Formation of Contiguous Stereotriads as Intermediates in the Stereocontrolled Synthesis of Medium-Ring Diterpenes

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Introduction

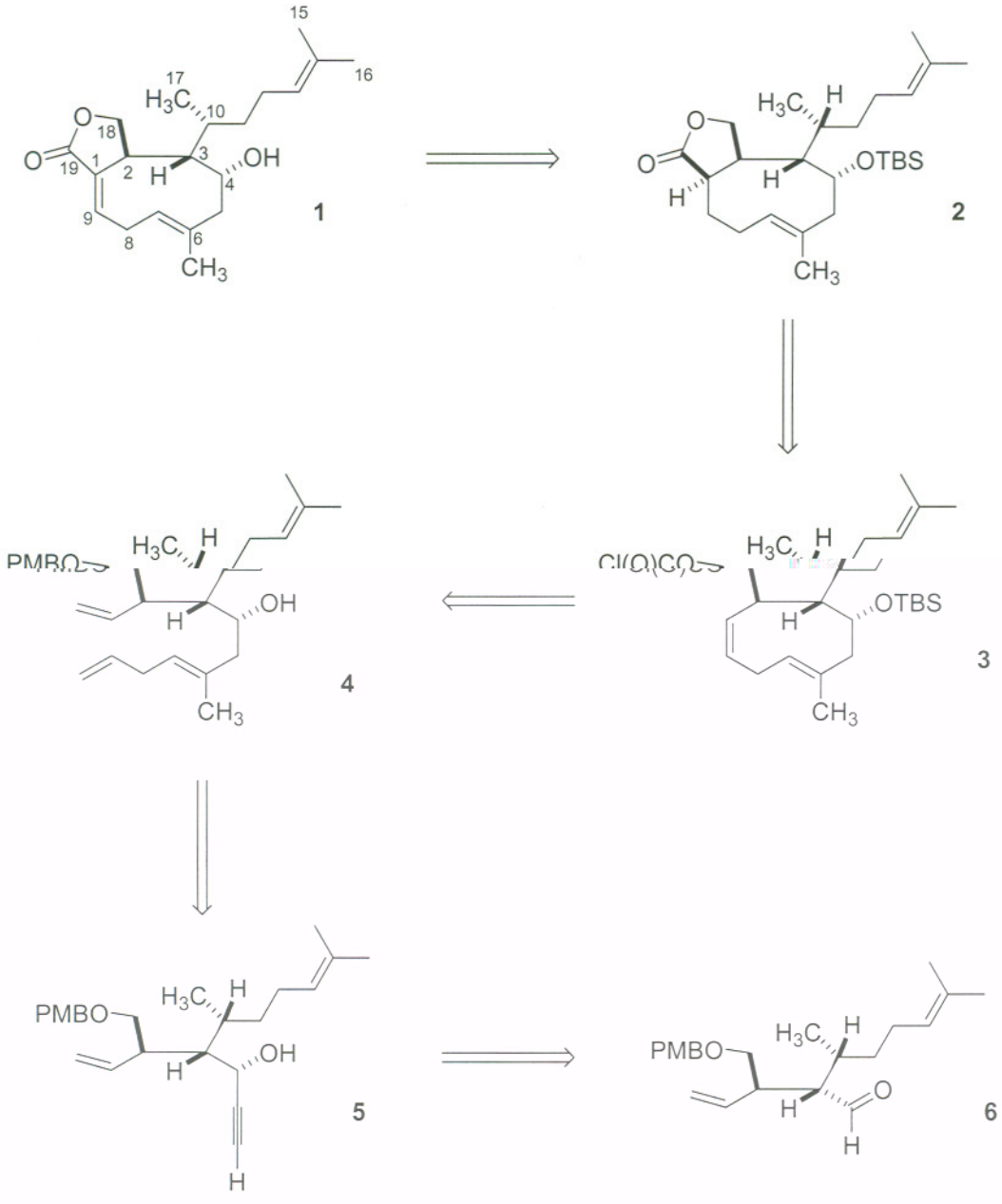
The formation of medium-sized carbocycles in organic natural products has been a longstanding problem for natural product chemists. Ring strain as a barrier to formation of

Retrosynthesis

Challenges exist in the total synthesis of **1** which will address the formation of the C_2, C_3 and C_{10} contiguous stereotriad (xenicane numbering). This stereotriad is problematic in the sense that the functionality at each chiral site is chemically similar to its neighboring substituents. Therefore, compound **6** has been deemed a key intermediate, as it contains the complex stereotriad backbone of **1**.

