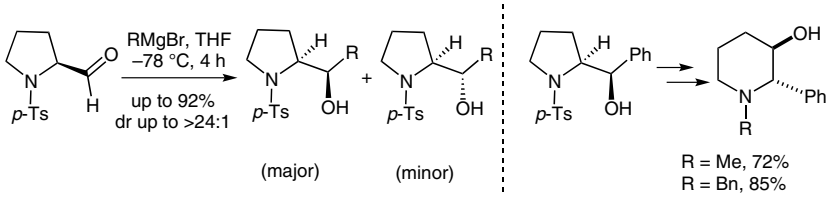
Synlett S. Chaudhuri et al. Letter

Highly Stereoselective Syntheses of Proline-Derived Vicinal Amino Alcohols through Grignard Addition onto *N*-Tosylprolinal

Saikat Chaudhuri
Amarchand Parida
Santanu Ghosh
Alakesh Bisai*

Department of Chemistry, Indian Institute of Science Education and Research Bhopal, Bhopal Bypass Road, Bhauri, Bhopal 462 066, Madhya Pradesh, India
alakesh@iiserb.ac.in



Received: 08.07.2015
Accepted after revision: 23.09.2015
Published online: 09.11.2015
DOI: 10.1055/s-0035-1560802; Art ID: st-2015-b0521-l

Abstract A highly diastereoselective Grignard addition to *N*-tosyl-L-prolinal has been developed to deliver a variety of proline-derived vicinal amino alcohols in good to excellent yields with high diastereoselectivities. A similar selectivity was also obtained by using *N*-tosyl-D-prolinal. The methodology has been applied to the synthesis of medicinally important 3-hydroxy-2-phenylpiperidines.

Key words prolinol, Grignard addition, diastereoselectivity, aziridinium ion, natural products

L-Proline-derived vicinal amino alcohols constitute a large class of enantioenriched scaffolds that are widely used in organic synthesis and catalysis.[1] These 1,2-amino alcohols have received considerable interest because of their efficiency as ligands in organometallic chemistry.[2] They are also structural targets in several natural products with important biological properties such as dolastatine 10,[3] which is a highly cytotoxic antineoplastic agent for cancer chemotherapy, symplostatins 1 and 3,[4] which have tumor-selective cytotoxic properties, and malevamide D[5] and isodolastatin H,[5] which have highly cytotoxic properties. Various auristatins[6] derived from L-prolinol that are synthetic analogues of the antineoplastic natural product dolastatin 10,[3] are also important in the field of antibody drug conjugates.[7,8] The pseudotetrapeptide protioenol lactone **1a** (Figure 1) is reported to be a potential alternate substrate for the inhibition of human leukocyte elastase.[9] Quinoline-based L-prolinol derivative **1b** is reported to be a new class of disruptors of biofilm formation in *V. cholerae*.[10] They are also common structural motifs of pyrrolizidine alkaloids[11] and phenanthroindolizidine alkaloids such as tylophoridicine E (**1c**) (Figure 1).[12]

Functionalized chiral piperidines are found in wide range of alkaloids and synthetic compounds showing a diverse range of biological activities (Scheme 1). Among these, 2-phenylpiperidin-3-ol derivatives **3a** and **3b** are vital for high-affinity binding to the human NK-1 receptor because they act as precursors of non-peptidic NK-1 receptor antagonists such as (+)-L-733,060 (**5a**),[13] (+)-GR-205,171 (**5b**),[14] and (+)-CP-99,994 (**5c**)[15] possessing a *cis*-relationship between the phenyl and the ether or amine group on the piperidine ring (Scheme 1). Furthermore, 3-hydroxy pipecolic acids **4a** and **4b**[16] are also significant chiral building blocks for the synthesis of biologically active natural products such as tetrazomine (**8**), which exhibits

