

Published in final edited form as:

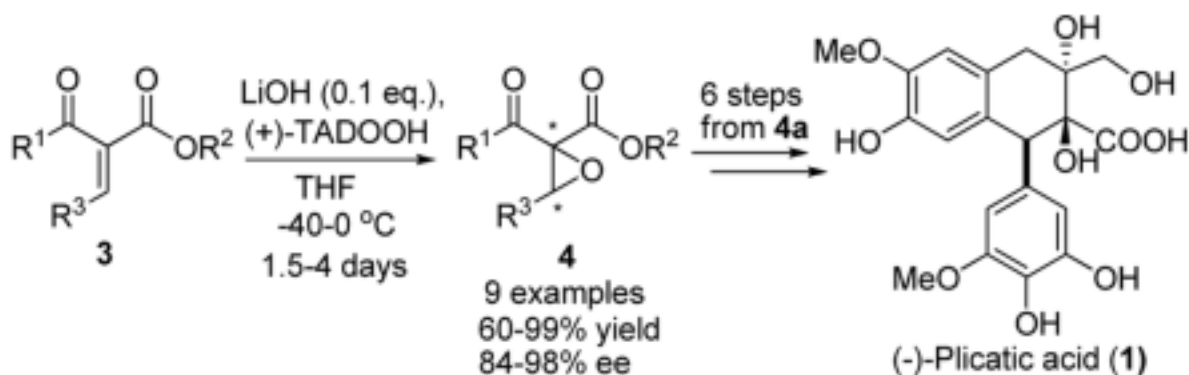
*J Am Chem Soc.* 2009 August 5; 131(30): 10384–10385. doi:10.1021/ja9039407.

## Asymmetric Total Synthesis of (–)-Plicatic Acid via a Highly Enantioselective and Diastereoselective Nucleophilic Epoxidation of Acyclic Trisubstituted Olefins

Bing-Feng Sun, Ran Hong, Yan-Biao Kang, and Li Deng\*

Department of Chemistry, Brandeis University, 415 South St., Waltham, MA 02454-9110, USA

### Abstract



The first total synthesis of (–)-plicatic acid has been achieved by a concise and enantioselective route. In this synthesis, a conceptually new strategy featuring an asymmetric epoxidation-intramolecular epoxy-ring-opening Friedel-Crafts reaction sequence was developed for the stereoselective construction of the 2,7'-cyclo lignane skeleton bearing contiguous quaternary-quaternary-tertiary stereocenters. The implementation of this strategy was enabled by the development of a modified protocol for the Seebach epoxidation with TADOOH, which affords an unprecedented, highly enantioselective and diastereoselective epoxidation with a range of  $\alpha$ -carbonyl- $\beta$ -substituted acrylates **3**.

Plicatic acid has been identified as the causative agent of occupational asthma.<sup>1a-d</sup> Furthermore, plicatic acid has been shown to cause inflammatory and allergic reactions, including increased concentrations of immunoglobulins, histamine, leukotrienes, eosinophil and T-cell levels in the blood.<sup>1e-g</sup> Plicatic acid was isolated in 1959 by MacLean and co-workers from western red cedar (*Thuja plicata*).<sup>2a</sup> The relative and absolute configurations were assigned by X-ray crystallographic analysis and optical rotatory dispersion (ORD) studies, respectively.<sup>2b-c</sup> A concise total synthesis of this natural product could establish a means for access to analogues that could be valuable for biomedical studies aiming to elucidate the molecular mechanism underlying the biological activities of plicatic acid. Our interest in the total synthesis of plicatic acid is also motivated by the synthetic challenges imposed by its

E-mail: deng@brandeis.edu.

 Supporting Information Available: Experimental procedures and characterization data for all new compounds, chiral chromatographic analyses for **2a**, **4b-i**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

rather unusual lignan skeleton that is densely functionalized and bears a motif of contiguous quaternary-quaternary-tertiary stereocenters.<sup>3</sup>

As illustrated in Scheme 1, our retrosynthetic analysis presents a new strategy to create the 2,7'-cyclo lignane skeleton in order to achieve a stereoselective construction of the B ring bearing the contiguous quaternary-quaternary-tertiary stereocenters. We envisaged that the key intermediate,  $\alpha$ -hydroxy ketone **2a**, could be synthesized from olefin *E*-**3a** by an asymmetric epoxidation followed by an intramolecular Friedel-Crafts reaction to open the epoxide ring in **4a**. The stereoselective construction of the quaternary center at C(8) is to be accomplished via a C(8') hydroxy-directed nucleophilic addition to the ketone in **2a**.