Scheme 1[5] outlines the retrosynthesis of **1** to the aldehyde, **6**. It has been proposed that the synthesis of **1** will proceed through lactone **2**, which can readily be converted to **1** via a Saegusa oxidation[6], followed by silyl deprotection of the alcohol functionality at C_4. The butyrolactone moiety of **2** may be generated via a palladium-catalyzed lactonization[7] of **3**, followed by reductive elimination in the presence of a hydride donor, such as sodium formate. Acyl chloride **3** is directly available from the nonconjugated diene **4**. This transformation may be accomplished via a ring-closing metathesis (RCM)[8] to construct the nine-membered carbocycle of the natural product, followed by TBS protection of the C_4 alcohol, PMB deprotection using DDQ, and conversion to the acyl chloride via treatment with phosgene. Triene **4** is available in three steps from alkyne **5**. This transformation takes place via an initial Negishi carbozirconation of **5**, followed by transmetallation via treatment with Me_2Zn, and finally a palladium-catalyzed coupling[9] to 2-propenyl acetate. Lastly, aldehyde **6** may be converted to **5** via a reagent controlled allylation with a nonracemic allenylborane[10].

Scheme 1

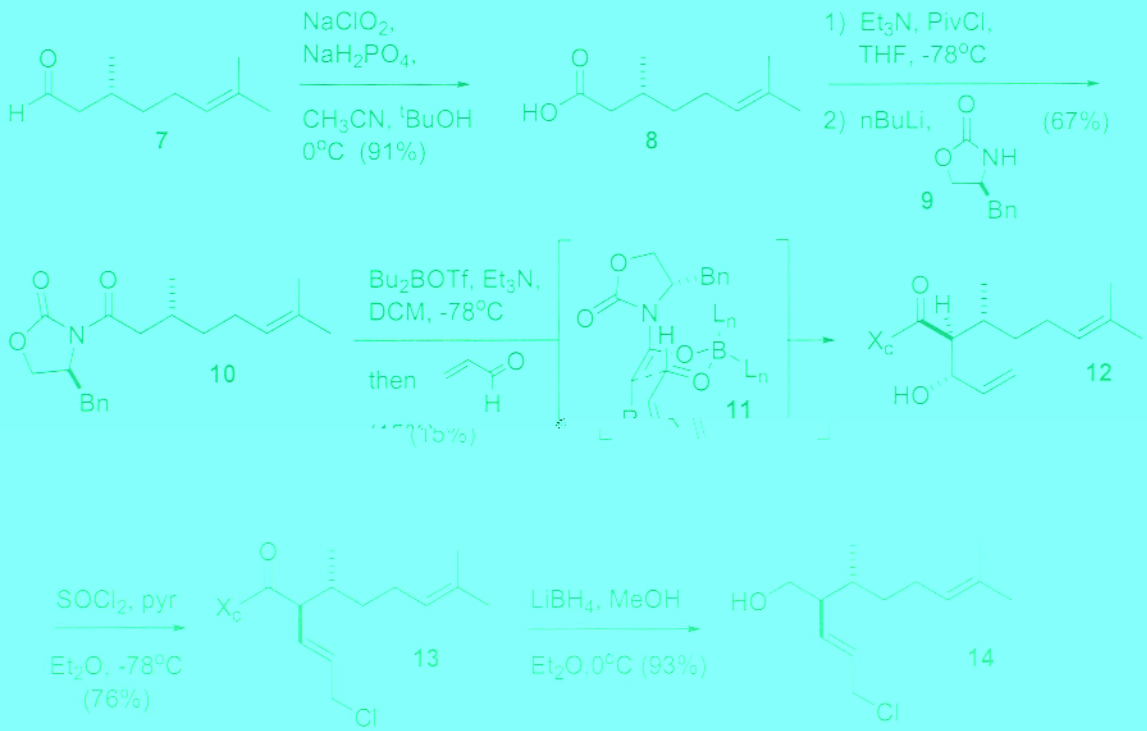


Currently, efforts are underway in our laboratory towards the construction of intermediate **6**. The goal of this effort is to convey work that has been done in the last three months towards the preparation of **6**, and to propose plans for future work