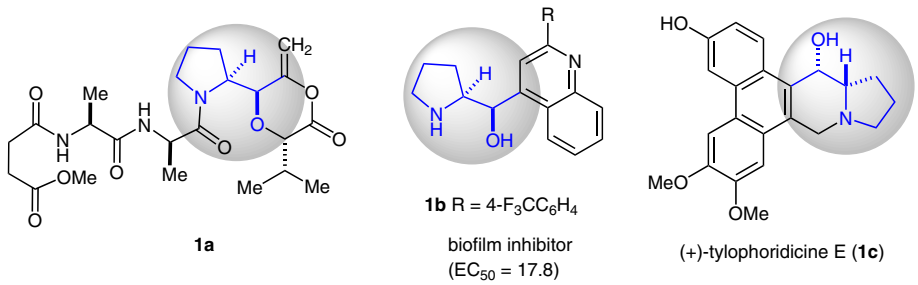
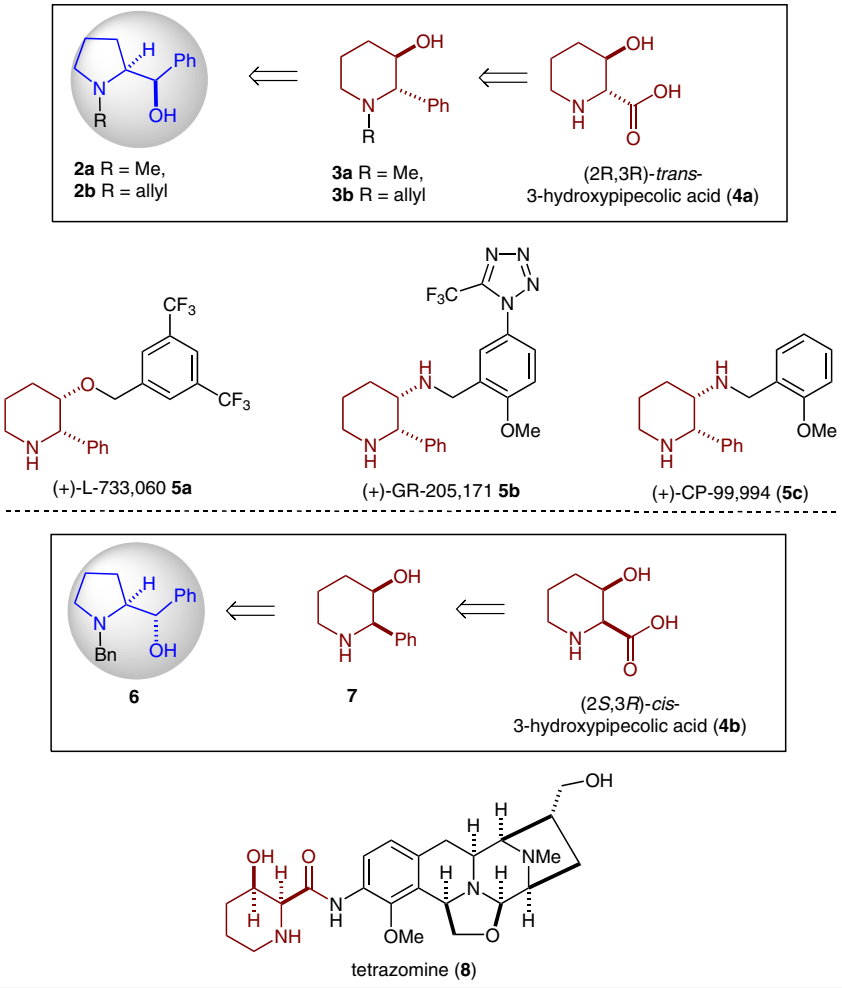


Figure 1 L-Prolinol derived enol lactone (**1a**), biofilm inhibitor (**1b**), and naturally occurring **1c**



Scheme 1 L-Prolinol **2a** and **2b**, and 2,3-disubstituted piperidines

antitumor and antibiotic properties.[17] Numerous synthetic strategies have been reported for the synthesis of compounds of type **3** and **4**.[16,18] One of the ways to synthesize 2-phenylpiperidin-3-ols **3a**, **3b**, and **7** is ring expansion of L-prolinol derivatives **2a**, **2b**, and **6**, respectively, via aziridinium ion intermediates,[19] which has been developed extensively by Lee,[19a] Cossy,[19b–f] and O'Brien[19g] (Scheme 1). Nevertheless, a highly stereoselective synthesis of L-prolinol derivatives **2a**, **2b**, and **6** remains a challenge to the synthetic community.

A survey of previous reports reveals that these prolinol derivatives are generally prepared by nucleophilic addition to N-protected prolinals such as **9a** and **9d**, bearing a benzyl or a carbalkoxy protecting group on the nitrogen atom (Figure 2). However, the addition of organometallic nucleophiles to aldehyde **9a**[20] usually results in lower diastereoselectivities. The same behavior is observed with aldehydes **9b**,[21] **9c**,[22] and **9d**.[23] However, good stereoselectivities can be achieved by means of double diastereoselection.[24] L-Prolinal **9e**, having an acid-sensitive *N*-trityl group, is reported to be good substrate for 1,2-addition of organometallic reagents.[25,10] Herein, we report the use of L-prolinal (**10**) and D-prolinal (*ent*-**10**), having an *N*-tosyl group[26] as a stable protecting group, in a highly diastereoselective Grignard addition, and we demonstrate the use of such an approach in organic synthesis.

