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A Synthetic Route to Valienamine: An Interesting Observation concerning Stereoelectronic Preferences in the S_N2' Reaction

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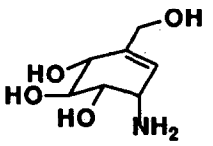
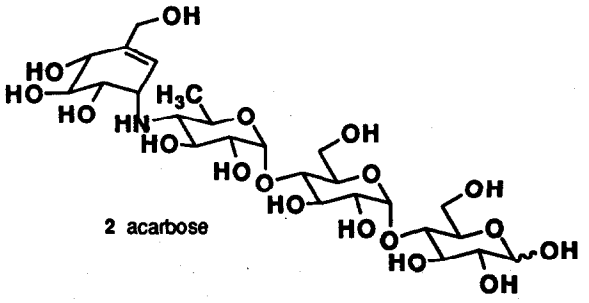
Abstract: Intramolecular allylic displacement of a spiroepoxide is used to reach (+)-valienamine.

Valienamine (**1**) is an unusual aminocyclitol which exhibits α-glucosidase inhibitory activity.[1,2] This cyclitol is also found as a conjugate to various novel carbohydrate structures in a number of biologically active natural products (pseudo-oligosaccharides).[3] Included among these is acarbose (**2**)[4] which is currently undergoing evaluation for the treatment of diabetes.[5]

Figure I



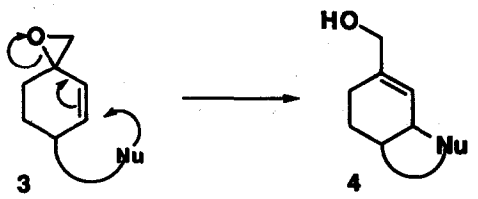
1 (+) - valienamine



2 acarbose

We report here a novel synthesis of (+)-valienamine.[6] An ancillary reason for undertaking this investigation was the expectation that the study of the projected key step (cf **3**—>**4**) would provide insight into stereoelectronic influences in the S_N2' reaction.[7,8] We were intrigued by this particular intramolecular variation of the reaction, since the leaving group remains anchored in the product via an sp^2 hybridized carbon. Interactions between the leaving group and nucleophile have been suggested in various rationalizations pertaining to the S_N2' reaction.[9] It was expected that the type of reaction under consideration, involving a leaving oxido-anion arising from a spiroepoxide, would provide insight into the stereoelectronic issues of bond formation relative to bond fragmentation, distinguished from issues of non-covalent interactions of nucleophile and leaving group. In this Letter we report an interesting synthesis of valienamine and the exploration of the stereoelectronic factor.

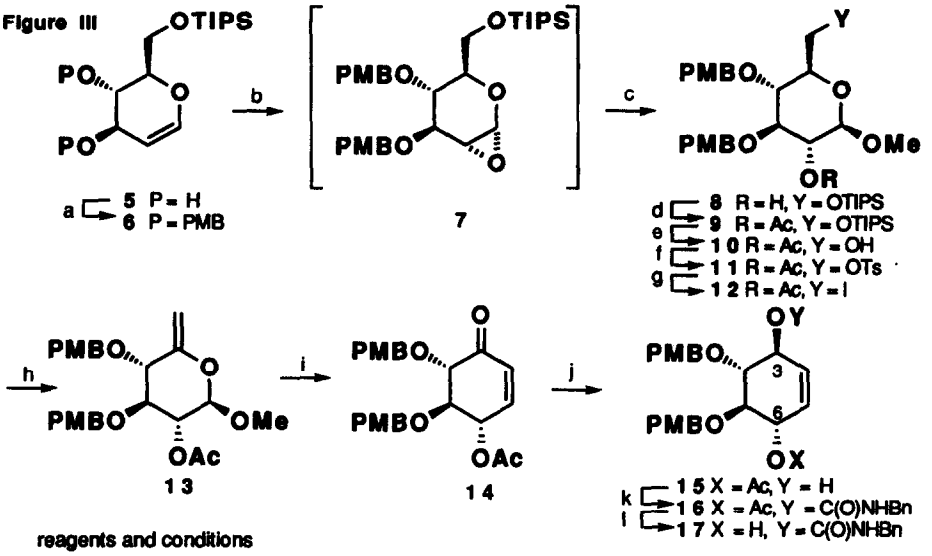
Figure II



3 4

As a subgoal, we focused on an intermediate such as **17** in which the oxygens at C_3 and C_6 were differentiated. One of these oxygens would bear a carbamate linkage and the other would be convertible to a ketone and then to the spiroepoxide. By recourse to a glucose derivative as a starting material, the desired enantiomer could become accessible. The C_2 symmetry of the idealized system related to **15-17** where X=Y allows added flexibility in designing straightforward routes.

