ORGANIC LETTERS

2003
Vol. 5, No. 11
1927−1929

Asymmetric Synthesis of (+)-L-733, 060 and (+)-CP-99, 994 Based on a New Chiral 3-Piperidinol Synthon†

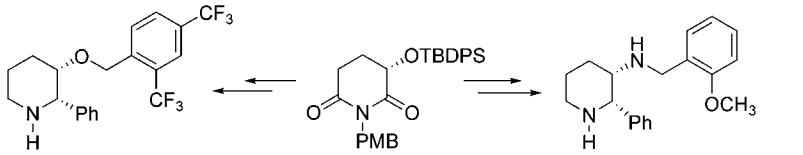
Pei-Qiang Huang,* Liang-Xian Liu, Bang-Guo Wei, and Yuan-Ping Ruan

Department of Chemistry, Xiamen University, Xiamen, Fujian 361005, P. R. China

pqhuang@xmu.edu.cn

Received March 23, 2003

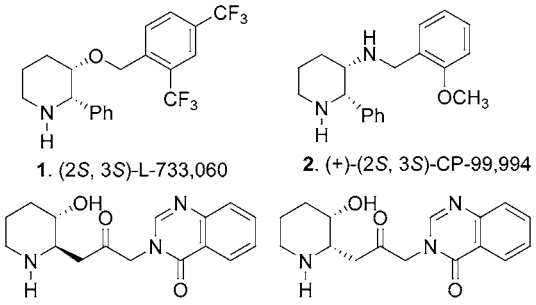
ABSTRACT



1. (+)-(2*S*, 3*S*)-L-733,060 (*S*)-**9** **2**. (+)-(2*S*, 3*S*)-CP-99,994

Selective and potent neurokinin substance P receptor antagonists (+)-L-733, 060 (1) and (+)-CP-99, 994 (2) have been synthesized starting from a new (3*S*)-piperidinol synthon derived from L-glutamic acid. The methods featured a C-2 regioselective reduction of glutarimide (9), Lewis acid-promoted Si to C-2 phenyl group migration of 10, and stereoselective reduction of acetylated oxime 19 as the key steps.

2-Alkyl-3-hydroxyl piperidines and 2-alkyl-3-aminopiperidines are structural units found in numerous bioactive natural products, drugs, and drug candidates. For example, (+)-L-733, 060 (**1**)[1] and (+)-CP-99, 994 (**2**)[2] are selective and potent neurokinin substance P receptor antagonists, which have been shown to possess potent antiemetic activity; febrifugine (**3**) and isofebrifugine (**4**) are well-known candidates of an antimalarial agent isolated from Chinese medicinal plants *Dichroa febrifuga*. The important bioactivities[1−3] associated both (+)-L-733, 060 (**1**) and (+)-CP-99, 994 (**2**) have stimulated the development of synthetic approaches.[1,2,4,5] However, only two racemic total synthesis[1,4c] of (±)-L-733, 060 and one asymmetric total synthesis of (+)-L-733, 060 have been reported very recently.[4e]



1. (2*S*, 3*S*)-L-733,060 **2**. (+)-(2*S*, 3*S*)-CP-99,994

3. febrifugine **4**. isofebrifugine

The success in the development of protected (*S*)-malimide-based synthetic methodology from these laboratories[6] led us to consider the protected 3-hydroxyglutarimide **9** as a suitable

† Dedicated to Professor Wei-Shan Zhou on the occasion of his 80th birthday.

(1) (a) Baker, R.; Harrison, T.; Hollingworth, G. J.; Swain, C. J.; Williams, B. J. EP 0 528, 495A1, 1993. (b) Harrison, T.; Williams, B. J.; Swain, C. J.; Ball, R. G. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2545.

(2) Desai, M. C.; Lefkowitz, S. L.; Thadeio, P. F.; Longo, K. P.; Snider, R. M. *J. Med. Chem.* **1992**, *35*, 4911.

(3) (a) Lotz, M.; Vaughan, J. H.; Carson, D. A. *Science* **1988**, *241*, 1218. (b) Perianan, A.; Snyderman, R.; Malfroy, B. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 520. (c) Moskowitz, M. A. *Trends Pharmacol. Sci.* **1992**, *13*, 307. (d) Zaman, S.; Woods, A. J.; Watson, J. W.; Reynolds, D. J. M.; Andrews, P. L. R. *Neuropharmacology* **2000**, *39*, 316.

(4) (a) Calvez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099. (b) Stadler, H.; Bos, M. *Heterocycles* **1999**, *51*, 1067. (c) Tomooka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc.* **2000**, *122*, 408. (d) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223. (e) Bhaskar, G.; Rao, B. V. *Tetrahedron Lett.* **2003**, *44*, 915.

