

Asymmetric Vinylogous Mannich Reactions: A Versatile Approach to Functionalized Heterocycles

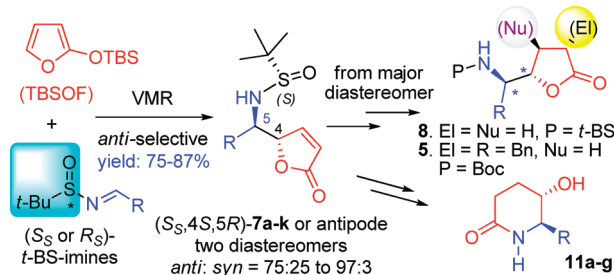
Shu-Tang Ruan,[†] Jie-Min Luo,[†] Yu Du,[†] and Pei-Qiang Huang^{*,†,‡}

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, P. R. China, and State Key Laboratory of Bioorganic and Natural Products Chemistry, 354 Fenglin Lu, Shanghai 200032, P. R. China

pqhuang@xmu.edu.cn

Received July 28, 2011

ABSTRACT



Asymmetric vinylogous Mannich reaction (VMR) of 2-(*tert*-butyldimethylsilyloxy)furan (TBSOF, **1**) with (*R_S*)- or (*S_S*)-*t*-BS-imines (**3**) furnished 5-aminoalkylbutenolides **7a–k** in 75–87% yields with *anti/syn* ratios ranging from 75:25 to 97:3. Butenolides **7a–f,k** were readily converted into substituted lactones **8** and **5** and 6-substituted 5-hydroxypiperidin-2-ones **11a–g**, which are, in turn, key intermediates for the synthesis of many bioactive compounds.

Functionalized heterocycles constitute the core structures of a large number of bioactive natural products and pharmaceuticals. Thanks to seminal work by Casiraghi, 2-trialkylsilyloxyfuran (e.g., TBSOF, **1**)-based reactions have become a powerful methodology for the efficient synthesis of highly functionalized heterocycles.^{1–3} In this regard, Martin's group has pioneered the use of vinylogous Mannich reactions (VMR)^{1–3} in the efficient synthesis of complex alkaloids.²

Similarly, Davis *p*-toluenesulfinimines⁴ and Ellman *N*-*tert*-butanesulfinimines (*t*-BS-imines, **3**)^{4b,5,6} have gained great success as versatile chiral amine templates in recent years.^{4,5} However, the use of cyclic silyl ketene acetal as a class of versatile nucleophiles for additions to these systems has largely been ignored.⁶

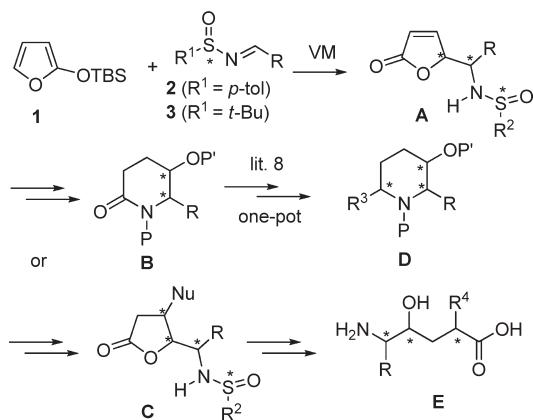
We envisioned that a combination of the powerful methodology of TBSOF-based vinylogous Mannich reaction (VMR) with this chiral sulfinamide-based methodology might provide a versatile and general approach to chiral nonracemic butenolides **A**, 6-substituted 5-hydroxypiperidin-2-ones **B**, functionalized lactones **C**, 2,6-disubstituted piperidin-3-ols **D**, and substituted γ -hydroxy- δ -amino acids **E** (Scheme 1).