Figure III



reagents and conditions

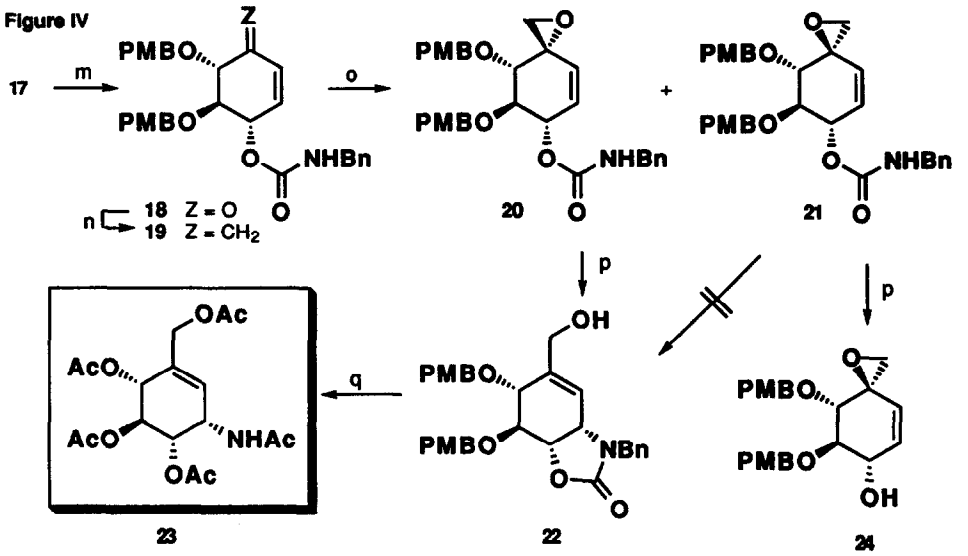
a) NaH, PMBCl, 74 %, b) dimethyldioxirane, acetone-CH_2Cl_2, c) MeOH, rt,d) Ac_2O, DMAP, Py, 76 % from **6**, e) TBAF, THF-EtOAc, 91%, f) TsCl, Py, DMAP, 93%, g) KI, DMF, 100 °, 2h, 94%, h) AgF, Py, rt, 1d, 97%, i) $HgCl_2$, acetone-water, reflux, 4h; MsCl, DMAP, py, rt, 5h, 72%, j) $NaBH_4$-$CeCl_3$, EtOH, -78°, 10 min, 92%, k) benzylisocyanate, benzene, reflux, overnight, 98%, l) K_2CO_3, MeOH, quant.

The readily available TIPS glucal (**5**) was converted to the bis PMB derivative **6**.[10] The latter was smoothly transformed to **9** by way of oxirane **7** and methyl glycoside **8**.[11] *The easy access to uniquely unprotected oxygens at C_2 of a β-glucoside is an oft used feature of the glycal methodology.*[12] Conversion of **9** to **13** was achieved by standard methods. Compound **13** served as the substrate for a Ferrier transformation.[13] The β-aldol thus elaborated was converted to **14** by mesylation and elimination. Reduction of the ketone under Luche conditions[14] gave **15** which was readily converted to **16** through the action of benzylisocyanate. Cleavage of the acetate afforded **17**.

Oxidation of **17** with PDC provided **18**. Methylenation of **18** by a modified Lombardo reaction[15] gave rise to **19**. Epoxidation of **19** with mCPBA led to a seperable mixture of **20** and **21** with only modest selectivity in the desired sense (**20:21**=2:1, 85% yield). Their availability was useful for probing the topography in the intramolecular S_N2' reaction.

Reaction of compound **20** with KHMDS in the presence of 18-C-6 gave rise to the desired valienamine derivative **22**[16] in 75% yield. Deprotection of **22**, as shown, followed by acetylation afforded the well characterized pentaacetylvalienamine (**23**)[16] (51% yield). We then studied the feasibility of this reaction with spiroepoxide **21**. In the event, all attempts to achieve conversion of **21** to **22** were unsuccessful. Under most of the basic conditions employed, **21** undergoes loss of benzyl isocyanate to provide **24** with some **21** recovered.

Figure IV



reagents and conditions
m) PDC, AcOH, EtOAc, rt, overnight, 85%, n) CH_2I_2, Zn, $TiCl_4$, THF, 15 min, 45%, o) mCPBA, $NaHCO_3$, CH_2Cl_2, p) KHMDS, 18-crown-6, THF, -78° - rt, 2.5h, q) Na, NH_3-THF, -78°; LiOH, 30% H_2O-EtOH, reflux; Ac_2O, pyridine, overnight, 51%

Since both **20** and **21** could, in principle, converge on the identical compound **22**, the striking differences in the reaction profiles must arise from kinetic factors, presumably of a stereoelectronic origin.[7,8] Thus, in the case of **20** both the attacking nitrogen of the carbamoylate function and the departing oxygen of the spiroepoxide can be axial in the chair form. In the case of **21**, this is not possible. Either the departing oxygen or the attacking nitrogen is poorly aligned relative to the π system. If the trans-trans disposed resident groups in **20** and **21** at carbons 2, 3 and 4 constitute a conformational lock, the crux of the stereoelectronic problem arises from the misalignment of the leaving oxygen with the 1,2-double bond. Since **21** undergoes substantial conversion to **24**, we could not use more forcing conditions to promote cyclization.

In summary, a synthesis of suitably protected versions of valienamine has been achieved. The strikingly different patterns of behavior of **20** and **21** suggest that the syn relationships in S_N2' reactions do not arise from a direct field interaction between the attacking and leaving groups,

but rather reflect a strong stereoelectronic preference. Further investigation of the scope of the effects is planned. The selection and fashioning of protecting arrangements for valienamine in anticipation of a coupling reaction with the carbohydrate domain for a synthesis of acarbose are also in progress. A synthetic route to the carbohydrate sector is reported in the following Letter.

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16 Structural assignments are consistent with NMR, IR and high resolution mass spectral analysis. The configurations of **20** and **21** follow from NMR measurements which will be discussed in detail in a full report.

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