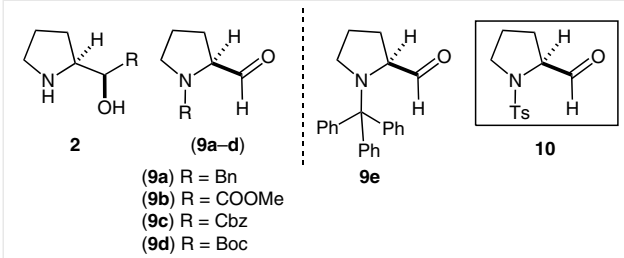
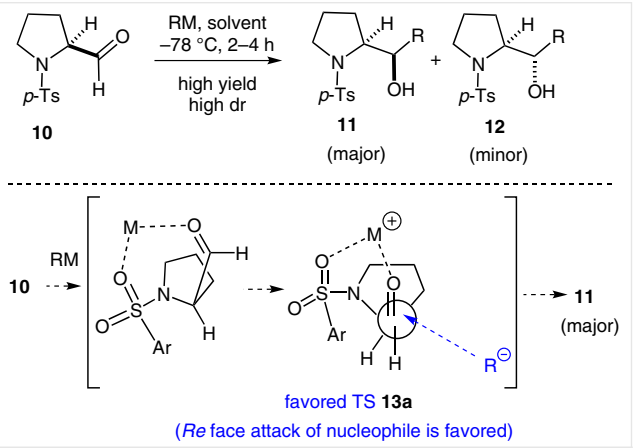


Figure 2 L-Prolinol (**2**) and N-protected L-prolinals **9a–e** and **10**

The proposed transition state of Grignard addition is shown in Scheme 2. We envisioned that the *p*-tolyl group of sulfonamide **10** adopts a position *trans* to the carbonyl moiety, thereby allowing metal coordination of the carbonyl oxygen and sulfonyl oxygen atoms (Scheme 2). In this situation, Grignard addition onto *N*-tosyl-L-prolinal (**10**) would follow a favored *Re*-face approach of nucleophile to afford L-prolinol **11** as the major product via **13a** as an organized transition state (TS) (Scheme 2).



Scheme 2 Proposed rationale for the observed diastereoselectivity

As proposed, at the outset, we carried out a large-scale synthesis of *N*-tosyl-L-prolinal (**10**) from L-proline in 87% overall yield starting from L-proline, as shown in Scheme 3. We found that direct reduction of **14c** afforded only 69% yield of *N*-tosyl-L-prolinal (**10**). Thus, we adopted a two-step synthesis of **10** from ester **14c** involving reduction of the ester using $LiAlH_4$ followed by Swern oxidation (Scheme 3).

With *N*-tosyl-L-prolinal **10** in hand, we then carried out PhMgBr addition to **10** in different solvents and at different temperatures (Table 1). After optimization (entries 1–8), we found that the reaction afforded **15a** as the major diastereomer in up to 92% yield with ca. 24:1 dr, when it was carried out in THF at –78 °C (entry 8). The X-ray crystal structure of **15a** unambiguously proved the formation of the major diastereoisomer (Figure 3).

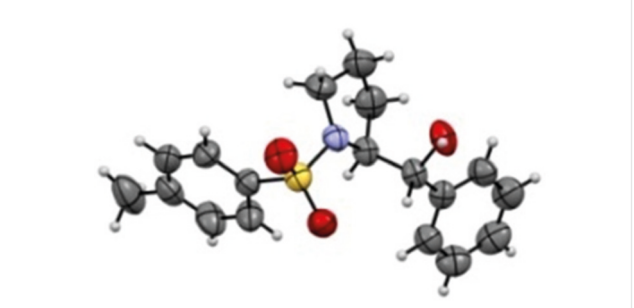
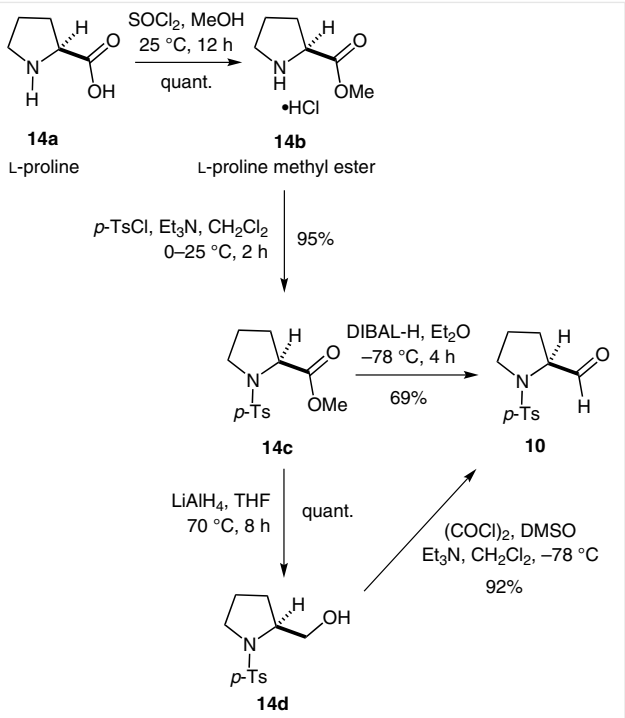
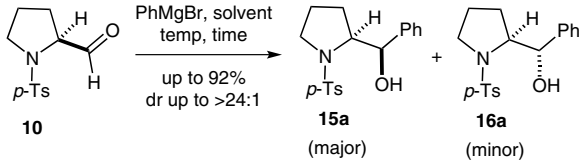


