Tetrahedron Letters,Vol.29,No.27,pp 3311-3314,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ASYMMETRIC SYNTHESIS XV[1] : ENANTIOSPECIFIC SYNTHESIS OF (+) and (-) ISONITRAMINES FROM A COMMON CHIRAL INTERMEDIATE[2,3].

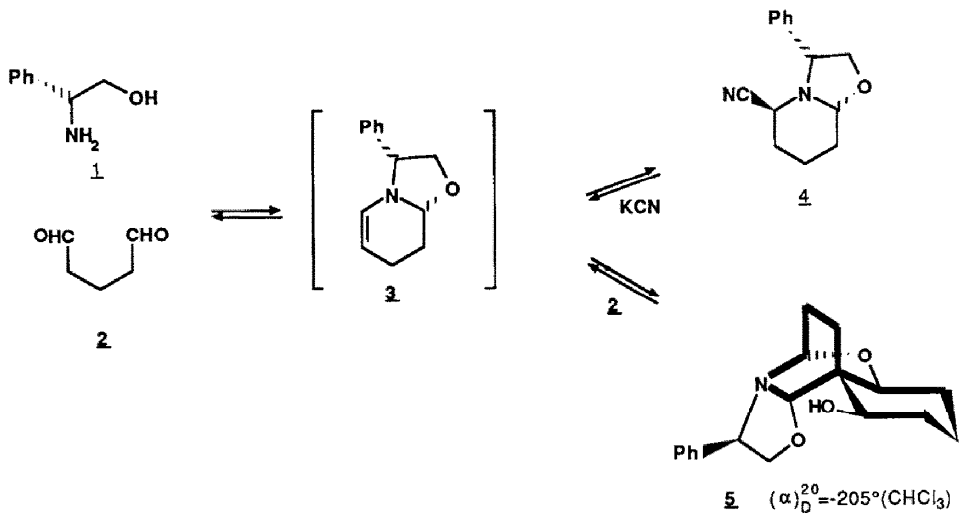
Jean-Charles Quirion, David S. Grierson, Jacques Royer and Henri-Philippe Husson*

Institut de Chimie des Substances Naturelles du CNRS, 91198 Gif s/Yvette Cédex, France

Abstract

The enantiospecific synthesis of (+) and (-) isonitramines 7 has been achieved from a common chiral intermediate 5 ; this key compound was formed by condensation of two molar equivalents of glutaraldehyde with one mole of (-) phenylglycinol.

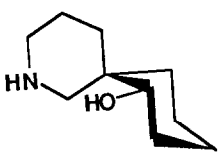
We have undertaken the development of a new and potentially general approach to the asymmetric synthesis of complex piperidine alkaloids involving the use of the chiral 1,4-dihydropyridine equivalent 4 (Scheme 1), prepared by condensation of glutaraldehyde 2 with (-)-phenylglycinol 1 in the presence of KCN[4]. In a continuation of our studies of



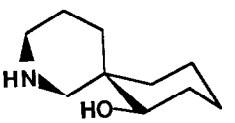
SCHEME 1

this reaction, it was found that on condensation of glutaraldehyde with 1 in the absence of KCN the initially formed Δ^2 piperideine intermediate 3 reacts with a second molecule of the dialdehyde to give the tetracyclic chiral compound 5, isolated in crystalline form[5]

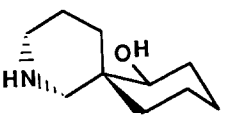
(45%, mp 136°C, ether/hexane) after column chromatography (silica, CH_2Cl_2-MeOH ; 98-2). As indicated in bold detail, this novel product contains within its structure a hydroxy substituted cyclohexane ring which is spirofused to the C-3 position of a piperidine ring, ie the same components that make up the structure of the piperidine alkaloids nitramine 6 and isonitramine 7[6] (Scheme 2). Although the structure and relative stereochemistry of 6 and 7 have been determined by X-ray diffraction and by synthesis of the racemic forms[8], the necessity to confirm the absolute configuration at C-7 was underlined[3].