The implementation of this synthetic strategy, however, required us to fill a significant gap in the current repertoire of asymmetric epoxidations, namely the lack of a highly diastereoselective and enantioselective nucleophilic epoxidation of trisubstituted electron-deficient olefins such as the  $\alpha$ -carbonyl- $\beta$ -substituted acrylates **3a**.<sup>4</sup> Accordingly, we first focused on the establishment of a highly enantioselective and diastereoselective asymmetric epoxidation of  $\alpha$ -carbonyl- $\beta$ -substituted acrylate **3b**. Through considerable experimentation, we discovered that Seebach's nucleophilic epoxidation with TADOOH as the terminal oxidant<sup>5</sup> could be promoted by a catalytic amount of LiOH, which, interestingly, proceeded smoothly in THF at 0 °C to transform **3b** into epoxide **4b** as a single diastereomer<sup>4f</sup> in 92% ee and 98% yield (**4b**, Table 1). Significantly, the scope of this modified Seebach epoxidation could be extended to a variety of acrylates (**3b-i**) bearing either an  $\alpha$ -alkoxycarbonyl or an  $\alpha$ -ketone group (**4b-i**, Table 1).

We next turned our attention to the application of this new protocol to the asymmetric epoxidation of the olefin intermediate *E*-**3a** (Scheme 2). Benzylation of eugenol (**5**) followed by oxidative cleavage of the olefin afforded aldehyde **7**, which was transformed into  $\beta$ -ketoester **8** in 92% yield using Roskamp's protocol.<sup>6</sup> The Knoevenagel condensation of **8** and **9** furnished olefin **3a** as a 5:3 *E/Z* mixture, which could be separated by chromatography. The *Z*-**3a** was found to isomerize to *E*-**3a** in the presence of pyridine in refluxing benzene. Thus, *E*-**3a** could be obtained in 80% overall yield from one cycle of Knoevenagel condensation-isomerization. Gratifyingly, the key LiOH-catalyzed asymmetric epoxidation of *E*-**3a** - with (*S,S*)-TADOOH generated epoxide **4a** in 98% ee and 83% yield. A screening of various Lewis acids revealed TfOH as the optimal catalyst, which effectively promoted the Friedel-Crafts reaction in a loading of 4.0 mol %. Thus,  $\alpha$ -hydroxy ketone **2** was obtained as a 4:1 diastereomeric mixture in favor of the desired diastereomer **2a** (Scheme 2), which was isolated in 70% yield by silica gel chromatography. Notably, the Friedel-Crafts reaction also proceeded in a highly regioselective manner as the other regioisomer was not detected.

With  $\alpha$ -hydroxy ketone **2a** in hand, a stereoselective addition of the hydroxymethyl group to the ketone in **2a** stood as the final obstacle for the construction of the full carbon skeleton of plicatic acid. Our initial attempts to realize a C8'-OH-directed addition with a metal reagent such as vinylmagnesium bromide,<sup>7a</sup> vinyl-lithium,<sup>7b</sup> vinylcesium chloride<sup>7c</sup> or benzyloxymethyl magnesium chloride<sup>7d</sup> were unsuccessful. These basic metal reagents only deprotonated the benzylic proton at C7 in **2a**, thereby leading to enolization, rather than nucleophilic addition to the C8-carbonyl group. We then explored an alternative strategy to execute a formal stereospecific addition of a hydroxymethyl group to the ketone with the C-C bond formation implemented under nearly neutral conditions (Scheme 2). Thus, the C8'-OH in **2a** was first silylated with ClSi(Me)<sub>2</sub>CH<sub>2</sub>Br to form **10** in 75% isolated yield (94% yield brsm). To our delight, **10** underwent a SmI<sub>2</sub>-mediated, intramolecular Barbier reaction<sup>8</sup> in the presence of 10 mol % of NiI<sub>2</sub><sup>9</sup> to afford hydroxysilane **11**, which was subjected to a Fleming-Tamao-Kumada oxidation<sup>10</sup> to furnish the triolester **12** in 50% overall yield from **10**. However, triolester **12** decomposed rapidly when subjected to hydrolysis by LiOH. On the other hand,

