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Unified Enantioselective, Convergent Synthetic Approach Toward the Furanobutenolide-Derived Polycyclic Norcembranoid Diterpenes: Synthesis of a Series of Ineleganoloids by Oxidation State Manipulation of the Carbocyclic Core

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ABSTRACT: Late-stage synthetic efforts to advance the enatio- and diastereoselectively constructed [6,7,5,5]-fused tetracyclic scaffold toward the polycyclic norditerpenoid ineleganolide are disclosed. The described investigations focus on oxidation state manipulation around the central cycloheptane ring. Computational evaluation of ground state energies of dihydroineleganolide are used to rationalize empirical observations and provide insight for further synthetic development, enhancing the understanding of the conformational constraints of these compact polycyclic structures. Advanced synthetic manipulations generated a series of natural product-like compounds termed the ineleganoloids.

INTRODUCTION

Natural products have proven invaluable for the development of pharmaceuticals, providing inspiration and serving as lead compounds for the treatment of ailments from cancer[1] to bacterial infection[1c,d,2] and neurological diseases.[1a,c,3] Additionally, through target-directed synthesis, natural products continue to inspire the development of novel reaction manifolds and the extension of chemical space.[4] The furanobutenolide-derived norcembranoid diterpenes are a class of biologically active natural products that have been sparsely explored and offer tremendous potential for both pharmaceutical and methodological development.[5] Among the members of this natural product family, ineleganolide (**1**) stands out due to the intricate functionalization of the compact and highly oxygenated structure paired with known antileukemic properties (Figure 1).[5f,6] Since the initial isolation and assignment of the structure in 1999 from the namesake soft coral *Sinularia inelegans*,[6j] ineleganolide (**1**) has been isolated from a number of other species belonging to the same genus[6a–i] along with the isomeric natural products horiolide (**2**)[7] and kavaranolide (**3**).[6c]

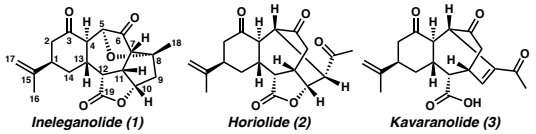
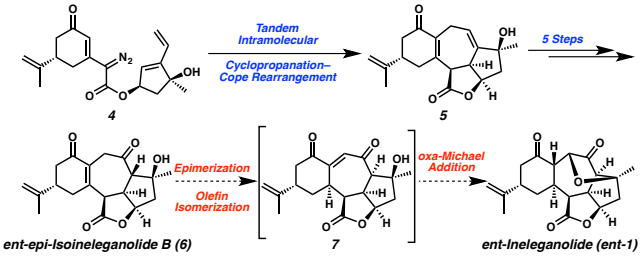


Figure 1. Ineleganolide (**1**) and Isomeric [6,7]-Polycyclic Furanobutenolide-Derived Norcembranoid Diterpenes.

Ineleganolide (**1**) poses a number of formidable synthetic challenges,[8,9] highlighted by nine stereogenic centers distributed across [6,7,5]-carbocyclic scaffold that is constrained within a highly cupped configuration by a bridging dihydrofuranone. Previously, we developed an enantioselective and diastereoselective approach toward the synthesis of the furanobutenolide-derived polycyclic norditerpenoids, resulting in synthetic access to the enantioenriched [6,7,5,5]-tetracyclic core of *ent*-ineleganolide (***ent*-1**) and representing the first completion of the carbocyclic scaffold of any member of the polycyclic furanobutenolide-derived norcembranoid natural product family (Scheme 1).[10,11] Completion of *ent*-ineleganolide (***ent*-1**) from *ent-epi*-isoineleganolide B (**6**), envisioned through olefin isomerization and ultimately intramolecular oxa-Michael addition from vinylogous diketone **7**, proved untenable.[12] Nevertheless, with synthetic access to the [6,7,5,5]-tetracyclic core of *ent*-ineleganolide (***ent*-1**) established, we sought to develop an alternative late-stage strategy that would enable access to the natural product itself. Presented herein are our efforts toward this end and, although ultimately proven unable to provide ineleganolide, have lead to a number of additional ineleganoloids that have been prepared through intriguing and unusual chemistry.

Scheme 1. Enantioselective Formation of the [6,7,5,5]-Tetracyclic Core of *ent*-Ineleganolide (*ent*-1)

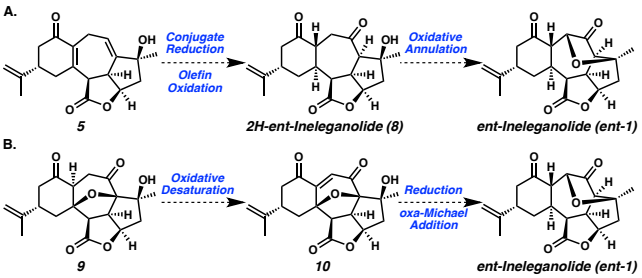


RESULTS AND DISCUSSION

Alternative access to *ent*-ineleganolide (***ent*-1**) was envisioned through two distinct strategies. Firstly, from synthetic intermediate diene **5**, *ent*-ineleganolide (***ent*-1**) could be synthesized using a sequential reduction-oxidation strategy (Scheme 2A). Conjugate reduction of the enone moiety within diene **5** would provide 2*H*-*ent*-ineleganolide (**8**) after oxidation of the remaining cycloheptenyl olefin. Completion of *ent*-ineleganolide (***ent*-1**) from 2*H*-*ent*-ineleganolide (**8**) would only require the formation of the final C–O bond and the bridging dihydrofuranone ring. This oxidative annulation could be accomplished either directly by oxidation of a C–H bond at the apical methylene or stepwise by an oxidative desaturation and ultimately an intramolecular oxa-Michael addition.

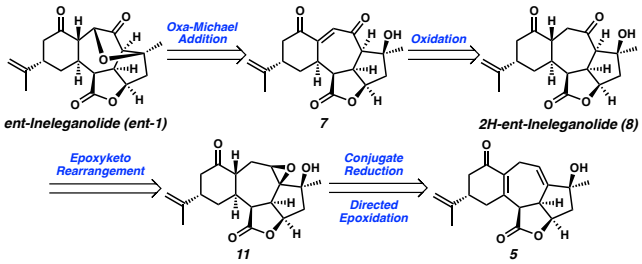
Contrastingly, *ent*-ineleganolide (***ent*-1**) might be synthesized from ketopyran **9** by an antipodal approach (Scheme 2B). In this approach, ketopyran **9** would undergo oxidation of the central cycloheptanone to install a transannular vinylogous diketone and furnish dihydropyranone **10**. Subsequently, a chemoselective reduction of the α-alkoxyketone C–O bond within dihydropyranone **10** in the presence of the unsaturated system would lead to spontaneous formation of the dihydrofuranone ring by intramolecular *oxa*-Michael addition and leave only a deoxygenation or a sequential dehydration-reduction to complete the natural product (***ent*-1**).

Scheme 2. Alternative Synthetic Strategies for the Completion of *ent*-Ineleganolide (*ent*-1)



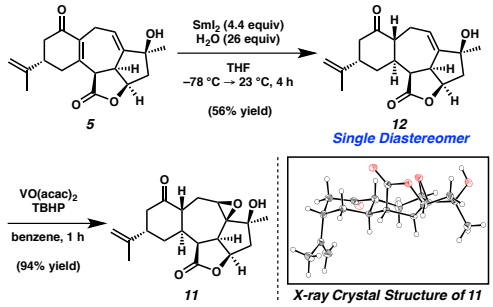
Late-stage synthetic efforts toward *ent*-ineleganolide (***ent*-1**) began with the sequential reduction-oxidation strategy from tetracyclic diene **5**. Retrosynthetically, access to *ent*-ineleganolide (***ent*-1**) was envisioned from vinylogous diketone **7**, furnishing the natural product following an intramolecular oxa-Michael addition (Scheme 3). Rather than accessing vinylogous diketone **7** by olefin isomerization from *ent*-isoineleganolide B (**6**, see Scheme 1), enedione **7** would be synthesized by the oxidation of saturated 1,4-diketone **8**. Alternatively, *ent*-ineleganolide (***ent*-1**) could be formed directly from 2*H*-*ent*-ineleganolide (**8**) through intramolecular oxidative annulation by C–H functionalization. 2*H*-*ent*-Ineleganolide (**8**) would be prepared from epoxide **11** by a *syn*-facial 1,2-hydride shift. Saturated ketone **11** would be synthesized by the sequential conjugate reduction and hydroxyl-directed epoxidation from diene **5**.

Scheme 3. Retrosynthetic Analysis of *ent*-Ineleganolide (*ent*-1) Employing Late-Stage Oxidation



The conjugate reduction of the tetrasubstituted enone moiety within tetracyclic diene **5** proved nontrivial. All attempts to reduce the conjugated system by the nucleophilic addition of hydride failed, likely due to the steric environment surrounding the fully-substituted β-position. Alternatively, we were pleased to discover the use of samarium diiodide (SmI_2) was a suitable reductant to enable the formation of saturated ketone **12** as a single diastereomer (Scheme 4). The use of water as an additive in an optimal ratio proved crucial for this transformation. The absence of an additive or the addition of MeOH, *t*-BuOH, LiCl, or fewer equivalents of H_2O prevented the complete consumption of starting material. Contrastingly, the addition of HMPA or the use of additional equivalents of H_2O resulted in diminished yield of tetracycle **12** through erosion of diastereoselectivity paired with over-reduction of the desired ketone product (**12**).

Scheme 4. Conjugate Reduction of Diene 5

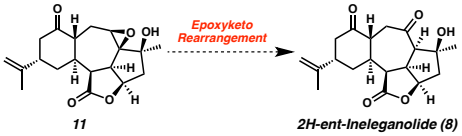


The hydroxyl-directed epoxidation of cycloheptene **12** was then accomplished under vanadium-catalyzed conditions to provide epoxide **11** in 94% yield. Epoxide **11** proved to be a crystalline white solid, enabling the unambiguous determination of relative configuration by single-crystal X-ray diffraction. This crystal structure confirmed not only the assignment of the epoxide, being correctly directed to the β-face of the molecule, but also the configuration of the *trans*-fusion at the [6,7]-ring junction, matching that found in *ent*-ineleganolide (***ent*-1**, see Scheme 3).

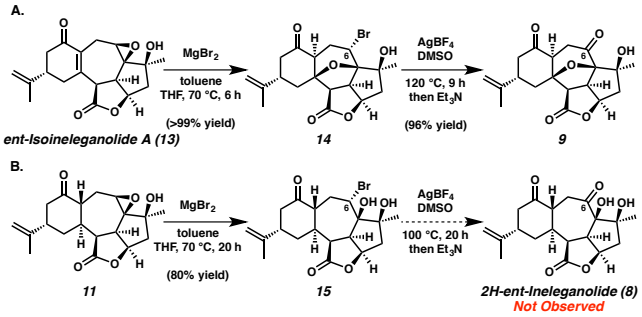
Similar to our experiences with a related epoxide,[11] advancement of epoxide **11** to 2*H*-*ent*-ineleganolide (**8**) through an epoxide rearrangement proved unfruitful under a variety of Lewis acidic conditions (Scheme 5). Thus, alternative access to 2*H*-*ent*-ineleganolide (**8**) was sought employing the method used successfully applied to the oxidized analogs, beginning

from *ent*-isoineleganolide A (**13**, Scheme 6A).[11,12] Nucleophilic opening of epoxide **13** was accomplished in the presence of stoichiometric magnesium(II) bromide in a mixed solvent system at 70 °C, providing bromide **14** in quantitative yield after concomitant transannular oxa-Michael addition. Subsequent installation of a ketone at C(6) was achieved under optimized Kornblum oxidation conditions to furnish ketopyran **9** in 96% yield.[13] The efficiency of this transformation was ascribed to the ability of the transannular ethereal oxygen to stabilize the intermediate carbocation.[10,11]

Scheme 5. Unsuccessful Epoxide Rearrangement of Epoxide 11



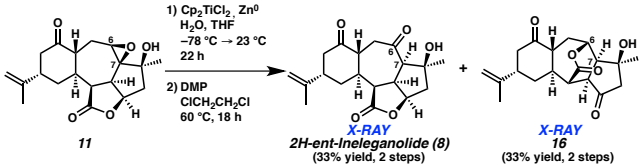
Scheme 6. Kornblum Oxidation for Formation of 1,4-Diketone Moiety



Application of this synthetic sequence to the reduced system began from epoxide **11**, which was first opened with magnesium(II) bromide to provide bromohydrin **15** in 80% yield after an extended reaction time (Scheme 6B). Unfortunately, Kornblum oxidation conditions failed to install the desired ketone at C(6). The only products observed from the attempted oxidation of bromide **15** were dehydration products after prolonged exposure to elevated temperature under the reaction conditions. This result reinforces the hypothesis that the transannular ether in secondary bromide **14** is critical for the efficacy of the Kornblum oxidation.

