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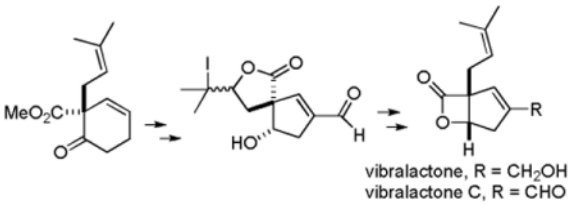
# Synthesis of (±)- and (-)-Vibralactone and Vibralactone C†

**Quan Zhou** and **Barry B. Snider***
*Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110*

## Abstract




Mander reductive alkylation of methyl 2-methoxybenzoate with prenyl bromide and hydrolysis of the enol ether afforded methyl 6-oxo-1-prenyl-2-cyclohexenecarboxylate. This was converted in five steps (reduction of the ketone, saponification, iodolactonization, ozonolysis and intramolecular aldol reaction) to a spiro lactone cyclopentenal. An efficient first synthesis of (±)-vibralactone was completed by retro-iodolactonization with activated Zn, formation of the β-lactone (vibralactone C), and reduction of the aldehyde. Except for the novel use of an iodolactone to protect both the prenyl double bond and carboxylic acid, no protecting groups were used. A similar sequence starting with asymmetric reductive alkylation of the (2*S*)-2-methoxymethoxymethylpyrrolidine amide of 2-methoxybenzoic acid with prenyl bromide afforded (-)-vibralactone confirming the absolute stereochemical assignment that was based on computational methods.

## Introduction

The unusual fused β-lactone vibralactone (**1**) was recently isolated from cultures of the Basidiomycete *Boreostereum vibrans* by Liu and coworkers (see Figure 1).[1] The structure was assigned by detailed spectroscopic analysis and the absolute stereochemistry was assigned by the B3LYP/aug-cc-pVDA//B3LYP/6-31G* computational method. Percyquinnin was originally assigned as a regioisomer of **1**,[2] but has since been shown to have the same planar structure as vibralactone (**1**).[1] Vibralactone inhibits pancreatic lipase with an $IC_{50}$ of 0.4 μg/mL and percyquinnin inhibits lipase with an $IC_{50}$ of 2 μg/mL.[2] 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 modification of either the prenyl side chain or the allylic alcohol. More recently, Liu reported the isolation of four minor congeners of vibralactone, vibralactone B (**4**), vibralactone C (**2**), vibralactone acetate (**3**) and 1,5-secovibralactone (**5**).[4]

The synthesis of vibralactone is a much more challenging problem than its small size would suggest because of the instability of the β-lactone ring and the presence of both an allylic alcohol and a side chain double bond.[5] There are two obvious approaches to form the β-lactone ring of vibralactone (**1**). The standard method of β-lactone formation would involve activation of the acid moiety of cis hydroxy acid **6** followed by displacement with the alkoxide to form the

†We dedicate this paper to Prof. E. J. Corey on the occasion of his 80th birthday.

snider@brandeis.edu.

β-lactone with retention of stereochemistry at the alcohol carbon (see Scheme 1).[6] Alternatively, the alcohol of trans hydroxy acid **7** could be converted to a good leaving group; β-lactone formation by an $S_N2$ reaction with the carboxylate as nucleophile would produce the same β-lactone with inversion at the alcohol carbon. This rarely used approach to β-lactones has recently been improved by Wu and Sun.[7]

Oxidative cleavage of the cyclohexene double bond of **9** and **10**, followed by an intramolecular aldol reaction should provide the cyclopentenal moieties of **6** and **7**, respectively. Unfortunately, the side chain double bond is more electron rich and will have to be protected before the cyclohexene double bond can be oxidatively cleaved. Iodolactonization[8] of the side chain double bond of **9** or **10** to give **11** would provide a suitable substrate for conversion to cyclopentenal **8**. However, both **9** and **10** have two double bonds that could undergo iodolactonization. Even if iodolactonization occurs selectively as expected and required at the more electron rich side chain double bond, stereoisomeric mixtures of γ- and δ-lactones that will complicate product analysis will be formed. Most importantly, it was not clear whether oxidative cleavage of the double bond and intramolecular aldol reaction to give cyclopentenal **8** could be accomplished in the presence of a reactive tertiary iodide. Retro-iodolactonization of **8** by zinc would form hydroxy acids **6** or **7** with both the side chain double bond and the free acid needed for lactone formation.

Diastereoselective reduction of ketone **13** will provide alcohols **9** and **10**. Surprisingly, this proved to be the most challenging step in the synthesis. Mander reductive alkylation[9] of methyl 2-methoxybenzoate (**12**) with prenyl bromide followed by acidic hydrolysis of the methyl enol ether will provide ready access to ketone **13**.

## Results and Discussion

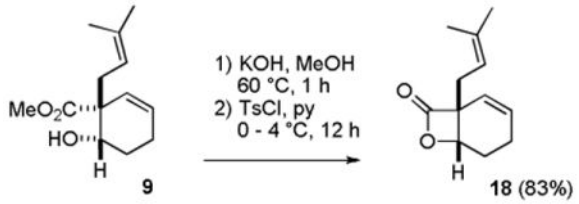
### Formation of and β-lactone formation from hydroxy esters 9 and 10

Reduction of methyl 2-methoxybenzoate (**12**) with K in liquid $NH_3$ at -78 °C, addition of 1,3-pentadiene to consume excess K, LiI to make the lithium dienolate, and prenyl bromide followed by slow warming to 25 °C afforded the alkylated cyclohexadiene **14** in 77% yield (see Scheme 2).[9] Methyl 3-(3-methyl-2-butenyl)-6-methoxy-1,5-cycloexadienecarboxylate, resulting from γ-alkylation of the dienolate, was formed as a minor byproduct, but was easily removed by chromatography. The enol ether of **14** was hydrolyzed with methanolic HCl to give ketone **13** in 84% yield. Reduction of ketone **13** with $NaBH_4$ in MeOH formed a 2:1 mixture of trans hydroxy ester **10** and cis hydroxy ester **9** in high yield. The stereochemistry of alcohols **9** and **10** was established by analysis of IR spectra obtained in dilute (0.1 M) $CCl_4$ solution and 1D NOESY NMR spectra. There were two equally intense peaks at 1734 $cm^{-1}$ (free carbonyl) and 1711 $cm^{-1}$ (hydrogen bonded carbonyl) in the IR spectrum of trans hydroxy ester **10**, whereas there was a medium peak at 1734 $cm^{-1}$ (free carbonyl) and a very strong peak at 1716 $cm^{-1}$ (hydrogen bonded carbonyl) in cis hydroxy ester **9**.[10] Irradiation of the C*H*OH hydrogen of **10** at δ 4.14 in a 1D NOESY experiment 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 of **9** at δ 3.79 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.

Magnus reported that similar ratios of products were produced in the $NaBH_4$ reduction of a related keto amide and also showed that $Zn(BH_4)_2$ gave the trans hydroxy amide with >99:1 selectivity.[11] Reduction of **13** with $Zn(BH_4)_2$ in ether[12] afforded trans hydroxy ester **10** in 69% yield. Reduction with $CaCl_2$ and $NaBH_4$, which selectively provides trans hydroxy esters from 1-alkyl-2-oxocyclohexanone carboxylates,[13] gave a 7.5:1 mixture of **10** and **9**, from which **10** was isolated in 69% yield.

