Synthesis of (±)-pseudoheliotridane by allylboration of 1-pyrroline

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Reaction of tricrotylborane with 1-pyrroline proceeds stereoselectively to give (*1R*,1'S**)-2-(1-methylallyl)pyrrolidine. The latter was converted to the pyrrolizidine alkaloid (±)-pseudoheliotridane through hydroboration—oxidation—intramolecular cyclization.

Key words: pyrrolizidine alkaloids, (±)-pseudoheliotridane; allylboration, stereochemistry, tricrotylborane; 1-pyrroline.

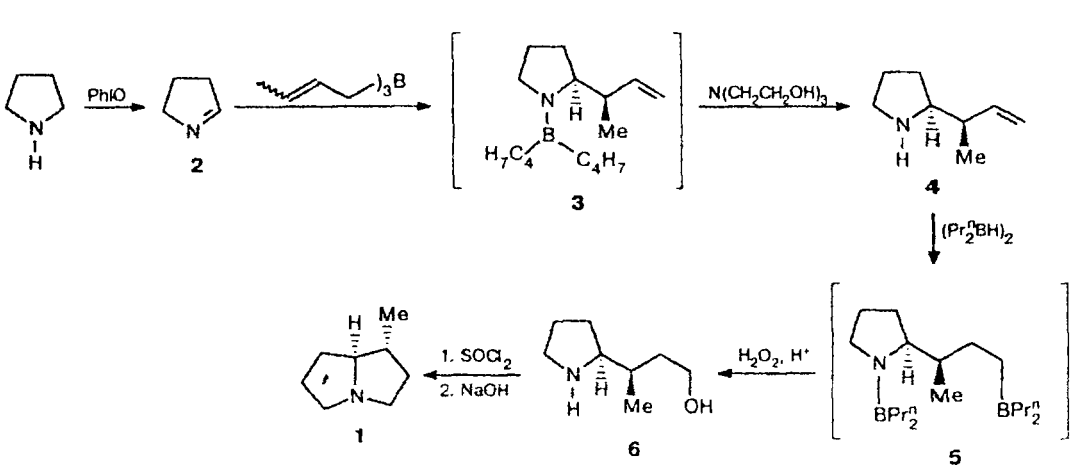
Pyrrolizidine alkaloids have attracted the attention of scientists for more than fifty years due to the broad spectrum of their biological activities,[1,2] fairly simple structures, and a number of stereochemical problems arising in their syntheses.[3,4] Alkaloids of this group are consistuents of a great number of plant sources all over the world; plants of *Borraginaceae*, *Compositae*, and *Leguminosae* families are especially rich in them. The alkaloids consist of two subunits, *viz.*, necine base and necic acid. 4-Azabicyclo[3.3.0]octane system is a general structural moiety of the necine base.

Recently, we discovered a number of new reactions of allylboranes with aromatic nitrogen-containing heterocyclic compounds.[5] α-Allylated heterocycles obtained by these reactions were used as the initial materials for the synthesis of nitrogen-containing bi- and tricyclic compounds,[6,7] including benzopyrrolizidine.

In the present paper, we report on the application of this approach to the synthesis of (±)-pseudoheliotridane (**1**), the parent compound of the alkaloid trachelanthamidine isolated from *Trachelanthus Korolkovi*.[8]

The key step of the synthesis consists in the reaction of the imine precursor, 1-pyrroline (**2**), with tricrotylborane. The addition of the crotyl moiety to the N=C bond occurs with rearrangement to give aminoborane (**3**) in which the B—N bond can be easily cleaved under the action of triethanolamine. As a result, virtually only one diastereoisomeric product (**4**) was obtained (Scheme 1),

Scheme 1



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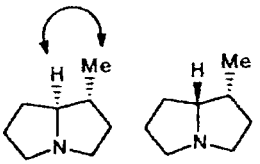
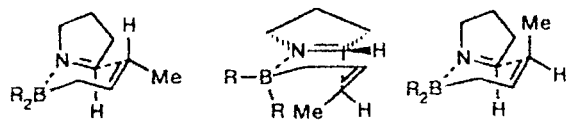
whose purity is higher than 93% (according to the NMR data). Such high diastereoselectivity is very surprising, because it is well known that the total ratio of *Z,E*-isomers of unsaturated groups in tricrotylborane is 3 : 7.[9]

