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Synthesis of the Prelog–Djerassi Lactone via an Asymmetric Hydroformylation/ Crotylation Tandem Sequence

Roberto M. Risi and Steven D. Burke*

Department of Chemistry, University of Wisconsin—Madison, 1101 University Avenue, Madison, Wisconsin 53706-1322, United States

burke@chem.wisc.edu

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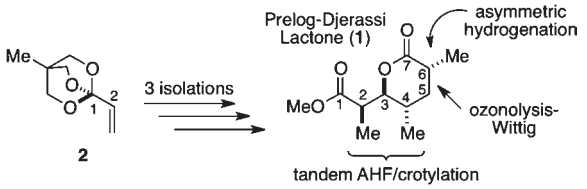
ABSTRACT



A synthesis of the Prelog–Djerassi lactone [(+)-1] has been accomplished in three isolations and 57% overall yield from the known vinyl ortho ester 2. A Rh(I)-catalyzed asymmetric hydroformylation/crotylation tandem sequence has been developed and used to set the C2–C4 stereochemistry. A Rh(I)-catalyzed asymmetric hydrogenation was employed to set the C6 sterechemistry, resulting in an unusually short and efficient enantioselective synthesis of this touchstone molecule from achiral starting material.

The Prelog–Djerassi lactone (**1**) was originally isolated in 1956 by Prelog and by Djerassi as an oxidative degradation product from neomethymycin, methymycin, narbomycin, and picromycin.[1,2] Rickards and Smith elucidated the full stereochemistry in 1970.[3,4] Since then, the PD lactone (**1**) has served as a touchstone molecule to showcase synthetic strategies and methods.[5] An instructive variety of strategies have been used to synthesize **1**, including two nonstereoselective approaches, the use of architecturally biased scaffolds, and carbohydrate-based syntheses. Many methods have been employed to construct this stereochemically rich lactone, including various aldol reactions, carbonyl crotylations, and pericyclic reactions such as [4 + 2] cycloaddition, the ene reaction, and Claisen- and [2,3] Wittig-rearrangements. Electrophilic additions to alkenes have also been used, including mercuric ion induced cyclization, acyclic 1,5-diene hydroboration, Sharpless asymmetric epoxidation, and phenyldimethylsilylcuprate 1,4-addition to an α,β-unsaturated ester.[5]

Since 1990 several syntheses have been published including one from *trans*-pulegenic acid,[6] three from the Roche ester,[7–9] a racemic synthesis from cyclopentanone,[10] a desymmetrization of a meso dialdehyde,[11] and an Ireland–Claisen rearrangement.[12] Clearly, the PD lactone (**1**) has provided a popular context to display a diverse range of methods and strategies for polypropionate natural product synthesis.

Mindful of these benchmarks, we wish to present herein a novel and efficient synthesis of (+)-PD lactone (**1**) based on a catalytic asymmetric hydroformylation/crotylation tandem sequence developed in our laboratory. Asymmetric hydroformylation (AHF) generates chiral, α-branched aldehydes

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(4) Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, *11*, 1025–1028.
(5) For a review of syntheses prior to 1990, see: Martin, S. F.; Guinn, D. E. *Synthesis* **1991**, *4*, 245–262.
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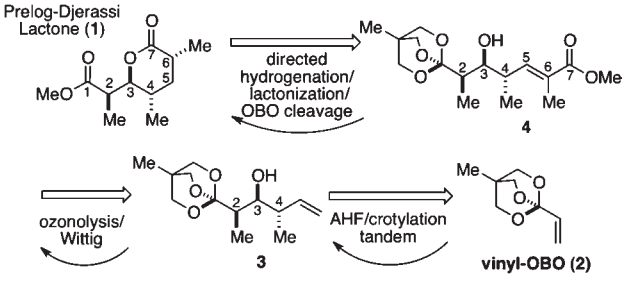
from alkenes.[13] Among the attributes of the catalytic AHF protocol are high atom economy, moderate temperature and pressure, low catalyst/ligand loadings, high substrate concentration, neutral conditions, and operational simplicity (pressure bottle). The only reagents, CO and H_2, are easily removed at the end of the reaction, yielding a substantially pure solution of the α-chiral branched aldehyde in high enantiomeric excess.[13] These characteristics suggest employing AHF in a tandem sequence.[14] Since crotylation of α-chiral aldehydes is well established,[15] we sought to couple this powerful reaction with the AHF in order to create three new asymmetric centers with the alternating of methyl, hydroxyl, and methyl substituents characteristic of polypropionates.

