Diastereoselective intramolecular nitroaldol entry to lycoricidine alkaloids

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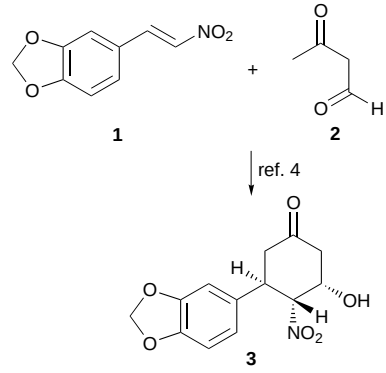
The alumina promoted 6-*exo*-*trig* intramolecular nitroaldol cyclization described proceeds in a highly diastereoselective manner *via* a proposed chelation controlled chair-like transition state, the major diastereomer having the correct relative configuration at three stereocentres as observed in the pancratistatin series of antitumor agents, in contrast to prior literature cyclization methods.

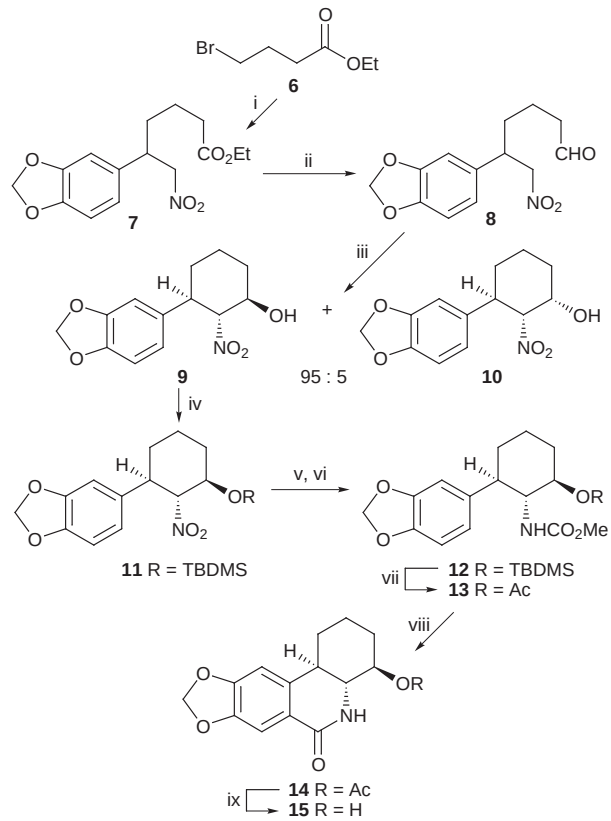
Nitroalkenes are valuable synthetic intermediates by virtue of their high reactivity and *umpolung* nature compared to carbonyl and amino substrates, to which they may be subsequently converted. They are highly reactive as Michael acceptors in conjugate addition processes[1] and dienophiles in Diels–Alder cycloadditions,[2] in addition to undergoing other valuable transformations.[3] Nitroalkenes are therefore valuable intermediates for the preparation of compounds of biological interest. Seebach has made extensive use of their high reactivity as Michael acceptors[1] and described applications towards the synthesis of alkaloids.[4] One attractive annulation strategy (Scheme 1) involves a combination Michael addition of a dianion onto the nitroalkene followed by subsequent intramolecular nitroaldol cyclization onto an appropriately functionalized carbonyl-containing side chain. This methodology has been applied towards the preparation of deoxylycorinone derivatives.[4] Other routes to lycoricidine-type alkaloids utilizing nitroalkenes have also been reported.[5]



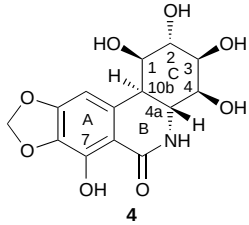
Scheme 1

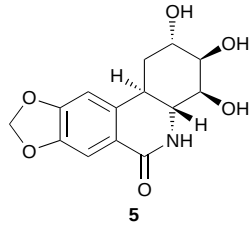
In consideration of the structure of the valuable anticancer alkaloids pancratistatin **4** and *trans*-dihydrolycoricidine **5**,[6] the development of an intramolecular nitroaldol cyclization exhibiting alternative diastereoselectivity to that of the base promoted example described above would be of great value. We are currently addressing the issue of the nature of the C-ring hydroxy substituents of compounds **4** and **5** with respect to the anticancer pharmacophore and require a means of access to deoxy derivatives of **5**. The observation that the three substituents on the cyclohexane C-ring at positions 4, 4a and 10b‡ in the desired natural diastereomeric series lie in *equatorial* positions led us to consider the possibility of a chelation controlled intramolecular nitroaldol cyclization as a means of controlling the relative stereochemistry. We now report a neutral alumina promoted nitroaldol cyclization that provides the desired diastereoselectivity.