The relative configuration of the pyrrolidine compound **4** was confirmed by its cyclization into (±)-pseudoheliotridane **1** (1-methylpyrrolizidine). Reaction of 2-(1-methylallyl)pyrrolidine **4** with an equimolar amount of tetrapropyldiborane gave *C,N*-bis-dipropylboryl compound (**5**). The standard treatment of **5** with alkaline hydrogen peroxide did not lead to complete deboronation of this product even upon prolonged refluxing. The target aminoalcohol (**6**) was obtained by a procedure of oxidation of organoboranes in an acid medium.[10] Subsequent direct cyclization of 2-(3-hydroxy-1-methylpropyl)pyrrolidine **6** under the action of thionyl chloride gave 1-methylpyrrolizidine **1** in 60% yield. To choose between the two possible diastereoisomers of 1-methylpyrrolizidine, *viz.*, pseudoheliotridane **1** and heliotridane **1a**,[8] we have carried out NOESY experiments. The NOE observed between H(8) and the methyl group unambiguously confirms structure **1**. In addition, the synthesized product **1** was identified by its conversion into a known picrate.[8,11,12]



1 **1a**

Therefore, pyrrolidine **4** has the structure of the *anti*-isomer, and its almost exclusive formation is caused by the stereospecificity of crotylboration of pyrroline **2** having *syn*-configuration of the C=N bond. The diastereoselectivity of addition of crotylborane to acyclic imines is very sensitive to steric interactions.[13] The predominance of *anti*-stereoselectivity observed in our case is probably associated with the formation of a transition state of the type C(*Z,E*), which is free from strong nonbonded interactions, whereas in alternative transition states, for example, B(*Z,Z*) and C(*Z,Z*), such interactions are possible.



C(*Z,E*) **B(*Z,Z*)** **C(*Z,Z*)**

The known syntheses of pseudoheliotridane **1** include cyclization of the corresponding precursors followed by separation of the diastereoisomers.[11,12] The method we propose is a new approach to the stereoselective design of this compound.

Experimental

All experiments with organoboron compounds were carried out under dry argon. The NMR spectra were recorded on Bruker AC-200P and Bruker AMX-400 NMR spectrometers. Assignments in the ^1H and ^{13}C NMR spectra were made using $^1H - ^1H$ COSY and $^1H - ^{13}C$ XHCORR procedures.

(2*S,2'*R**)-2-(1-Methylallyl)pyrrolidine (4).** Tricrotylborane (3.78 g, 21 mmol) was added dropwise to a solution of 1-pyrroline **2** (obtained from pyrrolidine (1.53 g, 21.5 mmol) and iodosobenzene (1.53 g, 21.5 mmol) by a known procedure[14]) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was stirred for 30 min at 20 °C and then refluxed for 30 min. The solvent was removed *in vacuo* and triethanolamine (5 g) was added to the residue. Distillation *in vacuo* gave pyrrolidine **4** (1.51 g, 56.5%), b.p. 76—77 °C. Found (%): C, 76.31; H, 11.97. $C_8H_{15}N$. Calculated (%): C, 76.74; H, 12.07. ^1H NMR ($CDCl_3$), δ: 0.98 (d, 3 H, CH_3, J = 6.7 Hz); 1.31 (m, 1 H, $H_AC(3)$); 1.70 (m, 2 H, $H_2C(4)$); 1.82 (m, 1 H, $H_A(3)$); 2.2 (m, 1 H, HC(2')); 2.15 (br.s, 1 H, NH); 2.7 (m, 1 H, HC(2)); 2.8 (m, 1H, $H_AC(5)$); 2.9 (m, 1 H, $H_BC(5)$); 5.00 (AB part of an ABX spectrum, 2 H, CH_2=C, δ_A = 4.95, δ_B = 5.05, J_{AX}= 10.3 Hz, J_{BX} = 17.2 Hz); 5.7 (ddd, 1 H, $H_XC(2')$, J_{XA} = 10.3 Hz, J_{XB} = 17.2 Hz, J = 8.3 Hz). ^{13}C ($CDCl_3$), δ: 17.6 (CH_3), 24.9 (C(4)); 29.4 (C(3)); 44.0 (C(2')); 46.2 (C(5)); 63.5 (C(2)); 114.0 ($\underline{C}H_2$=CH); 142.4 (CH_2=$\underline{C}$H).

