).

Scheme 3



The crude hydrazone **20a** was hydrolyzed without purification by treatment with silica gel in THF-water¹⁷ to afford the ketone **15a** in 73% yield from **8a**. In similar fashion, the 6-membered ring analog **15b** was prepared in 61% yield from α -epoxy ketone **8b**. The hydroxypyrrolidines **15a** and **15b** were smoothly converted to the dihydropyrroles **21a** and **21b** via the corresponding mesylates. Subsequent <u>N</u>-lodosuccinimide oxidation¹⁸ of **21a** and **21b** afforded <u>N</u>-tosylpyrroles **22a** and **22b** in 90% and 93% yields, respectively. On the other hand, DBU induced elimination of <u>p</u>-toluenesulfinic acid provided the <u>N</u>-H pyrroles **23a** and **23b** in good yields (Scheme 3).

Application of this strategy for the synthesis of more highly substituted ketopyrroles was also quite facile. For example, reaction of γ -methoxyallylsulfonyl anion **6a**⁵ with substituted tosylaziridine **26**¹⁹ regiospecifically²⁰ afforded racemic enone **27** in 73% yield after the standard acidic workup. Nucleophilic epoxidation generated **28** as a 1:1 mixture of diastereomeric epoxides, as expected. This mixture was directly treated with dimethylhydrazine in acidified ethyl acetate to generate β -hydroxy dimethylhydrazones **29** as a diastereomeric mixture as assayed by ¹H NMR. This mixture was also not separated, but further treated at 50-55 °C with wet THF in the presence of silica gel for 2.5 days to produce a 1:1 mixture of β -hydroxy ketones **30** in 78% overall yield from **28**. Completion of the target ketopyrrole **32** involved successive reaction of diastereomeric β -hydroxy ketones **30** with mesyl chloride followed by β -elimination to afford racemic dihydropyrrole **31** in 81% yield. Finally, aromatization with <u>N</u>-lodosuccinimide smoothly afforded ketopyrrole **32** in very high yield.



In conclusion, we have developed a new ketopyrrole annulation which features intramolecular conjugate-addition of a pendant sulfonamide moiety to an incipient azoene intermediate. Further applications of this strategy for synthesis of the ansa-bridged ring system of roseophilin is currently under study.

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References and Notes

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- ⁸ Sulfonylhydrazone stereochemistry was assigned by ¹³C-NMR (Bunnell, C. A.; Fuchs, P. L. J. Org. Chem. 1977, 42, 2614.)
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- ¹⁰ Treatment of α-epoxyhydrazone **9a** with many other bases (DBU, LDA, n-BuLi, NaH) and/or Lewis acids (BF₃•OEt₂, Et₃Al, LiClO₄) failed to afford **13a**.
- ¹¹ Molecular modeling results using CAChe v. 3.7.

¹² An alternative mechanism for production of **17a** would be via formation of **13a** followed by Shapiro reaction (see: Chamberlin, A. R.; Bloom, S. H. <u>Organic Reactions</u>, **1990**, *39*, 1, John Wiley, New York) of the <u>p</u>-tosylhydrazone moiety. Evidence which argues against such a possibility is the observation that the <u>p</u>-tosylhydrazone of **13b** generates a plethora of products when subjected to NaH/DMF/100 °C. In marked contrast, the <u>trisylhydrazone</u> of **15b** gives a 42% yield of the corresponding bicyclo [4.3.0] olefin which is **stable** to the reaction conditions above. For leading references to trisylhydrazone chemistry see: Nicolaou, K. C.; Yang, Z.; Sorensen, E. J.; Nakada, M. *J. Chem. Soc. Chem. Commun.* **1993**, 1024.

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