Lactone formation by $S_N2$ reaction with inversion by hydroxy group activation was examined using the now readily available trans hydroxy ester **10**. Hydrolysis of the methyl ester of **10** with KOH in MeOH at 60 °C provided the required trans hydroxy acid **15**. Wu and Sun examined the lactonization of acyclic β-hydroxy acids with inversion. This necessitated activation of the alcohol without also activating the carboyxlic acid because lactonization by acid activation will give the other stereoisomer.[7] Trans hydroxy acid **15** would have to 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 hydroxy group. Treatment of **15** with MsCl and $Et_3N$ in $CH_2Cl_2$ provided the mesylate mixed anhydride **16**. Hydrolysis of the more reactive mixed anhydride with $NaHCO_3$ in aqueous THF gave mesylate carboxylate **19**, which reacted further by an intramolecular $S_N2$ reaction with inversion (red arrow) to provide the desired lactone **18** in 33% overall yield from hydroxy ester **10**. Unfortunately, Grob fragmentation of **19** with loss of $CO_2$ (blue arrows) to give triene **17** in 46% overall yield from **10** was the major reaction. An even greater percentage of **17** 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.[7] This fragmentation process is quite distinct from the well-known decarboxylation of β-lactones that occurs on heating[14] since lactone **18** does not lose carbon dioxide to give triene **17** under the reaction conditions. The low yield of β-lactone **18** from trans hydroxy ester **10** suggested that **7** would not be a good precursor for vibralactone (**1**).

To our delight, lactone formation from cis hydroxy ester **9**, the minor product from the $NaBH_4$ reduction, proceeded cleanly and in high yield. Hydrolysis of the methyl ester of **9** with KOH in MeOH at 60 °C afforded the hydroxy acid. Treatment of the hydroxy acid with TsCl in pyridine as described by Adam[15] formed the hydroxy mixed anhydride, which cyclized providing lactone **18** in 83% yield (see eq 1).




(1)

## Synthesis of (±)-Vibralactone (1)

We now needed to develop a stereoselective route to cis hydroxy ester **9**. As expected, Mitsunobu reaction with the hindered secondary alcohol **10** failed, even using procedures optimized for hindered alcohols.[16] We were encouraged by Fraga's report that reduction of ethyl 1-allyl-2-oxocyclohexanecarboxylate with $(n\text{-Bu})_4NBH_4$ in MeOH gave an 8.2:1 mixture favoring the cis hydroxy ester.[13] Unfortunately, similar reductions of **10** are not nearly as selective; apparently the presence of the double bond in the ring has a significant effect on the reduction stereochemistry. We explored the reduction of **10** with $(n\text{-Bu})_4NBH_4$ and $Me_4NBH_4$ in a variety of solvents. The best result was obtained by reduction of **13** with $Me_4NBH_4$ in 1:1 THF/MeOH at 25 °C to afford a 3:2 mixture of **9** and **10** from which pure **9** was isolated in 42% yield (see Scheme 3). We also isolated a less polar 1:2 mixture of **9** and **10** in 40% yield that can be easily recycled to give ketone **13** in 94% yield by oxidation with Dess-Martin periodinane.

The desired iodolactones **20** (63%) and **21** (32%) were prepared by hydrolysis of the methyl ester of **9** with KOH in MeOH at 60 °C to provide the hydroxy acid, which was treated with $NaHCO_3$, $I_2$ and KI in aqueous THF. 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 **6**. The carbonyl absorptions at 1752 and 1749 $cm^{-1}$, respectively, establish that both isomers are γ-lactones. The methyl groups absorb between δ 1.92-2.0 as expected for $CMe_2I$ groups. X-ray crystal structure determination of the minor isomer **21** established the stereochemistry of the lactone ring and confirmed our stereochemical assignment of the hydroxy group (for details see Supporting Information). Ozonolysis at -78 °C followed by reduction of the ozonide with $Ph_3P$ afforded an unstable dialdehyde, which was immediately subjected to Corey's protocol ($Bn_2NH$•TFA in benzene)[17] to effect the intramolecular aldol reaction. This two-step sequence formed cyclopentenals **22** and **23** in 80% and 90% yields, respectively, from cyclohexenes **20** and **21**.

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 **22** or **23** with $NaBH_4$ gave a complex mixture, probably as a result of the instability of the tertiary iodide. Fortunately, retro-iodolactonization of **22** and **23** under mild conditions with activated Zn[18] in 4:1 THF/HOAc at 0 °C for 15 min regenerated prenyl acid **6** without pinacol coupling of the aldehyde.[19] Acid **6** decomposes if the concentration of HOAc is too high. Therefore, during work up, the reaction was partially concentrated, diluted with heptane, and concentrated to remove the 2:1 heptane-acetic acid azeotrope that boils at 92 °C.[20]

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 crude **6** with TsCl in pyridine for 12 h at 0 to 4 °C afforded mixed anhydride **24**, which cyclized to give β-lactone **2**, which has since been isolated and named vibralactone C, in 50% overall yield from **22** and 53% overall yield from **23**. Unfortunately, reduction of the aldehyde of vibralactone C (**2**) under standard conditions ($NaBH_4$ in MeOH) also hydrolyzed the unstable 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.[21] Reduction of vibralactone C (**2**) 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]

## Unsuccessful Attempts to Convert 10 to (±)-Vibralactone (1)

The conversion of cis hydroxy ester **9** to vibralactone (**1**) proceeded very efficiently, but the reduction of ketone **13** to **9** with $Me_4NBH_4$ was much less selective than the reduction of **13** to trans hydroxy ester **10** with either $Zn(BH_4)_2$ or $NaBH_4$ and $CaCl_2$. Therefore, we decided to convert **10** to trans hydroxy acid **7** and examine its conversion to **1** despite the competing fragmentation to give **17** that was observed in the conversion of trans cyclohexene hydroxy acid **19** to give β-lactone **18**. Hydrolysis of **10** followed by iodolactonization as described for the preparation of **20** and **21** gave iodolactones **25** and **26**, with unknown side chain stereochemistry, in 54% and 26% yield, respectively (see Scheme 4). Ozonolyis and aldol reaction as described for the preparation of cyclopentenals **22** and **23** afforded cyclopentenals **27** (73%) and **28** (82%), respectively. Unfortunately, retro-iodolactonization of either **27** or **28** to give trans hydroxy acid **7** was not as clean as the retro-iodolactionization of either **22** or **23** to give cis hydroxy acid **6**. For reasons that aren't clear, we obtained complex mixtures containing at best about 50% of **7** and uncharacterized side products. Attempts at forming **2** from this mixture by β-lactone formation with inversion by an $S_N2$ reaction were not promising.

