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ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-NITRAMINE

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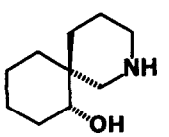
Abstract - A short enantioselective synthesis of the spirocyclic alkaloid (+)-Nitramine (1) is reported, the azaspiro ring system being formed via intramolecular ring-opening of the chiral epoxy sulfone 7.

Plants of the genus Nitraria have recently been found[1] to provide a family of 2-azaspiro-[5.5]-undecanols (e.g. Nitramine, 1, from Nitraria Schoberi) the structures of which closely resemble the basic molecular framework of the neurophysiologically important histrionicotoxin alkaloids[2]. These findings have prompted a number of synthetic studies[3] on the Nitraria alkaloids, including our own recent synthesis[3a] of racemic Nitramine. Following some initial confusion, the issue of the absolute stereochemistry of naturally occurring Nitramine and congeners has now been settled thanks to the work of Husson[3d] and Schultz[3e]. The absolute configuration of (+)-Nitramine is that shown below.



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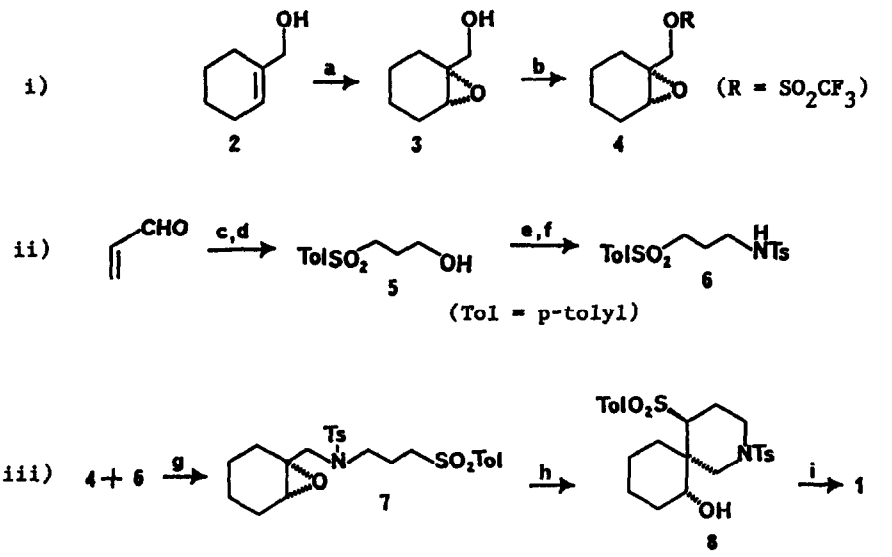
In this paper we present a short, convergent, and enantioselective synthesis of 1, the key intermediate being the chiral epoxy sulfone 7 (Scheme). We chose to introduce the two chiral centres of the target at an early stage of the synthesis via Sharpless asymmetric epoxidation[4] of 1-cyclohexenylmethanol, 2, which furnished the epoxy alcohol (+)-3. Recently, Sharpless and coworkers[4] described the preparation of (-)-3 which, by the Mosher ester technique[5], was shown convincingly to be of 93% e.e. In the course of our own studies we found that simple comparison of optical rotation data (at least those obtained for chloroform solutions) was not a reliable method for the estimation of optical purity since the $[\alpha]_D$ value was markedly concentration dependent. We therefore routinely checked the e.e. of our product by high-field ^1H NMR studies of the corresponding acetate in the presence of the chiral shift reagent $Eu(tfc)_3$. By this technique the optical purity of (+)-3 was found consistently to lie in the range

90-94% e.e., and the result of a typical run (92% e.e.) is shown in Fig. 1.



Scheme. (a) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (-)-diethyl tartrate, CH_2Cl_2, -40°C, 70% (b)$(CF_3SO_2)_2O$, Et_3N, THF, -20°C, product not isolated (c) 4-thiocresol, Na, EtOH, then $NaBH_4$, 86% (two steps) (d) H_2O_2, HOAc, 89% (e) CH_3SO_2Cl, Et_3N, THF, 97% (f) H_2NTs, NaH, DMF, 0°C to 60°C, 81% (g) NaH, DMF, 0°C,then add 6; then add 4 → 50°C, 71% (h) ^{n}BuLi (2 eq.), THF/HMPA, -20°C to RT, then quench at -78°C, 69% (i) Na(Hg), Na_2HPO_4, MeOH, 0°C, 74%.