Scheme 1. Synthesis Strategy



The synthesis strategy for **1** is shown in Scheme 1. The C2 stereochemistry would be established via an AHF of an appropriate vinyl ortho ester **2**[16,17] followed by a substrate controlled crotylation to set C3 and C4 in the requisite C2−C3 *syn*, C3−C4 *anti* relationship in homoallylic alcohol **3**. The C6 methyl as well as the C7 carbonyl would be incorporated via an ozonolysis/Wittig tandem to afford α,β-unsaturated ester **4**. Finally, a hydroxyl-directed cationic Rh(I)-catalyzed asymmetric hydrogenation[18] would set the C6 stereochemistry, which would be followed by unmasking of the ortho ester and lactonization to complete the synthesis of the PD lactone (**1**).

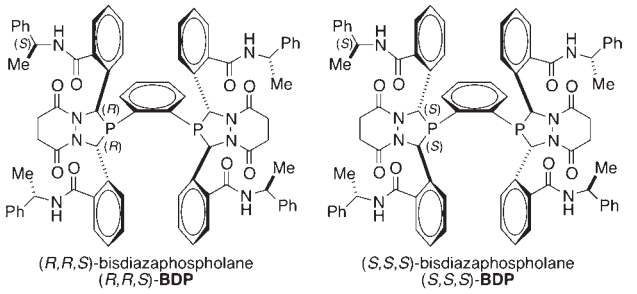


Figure 1. Landis' AHF Ligands.

Landis has developed bisdiazaphospholane (**BDP**) ligands (Figure 1) that enable highly regio- and enantioselective Rh(I)-catalyzed hydroformylation of numerous olefins, favoring branched (chiral) over linear (achiral) aldehydes.[13] We have initiated a program to develop and apply the AHF reaction using the **BDP** ligands to problems in synthesis.[19]

When considering masked acrylate substrates for the AHF/crotylation tandem sequence, an orthoester moiety was expected to maximize the steric distinction between the α-substituents on the aldehyde product for increased Felkin−Anh selectivity in the crotylation,[15] while avoiding the involvement of an enolizable β-dicarbonyl. With these objectives in mind, the known 1-vinyl-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane ortho ester [vinyl-OBO substrate (**2**) Scheme 1] was chosen.[16,17] Vinyl-OBO **2** smoothly underwent AHF with very low catalyst loading to afford the branched aldehyde **5** with excellent regio- and enantioselectivity (Scheme 2). To the same pot, *trans*-2-butenyl pinacolato boronic ester (**6**)[15a,b] was added at ambient temperature and reacted for 24 h to give the 2,3-*syn*, 3,4-*anti*-homoallylic alcohol **3**. The neutral conditions of both the AHF and the crotylation avoided epimerization of the α-chiral aldehyde and transferred stereogenicity from both **5** and **6** to **3** with high fidelity via the Zimmerman−Traxler transition state **T1**.[15,20] The harmonious combination of the AHF and the substrate-controlled crotylation efficiently telescopes the influence of the chiral catalyst to yield three new asymmetric centers in a single pot. Subjection of homoallylic alcohol **3** to an ozonolysis/Wittig olefination with ylide **7**[21] yielded the α,β-unsaturated methyl ester **4** in excellent yield and stereoselectivity.

Cationic Rh(I)- and Ir(I)-catalyzed, hydroxyl-directed olefin hydrogenations have been shown to transfer chirality

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(17) Ortho ester **2** is available in three steps from commercially available 3-methyl-3-oxetanemethanol via the scalable procedure described in the Supporting Information.