Figure 3 X-ray crystal structure of **15a** (CCDC 1405916)



Scheme 3 Synthesis of *N*-tosylprolinal **10**

Table 1 Optimization of PhMgBr Addition to **10**[a]

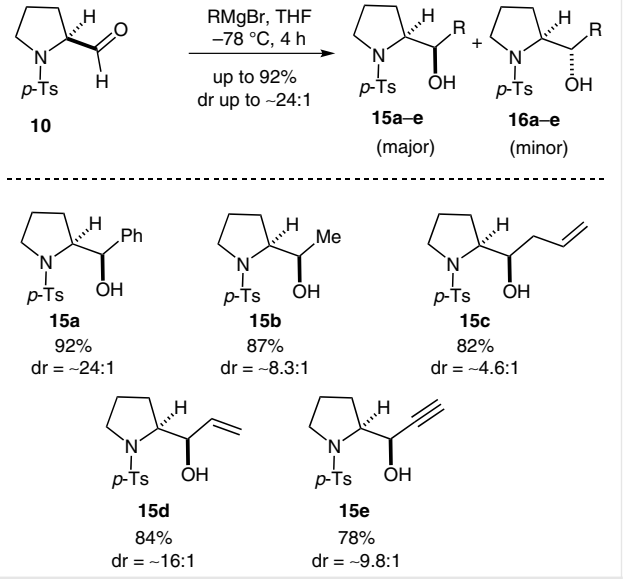


Entry	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	dr
1	THF	0	1	89	ca. 10:1
2	Et_2O	0	1	75	ca. 9:1
3	THF	–10	2	81	ca. 12:1
4	Et_2O	–10	2	70	ca. 10:1
5	THF	–30	3	82	ca. 15:1
6	THF	–50	3	84	ca. 16:1
7	THF	–70	3	86	ca. 20:1
8	THF	–78	4	92	ca. 24:1

[a] Reaction conditions: **10** (1.0 mmol), PhMgBr (1.3 equiv), THF (4 mL).
[b] Isolated yield after column chromatography.

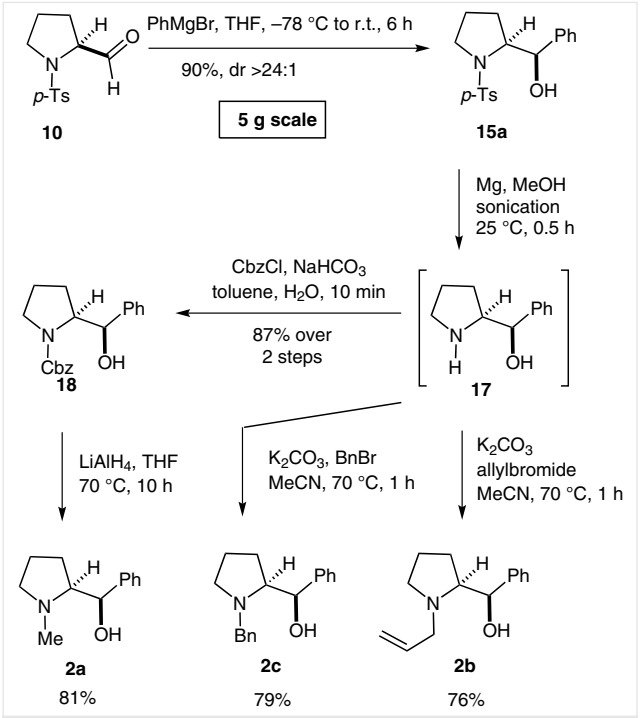
Interestingly, PhMgBr addition to *N*-tosyl-L-prolinal **10** could be carried out on a 5 g scale, which afforded major diastereomer **15a** with similar efficiency (90% yield with ca. 24:1 dr). We then tested Grignard reagent addition to *N*-tosyl-L-prolinal **10** (Scheme 4). To our delight, methyl and allylmagnesium bromide addition afforded products **15b** and **15c** in 82–87% yields with up to ca. 8.3:1 dr.[27,28] Vinylmag-

nesium bromide addition also furnished product **15d** in 84% isolated yield with ca. 16:1 dr. Importantly, products **15c** and **15d** could be used as starting material for the synthesis of a variety of pyrrolizidine alkaloids that are of immense biological importance.[29,30] Under the optimized conditions, ethynylmagnesium bromide also added to *N*-tosyl-L-prolinal **10** to afford product **15e** in 78% yield with ca. 9.8:1 dr. The latter can be utilized in organic synthesis by exploiting the reactivity of the acetylinic functionality.



