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Asymmetric Vinylogous Mannich Reactions: A Versatile Approach to Functionalized Heterocycles

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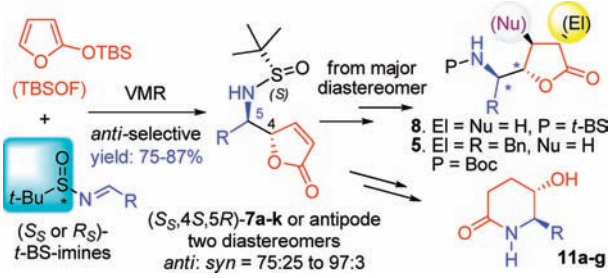
ABSTRACT



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*-toluenesulfinimines[4] 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 (IC_{50} = 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.

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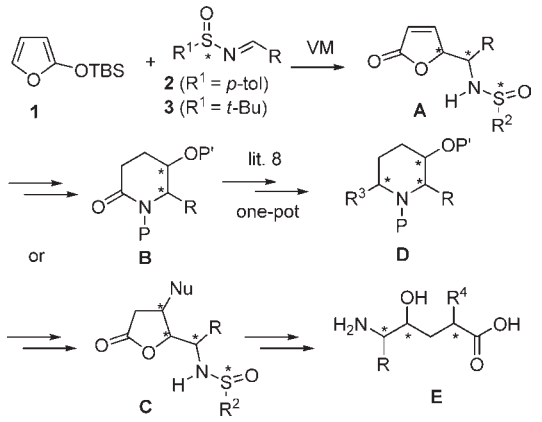
Scheme 1. Synthetic Potential of the Asymmetric VMR



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

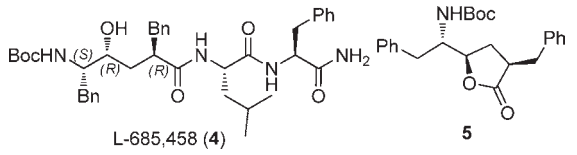
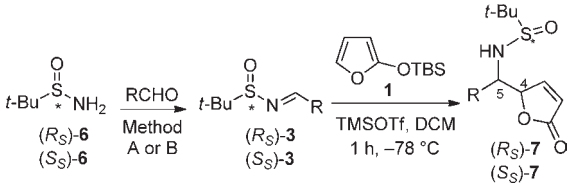


Figure 1. Structure of L-685,458 (**4**) and its lactone precursor **5**.

t-BS-Imines **3a**–**k** were prepared from either enantiomer of *N*-*tert*-butanesulfinamide (**6**) and aldehydes by the known methods[12] (Table 1). After screening the reaction conditions for the VMR, the optimal reaction conditions were defined as treating a CH_2Cl_2 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 compound[13] (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	*t*-BS*-imines **3** (% yield)[c]	major diastereomer of **7** (*anti*/*syn*)[d,f] (% yield)[e,f]
1	*n*-PrCHO	(S_S)-**3a** (85)[a]	(S_S,4*S*,5*R*)-**7a** (91:9) (82)
		(R_S)-**3a** (85)[a]	(R_S,4*R*,5*S*)-**7a** (93:7) (81)
2	*i*-PrCHO	(S_S)-**3b** (83)[a]	(S_S,4*S*,5*R*)-**7b** (97:3) (86)
		(R_S)-**3b** (90)[a]	(R_S,4*R*,5*S*)-**7b** (97:3) (84)
3	n-C_7H_{15}CHO	(S_S)-**3c** (75)[a]	(S_S,4*S*,5*R*)-**7c** (92:8) (87)
		(R_S)-**3c** (81)[a]	(R_S,4*R*,5*S*)-**7c** (90:10) (82)
4	$PhCH_2CHO$	(S_S)-**3d** (82)[a]	(S_S,4*S*,5*R*)-**7d** (91:9) (80)
		(R_S)-**3d** (82)[a]	(R_S,4*R*,5*S*)-**7d** (89:11) (78)
5	MeCHO	(R_S)-**3e** (90)[a]	(R_S,4*R*,5*S*)-**7e** (82:18) (76)
6	PhCHO	(S_S)-**3f** (82)[a]	(S_S,4*S*,5*R*)-**7f** (93:7) (75)
		(R_S)-**3f** (88)[a]	(R_S,4*R*,5*S*)-**7f** (93:7) (77)
7	3-$MeOPhCH_2CHO$	(S_S)-**3g** (78)[a]	(S_S,4*S*,5*R*)-**7g** (89:11) (84)
8	2,4-Cl_2PhCHO	(S_S)-**3h** (75)[b]	(S_S,4*S*,5*R*)-**7h** (81:19) (85)
9	2,5-$(MeO)_2$PhCHO	(S_S)-**3i** (80)[b]	(S_S,4*S*,5*R*)-**7i** (78:22) (82)
10	4-ClPhCHO	(S_S)-**3j** (86)[b]	(S_S,4*S*,5*R*)-**7j** (81:19) (78)
11	$BnOCH_2CHO$	(R_S)-**3k** (87)[a]	(R_S,4*R*,5*S*)-**7k** (75:25) (80)

[a] Method A: $MgSO_4$, PPTS, CH_2Cl_2, rt, 16 h. [b] Method B: $CuSO_4$, CH_2Cl_2, rt, 20 h. [c] Yield of isolated *E*-product. [d] Ratios determined by ^{1}H 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.