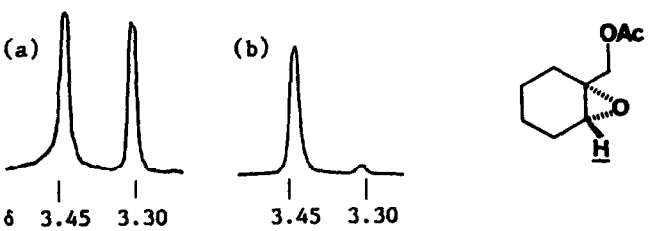
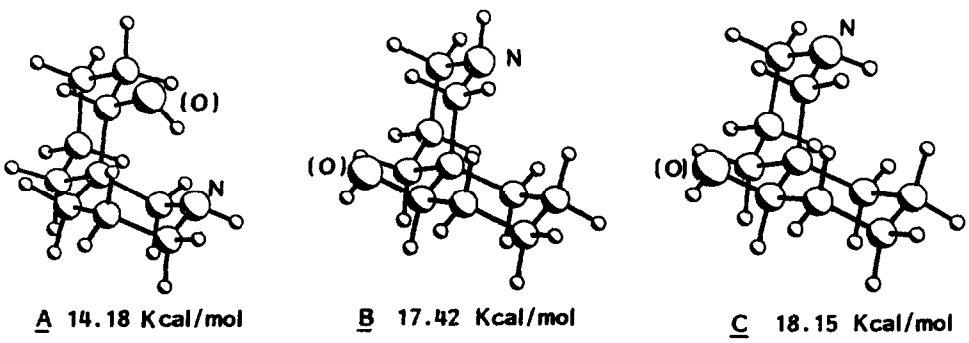


Fig. 1. Portion of the 300 MHz ^{1}H NMR spectrum (C_6D_6) of the acetate of 3, recorded in the presence of Eu(tfc)$_3$. Epoxide ring proton signals shown. (a) racemic material; (b) acetate of (+)-3, 92% e.e.

To allow introduction of a suitable side-chain, epoxy alcohol 3 was first converted to the (labile) triflate 4. The requisite appendage, in the form of sulfonamide 6, was rapidly constructed from acrolein, largely by use of the Pinnick methodology[6]. Union of 4 and the N -anion of 6 smoothly delivered the key (crystalline) spirocyclisation precursor 7, and exposure of this material to two equivalents of ^{n}butyllithium in THF/HMPA resulted in a clean intramolecular epoxide ring-opening reaction[7]. As noted in our earlier work on the racemic series[3a], a single diastereomer was the result of a low temperature quench[8] and this stereoselective reaction yielded the azaspirocycle having the absolute configuration shown for 8 in the Scheme. The sulfone moiety adopts an equatorial position on the piperidine ring, the adjacent proton showing J_{aa}= 12.5 Hz and J_{ae}= 4 Hz in the ^{1}H NMR spectrum. The complementary ^{1}H NMR spectroscopic evidence which formed the basis for the stereochemical assignment has already been discussed in some detail[3a], and for the present we prefer to confine the question of conformational analysis to the case of Nitramine itself (see below).

Conversion of 8 to the target was accomplished in acceptable yield (74%) by the use of buffered sodium amalgam in methanol[9], which provided (+)-Nitramine of ca. 93% optical purity and showing physical and spectral data in excellent accord with the literature values[3e].

By careful analysis and comparison of the 300 MHz ^{1}H NMR spectra of 8 and 1, we deduce that Nitramine (at least in 'dry' $CDCl_3$ solution) prefers to adopt a conformation characterised by an intramolecular O-H---N hydrogen bond. The evidence for this is the observation that the (axial) proton adjacent to the hydroxyl group, which in spirocycle 8 couples (J = 8 Hz) to the -OH, also shows a four-bond coupling (J = 0.9 Hz) to the axial component of the methylene group sandwiched between the nitrogen and the spiro carbon. Inspection of molecular models shows that the proposed H-bonded conformer would allow a perfect "W" arrangement[10] of the four bonds relevant to the observed long-range coupling, a situation which would not arise in alternative structures having the ring-flipped piperidine conformer. This conformational analysis is supported by the results of molecular mechanics calculations[11]. Calculated conformers are shown in Fig. 2.



A 14.18 Kcal/mol B 17.42 Kcal/mol C 18.15 Kcal/mol

Fig. 2. Calculated low-energy conformers of Nitramine. Conformer A is intramolecularly hydrogen-bonded.

