Pergamon

Tetrahedron Letters, Vol. 38, No. 2, pp. 271-272, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02301-5

First Asymmetric Synthesis of (2R, 3R)-3-Amino-1-benzyl-2-methyl-pyrrolidine via A Highly Diastereoselective Reductive Alkylation

Pei Qiang HUANG*, Si Li WANG, Hong ZHENG and Xiang Su FEI

Department of Chemistry, Xiamen University, Xiamen, Fujian 361005, CHINA

Abstract: The first asymmetric synthesis of (2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine, the parent diamine of antipsychotic agent, emonapride, from (S)-malic acid was achieved via a highly diastereroselective reductive alkylation. Copyright © 1996 Elsevier Science Ltd

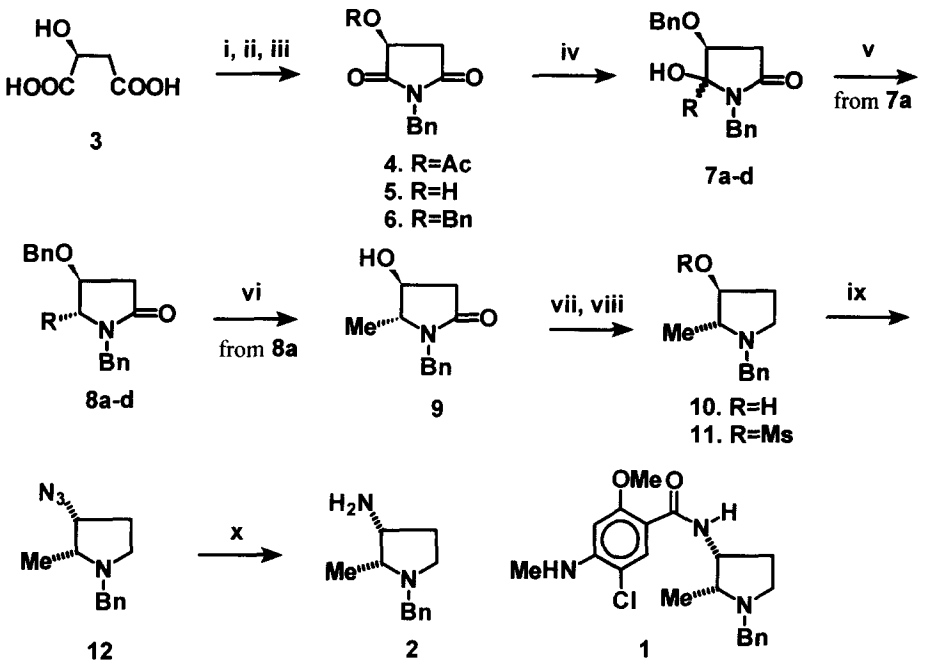
The 2-alkyl-3-aminopyrrolidines and 2-alkyl-3-hydroxypyrrolidines are key structural units present in many bioactive molecules such as anisomycin, preussin and emonapride **1**. The emonapride[1,2] **1** is a new promising antipsychotic drug with few side-effects[2], which currently attracts much pharmacological and clinical attention. However, only a few synthetic studies have been reported. The only reported synthesis[1,2] of racemic **1** relied on (±)-*cis*-3-amino-1-benzyl-2-methylpyrrolidine **2**. In this paper, we report a general asymmetric synthesis of the parent diamine (2R, 3R)-**2**, which is based on a highly diastereroselective reductive alkylation.

As shown in **Scheme 1**, acidic hydrolysis (EtOH, AcCl, 50°C) of **4** , prepared[3] from (S)-malic acid followed by *O*-benzylation led to a crystalline solid **6** [mp 76-77.5°C; $[\alpha]_D^{25}$ -34.7 (*c* 0.7 in $CHCl_3$)]. The key transformation, the conversion of **6** to **8a** was achieved as follows. Regioselective addition of methylmagnesium iodide to **6** afforded a 52:48 diastereomeric mixture of hydroxylactams **7a** in a combined yield of 89%. This mixture, although separable by flash chromatography, was used in the next step as it was, since the following Lewis acid mediated reduction was considered to proceed via an N-acyliminium[3,5]. Indeed, in the presence of 1.0 equivalent of trifluoroboron etherate, hydroxylactam **7a** was deoxygenated with an excess of triethylsilane (CH_2Cl_2, -78°C) to yield predominantly the *trans*-**8a** $[[\alpha]_D^{25}$ +77.6 (*c* 0.35 in $CHCl_3$)] (90%) and traces of *cis*-**8a**. The *trans*-diastereoselectivity was at least 95%. The stereochemistry of compound **8a** was tentatively assigned based on the observed vicinal coupling constants[3, 4] ($J_{4,5}$=6.5 Hz for *cis*-isomer and $J_{4,5}$=2.5 Hz for *trans*-isomer). This was further confirmed by converting **8a** to (2R, 3R)-**2**. Extension of this procedure to other Grignard reagents led to the corresponding products **8b-c** with similarly diastereoselectivity (95%-97%).

