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Synthesis of (±)-Vibralactone

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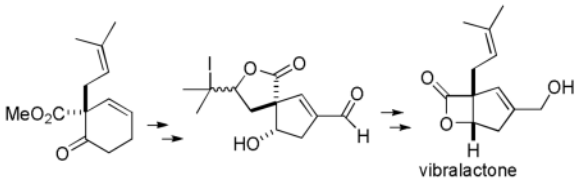
Abstract



Reductive alkylation of methyl 2-methoxybenzoate with prenyl bromide and hydrolysis afforded methyl 6-oxo-1-prenyl-2-cyclohexenecarboxylate. Reduction of the ketone, hydrolysis, iodolactonization, ozonolysis and intramolecular aldol reaction provided a spiro lactone cyclopentenal. Retro-iodolactonization with activated Zn, formation of the β-lactone, and reduction of the aldehyde completed an efficient first synthesis of (±)-vibralactone. No protecting groups were used except for the novel use of an iodolactone to protect both the prenyl double bond and carboxylic acid.

Liu and coworkers recently reported the isolation of the unusual fused β-lactone vibralactone (**1**) from cultures of the Basidiomycete *Boreostereum vibrans* (see Scheme 1).[1] The structure was assigned by detailed spectroscopic analysis and the absolute stereochemistry was assigned by computational methods. Vibralactone inhibits pancreatic lipase with an IC_{50} of 0.4 μg/mL. The pancreatic lipase inhibitor percyquinnin, which was originally assigned as a regioisomer of **1**,[2] has the same planar structure as vibralactone (**1**).[1] Pancreatic lipase inhibitors are clinically used for the treatment of obesity and improved drugs are needed.[3] This prompted us to undertake the synthesis of vibralactone (**1**), a new lead structure that should be readily amenable to analogue synthesis.

The instability of the β-lactone ring and the functional group density makes the synthesis of vibralactone a challenging problem despite its small size. We envisioned that the β-lactone ring of vibralactone (**1**) could be prepared from cis hydroxy acid **2** by activation of the acid group followed by β-lactonization with retention of stereochemistry.[4] Alternatively, vibralactone should be accessible from trans hydroxy acid **3** by conversion of the alcohol to a good leaving group and β-lactonization by an S_N2 reaction with inversion. This less common approach to β-lactone formation has recently been improved by Wu and Sun.[5] The cyclopentenal moiety of **2** and **3** should be readily available by oxidative cleavage of the cyclohexene double bond of **5** and **6**, respectively, followed by an intramolecular aldol reaction. Unfortunately, the cyclohexene double bond cannot be oxidatively cleaved in the presence of the more nucleophilic side chain double bond. This necessitated the protection of the side chain double bond of **5** or **6**, which might be accomplished by formation of iodolactone **7**.[6] However, iodolactonization could occur at either double bond of **5** or **6**. Even if iodolactonization occurs selectively as expected and required at the more nucleophilic side chain double bond, stereoisomeric mixtures of γ- and δ-lactones could be formed that would complicate product

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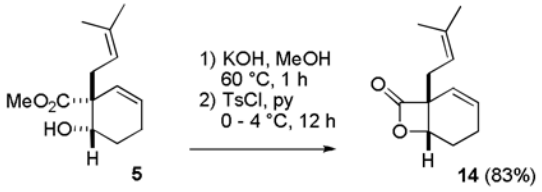
analysis. Furthermore, it was by no means certain that oxidative cleavage of the double bond and intramolecular aldol reaction to give cyclopentenal **4** could be accomplished in the presence of a reactive tertiary iodide. Retro-iodolactonization by zinc reduction of **4** would regenerate **2** or **3** with both the side chain double bond and the free acid needed for lactonization.

Alcohols **5** and **6** should be accessible by the diastereoselective reduction of ketone **9**, which surprisingly proved to be the most challenging step in the synthesis. Ketone **9** can be easily prepared by reductive alkylation[7] of methyl 2-methoxybenzoate (**8**) with prenyl bromide followed by acidic hydrolysis of the methyl enol ether.