## Synthesis of (-)-Vibralactone (1)

We now turned to the synthesis of (-)-vibralactone (**1**) using the Schultz asymmetric Birch reductive alkylation.[22, 23] Reductive alkylations of 2-alkoxymethylpyrrolidine 2-methoxybenzamides proceed in excellent yield with very high diastereoselectivity. Treatment of 2-methoxymethylpyrrolidine 2-methoxybenzamide (**29**) with K in liquid $NH_3$ at -78 °C,

addition of prenyl bromide, and slow warming to 25 °C afforded cyclohexadiene **30** in 65% yield as a single diastereomer whose stereochemistry was assigned by analogy to the products obtained with other alkylating agents (see Scheme 5).[22,23] Spectroscopic analysis of this mixture was complicated by the presence of amide rotamers. Hydrolysis of the enol ether of **30** with methanolic HCl gave ketone **31** in 75% yield. Unfortunately, all attempts at hydrolysis of the amide were unsuccessful. Acid hydrolysis cannot be used because of the reactivity of the side chain double bond. Base treatment will lead to a retro-Dieckmann reaction. Iodolactonization with the ring double bond has been used to cleave similar amides, but was unsuccessful with **31** or **32**.[11,23g-i] The reduction of keto amide of **31** was even more selective for the undesired trans hydroxy amide than the reduction of keto ester **13**.[11] No reaction occurred with $Me_4NBH_4$ in 1:1 THF/MeOH. Reduction with $Me_4NBH_4$ in MeOH at 25 °C afforded a 1:4 mixture of the cis- (desired) and trans- hydroxy amides **32**.

Reductive alkylation of 2-(methoxymethoxymethyl)pyrrolidine 2-methoxybenzamide (**33**) provided a solution to this problem as described by Schultz.[23b-d] Treatment of **33** with K in liquid $NH_3$ at -78 °C, addition of prenyl bromide, and slow warming to 25 °C afforded cyclohexadiene **34** in 76% yield as a single diastereomer whose stereochemistry was assigned by analogy to the products obtained with other alkylating agents (see Scheme 6). Hydrolysis of the MOM and enol ethers of **34** with methanolic HCl gave ketone **35**. In acid, hydroxy amide **35** rearranged to the ammonium ester **36**. Treatment with $NaHCO_3$ and methyl chloroformate provided carbamate ester **37** in 55% overall yield from **34**. We also obtained 15-20% of carbamate ester **39** in which MeOH had added to the side chain double bond during the MOM ether hydrolysis. Unfortunately, keto ester **13** was not formed on treatment of ester **37** with NaOMe in MeOH. A complex mixture, presumably resulting from retro-Dieckmann cyclization, was formed. Protection of the ketone as the enol ether with trimethyl orthoformate and sulfuric acid in MeOH, followed by ester exchange with NaOMe in MeOH afforded optically pure keto ester **14**, an intermediate in the synthesis of (±)-vibralactone (**1**). Unfortunately, the length of this sequence was not appealing.

Reduction of **37** with $Me_4NBH_4$ in 1:1 THF/MeOH was very slow, but in pure MeOH we obtained a 3:2 mixture of cis hydroxy ester **38** and the trans diastereomer. Flash chromatography afforded pure **38** in 39% yield along with 48% of a 1:3 mixture of **38** and the diastereomer, which was recycled by Dess-Martin oxidation to afford **37** in 91% yield. Reduction of keto esters **13** and **37** is much more selective for the desired cis hydroxy esters **9** and **38** (3:2) than the reduction of keto amide **31** to **32** (1:4). We hoped that the selectivity could be improved by the asymmetric reduction of **37**, a strategy that was not applicable to racemic keto ester **13**. Unfortunately, **37** was too hindered to react with chiral oxazaborolidine catalysts.[24] Benzylquininium and benzylquinidinium borohydrides reduce ketones with modest enantiomeric excess.[25] These reagents are very similar to $Me_4NBH_4$, the optimal reagent for obtaining the cis hydroxy ester. We hoped that we would obtain a higher yield of **38** with the matched reagent. Unfortunately, the same 3:2 mixture of **38** and the diastereomer was obtained with both benzylquininium and benzylquinidinium borohydrides.

The conversion of cis hydroxy ester **38** to vibralactone proceeded uneventfully. Hydrolysis with KOH in aqueous MeOH afforded the hydroxy acid that was obtained from methyl ester **9**. Iodolactionization afforded (-)-iodolactone **20** in 56% yield and (-)-iodolactone **21** in 27% yield. The absolute stereochemistry of (-)-**21** was confirmed by an X-ray crystal structure determination (for details see Supporting Information). Ozonolysis and aldol cyclization as in the racemic series afforded (-)-**22** and (-)-**23**, which were treated with Zn to give hydroxy acid **6** which was treated with TsCl and pyridine to give (-)-vibralactone C (**2**). Reduction as in the racemic series afforded (-)-vibralactone (**1**). The rotation of synthetic **1**, $[\alpha]^{25}_D$ = -129 (*c* 0.27, $CHCl_3$), is very close to that of natural **1**, $[\alpha]^{26}_D$ = -135.1 (*c* 0.52, $CHCl_3$). This confirms the assignment of stereochemistry based on the B3LYP/aug-cc-pVDA//B3LYP/6-31G*

computational method.[1] The rotation of synthetic **2**, $[\alpha]^{25}_{D}$ = -126.5 (*c* 0.4, $CHCl_3$), has the same sign, but is not close to that of natural **2**, $[\alpha]^{17}_{D}$ = -288.9 (*c* 0.08, $CHCl_3$). However, the latter value may not be very accurate because of the very low concentration.

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 **10** 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. Starting with 2-methoxymethoxymethylpyrrolidine 2-methoxybenzamide (**33**) we have prepared (-)-vibralactone (**1**) in eleven steps and 4.8% (higher if recycled trans hydroxy ester is included) overall yield. This synthesis is readily amenable to analogue preparation. Vibralactone C (**2**) was prepared, prior to its isolation,[4] as the ultimate precursor to vibralactone.

## Experimental Section

### Methyl 2-Methoxy-1-(3-methyl-2-butenyl)-2,5-cyclohexadiene-1-carboxylate (14)

*t*-BuOH (0.44 g, 6.0 mmol) was added to a solution of methyl 2-methoxybenzoate (**12**) (1.0 g, 6.0 mmol) in dry THF (5 mL) and the solution was cooled to -78 °C. Liquid ammonia (60 mL) was condensed into this mixture under nitrogen and potassium was added until the reaction mixture maintained a deep blue coloration for 5 min. 1,3-Pentadiene was added dropwise (2-20 drops) until the solution turned yellow-brown. Anhydrous lithium iodide (1.8 g, 13 mmol) was added and the solution was stirred for 1 h at -78 °C. A solution of prenyl bromide (2.69 g, 18 mmol) in dry THF (6 mL) was added. The resulting light yellow solution was stirred for another hour. The reaction was allowed to warm to 25 °C, and the ammonia was removed with a stream of nitrogen. Brine was added and the reaction mixture was extracted with $Et_2O$. The combined $Et_2O$ extracts were washed with 10% aqueous sodium thiosulfate solution, water, and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to give 2.44 g of crude **14** as a yellow oil. Flash chromatography (20:1 hexanes/EtOAc) gave 1.10 g (77%) of pure **14**: $^1$H NMR 5.88 (dt, 1, *J* = 9.6, 3.3), 5.42 (br d, 1, *J* = 9.6), 4.94 (t, 1, *J* = 7.6), 4.83 (dd, 1, *J* = 3.7, 3.7), 3.70 (s, 3), 3.52 (s, 3), 2.86 (dddd, 1, *J* = 22.4, 3.7, 3.3, 3.0), 2.77 (dddd, 1, *J* = 22.4, 3.7, 3.3, 3.0), 2.73 (dd, 1, *J* = 14.4, 7.6), 2.43 (dd, 1, *J* = 14.4, 7.6), 1.66 (s, 3), 1.59 (s, 3); $^{13}$C NMR 174.1, 152.8, 133.7, 126.9, 126.4, 119.3, 93.3, 54.2, 52.4, 51.8, 33.3, 26.4, 26.0, 17.9; IR (neat) 1735, 1689, 1235; HRMS (EI) calcd for $C_{14}H_{20}O_3$ ($M^+$) 236.1413, found 236.1415. The 22.4 Hz geminal coupling constant is characteristic of 1,4-cyclohexadienes.[26]

