

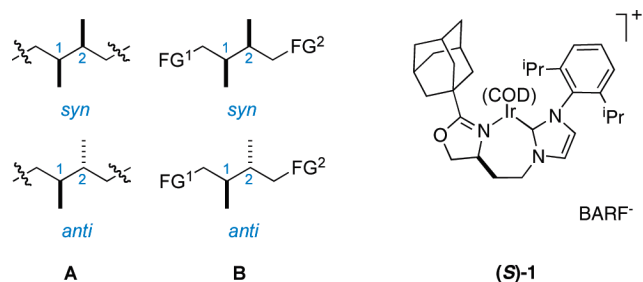
Synthesis of Vicinal Dimethyl Chirons by Asymmetric Hydrogenation of Trisubstituted Alkenes

Jian Zhao and Kevin Burgess*

Department of Chemistry, Texas A&M University, College Station, Texas 77840

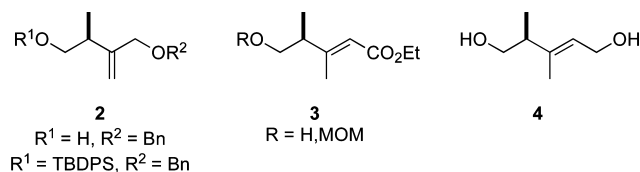
Received July 2, 2009; E-mail: burgess@tamu.edu

Chiral acyclic molecules with 1,2-dimethyl substitution patterns **A** are observed in some natural products.^{1–4} Synthetic methodologies to obtain these fragments are far from refined; older methods feature conjugate additions to α,β -unsaturated carbonyl systems equipped with chiral auxiliaries,⁵ and newer ones are based on asymmetric catalysts to deliver methyl Grignards to systems with γ -chiral centers.⁶ The latter approach will probably emerge as the most general and practical for many applications, though it is relatively untested now. Other routes are based on asymmetric desymmetrization of *meso*-1,2-dimethyl substrates,^{7,8} conjugate additions and enolate quenching,⁹ or modification of readily accessible chiral building blocks, but these lack generality with respect to either the substitution patterns that can be accessed or the stereoisomers that can be made. Here we demonstrate that useful chirons **B** can be obtained via asymmetric hydrogenation using the chiral carbene oxazoline catalyst **1**.^{10,11} The hydrogenation step does not generate any byproduct, requires minimal purification of the products, operates at ambient temperature, and should be amenable to scale-up.



Unlike many studies in asymmetric catalysis, the goal of this work was *not* to identify a range of substrates that could be hydrogenated with good stereoselectivities. Instead, the objective was to find *two* substrates that could be used to generate type **B** chirons, one for the *syn* and one for the *anti* form. To do this, substrates **2–8** were prepared from the Roche ester, and a series of hydrogenation experiments were performed to determine which combination of alkene substitution pattern and functional and protecting groups paired optimally with either **(S)-** or **(R)-1** to maximize the stereoselectivities. Full data for these experiments are given in the Supporting Information, but the important conclusion is that substrates **5** and **7** were the best identified (Figure 1).

All the hydrogenations shown in Figure 1 (and nearly all the reductions of **2–4**) were *catalyst* controlled. However, the vector that the substrates contributed to the stereoselectivities was significant and predictable. Thus steric factors seem to reinforce the matched selectivities observed for the homoallylic silyl ethers **5** and **7** while coordination effects are significant for the homoallylic alcohol **7** (Figure 1c and d).



Scheme 1 shows two illustrative applications of the methodology featured here. The first is a total synthesis of the (–)-lasiol, a

