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Synthesis of (+)-Disparlure via Enantioselective Iodolactonization

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Abstract

The BINOL-amidine organic catalyst **1** was previously shown to promote highly efficient enantioselective halolactonization reactions of olefinic acids. As part of these studies, it was discovered that the enantioenriched iodolactones could be easily converted into enantioenriched *cis*-1,2-disubstituted epoxides. This halolactonization-epoxidation sequence was applied to the synthesis of (+)-disparlure, which resulted in the shortest catalytic enantioselective synthesis to date, requiring only five steps and proceeding in 33% yield.

Graphical abstract

Electrophilic halocyclizations of olefinic carboxylic acids represent an important class of reactions that has been widely used in organic synthesis.¹ Consequently, the development of asymmetric variants of halolactonization reactions has received considerable attention in recent years, and some significant advances have been made.² We recently reported the discovery of the bifunctional organic catalyst **1** that promotes highly efficient enantioselective halolactonization reactions for a broad array of olefinic acids (Equation 1).³ The BINOL-amidine catalyst **1** was competitive with other catalysts in promoting enantioselective bromolactonizations of 4- and 5-aryl-4-pentenoic acids (**2a,b**), and at the time of its discovery was unique in its ability to effect bromolactonizations of 5-alkyl-4(*Z*)-pentenoic acids (**2c**) via 5-exo cyclizations to generate stereogenic carbonhalogen centers with excellent enantioselectivities.^{3a,4} Additionally, we subsequently found that **1** could be used to convert 5-substituted-4(*Z*)-pentenoic acids into the corresponding iodolactones with a high degree of enantioselectivity.^{3b}

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Supporting Information

Experimental procedures and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

(1)

As an integral part of developing useful applications of **1** and analogs thereof, we identified several unmet needs in the arena of enantioselective halolactonizations. For example, the enantioselective epoxidation of *Z*-disubstituted olefins in the absence of directing groups was a significant challenge,⁵ so there was an opportunity to invent efficient methods to generate such epoxides. Toward solving this problem, we discovered that chiral halolactones such as **4**, which were easily accessible via enantioselective halolactonizations of 4(*Z*)-alkenoic acids using **1** (Equation 1), could be readily transformed without erosion of enantiopurity into *cis*-1,2-disubstituted epoxides such as **5** upon treatment with Cs_2CO_3 in MeOH (Equation 2). We now report the application of this facile iodolactonization-epoxidation sequence to a concise enantioselective synthesis of (+)-disparlure, an important insect pheromone that is broadly used to manage gypsy moth populations.⁶

(2)

The gypsy moth, *Lymantria dispar*, is an invasive insect that is one of the most destructive exotic organisms in North America.⁷ During outbreaks, the insects cause severe deforestation that can have substantial negative ecological and economic ramifications. Bierl identified disparlure, (*Z*)-7,8-epoxy-2-methyloctadecane, as the sex attractant emitted by the female gypsy moth in 1970,⁸ and it was later established that (+)-disparlure (**6**) is the major attractant component.⁹ The management of gypsy moth populations has been successful in part due to the availability of pheromone-containing traps that are highly effective for detecting low density populations.¹⁰ Because of its utility in managing gypsy moth

populations and its scarcity from natural sources, disparlure has been the target of a myriad of synthetic investigations. Indeed, since its discovery, there have been more than 50 syntheses of racemic and enantiomerically-enriched disparlure.¹¹ Despite these many successes, there remains opportunity for improvement, so we designed an approach based upon our enantioselective iodolactonization methodology. In particular, we envisaged that (+)-disparlure (**6**) could be prepared from **7**, which would be accessible in two steps from the olefinic acid **9** via enantioselective halolactonization followed by reaction of the intermediate iodolactone **8** with methanolic base (Scheme 1).

Our synthesis commenced with the preparation of **9** through a two step procedure from commercially available pentynoic acid (**10**). In the event, alkylation of the dianion generated from **10** with 1-iododecane, followed by *in-situ* saponification of any ester byproduct furnished **11** in 82% yield. Partial reduction of the alkyne moiety of **11** was achieved through a P2-Ni hydrogenation to give the *Z*-alkenoic acid **9** in 85% yield. Gratifyingly, iodolactonization of **9** with *N*-iodosuccinimide (NIS) in the presence of *ent*-**1** and I₂ gave lactone **8** in 85% yield and 95:5 er. When **8** was processed via a one-pot sequence involving reduction of the lactone moiety followed by Wittig olefination, the requisite epoxide **12** was isolated in 62% yield. Not surprisingly based upon literature precedent,¹² we found that selective reduction of the double bond in **12** by catalytic hydrogenation was problematic because epoxide opening was a significant side reaction. However, after screening a variety of conditions, we ultimately discovered that hydrogenation of **12** using Pt₂O in hexanes delivered (+)-disparlure (**6**) in 90% yield. This synthesis of (+)-disparlure required only five steps from commercially available starting materials and proceeded in 33% overall yield from **10**, making this the shortest catalytic enantioselective synthesis of **6** to date.