### Methyl (1*R**, 6*S*)-6-Hydroxy-1-(3-methyl-2-butenyl)-2-cyclohexenecarboxylate (9)

$Me_4NBH_4$ (166 mg, 1.86 mmol) was added to a solution of ketone **13** (207 mg, 0.93 mmol) in MeOH (5 mL) and THF (5 mL) at 0 °C. The ice bath was removed and the reaction was stirred at 25 °C for 12 h. The solvent was removed under reduced pressure. The residue was diluted with EtOAc, and the resulting solution was washed with 10% aqueous HCl, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated to give 220 mg of crude **9** and **10**. Flash chromatography (12:1 hexanes/EtOAc) gave 85 mg (40%) of a 2:1 mixture of **10** and **9** followed by 88 mg (42%) of **9**: $^1$H NMR 5.78 (ddd, 1, *J* = 9.8, 3.7, 3.7), 5.67 (br d, 1, *J* = 9.8), 5.07 (dd, 1, *J* = 7.2, 7.2), 3.79 (ddd, 1, *J* = 9.2, 9.2, 3.0), 3.71 (s, 3), 3.28 (d, 1, *J* = 9.2, OH), 2.52-2.40 (m, 2), 2.25-2.05 (m, 2), 1.95-1.86 (m, 1), 1.84-1.73 (m, 1), 1.70 (br s, 3), 1.62 (br s, 3); $^{13}$C NMR 176.2, 135.2, 128.5, 127.6, 118.3, 71.1, 52.3, 52.0, 35.8, 27.4, 26.0, 23.5, 17.9; IR 3509, 3029, 1728, 1713; HRMS (EI) calcd for $C_{13}H_{20}O_3$ ($M^+$) 224.1413, found 224.1415.

### (3*S**,5*R*,10*S*)-10-Hydroxy-3-(1-iodo-1-methylethyl)-2-oxaspiro[4.5]dec-6-en-1-one (20) and (3*R**,5*R*,10*S*)-10-Hydroxy-3-(1-iodo-1-methylethyl)-2-oxaspiro[4.5]dec-6-en-1-one (21)

A solution of hydroxy ester **9** (316 mg, 1.41 mmol) in MeOH (15 mL) and 6 mL of 3.6 M aqueous KOH solution was heated at 60 °C for 3 h and cooled. The MeOH was removed under

reduced pressure. The residue was neutralized with 10% aqueous HCl to pH 1 ~ 2, and then treated with solid sodium bicarbonate until $CO_2$ evolution ceased. THF (15 mL), KI (468 mg, 2.82 mmol) and $I_2$ (716 mg, 2.82 mmol) were then added. The mixture was stirred overnight, quenched with 10% aqueous sodium thiosulfate solution, and extracted with EtOAc. The extracts were washed with water and brine, dried ($MgSO_4$), and concentrated to give 645 mg of crude lactones **20** and **21**. Flash chromatography (2:1 hexanes/EtOAc) gave 297 mg (63%) of **20** followed by 153 mg (32%) of **21**. A sample of **21** was recrystallized for X-ray crystal structure determination by dissolution in $Et_2O$ at 25 °C and cooling to 4 °C for 2 d.

Data for **20**: mp 92-93 °C (decomposition); $^1$H NMR 5.93 (ddd, 1, *J* = 10.0, 3.7, 3.7), 5.58 (br d, 1, *J* = 10.0), 4.17 (dd, 1, *J* = 10.4, 6.4), 3.76 (ddd, 1, *J* = 10.4, 7.6, 2.5), 2.56 (dd, 1, *J* = 12.4, 10.4), 2.46-2.38 (m, 1), 2.35 (d, 1, *J* = 7.6, OH), 2.33-2.26 (m, 1), 2.26 (dd, 1, *J* = 12.4, 6.4), 2.22-2.12 (m, 1), 2.00 (s, 3), 1.98 (s, 3), 1.91-1.83 (m, 1); $^{13}$C NMR 177.0, 130.9, 123.7, 84.0, 70.8, 51.4, 46.8, 38.6, 34.1, 31.4, 26.6, 23.9; IR 3444, 1752; HRMS (EI) calcd for $C_{12}H_{17}IO_3$ ($M^+$) 336.0229, found 336.0223.

Data for **21**: mp 104-107 °C (decomposition); $^1$H NMR 5.96 (ddd, 1, *J* = 10.0, 4.8, 2.4), 5.45 (br d, 1, *J* = 10.0), 3.87-3.78 (m, 2), 2.54 (dd, 1, *J* = 13.6, 7.2), 2.37-2.13 (m, 3), 2.26 (dd, 1, *J* = 13.6, 9.0), 2.00 (s, 3), 1.92 (s, 3), 1.88 (d, 1, *J* = 5.6, OH), 1.84-1.75 (m, 1); $^{13}$C NMR 177.0, 131.2, 126.7, 85.3, 75.2, 52.0, 50.6, 42.6, 33.2, 33.0, 27.4, 24.3; IR 3448, 1749; HRMS (EI) calcd for $C_{12}H_{17}IO_3$ ($M^+$) 336.0229, found 336.0221.