Reduction of **8** with K in liquid NH_3 at −78 °C, addition of LiI and prenyl bromide, and slow warming to 25 °C afforded the alkylated cyclohexadiene **10** in 77% yield (see Scheme 2).[7] Hydrolysis of the enol ether with methanolic HCl gave ketone **9** in 84% yield. Reduction of **9** with $NaBH_4$ in MeOH cleanly provided a 2:1 mixture of trans hydroxy ester **6** and cis hydroxy ester **5**.[8,9] Magnus reported similar ratios of products from the $NaBH_4$ reduction of a related keto amide and also found that $Zn(BH_4)_2$ gave the trans hydroxy amide with >99:1 selectivity.[10] Reduction of **9** with $Zn(BH_4)_2$ in ether[11] afforded trans hydroxy ester **6** in 69% yield. Reduction with $CaCl_2$ and $NaBH_4$, which selectively provides trans hydroxy esters from 1-alkyl-2-oxocyclohexanone carboxylates,[12] gave a 7.5:1 mixture of **6** and **5**, from which **6** was isolated in 69% yield.

We chose to carry out a model study exploring lactone formation with inversion by hydroxy group activation using the now readily available trans hydroxy ester **6**. Hydrolysis of the methyl ester with KOH in MeOH at 60 °C provided the required trans hydroxy acid. In their studies with acyclic β-hydroxy acids, Wu and Sun needed to activate the alcohol without activating the carboyxlic acid because lactonization by acid activation will give the other stereoisomer.[5] Trans hydroxy acid **11** would form a highly strained trans-fused β-lactone by reaction of the alcohol with an activated acyl group. Therefore there is no need to selectively activate the alcohol. Treatment of **11** with MsCl and Et_3N in CH_2Cl_2 afforded the mesylate mixed anhydride **12**. Hydrolysis of the more reactive mixed anhydride with $NaHCO_3$ in aqueous THF gave mesylate carboxylate **15**, which underwent an intramolecular S_N2 reaction with inversion (red arrow) to provide the desired lactone **14** in 33% overall yield from hydroxy ester **6**. Unfortunately, Grob fragmentation with loss of CO_2 (blue arrows) to give triene **13** in 46% overall yield from **6** was the major reaction. An even greater percentage of **13** was obtained using DBU or solid K_2CO_3 as bases in THF. This fragmentation reaction was previously noted by Wu and Sun, but has not been widely observed in β-lactone synthesis.[5] This fragmentation process is quite distinct from the well-known decarboxylation of β-lactones that occurs on heating;[13] lactone **14** is stable under the reaction conditions. These results suggested that trans hydroxy esters **6** and **3** are not ideal precursors for vibralactone (**1**) synthesis.

On the other hand, lactone formation from cis hydroxy ester **5**, the minor product from the $NaBH_4$ reduction, proceeded cleanly and in high yield. Hydrolysis of the methyl ester with KOH in MeOH at 60 °C afforded the hydroxy acid, which was treated with TsCl in pyridine to form the mixed anhydride, which cyclized to give lactone **14** in 83% yield (see eq 1).



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We therefore turned our attention to methods to selectively prepare the cis hydroxy ester **5**. As expected, Mitsunobu reaction with the hindered secondary alcohol **6** failed, even using procedures optimized for hindered alcohols.[14] Fraga reported that reduction of ethyl 1-allyl-2-oxocyclohexanonecarboxylate with $(n\text{-Bu})_4NBH_4$ in MeOH gave an 8.2:1 mixture favoring the cis hydroxy ester.[12] Eventually, we found that reduction of **9** with Me_4NBH_4 in 1:1 THF/MeOH at 25 °C afforded a 3:2 mixture of **5** and **6** from which pure **5** was isolated in 42% yield along with a 1:2 mixture of **5** and **6** in 40% yield (see Scheme 3). This mixture can easily be recycled by oxidation with Dess-Martin periodinane to give ketone **9** in 94% yield.

Hydrolysis of the methyl ester of **5** with KOH in MeOH at 60 °C provided the hydroxy acid, which was treated with $NaHCO_3$, I_2 and KI in aqueous THF to give the desired iodolactones **16** (63%) and **17** (32%). These iodolactones were separated to aid in characterization of intermediates, but can be carried through as a mixture because the sequence converges at cis hydroxy acid **2**. Both isomers are γ-lactones with carbonyl absorptions at 1752 and 1749 cm^{-1}, respectively. The methyl groups absorb between δ 1.92–2.0 as expected for CMe_2I. X-ray crystal structure determination of the minor isomer **17** established the stereochemistry of the lactone ring and confirmed our stereochemical assignment of the hydroxy group.[8] Ozonolysis at −78 °C followed by reduction of the ozonide with Ph_3P afforded a dialdehyde, which was immediately subjected to Corey's protocol (Bn_2NH•TFA in benzene)[15] to effect the intramolecular aldol reaction. This sequence converted cyclohexenes **16** and **17** to cyclopentenals **18** and **19** in 80% and 90% yields, respectively.