In place of a Kornblum oxidation strategy to access 2*H*-*ent*-ineleganolide (**8**), we began to pursue a reductive epoxide opening strategy employing Cp_2TiCl, which is generated in situ from $CpTiCl_2$ and a suitable reductant.[14] Initial exploration of this reductive epoxide opening proved immediately successful (Scheme 7). The use of H_2O as an additive results in the formation of the Cp_2TiCl aquo complex and thereby provides a sacrificial hydrogen atom donor.[14a,15] Subsequent oxidation under optimized conditions using Dess–Martin periodinane (DMP) in 1,2-dichloroethane at elevated temperature provided 2*H*-*ent*-ineleganolide (**8**) in 33% yield over two steps with the translactonized ketone **16** isolated in identical yield. The structures of both 2*H*-*ent*-ineleganolide (**8**) and lactone **16** were unambiguously determined by single crystal X-ray diffraction, confirming the desired relative configuration at C(7).

Scheme 7. Sequential Reductive Epoxide Opening and Carbinol Oxidation



In order to explore the conformational constraints of 2*H*-*ent*-ineleganolide (**8**), knowing the propensity of tetracyclic intermediates to adopt conformations distinct from that of ineleganolide,[6j,11a] we explored the in vacuo ground state energies (DFT/B3LYP/6-311+G**) of four different conformational isomers: $\mathbf{8}^{ax}$ and $\mathbf{8}^{equ}$ and $\mathbf{8A}^{ax}$ and $\mathbf{8A}^{equ}$ (Figure 2).[16] The two conformations in which the cyclohexanone ring adopts a chair conformation, placing the isopropenyl substituent in the axial position ($\mathbf{8}^{ax}$ and $\mathbf{8A}^{ax}$) are calculated to be energetically equivalent in the ground state, within the error of the calculation method (±0.23 kcal/mol), and have the lowest ground state energies of the calculated isomers, mirroring the preferred conformation of *ent*-ineleganolide (***ent*-$\mathbf{8}^{ax}$**) as determined on initial isolation by single crystal X-ray diffraction.[6j] The difference in energy between $\mathbf{8}^{ax}$ and $\mathbf{8A}^{ax}$ and the corresponding equatorial conformations, $\mathbf{8}^{equ}$ and $\mathbf{8A}^{equ}$, respectively, was calculated to be no more than 1.0 kcal/mol. Complimentarily, the X-ray crystal structure of the isolated 2*H*-*ent*-ineleganlolide shows $\mathbf{8}^{ax}$ is the preferred conformation. We were optimistic, however, that given the small ground state energy differences among these conformational isomers, we could induce an equilibrium between the isolated $\mathbf{8}^{ax}$ and one of the conformational isomers $\mathbf{8A}^{ax}$ or $\mathbf{8A}^{equ}$ en route the completion of the asymmetric total synthesis of *ent*-ineleganolide (***ent*-1**).

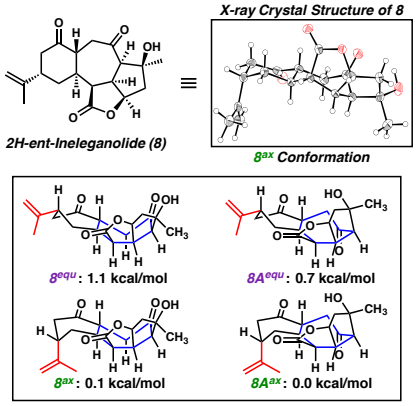
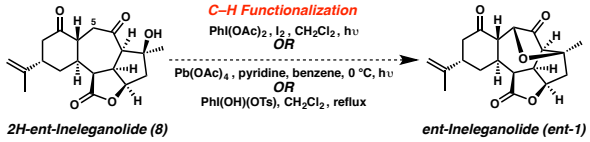


Figure 2. Computational Evaluation of Conformational Isomers of 2*H*-*ent*-Ineleganolide (**8**).

Toward this end, completion of the total synthesis would require the oxidation of 2*H*-*ent*-ineleganolide (**8**) in order to install the final requisite C–O bond and construct the characteristic bridging dihydrofuranone found within *ent*-ineleganolide (***ent*-1**). We envisioned accomplishing this transformation directly by C–H functionalization at C(5) (Scheme 8). We focused on the application of C–H functionalization methods that were known to accomplish the direct intramolecular formation a C–O bond from a free hydroxyl group. We tested methods based on the Suárez oxidation including the standard reaction conditions ($PhI(OAc)_2$, I_2, hv) and a series of modified Suarez oxidation conditions, which

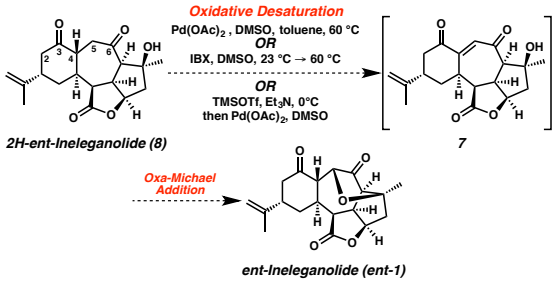
used mixed cyclohexane and dichloromethane solvent systems and exclude light.[17] Additionally, we attempted the oxidation of C(5) using lead(IV) acetate and light[18] as well as with functionalized hypervalent iodine reagents such as PhI(OH)(OTs).[19] Unfortunately, all reaction conditions explored failed to provide any product that was successfully oxidized at C(5).

Scheme 8. Attempted C(5) Oxidation by C–H Functionalization



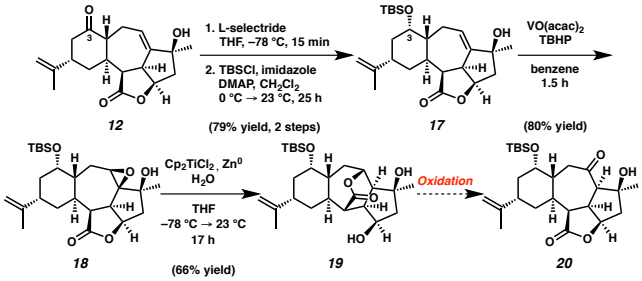
We also explored the potential to access *ent*-ineleganolide (***ent*-1**) through the oxidation of 2*H*-*ent*-ineleganolide (**8**), proceeding through vinylogous diketone **7**, which we hypothesized would undergo a spontaneous intramolecular oxa-Michael addition to furnish *ent*-ineleganolide (***ent*-1**, Scheme 9). Oxidative desaturation could be accomplished through either selective kinetic deprotonation relative to the cycloheptanone carbonyl at C(5) or by "thermodynamic" enolization relative to the cycloheptanone carbonyl at C(4). Complicated by potential enolization at C(2) and C(7), all attempts to accomplish this transformation by direct oxidation using palladium(II) salts (e.g., $Pd(OAc)_2$, $Pd(TFA)_2$),[20] hypervalent iodine reagents (e.g., IBX),[21] or various selenides (e.g., $(PhSeO)_2O$, PhSeCl then H_2O_2) failed to yield any trace of intermediate **7** or *ent*-ineleganolide (***ent*-1**), typically resulting in selective functionalization at C(2).[22] Similar nonproductive reactivity was observed when attempting the C(4)–C(5) oxidation by a Saegusa–Ito oxidation.[23] In order to avoid the undesired functionalization of the cyclohexanone ring, the selective reduction of the C(3) carbonyl was explored. While the selective reduction of the C(3) ketone in the presence of the C(6) carbonyl of 2*H*-*ent*-ineleganolide (**8**) could not be achieved, we sought to reduce the C(3) ketone at an earlier stage.

Scheme 9. Representative Reaction Conditions for Attempted C(4)–C(5) Oxidative Desaturation



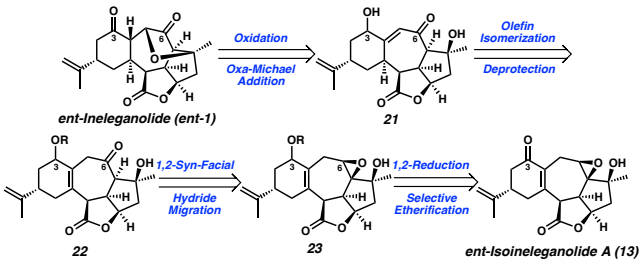
Stereoselective reduction of ketone **12** at C(3) was accomplished using L-selectride at low temperature (Scheme 10).[24] Subsequent silylation of the intermediate secondary alcohol provided tetracycle **17** in 79% yield over two steps. Epoxidation could then be smoothly accomplished to furnish epoxyalcohol **18** in 80% yield. Reductive epoxide opening of pentacycle **18** under optimized conditions using in situ generated titanium(III) resulted in concomitant translactonization, affording alcohol **19** in 66% yield as the sole product. Unable to manipulate lactone **19** further toward ineleganolide we again revised our retrosynthetic strategy.

Scheme 10. Advancement of Tetracycle 12 by Diastereoselective C(3) Reduction



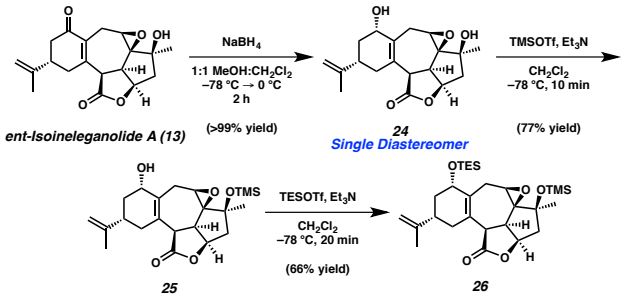
Armed with knowledge that selective late-stage functionalization of the tetracyclic core is complicated by the presence of the ketone functionality at C(3), access to *ent*-ineleganolide (***ent*-1**) was envisioned after oxidation of secondary alcohol **21** and ultimate intramolecular oxa-Michael addition (Scheme 11). Access to enone **21** was anticipated by the isomerization of olefin **22** into conjugation with the isolated ketone at C(6) followed by deprotection of the masked secondary C(3) hydroxyl group. Ketone **22** would be synthesized after the stereoselective epoxide rearrangement or sequential reductive epoxide opening-oxidation from epoxide **23**, which would be accessible from *ent*-isoineleganolide A (**13**) after selective 1,2-reduction of the conjugated system and subsequent protection.

Scheme 11. Retrosynthetic Analysis of *ent*-Ineleganolide (*ent*-1) Employing a Reduction at C(3)



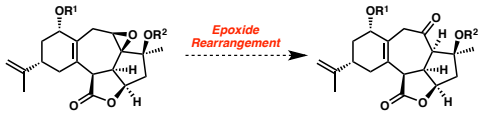
Exploration of the revised synthetic route began with the development of conditions that could accomplish the chemoselective 1,2-reduction of cyclohexenone **13** (Scheme 12). Gratifyingly, this transformation could be accomplished chemoselectively and diastereoselectively using sodium borohydride in a mixed CH_2Cl_2 and MeOH solvent system at low temperature to provide allylic alcohol **24** in quantitative yield as a single diastereomer.[25] With alcohol **24** in hand, the potential to accomplish an epoxide rearrangement on this reduced system was evaluated. To thoroughly evaluate this desired reactivity, selective protection of the hydroxyl groups on substrate **24** was accomplished, allowing for the isolation of monoprotected allylic alcohol **25** and bis-silyl ether **26**. Unfortunately, as with all other epoxides containing the [6,7,5,5]-core related to *ent*-ineleganolide (***ent*-1**), diol **27**, allylic alcohol **28**, and bis-silyl ether **29** all failed to undergo the desired 1,2-hydride shift (Scheme 13).