2,6-Disubstituted piperidin-3-ols (**D**) are a common framework shared by many bioactive alkaloids and azasugars. A number of methods have been developed for their synthesis. Many of them have used 5-hydroxypiperidin-2-ones **B** as key intermediates.⁷ Our group has recently developed a one-pot reductive alkylation of lactams such as **B** to give the corresponding piperidines **D**, which greatly improves the efficiency of this approach.⁸ On the other hand, substituted γ -hydroxy- δ -amino acids **E** are found as motifs of many bioactive compounds. For example, L-685,458 (**4**) is a potent inhibitor of γ -secretase (IC₅₀ = 17 nM) and of potential therapeutic benefit in the treatment of Alzheimer's disease and other neurological disorders (Figure 1).^{9,10} The γ -hydroxy- δ -amino acid

(1) For recent reviews on silyloxydiene, see: (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076–3154. (b) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525–1542.

(2) For reviews on vinylogous Mannich-type reactions, see: (a) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221–3242. (b) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895–904.

Scheme 1. Synthetic Potential of the Asymmetric VMR



residue of **4** could be synthesized by ring opening of lactone **5**.^{10a,11} We report herein the results of this investigation.

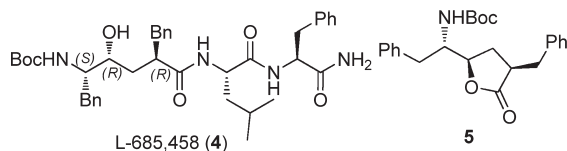


Figure 1. Structure of L-685,458 (**4**) and its lactone precursor **5**.

t-BS-Imines **3a–k** were prepared from either enantiomer of *N*-*tert*-butanesulfinamide (**6**) and aldehydes by the

(3) For selected examples on the *threo* (*syn*)-diastereoselective TMSF-based vinylogous Mannich-type reactions, see: (a) Harding, K. E.; Coleman, M. T.; Liu, L.-T. *Tetrahedron Lett.* **1991**, *32*, 3795–3798. (b) Martin, S. F.; Corbett, J. W. *Synthesis* **1992**, 55–56. (c) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773–5776. (d) Camilletti, C.; Poletti, L.; Trombini, C. *J. Org. Chem.* **1994**, *59*, 6843–6846. (e) Morimoto, Y.; Iwashita, M. *Synlett* **1995**, 1221–1222. (f) Martin, S. F.; Clark, C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236–3242. (g) Martin, S. F.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299–3300. (h) Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963–7966. (i) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567–1572. (j) Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059–1068. (k) Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2975–2987. (l) Battistini, L.; Rassu, G.; Pinna, L.; Zanardi, F.; Casiraghi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 765–773. (m) Pichon, M.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **1999**, *40*, 8567–8570. (n) Martin, S. F.; Bur, S. K. *Tetrahedron* **1999**, *55*, 8905–8914. (o) Martin, S. F.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990–6997. (p) Martin, S. F.; Lopez, O. D. *Tetrahedron Lett.* **1999**, *40*, 8949–8953. (q) Boto, A.; Hernandez, R.; Suarez, E. *Tetrahedron Lett.* **2000**, *41*, 2899–2902. (r) Pilli, R. A.; D'Oca, M. G. M.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709–9712. (s) Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445–3447. (t) de Oliveira, M. C. F.; Santos, L. S.; Pilli, R. A. *Tetrahedron Lett.* **2001**, *42*, 6995–6997. (u) Harding, K. E.; Southard, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 1845–1854. (v) González, A. S.; Arrayás, R. G.; Rivero, M. R.; Carretero, J. C. *Org. Lett.* **2008**, *10*, 4335–4337. (w) Hermange, P.; Dau, M. E. T. H.; Retailleau, P.; Dodd, R. H. *Org. Lett.* **2009**, *11*, 4044–4047.