Completion of the synthesis required reduction of the aldehyde to the alcohol, retro-iodolactonization to regenerate the unsaturated acid, and β-lactone formation. Reduction of **18** or **19** with $NaBH_4$ gave a complex mixture, probably as a result of the instability of the tertiary iodide. Fortunately, retro-iodolactonization of **18** and **19** under mild conditions with activated Zn[16] in 4:1 THF/HOAc at 0 °C for 15 min regenerated prenyl acid **2** without pinacol coupling of the aldehyde.[17] We chose to prepare the β-lactone prior to reduction of the aldehyde because this would not require the use of a protecting group for the primary alcohol. Treatment of **2** with TsCl in pyridine for 12 h at 0 to 4 °C afforded mixed anhydride **20**, which cyclized to give β-lactone **21** in 50% overall yield from **18** and 53% overall yield from **19**. Unfortunately, reduction of the aldehyde of **21** with $NaBH_4$ in MeOH also hydrolyzed the β-lactone to the hydroxy methyl ester. This problem was easily solved using a procedure developed by Corey and Schreiber for reductions of ketones in the presence of the β-lactone of omuralide.[18] Reduction of aldehyde **21** with $NaBH_4$ in 100:1 DME/H_2O for 40 min at 0 to 25 °C gave (±)-vibralactone (**1**) in 78% yield with spectral data identical to those reported.[1]

In conclusion, we have developed a ten-step synthesis of (±)-vibralactone (**1**) from methyl 2-methoxy benzoate and prenyl bromide that proceeds in 9% (higher if recycled **6** is included) overall yield. No protecting groups are used except for the novel use of an iodolactone to protect both the prenyl double bond and carboxylic acid. This synthesis is readily amenable to analogue preparation and we are currently adapting it to the preparation of optically pure vibralactone using the diastereoselective reductive alkylation of chiral benzamides.[19]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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8. The stereochemistry of alcohols 5 and 6 was established by an IR study in dilute (0.1 M) CCl_4 solution and a 1D NOESY experiment. Trans hydroxy ester 6 showed two equally intense peaks at 1734 cm $^{-1}$ (free carbonyl) and 1711 cm^{-1} (hydrogen bonded carbonyl) while cis hydroxy ester 5 showed one medium peak at 1734 cm^{-1} (free carbonyl) and a very strong peak at 1716 cm^{-1} (hydrogen bonded carbonyl).[9] In a 1D NOESY experiment, irradiation of the C*H*OH hydrogen at δ 4.14 in 6 showed NOEs to the hydroxy hydrogen at δ 2.77 and the ring hydrogens at δ 1.88–1.76. Irradiation of the C*H*OH hydrogen at δ 3.79 in 5 showed NOEs to the hydroxy hydrogen at δ 3.28 and the allylic side chain methylene group at δ 2.52–2.40 establishing that the hydrogen is cis to the prenyl side chain.
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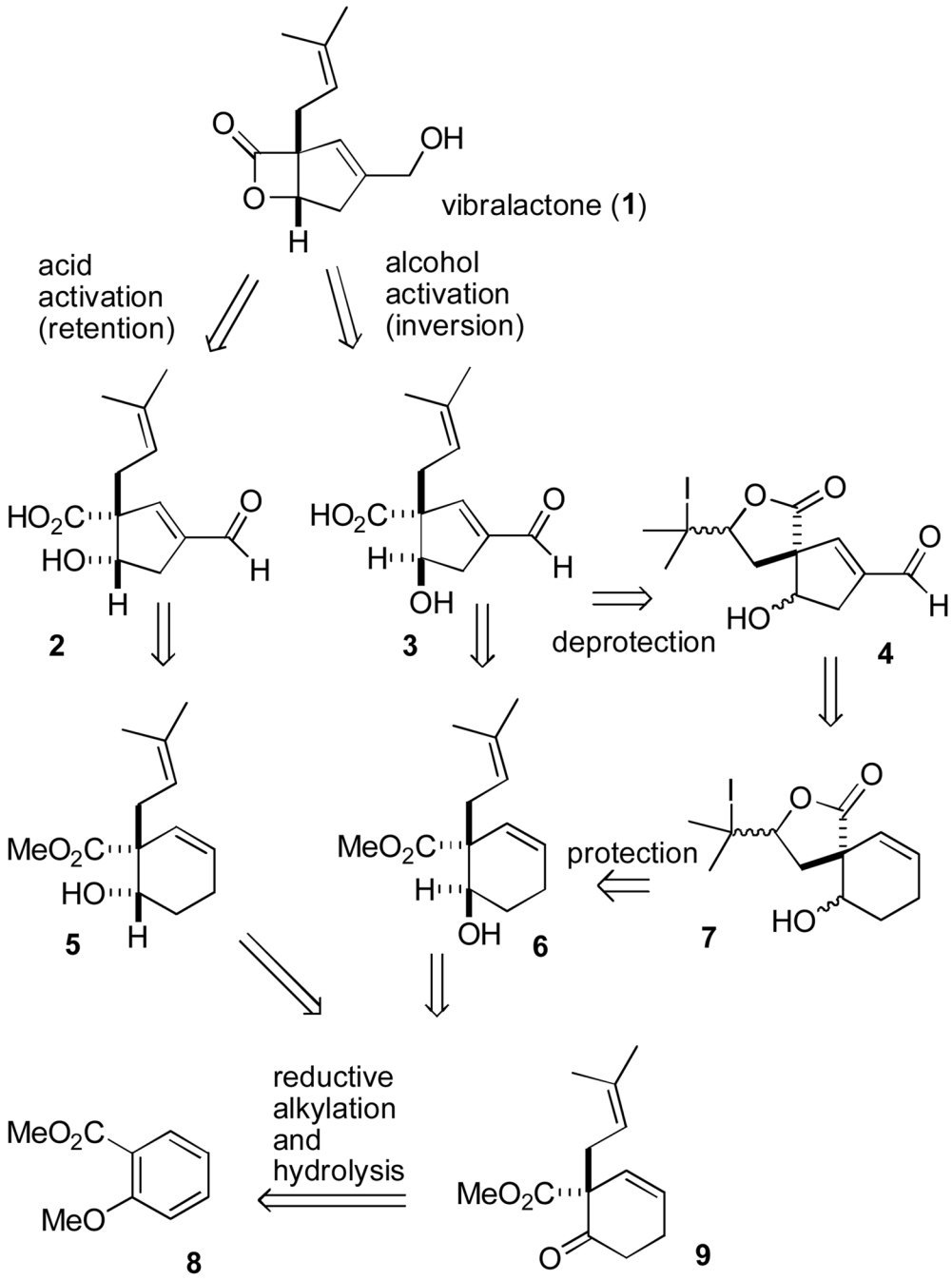

