Enantioselective Syntheses of (−)-Hastanecine and its Enantiomer using Malic Acid as a Chiral Educt

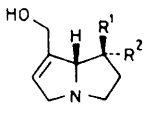
David J. Hart* and Teng-Kuei Yang

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210, U.S.A.

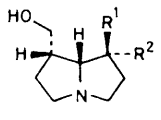
The pyrrolizidine base (−)-hastanecine (**5**) and its enantiomer (**19**) were prepared from *R*-(+) and *S*-(−)-malic acids, respectively.

The dihydroxypyrrolizidine bases (**1**)—(**6**) are incorporated into a large number of alkaloids[1] and total syntheses of racemic (**1**)—(**5**) have been recorded.[2] We report here the first enantioselective approach to these dihydroxypyrrolizidine bases within the context of syntheses of (−)-hastanecine (**5**) and its enantiomer (**19**).[3]

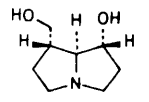
Our approach to (**5**) was patterned by our previously reported synthesis of (±)-trachelanthamidine (**7**).[4] The acid chloride (**8**)[4] was converted into the amine (**9**) *via* a straightforward reaction sequence [(i) NaN_3, acetone; (ii) PhH, reflux, 2 h; (iii) $KOBu^t$, Bu^tOH; (iv) CF_3CO_2H; 75% overall]. Treatment of (**9**) with (*R*)-acetoxysuccinic anhydride[5] (CH_2Cl_2, reflux) followed by cyclization of the resulting mixture of amido-acids (AcCl, CH_2Cl_2, 40 °C) gave the imide (**10**) {81%, $[\alpha]_D^{20}$ + 15.27° ($CHCl_3$)}. Sodium borohydride reduction of (**10**) in either ethanol or methanol proceeded regioselectively to give a mixture of diastereoisomeric hydroxy-amides (**11**) (83%). Rearrangement–cyclization[4] of (**11**) (HCO_2H, 24 h, 25 °C) gave a mixture of the formate (**12**) (60%) and the alcohol (**13**) (17%) which both afforded the diol (**14**) {95%, $[\alpha]_D$ + 6.8° (EtOH)} upon hydrolysis (NaOH, aqueous MeOH). The stereochemical assignment at C-2 of (**14**) is only tentative.[6] Proof of the stereochemistry at the three remaining asymmetric centres of (**14**) was obtained by completion of the synthesis of (−)-hastanecine (**5**) as follows. The benyzl-group was removed by hydrogenolysis (H_2, Pd/C, EtOH, 96%) and the resulting triol (**15**) was converted into the diacetate (**16**) (Ac_2O, pyridine, 94%). Treatment of (**16**) with mercury(II) oxide and iodine in carbon tetrachloride gave a mixture of iodides (**17**) (89%). Tri-n-butyltin hydride reduction of (**17**) gave the pyrrolizidinone (**18**) (91%) which was converted into (−)-hastanecine (**5**) upon treatment with lithium aluminium hydride {89%; m.p. 112.5—113.5 °C; lit.[7] 113—114 °C; $[\alpha]_D^{25}$ −10.0° (EtOH) as in ref. 7}. Synthetic (**5**) was identical (^{1}H n.m.r., i.r.) to a sample of (+)-hastanecine kindly supplied by Professor Culvenor. Substitution of (*S*)- for (*R*)-acetoxysuccinic anhydride in the above reaction sequence gave (+)-hastanecine (**19**), which was identical to (**5**) except for the direction of specific rotation.



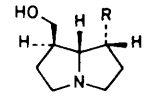
(**1**) Retronecine (R^1 = H, R^2 = OH)
(**2**) Heliotridine (R^1 = OH, R^2 = H)



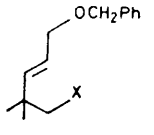
(**3**) Platynecine (R^1 = H, R^2 = OH)
(**4**) Dihydroxyheliotridane (R^1 = OH, R^2 = H)



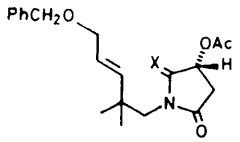
(**5**) Hastanecine



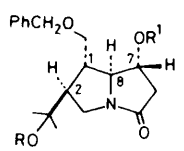
(**6**) Turneforcidine (R = OH)
(**7**) Trachelanthamidine (R = H)



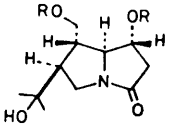
(**8**) X = COCl
(**9**) $X = NH_2$



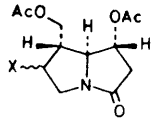
(**10**) X = O
(**11**) X = H, OH



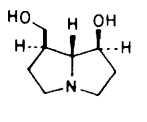
(**12**) R = CHO, R^1 = Ac
(**13**) R = H, R^1 = Ac
(**14**) R = R^1 = H



(**15**) R = H
(**16**) R = Ac



(**17**) X = I
(**18**) X = H



(**19**)

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3 Enantioselective syntheses of related monohydroxypyrrolizidine bases have been reported: D. J. Robins and S. Sakdarat, *J. Chem. Soc., Chem. Commun.*, 1979, 1181. See also H. Rueger and M. Benn, *Heterocycles*, 1982, **19**, 23.

4 D. J. Hart and T.-K. Yang, *Tetrahedron Lett.*, 1982, 2761.

5 Prepared from *R*-(+)-malic acid: B. Jones, *J. Chem. Soc.*, 1933, 788.

6 The C-2–C-8 relationship shown for (**14**) has been proven for structure (**2**) in ref. 4 by *X*-ray crystallography.

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