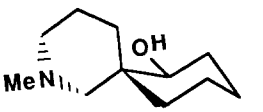
6



(+) 7



(-) 7

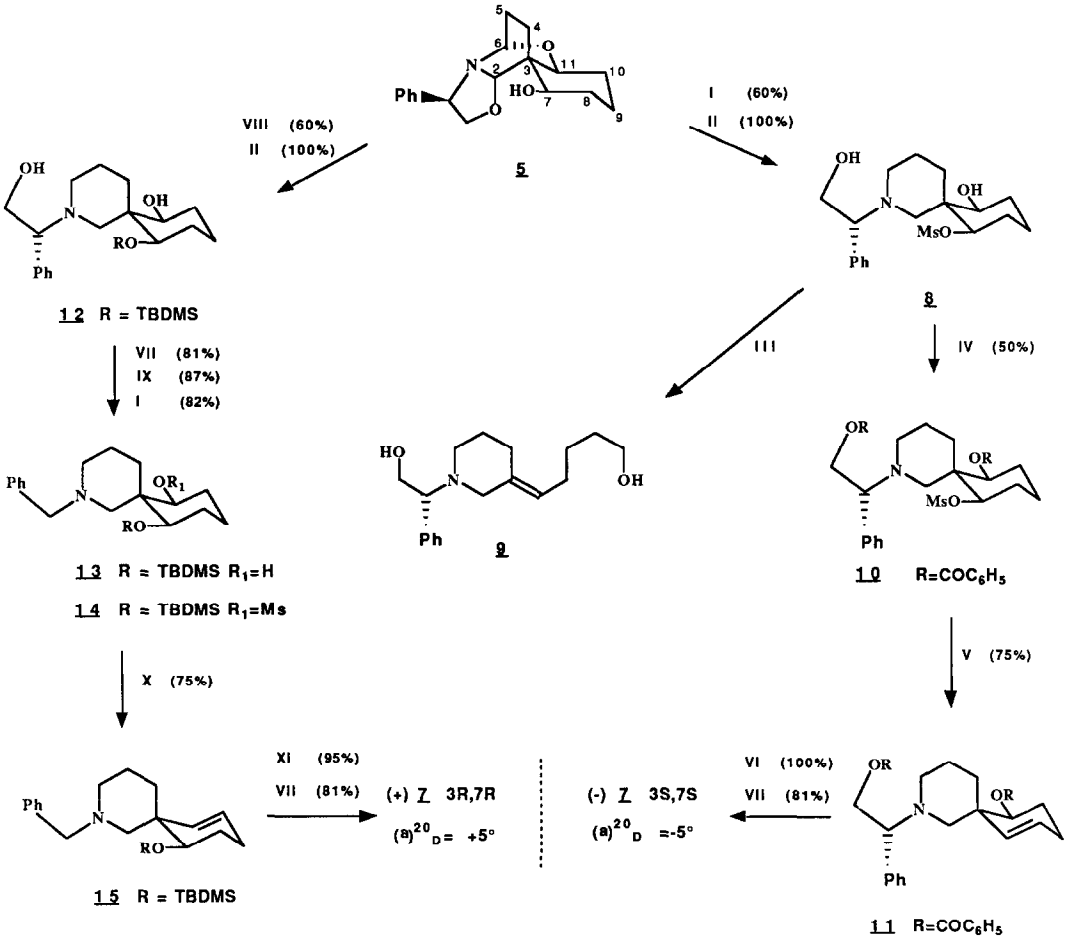


8

SCHEME 2

In this paper we describe the enantiospecific synthesis of both (+) and (-)-isonitramine 7 from 5 as a common starting synthon. Our strategy involves elimination of one or other of the oxygen functions from the cyclohexane ring of 5 and permits an unequivocal assignment of the 3R,7R absolute configuration to the natural (+)-enantiomer of this alkaloid.

Our initial plan was to deoxygenate synthon 5 directly through reaction of its C-7 O-mesylate derivative with either a hydride reducing agent or an appropriate base. Unfortunately in all cases starting material and/or polar degradation products were obtained. However, under carefully controlled conditions ($LiAlH_4$, ether, 0°C, 20 min) selective cleavage of the C-2 and C-6 aminoether bonds of this derivative was achieved producing the spiropiperidine 8 in essentially quantitative yield. Subsequent attempts to eliminate the mesylate function of 8 (Scheme 3) by reaction with $LiBEt_3H$ were also problematic as a competing Grob fragmentation was observed giving 9 as the principal product. Intermediate 8 was therefore converted into its bis-benzoate derivative 10 in order to avoid this problem. Reaction of this intermediate with DBU in DMSO (80°C, 96 h) was uneventful, leading to formation of the desired olefin 11, isolated as a colorless oil in 75% yield after flash chromatography on silica gel (CH_2Cl_2). Deprotection of the C-11 alcohol function of 11 was achieved using $LiAlH_4$. Final reduction of the olefin double bond and cleavage of the chiral appendage on nitrogen was accomplished under hydrogenation conditions (H_2, $Pd(OH)_2$-C, MeOH ; Y=81%). In this way isonitramine 7 was obtained as a colorless crystalline solid $[\alpha]_D^{20}$=-5° (c=2.1, $CHCl_3$), mp 100-101°C (sublim).