Three low-energy conformers (A, B, and C, with the final energies shown in Fig. 2) were found, all of which are chair-chair arrangements carrying an equatorial hydroxyl. The hydrogen-bonded conformer A (OH--- nitrogen lone-pair distance 1.26Å) is indeed suggested to be the one of lowest energy, while B and C, with the ring-flipped piperidine, differ from each other only in the orientation of the nitrogen lone-pair.

EXPERIMENTAL

General remarks. ^{1}H NMR spectra were obtained at 300 MHz, and ^{13}C spectra at 75 MHz, for $CDCl_3$/TMS solutions. IR spectra wre obtained for thin films or CH_2Cl_2 solutions, and only the strongest/structurally most important peaks are listed. Mass spectra were obtained using the chemical ionisation technique. Combustion analyses were performed by Mikro Kemi AB, Uppsala, Sweden. When necessary, solvents were dried and distilled under nitrogen using standard procedures, while reaction flasks and syringes were oven-dried (120°C) before use. Merck silica gel 60 (230-400 mesh) was used for flash chromatography.

Epoxy alcohol 3 was prepared according to the literature procedure[4] for the enantiomer. The spectral and physical data for our product were identical (except for sign of optical rotation) with those reported[4]. Material with $[\alpha]_D$ + 22.4° (c 2.5,$CHCl_3$) was shown to be of 92% e.e. (see Fig. 1).

Triflate 4. Epoxy alcohol 3 (0.64 g, 5 mmol) was dissolved with stirring under N_2 in dry THF (15 ml) and the solution was cooled to -20°C. Triethylamine (0.66 g, 6.5 mmol) was added, followed by trifluoromethanesulfonic anhydride (1.69 g, 6 mmol). The resultant solution was allowed to warm up slowly to 0°C (over 2 h) at which point TLC analysis (50% ether/pentane) showed complete reaction. The cold solution was washed quickly with $CuSO_4$.aq. and then with water, and finally dried over Na_2SO_4. The volume of the THF solution of the triflate was reduced to ca. 5 ml by rotary evaporation at 0°C, and the concentrated solution used immediately (see below). Attempts to isolate the triflate were unsuccessful, due to its instability.

Alcohol 5 was prepared by the general method of Pinnick[6]. 4-Thiocresol(14.9 g, 120 mmol) was dissolved with stirring in 95% ethanol (100 ml) and sodium (0.3 g) was added carefully. A solution of freshly distilled acrolein (5.61 g, 100 mmol) in 95% ethanol (40 ml) was added dropwise over 30 min, and the resultant solution stirred for 18 h at room temperature. $NaBH_4$ (1.9 g, 50 mmol) was added, and the reaction mixture was stirred for 2 h. A 2M aqueous solution of NaOH (10 ml) was added dropwise and the resultant mixture concentrated to low volume before thorough extraction with ether. The combined extracts were dried over Na_2SO_4 and evaporated to dryness to yield the sulfide as a viscous oil which slowly solidified in the freezer. This material was ^{1}H NMR spectroscopically pure and was used without further

purification. Yield: 15.65 g, 86% (based on acrolein). ^{1}H NMR: δ 7.30 and 7.10 (4H, AA'BB'm, J_{AB} = 9 Hz), 3.76 (2H, q, J = 7, $C\underline{H}_2O$, coupled to O$\underline{H}$), 2.98 (2H, t, J = 7, $SC\underline{H}_2$-), 2.30 (3H,s, Me), 1.86 (2H, qn, J = 7, -$CH_2C\underline{H}_2CH_2$-), 1.44 (1H, t, J = 7, O$\underline{H}$). IR: 3340 (b, OH) cm^{-1}.

The crude sulfide from above (15g, 82 mmol) was dissolved in glacial acetic acid (30 ml) and 30% H_2O_2 (30 ml) was slowly added dropwise. When addition was complete, the mixture was refluxed for 2 h, cooled, and worked up with 10% NaOH.aq. The product was extracted into ethyl acetate, the combined extracts were dried over Na_2SO_4, and the solvent was removed to yield compound 5 as a viscous colourless oil (19.05 g, 89%). This material was ^{1}H NMR spectroscopically pure. ^{1}H NMR: 7.79 and 7.35 (4H, AA'BB'm, J_{AB} = 9), 3.71 (2H, q, J = 6, $C\underline{H}_2O$, coupled to O$\underline{H}$), 3.21 (2H, m, O_2SCH_2), 2.42 (3H,s, Me), 1.96(2H, m, -$CH_2C\underline{H}_2CH_2$-), 1.83 (1H, t, J = 6, O$\underline{H}$). IR: 3500 (b,OH) 1300(s, sulfone), 1140(s, sulfone).