(4) For selected recent reviews on *p*-toluenesulfinimines, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8803–8030. See also: (c) Davis, F. A.; McCoull, W. J. *Org. Chem.* **1999**, *64*, 3396–3397.

known methods¹² (Table 1). After screening the reaction conditions for the VMR, the optimal reaction conditions were defined as treating a CH₂Cl₂ solution of TBSOF (**1**, 1.5 equiv) and *t*-BS-imine (**3a**, 1.0 equiv) with TMSOTf (1.0 equiv) at –78 °C for 1 h. Only two separable diastereomers **7a** (dr = 91:9) were obtained in a combined yield of 82%. The relative stereochemistry of the major product of (*S*_S)-**7a** was elucidated as *S*_S,4*S*,5*R* by X-ray diffraction analysis (cf. Supporting Information), while the minor diastereomer of (*R*_S)-**7k** was determined to be *R*_S,4*S*,5*S* by its conversion into a known compound¹³ (Supporting Information).

The reactions of either enantiomer of various *t*-BS-imines (**3a–k**) with TBSOF (**1**) are summarized in Table 1. In all

Table 1. Vinylogous Mannich Reactions of *t*-BS-Imines **3** with **1**

entry	aldehyde	<i>t</i> -BS*-imines 3 (% yield) ^c	major diastereomer of 7 (<i>anti/syn</i>) ^{d,f} (% yield) ^{e,f}
1	<i>n</i> -PrCHO	(<i>S</i> _S)- 3a (85) ^a (<i>R</i> _S)- 3a (85) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7a (91:9) (82) (<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7a (93:7) (81)
2	<i>i</i> -PrCHO	(<i>S</i> _S)- 3b (83) ^a (<i>R</i> _S)- 3b (90) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7b (97:3) (86) (<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7b (97:3) (84)
3	<i>n</i> -C ₇ H ₁₅ CHO	(<i>S</i> _S)- 3c (75) ^a (<i>R</i> _S)- 3c (81) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7c (92:8) (87) (<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7c (90:10) (82)
4	PhCH ₂ CHO	(<i>S</i> _S)- 3d (82) ^a (<i>R</i> _S)- 3d (82) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7d (91:9) (80) (<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7d (89:11) (78)
5	MeCHO	(<i>R</i> _S)- 3e (90) ^a	(<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7e (82:18) (76)
6	PhCHO	(<i>S</i> _S)- 3f (82) ^a (<i>R</i> _S)- 3f (88) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7f (93:7) (75) (<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7f (93:7) (77)
7	3-MeOPhCH ₂ CHO	(<i>S</i> _S)- 3g (78) ^a	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7g (89:11) (84)
8	2,4-Cl ₂ PhCHO	(<i>S</i> _S)- 3h (75) ^b	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7h (81:19) (85)
9	2,5-(MeO) ₂ PhCHO	(<i>S</i> _S)- 3i (80) ^b	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7i (78:22) (82)
10	4-ClPhCHO	(<i>S</i> _S)- 3j (86) ^b	(<i>S</i> _S ,4 <i>S</i> ,5 <i>R</i>)- 7j (81:19) (78)
11	BnOCH ₂ CHO	(<i>R</i> _S)- 3k (87) ^a	(<i>R</i> _S ,4 <i>R</i> ,5 <i>S</i>)- 7k (75:25) (80)

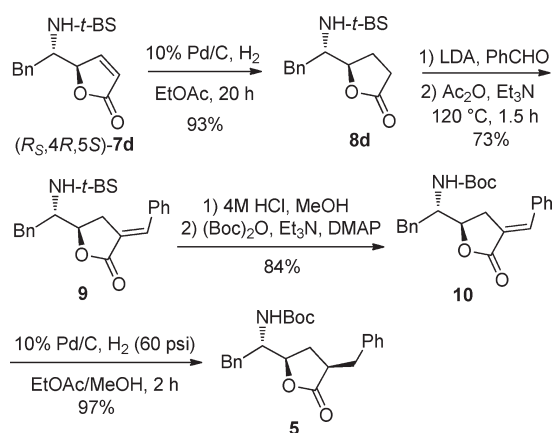
^a Method A: MgSO₄, PPTS, CH₂Cl₂, rt, 16 h. ^b Method B: CuSO₄, CH₂Cl₂, rt, 20 h. ^c Yield of isolated *E*-product. ^d Ratios determined by ¹H NMR analysis of crude mixtures. ^e Combined yield. ^f Small variations in both dr and yield between the two enantiomers of sulfinamide (entries 1, 3, 4) are due to errors in the measurement.