Scheme 12. Chemoselective Reduction of *ent*-Isoineleganolide A (13)



ent-Isoineleganolide A (13) — 24 — 25 — 26

Scheme 13. Attempted Epoxide Rearrangement

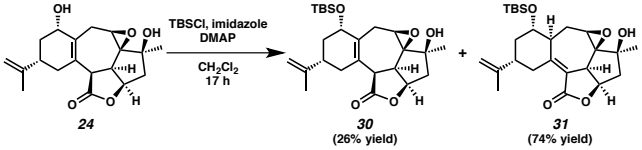


24 (R^1 = H, R^2 = H); 25 (R^1 = H, R^2 = TMS); 26 (R^1 = TES, R^2 = TMS)

27 (R^1 = H, R^2 = H); 28 (R^1 = H, R^2 = TMS); 29 (R^1 = TES, R^2 = TMS)

During this investigation, we sought to assess the reactivity of an analog of diol **24** that was functionalized with a silyl ether at solely the allylic secondary alcohol. Under standard imidazole-mediated silylation conditions employing a bulky silyl chloride, synthesis of silyl ether **30** was achieved in 26% yield (Scheme 14). Surprisingly allylic silyl ether **30** was the minor product. The remaining portion of diol **24** had been converted to α,β-unsaturated lactone **31** as the major product. Under optimized conditions, conjugated lactone **31** was produced in 74% yield.[26]

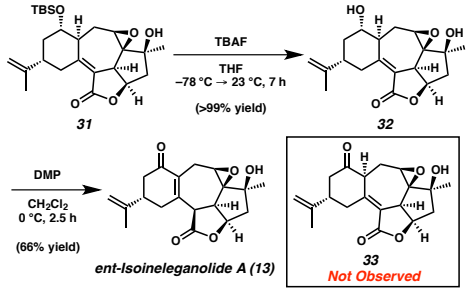
Scheme 14. Silyl Ether Formation with Unexpected Olefin Isomerization



24 — 30 — 31

Intrigued by α,β-unsaturated lactone **31**, the configurational stability of the isomerized olefin was explored. Deprotection of silyl ether **31** using TBAF provided secondary alcohol **32** in quantitative yield (Scheme 15). Unfortunately, oxidation of secondary alcohol **32** with DMP was accompanied by concomitant olefin migration back into conjugation at the [6,7] ring fusion providing *ent*-isoineleganolide A (**13**) in 66% yield. No trace of the desired α,β-unsaturated lactone (**33**) was detected. Although this oxidative route proved unfruitful, simply returning the original enone starting material (**13**) after 4 synthetic transformations, the investigation of the utility of silyl ether isomers **30** and **31** in synthetic efforts toward *ent*-ineleganolide (***ent*-1**) continued.

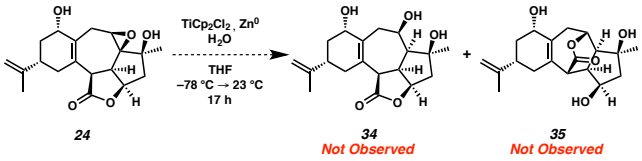
Scheme 15. Assessment of Configurational Stability of Unsaturated Lactone Moiety



31 — 32 — ent-Isoineleganolide A (13) — 33

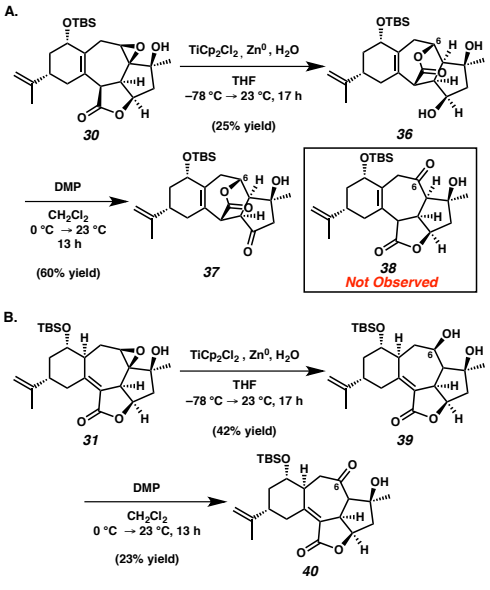
In order to advance toward *ent*-ineleganolide (***ent*-1**), the epoxide moiety within diol **24**, allylic ether **30**, or unsaturated lactone **31** would need to be converted into the requisite C(6) ketone. Unfortunately diol **24**, the precursor to silyl ether isomers **30** and **31**, proved to be an unsuitable substrate for titanium(III)-mediated reductive epoxide opening (Scheme 16).[27] Contrastingly, silyl ethers **30** and **31** proved to be competent substrates for this transformation (Schemes 17).[28] Epoxide opening of allylic silyl ether **30** provided translactonized alcohol **36** as the sole product in 60% yield (Scheme 17A). Subsequent oxidation failed to induce the desired retrotranslactonization, furnishing ketone **37** as the only isolable product without any trace of desired cycloheptanone **38**. Transannular lactone **37** was not immediately useful for continued advancement toward *ent*-ineleganolide (***ent*-1**).

Scheme 16. Attempted Reductive Opening of Epoxide 24



24 — 34 — 35

Scheme 17. Reductive Epoxide Opening of Isomeric Silyl Ethers 30 and 31



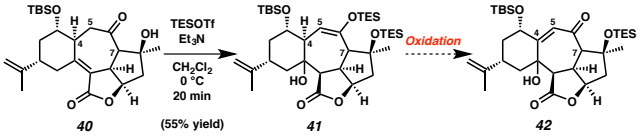
30 — 36 — 37 — 38 — 31 — 39 — 40

Alternatively, exposure of α,β-unsaturated lactone **31** to identical titanium(III)-mediated reductive conditions accomplished the desired epoxide opening while avoiding any translactonization, affording 1,3-diol **39** in 42% yield (Scheme

17B).[28] Interestingly, under these reducing and Lewis acidic conditions, the reduction of the α,β-unsaturated lactone moiety was not detected. Advancing diol **39** by oxidation of the secondary alcohol with DMP smoothly provided ketone **40** in 23% yield as the sole product.

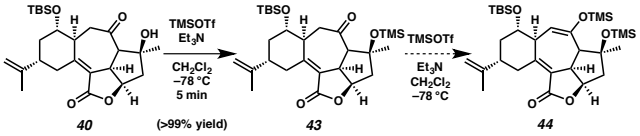
With ketone **40** in hand, we sought to accomplish the installation of the unsaturation required between C(4) and C(5) for the vinylogous diketone system and ultimate oxa-Michael addition to build the desired dihydrofuranone. Using triethylsilyl triflate (TESOTf) and Et_3N, desired enol ether **41** could be constructed, albeit with undesired concomitant hydration of the α,β-unsaturated lactone (Scheme 18). Unfortunately, we were unable to advance further toward *ent*-ineleganolide (***ent*-1**) at this stage as the oxidation of this enol ether **41** could not be accomplished.[29]

Scheme 18. Silyl Enol Ether Formation from Ketone 40



To test if the steric bulk of silyl enol ether **41** was preventing oxidation, silylation of tetracycle **40** was explored in a stepwise fashion. Tertiary alcohol **40** was first protected as trimethylsilyl (TMS) ether **43** (Scheme 19). Surprisingly, when ketone **43** was subjected to silyl enol ether formation conditions, although the starting material was fully consumed, no trace of either desired enol ether **44** or its hydrated analog were detected in the product mixture.[22]

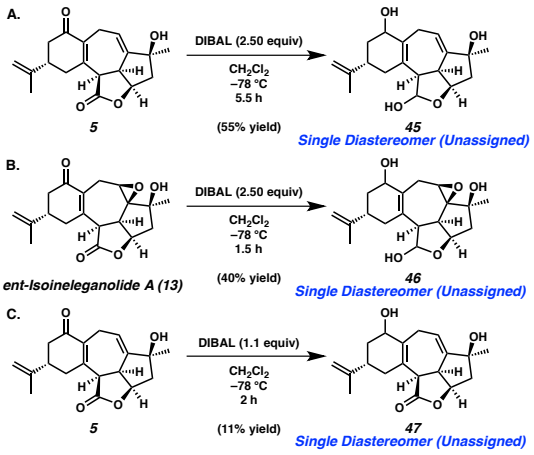
Scheme 19. Attempted Formation of TMS Enol Ether 44



Unfortunately, alternative advancement of ketone **40** or its diol precursor (**39**) by selective conjugate reduction of the unsaturated lactone could not be accomplished. Although the α,β-unsaturated lactone moiety within these compounds had enabled the installation of the C(6) ketone (i.e., **39**), the inability to advance further toward *ent*-ineleganolide (***ent*-1**) forced another reevaluation of the synthetic strategy.

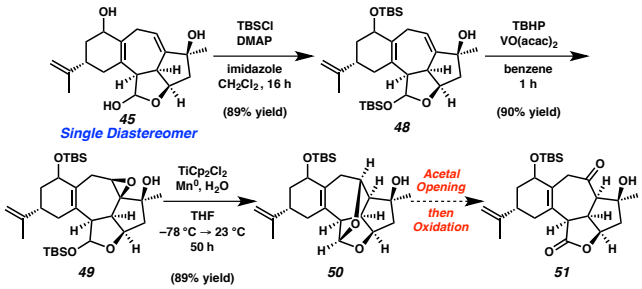
As such, development of an alternative pathway to avoid the problematic translactonization regularly observed using the titanium(III)-mediated epoxide openings began (cf. Schemes 7, 10, and 17). To prevent this undesired isomerization, the potential to mask the lactone as a lactol by reducing earlier synthetic intermediates was investigated. Beginning with either diene tetracycle **5** (Scheme 20A) or epoxide **13** (Scheme 20B), a completely diastereoselective double reduction could be accomplished in the presence of excess diisobutylaluminum hydride (DIBAL) at low temperature to afford either allylic alcohol **45** or epoxyalcohol **46**, respectively. The relative stereochemistry of reduction products **45** and **46** was not rigorously assigned. Although the selective reduction of the lactol was desired, reduction of the isolated ketone was the requisite precursor, as evidenced by the isolation of allylic alcohol **47** as the sole two-electron reduction product detectable (Scheme 20C). Since a late-stage oxidation would be required in this route to regenerate the lactone moiety, the advancement of the observed reduced lactols **45** and **46** could still be employed to advance toward *ent*-ineleganolide (***ent*-1**) in short sequence.

Scheme 20. Lactol Formation



Exploiting the higher yielding reduction of diene **5** compared to epoxide **13**, we chose to advance employing lactol **45**. Bis-silylation of secondary alcohol **45** using *tert*-butyldimethylsilyl chloride (TBSCl) under standard conditions provided lactol ether **48** in 89% yield (Scheme 21). Epoxidation of allyl alcohol **48** was then efficiently accomplished in 90% yield to furnish epoxide **49**. Titanium(III)-mediated epoxide opening accomplished the regioselective epoxide opening, smoothly furnishing a single product. The product observed had undergone an intramolecular transketalization, furnishing acetal **50** in 89% yield.[28] Yet again, an intermediate was produced that was not useful for the progression toward *ent*-ineleganolide (***ent*-1**) as opening of the acetal under acidic or oxidative conditions could not be achieved. Oxidative reactions using SO_3•pyridine in DMSO, DMP in wet CH_2Cl_2, other hypervalent iodine oxidants in wet solvents, and chromium oxidants all proved ineffective, routinely quantitatively returning the starting material after reaction times up to 7 days at elevated temperatures.

