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A SYNTHESIS OF dl-ISORETRONECANOL

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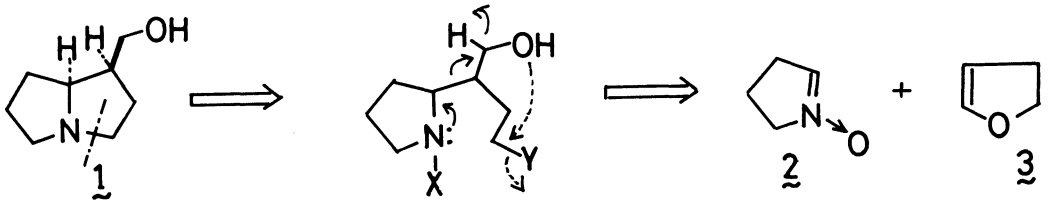
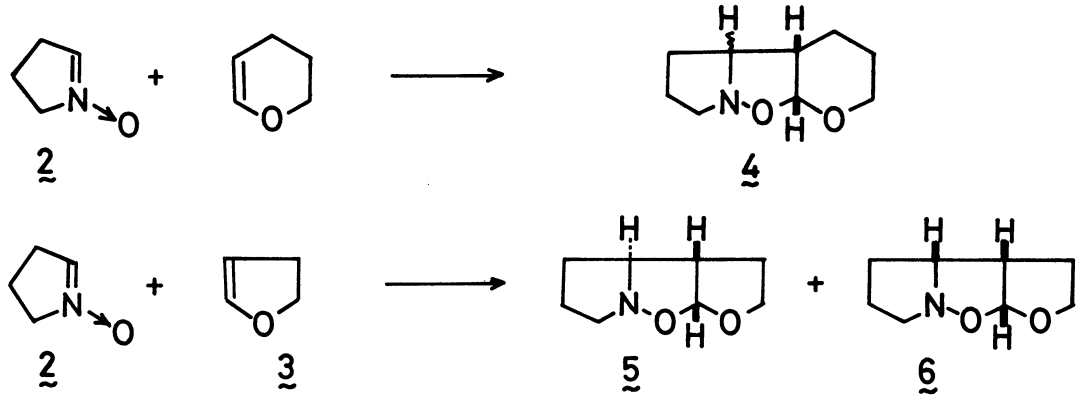
Isoretronecanol was stereoselectively synthesized using 1,3-dipolar addition of pyrroline oxide to dihydrofuran and a new cyclization of δ-amino alcohol to pyrrolidine.

Pyrrolizidine alkaloids are distributed in various plant species mainly of Compositae[1] and are known to have wide range of physiological activities.[2] In these alkaloids, isoretronecanol(1) was found as the base component of alkaloids of Mimusops species[3] and the (+)-enantiomer of this alkaloid, lindelofidine, was also isolated from a plant of Thesium spp.[4] We wish to report a new stereoselective synthesis of (±)-isoretronecanol.[5]

Retrosynthetic analysis[6] of isoretronecanol(1) indicated that one of efficient means of assembling the molecular framework would involve 1,3-dipolar addition of readily available 1-pyrroline 1-oxide to dihydrofuran. Although the regioselectivity

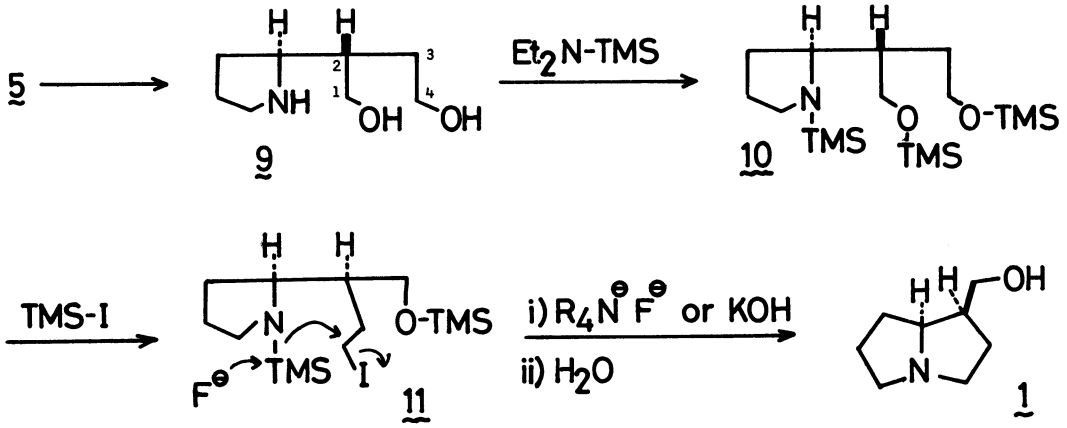


of 1,3-dipolar cycloaddition of nitrones to ordinary ethylene bonds was thoroughly studied,[7] that to hetero-substituted ethylenes was not well documented.[8] We examined first the reaction of 1-pyrroline 1-oxide(2) and dihydropyran. Reaction of the nitrone(2) with dihydropyran occurred upon heating in benzene solution at 140°C for 1 h to afford a single adduct(4) in 28% yield.[9] The NMR spectrum of 4 revealed a doublet at δ5.06(J=4Hz) due to an anomeric proton, showing that the reaction proceeded regiospecifically. This finding encouraged further exploration of this approach. In the same condition, dihydrofuran(3) reacted more smoothly than dihydropyran to afford two adducts[9] in 91% and 3% yield, which were separated by chromatog-