(5) For selected reviews on the chemistry of *t*-BS-imines, see: (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600–3740. (b) Ferreira, F.; Botuha, C.; Chemla, F.; Pérez-Luna, A. *Chem. Soc. Rev.* **2009**, *38*, 1162–1186. (c) Lin, G.-Q.; Xu, M.-H.; Zhong, Y.-W.; Sun, X.-W. *Acc. Chem. Res.* **2008**, *41*, 831–840. (d) Ellman, J. A.; Owens, T. D.; Tang, T.-P. *Acc. Chem. Res.* **2002**, *35*, 984–995. For selected examples, see: (e) Tang, M. T.; Volkman, S. K.; Ellman, J. A. *J. Org. Chem.* **2001**, *66*, 8772–8778. (f) Staas, D. D.; Savage, K. L.; Homnick, C. F.; Tsou, N. N.; Ball, R. G. *J. Org. Chem.* **2002**, *67*, 8276–8279. (g) Zhong, Y.-W.; Dong, Y.-Z.; Fang, K.; Izumi, K.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956–11957.

cases, two diastereomers were obtained in yields that varied from 75% to 87% with a dr that ranged from 75:25 to 97:3.

We next turned our attention to the synthesis of the precursor (2*R*,4*R*,5*S*-5) of the γ -hydroxy- δ -amino acid residue of L-685,458 (**4**). Catalytic hydrogenation of (*R_S*,4*R*,5*S*)-**7d** (Table 1, entry 4) gave lactone (*R_S*)-**8d** in 93% yield (Scheme 2). Deprotonation of (*R_S*)-**8d** with LDA and reaction of the resulting enolate with benzaldehyde gave the desired carbinol, which without separation was dehydrated (Ac₂O, Et₃N, 120–140 °C) to afford α,β -unsaturated lactone **9** in 73% yield. Cleavage of the chiral auxiliary (4 M HCl, MeOH) followed by reprotection gave the known *N*-Boc-protected derivative **10** in 84% yield. Hydrogenation of **10** (10% Pd/C, 60 psi H₂) produced the known lactone **5** in 97% yield as a single diastereomer (Scheme 2).^{10a} Its physical and spectroscopic data were identical with those reported {[α]_D²⁰ –68.9 (*c* 1.04, CHCl₃), lit.^{10a} [α]_D²⁰ –69.5 (*c* 1.02, CHCl₃); mp 127.0–128.6 °C, lit.^{11b} mp 127–128.5 °C}.

Scheme 2. Synthesis of Lactone Precursor **5**



(6) For addition of silyl ketene acetals to chiral sulfinimines, see: (a) Kawęcki, R. *J. Org. Chem.* **1999**, *64*, 8724–8727. (b) Jacobsen, M. F.; Skrydstrup, T. *J. Org. Chem.* **2003**, *68*, 7112–7114. For addition of dienolates to chiral sulfinimines, see: (c) Kawęcki, R. *Tetrahedron* **2001**, *57*, 8385–8390. (d) Gu, C.-L.; Liu, L.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2009**, *74*, 5754–5757. For addition of TBSOP with a *p*-toluenesulfinimine, see: (e) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445–5453. See also: (f) Turcaud, S.; Martens, T.; Sierceki, E.; Péard-Viret, J.; Royer, J. *Tetrahedron Lett.* **2005**, *46*, 5131–5134.