Scheme 21. Advancement of Lactol 45

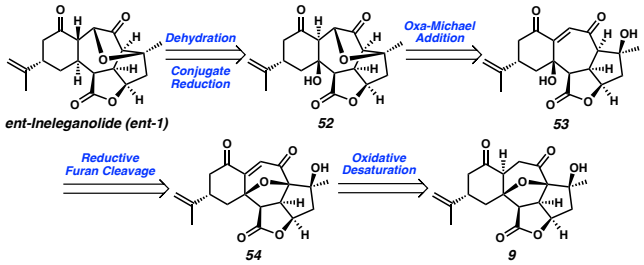


Unable to advance acetal **50** further, we had again encountered an unsuccessful synthetic strategy pairing early-stage reduction with late-stage oxidation. Thus, we turned to the antipodal retrosynthetic strategy employing an early-stage oxidation, requiring a late-stage reduction to complete *ent*-ineleganolide (***ent*-1**, cf. Scheme 2B).

Alternative completion of the asymmetric total synthesis of *ent*-ineleganolide (***ent*-1**) was envisioned after dehydration of ketofuran **52** paired with ultimate conjugate reduction (Scheme 22). Synthesis of dihydrofuranone **52** would be accomplished by an intramolecular oxa-Michael addition from vinylogous diketone **53**. Access to enedione **53** was envisioned through the selective reductive opening of dihydropy-

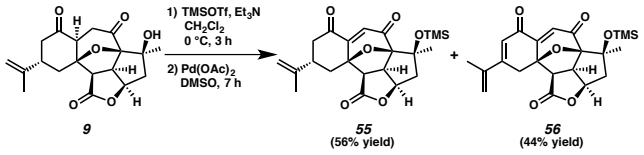
ranone **54**. Access to dihydropyranone **54** would be achieved after the oxidation of saturated 1,4-diketone **9**.

Scheme 22. Retrosynthetic Analysis of *ent*-Ineleganolide (*ent*-1) Employing Late-Stage Reduction



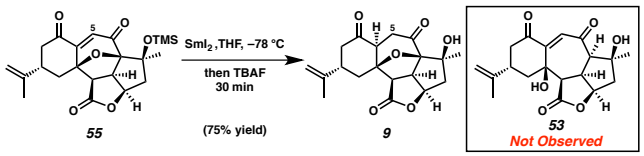
Evaluation of this synthetic route began with the previously synthesized intermediate ketopyran **9** (Scheme 23).[10,11] Formation of the thermodynamic TMS enol ether at C(3) enabled the subsequent Saegusa-Ito oxidation, smoothly furnishing vinylogous diketone **55** in 56% yield as the major product. Unfortunately, even under optimized conditions, the production of polyunsaturated diketone **56** could not be avoided, which was isolated in 44% yield.[30]

Scheme 23. Oxidation of 1,4-Diketone 9



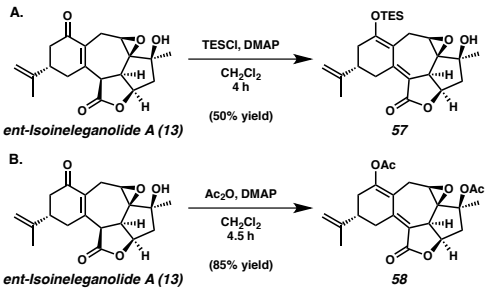
With vinylogous diketone **55** in hand, the investigating reductive α-alkoxyketone cleavage procedures commenced. These studies focused on the use of SmI_2 considering that this reagent is known to accomplish related transformations[31] and has been used previously for the α-alkoxyketone cleavage of saturated 1,4-diketone **9**.[10,11] The use of SmI_2 in the absence of an additive or with H_2O, LiCl, LiBr, HMPA, or *t*-BuOH all failed to provide any trace of enedione **53** (Scheme 24). Rather, all conditions selectively reduced the conjugated system. For example, exposure of enedione **55** to SmI_2 at low temperature followed sequentially by TBAF-mediated tertiary silyl ether cleavage produced saturated diketone **9** in 75% yield.

Scheme 24. Reduction of Vinylogous Diketone 55



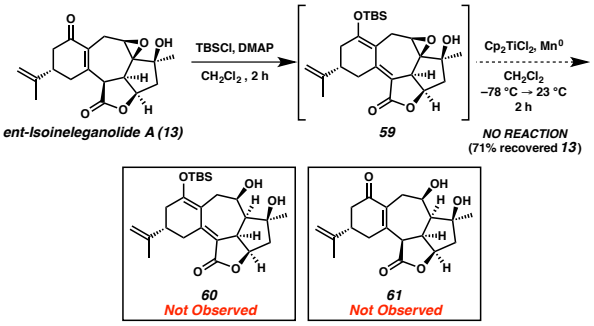
Unable to advance further toward *ent*-ineleganolide (***ent*-1**) using dihydropyranone **55**, but inspired by access to dihydropyranone **55** as the first intermediate with oxidation of C(5), we regressed further in the synthetic route to find other substrates that could be oxidized in a productive fashion. We were pleased to find that *ent*-isoineleganolide A (**13**) could be selectively enolized at the γ-position of the conjugated system when DMAP was used as the base (Scheme 25). Formation of both dienol ether **57** (Scheme 25A) and dienol acetate **58** (Scheme 25B) could be achieved using TESCl and acetic anhydride, respectively. Although TES dienol ether **57** could be isolated and purified on small scale, attempts to increase the scale of its production routinely resulted in hydrolysis during purification and reformation of starting material **13**. Although the formation of the analogous triisopropylsilyl (TIPS) dienol ether could not be accomplished under similar conditions, the TBS analog could be formed using TBSCl in place of TESCl, furnishing a significantly more stable product that was used for further synthetic studies.

Scheme 25. Dienol Ether Formation



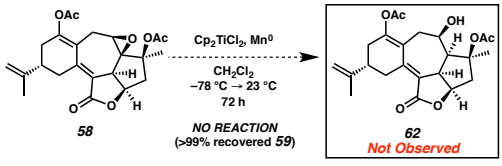
In order to advance the dienol ether substrates toward *ent*-ineleganolide (***ent*-1**), exploration of the employment of the previously utilized titanium(III)-mediated reductive epoxide opening conditions was explored. *ent*-Isoineleganolide A (**13**) was first converted into the TBS dienol ether **59** and was subsequently exposed to titanium(III)-mediated reductive conditions (Scheme 26). Not only did hydrolysis of dienol ether **59** occur under the reaction conditions, but solely the recovery of starting material **13** was observed without the detection of desired product **60** or hydrolysis product **61**.

Scheme 26. Attempted Reductive Epoxide Opening of Dienol Ether 59



Comparably, dienol acetate **58** proved an incompetent substrate for reductive epoxide opening under the same conditions (Scheme 27). Rather than producing desired product **62**, quantitative return of the staring material (**58**) was observed.

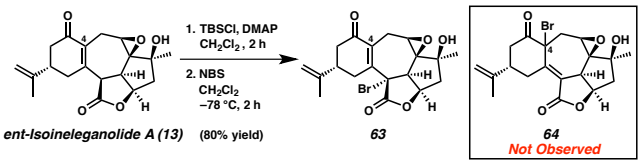
Scheme 27. Attempted Reductive Epoxide Opening of Dienol Ether 58



Leaving the epoxide opening for a later stage, the oxidative advancement of these dienol ether intermediates (**57** and **58**) was explored. In an attempt to functionalize *ent*-isoineleganolide A (**13**) at C(4), we first formed the TBS dienol ether (Scheme 28). Exposure of this intermediate to NBS in dichloromethane at room temperature afforded solely α-bromolactone **63** rather than α-bromoketone **64**.[32] We did not believe γ-bromide **63** was useful for progression toward

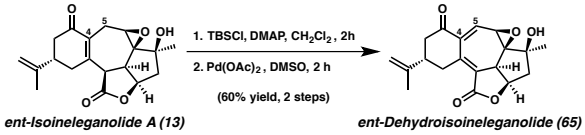
ent-ineleganolide (***ent*-1**), thus alternative oxidative procedures were explored.

Scheme 28. Construction of α-Bromolactone 63

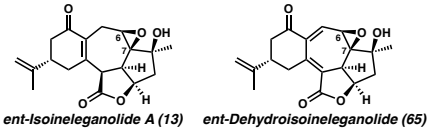


During that investigation, we were gratified to find C(4)–C(5) oxidation of *ent*-isoineleganolide A (**13**) could indeed be accomplished (Scheme 29). Beginning again with the formation of the TBS dienol ether from epoxide **13**, oxidation using stoichiometric palladium(II) acetate in DMSO provided *ent*-dehydroisoineleganolide (**65**) in 60% yield. Unfortunately, this transformation was plagued by routinely low yields on increased scale, but afforded enough material to continue synthetic explorations.

Scheme 29. Oxidation of *ent*-Isoineleganolide A (13) to Cycloheptadiene 65



ent-Dehydroisoineleganolide (**65**) was characterized by unique spectroscopic features, including an unexpected ^{13}C NMR spectrum. For example, consider *ent*-isoineleganolide A (**13**) and the ^{13}C NMR shifts of C6 and C7 at 54.5 ppm and 70.2 ppm, respectively (Figure 3). These shifts were characteristic with the remaining epoxytetracycles synthesized throughout this study (e.g., **11**, **18**, **24**–**26**, **30**–**31**, **57**–**58**, **63**). In contrast, while the carbon shift of the secondary epoxide carbon C6 of *ent*-dehydroisoineleganolide (**65**) is within the expected range at 52.1 ppm, the tertiary epoxide carbon C7 is found at 94.9 ppm. We hoped that the spectral data associated with *ent*-dehydroisoineleganolide (**65**) was indicative of a reactivity profile that could be exploited.

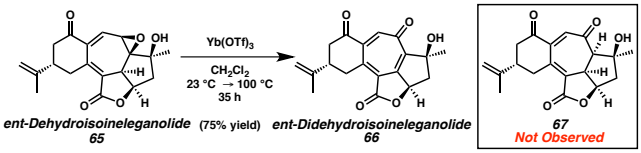


Compound	Carbon	δ (ppm in $CDCl_3$)
13	C6	54.4
65	C6	52.1
13	C7	70.2
65	C7	94.9

Figure 3. Comparison of ^{13}C NMR Shifts of Enone **13** and Diene **65**.

Any further advancement toward *ent*-ineleganolide (***ent*-1**) would now require the opening of the epoxide moiety. Unfortunately, *ent*-dehydroisoineleganolide (**65**) was extremely reactive under titanium(III)-mediated reductive epoxide opening conditions, largely decomposing upon initiation of the reaction and routinely furnishing a complex mixture of products. Additionally, all attempts to accomplish a Lewis acid-mediated 1,2-hyride shift and generation of the vinylogous diketone (**67**) were unfruitful. In fact, the only productive reactivity observed during this screen was the production of cycloheptatrienone **66** from *ent*-dehydroisoineleganolide (**65**) in 75% yield in the presence of $Yb(OTf)_3$ (Scheme 30).