### (3*S**,5*R*,9*S*)-3-(1-Iodo-1-methylethyl)-9-hydroxy-1-oxo-2-oxaspiro[4.4]non-6-ene-7-carboxaldehyde (22)

A solution of **20** (170 mg, 0.50 mmol) in a mixture of dry $CH_2Cl_2$ (10 mL) and MeOH (10 mL) was ozonolyzed at -78 °C until the solution turned light blue and then purged with oxygen until the blue color disappeared. The solution was then treated with $PPh_3$ (157 mg, 0.60 mmol) and allowed to slowly warm to 25 °C. To this solution was added 40 mL of dry benzene and the solution was then concentrated to 5 mL. Another 10 mL of dry benzene was added and the solution was concentrated to 5 mL again. Finally another 10 mL dry benzene and $Bn_2NH$•TFA (30 mg, 0.10 mmol) was added and the solution was stirred overnight. The solvent was removed under reduced pressure to give crude **22**. Flash chromatography (2:1 hexanes/EtOAc) gave 140 mg (80%) of pure **22**: $^1$H NMR 9.73 (s, 1), 6.61 (br s, 1), 4.52 (ddd, 1, *J* = 8.4, 8.4, 8.8), 4.20 (dd, 1, *J* = 9.7, 6.7), 3.01 (dd, 1, *J* = 16.4, 8.4), 2.76 (br dd, 1, *J* = 16.4, 8.4), 2.76 (d, 1, *J* = 8.8, OH), 2.59 (dd, 1, *J* = 13.6, 6.7), 2.52 (dd, 1, *J* = 13.6, 9.7), 2.02 (s, 3), 1.99 (s, 3); $^{13}$C NMR 188.8, 174.7, 147.7, 144.8, 85.5, 79.0, 61.7, 45.6, 37.4, 36.2, 34.1, 31.3; IR 3460, 1763, 1683, 1188; HRMS (CI) calcd for $C_{12}H_{16}IO_4$ ($MH^+$) 351.0094, found 351.0091.

An identical reaction with (-)-**20** afforded (-)-**22**: $[\alpha]^{25}_D$ = -66.1 (c 0.95, $CHCl_3$).

### (1*R**,5*S*)-1-(3-methyl-2-buten-1-yl)-7-oxo-6-oxabicyclo[3.2.0]hept-2-ene-3-carboxaldehdye (Vibralactone C, 2)

A slurry of iodolactone **23** (128 mg, 0.36 mmol) in THF (6 mL) and activated Zn (351 mg, 5.4 mmol) was treated with AcOH (1.5 mL). The mixture was stirred at 0 °C for 15 min, diluted with EtOAc, and filtered through a pad of silica gel. The combined filtrates were concentrated under reduced pressure to about 5 mL volume. 20 mL of heptane was added and the resulting solution was again concentrated under reduced pressure to give 126 mg of crude hydroxy acid **6**. Addition of heptane and reconcentration aided in the removal of acetic acid.

A solution of crude hydroxy acid **6** in dry pyridine (6 mL) was cooled at 0 °C and TsCl (103 mg, 0.54 mmol) was added. The mixture was stirred at 0 °C for 1 h, and then sealed and placed in a refrigerator (4 °C) overnight. The mixture was poured onto crushed ice and extracted with

EtOAc. The combined extracts were washed with saturated $NaHCO_3$, water, and brine, dried ($MgSO_4$) and concentrated to give 51 mg of crude **2**. Flash chromatography on MeOH-deactivated silica gel (4:1 hexanes/EtOAc) gave 40 mg (53%) of **2**: $^1$H NMR 9.84 (s, 1), 6.67 (s, 1), 5.12 (br t, 1, *J* = 7.2), 4.90 (d, 1, *J* = 6.1), 3.06 (d, 1, *J* = 19.6), 2.90 (dd, 1, *J* = 19.6, 6.1), 2.75 (dd, 1, *J* = 15.2, 7.6), 2.59 (dd, 1, *J* = 15.2, 7.6), 1.74 (br s, 3), 1.66 (br s, 3); $^{13}$C NMR 188.9, 170.0, 146.8, 144.6, 137.2, 116.2, 78.0, 76.6, 34.2, 27.3, 25.8, 18.0; IR 1819, 1684, 1612, 1106; HRMS (EI) calcd for $C_{12}H_{14}O_3$ ($M^+$) 206.0943, found 206.0942.

An identical reaction with (-)-**23** afforded (-)-**2**: $[\alpha]^{25}_D$ = -126.5 (c 0.4, $CHCl_3$) [lit.[4] $[\alpha]^{17}_D$ = -288.9 (c 0.08, $CHCl_3$)].

Following the procedure for conversion of **23** to **2**, a slurry of iodolactone **22** (89 mg, 0.25 mmol) in THF (6 mL) and activated Zn (330 mg, 5.0 mmol) was treated with AcOH (1.5 mL) to give 91 mg of crude hydroxy acid **6**. A solution of crude hydroxy acid **6** in dry pyridine (6 mL) was cooled at 0 °C and treated with TsCl (96 mg, 0.50 mmol) to give 53 mg of crude **2**. Flash chromatography on MeOH-deactivated silica gel (4:1 hexanes/EtOAc) gave 26 mg (50%) of **2**.

An identical reaction with (-)-**22** afforded (-)-**2**: $[\alpha]^{25}_D$ = -126.5 (c 0.4, $CHCl_3$) [lit.[4] $[\alpha]^{17}_D$ = -288.9 (c 0.08, $CHCl_3$)].

### (1*R**,5*S*)-3-(Hydroxymethyl)-1-(3-methyl-2-buten-1-yl)-6-oxabicyclo[3.2.0]hept-2-en-7-one (Vibralactone, 1)

$NaBH_4$ (8 mg, 0.2 mmol) was added to a stirred solution of aldehyde **2** (20 mg, 0.1 mmol) in DME (5 mL) and $H_2O$ (two drops) at 0 °C. The solution was stirred for 10 min and allowed to warm to 25 °C over 30 min. The solvent was removed under reduced pressure. The residue was taken up in EtOAc and the solution was washed with water and brine, dried ($MgSO_4$), and concentrated to give 22 mg of crude **1**. Flash chromatography (2:1 hexanes/EtOAc) gave 15.6 mg (78%) of pure vibralactone (**1**): $^1$H NMR 5.62 (br s, 1), 5.13 (br dd, 1, *J* = 7.6, 7.6), 4.81 (d, 1, *J* = 4.4), 4.25 (br d, 2, *J* = 4.8), 2.77 (dd, 1, *J* = 19, 4.4), 2.75 (d, 1, *J* = 19), 2.62 (dd, 1, *J* = 15.2, 7.6), 2.43 (dd, 1, *J* = 15.2, 7.6), 1.72 (br s, 3), 1.64 (br s, 3), 1.65-1.63 (1, OH, partially obscured by Me group); $^{13}$C NMR 172.9, 146.5, 136.0, 122.5, 117.2, 78.4, 75.1, 61.4, 37.3, 27.6, 25.8, 18.0; IR 3407, 1815, 1110; HRMS (CI) calcd for $C_{12}H_{17}O_3$ ($MH^+$) 209.1178, found 209.1176.

An identical reaction with (-)-**2** afforded (-)-**1**: $[\alpha]^{25}_D$ = -129 (c 0.27, $CHCl_3$) [lit.[1] $[\alpha]^{26}_D$ = -135.1 (c 0.52, $CHCl_3$).