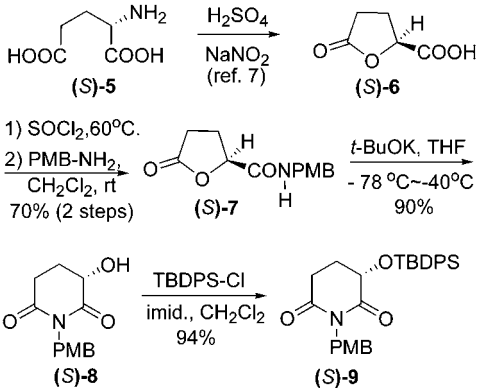
(5) (a) Chandrasekhar, S.; Mohanty, P. K. *Tetrahedron Lett.* **1999**, *40*, 5071. (b) Tsuritani, N.; Yamada, K.; Yoshikawa, N.; Shibasaki, M. *Chem. Lett.* **2002**, 276. (c) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2002**, *43*, 7979. For the synthesis of racemic CP-99, 994, see: (d) Desai, M. C.; Thadeio, P. F.; Lefkowitz, S. L. *Tetrahedron Lett.* **1993**, *34*, 5831.

10.1021/ol034505g CCC: $25.00
Published on Web 05/07/2003

multifunctional 3-hydroxypiperidine synthon. We now report the asymmetric synthesis of (+)-L-733, 060 and (+)-CP-99, 994 based on this new chiral nonracemic 3-piperidinol synthon.

In the malimide-based methodology, (*S*)-malic acid[6] has been conveniently used as the chiral pool. For the synthesis of (*S*)-3-hydroxyglutarimide (**8**), although the requisite higher homologue of malic acid is not a naturally occurring compound, it occurred to us that this compound could be derived from inexpensive and easily available (*S*)-glutamic acid via the well-established diazodation method.[7] Thus, (*S*)-glutamic acid was selected as the chiral pool for our synthesis.

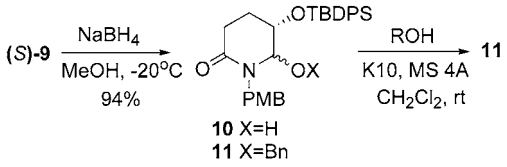
Scheme 1



The synthesis started with (*S*)-glutamic acid (Scheme 1). Thus, (*S*)-glutamic acid (**5**) was converted to (*S*)-**6** by the well-established diazodation procedure.[7] Treatment of γ-lactone-carboxylic acid (*S*)-**6** with thionyl chloride at 60 °C provided the corresponding acid chloride, which without further purification, was treated with *p*-methoxybenzylamine to give lactone-amide (*S*)-**7** {mp 92−93 °C, $[\alpha]^{20}_D$ −4.9° (*c* 0.9, $CHCl_3$)}. The overall yield from (*S*)-**6** to (*S*)-**7** was 70%. The ring expansion for the conversion of lactone-amide (*S*)-**7** to glutarimide (*S*)-**8** was achieved via the treatment of (*S*)-**7** with LDA at −78 °C. In this way, the yield of (*S*)-**8** was about 50%. Better results could be obtained by using 0.2−0.5 molar equiv of potassium *tert*-butoxide at low temperature (−78 °C). In this manner, the desired glutarimide (*S*)-**8** could be obtained in excellent yield {90%, colorless crystalline, mp 98−99 °C, $[\alpha]^{20}_D$ −70° (*c* 1.0, $CHCl_3$)}. The enantiomeric excess of (*S*)-**8** was at least 98%, as determined by chiral HPLC analysis [Chirex (*S*)-leu and (*S*)-NEA] by comparing with a partially racemized sample of (*S*)-**8**. The hydroxyl group in **8** was protected with *tert*-butyldiphenyl silyl chloride under standard conditions (TBDPSCl, imidazole, CH_2Cl_2), which afforded glutarimide (*S*)-**9** in 94% yield.