Scheme 1.
Retrosynthesis of (±)-Vibralactone (**1**)

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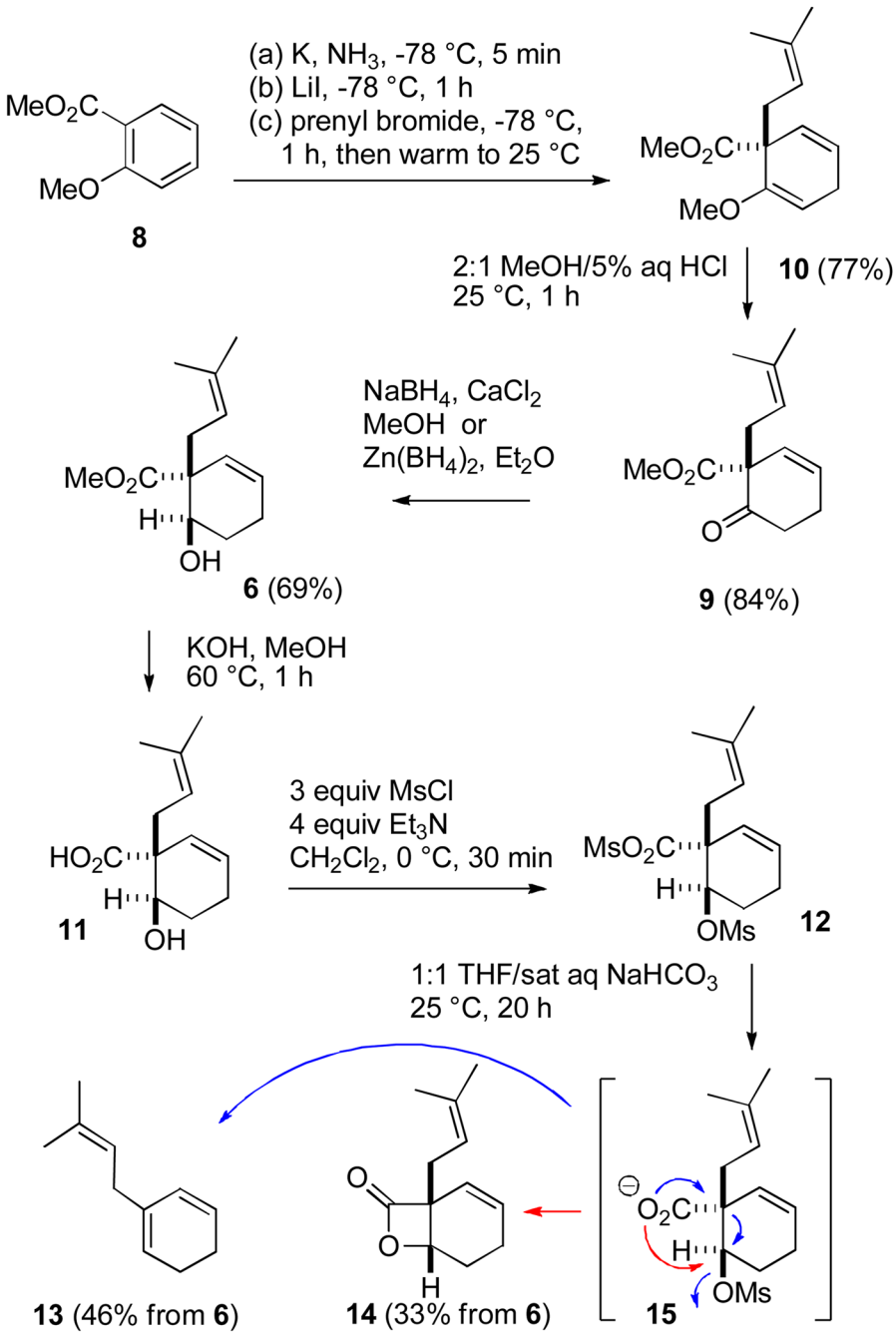