upon treatment with the slightly basic sodium propanethiolate, **12** was converted to carboxylate **13** in 97% yield.<sup>11</sup> Global debenzoylation of **13** followed by cationic exchange delivered synthetic (–)-plicatic acid (**1**) in 72% yield. Extensive spectroscopic and chromatographic analysis of a 1:1 mixture of synthetic and natural (–)-plicatic acid showed the two to be indistinguishable.<sup>12</sup>

In summary, the first asymmetric total synthesis of (–)-plicatic acid was accomplished in 12 steps and 14% overall yield from eugenol. In this synthesis a conceptually new strategy featuring an asymmetric epoxidation-intramolecular epoxy-ring-opening Friedel-Crafts reaction sequence was developed for the stereoselective construction of a structurally complex 2,7'-cyclo lignane skeleton. The implementation of this strategy was enabled by the development of a modified protocol for the Seebach epoxidation with TADOOH, which affords an unprecedented, highly enantioselective and diastereoselective epoxidation with a range of  $\alpha$ -carbonyl- $\beta$ -substituted acrylates **3**.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

**Acknowledgment.** We are grateful for financial support from National Institute of Health (GM-61591). We thank Dr. C. R. Daniels of Forintek Canada Corp. for kindly providing us with an authentic sample of natural (–)-plicatic acid.