Sulfonamide 6. The alcohol 5 (5.35 g, 25 mmol) was dissolved with stirring under N_2 in dry THF (15 ml). The solution was cooled to 0°C before addition of triethylamine (3.28g, 32.5 mmol) and methanesulfonyl chloride (3.15 g, 27.5 mmol). The mixture was stirred at 0°C for 5 h, poured into ice-cold 5% HCl, and extracted with CH_2Cl_2 (3x25 ml). The combined extracts were dried over Na_2SO_4 and the solvents removed to yield the mesylate as a colourless low-melting solid. This material was used without further purification. ^{1}H NMR: 7.80 and 7.39 (4H, AA'BB'm, J_{AB} = 9), 4.32 (2H, t, J = 7, $C\underline{H}_2OMs$), 3.19 (2H, m, $O_2SC\underline{H}_2$), 3.00 (3H,s, mesyl Me), 2.44 (3H,s, Me), 2.18 (2H, m, -$CH_2C\underline{H}_2CH_2$-). Yield: 7.08 g, 97%.

Sodium hydride (1.28 g of 60% dispersion in mineral oil, 32 mmol) was washed thrice with dry pentane under nitrogen, and the last traces of pentane were removed at aspirator pressure. The remaining solid was placed under nitrogen atmosphere and cooled to 0°C before addition of dry DMF (90 ml). The resultant slurry was stirred at 0°C during addition of a solution of p -toluenesulfonamide (5.14 g, 30 mmol) in dry DMF (25 ml). The resultant mixture was stirred for 2 h before addition of a solution of the mesylate from above (5.84 g, 20 mmol) in dry DMF (15 ml). When addition was complete, the reaction mixture was heated to 60°C and stirred at that temperature overnight. The cooled mixture was partitioned between ether and water, the ethereal layer was dried over Na_2SO_4, and the solvent was removed to yield the crude sulfonamide which was purified by recrystallisation from ether/CH_2Cl_2. There was obtained 5.95 g (81%) of the pure sulfonamide as colourless needles, m.p. 162-163°C. ^{1}H NMR: 7.76, 7.71 and 7.38, 7.30 (8H, 2xAA'BB', J_{AB} = 9), 4.71 (1H, t, J = 6.5, N$\underline{H}$), 3.14 (4H, m, $O_2SC\underline{H}_2$ and $NC\underline{H}_2$), 2.47 (3H,s, Me), 2.43 (3H,s, Me), 1.99 (2H, qn, J = 5.5, -$CH_2C\underline{H}_2CH_2$-). IR: 3250, 1320, 1300, 1160, 1140. MS(CI): m/z 368 (M^++1, 100%). Anal. Calcd for $C_{17}H_{21}NO_4S_2$: C,55.56; H, 5.76; N, 3.81. Found: C, 55.40; H, 5.75; N, 3.51%.

Epoxide 7. Sulfonamide 6 (2.39 g, 6.5 mmol) was converted to its N-anion as described above for p-toluenesulfonamide (NaH, 0.28 g of 60% dispersion, 7 mmol, 20 ml DMF, 0°C). The solution of the anion was stirred under nitrogen at room temperature during the rapid addition of the previously described THF solution of triflate 4 (from 5 mmol of 3). The reaction mixture was then heated to 50°C and stirred at that temperature overnight. Work-up as described above for 6 was followed by flash chromatography (75% ether-pentane). There was obtained 1.69 g (71% based on epoxy alcohol 3) of epoxide 7 as a colourless crystalline solid, m.p. 143-144°C (ether-pentane). ^{1}H NMR: 7.82,7.63, 7.35, 7.29 (8H, 2xAA'BB', J_{AB} = 9), 3.41 (1H, d, J = 15, OC-CH-N), 3.20 (2H, m, NCH_2CH_2), 3.13 (2H, t, J = 8, O_2SCH_2), 2.93 (1H, b"d", J = 3, epoxy), 2.85 (1H, d, J = 15, OC-CH-N), 2.46 (3H, s, Me), 2.41 (3H,s, Me), 2.05 (2H, m), 1.92-1.60 (4H,m), 1.38 (2H, m), 1.32 (2H, m). IR: 1330, 1300, 1210 (epoxy), 1150, 920 (epoxy). MS(CI): m/z 478 (M^++1, 1%). $[\alpha]_D$ +9.2° (c 0.34, CH_2Cl_2). Anal. Calcd for $C_{24}H_{31}NO_5S_2$: C, 60.35; H, 6.54; N, 2.93. Found: C, 60.15; H, 6.40; N, 2.70%.