### (2*S*)-2-[(Methoxymethoxy)methyl]-1-[[(1*R*)-2-methoxy-1-(3-methyl-2-butenyl)-2,5-cyclohexadien-1-yl]carbonyl]-pyrrolidine (34)

A solution of benzamide **33**[23c] (540 mg, 1.93 mmol) and *t*-BuOH (143 mg, 1.93 mmol) in THF (5 mL) and liquid ammonia (60 mL) at -78 °C was treated with potassium metal in small pieces until the reaction mixture maintained a deep blue coloration for 20 min. A solution of prenyl bromide (863 mg, 5.79 mmol) in THF (4 mL) was added. The reaction was stirred at -78 °C for an hour and was allowed to slowly warm to 25 °C while the ammonia was evaporated. Water was added and the reaction was extracted with EtOAc. The combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated to give 1.32 g of crude prenyl amide **34**. Flash chromatography (3:1 hexanes/EtOAc) gave 517 mg (76%) of pure **34** as a 3:1 mixture of rotamers: $[\alpha]^{25}_D$ = -40.3 (*c* 1.62, $CHCl_3$); $^1$H NMR 5.84 (dt, 1, *J* = 9.6, 3.3), 5.38 (br d, 0.75 × 1, *J* = 9.6), 5.35 (br d, 0.25 × 1, *J* = 9.6), 4.99 (dd, 1, *J* = 7.6, 7.6), 4.71 (dd, 1, *J* = 3.7, 3.7), 4.63 (d, 1, *J* = 5.6), 4.61 (d, 0.75 × 1,*J* = 5.6), 4.59 (d, 0.25 × 1, *J* = 5.6), 4.40-4.26 (m, 1), 3.77 (dd, 0.75 × 1, *J* = 9.5, 3.5), 3.73 (dd, 0.25 × 1, *J* = 9.5, 3.5), 3.70-3.62 (m, 1), 3.54-3.23 (m, 2),

3.48 (s, 0.25 × 3), 3.47 (s, 0.75 × 3), 3.36 (s, 0.75 × 3), 3.35 (s, 0.25 × 3), 2.89-2.69 (m, 3), 2.49 (dd, 0.75 × 1, *J* = 14.4, 6.8), 2.38 (dd, 0.25 × 1, *J* = 14.4, 6.8), 1.94-1.69 (m, 4), 1.65 (s, 3), 1.56 (s, 3); $^{13}$C NMR 170.94 (0.25 × 1), 170.45 (0.75 × 1), 153.18 (0.75 × 1), 153.79 (0.25 × 1), 133.19 (0.25 × 1), 133.14 (0.75 × 1), 127.11 (0.25 × 1), 126.53 (0.75 × 1), 125.83 (0.75 × 1), 125.53 (0.25 × 1), 120.03 (0.75 × 1), 119.99 (0.25 × 1), 96.79 (0.75 × 1), 96.63 (0.25 × 1), 92.58 (0.25 × 1), 92.51 (0.75 × 1), 67.57 (0.75 × 1), 67.44 (0.25 × 1), 58.26 (0.75 × 1), 58.05 (0.25 × 1), 55.15 (0.25 × 1), 55.10 (0.75 × 1), 54.04 (0.25 × 1), 54.00 (0.75 × 1), 52.2, 46.35 (0.25 × 1), 46.13 (0.75 × 1), 34.9, 26.80 (0.75 × 1), 26.76 (0.25 × 1), 26.66 (0.25 × 1), 26.59 (0.75 × 1), 26.1, 24.83 (0.75 × 1), 24.77 (0.25 × 1), 17.86 (0.75 × 1), 17.84 (0.25 × 1); IR (neat) 1685, 1635; HRMS (EI) calcd for $C_{20}H_{31}NO_4$ ($M^+$) 349.2253, found 349.2256.

### Methyl (2*S*)-2-[[[[(1*R*)-1-(3-Methyl-2-butenyl)-6-oxo-2-cyclohexen-1-yl]carbonyl]oxy] methyl]-1-pyrrolidinecarboxylate (37)

A solution of **34** (375 mg, 1.07 mmol) in methanol (3 mL) and 10% aqueous HCl (1.5 mL) in a sealed tube was irradiated in a microwave oven at 65 °C for 8 min and cooled to 25 °C. The solution was then neutralized with saturated $NaHCO_3$ to pH 6 and concentrated. The residue was extracted with $CH_2Cl_2$ (20 mL × 3). The combined $CH_2Cl_2$ layers were washed with brine, dried ($Na_2SO_4$), and concentrated to give 449 mg of crude amine **36**, which was immediately dissolved in dry $CH_2Cl_2$ (6 mL). This solution was cooled to 0 °C and treated with solid $NaHCO_3$ (90 mg, 1.07 mmol) and methyl chloroformate (100 μL, 1.28 mmol). The solution was stirred 1 h at 0 °C and another 2 h at 25 °C. Water was added, and the reaction mixture was extracted with $CH_2Cl_2$. The organic layers were washed with brine, dried ($Na_2SO_4$), and concentrated to give 300 mg of crude **37**. Flash chromatography (2:1 hexanes/EtOAc) gave 206 mg (55%) of pure **37**, which is a 1:1 mixture of rotamers:[27] $[\alpha]^{25}_D$ = -81.8 (*c* 1.16, $CHCl_3$); $^1$H NMR 6.07 (br, 1, $W_{1/2}$ = 20.0), 5.69 (br d, 1, *J* = 9.6), 4.97 (br, 1, $W_{1/2}$ = 14.0), 4.28-3.94 (m, 3), 3.70 (br s, 0.5 × 3), 3.69 (br s, 0.5 × 3), 3.53-3.26 (m, 2), 2.78-2.37 (m, 6), 2.03-1.71 (m, 4), 1.66 (br s, 3), 1.60 (br s, 3); $^{13}$C NMR 207.0, 170.7, 155.4, 135.5, 129.3, 128.5, 118.0, (65.5, 65.1), 60.3, (55.9, 55.2), (52.4, 52.3), (46.9, 46.5), 38.0, 33.5, (28.6, 27.7), 25.9, 25.4, (23.8, 22.9), 17.9; IR (neat) 1740, 1702, 1450, 1385, 1214; HRMS (EI) calcd for $C_{19}H_{27}NO_5$ ($M^+$) 349.1889, found 349.1888.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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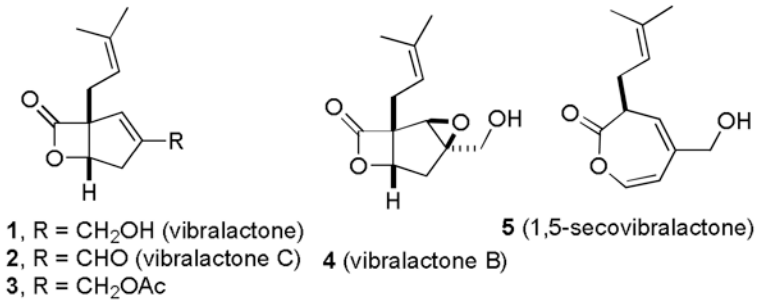
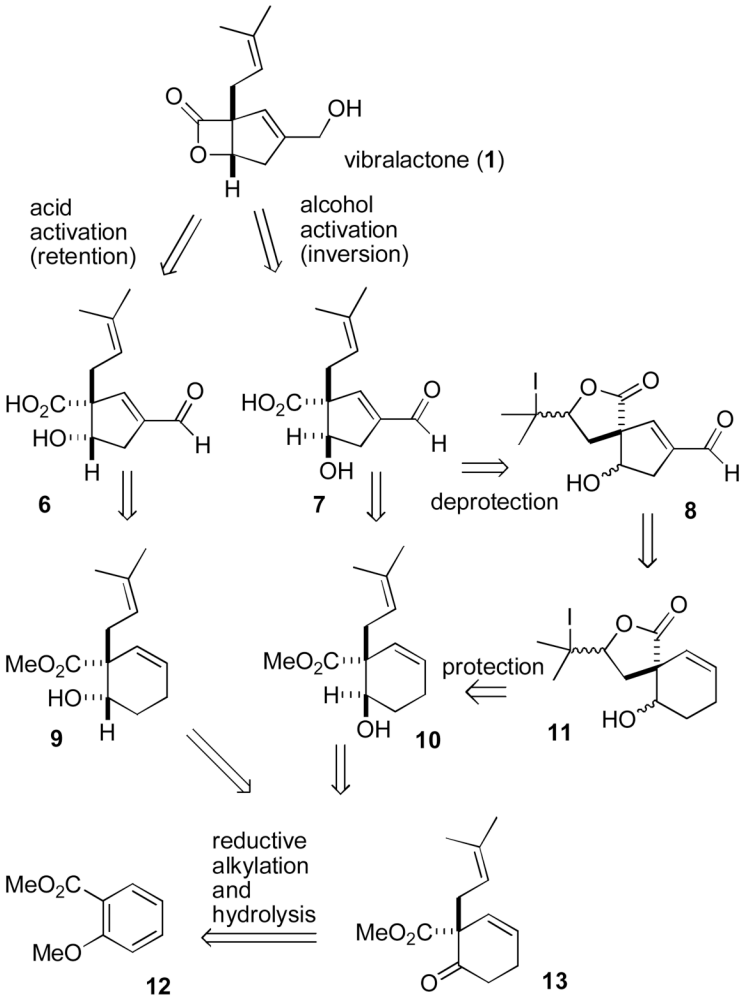