raphy. The structures(5 and 6) including the stereochemistry of the two products were assigned from the spectral properties and the reaction mechanism. It was reported that 1,3-dipolar cycloadditions of a conjugated nitrone, C-phenyl-N-methylnitrone, to conjugated alkenes such as styrene and alkyl acrylate afford mainly endo-adduct with small amount of exo-adduct because of secondary orbital interactions.[10] But unconjugated alkenes were known to give exclusively exo-addition product owing to disfavored steric interaction of the rest of molecule in the endo-mode of addition.[10] Thus, unconjugated nitrone(2) and dihydrofuran(3) would react through exo-oriented transition state(7) rather than endo-transition state(8) to afford an adduct having

the stereostructure(5). This was finally confirmed by converting it into isoretronecanol.



The major adduct(5) was reduced with lithium aluminium hydride by refluxing in tetrahydrofuran for 40 h to afford an aminodiol(9)[9] in quantitative yield. Many efforts to cyclize the aminodiol directly to pyrrolizidine ring using the reagents such as thionyl chloride[11] or hydrobromic acid only resulted in a trace amount of isoretronecanol(1). But the aminodiol(9) was converted into the alkaloid in a high yield using the following new method. The amino and hydroxyl groups of the aminodiol(9) were thoroughly silylated by heating with N-(trimethylsilyl)diethylamine at 145°C for 3 h. After the excess reagent was removed, the trisilylated 10 was treated with one equivalent of trimethylsilyl iodide in chloroform at 50°C for 12.5 h. This iodide was anticipated to attack mainly at sterically less hindered carbon-4 of 10 leading to an iodide(11). Without the isolation of the reaction product, mixture was further treated with benzyltrimethylammonium fluoride at room temp and then at 50°C for 0.5 h to afford isoretronecanol in 58% yield [ν(film) 3380, 1460, 1110, 1080, 1040 cm^{-1}; $\delta(CDCl_3)$ 1.2-2.1(6H,m), 2.2-3.4(6H,m), 3.60(2H,d,J=7Hz), 5.58(1H,brs); picrate mp 188.5-189.0°C,lit[5] mp 188-189°C]. Addition of potassium hydroxide to the iodide (11) also afforded the alkaloid(1) in 45% yield. The synthetic compound showed the same spectral properties with those of authentic sample.[12,13]

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8) Addition to an enamine has been reported by O.Tsuge, M.Tashiro, and Y.Nishihara, Tetrahedron Lett., 3769 (1967).

9) Satisfactory analytical data were obtained for each synthetic intermediate using purified and chromatographically homogeneous samples. The physical and analytical properties of the intermediates in this synthesis are as follows:
4; Bp 80-85°C/0.06mmHg(by short path distillation); $\nu(CHCl_3)$ 1075, 1050 cm^{-1}; $\delta(CCl_4)$ 1.3-2.2(9H,m), 2.7-4.0(5H,m), 5.06(1H,d,J=4Hz); Found:C, 63.45;H, 8.96; N, 8.27%. Calcd for $C_9H_{15}O_2N$:C, 63.87;H, 8.93;N, 8.27%.
5; Bp 86.0-87.5°C/4mmHg; $\nu(CHCl_3)$ 1075, 995, 920 cm^{-1}; $\delta(CCl_4)$ 1.2-2.4(6H,m), 2.5-3.5(4H,m), 3.5-4.2(2H,m),5.50(1H,d,J=5Hz); Found:C, 61.57;H, 8.41;N, 9.00%. Calcd for $C_8H_{13}O_2N$:C, 61.91;H, 8.44;N, 9.02%.
6; Bp 62°C/0.007mmHg(by short path distillation); $\nu(CHCl_3)$ 1125, 1075, 1050, 995, 950 cm^{-1}; $\delta(CCl_4)$ 1.3-2.3(6H,m), 2.5-4.1(6H,m), 5.52(1H,d,J=5Hz); MS:found 155.0944; calcd for $C_8H_{13}O_2N$: 155.0945.
9; ν(film) 3320, 1410, 1050 cm^{-1}; $\delta(CDCl_3)$ 1.2-2.1(6H,m), 2.8-3.4(4H,m), 3.5-3.9 (4H,m), 4.57(3H,s); Triacetate of 9: bp 125°C/0.09mmHg(by short path distillation); Found:C, 58.65;H, 8.17;N, 5.17%. Calcd for $C_{14}H_{23}O_5N$:C, 58.93;H, 8.12; N, 4.90%.

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12) All the chemical shifts of the synthetic compound had been slightly different from the values reported by Pinnick and Chang,[5] but the published values were found to be uncalibrated on the reference tetramethylsilane by inspection of the spectrum provided from Professor Pinnick.

13) The authors express thir appreciation to Professor H.W.Pinnick, The University of Georgia, for generously supplying the NMR copy of the synthetic isoretronecanol, and to Professor L.W.Smith, CSIRO, Australia, for kindly sending of the copy of NMR spectra of natural isoretronecanol.

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