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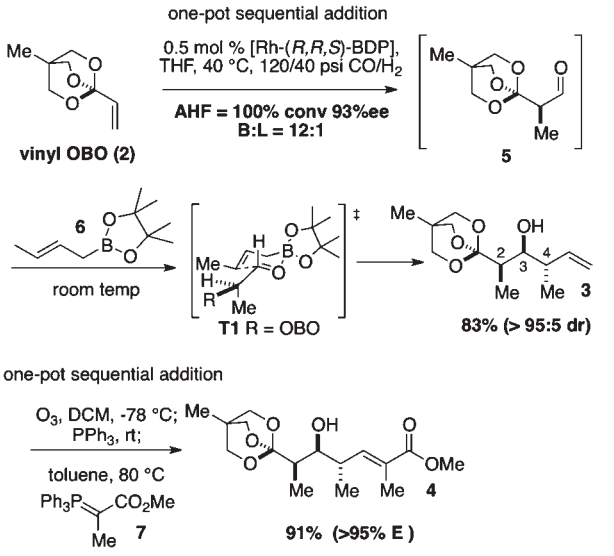
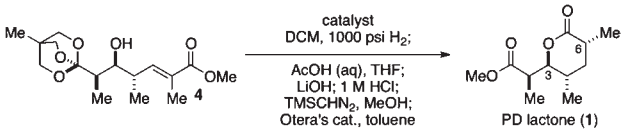
Scheme 2. Tandem AHF/Crotylation and Ozonolysis/Wittig Olefination



in unsaturated esters similar to **4**.[18,22,23] We explored several catalyst systems for the hydrogenation (Scheme 3, Table 1) followed by a one-pot conversion of the hydrogenation product to the targeted PD lactone (**1**), in which the hydrogenation diastereoselectivity (C6 α-Me desired) was determined.[24] Simple hydrogenation with Pd/C imparted no diastereoselectivity while [Rh(nbd)(dppb)]BF_4 gave a 2.5:1 mixture of products favoring the desired diastereomer. Crabtree's catalyst[22] (entry 3) gave slightly better selectivity (3:1), and Burgess' cationic Ir(I) catalyst[23] (entry 4) gave lower selectivity (1.6:1). Incorporating a chiral ligand with the hydroxyl-directed Rh(I)-catalyzed hydrogenation has been shown to increase the diastereoselectivity via double stereodifferentiation.[18] Using [Rh(COD)-(*S*)-BINAP]BF_4 afforded a 5:1 mixture in favor of the PD lactone (**1**). Superior results were obtained when the noncoordinating perchlorate counterion was incorporated into the catalyst (entry 6), affording a much higher diastereoselectivity (> 31:1).

Scheme 3. Directed Hydrogenation/Lactonization/OBO Cleavage



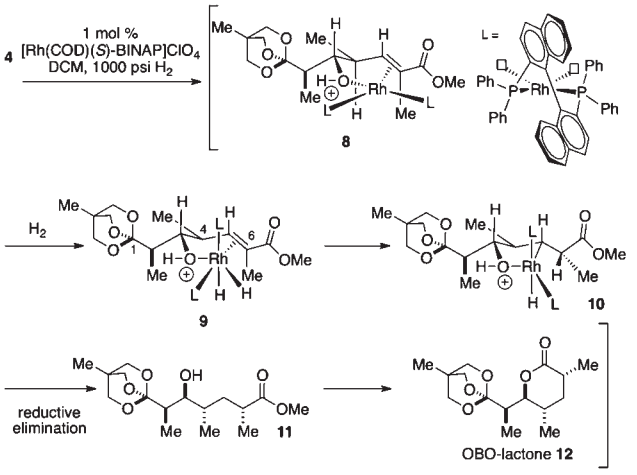
The proposed model for the optimized diastereoselectivity of entry 6 is presented in Scheme 4.[18] Initial coordination of both the hydroxyl group and the olefin face shown with the rhodium would put the C4 methyl and the bulky OBO containing substituent in equatorial positions on the chairlike complex **8**. Insertion of dihydrogen would generate intermediate **9**, followed by alkene insertion to give **10** and reductive elimination to afford the open chain methyl ester **11**, which spontaneously underwent lactonization to afford OBO-lactone **12**.

