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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.
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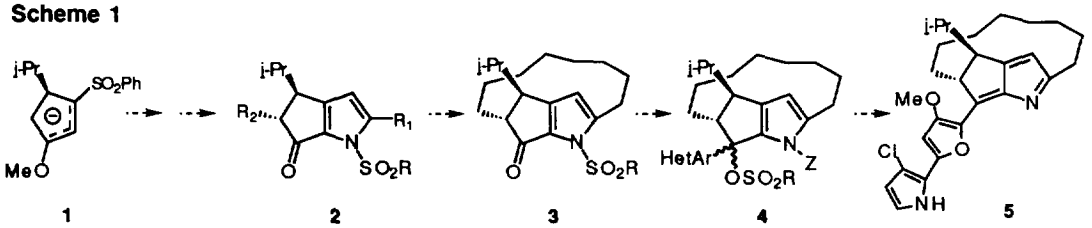
Roseophilin **5** is a topographically interesting ansa-bridged 1-azafulvene which exhibits submicromolar cytotoxicity against several human cancer cell lines.[2] The recent publication of the synthesis and reactions of the roseophilin heterobiaryl moiety[3] prompted us to report a new annulation method 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 synthesis[5] might provide efficient access to the requisite fused pyrroles (Scheme 1).

Scheme 1

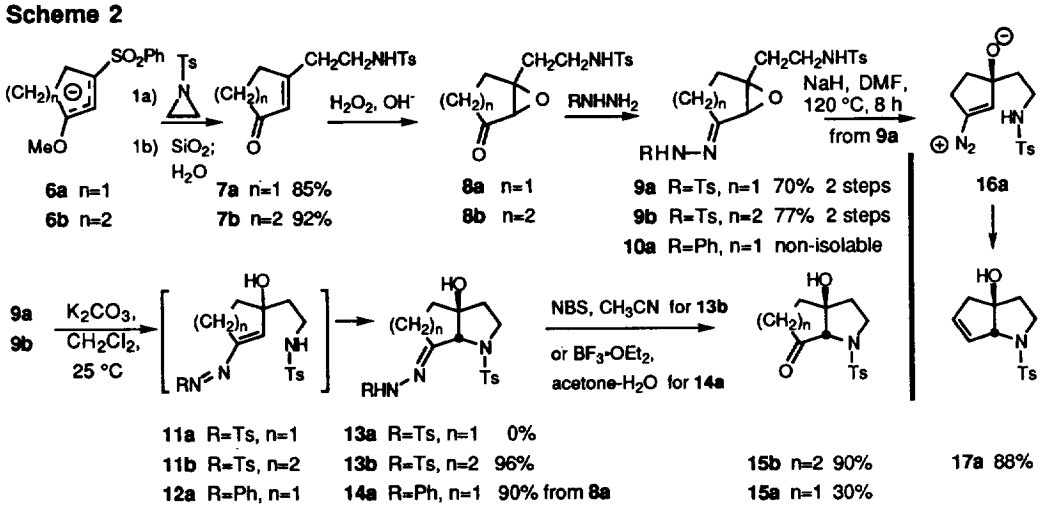


1 **2** **3** **4** **5**

As expected, synthesis of δ-(sulfonyl)amino enones **7a**[5] and **7b** was a straightforward prospect. Epoxidation[6] followed by treatment with tosylhydrazine in ether[7] afforded the stereochemically homogeneous[8] *anti* α-epoxytosylhydrazones **9a** and **9b** in high overall yield. At this stage we treated **9b** with K_2CO_3 which afforded **13b** in 96% yield via the intermediacy of azoene **11b** (Scheme 2). Subsequent hydrolysis of hydrazone **13b** with NBS[9] 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 calculated[11] 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]