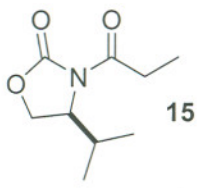
Completed Work

Work completed towards intermediate **6** is outlined in **Scheme 2.** The synthesis of **6** began from the commercially available (*R*)-(+)-citronellal (**7**), which was subjected to perchlorite oxidation conditions for conversion of the aldehyde to the corresponding (*R*)-(+)-citronellic acid **8**. Transformation to imide **10** occurred via treatment with Et_3N and pivaloyl chloride to give a mixed anhydride, which was then immediately introduced to the deprotonated phenylalanine-derived oxazolidinone **9**. Generation of the *Z*(O) enolate of **10** followed by addition of acrolein afforded the expected *syn* aldol product **12**, via **11**, as the major product[11]. Alcohol **12** was treated with thionyl chloride in the presence of pyridine to give allyl chloride **13**, which was then subjected to $LiBH_4$ reduction to afford alcohol **14**.

Scheme 2



The conversion of imide **10** to alcohol **12** has been the main focus of work in the last three months, as yields of 10-15% prevented further progress towards **6**. In initial studies of aldol reactions utilizing boron enolates and chiral oxazolidinones, Evans and coworkers introduced an aldol reaction involving an imide derived from propanoic acid (**15**), which was then utilized for aldol condensations with various aldehydes[11]. In the present synthesis, however, the stereochemical complexity of the imide and resulting enolate are considerably amplified with the introduction of a β-stereocenter and an extended hydrocarbon chain (**10**). While literature precedence for such an aldol condensation is minimal, the Williams' laboratories have previously addressed related issues[12] and have reported an optimized protocol for a similar system. Therefore, this reported procedure was adopted as a starting point from which the current study was to begin.



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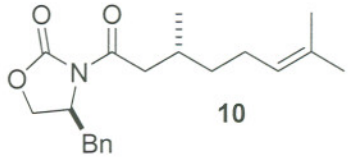

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Initial trials under these conditions afforded little or no product while nearly quantitative yields of starting material were recovered. Therefore, efforts towards optimization have resulted in a current procedure providing improved yields of 10-15%, although affording diastereoselectivites of 3-4:1. Both of these finding are in stark contrast to those reported by Evans and suggests further optimization is required. However, it should be noted that the improvement in the yield suggests the potential for a viable reaction and, therefore, a need for further efforts towards optimization.

Future Work

Future work towards the synthesis of intermediate **6** will take on a two-fold nature with optimization of the Evans' aldol condensation and completion of the synthesis of intermediate **6**. Herein both aspects of the synthesis and the necessary steps needed for their completion will be discussed.

