Tetrahedron: Asymmetry Vol. 2, No. 10, pp. 945-948, 1991
Printed in Great Britain

0957-4166/91 $3.00+.00
Pergamon Press plc

Synthesis of Unnatural 2R,5S-5-Hydroxypipecolic Acid Via Homochiral Acyliminium Ion - Pipecolic Acids- Part III.

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(*Received* 15 *July* 1991)

Abstract: Stereoselective functionalization of S-5-hydroxy-2-piperidone **1** via acyliminium ion was demonstrated to maintain the unnatural enantiomer of trans-5-hydroxypipecolic acid **6**.

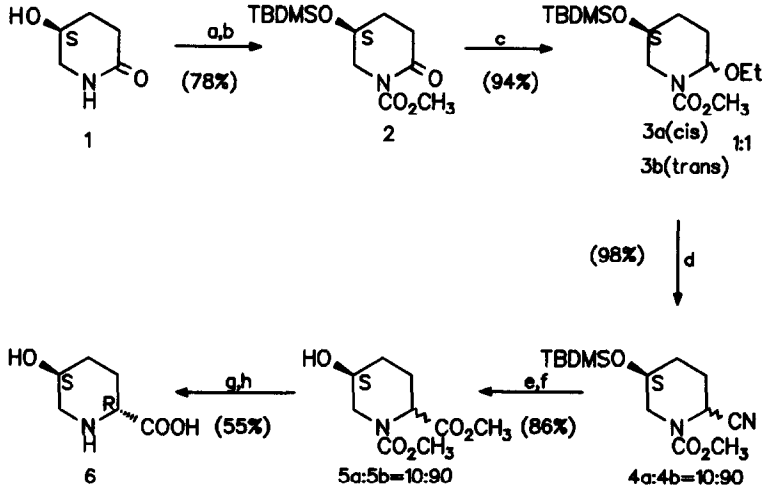
Substituted pipecolic acids are the subject of much current investigations[2]. As an extension of our study of the structure-activity relationship of DAVA (δ-amino valeric acid) derivatives as $GABA_B$-receptor ligands[3] we, became interested in the pharmacological activity of substituted pipecolic acids, especially because it is known that pipecolic acid inhibits the cellular uptake of ^{3}H-GABA and enhances the GABA response in single neurons of rat brains[4].

As part of our synthetic program on DAVA derivatives from homochiral 5-hydroxy-2-piperidones[5], we postulated that **1** and derivatives thereof, easily accesssible from S-glutamic acid, might be stereoselectively transformed into 5-hydroxypipecolic acid via an acyliminium ion[6].

Having readily introduced TBDMS as the OH-protecting group into **1** by standard methods, we found that introduction of the methoxycarbonyl group was best accomplished by Manders reagent[7] ($NCCO_2CH_3$,BuLi,THF,-78°C). Other alkoxycarbonyl groups like Boc and Cbz proved less suitable in the next reaction step, because considerable amounts of the corresponding enamines and dimers could be detected as side products[8]. In the case of N-tosyl protection, sodium borohydride reduction furnished only ring opened S-5-tosylamino-4-tert-butyldimethylsiloxy-1-pentanol.

Quantitative reduction of the cyclic imide **2** with sodium borohydride in ethanol/HCl (0°C) proceeded via an α-hydroxycarbamate as an intermediate to **3** and could be monitored by TLC. To prevent formation of ring opened product by ethanolysis of lactam (observed at high pH), carefully controlled reaction conditions were necessary. By addition of ethanolic hydrogen chloride solution, the reaction solution pH was maintained

initially at 8-9, then gradually lowered to 3-4. This procedure was controlled by a glass electrode. By this manner **3a/b** could be isolated by extractive workup as a 1:1 diastereomeric mixture. This 1:1 mixture of cyclic α-alkoxycarbamate compounds was transformed via the homochiral acyliminium ion by treatment with anhydrous $ZnCl_2$/trimethylsilylcyanide[8] to **4a/b** in a cis/trans ratio of 10:90, determined by ^{1}H-NMR spectroscopy[9] of the crude reaction product. Other Lewis acids like $TiCl_4$ or $Zn(CN)_2$ gave poorer yields of **4a/b**. Pinner reaction[10] of **4a/b** furnished **5a/b** which was hydrolysed to the amino acid hydrochloride **6·HCL**. This in turn crystallized as pure trans diastereomer from the reaction mixture. Ion exchange with Serdolit AWM provided 2R,5S-5-hydroxypipecolic acid **6**.[11] **Ent-6** can be prepared from **R-1** following the same procedure, and has been isolated e.g. from dates[12] and morus alba.[13]



a: TBDMSCl,imidazole,DMF; b: BuLi,THF,-78°C,$NCCO_2CH_3$; c: $NaBH_4$,EtOH,0°C,EtOH/HCl to pH 3-4; d: Me_3SiCN,$ZnCl_2$,CH_2Cl_2,-78°C --> r.t.; e: HCl/Et_2O,MeOH; f: H_2O,$NaHCO_3$; g: HCl/H_2O, ; h: Serdolit AWM,H_2O.