Protected glutarimide **9** was reduced with sodium borohydride at low temperatures (between −20 and −10 °C, 50 min), which afforded predominantly the desired regioisomer **10** in 10:1 regioselectivity (Scheme 2). The regioisomer **10**

Scheme 2



consisted of two separable diastereomers in 82:18 ratio. The stereochemistry of the major diastereomer was tentatively assigned as *cis* on the basis of the smaller coupling constants ($J_{5,6}$ = 2.2 Hz) of major diastereomer ($J_{5,6}$ = 3.1 Hz for minor diastereomer). Both diastereomers of **10** could be purified by recrystallization {major diastereomer, mp 165−166 °C, $[\alpha]^{20}_D$ −54.8° (*c* 1.3, $CHCl_3$); minor diastereomer, mp 174.5−175.5 °C, $[\alpha]^{20}_D$ +31.7° (*c* 0.9, $CHCl_3$)}. The deoxygenative phenylation of **10** was first attempted using Tomooka's conditions.[4c] Since the reaction was presumed to proceed via an *N*-acyliminium,[4c,8] which could be derived from both diastereomers of **10**, the diastereomeric mixture of **10** could be used as it was. Thus, in the presence of montmorillonite clay (K10) and 4 Å molecular sieves, the diastereomeric mixture of **10** was treated with benzyl alcohol. However, the desired phenyl migration product was not observed, we obtained instead aza-acetal **11** as a diastereomeric mixture. Since the reaction depended, on one hand, on the formation of the *N*-acyliminium and, on the other hand, the attack of a nucleophile (e.g., benzyl alcohol) at silicon atom (which enhances the migration of the phenyl group), to facilitate the nucleophilic attack at hindered silicon atom, water was selected as a smaller nucleophile. However, when stirring a suspension of **10**, water, and K10, we observed only the epimerization of *cis*-**10** to thermodynamically more stable *trans*-**10**. Although the reaction did not lead to the desired phenyl migration product, the observed epimerization allowed to confirm the *cis* stereochemistry assigned previously for the major diastereomer of **10**.

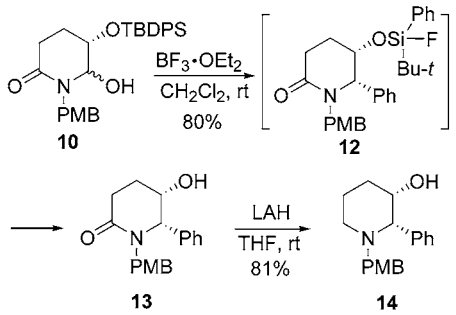
At this stage, the use of Lewis acid as a promoter was considered. Gratefully, when **10** was stirred with $BF_3{\cdot}OEt_2$ at room temperature for 3 days, the phenyl migration proceeded smoothly, and **13** was isolated in 80% yield (>95% *cis*) after workup (Scheme 3). Reduction of **13** with

(6) (a) Huang, P.-Q.; Wang, S. L.; Zheng, H.; Fei, X. S. *Tetrahedron Lett.* **1997**, *38*, 271. (b) Huang, P.-Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547. (c) Huang, P.-Q.; Wang, S. L.; Ruan, Y. P.; Gao, J. X. *Nat. Prod. Lett.* **1998**, *11*, 101. (d) Huang, P.-Q.; Ye, J. L.; Chen, Z.; Ruan, Y. P.; Gao, J. X. *Synth. Commun.* **1998**, *28*, 417. (e) Huang, P. -Q.; Chen, Q. F.; Chen, C.-L.; Zhang, H.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 3827. (f) Huang, P.-Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309. (g) Zheng, X.; Huang, P.-Q.; Ruan, Y. P.; Lee, A. W. M.; Chan, W. H. *Heterocycles* **2001**, *55*, 1505. (h) Zheng, X.; Huang, P.-Q.; Ruan, Y. P.; Lee, A. W. M.; Chan, W. H. *Nat. Prod. Lett.* **2002,** *16*, 53. (i) Huang, P.-Q.; Zheng, X. *Arkivoc* **2003**, Part ii, 7 (http://www.arkat-usa.org).

(7) Gringore, O. H.; Rouessac, F. P. In *Organic Synthesis*; Freeman, J. P. Ed.; John Wiley & Sons: New York, 1990; Coll. Vol. VII, p 99.

(8) For a recent review, see: Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

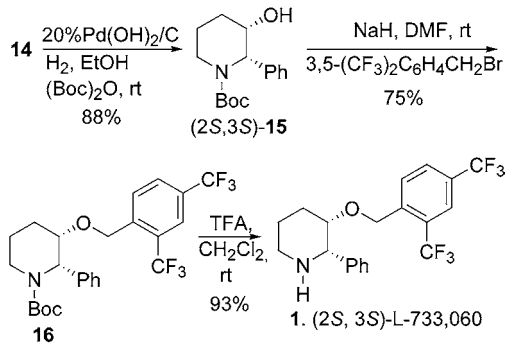
Scheme 3



lithium aluminum hydride at room temperature then provided piperidine (2*S*,3*S*)-**14** in 81% yield.