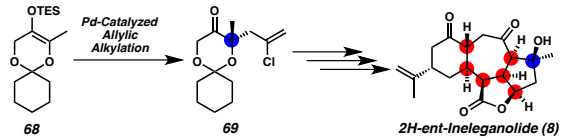
Scheme 30. Formation of *ent*-Didehydroisoineleganolide (66)



CONCLUSIONS

We have disclosed a research program dedicated to developing synthetic access to the core structures of the polycyclic furanobutenolide-derived norcembranoid diterpene natural products. Enantioselective construction of the tetracyclic core of ineleganolide (**1**) employed a palladium-catalyzed asymmetric allylic alkylation for the formation of a fully substituted chiral tertiary ether center (blue, Scheme 31). This stereocenter was then used to relay chiral information to *all* remaining stereocenters within the [7,5,5]-tricyclic portion of the ineleganolide core (red) through a diastereoselective reduction followed by a key cyclopropanation-Cope rearrangement cascade.[10,11,33]

Scheme 31. Asymmetric Allylic Alkylation Stereoselectively Determines All Remaining Chiral Information



Although the synthesis of neither ineleganolide (**1**) nor any member of the polycyclic furanobutenolide-derived norcembranoid diterpene natural product family has yet been accomplished, this synthetic program has facilitated the construction of the core of any member for the first time and the first synthetic isomers and analogs of ineleganolide (**1**). These natural product-like ineleganoloids advanced the understanding of the conformational restraints influencing chemistry of the highly compact norcembranoid diterpene scaffold and have led to the identification of biologically active ineleganolide analogs (Figure 4).[10,11] Currently, the biological activity this class of synthetic, natural product-like compounds is in the process of being evaluated in collaboration with Eli Lilly[34] and the City of Hope.[35]

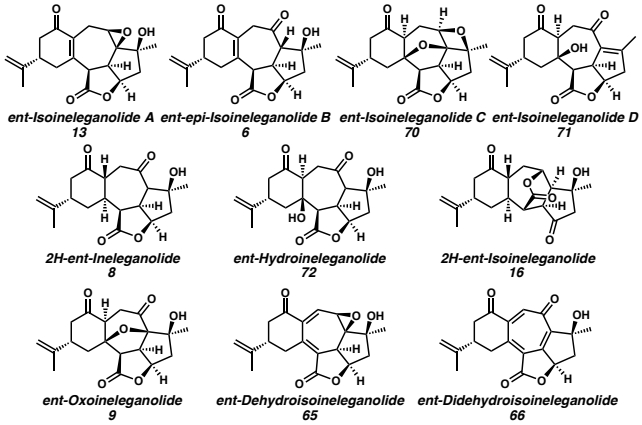


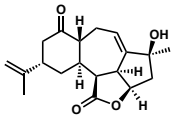
Figure 4. The Synthetic Natural Product-Like Ineleganoloids.

Throughout the course of this research program, we have thoroughly explored the limits of chemical transformation on complex, constrained fused cycloheptane polycycles. The understanding of this chemistry will not only benefit continued efforts toward the completion of the first asymmetric total synthesis of ineleganolide (**1**), but also will be broadly applicable to other total synthetic and semi-synthetic efforts toward the polycyclic furanobutenolide-derived norcembranoids as well as other terpenoid and alkaloid natural products. Perhaps then, the greater value in total synthesis is truly derived from the journey taken rather than that simply found at the finish line.

ASSOCIATED CONTENT

Experimental Section

General Methods. Unless stated otherwise, reactions were performed at ambient temperature (23 °C) in flame-dried or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina),[36] being stirred with a Teflon®-coated magnetic stirring bar. Commercially available reagents were used as received unless otherwise noted. Et_3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Reagent grade acetone was obtained from Sigma-Aldrich and used as received. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Diene **5**,[10] *ent*-Isoineleganolide A (**13**),[10] *ent*-oxoineleganolide (**9**),[10] were prepared by known methods. Reactions requiring external heat were modulated to the specified temperatures using an IKAmag temperature controller. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (250 nm) and visualized by UV fluorescence quenching, potassium permanganate, or *p*-anisaldehyde staining. Silicycle SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 (600 MHz and 151 MHz, respectively), Varian Inova 500 (500 MHz and 126 MHz, respectively), Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 MHz and 101 MHz, respectively), or a Varian Mercury 300 spectrometer (300 MHz and 76 MHz, respectively) and are reported in terms of chemical shift relative to residual $CHCl_3$ (in $CDCl_3$, δ 7.26 and δ 77.16, respectively) or C_6D_5H (in C_6D_6, δ 7.16 and δ 128.06, respectively). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were acquired using an Agilent 6200 Series TOF mass spectrometer with an Agilent G1978A Multimode source in atmospheric pressure chemical ionization (APCI) or mixed (MultiMode: ESI-APCI) ionization mode or were obtained from the Caltech Mass Spectral Facility using either a JEOL JMS-600H High Resolution Mass Spectrometer in fast atom bombardment (FAB+) or electron ionization (EI+) mode or an LCT Premier XE TOF mass spectrometer equipped with an electrospray ionization source (ES+). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path length cell at 589 nm.



12

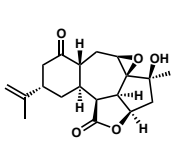
(2a*R*,2a^1*S*,4*S*,6a*R*,9*S*,10a*S*,10b*S*)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)-2a^1,3,4,6,6a,8,9,10,10a,10b-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,7(2a*H*)-dione (12).

Preparation of a 0.07 M Stock Solution SmI_2

Into each of two Schlenk tubes was added freshly filed samarium metal (150 mg, 1.00 mmol, 6.25 equiv). The reaction vessel was then thoroughly flame-dried, backfilled with argon, and allowed to cool to ambient temperature (ca. 23 °C). To each reaction vessel was added THF (10.0 mL) that had previously been sparged with argon for 60 minutes and cooled to 0 °C (ice/H_2O bath) with stirring. Diiodoethane (200 mg, 0.71 mmol, 4.44 equiv) was then added to each Schlenk tube in separate 100 mg portions 30 minutes apart. After the addition of the second portion, the Schlenk tubes were removed from the cooling bath, allowed to warm to ambient temperature (ca. 23 °C), and the pale yellow solution was stirred overnight (ca. 14 h) causing the reaction to become deep blue, indicating formation of SmI_2.

*Reduction of Diene **5***

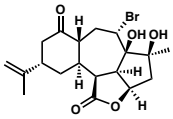
Each Schlenk tube was cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (75 μL, 4.16 mmol, 26.0 equiv). After stirring for 5 minutes, the addition of diene **5** (50 mg, 0.16 mmol, 1.00 equiv) as solution in thoroughly sparged THF (1.60 mL) was accomplished quickly dropwise over 4 minutes. After 2 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 2 h, the Schlenk tube was removed from the cooling bath and allowed to warm. After 20 minutes, before warming all the way to ambient temperature (ca. 23 °C), the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The dark blue reaction mixture was quenched by the addition of hexanes (10.0 mL) and H_2O (0.10 mL). After stirring for 5 minutes, both reaction mixtures were combined, filtered through a pad of silica gel (50% acetone in hexanes eluent), and concentrated in vacuo. The crude tan solid was purified by silica gel column chromatography (20% acetone in hexanes eluent) to afford allylic alcohol **12** (56 mg, 56% yield) as an amorphous white solid: R_f = 0.21 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.32–6.24 (m, 1H), 4.93–4.86 (m, 1H), 4.74–4.70 (m, 1H), 4.63 (dt, *J* = 1.8, 0.9 Hz, 1H), 3.37 (dq, *J* = 6.0, 2.9 Hz, 1H), 3.12 (ddd, *J* = 15.9, 9.7, 1.7 Hz, 1H), 2.99–2.89 (m, 2H), 2.84 (dq, *J* = 7.8, 4.4 Hz, 1H), 2.68 (ddd, *J* = 15.1, 3.2, 2.3 Hz, 1H), 2.62 (ddd, *J* = 15.2, 6.0, 0.9 Hz, 1H), 2.40–2.29 (m, 2H), 2.19 (tt, *J* = 11.4, 3.8 Hz, 1H), 2.08 (dd, *J* = 15.7, 4.3 Hz, 1H), 2.02 (s, 1H), 1.83 (dtd, *J* = 14.1, 3.8, 2.0 Hz, 1H), 1.74 (dt, *J* = 1.5, 0.7 Hz, 3H), 1.73–1.65 (m, 1H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 210.3, 174.8, 149.9, 146.2, 128.2, 113.0, 83.1, 79.4, 49.7, 49.4, 48.4, 45.8, 44.5, 40.0, 39.8, 32.4, 30.0, 26.9, 22.5; IR (Neat Film, NaCl) 3479, 2965, 1760, 1699, 1444, 1372, 1224, 1138, 992, 900, 754 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_4$ $[M–H]^–$: 315.1596, found 315.1600; $[\alpha]_D^{25.0}$ –17.7° (*c* 0.400, $CHCl_3$).



11

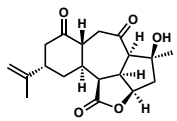
(2*S*,2a*S*,2a^1*R*,3a*R*,4a*R*,7*S*,8a*S*,8b*S*,10a*R*)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-

***bc*]furan-5,9(2*H*,3a*H*)-dione (11).** To a pale yellow stirred solution of allylic alcohol **12** (50 mg, 0.16 mmol, 1.00 equiv) in a vial open to air in benzene (5.3 mL) was added $VO(acac)_2$ (0.5 mg, 0.0016 mmol, 0.01 equiv). After 5 minutes, to this dark green solution was added *t*-butyl hydroperoxide (TBHP, 36 mL, 0.018 mmol, 1.10 equiv) as a 5 M solution in decane dropwise causing the reaction to immediately became deep ruby red. After 1 h, the reaction had lost all red color and become pale yellow and the consumption of starting material was complete as determined by TLC (1:4 Acetone:Hexanes eluent). The reaction was concentrated in vacuo and the crude tan solid was purified by silica gel column chromatography (25% acetone in hexanes eluent) to afford epoxide **11** (47 mg, 94% yield) as a white crystalline solid. Colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of epoxide **11** in EtOAc, mp: 183–185 °C: R_f = 0.15 (1:4 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.87 (s, 1H), 4.79–4.73 (m, 1H), 4.63–4.57 (m, 1H), 3.34 (d, *J* = 7.1 Hz, 1H), 3.24 (ddd, *J* = 15.9, 7.2, 1.8 Hz, 1H), 3.05 (dd, *J* = 6.0, 4.4 Hz, 1H), 2.97 (ddd, *J* = 13.5, 11.8, 4.5 Hz, 1H), 2.84 (dd, *J* = 6.5, 3.4 Hz, 1H), 2.76 (dd, *J* = 6.0, 3.5 Hz, 1H), 2.67 (m, 2H), 2.63 (dd, *J* = 15.3, 6.0 Hz, 1H), 2.48 (bs, 1H), 2.38 (dd, *J* = 15.8, 6.7 Hz, 1H), 2.18 (d, *J* = 15.8 Hz, 1H), 1.89–1.74 (m, 2H), 1.74 (s, 3H), 1.53 (dd, *J* = 15.8, 10.8 Hz, 1H), 1.31 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 210.3, 173.8, 146.2, 113.0, 79.2, 75.3, 71.4, 54.4, 46.8, 46.2, 45.3, 44.3, 44.2, 39.7, 38.0, 31.8, 26.3, 25.6, 22.4; IR (Neat Film, NaCl) 3518, 2963, 2931, 1766, 1703, 1442, 1370, 1259, 1131, 985, 893, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_5$ $[M+H]^+$: 333.1702, found 333.1716; $[\alpha]_D^{25.0}$ +13.2° (*c* 0.200, $CHCl_3$).

