Pergamon

Tetrahedron Letters, Vol. 37, No. 12, pp. 2031-2034, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00191-8

Synthesis of Both Enantiomers of *trans* 3-Hydroxypipecolic Acid.

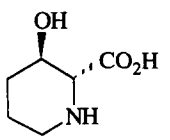
Christine Greck, Franck Ferreira and Jean Pierre Genêt

Laboratoire de Synthèse Organique, associé au CNRS ; Ecole Nationale Supérieure de Chimie de Paris
11, rue Pierre et Marie Curie ; 75231 Paris Cédex 05.

***Abstract** : The first syntheses of enantiomerically pure (2R, 3R) and (2S, 3S) 3-hydroxypipecolic acids* **1** *and* **2** *respectively, have been achieved from methyl 7-methyl-3-oxo-6-octenoate. Key steps involved asymmetric hydrogenation and electrophilic amination.*

The synthesis of optically active α-amino β-hydroxy acids has been of great interest owing to their use as chiral building blocks for organic synthesis[1] or as components of biologically active peptides.[2] Hydroxylated pyrrolidine, piperidine, pyrrolizidine and indolizidine alkaloids receive considerable attention due to their well established action as glycosidase inhibitors.[3] Syntheses of polyhydroxypipecolic acids as 3,4-dihydroxy and 3,4,5-trihydroxy have been previously reported and these compounds have been screened as potential inhibitors of HIV replication.[4] Surprisingly, the synthesis of 3-hydroxypipecolic acid was less documented. 3-Hydroxypipecolic acid is an α-amino β-hydroxy acid with a monohydroxylated piperidine ring. To our knowledge, only two enantioselective preparations of the *cis* stereomer have been proposed in the literature from L-serine[5a] or by baker's yeast reduction of the corresponding ketoester.[5b]

In this letter, we present a rapid stereocontrolled route to both enantiomers **1** and **2** of the *trans* stereomer. In connection to our previous work on the asymmetric synthesis of α-amino β-hydroxy acids, the syntheses of **1** and **2** were based on sequential catalytic hydrogenation and electrophilic amination.[6]



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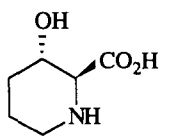

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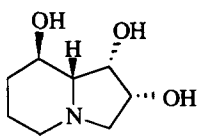
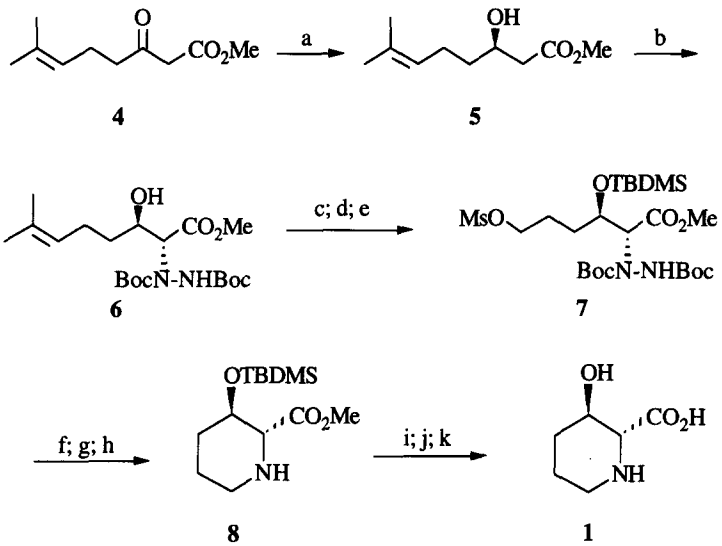


3

(2*R*, 3*R*)-3-Hydroxypipecolic acid **1** has the same configuration as the piperidine ring of (-)-swainsonine **3**. **3** and its epimers exhibit potent α-D-mannosidase activity.[7] **1** and **2** are potential chiral precursors for the synthesis of this class of compounds.

Using our methodology,[6] two stereogenic centers in *anti* relationship could be created on a flexible chain starting from the β-ketoester **4**. The β-hydroxyester function was generated by enantioselective hydrogenation of **4**, catalyzed by chiral ruthenium complexes. The nitrogen atom was introduced with the desired relative stereochemistry, by the diastereoselective electrophilic amination. The carbon-carbon unsaturation of **4** at C-6 could be then easily transformed to an alcohol which, after activation, allows the cyclization to the piperidine ring.

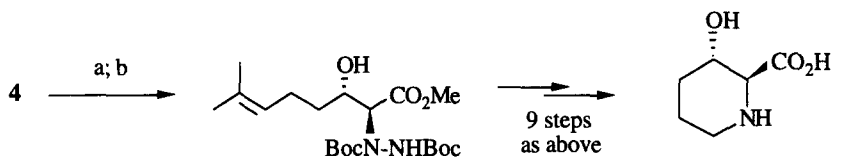


(a) - H_2, 1 atm.; $RuBr_2$[(*R*)-Binap], 2%; MeOH, 50°C. (98%; ee=97%). (b) - MeZnBr, 1 eq., 0°C; LDA, 2 eq., -78°C; DBAD, 2 eq., -78°C; NH_4Cl, H_2O. (55%; de>98%). (c) - TBDMSOTf, 2,6-lutidine, -78°C. (d) - O_3, CH_2Cl_2, -78°C; BH_3-Me_2S. (e) - MsCl, py, 0°C. (65% from **6**). (f) - TFA, CH_2Cl_2. (g) - H_2, Raney Ni,ultrasound (h) - Et_3N, CH_2Cl_2. (75% from **7**). (i) - HF, CH_3CN, 50°C. (j) - K_2CO_3, MeOH, H_2O. (k) - Amberlite CG 50. (80% from **8**).