When **14** was subjected to hydrogenolysis conditions [H_2, 1 atm, 20% $Pd(OH)_2$, MeOH] in the presence of $(Boc)_2O$, one-pot selective *N*-debenzylation−butoxycarbonylation occurred. In this way, (2*S*,3*S*)-**15** {mp 71−72 °C, $[\alpha]_D$ +53.8° (*c* 1.0, $CHCl_3$); lit.[4e] $[\alpha]_D$ +38.3° (*c* 1.92, $CHCl_3$)} was obtained in a yield of 88% (Scheme 4).

Scheme 4

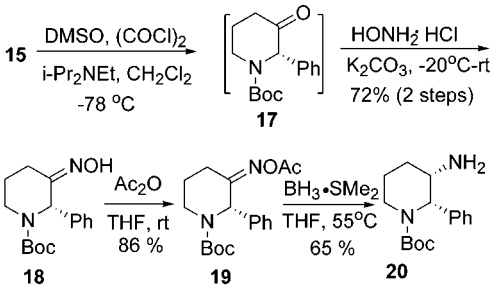


The following step involved the etherification. This was achieved by sodium hydride deprotonation of **15** followed by reaction with 3,5-bis(trifluoromethyl)benzyl bromide, which gave **16** in 75% yield {$[\alpha]^{28}_D$ +36.9° (*c* 1.0, $CHCl_3$); lit.[4e] $[\alpha]_D$ +30.38° (*c* 1.55, $CHCl_3$)}. Finally, *N*-Boc deprotection of **16** using TFA afforded the desired (2*S*, 3*S*)-L-733, 060 (**1**), which was characterized as its hydrochloride {mp 213-215 °C; lit.[1a] 215−216 °C; $[\alpha]^{28}_D$ +84.5° (*c* 0.8, MeOH); lit.[1a] $[\alpha]^{23}_D$ +87.3° (*c* 1.0, MeOH)}.

The synthesis of (+)-CP-99, 994 began with the key intermediate (2*S*,3*S*)-**15** (Scheme 5). (2*S*,3*S*)-3-Piperidinol **15** was converted to oxime (*S*)-**18** by Swern oxidation [9] [DMSO, $(COCl)_2$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C], followed by reaction with hydroxylamine hydrochloride ($HONH_2$·HCl, K_2CO_3, MeCN). Oxime **18** was then acetylated to afford **19**. The key reduction step was achieved using borane dimethyl sulfite complex[5c] (H_3B·SMe_2, 65%), which established the 2,3-*cis*-stereochemistry of **20**.

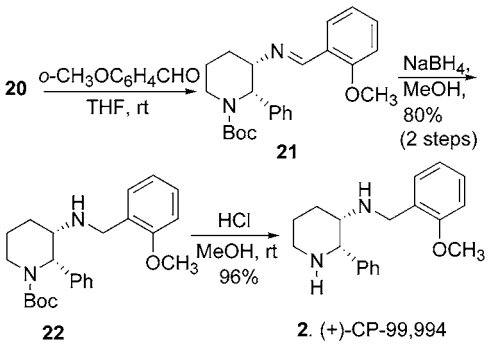
(9) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

Scheme 5



(2*S*,3*S*)-3-Aminopiperidine derivative **20** was then subjected to reductive alkylation conditions (*o*-$CH_3OC_6H_4CHO$, THF; $NaBH_4$, MeOH, rt), which afforded, surprisingly, an adduct of the desired **22** with *o*-methoxybenzyl alcohol in 80% yield {colorless oil, $[\alpha]^{28}_D$ +25.7° (*c* 0.9, $CHCl_3$)} (Scheme 6). Finally, treatment of the **22**−*o*-methoxybenzyl

Scheme 6



alcohol adduct with a methanolic solution of hydrochloric acid at room temperature gave the desired (+)-(2*S*,3*S*)-CP-99, 994 (**2**) in 96% yield, which was characterized as its dihydrochloride {mp 253−254 °C; $[\alpha]^{28}_D$ +75.1° (*c* 0.6, MeOH); lit.[2] mp 255 °C; $[\alpha]^{23}_D$ +77° (*c* 1.0, MeOH); lit.[5c] mp 254.5 °C; $[\alpha]^{23}_D$ +75.5° (*c* 1.1, MeOH)}.

In conclusion, (+)-L-733, 060 and (+)-CP-99, 994 were synthesized from easily available chiral building block (*S*)-**8**. Work is in progress for further application of this new chiral 3-piperidinol synthon in the asymmetric synthesis of other 3-piperidinol-related natural products.

Acknowledgment. The authors are grateful to the National Science Fund for Distinguished Young Investigators, the NNSF of China, and the Fund for doctoral sites of the Ministry of Education for financial support.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034505G