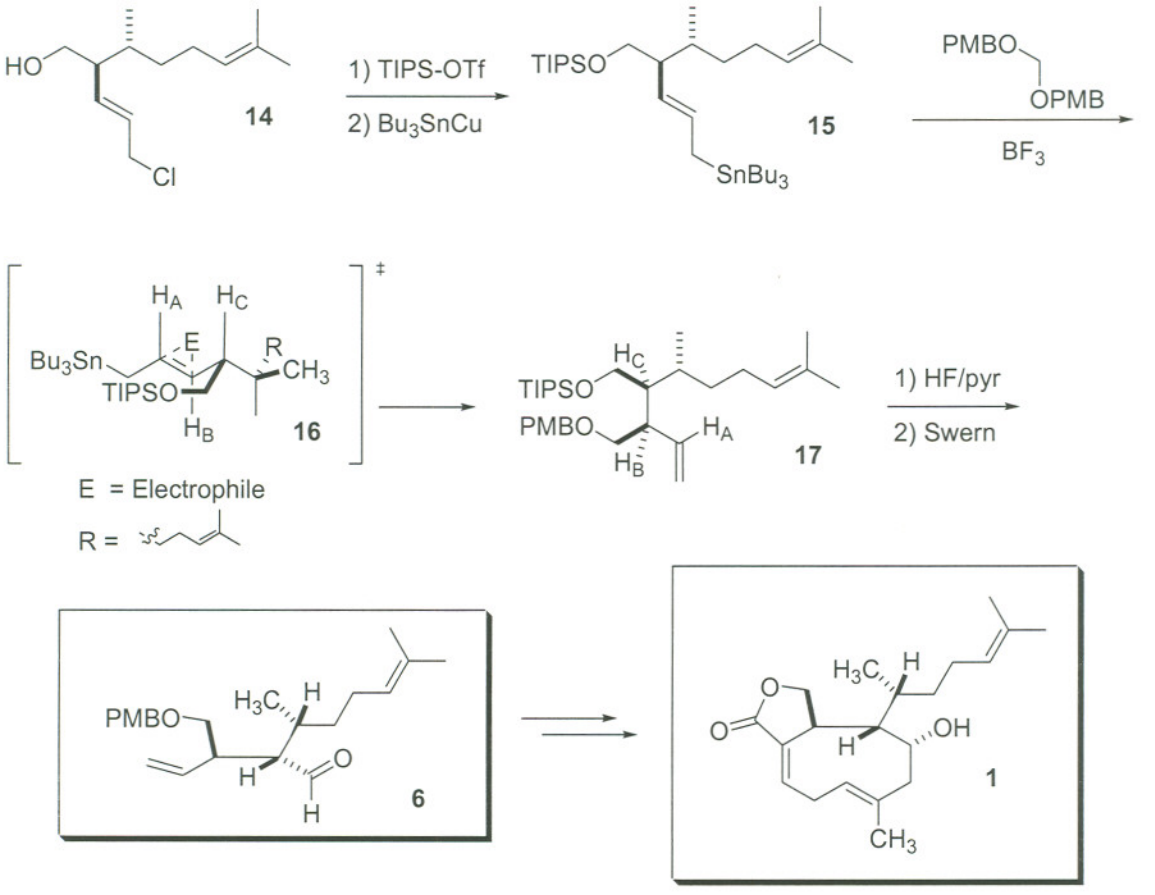
The conversion of imide **10** to aldol product **12** has several factors limiting its facile completion. As noted, protocols exist for systems similar to those in the current study[12]. However, upon careful investigation, it was found that this procedure differed from those in reports by Evans and coworkers. In the seminal paper, nBu_2BOTf and diisopropylethylamine were introduced into a solution containing imide **15** in CH_2Cl_2 at $0^{\circ}C$. This solution stirred for 0.5 hours and reportedly allowed for complete enolization. However, in the Williams paper, an adapted protocol involving the addition of nBu_2BOTf to the imide at $-78^{\circ}C$, followed by stirring for 1 hour, addition of Et_3N at $-78^{\circ}C$, stirring for 15 minutes, warming to $0^{\circ}C$ and then stirring for an additional 45 minutes reportedly was necessary to allow for complete enolization. This necessary change in procedure may be attributable to the fact that as the alkyl chain of the imide increases in length and stereocenters are introduced into this chain, steric congestion prevents facile deprotonation, therefore resulting in a slower rate of enolization. Consequently, future studies will involve quenches – via deuterated methanol – of the enolate at intervals that will allow for insight as to optimal times necessary for coordination of boron to the imide and enolization by Et_3N. These findings will help address the issue of poor yields in the current system.

Poor diastereoselectivity has also been a point of concern in the current study when compared to previous reports. The current study mirrors that reported by Evans for the addition of the aldehyde to the enolate[11]. This step was performed at -78°C and is stirred for 15 minutes at which point the solution is warmed to 0°C and stirred for an additional 45 minutes. It has been observed that upon addition of the aldehyde at -78°C, a conversion of reactant to product is immediately visible via TLC. However, as the reaction is warmed to 0°C, an additional product becomes visible. This compound has not been isolated as it appears very close to the product spot on the TLC plate. This may be a major factor in the observed poor diastereoselctivity, as temperatures above -78°C may cause a decrease in aldehydic facial selectivity. In order to address this issue, future studies will include efforts to examine the temperature restraints in the current system. Carrying out this reaction without a ramp in temperature may be necessary in order to maintain diastereoselctivity. In addition, future studies will examine the temperature threshold at which a second product formation occurs. These studies will address the issue of poor diastereoselectivity in the current system, and, consequently, further the efforts towards optimization of the step.