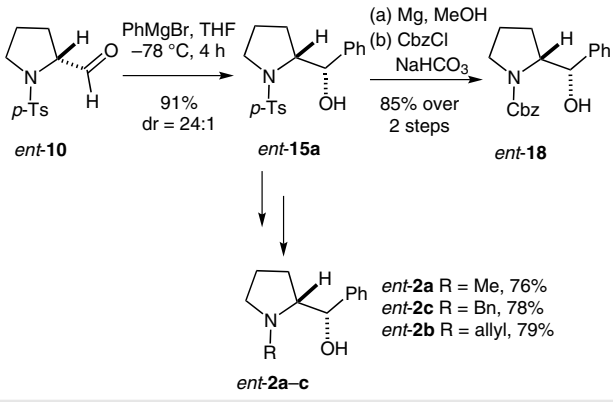
Scheme 4 Substrate scope of 1,2-addition. *Reagents and conditions*: **10** (1.0 mmol), Grignard reagent (1.3 equiv), THF (5 mL), –78 °C. Isolated yield after column chromatography.

To make the strategy more synthetically useful, we became interested in cleaving the *N*-tosyl protecting group of **15a**. To this end, **15a** was treated with Mg in MeOH to afford secondary aminoalcohol **17**, which was further reacted with CbzCl to afford **18** in 87% yield in two steps. Carbamate **18** was reduced in the presence of lithium aluminum hydride to afford aminoalcohol **2a** in 81% yield (Scheme 5). In another sequence, crude amino alcohol **17** was reacted directly with alkylhalides in the presence of K_2CO_3 in acetonitrile to afford aminoalcohols **2b** and **2c** in 76 and 79% yield, respectively. Interestingly, (2*S*,3*R*)-2-phenyl-3-hydroxypiperidine is known to be an intermediate for the synthesis of (2*R*,3*R*)-*trans*-3-hydroxypipecolic acid **4a** (Scheme 1) as reported by Cossy et al.[19c]



Scheme 5 Stereoselective syntheses of proline-based vicinal aminoalcohols **2a–c**

Furthermore, to access enantiomeric pairs of proline-based vicinal aminoalcohols **2a–c**, we synthesized *N*-tosyl-D-prolinal *ent*-**10** from D-proline by following the route presented in Scheme 3 (see the Supporting Information for details). As expected, phenylmagnesium addition to *N*-tosyl-D-prolinal *ent*-**10** afforded *ent*-**15a** with similar efficiency (Scheme 6). Vicinal aminoalcohol *ent*-**15a** was further elaborated to access *ent*-**18** and *ent*-**2a–c** with similar efficiencies (see the Supporting Information for details).



Scheme 6 Stereoselective synthesis of *ent*-**2a–c** from D-proline

In conclusion, *N*-tosyl-L-prolinal **10**[31] has been identified as a good substrate for 1,2-addition of Grignard reagents to afford a variety of vicinal amino alcohols **15a**–**c**. The *N*-tosyl group of **15a** can be removed efficiently by using Mg in MeOH at room temperature to afford *N*-alkyl aminoalcohols **2a**–**c**. We have also synthesized *ent*-**2a**–**c** with similar efficiency from *N*-tosyl-D-prolinal *ent*-**10**. These substrates are important precursors for the synthesis of 2,3-disubstituted piperidines. Further studies to extend the application of this methodology to the synthesis of naturally occurring alkaloids are currently under active investigations in our laboratory.

Acknowledgment

A.B. thanks the SERB, Department of Science and Technology (DST), India, for generous funding. We also thank the BRNS, Department of Atomic Energy (DAE) for a research grant through a Young Scientist Research Award (YSRA). S.C. thanks the UGC for a senior Research Fellowship (SRF). A.P. and S.G. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for JRF and SRF, respectively. We sincerely thank the Department of Chemistry, IISER Bhopal for infrastructure.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560802.

References and Notes

(1) (a) Halskov, K. S.; Kniep, F.; Lauridsen, V. H.; Iversen, E. H.; Donslund, B. S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2015**, *137*, 1685. (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.

(2) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Trost, B. M.; Shin, S.; Sclafani, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602. (c) Trost, B. M.; Bartlett, M. J. *Acc. Chem. Res.* **2015**, *48*, 688; and references therein.

(3) For the isolation of dolastatin 10, see: (a) Luesch, H.; Moore, R. E.; Paul, V. J.; Mooberry, S. L.; Corbett, T. H. *J. Nat. Prod.* **2001**, *64*, 907. (b) Salvador-Reyes, L. A.; Engene, N.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2015**, *78*, 486.

(4) For the isolation of symplostatin 1, see: Harrigan, G. G.; Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Nagle, D. G.; Paul, V. J.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Nat. Prod.* **1998**, *61*, 1075.

(5) For the isolation of malevamide D, see: Horgen, F. D.; Kazmierski, E. B.; Westenburg, H. E.; Yoshida, W. Y.; Scheuer, P. J. *J. Nat. Prod.* **2002**, *65*, 487.