The keto group of **4** was hydrogenated under mild conditions, in the presence of $RuBr_2$[(*R*)-Binap] catalyst generated *in situ* from Ru(Cod)(2-methylallyl)$_2$.[8] (*R*)-Methyl-3-hydroxy-7-methyl-6-octenoate **5** was obtained with a good yield (98%) and high enantioselectivity (97% ee). With $RuBr_2$[(*R*)-MeOBiphep] as catalyst the enantiomeric excess was 93%. This reaction at atmospheric pressure was completely chemoselective, the reduction of the carbonyl function was only observed : we did not notice any hydrogenation of the double bond.[9] The ester enolate of **5** was aminated with di*t*-butylazodicarboxylate (DBAD) in presence of methylzinc bromide at -78°C to produce the corresponding α-hydrazino β-hydroxyester **6** in 55% yield.[10] This amination was highly diastereoselective and the N,N-protected hydrazine group was introduced in *anti* relationship to the hydroxyl function of the β-hydroxyester **5**. After protection of the hydroxyl function with a *t*-butyldimethylsilyl group, the double bond was ozonolyzed and the ozonide was reduced with BH_3-Me_2S. The resulting primary alcohol was directly mesylated. **7** was obtained in 65% overall yield over 4 steps from **6**. At this stage, compound **7** presented all the functionalities

required for the obtention of (2*R*, 3*R*)-3-hydroxypipecolic acid **1**. To achieve the piperidine formation, *t*-butyloxycarbamates were cleaved with trifluoroacetic acid in dichloromethane and the hydrazine was hydrogenolyzed in presence of Raney Ni under ultrasound.[11] Under these conditions, some cyclized product was observed by TLC. Completion of the ring closure was performed under basic conditions with triethylamine and *O*-protected 3-hydroxypipecolic acid methyl ester **8** was isolated in 75% yield. By ^1H NMR, a coupling constant ^3J=8.6 Hz was observed for the proton at C(2). This value confirmed a *trans* relationship between the *t*-butyldimethylsilyl ether and the methyl ester groups of **8**. Deprotection of the alcohol under standard conditions with tetrabutylammonium fluoride gave degradation products. However, desilylation of **8** realized at 50°C with hydrogen fluoride in acetonitrile produced the alcohol quantitatively. After saponification of the ester and chromatography over an ion exchange resin, (2*R*, 3*R*)-3-hydroxypipecolic acid **1** was cleanly obtained in 90% yield.[12]

(2*S*, 3*S*)-3-Hydroxypipecolic acid **2** was synthetized in the same manner using RuBr2[(*S*)-Binap] catalyst for the hydrogenation of **4**. The synthesis was concluded in a similar manner as above. Spectral data of **2** were identical with those obtained for **1** and the specific rotation was opposite.[13]



9 **2**

(a) - H_2, 1 atm.; RuBr2[(*S*)-Binap], 2%; MeOH, 50°C. (98%; ee=97%). (b) - MeZnBr, 1 eq., 0°C; LDA, 2 eq., -78°C; DBAD, 2 eq., -78°C; NH_4Cl, H_2O. (55%; de>98%).

The hydroxypipecolic acid **2** could be an interesting chiral intermediate for the total synthesis of the enantiomer of (-)-swainsonine : the first stereoselective synthesis of (+)-swainsonine was recently reported from L-glutamic acid.[14]

This synthetic route provides an efficient and general method for obtaining both enantiomers of functionalized piperidines and could be a convenient approach of indolizidines using the six membered ring as starting chiral building block. This methodology can be used to synthesize a variety of *anti* α-amino β-hydroxyacids containing other functions as well. The synthesis of polyhydroxylated indolizidine alkaloids is currently under investigation.

Acknowledgement : We thank the Ministère de la Recherche et de l'Enseignement Supérieur for a grant to F.F. (1993 - 1996).

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9 - **4** was hydrogenated using [(*S*)-Binap Ru $Br_2]_2.Et_3N$ at 4 atm and 80°C : Taber, D.F.; Silverberg, L.J. *Tetrahedron Lett.* **1991**, *32*, 4227-4230.

10 - **6** : ^1H NMR (200 MHz, $CDCl_3$) δ(ppm) : 6.60 (broad s, 1H); 5.10 (t, J=6.5 Hz, 1H); 4.90 (broad m, 1H); 3.76 (s, 3H); 2.15 (m, 2H); 1.67 (s, 3H); 1.63 (m, 2H); 1.61 (s, 3H); 1.45 (s, 18H). $[\alpha]_D^{20}$ = +22 (c=1, EtOH).

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12 - **1** : ^1H NMR (200 MHz, D_2O) δ(ppm) : 3.97 (ddd, J=7.1, 3, 3 Hz, 1H); 3.47 (d, J=7.1 Hz, 1H); 3.16 (m, 1H); 2.93 (m, 1H); 1.79 (m, 2H); 1.53 (m, 2H). $[\alpha]_D^{20}$ = -14 (c=0.5, aq.HCl 10%).

13 - **2** : $[\alpha]_D^{20}$ = +13 (c=0.4, aq.HCl 10%).

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(*Received in France* 12 *December* 1995; *accepted* 29 *January* 1996)