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An Asymmetric Synthesis of (+)-Isonitramine by 'Triple Allylic Strain-Controlled' Intramolecular S_N2' Alkylation

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Abstract: The spirocyclic alkaloid (+)-isonitramine (**1**) has been synthesized in a stereoselective manner utilizing a novel '*triple allylic strain-controlled*' intramolecular lactam enolate S_N2' alkylation.

(+)-Isonitramine (**1**), a spirocyclic alkaloid produced by plants of the genus *Nitraria*,[3] has received considerable synthetic attention because of its unusual 2-azaspiro[5.5]undecane skeleton and the potential for biological activity of this class of γ-aminoalcohols.[4] We recently reported a highly stereoselective synthesis of (±)-isonitramine by an intramolecular S_N2' cyclization.[4m] Described herein is an asymmetric synthesis of (+)-isonitramine (**1**) using a novel '*triple allylic strain-controlled*' intramolecular lactam enolate S_N2' alkylation which is summarized in the scheme below.[5]

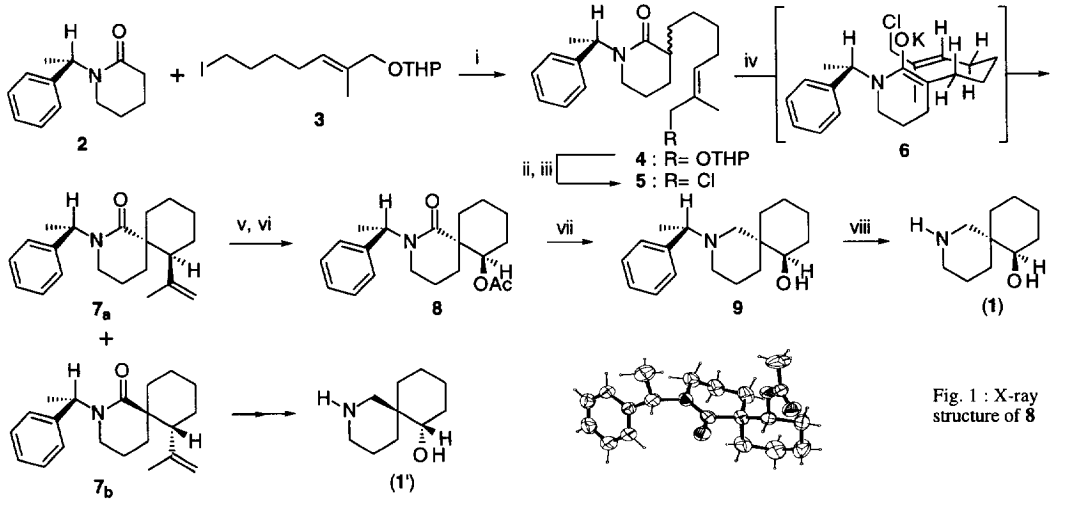

Fig. 1 : X-ray structure of **8**

Reagents: i) LDA, THF, -78 °C, 30 min, then, rt, 1 h (94%); ii) PPTS, EtOH, 55 °C, 24 h (88%); iii) CCl_4, *n*-Bu_3P, rt, 2 h (98%); iv) KHMDS, toluene, 70 °C, 4 h (70% total yield); v) OsO_4(0.1 eq), $NaIO_4$, acetone : H_2O (4 : 1), rt, 15 h (95%); vi) $(CF_3CO)_2O$, 70% H_2O_2, methylene chloride, Na_2HPO_4, rt, 15 h (79%); vii) LAH, ether, -30 °C to rt, 1 h (94%); viii) $Pd(OH)_2$ on carbon, MeOH, rt, 2 h (87%).

Treatment of the (*S*)-*N*-1'-phenethyl valerolactam **2**[6] with LDA followed by alkylating agent **3** in THF gave the corresponding alkylated δ-lactam **4** as a mixture of diastereoisomers in 94% yield. Removal of THP protecting group with PPTS[7] and subsequent chlorination of the resulting allylic alcohol by the protocol described by Hooz[8] gave a 1 : 1 mixture of the key cyclization substrate **5** in 86% yield for the two steps. Slow addition of allylic chloride **5** to a refluxing THF solution of KHMDS furnished the desired spirocyclic lactam **7**$_a$

as the major isomer, along with $\mathbf{7_b}$ in a 3.2 : 1 ratio in 67% total yield.[9] In subsequent experiments, the ratio of 1,4-induction was increased to 6.2 : 1 by using toluene as solvent under comparable conditions. The observed high stereoselectivity can best be rationalized by considering that the reaction proceeds via *'triple allylic strain-controlled'* transition state geometry **6** where the *'H-eclipsed'* allylic chloride moiety reacts from the less hindered face of the preferred *'doubly H-eclipsed'* conformation of the lactam enolate.[10]

When the spirolactam $\mathbf{7_a}$ was subjected to Lemieux-Johnson oxidation followed by Baeyer-Villiger reaction, ester **8** was obtained as white crystals in 73% overall yield for the two steps.[4l] X-ray crystallographic analysis established the relative configuration of **8** (Figure 1).[11] LAH reduction of the lactam ester **8** followed by hydrogenolysis of the resulting aminoalcohol **9** with Pearlman's catalyst afforded the desired (+)-isonitramine (**1**) ($[\alpha]^{20}_D$ = +4.4°, c = 0.67, $CHCl_3$ (lit.[4i]) $[\alpha]^{20}_D$ = +5°, c = 1.2, $CHCl_3$)) in 87% overall yield, after purification by column chromatography on basic alumina. ^1H and ^{13}C NMR data of the synthetic (+)-isonitramine (**1**) were in good agreement with those kindly provided by Professor Husson.[12] The minor isomer $\mathbf{7_b}$ was also converted into (-)-isonitramine (**1'**) (($[\alpha]^{26}_D$ = -4.5°, c = 0.24, $CHCl_3$ (lit.[4i]) $[\alpha]^{20}_D$ = -5°, c = 2.1, $CHCl_3$)) by a reaction sequence analogous to (**1**).

In summary, we have synthesized (+)-isonitramine (**1**) by a novel *'triple allylic strain-controlled'* intramolecular lactam enolate S_N2' alkylation route with a high degree of 1,4-induction.

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9. All new compounds exhibited satisfactory spectroscopic data. The ratio of stereoisomers was determined by rigorous analysis of 600 MHz ^1H NMR spectra. Compound $\mathbf{7_a}$: **IR** (neat) ν 1624 cm^{-1}; **^1H NMR** ($CDCl_3$, 400 MHz) δ 1.38 (d, J = 7.2 Hz, 3H), 1.67 (s, 3H), 1.27 - 1.91 (m, 12H), 2.66 - 2.70 (m, 1H), 2.84 - 2.88 (m, 1H), 2.91 - 2.98 (m, 1H), 4.64 (s, 1H), 4.80 (s, 1H), 6.06 (q, J = 7.2 Hz, 1H), 7.15 - 7.26 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 15.1, 20.1, 20.9, 24.1, 24.6, 26.1, 26.5, 35.9, 41.6, 45.9, 48.0, 49.9, 112.5, 126.9, 127.0, 128.3, 141.2, 148.1, 175.2; **HRMS** calcd for $C_{21}H_{29}NO$ (M^+) 311.2249, found 311.2249; $[\alpha]^{18}_D$ = -184.5° (c = 1.52, $CHCl_3$).
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11. Details of X-ray crystallographic study will be reported elsewhere.
12. We thank Professor H.-P. Husson (CNRS, France) for sending us copies of reference spectra of (+)-isonitramine (**1**).

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