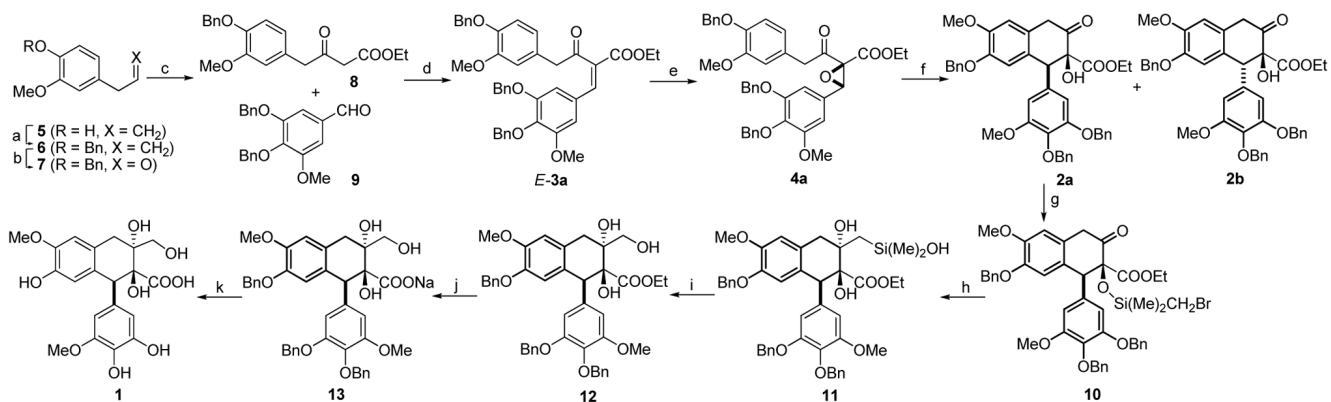
## References

1. (a) Chan-Yeung M, Giclas PC, Henson PM. *J Allerg Clin Immunol* 1980;65:333. (b) Cartier A, Chan H, Malo JL, Pineau L, Tse KS, Chan-Yeung M. *J Allerg Clin Immunol* 1986;77:639. (c) Frew A, Chang JH, Chan H, Quirce S, Noertjojo K, Keown P, Chan-Yeung M. *J Allerg Clin Immunol* 1998;101:841. (d) Weissman DN, Lewis DM. *Occup Med* 2000;15:385. [PubMed: 10769344] (e) Chan-Yeung M. *J Allerg Clin Immunol* 1982;70:32. (f) Vedal S, Chan-Yeung M, Enarson DA, Chan H, Dorken E, Tse KS. *J Allerg Clin Immunol* 1986;78:1103. (g) Chan-Yeung M, Chan H, Tse KS, Salari H, Lam S. *J Allerg Clin Immunol* 1989;85:762.
2. (a) Gradner JAF, Barton GM, MacLean H. *Can J Chem* 1959;37:1703. (b) Gradner JAF, Swan EP, Sutherland SA, MacLean H. *Can J Chem* 1966;44:52. (c) Swan RJ, Klyne W, MacLean H. *Can J Chem* 1967;45:321. For a survey of chiroptical studies on tetralin lignans, see: Hulbert PB, Klyne W, Scopes PM. *J Chem Res (S)* 1981:27.
3. For selected recent lignans syntheses, see: (a) Sefkow M. *Top Curr Chem* 2005;243:185. (b) Wu Y, Zhao J, Chen J, Pan C, Li L, Zhang H. *Org Lett* 2009;11:597. [PubMed: 19105659] (c) Kiran M, Subrata G. *Tetrahedron Lett* 2008;49:3433. (d) Fukuyama Y, Harada K, Esumi T, Hojyo D, Kujime Y, Kubo N, Kubo M, Hioki H. *Heterocycles* 2008;76:551. (e) Angle SR, Choi I, Tham FS. *J Org Chem* 2008;73:6268. [PubMed: 18646863] (f) Mitra S, Gurralla SR, Coleman RS. *J Org Chem* 2007;72:8724. [PubMed: 17929867] (g) Coleman RS, Gurralla SR. *Org Lett* 2005;7:1849. [PubMed: 15844922]
4. For examples and reviews of asymmetric epoxidations of electron-deficient olefins, see: (a) Wang X, Reisinger CM, List B. *J Am Chem Soc* 2008;130:6070. [PubMed: 18422314] (b) Wang B, Wu XY, Wong OA, Nettles B, Zhao MX, Chen D, Shi Y. *J Org Chem* 2009;74:3986. [PubMed: 19388627] (c) Lu X, Liu Y, Sun B, Cindric B, Deng L. *J Am Chem Soc* 2008;130:8134. [PubMed: 18529055] (d) Reisinger CM, Wang X, List B. *Angew Chem Int Ed* 2008;47:8112. (e) Shi Y. *Acc Chem Res* 2004;37:488. [PubMed: 15311947] For a recently reported stereospecific, base-catalyzed epoxidation, see (f) Švenda J, Myers AG. *Org Lett* 2009;11:2437. [PubMed: 19397300]
5. Aoki M, Seebach D. *Helv Chim Acta* 2001;84:187.
6. Holmquist CR, Roskamp EJ. *J Org Chem* 1989;54:3258.
7. (a) Bull JR, Sickel ES. *J Chem Soc, Perkin Trans 1* 2000:4476. (b) Pettus TRR, Wwang J. *Tetrahedron Lett* 2004;45:5895. (c) Imamoto T, Sugiura Y. *J Organomet Chem* 1985;285:4233. (d) McAuliffe JC, Stick RV. *Aust J Chem* 1997;50:193. For Lewis acid promoted nucleophilic addition to ketones with

lithium or magnesium reagents, see: (e)Aubrecht KB, Winemiller MD, Collum DB. *J Am Chem Soc* 2000;122:11084. and references therein.