(6) For auristatins, see: Pettit, G. R.; Hogan, F.; Toms, S. *J. Nat. Prod.* **2011**, *74*, 962.

(7) Maderna, A.; Doroski, M.; Subramanyam, C.; Porte, A.; Leverett, C. A.; Vetelino, B. C.; Chen, Z.; Risley, H.; Parris, K.; Pandit, J.; Varghese, A. H.; Shanker, S.; Song, C.; Sukura, S. C. K.; Farley, K. A.; Wagenaar, M. M.; Shapiro, M. J.; Musto, S.; Lam, M.-H.; Loganzo, F.; O'Donnell, C. J. *J. Med. Chem.* **2014**, *57*, 10527.

(8) (a) Pettit, G. R.; Anderson, C. R.; Gapud, E. J.; Jung, M. K.; Knight, J. C.; Hamel, E.; Pettit, R. K. *J. Nat. Prod.* **2005**, *68*, 1191. (b) For a review, see: Maderna, A.; Leverett, C. A. *Mol. Pharmaceutics* **2015**, *12*, 1798.

(9) For the synthesis of **1a**, see: Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624.

(10) León, B.; Fong, J. C. N.; Peach, K. C.; Wong, W. R.; Yildiz, F. H.; Linington, R. G. *Org. Lett.* **2013**, *15*, 1234.

(11) (a) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741. (b) Snider, B. B.; Gao, X. *Org. Lett.* **2005**, *7*, 4419. (c) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861. (d) El-Naggar, M.; Piggott, A. M.; Capon, R. J. *Org. Lett.* **2008**, *10*, 4247. (e) Zhang, H.; Zhang, C.-R.; Zhu, K.-K.; Gao, A.-H.; Luo, C.; Li, J.; Yue, J.-M. *Org. Lett.* **2013**, *15*, 120.

(12) For tylophoridicine E, see: Stoye, A.; Peez, T. E.; Opatz, T. *J. Nat. Prod.* **2013**, *76*, 275; and references cited.

(13) (a) Liu, L.-X.; Ruan, Y.-P.; Guo, Z.-Q.; Huang, P.-Q. *J. Org. Chem.* **2004**, *69*, 6001. (b) Tsai, M.-R.; Chen, B.-F.; Cheng, C.-C.; Chang, N.-C. *J. Org. Chem.* **2005**, *70*, 1780.

(14) For (+)-GR-205,171 (**5b**), see: Fabio, R. D.; Griffante, C.; Alvaro, G.; Pentassuglia, G.; Pizzi, D. A.; Donati, D.; Rossi, T.; Guercio, G.; Mattioli, M.; Cimarosti, Z.; Marchioro, C.; Provera, S.; Zonzini, L.; Montanari, D.; Melotto, S.; Gerrard, P. A.; Trist, D. G.; Ratti, E.; Corsi, M. *J. Med. Chem.* **2009**, *52*, 3238.

(15) Clavez, O.; Langlois, N. *Tetrahedron Lett.* **1999**, *40*, 7099.

(16) For 3-hydroxypipecolinic acid, see: (a) Kumar, P.; Bodas, M. S. *J. Org. Chem.* **2005**, *70*, 360. (b) Liang, N.; Datta, A. *J. Org. Chem.* **2005**, *70*, 10182. (c) Kalamkar, N. B.; Kasture, V. M.; Dhavale, D. D. *J. Org. Chem.* **2008**, *73*, 3619. (d) Chiou, W.-H.; Lin, G.-H.; Liang, C.-W. *J. Org. Chem.* **2010**, *75*, 1748. (e) Kokatla, H. P.; Lahiri, R.; Kancharla, P. K.; Doddi, V. R.; Vankar, Y. D. *J. Org. Chem.* **2010**, *75*, 4608.

(17) (a) Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **2001**, *66*, 3133. (b) Scott, J. D.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2951. (c) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148.

(18) (a) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517. (b) Kise, N.; Ohya, K.; Arimoto, K.; Yamashita, Y.; Hirano, Y.; Ono, T.; Ueda, N. *J. Org. Chem.* **2004**, *69*, 7710. (c) Liu, R.-H.; Fang, K.; Wang, B.; Xu, M.-H.; Lin, G.-Q. *J. Org. Chem.* **2008**, *73*, 3307. (d) Huy, P. H.; Koskinen, A. M. P. *Org. Lett.* **2013**, *15*, 5178.