SCHEME 3

Reagents : I) MsCl, DMAP, CH_2Cl_2 ; II) $LiAlH_4$, Et_2O, 0°C, 20 min ; III) $LiBEt_3H$, toluene, reflux ; IV) C_6H_5COCl, DMAP, CH_2Cl_2 ; V) DBU, DMSO, 80°, 96h ; VI) $LiAlH_4$, THF, 20°C, 15min ; VII) H_2, $Pd(OH)_2/C$, MeOH, 18h ; VIII) $tBuMe_2SiCl$, imidazole, DMF ; IX) $C_6H_5CH_2Br$, $NaHCO_3$, DMF, 60°C ; X) DBU, C_6H_6, reflux, 96h ; XI) HF, H_2O-CH_3CN.

For the synthesis of (+)-isonitramine the C-7 hydroxyl group of 5 was protected as its t-butyl dimethylsilyl ether (Y=60%) before ring opening to 12 with $LiAlH_4$. On treatment of 12 with MsCl a mixture of polar products was obtained indicating that the bis mesylate derivative of this molecule is unstable. An exchange of substituents on nitrogen was thus made involving reaction of 12 under hydrogenolysis conditions (H_2, $Pd(OH)_2$-C, MeOH, Y=87%) followed by reaction of the resulting secondary amine with benzyl bromide. A clean reaction was observed on subsequent reaction of compound 13 with MsCl giving 14 in 82% yield. Reaction of this intermediate with DBU in refluxing benzene (96h) was also clean, producing olefin 15 in 75% isolated yield. Deprotection of the hydroxyl group of 15 (HF, CH_3CN-H_2O, Y=95%) followed by reaction under hydrogenolysis conditions gave (+)-isonitramine 7 (75% yield for the two steps) as a colorless crystalline solid $[\alpha]_D^{20}$ =+5° (c=1.2 ; $CHCl_3$), mp=100-101°C.

Our synthetic (-)-isonitramine was reacted with methyl iodide at reflux in ethanol giving (-) sibirine $[\alpha]_D^{20}$ =-22.5° (c=0.8 ; $CHCl_3$) and not (+)-sibirine as reported in the literature[6]. As the (+) enantiomer of sibirine corresponds to the natural product it follows that natural isonitramine is dextrorotatory. Furthermore as the absolute value for the rotation of our (+) and (-) isonitramine is the same, the literature values[6] should be regarded as being incorrect.

References and notes

1 For Part XIV see S. Arseniyadis, P.Q. Huang and H.-P. Husson, Tetrahedron Lett., 1988, 29, 1391.

2 First disclosure presented by H.-P. Husson in a plenary lecture at the Biologically Active Nitrogen-Containing Natural Products : Structure, Biosynthesis and Synthesis Symposium, Chapel Hill, North Carolina, USA, July 1985. It should be noted however, that the structure initially reported for synthon 5 is isomeric with the structure determined later by X-ray diffraction[5].

3 A second enantioselective synthesis of the nitramine alkaloids has recently appeared : P.J. Mc Closkey and A. Schultz, Heterocycles, 1987, 25, 437, in which the problem concerning the $[\alpha]_D$ values for the natural compounds is brought to light (in agreement with our concluding remarks).

4 L. Guerrier, J. Royer, D.S. Grierson and H.-P. Husson, J. Am. Chem. Soc., 1983, 105, 7754.

5 The absolute configuration of 5 has been determined by X-ray analysis of its p-bromobenzoate ester. Discussion on the formation of 5 based upon molecular mechanic calculations will be reported at a later date.

6 Nitramine, isonitramine and sibirine (N-CH_3 isonitramine) have been isolated from the plants of the genus Nitraria (Zygophyllaceae) by russian chemists : Z. Osmanov, A.A. Ibragimov and S. Yu Yunusov, Chem. Nat. Prod., 1977, 607.

7 A.A. Ibragimov, Z. Osmanov, B. Tashkodzhaev, N.D. Abdullaev, M.R. Yagudaev and S. Yu Yunusov, Chem. Nat. Prod., 1982, 458.

8 a) B.B. Snider and C.P. Cartaya-Marin, J. Org. Chem., 1984, 49, 1688 ; b) J.B. Mieczkowski, Bull. Polish Acad. Sc. Chem., 1985, 33, 13 ; c) A.P. Kozikowski and P.W. Yuen, J. Chem. Soc. Chem. Commun., 1985, 847 ; d) L.H. Hellberg, C. Beeson and R. Somanathan, Tetrahedron Lett., 1986, 27, 3955 ; e) W. Carruthers and R.C. Moses, J. Chem. Soc. Chem. Commun., 1987, 509.

9 The spectral data for all compounds were in accord with their proposed structures. Satisfactory microanalyses and/or high-resolution mass spectra were obtained for these products.

(Received in France 16 April 1988)