Alcohol 8. Epoxide 7 (1.43 g, 3 mmol) was dissolved with stirring under nitrogen in dry THF (30 ml) and dry HMPA (3.5 ml). The solution was cooled to -20°C before dropwise addition of ^{n}butyllithium (3.75 ml of 1.6M hexane solution, 6 mmol). During the addition the reaction mixture changed from colourless to yellow to deep red. The resultant solution of the dianion was allowed to reach room temperature overnight (reaction complete according to TLC analysis) and was then cooled to -78°C. The reaction was quenched by the rapid addition of 10% aqueous $NaHSO_4$. The partly frozen mixture was allowed to reach room temperature slowly, and the resultant pale yellow mixture was partitioned between ether and water. The organic phase was dried over Na_2SO_4 and concentrated to give the crude product which was purified by flash chromatography (75% ether-pentane). There was obtained 0.987 g (69%) of the spirocycle 8 as a foamy solid (single sulfone diastereomer). ^{1}H NMR: 7.75, 7.60, 7.35, 7.27 (8H, 2xAA'BB'm, J_{AB} = 9), 3.95 (1H, dd, J = 12.5, 4, CH SO_2Tol), 3.84 (1H, dddd, J = 13, 8, 4, 0.9, CHOH, coupled to OH and long-range coupling, see text), 3.39 (1H, bd, J = 15, OC-CH_{ax}-N, long-range coupled to CHOH), 3.17 (1H, d, J = 15, OC-CH_{eq}-N), 2.93-2.82 (3H, m, CH_2CH_2N and OH), 2.43 (3H,s, Me), 2.40 (3H,s, Me), 2.29 (2H,m), 2.00 (2H, m), 1.79-1.55 (4H, m), 1.34- 1.11 (2H, m). ^{13}C NMR: 144.56 143.78, 136.05, 135.12, 129.89, 129.84, 128.48, 126.78, 70.94, 58.73, 56.03, 46.82, 44.51, 39.52, 25.47, 24.65, 23.75, 23.30, 21.64, 21.49. IR: 3500 (b, OH), 1340, 1300, 1160, 1140. MS(CI): m/z 460 (M^++1 minus H_2O). $[\alpha]_D$ +12.7° (c 0.58, CH_2Cl_2). Anal. Calcd for $C_{24}H_{31}NO_5S_2$: C, 60.35; H, 6.54; N, 2.93. Found: C, 60.12; H, 6.55; N,2.90%.

(+)-Nitramine, 1. The alcohol 8 (0.477 g, 1 mmol) was dissolved with stirring in dry methanol (10 ml) and Na_2HPO_4 (1.42 g, 10 mmol) was added. The mixture was cooled to -20°C and finely powdered, freshly prepared, 6% sodium amalgam (3.75 g) was added in

portions. The reaction mixture was allowed to reach 0°C and stirred at that temperature overnight. The methanol was decanted and the solvent was removed to give the crude product which was purified by flash chromatography ($CHCl_3$-methanol-NH_4OH gradient). There was obtained 0.125 g (74%) of (+)-Nitramine as a colourless oil. $[\alpha]_D$ +21.3° (c 1.52, CH_2Cl_2); Lit.[3e]: +23.0° (c 1.58, CH_2Cl_2). The ^1H and ^{13}C NMR data were in excellent accord with those reported[3c,e]. ^1H NMR: 5.70 (2H, bs, OH and NH), 3.54 (1H, ddd, J = 10, 4.4, 0.9, CHOH, long-range coupled, see text), 3.45 (1H, d, J = 12, OC-CH_{eq}-N), 2.96 (1H, m), 2.60 (1H, td, J = 11, 3), 2.39 (1H, dd, J = 12, 0.9, OC-CH_{ax}-N), 2.10 (1H, m), 1.97-0.90 (11H, m). MS(CI): m/z 170 (M^++1).

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