**1**, R = $CH_2OH$ (vibralactone)
**2**, R = CHO (vibralactone C)
**3**, R = $CH_2OAc$

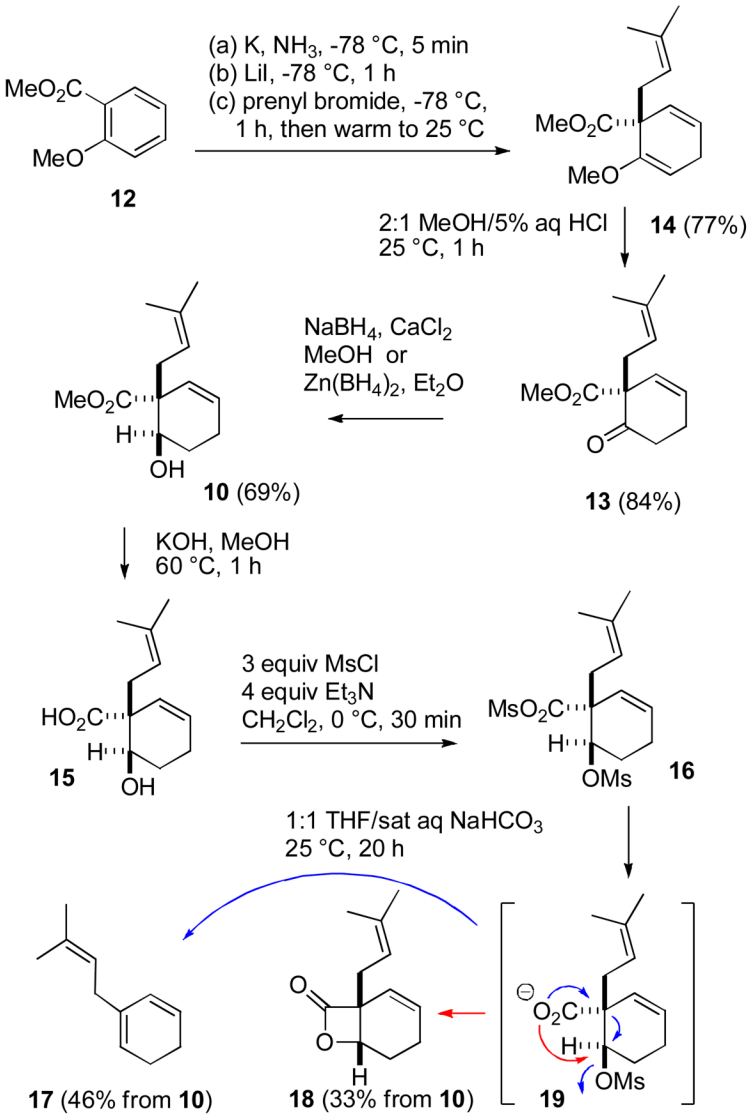
**4** (vibralactone B)

**5** (1,5-secovibralactone)

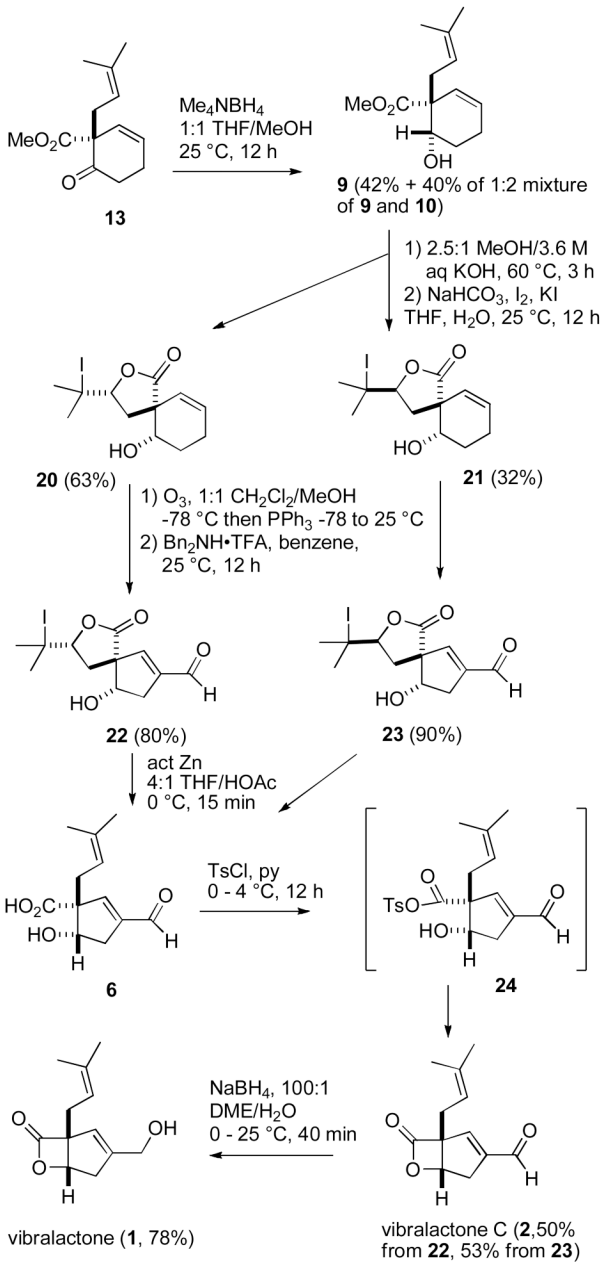
**FIGURE 1.**
Structures of vibralactone (**1**), vibralactone B (**4**), vibralactone C (**2**), and 1,5-secovibralactone (**5**).