Scheme 2.
Synthesis of Model β-Lactone **14**

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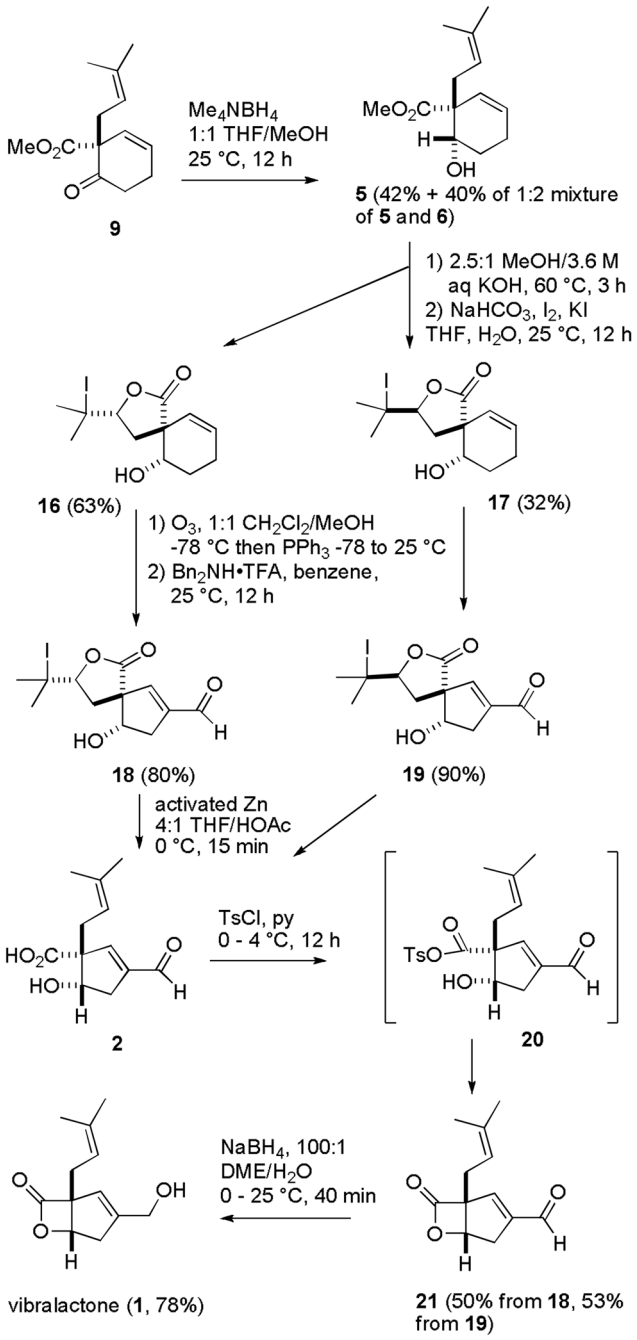

Scheme 3.
Synthesis of (±)-Vibralactone (**1**)