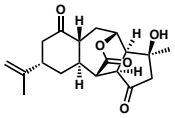


15

(2a*R*,2a^1*R*,4*S*,4a*R*,5*S*,6a*R*,9*S*,10a*S*,10b*S*)-5-bromo-4,4a-dihydroxy-4-methyl-9-(prop-1-en-2-yl)dodecahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,7(2a*H*)-dione (15). To a stirred colorless solution of epoxide **11** (8 mg, 0.024 mmol, 1.00 equiv) in a mixture of toluene (1.6 mL) and THF (0.4 mL) in a nitrogen-filled glovebox was added $MgBr_2$ (22 mg, 0.12 mmol, 5.00 equiv) in a single portion. The reaction mixture was then sealed and heated to 70 °C. After 15 h, the consumption of starting material was complete as determined by TLC (3:7 Acetone:Hexanes eluent). The golden yellow solution was removed from the glovebox. The reaction mixture was concentrated in vacuo and the crude tan solid was purified by silica gel column chromatography (20% acetone in hexanes eluent) to afford bromide **15** (8 mg, 80% yield) as an amorphous white solid: R_f = 0.38 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.96 (ddd, *J* = 9.6, 4.1, 2.9 Hz, 1H), 4.89 (dd, *J* = 2.2, 1.1 Hz, 1H), 4.80–4.74 (m, 1H), 4.65 (dt, *J* = 1.7, 0.8 Hz, 1H), 3.17 (d, *J* = 2.6 Hz, 1H), 2.88–2.70 (m, 6H), 2.51 (ddd, *J* = 14.6, 6.5, 1.0 Hz, 1H), 2.39–2.31 (m, 2H), 2.26 (dd, *J* = 12.0, 10.8 Hz, 1H), 2.20 (d, *J* = 9.6 Hz, 1H), 2.15–2.09 (m, 2H), 1.98 (s, 3H), 1.88 (tt, *J* = 12.5, 3.1 Hz, 1H), 1.75 (dt, *J* = 1.4, 0.7 Hz, 3H), 1.61 (dd, *J* = 11.4, 4.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 209.0, 176.1, 146.1, 113.3, 98.1, 72.5, 69.5, 68.4, 51.0, 49.9, 46.9, 46.8, 44.2, 43.2, 40.4, 33.7, 33.0, 26.1, 22.6; IR (Neat Film, NaCl) 3437, 2926, 1766, 1708, 1444, 1262, 1109, 1014, 799 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{26}O_5{}^{79}Br$ $[M+H]^+$: 413.0964, found 413.0965; $[\alpha]_D^{25.0}$ –8.1° (*c* 0.150, $CHCl_3$).



2H-ent-Ineleganolide (8)



16

(2a*R*,2a^1*R*,4*S*,4a*R*,6a*R*,9*S*,10a*S*,10b*S*)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)dodecahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,5,7-trione (2*H*-*ent*-Ineleganolide, 8) and (1*S*,3a*R*,4*S*,4a*S*,6*S*,8a*R*,10*R*,10a*S*)-1-hydroxy-1-methyl-6-(prop-1-en-2-yl)dodecahydro-10,4-(epoxymethano)benzo[*f*]azulene-3,8,12-trione (16).

Preparation of 0.50 M Solution of Titanocene Monochloride (Cp_2TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with zinc(0) dust (647 mg, 9.90 mmol, 3.00 equiv) and titanocene dichloride (Cp_2TiCl_2, 822 mg, 3.30 mmol, 1.00 equiv). The flask was then evacuated and back filled with argon (3 x 5 minute cycles). To the reaction vessel was then added THF (6.6 mL) that had previously been sparged with argon for 60 minutes and stirring commenced. After 1.5 h, the bright red reaction mixture had become dark green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp_2TiCl.

*Reductive Opening of Epoxide **11***

A stirred solution of epoxide **11** (26 mg, 0.078 mmol, 1.00 equiv) in THF (2.5 mL) was sparged with argon for 1 h, resulting in a reaction volume of 1.5 mL. The homogeneous, off-white reaction mixture was then cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (108 μL, 6.00 mmol, 76.9 equiv). After stirring for 5 minutes, Cp_2TiCl (1.50 mmol, 0.50 M in THF, 19.2 equiv) was added dropwise over 8 minutes. After 2 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 1.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After an additional 18.5 h, the consumption of starting material was complete as determined by TLC (3:7 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH_2PO_4 (1.0 mL) and brine (1.0 mL), sparged with compressed air for 5 minutes, and allowed to stir for an additional 15 minutes. The reaction mixture was then filtered through a Celite® plug, washing with 50% acetone in hexanes eluent. The combined organics were concentrated in vacuo and immediately purified by silica gel column chromatography (50% EtOAc in CH_2Cl_2 eluent), furnishing a mixture of diol products (21 mg, 81% yield) that was directly carried on without further purification.

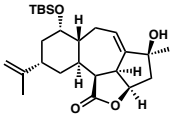
Oxidation of Intermediate Diol Products

To a portion of the diol products (8 mg, 0.024 mmol, 1.00 equiv) in wet DCE[37] (3.0 mL) was added DMP (60 mg, 0.14 mmol, 5.82 equiv) at ambient temperature (ca. 23 °C) with stirring. The reaction vessel was then sealed and heated to 65 °C. After 18 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:CH_2Cl_2 eluent). The reaction vessel was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The reaction mixture was then quenched by the addition of saturated NaS_2O_3 (3.0 mL) and saturated $NaHCO_3$ (3.0 mL). After stirring to 10 minutes, the reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organics were then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude brown solid was purified by silica gel column chromatography (25% acetone in hexanes eluent) to furnish 2*H*-*ent*-ineleganolide (**8**, 4 mg, 50% yield) and diketone **16** (4 mg, 50% yield), both as crystalline white solids.

2*H*-*ent*-Ineleganolide (8): Colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in

heptane into a solution of 2*H*-*ent*-ineleganolide (**8**) in EtOAc, mp: 218–220 °C: R_f = 0.23 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.96–4.92 (m, 1H), 4.80 (ddd, *J* = 7.2, 6.2, 3.8 Hz, 1H), 4.68 (dt, *J* = 1.7, 0.8 Hz, 1H), 3.62 (q, *J* = 1.3 Hz, 1H), 3.21 (td, *J* = 9.3, 6.2 Hz, 1H), 3.08 (d, *J* = 9.6 Hz, 1H), 3.03 (dd, *J* = 9.0, 1.7 Hz, 1H), 2.96 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.89–2.78 (m, 3H), 2.73 (dt, *J* = 14.7, 2.3 Hz, 1H), 2.67 (ddd, *J* = 14.7, 6.1, 1.0 Hz, 1H), 2.51–2.37 (m, 3H), 2.24–2.15 (m, 1H), 1.91 (ddd, *J* = 10.9, 6.0, 2.6 Hz, 1H), 1.78–1.74 (m, 3H), 1.28 (t, *J* = 1.0 Hz, 3H).; ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 213.8, 208.2, 174.1, 145.7, 113.7, 80.9, 80.4, 61.8, 48.0, 46.4, 46.3, 46.1, 44.0, 43.2, 40.3, 37.0, 34.0, 28.7, 22.6; IR (Neat Film, NaCl) 3501, 2965, 2925, 1761, 1698, 1440, 1368, 1318, 1262, 1160, 1081, 1030, 1003, 800, 758 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_5$ $[M+H]^+$: 333.1702, found 333.1714; $[\alpha]_D^{25.0}$ –32.6° (*c* 0.150, $CHCl_3$).

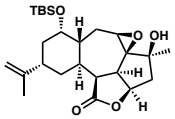
Diketone 16: Colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of diketone **16** in EtOAc, mp: 230–232 °C: R_f = 0.14 (3:7 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.28 (d, *J* = 9.2 Hz, 1H), 4.90 (d, *J* = 1.8 Hz, 1H), 4.66 (s, 1H), 3.02 (d, *J* = 1.8 Hz, 1H), 2.87 (d, *J* = 10.8 Hz, 1H), 2.84 (d, *J* = 5.6 Hz, 1H), 2.72–2.62 (m, 2H), 2.58–2.49 (m, 2H), 2.45 (d, *J* = 16.9 Hz, 1H), 2.41 (d, *J* = 10.8 Hz, 1H), 2.27 (td, *J* = 12.5, 5.4 Hz, 1H), 2.13–2.07 (m, 2H), 1.90 (s, 1H), 1.82–1.70 (m, 4H), 1.71 (dd, *J* = 15.0, 12.1 Hz, 1H), 1.49 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 211.5, 208.9, 170.4, 146.3, 113.4, 75.0, 73.6, 53.1, 51.2, 50.1, 49.8, 47.5, 44.1, 41.7, 40.8, 34.4, 31.8, 28.7, 22.7; IR (Neat Film, NaCl) 3449, 2943, 1742, 1661, 1451, 1378, 1260, 1103, 1041, 801 cm^{-1}; HRMS (EI+) *m/z* calc'd for $C_{19}H_{24}O_5$ $[M\bullet]^+$: 332.1624, found 332.1620; $[\alpha]_D^{25.0}$ +7.8° (*c* 0.100, $CHCl_3$).



17

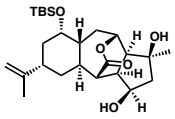
(2a*R*,2a^1*S*,4*S*,6a*R*,7*S*,9*S*,10a*S*,10b*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,6,6a,7,8,9,10,10a,10b-dodecahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1-one (17). To a stirred colorless solution of ketone **12** (10 mg, 0.032 mmol, 1.00 equiv) in THF (2.50 mL) at –78 °C (*i*-PrOH/dry ice bath) was added L-Selectride® (100 mL, 1.0 M in THF, 3.00 equiv) slowly dropwise over 2 minutes. After 15 minutes, the consumption of starting material was complete as determined by TLC (3:7 Acetone:Hexanes eluent). The light yellow reaction mixture was quenched by the addition of saturated NH_4Cl (2.00 mL), removed from the cooling bath, and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 8 mL). The combined organics were then dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an amorphous white solid that was carried on without further purification, assuming quantitative yield.

To a solution of the crude white solid in CH_2Cl_2 (0.65 mL) were added imidazole (22 mg, 0.32 mmol, 10.0 equiv) and DMAP (0.7 mg, 0.006 mmol, 0.20 equiv) at ambient temperature (ca. 23 °C). The pale yellow reaction mixture was the cooled to 0 °C (ice/H_2O bath) at which time TBSCl (15 mg, 0.096 mmol, 3.00 equiv) was added as a solution in CH_2Cl_2 (0.25 mL) quickly dropwise. After 15 minutes, the reaction was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After 18 h, additional imidazole (50 mg, 0.74 mmol, 23.1 equiv), DMAP (10 mg, 0.082, 2.56 equiv), and TBSCl (30 mg, 0.20 mmol, 6.35 equiv) were added sequentially as solids, each in a single portion. After 6 h, the consumption of starting material was complete as determined by TLC (3:7 Acetone:Hexanes eluent). The reaction mixture was concentrated in vacuo and the resultant crude white solid was purified by silica gel column chromatography (15% acetone in hexanes eluent) to provide silyl ether **17** (79% yield, 2 steps) as an amorphous white solid: R_f = 0.19 (3:17 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (ddd, *J* = 8.8, 5.0, 2.9 Hz, 1H), 4.77–4.64 (m, 3H), 3.86 (dt, *J* = 4.9, 2.6 Hz, 1H), 3.36 (tt, *J* = 5.9, 2.6 Hz, 1H), 2.97 (dd, *J* = 5.7, 3.9 Hz, 1H), 2.77–2.66 (m, 1H), 2.45–2.32 (m, 2H), 2.14–2.00 (m, 4H), 1.99–1.82 (m, 3H), 1.74 (dt, *J* = 1.2, 0.6 Hz, 3H), 1.73–1.66 (m, 1H), 1.61 (tt, *J* = 11.0, 3.1 Hz, 1H), 1.37 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 175.4, 149.7, 149.0, 129.9, 108.3, 83.0, 79.4, 73.1, 50.3, 50.2, 45.9, 39.7, 36.6, 36.5, 35.2, 33.4, 32.8, 29.7, 26.1, 21.9, 18.2, –3.9, –4.5; IR (Neat Film, NaCl) 3501, 2927, 2855, 1767, 1444, 1360, 1256, 1151, 1069, 1003, 959, 836, 807, 773 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_4Si$ $[(M+H)–H_2]^+$: 431.2618, found 431.2611; $[\alpha]_D^{25.0}$ –8.1° (*c* 0.250, $CHCl_3$).