Table 1. Catalyst Screen

entry	catalyst	% yield[a]	dr (α:β) for C6-Me[a]
1	10% Pd/C	39	1:1
2	15% [Rh(nbd)(dppb)]BF_4	61	2.5:1
3	0.9% [Ir(pyr)(Cy_3P)]PF_6	66	3:1
4	3% Burgess cat.	63	1.6:1
5	5% [Rh(COD)(*S*)-BINAP]BF_4	30	5:1
6	1% [Rh(COD)(*S*)-BINAP]ClO_4	76	>31:1

[a] Yield and diastereomer ratio measured on **1** before recrystallization; dr determined by comparing integrations of C3-$^{12}C-^{1}H$ minor diastereomer vs $^{13}C-^{1}H$ satellite of **1** in C_6D_6 at 600 MHz.[24] See Supporting Information for details.

Scheme 4. Directed Asymmetric Hydrogenation



Following the hydrogenation of **4** to afford OBO-lactone **12** (Scheme 5), the acid catalyzed decomposition of the OBO-ortho ester gave diol ester **13**,[25] which upon saponification gave a mixture of **14** and **15**. Esterification of the C1 carboxylic acid with $TMSCHN_2$[26] produced a

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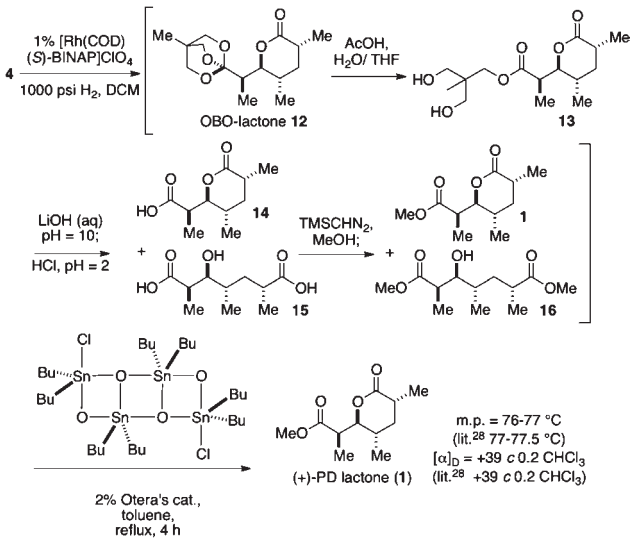
Scheme 5. Conversion of **4** to (+)-Prelog–Djerassi Lactone (**1**)



mixture of **1** and a minor amount of **16** that converged to only **1** via neutral lactonization with Otera's catalyst.[27]

In conclusion, the Prelog–Djerassi lactone [(+)-**1**] has been synthesized in three isolations and 57% overall yield from vinyl-OBO **2**.[16,17] Featured in this synthesis is the development of an AHF/crotylation tandem sequence yielding **3**, in which three of the four needed asymmetric centers are set in a single pot.

An ozonolysis/Wittig homologation afforded the α,β-unsaturated methyl ester **4** containing C1–C7 of the PD lactone (**1**) in good yield with excellent selectivity. Finally a hydroxyl-directed cationic Rh(I)-catalyzed asymmetric hydrogenation[18] set the C6 stereocenter with excellent (>31:1) diastereoselectivity. In the same pot, the OBO-ortho ester was hydrolyzed,[25] the carboxylic acid was esterified with $TMSCHN_2$,[26] and lactonization with Otera's catalyst[27] yielded the PD lactone (**1**). Further investigations into the development of efficient AHF-based strategies for natural products synthesis are underway.

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Supporting Information Available. Experimental procedures and characterization data for new compounds, vinyl OBO **2**, (+)-PD lactone (**1**), SFC derivatives, and NMR data for dr determination. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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