Michael addition of the copper–zinc reagent[7] derived from ethyl 4-bromobutyrate **6** (Scheme 2) to the piperonal derived nitroalkene **1** proceeded cleanly to give the ester **7**. Selective reduction of the ester with DIBAL-H gave aldehyde **8**, the key substrate for the intramolecular nitroaldol. Our analysis of the possibility of a chelation controlled chair-like transition state



Scheme 2 *Reagents and conditions*: i, Zn, LiI (0.25 equiv.), DMF, 75 °C, 5 h; then CuCN (1 equiv.), LiCl (2 equiv.), THF, 0 °C, 5 min; cool to −78 °C, then **1**, −78 to 0 °C, 5 h, 81%; ii, DIBAL-H (1.3 equiv.), CH_2Cl_2, −78 °C, 5 h; iii, Activity 1 (Brockmann) alumina, 20 °C, 48 h, 71% from **7**; iv, TBDMSCl (1.3 equiv.), imidazole (2.5 equiv.), DMF, 20 °C, 24 h, 96%; v, Raney Ni, 650 psi H_2, MeOH, 20 °C, 4 h, 100%; vi, $ClCO_2Me$ (1.5 equiv.), 0 °C, CH_2Cl_2, Et_3N, 5 h, 96%; vii, Ac_2O, $FeCl_3$ (0.2 equiv.), 0 °C , 10 min, 85%; viii, Tf_2O (5.0 equiv.), DMAP (3.0 equiv.), CH_2Cl_2, 0–15 °C, 15 h; then 2 M HCl (aq.), THF, 18 °C, 14 h, then Ac_2O, DMAP, Et_3N, 0–18 °C, 12 h, 85%; ix, NaOMe (1.1 equiv.), THF–MeOH, 0–18 °C, 12 h, 96%





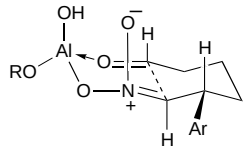


Fig. 1

(Fig. 1) for the intramolecular cyclization in conjunction with earlier reports[8a,b] on basic alumina promoted *inter*molecular nitroaldol reactions led to the following procedure. Aldehyde **8** was dissolved in CH_2Cl_2 and treated with *neutral* alumina at ambient temperature while solvent was removed under a nitrogen flow. Clean cyclization slowly occurred giving two diastereomers, **9** and **10**, in the ratio of 95 : 5. Importantly, no dehydration is observed when neutral alumina is employed at room temperature; however simply warming to 40 °C can result in the formation of nitroalkenes.[8a] Separation of the compounds was readily achieved (neutral alumina, CH_2Cl_2–MeOH, 95 : 5) and to our delight the *major* isomer proved to be **9**, as evidenced by ^{1}H NMR analysis (H-4a δ 4.45, dd, J = 11.2, 9.8 Hz). The high diastereoselectivity observed is consistent with the transition state model we propose in which an alumina–nitronate bischelated intermediate undergoes intramolecular cyclization *via* a late, chair-like transition state in which all developing substituents occupy equatorial-like positions. This model should prove useful in the prediction of diastereoselectivity in related 6-*exo*-*trig* nitroaldol reactions.

The utility of this diastereoselective cyclization was demonstrated by elaboration of the nitroaldol product **9** (Scheme 2) to lycoricidine analogue **15** retaining the desired natural stereochemistry. The alcohol of **9** was first protected§ to give the silyl ether **11**, which was quantitatively reduced over Raney Ni and protected to give the carbamate **12**. Attempts to cyclize this silyl protected carbamate by the method of Banwell[9] failed due to the instability of the TBDMS group under the cyclization conditions. The protecting group was therefore changed using the one-pot procedure of Ganem[10] providing the acetate **13**, which was cyclized[9] to give the tetracycle **14**. The yield on the Bischler–Napieralski cyclization was optimized by extending the hydrolysis time to 14 h, and employing an aqueous HCl–THF mixture instead of the reported aqueous AcOH. This also resulted in a small amount of acetate hydrolysis, as was observed under Banwell's conditions.[9] An overall yield of 85% of **14** could be realized from **13** when a final re-acetylation step was employed. Banwell's cyclization protocol is clearly more efficient than earlier methods in effecting this key transformation.[9] Finally, clean removal of the acetate protecting group provided us with the desired analogue 2,3-dideoxy-*trans*-dihydrolycoricidine **15**.

The diastereoselective nitroaldol cyclization described above provides a valuable access to deoxy derivatives of alkaloids **4** and **5**, both of which exhibit a high degree of anticancer activity,[6] having the correct relative stereochemistry at key positions C-4, C-4a and C-10b. Alkaloid **5** is currently the simplest known derivative that exhibits the full spectrum of anticancer activity.[6] The chemistry reported allows access to the simplified C-ring analogue **15**, lacking two hydroxy groups from **5**, which will provide valuable information concerning the pharmacophore of these alkaloids.

Further modifications of the C-ring based on the proposed transition state model and anticancer evaluation is currently in progress and will be reported shortly.

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Notes and References

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‡ The pancratistatin ring numbering system (ref. 6) is used throughout.

§ Compound **9** could be protected as the acetate, however intramolecular acyl transfer occurred when the nitro substituent was reduced, giving the acetamide.

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