Experimental

Methyl 5-tert-Butyldimethylsiloxy-2-ethoxy-piperidine-1-carboxylate (3)

$NaBH_4$ (145 mg, 3.83 mmol) was added to an ice-cooled solution of **2**[14] (1.00g, 3.48 mmol) in EtOH (20 ml). This suspension was continously treated dropwise with 0.8 N-HCl/EtOH at 0°C and the reaction progress was monitored by glass electrode and TLC ($CHCl_3$/EtOAc 9+1). After reduction of 2 (R_F=0.37) to the α-hydroxycarbamate (R_F=0.17) at pH 8-9, the pH was

lowered, conversion of α-hydroxycarbamate to **3** (R_F=0.70) took place, and was completed at pH 3 (60min). The mixture was diluted with aq. $NaHCO_3$, extracted with CH_2Cl_2, dried, filtered, evaporated, and chromatographed on silicagel ($CHCl_3$/EtOAc 9+1) to give a 1:1 mixture of **3a** (2R,5S) and **3b** (2S,5S) as a colorless oil (1.04 g, 94%). Calcd.: C 56.75 H 9.84 N 4.41 found: C 57.08 H 10.01 N 4.43.

Methyl 5-tert-Butyldimethylsiloxy-2-cyan-piperidine-1-carboxylate (4)

A suspension of powdered $ZnCl_2$ (390 mg, 2.86 mmol) and CH_2Cl_2 (20 ml) was cooled to -78°C and **3a/b** (826 mg, 2.60 mmol) was added under N_2-atmosphere. This mixture was treated with trimethylsilylcyanide (515 mg, 5.20 mmol). After 2.5 hr. at -78°C, the mixture was allowed to warm to an ambient temperature and stirring was continued over night (14 hr.). The reaction mixture was quenched with dil. Na_2CO_3 solution, extracted with CH_2Cl_2, dried, filtered and evaporated to yield a 10:90 mixture[9] of **4a** (2S,5S) and **4b** (2R,5S) as a colorless oil. (763 mg, 98%). Calcd.: C 56.34 H 8.78 N 9.39 found: C 56.08 H 8.85 N 9.51. 50MHz-^{13}C-NMR($CDCl_3$): **4a**(cis): δ(ppm)= -4.9, 17.8,25.5(TBDMS), 27.1(C-3), 30.3(C-4), 43.2(C-2), 47.8(C-6), 53.3(OCH_3), 66.4(C-5), 116.8(CN), 155.0($\underline{C}O_2Me$) - **4b**(trans): δ(ppm)= -5.2,17.8,25.4 (TBDMS), 22.3(C-3), 27.7(C-4), 43.9(C-2), 47.3(C-6), 53.0(OCH_3), 63.4(C-5), 117.3(CN), 155.8($\underline{C}O_2Me$).

Dimethyl 5-Hydroxy-piperidine-1,2-dicarboxylate (5)

4a/b (660 mg, 2.08 mmol) was dissolved in Et_2O (30 ml) and MeOH (10 ml), cooled to 0°C and saturated with gaseous HCl. After storage (70 hr.) at 4°C, the volatiles were evaporated, the residue treated with dil. $NaHCO_3$ solution and MeOH (each 10 ml), and stirred at ambient temperature (3 hr.). Extraction with CH_2Cl_2, drying, filtration and evaporation yielded a 10:90 mixture of **5a** (2S,5S) and **5b** (2R,5S) as a colorless oil (390 mg, 86%).

2R,5S-5-Hydroxy-piperidine-2-carboxylic acid (6)

5a/b (217 mg, 1.00 mmol) was refluxed for 4 hr. in 6 N-HCl and then evaporated. The residue was treated with EtOH and acetone to induce crystallization. The colorless crystals were collected, washed with EtOH and acetone and identified (^{1}H-,^{13}C-NMR) as pure trans diastereomer: **6·HCl** (130 mg, 80% based on **5b**). **6·HCl** was transformed into free amino acid **6** by passing through an ion exchange column Serdolit AWM (elution with H_2O): colorless crystals, recovery 78%; m.p. 246-248°C (dec.); α_D= +22.8 (c=1, H_2O). Calcd.: C 49.65 H 7.64 N 9.65 found: C 49.44 H 7.76 N 9.56. - 200MHz-^{1}H-NMR(D_2O): δ(ppm)= 1.70(1H,m,H_a-4), 1.82(1H,m,H_a-3), 2.12(1H,m,H_e-4), 2.35 (1H,m,H_e-3), 2.88(1H,dd,J_{6a6e}=12.3Hz,J_{5a6a}=9.6Hz,H_a-6), 3.49(1H,ddd,J_{6a6e}=12.3 Hz,J_{5a6e}=4.1Hz,J_{4e6e}=1.6Hz,H_e-6), 3.65(1H,dd,J_{2a3a}=10.5Hz,J_{2a3e}=3.8Hz,H_a-2),4.00

(1H,tt,$J_{4a5a}\approx J_{5a6a}$=9.6Hz,$J_{4e5a}\approx J_{5a6e}$=4.1Hz,H_a-5). - 50MHz-^{13}C-NMR(D_2O): δ(ppm): 24.7(C-3), 30.8(C-4), 48.2(C-6), 59.0(C-2), 64.1(C-5), 174.3(CO_2H).

Acknowledgement: We thank the Fonds der Chemischen Industrie for financial support and Mrs. A. Betz for the preparation of starting material.

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14. **2** was obtained from S-5-Hydroxy-2-piperidone[5a] in 78% yield as colorless crystals: m.p. 68°C (ligroin), α_D=+10.9 (c=1,MeOH).