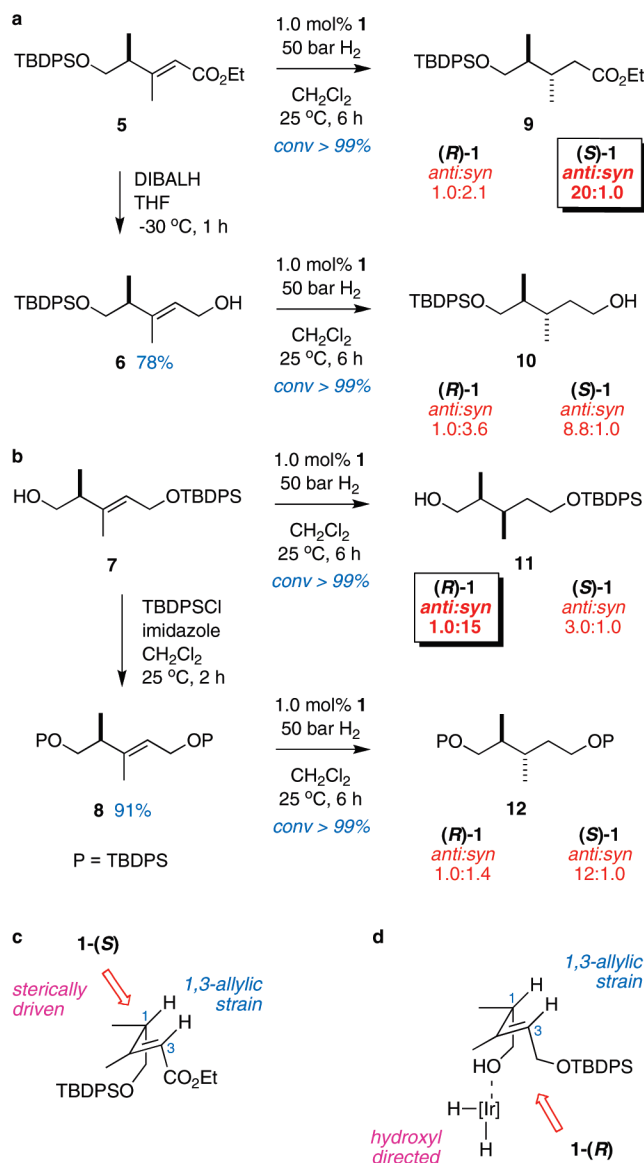
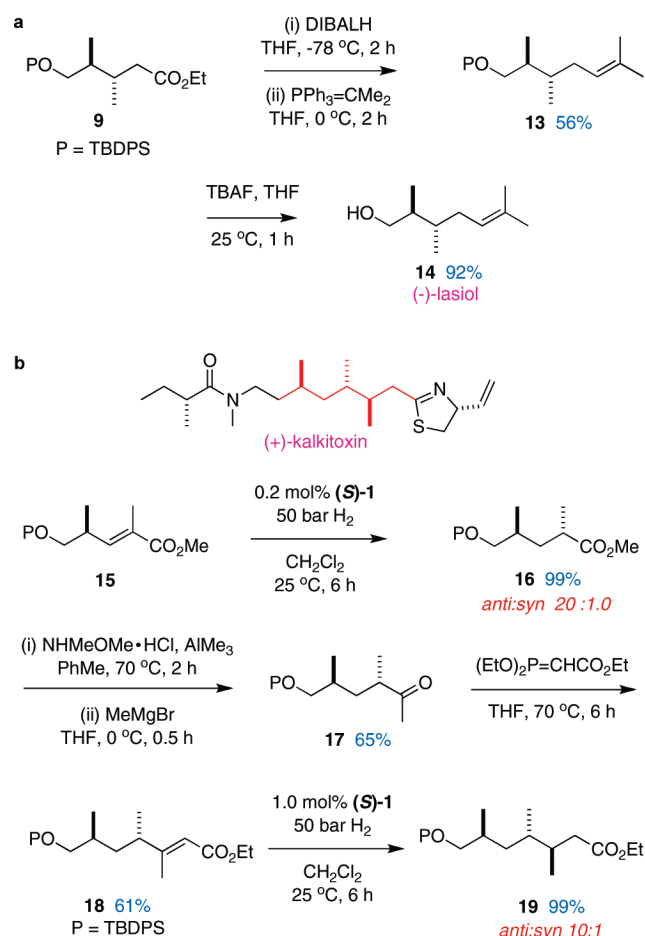


Figure 1. Key data for identification of substrates to afford the chirons **B**: *anti* (a); *syn* (b). Models to explain the substrate vector in these catalyst controlled reactions for homoallylic (c) silyl ethers and (d) alcohols.