18

(2*S*,2a*S*,2a^1*R*,3a*R*,4a*R*,5*S*,7*S*,8a*S*,8b*S*,10a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)dodecahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (18). To a pale yellow stirred solution of allylic alcohol **17** (5 mg, 0.012 mmol, 1.00 equiv) in a vial open to air in benzene (2.0 mL) was added $VO(acac)_2$ (0.6 mg, 0.0024 mmol, 0.2 equiv). After 5 minutes, to this dark green solution was added *t*-butyl hydroperoxide (TBHP, 3 mL, 0.014 mmol, 1.10 equiv) as a 5 M solution in decane dropwise causing the reaction to immediately become deep ruby red. After 1.5 h, the reaction had lost all red color and become pale yellow and the consumption of starting material was complete as determined by TLC (3:17 Acetone:Hexanes eluent). The reaction was concentrated in vacuo and the crude tan solid was purified by silica gel column chromatography (15% acetone in hexanes eluent) to afford epoxide **18** (4 mg, 80% yield) as an amorphous white solid: R_f = 0.19 (3:17 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.74 (ddd, *J* = 6.6, 4.5, 1.3 Hz, 1H), 4.68 (qt, *J* = 1.9, 0.9 Hz, 2H), 3.87 (dt, *J* = 5.0, 1.7 Hz, 1H), 3.28 (d, *J* = 6.8 Hz, 1H), 3.04 (dd, *J* = 6.0, 4.5 Hz, 1H), 2.79 (dd, *J* = 6.2, 2.7 Hz, 2H), 2.53 (d, *J* = 1.2 Hz, 1H), 2.37 (dd, *J* = 15.7, 6.6 Hz, 1H), 2.17 (d, *J* = 15.7 Hz, 1H), 2.11 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.03–1.83 (m, 6H), 1.76–1.69 (m, 3H), 1.64 (ddd, *J* = 14.3, 7.8, 2.1 Hz, 1H), 1.35–1.30 (m, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 174.3, 149.7, 108.3, 79.0, 77.4, 75.4, 73.6, 71.5, 55.4, 48.4, 45.5, 44.8, 36.6, 36.4, 35.4, 33.5, 32.7, 32.3, 26.1, 25.6, 21.7, 18.1, –3.9, –4.5; IR (Neat Film, NaCl) 3521, 2928, 2856, 1771, 1645, 1463, 1361, 1257, 1163, 1069, 986, 963, 878, 836, 774 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_5Si$ $[(M+H)–H_2]^+$: 447.2567, found 447.2572; $[\alpha]_D^{25.0}$ +19.9° (*c* 0.200, $CHCl_3$).



19

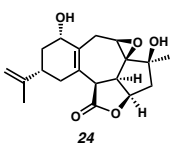
(1*S*,3*R*,3a*R*,4*S*,4a*S*,6*S*,8*S*,8a*R*,10*R*,10a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-1,3-dihydroxy-1-methyl-6-(prop-1-en-2-yl)tetradecahydro-10,4-(epoxymethano)benzo[*f*]azulen-12-one (19).

Preparation of 0.50 M Solution of Titanocene Monochloride (Cp_2TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with zinc(0) dust (647 mg, 9.90 mmol, 3.00 equiv) and titanocene dichloride (Cp_2TiCl_2, 822 mg, 3.30 mmol, 1.00 equiv). The flask was then evacuated and back filled with argon (3 x 5 minute cycles). To the reaction vessel was then added THF (6.6 mL) that had previously been sparged with argon for 60 minutes and stirring commenced. After 1.5 h, the bright red reaction mixture had become dark green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp_2TiCl.

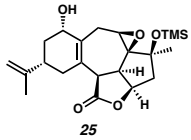
Epoxide Opening with Cp_2TiCl

A stirred solution of epoxide **18** (5 mg, 0.013 mmol, 1.00 equiv) in THF (1.5 mL) was sparged with argon for 1 h, resulting in a reaction volume of 0.5 mL. The homogeneous, off-white reaction mixture was then cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (18 μL, 1.00 mmol, 76.9 equiv). After stirring for 5 minutes, Cp_2TiCl (0.25 mmol, 0.50 M in THF, 19.2 equiv) was added dropwise over 3 minutes. After 2 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 2.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature. After an additional 12 h, the consumption of starting material was complete as determined by TLC (3:17 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH_2PO_4 (0.25 mL) and brine (0.25 mL), sparged with compressed air for 5 minutes, and allowed to stir for an additional 15 minutes. The reaction mixture was then filtered through a Celite® plug, washing with 50% acetone in hexanes eluent. The combined organics were concentrated in vacuo and immediately purified by silica gel column chromatography (40% EtOAc in CH_2Cl_2 eluent) to furnish diol **19** (4 mg, 66% yield) as an amorphous white solid: R_f = 0.42 (1:1 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (d, *J* = 8.7 Hz, 1H), 4.69 (t, *J* = 1.8 Hz, 1H), 4.67 (q, *J* = 1.6 Hz, 1H), 4.33 (q, *J* = 4.3 Hz, 1H), 3.72 (q, *J* = 2.8 Hz, 1H), 3.20 (s, 1H), 2.67–2.58 (m, 2H), 2.50 (d, *J* = 5.1 Hz, 1H), 2.28–2.20 (m, 1H), 2.19–2.05 (m, 2H), 2.05–1.91 (m, 4H), 1.75–1.66 (m, 5H), 1.64–1.52 (m, 2H), 1.34 (dddd, *J* = 12.1, 9.0, 6.0, 2.9 Hz, 1H), 1.28 (s, 3H), 0.80 (s, 9H), 0.00 (d, *J* = 3.0 Hz, 3H), –0.06 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 174.76, 148.41, 108.35, 81.39, 76.21, 74.16, 70.00, 52.77, 50.22, 48.81, 48.35, 42.47, 37.26, 36.95, 35.81, 34.91, 34.69, 27.47, 25.95, 23.23, 18.18, –3.84, –4.81.; IR (Neat Film, NaCl) 3391, 2927, 2855, 1726, 1444, 1386, 1252, 1173, 1081, 1056, 881 838, 774 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{43}O_5Si$ $[M+H]^+$: 451.2880, found 451.2890; $[\alpha]_D^{25.0}$ –2.9° (*c* 0.200, $CHCl_3$).



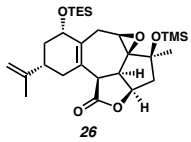
24

(2*S*,2a*S*,2a^1*R*,3a*R*,5*S*,7*S*,8b*R*,10a*R*)-2,5-dihydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,3a,4,5,6,7,8,8b,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (24). To a stirred solution of *ent*-isoineleganolide A (**13**, 11 mg, 0.033 mmol, 1.00 equiv) in MeOH (0.3 mL) and CH_2Cl_2 (0.3 mL) at –78 °C (*i*-PrOH/dry ice bath) was added $NaBH_4$ (4 mg, 0.10 mmol, 3.00 equiv) as a solid in single portion. After 1 h, the homogenous colorless reaction mixture was warmed to 0 °C (ice/H_2O bath). After an additional 1 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (80 mL), removed from the cooling bath, and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then filtered through a silica gel plug, eluting with EtOAc. The combined organics were concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (95% EtOAc in hexanes eluent) to provide allylic alcohol **24** (11 mg, >99% yield) as an amorphous white solid: R_f = 0.17 (19:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.79–4.68 (m, 3H), 4.21 (t, *J* = 8.3 Hz, 1H), 3.35 (dd, *J* = 6.1, 4.5 Hz, 1H), 3.32 (d, *J* = 5.2 Hz, 1H), 3.21 (d, *J* = 6.1 Hz, 1H), 3.01–2.93 (m, 1H), 2.92–2.84 (m, 2H), 2.42–2.32 (m, 2H), 2.29 (d, *J* = 16.0 Hz, 1H), 2.22–2.15 (m, 1H), 1.79–1.70 (m, 4H), 1.42 (td, *J* = 12.3, 9.7 Hz, 1H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 173.8, 148.4, 129.7, 126.8, 109.4, 79.6, 75.2, 73.8, 70.4, 55.5, 48.8, 45.7, 44.1, 38.5, 38.1, 37.2, 28.0, 26.5, 21.0; IR (Neat Film, NaCl) 3441, 2930, 1771, 1645, 1436, 1373, 1234, 1140, 986, 890, 757 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_5$ $[M+H]^+$: 333.1702, found 333.1695; $[\alpha]_D^{25.0}$ +0.5 ° (*c* 0.550, $CHCl_3$).



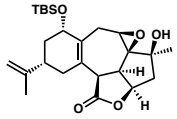
25

(2*S*,2a*S*,2a^1*R*,3a*R*,5*S*,7*S*,8b*R*,10a*R*)-5-hydroxy-2-methyl-7-(prop-1-en-2-yl)-2-((trimethylsilyl)oxy)-1,2a^1,3a,4,5,6,7,8,8b,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (25). To a stirred solution of allylic alcohol **24** (11 mg, 0.033 mmol, 1.00 equiv) in CH_2Cl_2 (0.7 mL) at –78 °C (*i*-PrOH/dry ice bath) was added Et_3N (92 ml, 0.66 mmol, 20.0 equiv) dropwise. After 5 minutes, TMSOTf (31 mL, 0.10 mmol, 3.00 equiv) was added slowly dropwise. After an additional 10 minutes, the consumption of starting material was complete as determined by TLC (19:1 EtOAc:Hexanes eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (80 mL), removed from the cooling bath, and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then filtered through a silica gel plug, eluting with 100% EtOAc. The combined organics were concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (40% EtOAc in hexanes eluent) to furnish silyl ether **25** (10 mg, 77% yield) as an amorphous white solid: R_f = 0.36 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.83–4.67 (m, 3H), 4.33–4.22 (m, 1H), 3.35–3.30 (m, 2H), 3.17 (d, *J* = 6.2 Hz, 1H), 3.00–2.90 (m, 1H), 2.83 (ddt, *J* = 16.6, 4.0, 2.1 Hz, 1H), 2.68 (dd, *J* = 19.7, 5.5 Hz, 1H), 2.55 (bs, 1H), 2.44–2.25 (m, 3H), 2.13–2.04 (m, 1H), 1.83–1.69 (m, 4H), 1.48–1.38 (m, 1H), 1.33 (s, 3H), 0.18 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 173.8, 148.4, 129.8, 127.0, 109.4, 79.6 (d, *J* = 4.1 Hz), 75.2, 74.8, 70.4, 55.6, 48.8, 45.7, 44.2, 38.6, 38.4, 37.3, 28.5, 26.5, 20.8, 0.6; IR (Neat Film, NaCl) 3429, 2959, 1764, 1371, 1250, 1142, 1056, 887, 841 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{33}O_5Si$ $[M+H]^+$: 405.2097, found 405.2088; $[\alpha]_D^{25.0}$ +60.4° (*c* 0.250, $CHCl_3$).

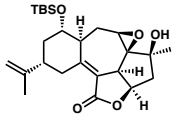


26

(2*S*,2a*S*,2a^1*R*,3a*R*,5*S*,7*S*,8b*R*,10a*R*)-2-methyl-7-(prop-1-en-2-yl)-5-((triethylsilyl)oxy)-2-((trimethylsilyl)oxy)-1,2a^1,3a,4,5,6,7,8,8b,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (26). To a stirred solution of allylic alcohol **25** (5 mg, 0.012 mmol, 1.00 equiv) in CH_2Cl_2 (0.3 mL) at –78 °C (*i*-PrOH/dry ice bath) was added Et_3N (35 ml, 0.25 mmol, 20.8 equiv) dropwise. After 5 minutes, TESOTf (15 mL, 0.060 mmol, 5.00 equiv) was added slowly dropwise. After an additional 20 minutes, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:Hexanes eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (80 mL), removed from the cooling bath, and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then filtered through a silica gel plug, eluting with EtOAc. The combined organics were concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (10% EtOAc in hexanes eluent) to afford bis-silyl ether **26** (4 mg, 66% yield) as an amorphous white solid: R_f = 0.14 (1:9 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.84–4.72 (m, 2H), 4.70 (s, 1H), 4.33–4.21 (m, 1H), 3.25 (dd, *J* = 6.4, 4.7 Hz, 1H), 3.20 (d, *J* = 5.4 Hz, 1H), 3.10 (d, *J* = 6.4 Hz, 1H), 2.93–2.84 (m, 2H), 2.65 (dd, *J* = 19.5, 5.5 Hz, 1H), 2.41–2.32 (m, 2H), 2.28 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.10–2.03 (m, 1H), 1.76–1.70 (m, 4H), 1.41 (td, *J* = 12.7, 10.0 Hz, 1H), 1.31 (s, 3H), 0.93 (t, *J* = 7.9 Hz, 9H), 0.68–0.54 (m, 6H), 0.18 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 173.7, 148.6, 130.0, 127.0, 109.3, 79.3, 77.0, 74.9, 69.6, 53.8, 48.6, 44.5, 43.4, 38.6, 38.5, 37.2, 29.7, 28.7, 20.8, 7.2, 6.5, 0.6; IR (Neat Film, NaCl) 3464, 2956, 1766, 1665, 1451, 1376, 1249, 1143, 1047, 890, 841, 795, 744 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{47}O_5Si_2$ $[M+H]^+$: 519.2962, found 519.2959; $[\alpha]_D^{25.0}$ +53.6° (*c* 0.100, $CHCl_3$).