(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) Camiletti, C.; Poletti, L.; Trombini, C. *J. Org. Chem*. **1994**, *59*, 6843–6846. (e) Morimoto, Y.; Iwahashi, 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.

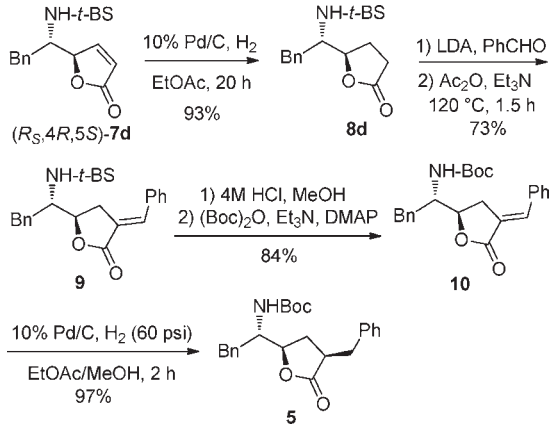
(4) For selected recent reviews on *p*-toluenesulfinimines, see: (a) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869–8905. (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8803–8030. See also: (c) Davis, F. A.; McCoull, W. *J. Org. Chem*. **1999**, *64*, 3396–3397.

(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.

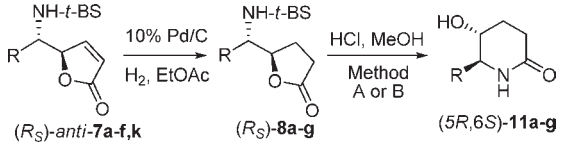
We next turned our attention to the synthesis of the precursor (2*R*,4*R*,5*S*-**5**) of the γ-hydroxy-δ-amino acid residue of L-685,458 (**4**). Catalytic hydrogenation of (*R*$_S$,4*R*,5*S*)-**7d** (Table 1, entry 4) gave lactone (*R*$_S$)-**8d** in 93% yield (Scheme 2). Deprotonation of (*R*$_S$)-**8d** with LDA and reaction of the resulting enolate with benzaldehyde gave the desired carbinol, which without separation was dehydrated (Ac_2O, Et_3N, 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 H_2) 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 {$[\alpha]^{20}_D$ −68.9 (*c* 1.04, $CHCl_3$), lit.[10a] $[\alpha]^{20}_D$ −69.5 (*c* 1.02, $CHCl_3$); mp 127.0−128.6 °C, lit.[11b] mp 127−128.5 °C}.

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



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 K_2CO_3 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 {$[\alpha]^{20}_D$ −34.4 (*c* 1.2, MeOH); lit.[15] $[\alpha]^{23}_D$ −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	(*R*$_S$)-**8** (% yield)[c]	(5*R*,6*S*)-**11** (% yield)[c]
1	*n*-$PrCH_2$	**8a** (91)	**11a** (70),[a] (87)[b]
2	*i*-$PrCH_2$	**8b** (95)	**11b** (80),[a] (72)[b]
3	*n*-$C_6H_{13}CH_2$	**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: K_2CO_3, MeOH, rt. [c] Isolated yield.

Compound **11g** was protected with TBSCl (imid., DMAP, CH_2Cl_2) to produce TBS ether **12**, whose spectral data were identical with those reported.[16,17b] The synthesis of **12** constitutes a formal synthesis of (−)-deoxoprosophylline (**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

(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.; Sierecki, E.; Pérard-Viret, J.; Royer, J. *Tetrahedron Lett.* **2005**, *46*, 5131–5134.

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(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. *Chem.—Eur. J.* **2010**, *16*, 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.; Neduvelil, 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.

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(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.

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

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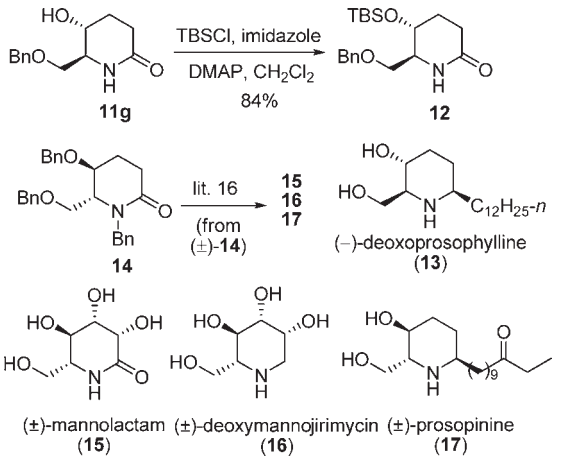
Scheme 3. Synthetic Applications of Piperidin-2-one **11g**



the *re* face of the imine is sterically shielded by the *O*-LA, the nucleophile TBSOF[3l,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

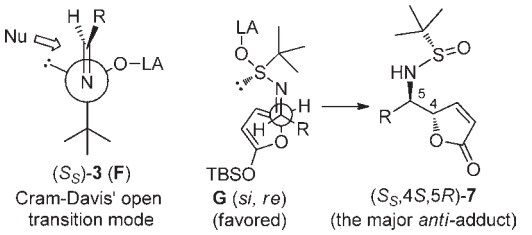


Figure 2. Plausible transition state for the VMR.

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 prosopinine (**17**).

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Supporting Information Available. Detailed experimental procedures, characterizations, and copies of ^{1}H and ^{13}C 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.