Once the conversion of imide **10** to alcohol **12** is optimized, few steps remain in the construction of intermediate **6** from **14**. These steps are outlined in **Scheme 3**[5]. Simple TIPS protection, followed by S_N2 displacement of the chloride by tributylstanyl cuprate may afford stannane **15**. Lewis acid-assisted electrophlic attack of the olefin in **15** will give **17**, which will then contain the desired stereotriad core of **6**. This diastereoselectivity is hypothesized to arise due to minimization of $A^{1,3}$ strain in the transition state[13], as illustrated in **16**. Lastly, deprotection of the silyl ether group,

followed by oxidation to the aldehyde will afford intermediate **6**, which may then be introduced into the aforementioned **Scheme 1**, towards completion of 4-hydroxydictylactone **1**.

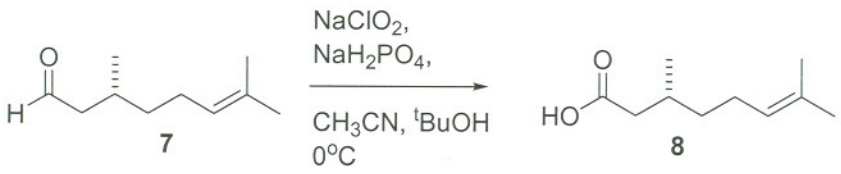
Scheme 3



Experimental Section

General Experimental Notes

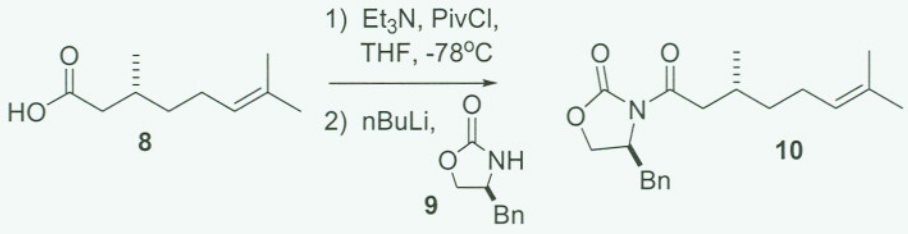
All reactions in the current study were performed in flame-dried flasks and under inert argon atmosphere. In addition, all solvents and liquid reagents were freshly distilled prior to experiment.



(*R*)-3,7-Dimethyloct-6-enoic acid (8)

To a solution of **7** (4.10mL, 22.6mmol), acetonitrile (280mL), and *tert*-butanol (280mL) at 0°C, was added 2-methyl-2-butene (95mL). Solution was allowed to stir at 0°C while in a separate flask, NaH_2PO_4 (24.63g, 181.0mmol) was dissolved in H_2O (200mL). To this aqueous solution, $NaClO_2$ (18.41g, 203.0mmol) was added very slowly. Once $NaClO_2$ was completely dissolved, the aqueous solution was added dropwise to the prepared organic solution. Heterogeneous mixture was allowed to stir at 0°C for 45 minutes at which time TLC indicated reaction completion. Solution was then diluted with ether, washed with saturated $Na_2S_2O_{3\,(aq)}$ (2 x 300mL) and saturated $NaCl_{(aq)}$ (2 x 300ml), dried over $MgSO_4$, and concentrated to yield a colorless oil. Crude product was then purified via flash chromatography eluting with hexanes/EtOAc (8:1) to give acid **8** as a clear oil (3.59g, 91%). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.09 (t, J = 6.2 Hz, 1H), 2.37 (dd, A of ABX, J_{AB} = 15.0 Hz, J_{AX} = 5.9 Hz, 1H), 2.15 (dd, B of ABX, J_{AB} = 15.0 Hz,

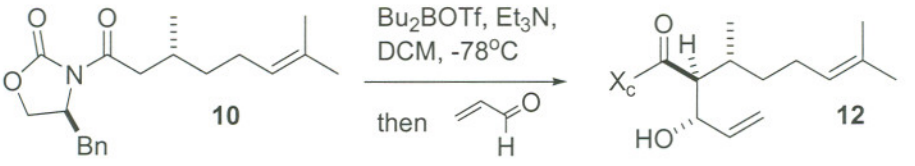
J_{BX} = 8.4 Hz, 1H), 2.03-1.94 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.51-1.17 (m, 3H), 0.98 (d, J = 6.6 Hz, 3H).



