

A Short Diastereoselective Total Synthesis of (\pm)-Vibralactone

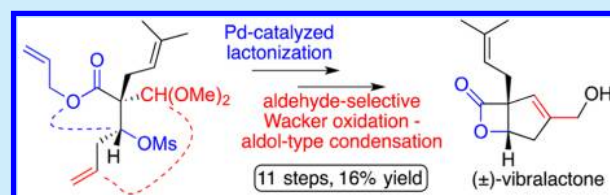
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S Supporting Information

ABSTRACT: A total synthesis of the (\pm)-vibralactone has been achieved in 11 steps and 16% overall yield from malonic acid. Key steps include a highly diastereoselective allylation of an α -formyl ester containing an all carbon α -quaternary center, a Pd-catalyzed deallylative β -lactonization, and an aldehyde-selective Wacker oxidation of a terminal alkene.



Vibralactone (**1**) is a terpenoid natural product, which inhibits pancreatic lipase (IC_{50} $0.4 \mu\text{g mL}^{-1}$) with *in vitro* activity comparable to that of the FDA approved obesity therapeutic tetrahydrolipstatin (**2**, IC_{50} $0.36 \mu\text{g mL}^{-1}$, Figure 1).^{1,2} Isolation of (–)-vibralactone was first reported by Liu et

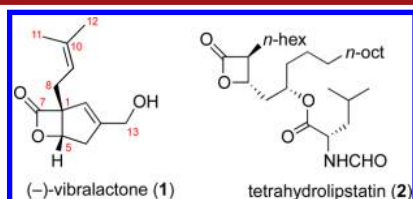


Figure 1. Structures of pancreatic lipase inhibitors (–)-vibralactone and tetrahydrolipstatin.

al. in 2006 by extraction from cultures of Basidiomycete *Borestereum vibrans*, leading to the elucidation of its unusual fused β -lactone structure and discovery of lipase inhibitory activity.³ Shortly after its isolation, Snider and co-workers reported total syntheses of racemic and, subsequently, (–)-vibralactone employing an auxiliary controlled Birch reduction–prenylation strategy to form the C1 all-carbon quaternary center with high diastereoselectivity.^{4,5} Their asymmetric synthesis was achieved in 11 steps and 4.8% overall yield from a 2-methoxybenzamide derivative functionalized with a prolinol chiral auxiliary.

The synthetic route devised by Snider's group was adopted by Zeiler et al.⁶ to provide vibralactone and modified derivatives, which were used to label and study the assembly of two isoforms of caseinolytic peptidase (ClpP1 and ClpP2) from *Listeria monocytogenes*.⁷ Interest in β -lactones as covalent inhibitors of therapeutically relevant enzymes, combined with challenges associated with formation of the strained and sterically congested bicyclic lactone framework of vibralactone, led us to consider a synthesis of this natural product. Here we describe an approach to (\pm)-vibralactone based upon diastereoselective construction of an acyclic β -hydroxyketone

intermediate **3** and a palladium-catalyzed deallylative cyclization to form the β -lactone ring.

Our strategy centered on a diastereoselective synthesis of densely functionalized acyclic intermediate **3**, wherein the relative stereochemistry at the C5 carbinol would be directed by the adjacent C1 all-carbon quaternary center under conditions of chelation control (Figure 2). Lactone ring

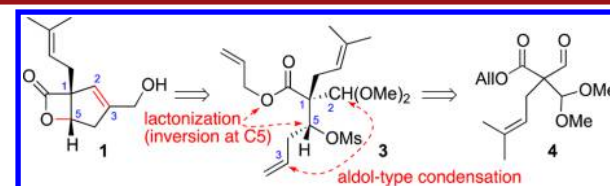
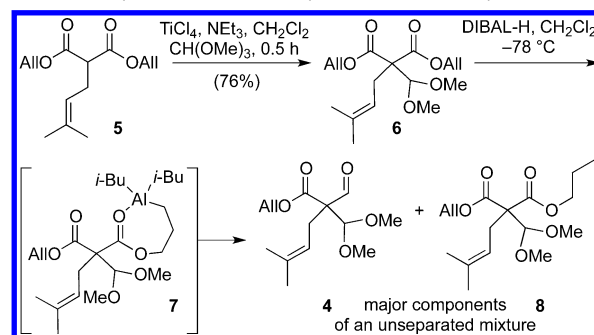


Figure 2. Vibralactone synthesis plan.

formation would require inversion at C5 by means of a new Pd-catalyzed deallylative lactonization, and the cyclopentene ring closure would employ a modified aldol-type condensation.

