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

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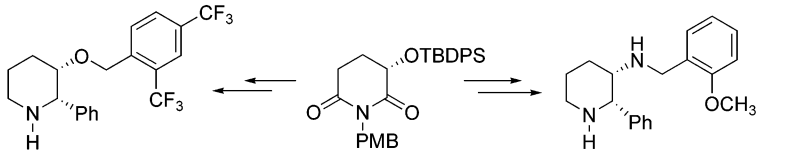
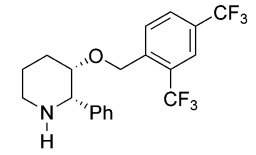
ABSTRACT



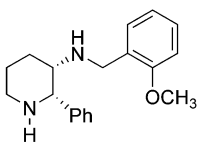
1. (+)-(2*S*, 3*S*)-L-733,060 (*S*)-**9** **2**. (+)-(2*S*, 3*S*)-CP-99,994

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.

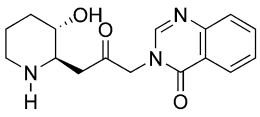
2-Alkyl-3-hydroxyl piperidines and 2-alkyl-3-aminopiperidines are structural units found in numerous bioactive natural products, drugs, and drug candidates. For example, (+)-L-733, 060 (**1**)[1] and (+)-CP-99, 994 (**2**)[2] are selective and potent neurokinin substance P receptor antagonists, which 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]



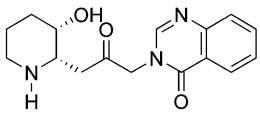
1. (2*S*, 3*S*)-L-733,060



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.

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(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.

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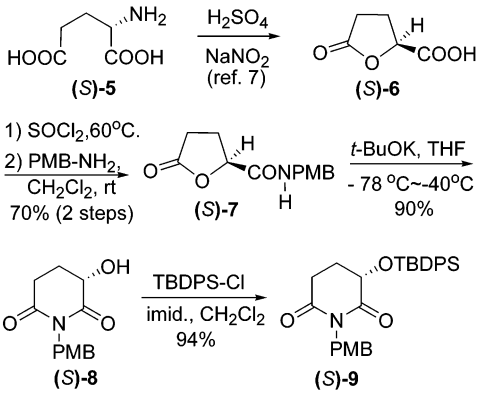
multifunctional 3-hydroxypiperidine synthon. We now report the asymmetric synthesis of (+)-L-733, 060 and (+)-CP-99, 994 based on this new chiral nonracemic 3-piperidinol synthon.

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.

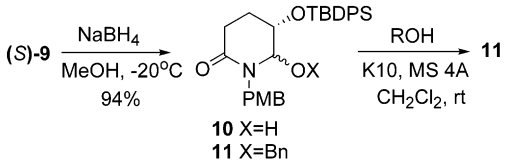
Scheme 1



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**.

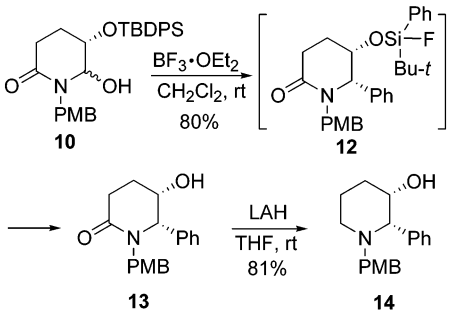
At this stage, the use of Lewis acid as a promoter was considered. Gratefully, when **10** was stirred with $BF_3{\cdot}OEt_2$ at room temperature for 3 days, the phenyl migration proceeded smoothly, and **13** was isolated in 80% yield (>95% *cis*) after workup (Scheme 3). Reduction of **13** with

(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.

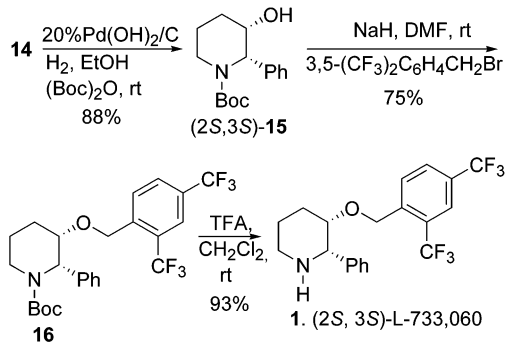
Scheme 3



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

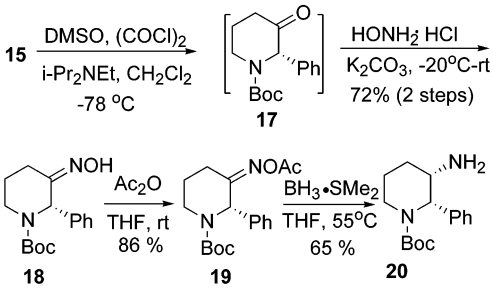


The following step involved the etherification. This was achieved by sodium hydride deprotonation of **15** followed by reaction with 3,5-bis(trifluoromethyl)benzyl bromide, which gave **16** in 75% yield {$[\alpha]^{28}_D$ +36.9° (*c* 1.0, $CHCl_3$); lit.[4e] $[\alpha]_D$ +30.38° (*c* 1.55, $CHCl_3$)}. 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**.

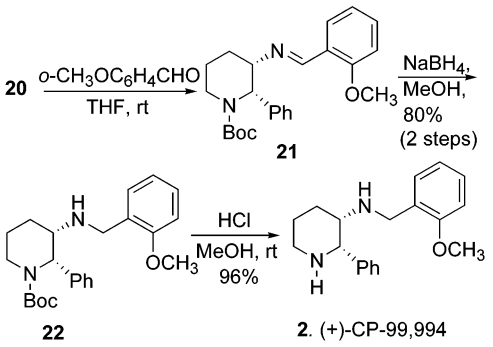
(9) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.

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.

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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.

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