(*S*)-4-Benzyl-3-((*R*)-3,7-dimethyloct-6-enoyl)oxazlidin-2-one (10)

To a solution of **8** (4.68mL, 25.45mmol) in THF (65mL) was added Et_3N (4.26mL, 30.55mmol) via syringe. Solution was allowed to cool to -78°C at which time pivaloyl chloride (3.46mL, 28.00mmol) was added via syringe, resulting in the precipitation of a yellowish salt. This solution was allowed to stir at -78°C for 30 minutes. In a separate flask, **9** (4.64g, 30.55mmol) was dissolved in THF (65mL) and cooled to -78°C. To this solution was added nBuLi (13.24 mL, 33.09mmol). The resulting orange solution was allowed to stir at -78°C for 10 minutes, and then was cannulated into the solution containing the mixed anhydride. This solution returned to a clear color and was then stirred for 2.5 hours at a constant -78°C. Upon reaction completion, solution was washed with H_2O (3 x 25mL) and saturated $NaCl_{(aq)}$ (3 x 25mL), dried over $MgSO_4$, and concentrated to yield a yellowish oil. Crude product was then purified via flash chromatography using hexanes/EtOAc (9:1) as an eluent to give purified imide **10** (5.57g, 67%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 5.11 (t, J = 6.2 Hz, 1H), 4.68 (ddt, J = 10.3. 7.0, 3.3 Hz, 1H), 4.20-4.13 (m, 1H), 3.32 (dd, J = 13.5, 3.3

Hz, 1H), 2.88-2.72 (m, 2H), 2.13-1.96 (m, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.48-1.41 (m, 3H), 1.31-1.19 (m, 1H), 1.01 (d, J = 6.2Hz, 3H).

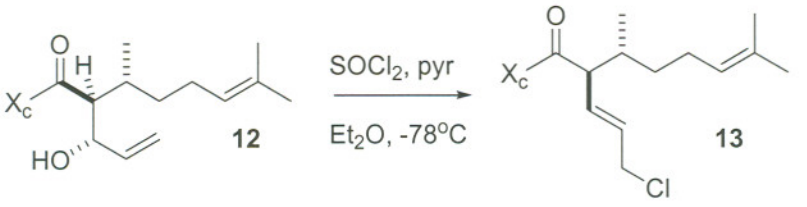


(*S*)-4-Benzyl-3-((2*S*,3*R*)-2-((*S*)-1-hydroxyallyl)-3,7-dimethyloct-6-enoyl)oxazolidin-2-one (12)

Not Optimized

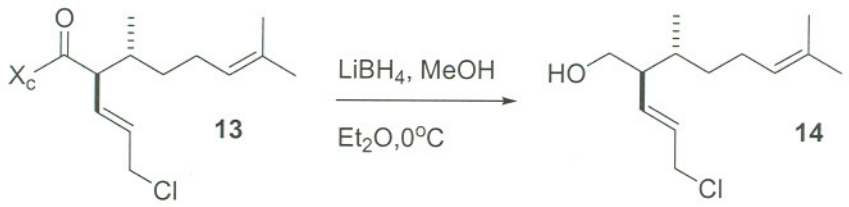
Oxazolidinone **10** (549mg, 1.67mmol) was dissolved in 1mL of freshly distilled benzene and placed on rotavap until solvent completely evaporated. This was repeated twice more and was then placed on high vacuum for 1 hour in order to ensure that any azeotrope of **10** had been removed. Under argon, **10** was then dissolved in DCM (8.35mL) and solution was cooled to -78°C. To this solution, freshly distilled Bu_2BOTF (417.2μL, 1.84mmol) was added dropwise, resulting in a yellow solution that was then allowed to stir at -78°C for 1 hour. To this solution was added freshly distilled Et_3N (302.5μL, 2.17mmol), resulting in the solution returning to a clear color. This solution was allowed to continue stirring at -78°C for 15 minutes and was then warmed to 0°C.Solution was stirred at this temperature for 45 minutes. Solution was returned to -78°C and acrolein (135.1μL, 2.00mmol) (U-tube distillation over Na_2SO_4) was then

