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Efficient Synthesis of Indolizidine Alkaloids from γ -Hydroxy- α,β -unsaturated Sulfones

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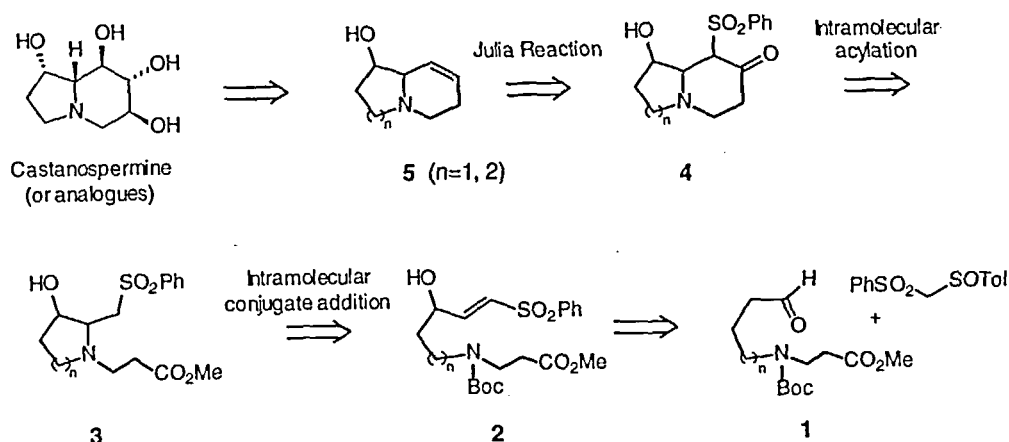
An efficient and stereoselective synthesis of polyhydroxylated indolizidine alkaloids from readily available N-substituted γ -hydroxyvinyl sulfones is described.

Naturally occurring polyhydroxylated indolizidine alkaloids, such as castanospermine or swainsonine, have been shown to be powerful inhibitors of many glycosidases. However, most of the reported syntheses of this kind of natural products utilize monosaccharides as starting materials which limits the flexibility for structural modifications.¹

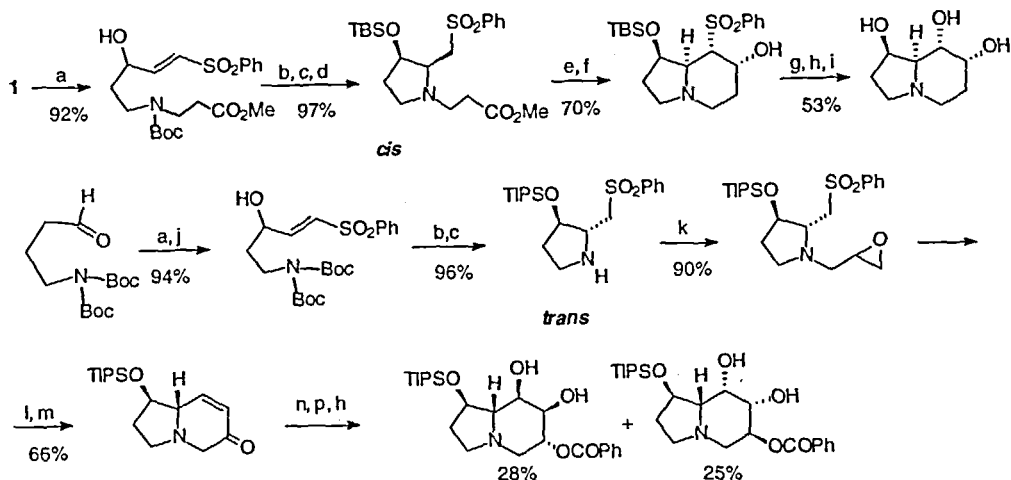
As a part of our current interest concerning the use of γ -oxygenated- α,β -unsaturated sulfones as versatile intermediates in enantioselective and stereoselective synthesis, we have developed a new approach to the synthesis of polyhydroxylated indolizidine alkaloids.² As it is shown in the retrosynthetic scheme, all the key steps are based on the reactivity of the sulfonyl group: a) condensation of sulfonyl sulfinyl methanes with the N-substituted aldehydes **1** gives the required N-substituted γ -hydroxy- α,β -unsaturated sulfones **2**; b) intramolecular conjugate addition to the vinylsulfone moiety of **2** yields quantitatively the pyrrolidine (n=1) or piperidine (n=2) intermediates **3**; c) intramolecular Claisen-like condensation of **3** yields quantitatively the ketosulfones **4**, having indolizidine structure; d) finally, removal of the sulfonyl group by Julia reaction lead to a C=C bond (olefins **5**) suitable for stereoselective dihydroxylation reactions.

Interestingly, the stereoselectivity of the intramolecular conjugate addition is highly dependent on the steric size of the γ -oxygenated moiety. Thus, whereas *cis*-pyrrolidines are formed majoritarilly from the γ -hydroxyvinyl sulfone, *trans*-

pyrrolidines and *trans*-piperidines are obtained stereoselectively from the γ -OTIPS derivatives.³



As two representative examples, in the following schemes are summarized the stereoselective synthesis of a trihydroxylated and a tetrahydroxylated indolizidine alkaloid.



(a) $\text{PhSO}_2\text{CH}_2\text{SOTol}$, piperidine, 0°C ; (b) CF_3COOH ; (c) Et_3N , THF, -78°C ; (d) CITBS, imidazole; (e) LHMDS, THF, 0°C ; (f) LiEt_3BH , -78°C ; (g) Na(Hg) ; (h) OsO_4 , Et_3N ; (i) HCl 5N ; (j) TPSTf, 2,6-Lutidine; (k) $\text{PhSO}_2\text{CH}_2\text{SOTol}$, K_2CO_3 , CH_3CN ; (l) MeMgI , THF, 0°C ; (m) $(\text{COC})_2$, DMSO, Et_3N ; (n) DBAL, THF, -78°C ; (p) PhCOCl , Py.

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