(7) For a recent review, see: Wijdeven, M. A.; Willemsen, J.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2010**, 2831–2844.

(8) (a) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037–3040. (b) Xiao, K.-J.; Wang, Y.; Ye, K.-Y.; Huang, P.-Q. *Eur. J. Org. Chem.* **2010**, 12792–12796.

(9) Li, Y.-M.; Xu, M.; Lai, M.-T.; Huang, Q.; Castro, J. L.; DiMuzio-Mower, J.; Harrison, T.; Lellis, C.; Nadin, A.; Neduvilil, J. G.; Register, R. B.; Sardana, M. K.; Shearman, M. S.; Smith, A. L.; Shi, X.-P.; Yin, K.-C.; Shafer, J. A.; Gardell, S. J. *Nature* **2000**, *405*, 689–694.

(10) For the synthesis of L-685,458, see: (a) Nadin, A.; López, J. M. S.; Neduvilil, J. G.; Thomas, S. R. *Tetrahedron* **2001**, *57*, 1861–1864. (b) Dias, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, 603–622.

(11) (a) McWilliams, J. C.; Armstrong, J. D., III; Zheng, N.; Bhupathy, M.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1996**, *118*, 11970–11971. (b) Litera, J.; Budesinsky, M.; Urban, J.; Soucek, M. *Collect. Czech. Chem. Commun.* **1998**, *63*, 231–244.

We next focused on the synthesis of 6-substituted 5-hydroxypiperidin-2-ones. Butenolides (*R_S*,4*R*,5*S*)-**7a–f,k** were hydrogenated to give the corresponding lactones (*R_S*)-**8a–g** in good yield (Table 2). Cleavage of the sulfinyl group under acidic conditions followed by base-promoted cyclization (DBU in toluene or K₂CO₃ in MeOH)¹⁴ produced the 6-substituted 5-hydroxypiperidin-2-ones **11a–g**. Among the synthesized products, **11b**, **11d–g** or their enantiomers are known compounds. The physical and spectroscopic data of **11d** were identical with those reported {[α]_D²⁰ –34.4 (*c* 1.2, MeOH); lit.¹⁵ [α]_D²³ –37.9 (*c* 1.2, MeOH)}, and the data of the others are available in the Supporting Information.

Table 2. Synthesis of 6-Substituted 5-Hydroxypiperidin-2-ones **11a–g**

entry	R	(<i>R_S</i>)- 8 (% yield) ^c	(5 <i>R</i> ,6 <i>S</i>)- 11 (% yield) ^c
1	<i>n</i> -PrCH ₂	8a (91)	11a (70), ^a (87) ^b
2	<i>i</i> -PrCH ₂	8b (95)	11b (80), ^a (72) ^b
3	<i>n</i> -C ₆ H ₁₃ CH ₂	8c (92)	11c (77) ^b
4	PhCH ₂	8d (93)	11d (78) ^a
5	CH ₃	8e (93)	11e (65) ^a
6	Ph	8f (92)	11f (76) ^b
7	BnOCH ₂	8g (89)	11g (70) ^b

^a Method A: DBU, toluene, reflux. ^b Method B: K₂CO₃, MeOH, rt. ^c Isolated yield.

Compound **11g** was protected with TBSCl (imid., DMAP, CH₂Cl₂) to produce TBS ether **12**, whose spectral data were identical with those reported.^{16,17b} The synthesis of **12** constitutes a formal synthesis of (–)-deoxoprosopphylline (**13**).¹⁶ In addition, Rapoport and co-workers have converted *ent*-**11g** into **14**; moreover, **14** is a versatile intermediate that can be elaborated to **15**, **16**, and **17** (Scheme 3).¹⁷

A plausible interpretation of stereochemical outcome in these VMR processes is depicted in Figure 2. Since only 1 equiv of Lewis acid (TMSOTf) is required for the reaction, a monocoordinated species with the preferred conformation^{4c} shown by **F** is thought to be involved. Because

(12) Liu, G.-C.; Cogan, D. A.; Owens, T. D.; Tang, T.-P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 1278–1284.