O-debenzylation of **8a** (10% Pd/C, H_2 1 atm , 95% EtOH) yielded hydroxylactam **9** $[[\alpha]_D^{25}$ +83.6 (*c* 1.0 in $CHCl_3$)] in 95% yield. Amide reduction (LAH, THF, reflux, 92%) followed by *O*-mesylation (MsCl, NEt_3, DMAP, CH_2Cl_2, 93%) afforded **11** $[[\alpha]_D^{25}$ -51.8 (*c* 0.4 in $CHCl_3$)] in high overall yield. Mesylate **11** was subjected to an S_N2 reaction with sodium azide in hot DMF to give β-azidoamine (2R, 3R)-**12** in 87% yield. Lithium aluminum hydride reduction then provide the desired (2R, 3R)-3-amino-1-benzyl-2-methylpyrrolidine **2** [6] $[[\alpha]_D^{25}$ -88.5 (*c* 0.4 in $CHCl_3$)] in 88% yield. Since racemic **2** has been aroylated to give to emonapride **1**[1,2], our work thus constitutes a formal synthesis of emonapride **1**.

In summary, we have developed an efficient and general asymmetric alkylation-reduction procedure leading to *trans*-5-alkyl-4-hydroxy-2-pyrrolidinones. Based on this transformation, the first asymmetric

synthesis of (2R, 3R)-**2**, a key intermediate for antipsychotic agent, emonapride **1**, was achieved.



Scheme 1. Reagents and conditions: i, ref. 3b; ii, EtOH, AcCl, 50°C, 96%; iii, BnBr, Ag_2O, Et_2O, room temp., 92%; iv. RMgX (a. R = Me, b. R = Bn, c. R = *n*Bu, d. R = *i*Bu), THF, -78°C ,83-94%; v. Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78°C, 76-90%; vi. H_2, 10% Pd/C, 95%EtOH, 95%; vii. $LiAlH_4$, THF, reflux, 92%; viii. MsCl, NEt_3, DMAP, CH_2Cl_2, r. t., 93%; ix. NaN_3, DMF, 50°C, 87%; x. $LiAlH_4$, THF, reflux, 88%.

ACKNOWLEDGMENTS We wish to thank the State Education Committee, FOK YING TUNG Education Foundation and the NSF of China for financial support. The NSF of Fujian province is also thanked for additional support.

REFERENCES AND NOTES

1. (a) Murakami, K.; Takahashi, M.; Hirata, Y.; Takashima, M.; Iwanami, S.; Hasegawa, O.; Nozaki, Y.; Tashikawa, S.; Takeda, M.; Usuda, S., U. S. Patent 4 097 487, **1978**; (b) Takashima, M.; Iwanami, S.; Usuda, S.; U. S. Patent 4 210 660 ,**1980**.
2. Iwanami, S.; Takashima, M.; Hirata, Y.; Hasegawa, O.; Usuda, S., *J. Med. Chem.*, **1981**, *24*, 1224.
3. (a) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.*, **1990**, *31*, 4949; (b) Koot, W. J.; Ginkel, R. V.; Kranenburg, M.; Hiemstra, H.; Louwrier, S.; Moolenaar, M. J.; Speckamp, W. M. *Tetrahedron Lett.*, **1991**, *32*, 401.
4. Jouin, P.; Castro, B.; Nisato, D. *J. Chem. Soc. Perkin Trans. 1*, **1987**, 1177.
5. (a) Evans, D. A.; Thomas, E. W.; Cherpeck, R. E. *J. Am. Chem. Soc.*, **1982**, *104*, 3695 ; (b) Dijkink, J.; Speckamp, W. N. *Heterocycles*, **1979**, *12*, 1147.
6. Selected spectroscopic data of compound (2R, 3R)-**2**, MS(m/e, relative intensity %): 183(M^+, 33), 147(26), 132(9), 91(100); HRMS calcd. for $C_{12}H_{15}N$: 173.1204, found: 173.1215; ^{1}HNMR (500MHz, $CDCl_3$) δ: 1.16(d, 3H) , 1.49(m, 1H), 2.09(m, 2H), 2.19(s, 2H), 2.39(br, 1H), 2.92(m, 1H), 3.16(d, 1H), 3.29(br, 1H), 3.99(d, 1H), 7.31(m, 5H) ppm.

(*Received in China* 11 *July* 1996; *revised* 4 *October* 1996; *accepted* 29 *October* 1996)