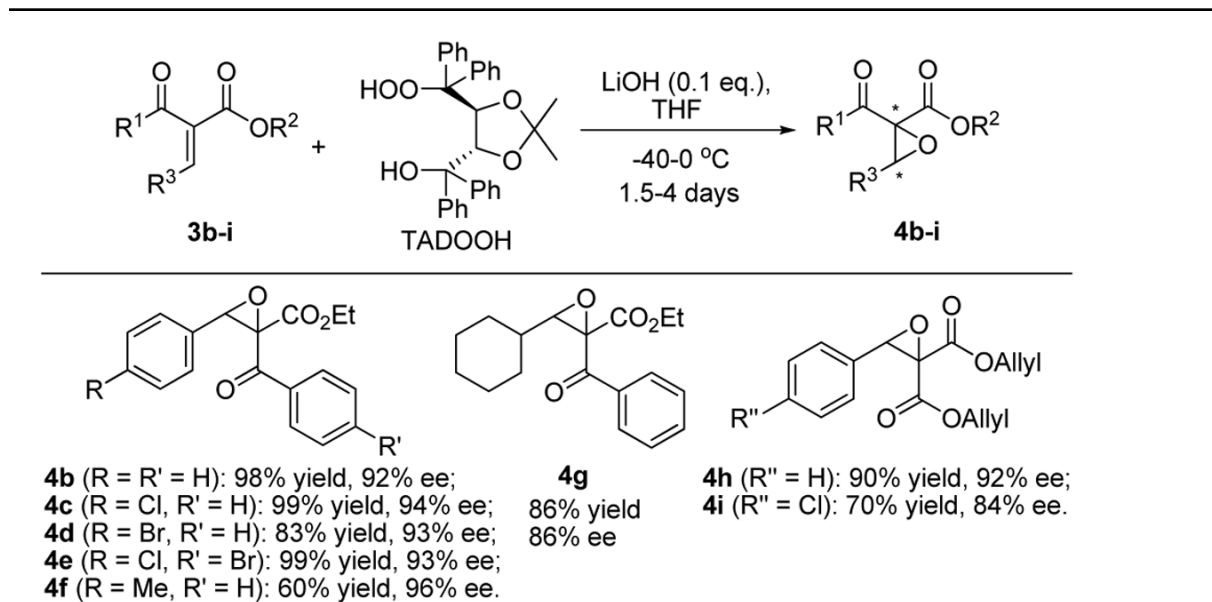
8. (a) Park HS, Lee IS, Kwon DW, Kim YH. *Chem Comm* 1998:2745. (b) Miller RS, Sealy JM, Shabangi M, Kuhlman ML, Fuchs JR, Flowers RA II. *J Am Chem Soc* 2000;122:7718.
9. (a) Machrouhi F, Hamann B, Namy JL, Kagan H. *Synlett* 1996;7:633. (b) Miquel N, Doisneau G, Beau JM. *Angew Chem Int Ed* 2000;39:4111.
10. (a) Tamao K, Ishida N, Tanak T, Kumada M. *Organometallics* 1983;2:1694. (b) Tamao K, Ishida N, Kumada M. *J Org Chem* 1983;48:2122.
11. (a) Vaughan WR, Baumann JB. *J Org Chem* 1962;27:739. (b) Lal K, Ghosh S, Salomon RG. *J Org Chem* 1987;52:1072.
12. See Supporting Information for details.



**Scheme 2.****Total Synthesis of (-)-Plicatic Acid (1)**

<sup>a</sup> Conditions: (a) NaH, BnBr, quant. (b) (1) NMO, cat. OsO<sub>4</sub>; (2) NaIO<sub>4</sub>, quant. (c) N<sub>2</sub>CHCOOEt, cat. SnCl<sub>2</sub>, 92%. (d) **9**, piperidine, PhCOOH, 80% (after one cycle), *E/Z* = 5:3. (e) (*S,S*)-TADOOH, cat. LiOH, 83%, 98% ee. (f) TfOH (0.04 eq.), 0 oC to r.t., 70% **2a**, 17% **2b**. (g) ClSi(Me)<sub>2</sub>CH<sub>2</sub>Br, imidazole, 75% (94% brsm). (h) SmI<sub>2</sub>, NiI<sub>2</sub> (0.1 eq.), 0 oC, 58%. (i) H<sub>2</sub>O<sub>2</sub>, NaHCO<sub>3</sub>, 87% (90% brsm). (j) *n*-PrSNa, DMF, 97%. (k) H<sub>2</sub>, Pd/C, MeOH, then Dowex-50, 72%.

**Table 1**  
Asymmetric Nucleophilic Epoxidation of Various Acyclic Trisubstituted Olefins



<sup>a</sup>See Supporting Information for details of reaction conditions.

<sup>b</sup>Isolated yields are reported.

<sup>c</sup>Ee's were determined by HPLC analysis.