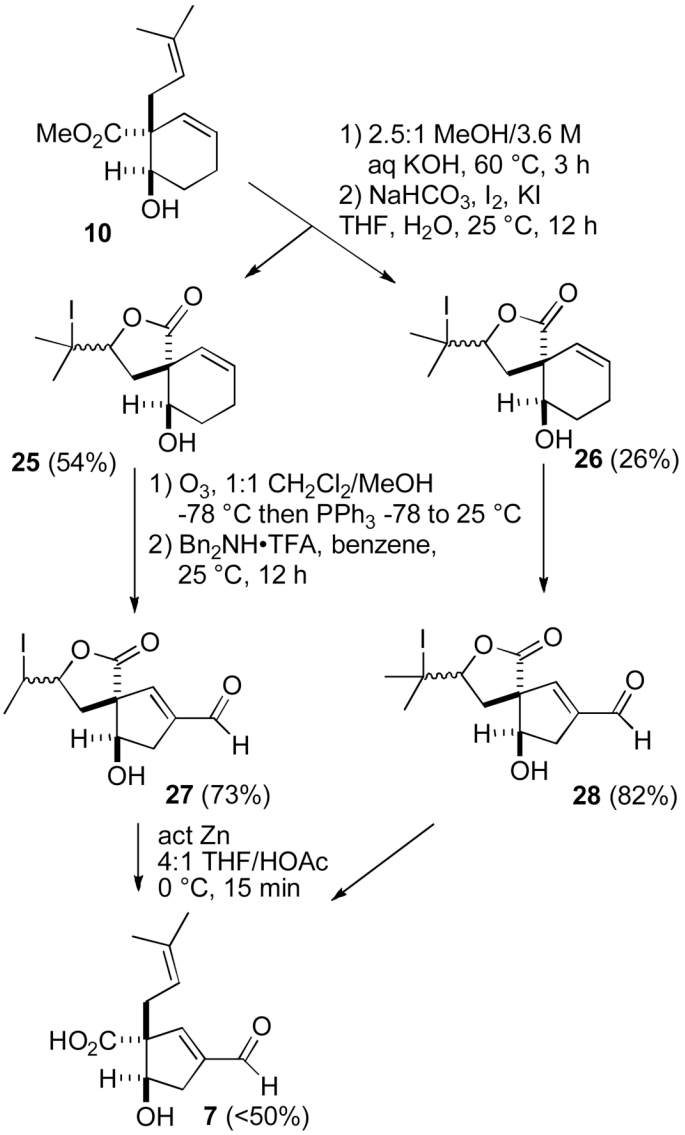

**Scheme 1. Retrosynthesis of (±)-Vibralactone (1)**



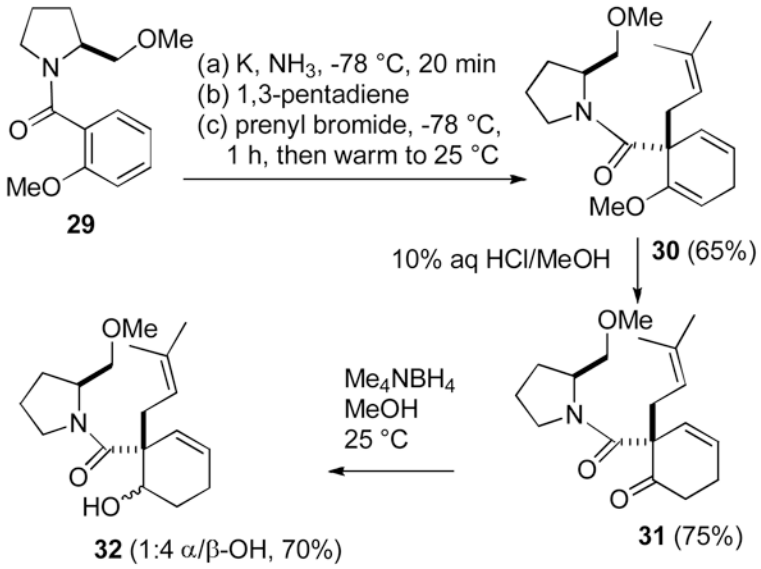

**Scheme 2. Synthesis of Model β-Lactone 18**



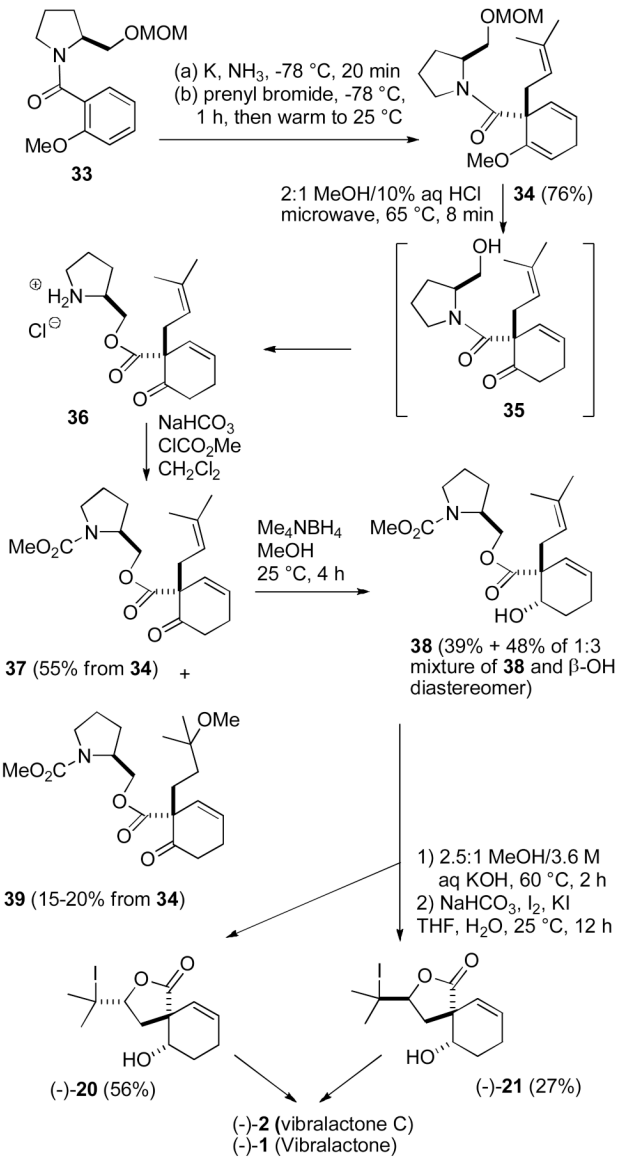

**Scheme 3. Synthesis of (±)-Vibralactone (1)**




**Scheme 4. Attempted Formation of trans Hydroxy Acid 7**




**Scheme 5. Reductive alkylation of 29**




**Scheme 6. Synthesis of (-)-Vibralactone (1)**