In summary, we have demonstrated that enantioselective iodolactonization reactions promoted by the bifunctional BINOL-amidine catalysts **1** and *ent*-**1** can give rapid access to enantioenriched *cis*-disubstituted epoxides. In order to exemplify the utility of this methodology, it was applied to prepare (+)-disparlure in the shortest catalytic enantioselective synthesis of (+)-disparlure reported to date.¹³ Other applications of **1** and related catalysts in organic synthesis will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Gribble GW. Chem Soc Rev. 1999; 28:335–346.(b) Ranganathan S, Muraleedharan KM, Vaish NK, Jayaraman N. Tetrahedron. 2004; 60:5273–5308.(c) Lava MS, Banerjee AK, Cabrera EV. Curr Org Chem. 2009; 13:720–730.(d) Snyder SA, Treitler DS, Brucks AP. Aldrichim Acta. 2011; 44:27.
2. For reviews on enantioselective halolactonization see:(a) Chen G, Ma S. Angew Chem, Int Ed. 2010; 49:8306.(b) Tan CK, Zhou L, Yeung YY. Synlett. 2011; 2011:1335.(c) Castellanos A,

- Fletcher SP. *Chem - Eur J*. 2011; 17:5766. [PubMed: 21509840] (d) Tan CK, Yeung YY. *Chem Commun*. 2013; 49:7985. (e) Nolsøe JM, Hansen TV. *Eur J Org Chem*. 2014; 2014:3051.
3. (a) Paull DH, Fang C, Donald JR, Pansick AD, Martin SF. *J Am Chem Soc*. 2012; 134:11128–11131. [PubMed: 22726214] (b) Fang C, Paull DH, Hethcox JC, Shugrue CR, Martin SF. *Org Lett*. 2012; 14:6290–6293. [PubMed: 23199100]
4. Tan CK, Le C, Yeung Y-Y. *Chem Commun*. 2012; 48:5793–5795.
5. For recent advances in enantioselective epoxidations of olefins with organocatalysts see: (a) Burke CP, Shi Y. *Org Lett*. 2009; 11:5150–5153. [PubMed: 19824657] (b) Zhu Y, Wang Q, Cornwall R, Shi Y. *Chem Rev*. 2014; 114:8199–8256. [PubMed: 24785198]
6. Lance DR, Leonard DS, Mastro VC, Walters ML. *J Chem Ecol*. 2016; 42:590–605. [PubMed: 27492468]
7. Liebhold AM, Halverson JA, Elmes GA. *J Biogeogr*. 1992; 19:513–520.
8. Bierl BA, Beroza M, Collier CW. *Science*. 1970; 170:87–89. [PubMed: 5452898]
9. (a) Iwaki S, Marumo S, Saito T, Yamada M, Kazumasa K. *J Am Chem Soc*. 1974; 96:7842–7844. (b) Plettner E, Lazar J, Prestwich EG, Prestwich GD. *Biochemistry*. 2000; 39:8953–8962. [PubMed: 10913308]
10. Liebhold AM, Tobin PC. *Annu Rev Entomol*. 2008; 53:387–408. [PubMed: 17877456]
11. For recent syntheses, see: (a) Koumbis AE, Chronopoulos DD. *Tetrahedron Lett*. 2005; 46:4353–4355. (b) Inkster JAH, Ling I, Honson NS, Jacquet L, Gries R, Plettner E. *Tetrahedron Asymmetry*. 2005; 16:3773–3784. (c) Zhang S, Sun H, Li B. *Acta Chim Sin*. 2007; 65:2433–2436. (d) Prasad KR, Anbarasan P. *J Org Chem*. 2007; 72:3155–3157. [PubMed: 17367199] (e) Kovalenko VN, Masalov NV, Kulinkovich OG. *Russ J Org Chem*. 2009; 45:1318–1324. (f) Kim SG. *Synthesis*. 2009:2418–2422. (g) Chen H, Gong Y, Gries RM, Plettner E. *Bioorg Med Chem*. 2010; 18:2920–2929. [PubMed: 20347316] (h) Dubey AK, Chattopadhyay A. *Tetrahedron Asymmetry*. 2011; 22:1516–1521. (i) Wang Z, Zheng J, Huang P. *Chinese J Chem*. 2012; 30:23–28. (j) Herbert MB, Marx VM, Pederson RL, Grubbs RH. *Angew Chemie Int Ed*. 2013; 52:310–314. (k) Bethi V, Kattanguru P, Fernandes RA. *Eur J Org Chem*. 2014:3249–3255. (l) Garg Y, Tiwari AK, Pandey SL. *Tetrahedron Lett*. 2017; 58:3344–3346.
12. (a) Dragovich PS, Prins TJ, Zhou R. *J Org Chem*. 1995; 60:4922–4924. (b) Sajiki H, Hattori K, Hirota K. *Chem Commun*. 1999:1041–1042. (c) Kwon MS, Park IS, Jang JS, Lee JS, Park J. *Org Lett*. 2007; 9:3417–3419. [PubMed: 17661475]
13. To the best of our knowledge, the shortest enantioselective synthesis of (+)-disparlure was achieved in five steps through the use of a chiral sulfoxide auxiliary: Satoh T, Oohara T, Ueda Y, Yamakawa K. *J Org Chem*. 1989; 54:3130–3136.

Scheme 1.
Synthetic strategy towards (+)-disparlure

Scheme 2.
Synthesis of (+)-disparlure from pentynoic acid