(13) Kumar, P. S.; Kumar, G. D. K.; Baskaran, S. *Eur. J. Org. Chem.* **2008**, 6063–6067.

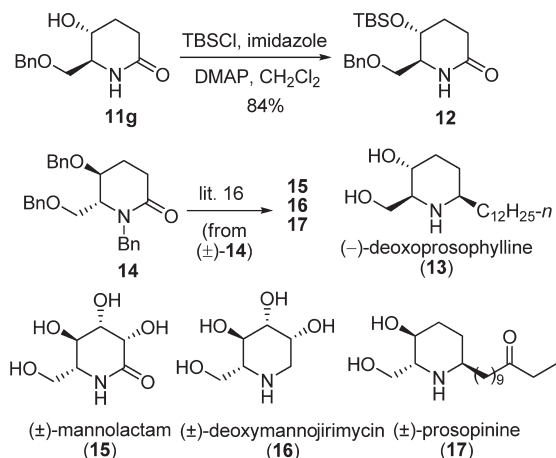
(14) Liu, L.; Wang, X.; Li, C.-Z. *Org. Lett.* **2003**, *5*, 361–363.

(15) Andrés, J. M.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron Lett.* **2006**, *47*, 5317–5320.

(16) Liu, R.-C.; Wei, J.-H.; Wei, B.-G.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2008**, *19*, 2731–2734.

(17) (a) Cook, G. R.; Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 3575–3584. (b) Campbell, J. A.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1995**, *60*, 4602–4616. (c) Chen, B.-F.; Tasi, M.-R.; Yang, C.-Y.; Chang, J.-K.; Chang, N.-C. *Tetrahedron* **2004**, *60*, 10223–10231.

Scheme 3. Synthetic Applications of Piperidin-2-one **11g**



the *re* face of the imine is sterically shielded by the *O*-LA, the nucleophile TBSOF^{31,s,u} probably approaches from the *si* face of the imine, via the favored transition state **G**, to form the 4,5-*erythro* (*anti*)-adduct as the major diastereomer.

In summary, 4,5-*anti*-selective vinylogous Mannich reactions between *t*-BS-imines **3a–k** and TBSOF (**1**) have been developed. They provide a versatile and general asymmetric approach to 4,5-*anti*-4-aminoalkylbutenolides **7** and 6-substituted *trans*-5-hydroxypiperidin-2-ones **11**, as well as functionalized lactones **5** and **8**. Lactone **5** is a key intermediate for the asymmetric synthesis of the potent γ -secretase inhibitor L-685,458 (**4**), while the synthesis of

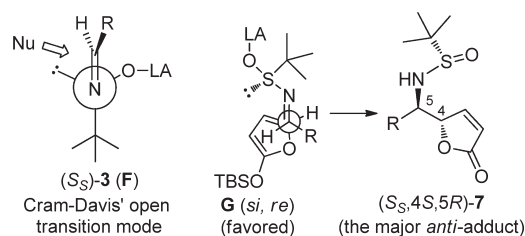


Figure 2. Plausible transition state for the VMR.

compound **12** constitutes a formal asymmetric synthesis of (-)-deoxoprosophylline (**13**). In addition, compound **11g** serves as a key intermediate for the asymmetric synthesis of mannolactam (**15**), deoxymannojirimycin (**16**), and proso-pinine (**17**).

Acknowledgment. The authors are grateful to the National Basic Research Program (973 Program) of China (Grant No. 2010CB833200) and NSF of China (20832005; 21072160) for financial support.

Supporting Information Available. Detailed experimental procedures, characterizations, and copies of ¹H and ¹³C NMR spectra of all new compounds; X-ray structure and crystallographic data in CIF format of compound (S_S)-**7a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.