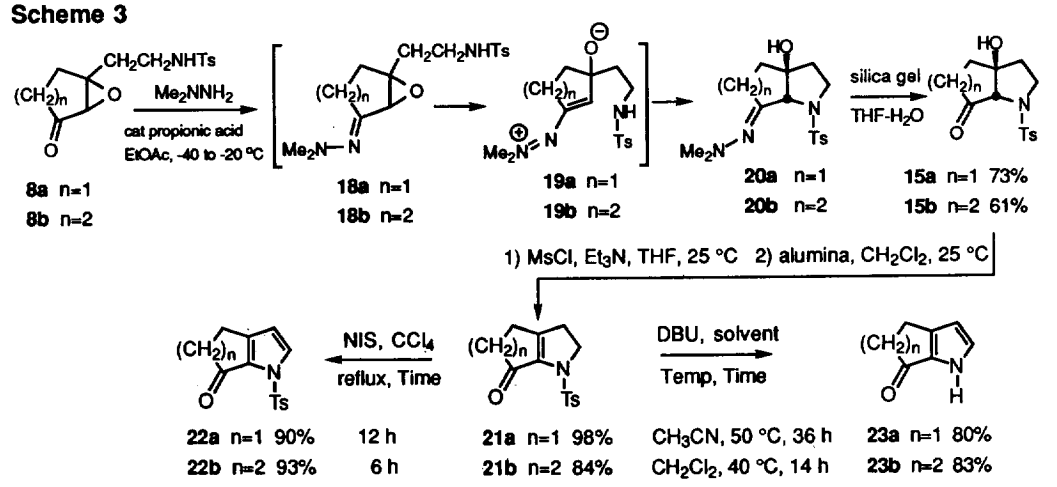
Since Gründemann has shown that reaction of acyclic α-epoxy ketones with phenylhydrazine affords γ-hydroxy azoenes,[13] we reasoned that the more basic hydrazine lone pair of intermediate **10a** might facilitate opening of the oxirane. Thus the epoxy ketone **8a** was treated with phenylhydrazine in 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 ≈ 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 BF_3•OEt_2 (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).

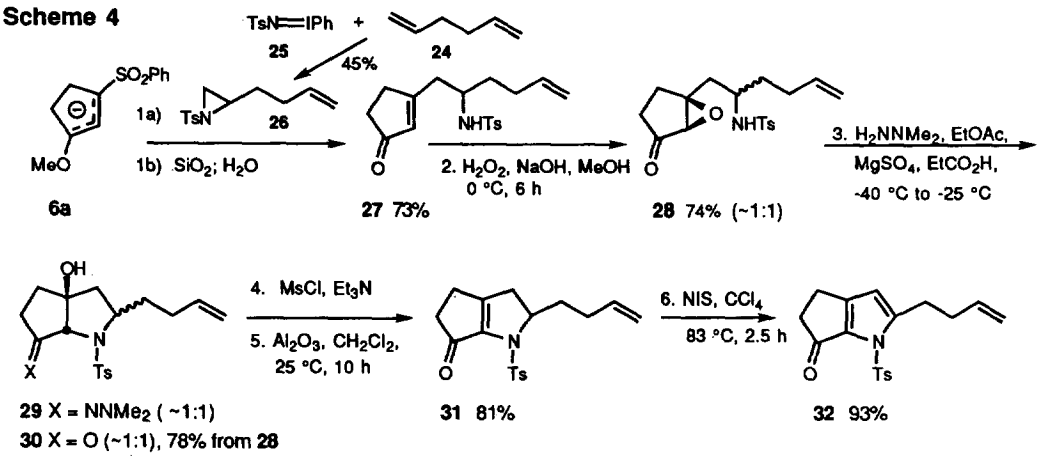
Scheme 3



The crude hydrazone **20a** was hydrolyzed without purification by treatment with silica gel in THF-water[17] 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 N-Iodosuccinimide oxidation[18] of **21a** and **21b** afforded N-tosylpyrroles **22a** and **22b** in 90% and 93% yields, respectively. On the other hand, DBU induced elimination of p-toluenesulfinic acid provided the N-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] regiospecifically[20] 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 ^{1}H 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 N-Iodosuccinimide smoothly afforded ketopyrrole **32** in very high yield.

Scheme 4



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 ^{13}C-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 (BF_3•OEt_2, Et_3Al, $LiClO_4$) 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. Organic Reactions, **1990**, *39*, 1, John Wiley, New York) of the p-tosylhydrazone moiety. Evidence which argues against such a possibility is the observation that the p-tosylhydrazone of **13b** generates a plethora of products when subjected to NaH/DMF/100 °C. In marked contrast, the trisylhydrazone 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.

13 Gründemann, E. *Angew. Chem.* **1969**, *81*, 467; Ohloff, G.; Uhde, G. *Helv. Chim. Acta.* **1970**, *53*, 531.

14 Azoene **12a** could be isolated in ~90% yield by flash chromatography on silica gel and was characterized by ^1H-NMR in $CDCl_3$ during which time it underwent cyclization to **14a**.

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18 For NBS or DDQ oxidation of pyrrolines, see Shim, Y. K., *et al. Synthesis* **1990**, 753; NBS oxidation of **21a,b** gave some brominated compound along with the pyrroles. DDQ oxidation gave **22a,b** in only moderate yield (~60%).

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