(1*S,2'*R**)-2-(3-Hydroxy-1-methylpropyl)pyrrolidine (6).** A 1.96 *M* THF solution of $(Pr_2BH)_2$ (5.8 mL, 11.35 mmol) was added dropwise to a solution of pyrrolidine **4** in THF (15 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then warmed to 20 °C. The excess of hydride was decomposed by addition of MeOH (several drops). The solvent was removed *in vacuo*, and the residue was dissolved in EtOH (10 mL). A solution of H_2SO_4 (1.5 mL) in water (10 mL) and a 30% solution of H_2O_2 (6 mL) were added to the resulting ethanol solution. The mixture was stirred for 5 days at 50 °C and concentrated *in vacuo* to dryness. The residue was treated with the minimum amount of 20% NaOH solution to make it basic, and the solution was concentrated to dryness. The product was extracted from the dry residue with hot THF (3 × 10 mL). After removal of the THF, the residue was distilled to give aminoalcohol **6** (0.67 g, 41.3%), b.p. 91—94 °C (1 Torr), n_D^{20} 1.4847. Found (%): C, 67.00; H, 12.03; N, 9.80. $C_8H_{17}NO$. Calculated (%): C, 67.09; H, 11.96; N, 9.78. ^1H NMR ($CDCl_3$) δ: 0.78 (d, 3 H, CH_3, J = 6.9 Hz); 1.17 (m, 1 H, H=$H_AC(3)$); 1.39 (m, 1 H, HC(2')); 1.43 (m, 2 H, $H_2C(2'')$); 1.53 (m, 1 H, $H_AC(4)$); 1.61 (m, 1 H, $H_BC(4)$); 1.73 (m, 1 H, $H_BC(3)$); 2.54 (m, 1 H, HC(2)); 2.68 (m, 1 H, $H_AC(5)$); 2.75 (m, 1 H, $H_BC(5)$); 3.36 (m, 1 H, $H_AC(2''')$); 3.49 (m, 1 H, $H_BC(2''')$). ^{13}C NMR ($CDCl_3$), δ: 18.65 (CH_3); 25.3 (C(4)); 30.25 (C(3)); 37.6 (C(1')); 38.2 (C(2')); 45.9 (C(5)); 59.9(CH_2O); 64.2 (C(2)).

(±)-Pseudoheliotridane (1). A solution of aminoalcohol **6** (0.6 g, 4.2 mmol) and $SOCl_2$ (0.5 g) in benzene (15 mL) was refluxed for 1 h. The precipitate that formed was filtered off and treated with the minimum amount of a 20% NaOH solution. The resulting free base was extracted with ether (3×10 mL), dried, and, after removal of the sovent *in vacuo*, yielded compound **1** (0.36 g, 70%), b.p. 62—63 °C (20 Torr), n_D^{20} 1.4612 (*cf.* Ref. 11) Found (%): C, 76.60; H, 11.92. $C_8H_{15}N$. Calculated (%): C, 76.74; H, 12.07. ^1H ($CDCl_3$), δ: 0.82 (d, 3 H, CH_3, J = 6.5 Hz); 1.25 (m, 2 H, $H_AC(7)$); 1.31 (m, 1 H, $H_AC(2)$); 1.41 (m, 1 H, HC(1)); 1.56 (m, 2 H, $H_2C(6)$); 1.67 (m, 1 H, $H_BC(7)$); 1.76 (m, 1 H, $H_BC(2)$); 2.27 (m, 1 H, $H_AC(3)$); 2.34 (m, 1 H, $H_AC(5)$); 2.73 (m, 1 H, $H_BC(5)$); 2.80 (m, 1 H, HC(8)); 2.95 (m, 1 H, $H_BC(3)$). ^{13}C NMR ($CDCl_3$) δ: 17.6 (CH_3); 25.45 (C(6)); 30.65 (C(7)); 35.55 (C(2)); 40.3 (C(1)); 54.8 (C(5)); 55.0 (C(3)); 71.5 (C(8)).

(±)-Pseudoheliotridane picrate. A saturated solution of picric acid in ethanol was added to an ethanolic solution of base **1** (0.2 g). The yellow precipitate that formed was filtered off to give the picrate (0.48 g, 85%), m.p. 233—235 °C (from ethanol) (*cf.* Refs. 11 and 12).

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