(19) (a) Lee, J.; Hoang, T.; Lewis, S.; Weissman, S. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 6223. (b) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693. (c) Métro, T.-X.; Appenzeller, J.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2006**, *8*, 3509. (d) Cochi, A.; Burger, B.; Navarro, C.; Pardo, D. G.; Cossy, J.; Zhao, Y.; Cohen, T. *Synlett* **2009**, 2157. (e) Cochi, A.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2011**, *13*, 4442. (f) Rioton, S.; Orliac, A.; Antoun, Z.; Bidault, R.; Pardo, D. G.; Cossy, J. *Org. Lett.* **2015**, *17*, 2916. (g) Bilke, J. L.; Moore, S. P.; O'Brien, P.; Gilday, J. *Org. Lett.* **2009**, *11*, 1935.

(20) (a) Andrés, J. M.; Pedrosa, R.; Pérez, A.; Pérez-Encabo, A. *Tetrahedron* **2001**, *57*, 8521. (b) Ma, D.; Pan, Q.; Han, F. *Tetrahedron Lett.* **2002**, *43*, 9401.

(21) (a) Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Heterocycles* **1986**, *24*, 1045. (b) Reed, P. E.; Katzenellenbogen, J. A. *J. Org. Chem.* **1991**, *56*, 2624. (c) Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5469. (d) Mahboobi, S.; Popp, A.; Burgemeister, T.; Schollmeyer, D. *Tetrahedron: Asymmetry* **1998**, *9*, 2369; and references cited therein.

(22) (a) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64*, 1410. (b) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316.

(23) (a) Soai, K.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1986**, 412. (b) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (c) Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* **2002**, *43*, 7503.

(24) (a) Funabiki, K.; Shibata, A.; Iwata, H.; Hatano, K.; Kubota, Y.; Komura, K.; Ebihara, M.; Matsui, M. *J. Org. Chem.* **2008**, *73*, 4694. (b) Marquez, F.; Montoro, R.; Llebaria, A.; Lago, E.; Molins, E.; Delgado, A. *J. Org. Chem.* **2002**, *67*, 308. (c) Pettit, G. R.; Grealish, M. P. *J. Org. Chem.* **2001**, *66*, 8640. (d) Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkóczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287. (e) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (f) Soai, K.; Ookawa, A. *Chem. Commun.* **1986**, 412.

(25) (a) Bejjani, J.; Chemla, F.; Audouin, M. *J. Org. Chem.* **2003**, *68*, 9747. (b) For use of **9e** in total synthesis, see: Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562.

(26) MeMgBr addition to 4-(*S*)-TBS-protected-*N*-tosyl-D-prolinal afforded the products in 1.32:1 dr, see: Remuzon, P.; Bouzard, D.; Guiol, C.; Jacquet, J.-P. *J. Med. Chem.* **1992**, *35*, 2898.

(27) The diastereoselectivities in case of allylmagnesium halide addition to *N*-trityl-L-prolinal (**9e**) afforded the products with <2:1 dr [see ref. 25a].

(28) **Addition of Grignard Reagents to the Aldehyde; General Procedure:** To a stirred solution of crude **10** (253 mg, 1.0 mmol, 1.0 equiv) in anhydrous THF at –78 °C was added RMgBr (1.3 mmol, 1.3 equiv) slowly over a period of 5 min, and stirring was continued for 4 h. The reaction was quenched with sat. aq NH_4Cl (2 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude mixture was purified by column chromatography to afford the desired product **15**.

(*R*)-Phenyl [(*S*)-1-Tosylpyrrolidin-2-yl] methanol [(–)-15a)]: White crystalline solid; R_f 0.51 (EtOAc–hexane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 8.25 Hz, 2 H), 7.38 (m, 2 H), 7.29–7.32 (m, 4 H), 7.20–7.24 (m, 1 H), 5.22 (m, 1 H), 3.76–3.80 (m, 1 H), 3.29–3.35 (m, 2 H), 3.21–3.27 (m, 1 H), 2.39 (s, 3 H), 1.77–1.86 (m, 1 H), 1.51–1.60 (m, 1 H), 1.14–1.32 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 140.6, 134.0, 129.9, 128.2, 127.7, 127.4, 126.2, 75.0, 66.1, 50.6, 25.7, 24.4, 21.6. IR (film): 3499, 3120, 2980, 1795, 1654, 1560, 1510, 1499, 1475, 1460, 930, 750 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{18}H_{22}NO_3S]^+$: 332.1315; found: 332.1333. $[\alpha]_D^{20.7}$ –156.4 (*c* = 0.042, MeOH).

(*R*)-1-[(*S*)-1-Tosylpyrrolidin-2-yl]ethanol [(–)-15b)]: Colorless oil; R_f 0.40 (EtOAc–hexane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.12 Hz, 2 H), 7.29 (d, *J* = 8.01 Hz, 2 H), 4.15 (m, 1 H), 3.44–3.48 (m, 1 H), 3.27–3.37 (m, 2 H), 2.67 (br, 1 H), 2.39 (s, 3 H), 1.67–1.87 (m, 2 H), 1.50–1.62 (m, 1 H), 1.22–1.31 (m, 1 H), 1.12 (d, *J* = 6.45 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 134.1, 129.8, 127.6, 69.0, 65.8, 50.5, 26.1, 24.5, 21.5, 18.4. IR (film): 3503, 1654, 1561, 1402, 1331, 1159, 1059, 983, 662 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{13}H_{20}NO_3S]^+$: 270.1158; found: 270.1181. $[\alpha]_D^{22.2}$ –64.6 (*c* = 0.47, CH_2Cl_2).

