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STEREOCONTROLLED SYNTHESIS OF THE SPIROCYCLIC ALKALOID (±)-NITRAMINE

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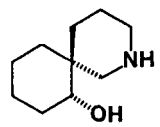
Summary. A short and completely stereocontrolled total synthesis of the title alkaloid is described, the key step being spirocyclisation of the epoxy sulfone 4.

Nitramine, 1, an alkaloid possessing the unusual 2-azaspiro-[5.5]-undecane skeleton has been isolated from Nitraria schoberi[1]. The molecular framework of this alkaloid and congeners[1] resembles that of the histrionicotoxins, a class of 1-azaspiro-[5.5]-undecan-8-ols which has attracted widespread pharmacological and synthetic interest[2].



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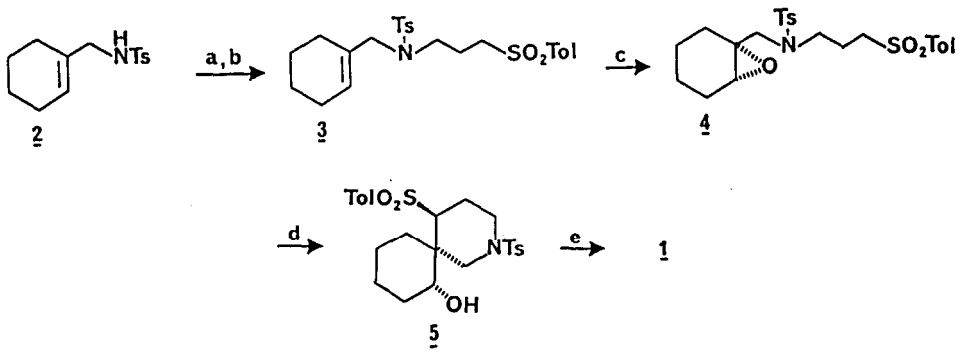
In view of our own interest in the histrionicotoxins[3] and since both Nitramine itself and analogous structures should be reasonable candidates for biological testing, we have developed a concise total synthesis of the title alkaloid. Our route, which is short (five operations) and completely stereocontrolled should also be applicable to enantioselective synthesis.[4] The synthesis of racemic Nitramine is shown in Scheme 1.



2 3 4 5

SCHEME 1. (a) BuLi,then excess $Br(CH_2)_3Br$,THF, 83% yield. (b) sodium p-toluenesulfinate,DMF, 80%. (c) mCPBA,CH_2Cl_2, 95%. (d) BuLi (2 eq.) THF/HMPA (9:1) -20°C to RT,then quench at -78°C, 73%. (e) Na(Hg),Na_2HPO_4,MeOH, 0°C to RT, 76%. For simplicity,only one enantiomer of 4 and 5 is shown.

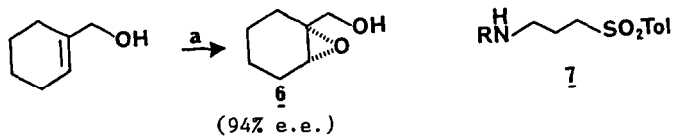
The N-tosyl derivative, 2, of the readily available[5] 1-cyclohexenylmethylamine was alkylated (BuLi, then excess 1,3-dibromopropane) and the relevant terminal bromide was then displaced by the para-toluenesulfinate ion. The resultant crystalline sulfone (3, m.p. 117-119°C) was then transformed (mCPBA) to 4 (m.p. 131-132°C) thus setting the stage for the crucial spirocyclisation step. Conversion of 4 to the spirocycle 5 obviously requires attack at a fully substituted oxirane carbon, and while this may be considered difficult it should be by no means impossible providing a suitably powerful nucleophile is available[6]. In the event, generation of the dianion of sulfone 4 at -20°C in a mixture of THF and HMPA followed by warming of the reaction mixture to ambient temperature led smoothly and consistently to the desired spirocycle 5 in 68-73% isolated yield. Use of the mono-anion of 4 led to poor and irreproducible results. Interestingly, if the cyclisation reaction was quenched at room temperature, 5 was obtained as an oily mixture of sulfone diastereomers which displayed a complex ^{1}H NMR spectrum, the tosyl methyls of the sulfone and sulfonamide moieties appearing as four well separated singlets; a low-temperature quench (-78°C) delivered a single, nicely crystalline, product (m.p. 93°C, dec.) having a clean and easily interpretable spectrum. From inspection of molecular models and careful analysis of coupling constants and the COSY spectrum of the cyclisation product, we assign the stereochemistry shown for 5 with the (equatorial) sulfone moiety in the β relative configuration. Our assignment is based on the observation of a long-range coupling between the (axial) proton adjacent to the hydroxyl and the axial component of the diastereotopic methylene group situated between the nitrogen and the spiro carbon. The observed coupling is no doubt a consequence of the perfect "W" arrangement of the relevant four bonds[7]. Such long-range "W" coupling would not be expected for the only reasonable alternative structure having the (equatorial) sulfone in the α relative configuration and the ring-flipped conformer of the piperidine ring. Although the observed diastereoselectivity is of no consequence for the overall result of the present synthesis, it is nevertheless of interest in its own right. Indeed, while our studies were nearing completion Trost and Merlic[8] published an intriguing paper describing high diastereoselectivity due to the selective protonation of sulfone-stabilised anions.

With the spirocycle 5 in hand, we sought to remove both sulfone and sulfonamide groups in one step. The use of conventional methods gave disappointing results, but success was achieved (76% isolated yield of Nitramine) by using the Trost sodium amalgam procedure[9]. As pointed out recently by Holmes[10] (apparently the first to use this technique for sulfonamide cleavage) the use of freshly prepared reagent was imperative. The overall yield for the synthesis was thus 35% for five simple operations from the readily available 2, and the spectral and physical data of our product were in excellent accord with those reported[4].

Using chromatographically purified material and rigorously dried deuteriochloroform for high-field (300 MHz) ^{1}H NMR studies, we have observed a hitherto unreported

long-range (0.9 Hz) coupling constant corresponding exactly to that found for 5, which can be attributed to a similar four-bond "W" array in a favourable conformation characterised by an intramolecular O-H---N hydrogen bond (a situation reminiscent of that found in the histrionicotoxin series[2,3]).

In conclusion, we note that the ready availability[11,12] of the chiral epoxide 6 of high enantiomeric purity and the requisite side-chain 7 (Scheme 2) should allow adaptation of the present methodology to a short and more convergent synthesis of the natural enantiomer of Nitramine. Results will be reported separately.



SCHEME 2. (a) Sharpless asymmetric epoxidation, 83% yield.

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