The initial synthetic work commenced with the prenylation of diallyl malonate to afford **5** (Scheme 1), which participated

Scheme 1. Synthesis of Aldehyde 4 from Diallyl Malonate

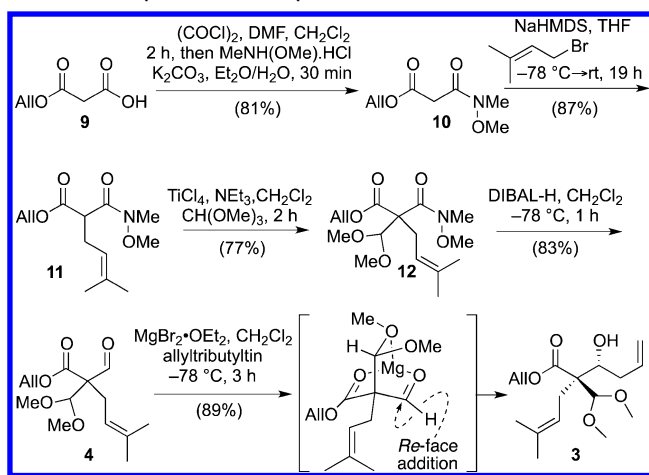


Received: October 6, 2016

in an unique malonate dimethoxymethylation reaction induced under soft enolization conditions using TiCl_4 , NEt_3 and trimethylorthoformate.⁸ While this reaction proved efficient for the production of the diallyl malonate **6**, our efforts to achieve a selective reduction of **6** with DIBAL-H were thwarted by the formation of multiple products stemming from hydroalumination of the allyl groups. The predominating components of the mixture were the desired aldehyde **4** and the propyl ester **8**. The observation of olefin reduction underscored the highly hindered nature of malonate derivative containing the all carbon quaternary center, and consequential attenuated reactivity of the ester carbonyl groups. It is possible that the ester carbonyl of the postulated hydroaluminated intermediate **7** is activated toward DIBAL-H reduction by internal Lewis acid activation, accounting for the predominant formation of aldehyde **4** and propyl ester **8** as a significant impurity.

In order to achieve access to the aldehyde **4**, our attention turned to the possibility of chemoselective reduction of a mixed allyl ester/Weinreb amide derivative (Scheme 2). Selective

Scheme 2. Synthesis of Acyclic Vibrallactone Precursor **3**



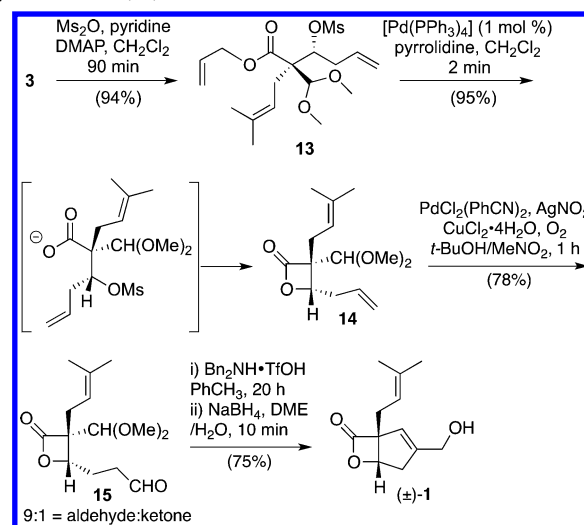
reduction of Weinreb amides in the presence of hindered esters has been reported,⁹ although we are not aware of any examples for sterically unbiased systems. The reduction substrate **12** was prepared from allyl malonate by Weinreb amide formation, followed by the prenylation–dimethoxymethylation sequence described above. Submission of Weinreb amide **12** to DIBAL-H at low temperature resulted in a clean transformation to the required aldehyde intermediate **4**. Importantly, the aldehyde **4** contained the all-carbon quaternary center bearing three suitably functionalized groups for further selective chemical transformation toward vibrallactone.