(*R*)-1-[(*S*)-1-Tosylpyrrolidin-2-yl]but-3-en-1-ol [(–)-15c)]: Colorless oil; R_f 0.43 (EtOAc–hexane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.23 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.80–5.90 (m, 1 H), 5.07–5.13 (m, 2 H), 4.05–4.09 (m, 1 H), 3.49–3.53 (m, 1 H), 3.26–3.38 (m, 2 H), 2.39 (s, 3 H), 2.14–2.26 (m, 2 H), 1.83–1.92 (m, 1 H), 1.70–1.77 (m, 1 H), 1.50–1.58 (m, 1 H), 1.22–1.31 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 134.8, 134.1, 129.8, 127.7, 127.6, 117.4, 72.2, 64.4, 50.3, 37.8, 25.8, 24.6, 21.5. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{22}\ NO_3S]^+$: 296.1315; found: 296.1336. $[\alpha]_D^{22.8}$ –90.3 (*c* = 0.43, CH_2Cl_2).

(*R*)-1-[(*S*)-1-Tosylpyrrolidin-2-yl]prop-2-en-1-ol [(–)-15d)]: Colorless gel; R_f 0.49 (EtOAc–hexane, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.71 (m, 2 H), 7.30 (d, *J* = 7.95 Hz, 2 H), 5.79–5.86 (m, 1 H), 5.30–5.36 (dt, *J* = 17.27, 1.58 Hz, 1 H), 5.17–5.21 (dt, *J* = 10.56, 1.55 Hz, 1 H), 4.46 (br, 1 H), 3.59–3.63 (m, 1 H), 3.26–3.39 (m, 2 H), 2.96 (d, *J* = 4.61 Hz, 1 H), 2.4 (s, 3 H), 1.70–1.83 (m, 2 H), 1.53–1.62 (m, 1 H), 1.22–1.30 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 136.4, 134.0, 129.8, 127.6, 116.8, 74.5, 64.6, 50.6, 26.7, 24.5, 21.5; IR (film): 3584, 3099, 2981, 2059, 1870, 1655, 1544, 1474, 1154, 933 cm^{-1}. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $[C_{14}H_{19}NO_3S]^+$: 282.1158; found: 282.1178. $[\alpha]_D^{27.0}$ –102.24 (*c* = 0.0352, MeOH).

(*R*)-1-[(*S*)-1-Tosylpyrrolidin-2-yl]prop-2-yn-1-ol [(–)-15e)]: White crystalline solid; R_f 0.47 (EtOAc–hexane, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.07 Hz, 2 H), 7.31 (d, *J* = 7.97 Hz, 2 H), 4.67 (br, 1 H), 3.67–3.70 (m, 1 H), 3.45–3.50 (m, 1 H), 3.42 (br s, 1 H), 3.29–3.34 (m, 1 H), 2.43 (d, *J* = 1.96 Hz, 1 H), 2.42 (s, 3 H), 1.96–2.0 (m, 1 H), 1.85–1.93 (m, 1 H), 1.73–1.80 (m, 1 H), 1.70 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 133.9, 129.9, 127.6, 81.8, 74.4, 65.3, 64.3, 50.9, 27.9, 24.5, 21.6; IR (film): 3500, 3110, 2270, 1460, 1420, 1339, 1158, 1094 cm^{-1}. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $[C_{14}H_{17}NO_3S$ + Na]$^+$: 302.0821; found: 302.0845. $[\alpha]_D^{20.7}$ –105 (*c* = 0.042, MeOH).

(29) (a) Tasso, B.; Novelli, F.; Sparatore, F.; Fasoli, F.; Gotti, C. *J. Nat. Prod.* **2013**, *76*, 727. (b) El-Naggar, M.; Piggott, A. M.; Capon, R. J. *Org. Lett.* **2008**, *10*, 4247. (c) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861. (d) Snider, B. B.; Gao, X. *Org. Lett.* **2005**, *7*, 4419. (e) Roche, C.; Delair, P.; Greene, A. E. *Org. Lett.* **2003**, *5*, 1741.

(30) (a) Pyrrolizidine alkaloids, see: Robertson, J.; Stevens, K. *Nat. Prod. Rep.* **2014**, *31*, 1721; and references cited. (b) For a review on indolizidine alkaloids, see: Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139; and references cited therein.

(31) For the use of *N*-tosyl-l-prolinal (**10**) in organic synthesis, see: Zhang, Z.; Wang, F.; Mu, X.; Chen, P.; Liu, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 7549.