added, stirred for 15 minutes, and then warmed to 0°C. Reaction was monitored via TLC until starting material was no longer converting to product (approximately 1hour), at which time ph 7.0 buffer (4mL) and methanol (4mL) were added in order to quench the reaction. After 10 minutes of stirring, a 2:1 mixture of methanol/H_2O_2 (30%) was added and stirred for 20 minutes. Reaction was then diluted in Et_2O and washed with $NaHCO_3$ and NaCl (2 x 10mL each), dried over $MgSO_4$ and concentrated to yield a yellowish oil. Crude product was purified via flash chromatography using an 8:1 hexanes/EtOAc to give alcohol **12** (100.6mg, 15%) as a yellowish oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.35-7.23 (m, 5H), 6.01 (ddd, J = 17.6, 10.3, 7.3 Hz, 1H), 5.32-5.21 (m, 2H), 5.08 (t, J = 7.0 Hz, 1H), 4.73 (ddt, J = 10.6, 7.3, 3.7 Hz, 1H), 4.54 (dt, J = 6.6, 2.9 Hz, 1H), 4.27 (t, J = 7.3 Hz, 1H), 4.17-4.10 (m, 2H), 3.41 (dd, J = 13.2, 3.7 Hz, 1H), 2.62 (dd, J = 13.2, 10.2 Hz, 1H), 2.15-1.90 (m, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 1.30-1.19(m, 3H), 1.03 (d, J = 6.6 Hz, 3H).



(*S*)-4-Benzyl-3-((2*S*,3*R*)-2-((*E*)-3-chloroprop-1-enyl)-3,7-dimethyloct-6-enoyl)oxazolidin-2-one (13)

In a clean, dried flask, **12** (40mg, 0.104mmol) was dissolved in 0.52mL Et_2O and cooled to -78°C. To the stirring solution was added freshly distilled pyridine (26μL, 0.260mmol). After stirring for 10 minutes, freshly distilled thionyl chloride (U-tube distillation without drying agent) (19μL, 0.26mmol) was added to the solution, which resulted in the precipitation of a white solid. Reaction was stirred for 1 hour at -78°C, warmed to 0°C, and then stirred for 4 hours. Reaction was quenched with saturated $NaHCO_{3\,(aq)}$, aqueous and organic layers were separated, and aqueous layers were extracted with Et_2O. Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to yield a yellowish oil. Crude product was purified via flash chromatography, eluting with hexanes/EtOAc (9:1 – 4:1) , providing chloride **13** (32mg, 76%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.39–7.05 (m, 5H), 5.91-5.78 (m, 2H), 5.11-5.07 (m, 1H), 4.69 (ddt, *J* = 10.2, 6.8, 3.2 Hz, 1H), 4.42 (dd, *J* = 8.4, 7.9 1H), 4.21-4.07 (m, 2H), 4.06 (d, *J* = 5.9 Hz, 2H), 3.39 (dd, *J* = 13.3, 3.3 Hz, 1H), 2.69 (dd, *J* = 13.1, 10.2 Hz, 1H), 2.16-1.82 (m, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.59-1.49 (m, 1H), 1.20-1.09 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H).



(2*S*,3*R*,*E*)-2-(3-Chloroprop-1-enyl)-3,7-dimethyloct-6-en-1-ol (14)

Chloride **13** (49.2mg, 0.124mmol) was dissolved in Et_2O (0.60mL) and solution was cooled to 0°C. To this solution was added methanol (10μL, 0.248mmol), followed by $LiBH_4$ (5.4mg, 0.248mmol). Reaction was allowed to stir until completion (3 hours) at which point saturated $NaHCO_3$ was added as a quench. Solution continued to stir for 45 minutes, after which layers were extracted with Et_2O. Organic layers were then combined, dried over $MgSO_4$, filtered and concentrated to yield a colorless liquid. Crude product was purified via flash chromatography, eluting with hexanes/EtOAc (9:1 – 4:1) , providing **14** (26mg, 93%) as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.68 (dt, J = 15.2, 6.6 Hz, 1H), 5.59 (dd, J = 15.4, 8.9 Hz, 1H), 5.05-4.98 (m, 1H), 4.00 (d, J = 6.4 Hz, 2H), 3.67-3.60 (m, 1H), 3.42 (dd, J = 10.4, 8.7 Hz, 1H), 2.09 (ddt, J = 8.8, 6.1, 5.1 Hz, 1H), 2.05-1.75 (m, 2H), 1.68 (s, 3H), 1.55 (s, 3H), 1.53-1.45 (m, 1H), 1.38 (dddd, J = 13.3, 10.0, 6.6, 3.5 Hz, 1H), 1.02 (ddt, J = 14.7, 9.4, 5.1 Hz, 1H), 0.85 (d, J = 6.8 Hz, 3H).

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