Scheme 1^a

^a (a) Total synthesis of (–)-lasiol. (b) Synthesis of the 1,3,4-stereochemical triad of (+)-kalkitoxin.

substance isolated from male *Lasius meridionalis* ants, in three steps from the hydrogenation product **9**.^{6,12,13} The second is a synthesis of the central asymmetric region of the neurotoxin (+)-kalkitoxin.¹⁴ This began with another of our hydrogenation methodologies, which also uses catalyst **1**, to generate the *anti*-1,3-dimethyl chirons **16**.^{15–17} This was elaborated to the α,β -unsaturated ester **18**, which then was hydrogenated with catalyst **1** to afford compound **19** with a good diastereomeric excess. Palladium-mediated hydrogenations, and conjugate additions of hydride, have been reported for very similar substrates but gave disappointing selectivities.¹⁸ Otherwise, all previous syntheses of (+)-kalkitoxin featured conjugate additions to systems functionalized with a chiral auxiliary.^{14,18,19}

Chiral analogues^{20,21} of Crabtree's catalyst²² are almost uniquely suitable for asymmetric hydrogenations of optically active substrates

with no obvious coordinating groups.²³ As in the syntheses of 1,3-dimethyl-,^{15–17} 1,3-hydroxymethyl-,²⁴ and 1,2-hydroxymethyl-²⁵ synthons, the key issue tends to be enhancement of *catalyst control* by adjusting the *substrate vector* by changing peripheral masking or functional groups. Throughout, the range of substrates that can be processed with high selectivities is less important than finding the right situation to prepare privileged chirons that are ubiquitously useful in syntheses of optically active molecules. The Roche ester and catalyst **1** are available as both optical antipodes so the methodology described here achieves this for α,ω -functionalized 1,2-dimethyl chirons.

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Supporting Information Available: Experimental data for the new compounds reported. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Nakamura, S.; Kikuchi, F.; Hashimoto, S. *Tetrahedron: Asymmetry* **2008**, *19*, 1059–1067.
- (2) Takeda, Y.; Shi, J.; Oikawa, M.; Sasaki, M. *Org. Lett.* **2008**, *10*, 1013–1016.
- (3) Rizvi, S. A. I.; Varshney, S. C.; Abbas, S. L.; Jahan, N. *Phytochemistry* **1972**, *11*, 1823–6.
- (4) Hwu, J. R.; Hsu, M.-H.; Huang, R. C. C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1884–1888.
- (5) Coleman, R. S.; Gurrall, S. R.; Mitra, S.; Rao, A. *J. Org. Chem.* **2005**, *70*, 8932–8941.
- (6) van Zijl, A. W.; Szymanski, W.; Lopez, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 6994–7002.
- (7) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543.
- (8) Johnson, J. B.; Bercot, E. A.; Williams, C. M.; Rovis, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4514–4518.
- (9) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491.
- (10) Perry, M. C.; Cui, X.; Powell, M. T.; Hou, D.-R.; Reibenspies, J. H.; Burgess, K. *J. Am. Chem. Soc.* **2003**, *125*, 113–123.
- (11) Powell, M. T.; Hou, D.-R.; Perry, M. C.; Cui, X.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 8878–8879.
- (12) Vasil'ev, A. A.; Vielhauer, O.; Engman, L.; Pietzsch, M.; Serebryakov, E. P. *Russ. Chem. Bull.* **2002**, *51*, 481–487.
- (13) Vasil'ev, A. A.; Engman, L.; Serebryakov, E. P. *Mendeleev Commun.* **2000**, 101–103.
- (14) Yokokawa, F.; Asano, T.; Okino, T.; Gerwick, W. H.; Shioiri, T. *Tetrahedron* **2004**, *60*, 6859–6880.
- (15) Zhou, J.; Zhu, Y.; Burgess, K. *Org. Lett.* **2007**, *9*, 1391–1393.
- (16) Zhou, J.; Ogle, J. W.; Fan, Y.; Banphavichit, V.; Zhu, Y.; Burgess, K. *Chem.-Eur. J.* **2007**, *13*, 7162–7170.
- (17) Zhou, J.; Burgess, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1129–1131.
- (18) White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092–2102.
- (19) LePage, K. T.; Goeger, D.; Yokokawa, F.; Asano, T.; Shioiri, T.; Gerwick, W. H.; Murray, T. F. *Toxicol. Lett.* **2005**, *158*, 133–9.
- (20) Lightfoot, A.; Schnider, P.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2897–9.
- (21) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.
- (22) Crabtree, R. H. *Acc. Chem. Res.* **1979**, *12*, 331–337.
- (23) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296.
- (24) Zhu, Y.; Burgess, K. *J. Am. Chem. Soc.* **2008**, *130*, 8894–8895.
- (25) Zhao, J.; Burgess, K. *Org. Lett.* **2008**, *11*, 2053–2056.

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