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Inversion at the Bridgehead Nitrogen of the 1-Azabicyclo[4.4.0]decane Ring System

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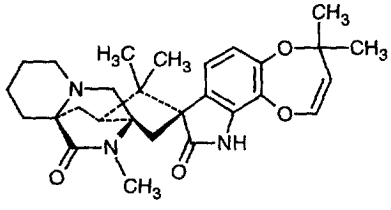
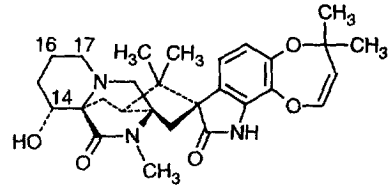
Abstract: Single crystal X-ray analyses conducted on 14-(R)-hydroxymarcfortine A **2** containing a 1-azabicyclo[4.4.0]decane ring system showed the unit cell to consist of two invertomers which differ in conformation at the bridgehead nitrogen. When the proton NMR spectra of **2** were recorded at low temperatures separate signals for each invertomer were observed.

Barriers to nitrogen inversion may be considered as useful probes for understanding structural effects in organic molecules. The factors that influence this inversion have been widely discussed.[1] Some *N*-methyl bicyclic amines[2] including the natural alkaloid 9-*O*-demethylhomolycorine have shown nitrogen inversion despite high inversion barriers.[3] Inversion at nitrogen has also been reported in a 7-azabicyclo[2.2.1]heptane ring system.[4] Such inversions must overcome the angle strain imposed by a quasi-trigonal (planar) transition state.[5] Inversion at the bridgehead nitrogen of the still more highly constrained 1-azabicyclo[4.4.0]decane ring



Marcfortine A (1)



2

system has not been reported until now. Single crystal X-ray analyses conducted on 14-(R)-hydroxymarcfortine A **2** showed that the crystal contains two invertomers which differ in conformation at the bridgehead nitrogen with each residing equally in the same unit cell (*Fig. 1*).[6] We originally prepared 14-(R)-hydroxymarcfortine A **2** from marcfortine A **1**, a fungal metabolite of *Penicillium roqueforti* reported by Polonsky et al.,[7] to investigate the significance of the hydroxyl group on anthelmintic activity.[8] Marcfortine A was converted in a multistep synthesis to compound **3** which was reduced (BH_3•$S(CH_3)_2$, THF) to **2** by way of intermediate **4** having an sp^2–hybridized nitrogen (Scheme 1). The question of whether the reduction of **4** to **2**

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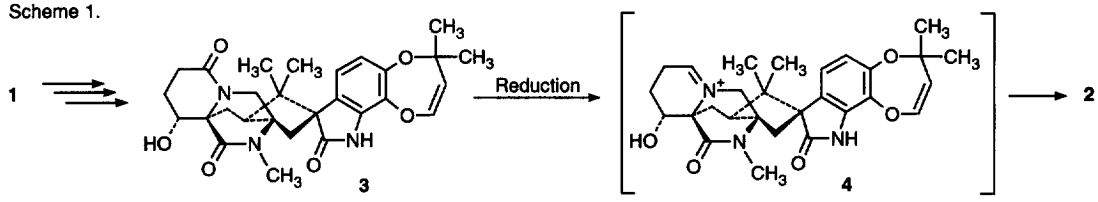
occurs equally at both diastereotopic faces of the carbon-nitrogen double bond thereby producing the two invertomers of this report is moot in light of the rapid inversion seen by proton NMR at room temperature. Unlike compound **2**, marcfortine A **1** crystallizes to give an isomerically homogeneous unit cell as shown by

Scheme 1.



X-ray analysis and does not appear to undergo bridgehead-nitrogen inversion since low temperature NMR studies failed to reveal the presence of invertomers.

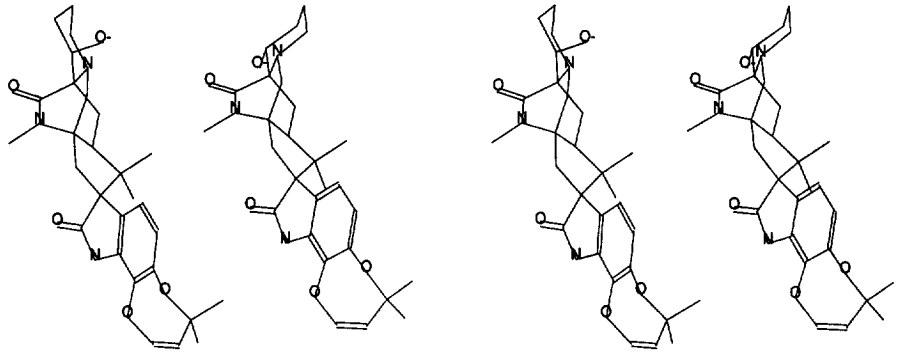


Figure 1. Relaxed stereoview from the X-ray analysis [9] of compound **2** showing the invertomer related to marcfortine A **1** (left hand structure of pair) and the invertomer peculiar to compound **2** (right hand structure of pair). Solvent molecules and hydrogens were omitted for clarity.