Completion of the carbon skeleton of vibrallactone required allylation of aldehyde **4** containing the quaternary all-carbon α -center (Scheme 2). Linclau and co-workers discussed substituent and conformational effects controlling diastereoselectivity of nucleophilic addition to malonaldehydes containing a quaternary carbon in the presence of MgBr_2 .¹⁰ Examples of diastereoselective additions to α -formyl esters^{11,12} and α -formyl ketones¹³ that contain α -quaternary stereogenic centers have also been described. In the present work, we applied MgBr_2 promoted allylation conditions to aldehyde **4** and we were delighted to observe the formation of β -hydroxyester **3** as a single diastereoisomer in 89% yield with no acetal cleavage. The sense of diastereoselectivity can be explained by a chelation

model where the dimethoxymethyl group blocks nucleophilic addition to the *Si*-face of the aldehyde carbonyl.

With highly functionalized intermediate **3** in hand, formation of the β -lactone was investigated. A classical method entails lactonization of β -halocarboxylate salts with inversion of configuration, although Grob fragmentation leading to olefin byproducts can be a limitation.¹⁴ This approach has been extended to basic hydrolysis of esters, or larger ring lactones, possessing a leaving group β to the carboxylate intermediate,¹¹ as well as selective monotosylation of β -hydroxy acid dianions followed by treatment of the resulting acid with NaHCO_3 .¹⁵ Two-step approaches entailing hydrogenolysis of a benzyl ester or acid catalyzed ester or amide hydrolysis followed by β -lactonization under basic conditions have also been described.^{16,17} We considered the possible application of a direct deallylative cyclization, catalyzed by $\text{Pd}(0)$ under less basic conditions that are more forgiving toward a strained lactone product (Scheme 3). Therefore, secondary alcohol **3** was

Scheme 3. Pd-Catalyzed Deallylative Lactonization and Synthesis of (\pm)-Vibrallactone



activated by mesylation to afford **13**, which was subjected to palladium-catalyzed deallylation conditions. The outcome was a remarkably rapid reaction resulting in the desired intramolecular substitution to form β -lactone **14** in 95% yield. Formation of **14** also enabled confirmation of the required relative stereochemistry (NOESY) for completion of the total synthesis of vibrallactone. To the best of our knowledge, this deallylative cyclization constitutes a novel approach to the synthesis of β -lactones, and its potential broader application is under investigation in our laboratory.

To close the bicycle, oxidative functional group interconversion of the terminal alkene to an aldehyde **15** was needed, and we were attracted to a recent report from the Grubbs group of an aldehyde-selective Wacker oxidation using $\text{PdCl}_2(\text{PhCN})_2$, CuCl_2 , and AgNO_2 .¹⁸ Pleasingly, the methodology delivered the desired aldehyde **15** in good yield and with a respectable selectivity of 9:1 over the ketone product, which was not separated at this stage. The final C–C bond formation step of the synthesis was an aldol-type condensation of the monoacetal **15**; Snider and co-workers employed an aldol condensation of a dialdehyde promoted by $\text{Bn}_2\text{NH}\cdot\text{TFA}$ to form a cyclopentene intermediate in their synthesis of vibrallactone.^{4,5} However, submission of our substrate **15** to the trifluoroacetate salt

catalyzed enamine aldolization conditions failed to deliver any conversion of starting material. Gratifyingly, the more strongly acidic $[\text{Bn}_2\text{NH}_2]^+\text{TfO}^-$ salt proved highly effective, delivering an enal (vibrallactone C), which was reduced to the allylic alcohol, completing the synthesis of the natural product (\pm)-vibrallactone in 75% yield over the final two steps.

In summary, we have described a total synthesis of (\pm)-vibrallactone in 16% overall yield over 11 steps from malonic acid. Key features of the synthesis include near-perfect diastereofacial selectivity achieved establishing the C5 stereogenic center using a chelation controlled allylation and a novel Pd-catalyzed β -lactone formation. The approach should be amenable to the synthesis of vibrallactone analogues containing different groups at C1, as well as recently reported vibrallactone oximes isolated from *Basidiomycete Boreostereum vibrans*.¹⁹

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.6b03007](https://doi.org/10.1021/acs.orglett.6b03007).

Experimental details and procedures, compound characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge financial support from EPSRC (EP/K039466/1, EP/L050506/1, and EP/P505739/1), the Royal Society (L. J. B.) for a Dorothy Hodgkin Fellowship, Region Normandie, and the European Regional Development Fund (ERDF) for cofinancing the AI-Chem project through the INTERREG IV A France (Channel) - England cross-border cooperation Programme.

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