Proton NMR spectra of **2** obtained at room temperature (300 MHz, 1:1 - CD_2Cl_2:CD_3OD) showed only one set of peaks due to rapid inversion on the NMR time-scale. For example, one methylene hydrogen at C17 appeared at δ2.44 (doublet of triplet). At temperatures below 228 K, the same C17 proton signal decoalesces

into two resolved signals ($\Delta\nu_{est.}$=26Hz) (*Fig. 2*). The calculated activation barrier for inversion is 11.5 ± 0.1 kcal mol^{-1} which is intermediate in value compared to other amine inversion processes.[1] At still lower

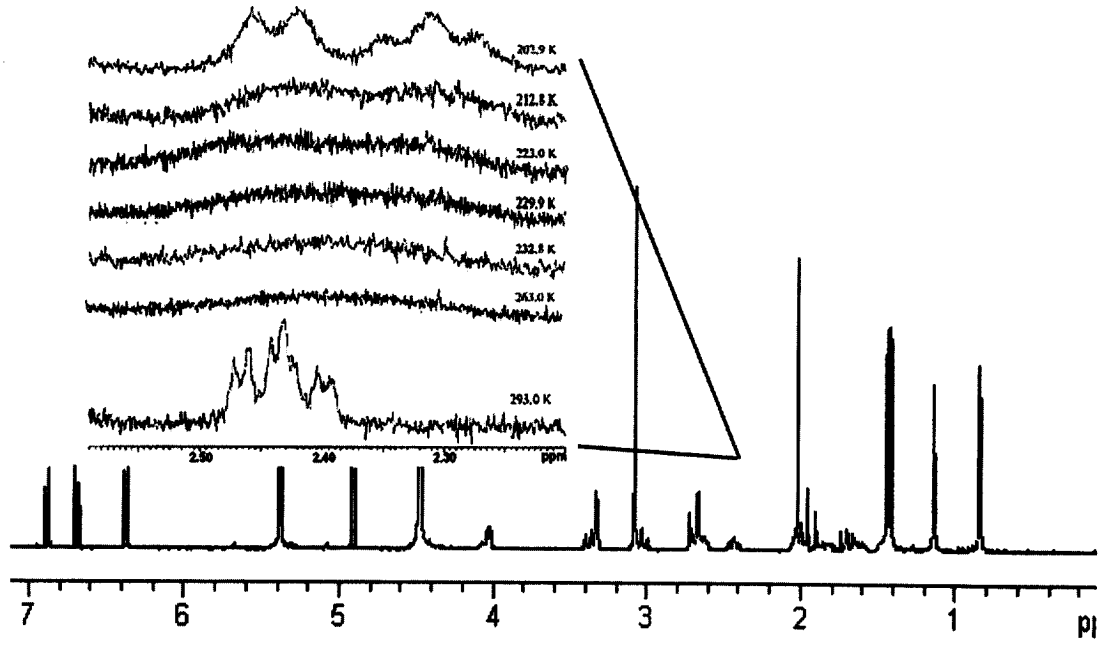


Figure 2. Proton NMR spectra of compound **2** (300 MHz, 1:1 - CD_2Cl_2:CD_3OD) obtained at low temperatures.

temperatures, the decoalesced C17 signals[10] further differentiated into an apparent doublet and a triplet at 203 K. The apparent triplet arises from an added coupling with a C16 proton and demonstrates different conformations for the two invertomers.

The tendency of compound **2** to undergo inversion can be attributed to the strain introduced by the 14-(R)-hydroxyl group which occupies an axial position in the invertomeric state related to marcfortine A **1** but takes up the equatorial position on inversion of the bridgehead nitrogen. The hydroxyl group is absent in marcfortine A **1** which consequently shows no inversion.

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6. **Single-Crystal Structure Determination:** $C_{28}H_{35}N_3O_5$; Space group $P2_12_12_1$; cell parameters: *a* = *11.910(1)*, *b* = *17.400(1)*, *c* = *24.340(2)* ; molecular weight = 493.61; Z = 8; calculated density = 1.2998g/cm^3. A colorless, clear, prism-shaped crystal (0.3X0.4X0.1 mm) was selected and mounted on a glass fiber. The data was collected on a Mar Research Imaging Plate controlled by a SGI computer, at low temperature (-100 °C), with crystal-monochromatized Mo*Ka* radiation [l(Mo*Ka*)=0.71069]. All 3,002 unique reflections were measured to a $2q_{max}$ of 55 for Laue group mmm; 2,173 intensities were > 4s. The DENZO software was used for the data reduction. The structure was solved by direct methods, using MULTAN on IBM mainframe computer. The trial solution obtained 43 non-hydrogen atomic positions. All 72 non-hydrogen atoms were found from the following Fourier maps. Least squares refinement included all nonhydrogen atomic coordinates and anisotropic thermal parameters. Refinement on F^2 for all reflections. Weighted R-factors Rw and all goodnesses of fit S are based on F^2, conventional R-factors are based on F. The observed criterion of $F^2 > 2s(F^2)$ is used only for calculating _R_factor_obs etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F, and R-factors based on all data will be even larger. In the final refinement, with 2,173 reflections have intensities > 4s : R = 0.066; S = 3.42. R = 0.080 with all 3,002 reflections. The two molecules in the asymmetrical unit have different conformations.
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9. The original X-ray coordinates were transferred to our proprietary computer modeling system, Mozaic®, and the two invertomers modeled side by side.
10. To verify the assignment of decoalesed proton signals on C17 at 203 K a correlated spectrum (COSY) was obtained. Both signals at 2.44 and 2.31 ppm showed separate cross peaks at 2.62 ppm. A single cross peak at the resonance frequency was observed in the 293 K COSY.