30

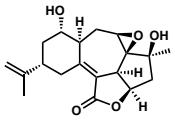


31

(2*S*,2a*S*,2a^1*R*,3a*R*,5*S*,7*S*,8b*R*,10a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,3a,4,5,6,7,8,8b,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (30) and (2*S*,2a*S*,2a^1*R*,3a*R*,4a*S*,5*S*,7*S*,10a*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,3a,4,4a,5,6,7,8,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (31). To a stirred solution of allylic alcohol **24** (65 mg, 0.20 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) were added imidazole (2.72 g, 40.0 mmol, 200.0 equiv) and DMAP (98 mg, 0.80 mmol, 4.00 equiv) as solids sequential, each in a single portion. After 5 minutes, to the resulting homogenous, pale yellow solution was added TBSCl (3.01 g, 20.0 mmol, 100.0 equiv) as a solution in CH_2Cl_2 (7.5 mL) quickly dropwise over 5 minutes. After 17 h, the consumption of starting material was complete as determined by TLC (19:1 EtOAc:Hexanes eluent). The reaction mixture was then filtered through a Celite® plug, washing with CH_2Cl_2 eluent. The combined organics were concentrated in vacuo and purified by silica gel column chromatography (15% acetone in hexanes eluent) to furnish diol allylic silyl ether **30** (23 mg, 26% yield) as an amorphous white solid and unsaturated lactone **31** (66 mg, 74% yield) as an amorphous white solid.

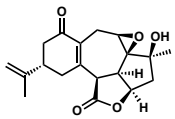
Allylic Silyl Ether 30: R_f = 0.20 (3:17 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.78–4.67 (m, 3H), 4.26 (bt, *J* = 8.0 Hz, 1H), 3.35 (dd, *J* = 6.1, 4.5 Hz, 1H), 3.31 (d, *J* = 5.4 Hz, 1H), 3.17 (dd, *J* = 5.8, 1.9 Hz, 1H), 2.97–2.78 (m, 2H), 2.78–2.67 (m, 1H), 2.55 (bs, 1H), 2.42–2.24 (m, 3H), 2.06 (ddt, *J* = 12.2, 6.3, 2.3 Hz, 1H), 1.79–1.69 (m, 4H), 1.40 (ddd, *J* = 13.5, 12.4, 10.3 Hz, 1H), 1.34 (s, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 173.9, 148.6, 130.5, 126.5, 109.4, 79.7, 75.3, 75.0, 70.5, 55.8, 48.9, 45.8, 44.3, 38.7, 38.5, 37.4, 28.6, 26.6, 26.2, 20.9, 18.4, –3.5, –4.6; IR (Neat Film, NaCl) 3465, 2930, 2857, 1771, 1463, 1370, 1256, 1140, 1102, 1056, 988, 972, 883, 836, 774 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_5Si$ $[M+H]^+$:447.2567, found 447.2552; $[\alpha]_D^{25.0}$ +87.5 ° (*c* 0.400, $CHCl_3$).

Unsaturated Lactone 31: R_f = 0.29 (3:17 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.80 (ddd, *J* = 9.3, 7.8, 7.2 Hz, 1H), 4.75 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.73 (s, 1H), 4.16–4.07 (m, 1H), 3.88 (ddd, *J* = 10.1, 9.0, 4.3 Hz, 1H), 3.81 (dt, *J* = 9.3, 2.5 Hz, 1H), 3.37 (ddd, *J* = 5.4, 2.0, 0.7 Hz, 1H), 2.61–2.51 (m, 2H), 2.41 (dtd, *J* = 9.3, 4.7, 2.4 Hz, 1H), 2.38–2.32 (m, 1H), 2.14 (tt, *J* = 11.7, 4.1 Hz, 1H), 2.08–1.97 (m, 2H), 1.97–1.90 (m, 1H), 1.86 (ddd, *J* = 13.7, 11.1, 2.5 Hz, 1H), 1.74 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.43 (td, *J* = 12.5, 10.2 Hz, 1H), 1.32 (d, *J* = 0.9 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 169.7, 158.8, 148.2, 116.1, 109.6, 74.5, 73.5, 73.3, 70.9, 54.3, 51.6, 48.1, 41.5, 41.0, 40.4, 32.6, 26.0, 23.5, 22.7, 20.6, 18.2, –3.9, –4.7; IR (Neat Film, NaCl) 3494, 2929, 2857, 1742, 1645, 1455, 1360, 1259, 1176, 1121, 1078, 1053, 957, 918, 898, 837, 775 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_5Si$ $[M+H]^+$: 447.2567, found 447.2577; $[\alpha]_D^{25.0}$ +56.1° (*c* 0.600, $CHCl_3$).



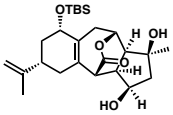
32

(2*S*,2a*S*,2a^1*R*,3a*R*,4a*S*,5*S*,7*S*,10a*R*)-2,5-dihydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,3a,4,4a,5,6,7,8,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (32). To a stirred solution of silyl ether **31** (4 mg, 0.009 mmol, 1.00 equiv) in THF (0.6 mL) at –78 °C (*i*-PrOH/dry ice bath) was added TBAF (11 mL, 1 M in THF, 1.22 equiv) slowly dropwise. After 3 h, the reaction was introduced to a 0 °C bath (ice/H_2O). After a further 4 h, the consumption of starting material was complete as determined by TLC (1:4 Acetone:Hexanes eluent). The reaction was removed from the cooling bath and immediately concentrated in vacuo. The crude dark brown oil was purified by silica gel column chromatography (EtOAc eluent) to provide epoxide **32** (3 mg, >99% yield) as an amorphous white solid: R_f = 0.31 (EtOAc eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.83 (dt, *J* = 9.2, 7.4 Hz, 1H), 4.77 (dt, *J* = 1.7, 0.9 Hz, 1H), 4.75 (q, *J* = 1.5 Hz, 1H), 3.96 (dd, *J* = 14.0, 4.7 Hz, 1H), 3.93–3.86 (m, 1H), 3.84 (dt, *J* = 9.2, 2.5 Hz, 1H), 3.43 (dd, *J* = 4.8, 2.2 Hz, 1H), 2.63–2.52 (m, 2H), 2.42 (dddd, *J* = 8.3, 6.2, 4.3, 2.2 Hz, 1H), 2.32 (bs, 1H), 2.26–2.03 (m, 4H), 1.93 (dd, *J* = 13.3, 7.3 Hz, 1H), 1.75 (t, *J* = 1.1 Hz, 3H), 1.44 (ddd, *J* = 12.4, 11.7, 10.5 Hz, 1H), 1.33 (t, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 169.6, 158.0, 148.0, 116.9, 109.8, 74.6, 73.5, 72.7, 70.4, 54.3, 50.8, 48.0, 41.6, 40.8, 40.1, 31.9, 23.5, 23.0, 20.8; IR (Neat Film, NaCl) 3418, 2964, 2925, 2855, 1732, 1644, 1446, 1372, 1260, 1177, 1103, 1048, 1029, 911, 802, 732 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{25}O_5$ $[M+H]^+$: 333.1702, found 333.1688; $[\alpha]_D^{25.0}$ +14.3° (*c* 0.150, $CHCl_3$).



***ent*-Isoineleganolide A (13)**

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,8b*R*,10a*R*)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,4,6,7,8,8b,10a-octahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-5,9(2*H*,3a*H*)-dione (*ent*-Isoineleganolide A, 13). To a stirred solution of unsaturated lactone **32** (3 mg, 0.009 mmol, 1.00 equiv) in wet CH_2Cl_2 (1.3 mL) at 0 °C (ice/H_2O bath) was added Dess–Martin periodinane (DMP, 8 mg, 0.018 mmol, 2.00 equiv) as a solid in a single portion. After 2.5 h, the consumption of starting material was complete as determined by TLC (EtOAc eluent). The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (2 mL) with vigorous stirring. After 15 minutes, the reaction was diluted with CH_2Cl_2 (5 mL) and poured onto saturated aqueous $NaHCO_3$ (2 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (3 x 2 mL). The combined organics were concentrated in vacuo. The crude golden solid was purified by silica gel column chromatography (85% EtOAc in hexanes eluent) to provide *ent*-isoineleganolide A (**13**, 2 mg, 66% yield) as a crystalline white solid: characterization match those reported previously.[8]



36

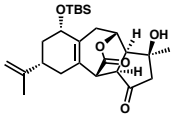
(1*S*,3*R*,3a*R*,4*R*,6*S*,8*S*,10*R*,10a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-1,3-dihydroxy-1-methyl-6-(prop-1-en-2-yl)-1,2,3,3a,4,5,6,7,8,9,10,10a-dodecahydro-10,4-(epoxymethano)benzo[*f*]azulen-12-one (36).

Preparation of 0.50 M Solution of Titanocene Monochloride (Cp_2TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with zinc(0) dust (647 mg, 9.90 mmol, 3.00 equiv) and titanocene dichloride (Cp_2TiCl_2, 822 mg, 3.30 mmol, 1.00 equiv). The flask was then evacuated and back filled with argon (3 x 5 minute cycles). To the reaction vessel was then added THF (6.6 mL) that had previously been sparged with argon for 60 minutes and stirring commenced. After 1.5 h, the bright red reaction mixture had become dark green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp_2TiCl.

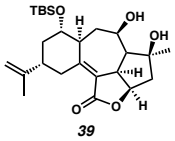
Epoxide Opening with Cp_2TiCl

A stirred solution of epoxide **30** (8 mg, 0.018 mmol, 1.00 equiv) in THF (2.0 mL) was sparged with argon for 1 h, resulting in a reaction volume of 0.8 mL. The homogeneous, off-white reaction mixture was then cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (27 µL, 1.50 mmol, 55.6 equiv). After stirring for 5 minutes, Cp_2TiCl (0.38 mmol, 0.50 M in THF, 14.1 equiv) was added dropwise over 3 minutes. After 2 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 2.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature. After an additional 12.5 h, the consumption of starting material was complete as determined by TLC (3:17 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH_2PO_4 (0.25 mL) and brine (0.25 mL), sparged with compressed air for 5 minutes, and allowed to stir for an additional 15 minutes. The reaction mixture was then filtered through a Celite® plug, washing with 50% acetone in hexanes eluent. The combined organics were concentrated in vacuo and purified *twice* by silica gel column chromatography (first column: 45% EtOAc in CH_2Cl_2 eluent, second column: 40% EtOAc in CH_2Cl_2 eluent) to furnish diol **36** (2 mg, 25% yield) as an amorphous white solid: R_f = 0.40 (1:1 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.00 (dd, *J* = 4.5, 2.6 Hz, 1H), 4.74 (p, *J* = 1.7 Hz, 1H), 4.71 (dd, *J* = 1.9, 0.9 Hz, 1H), 4.33 (tt, *J* = 4.9, 2.1 Hz, 1H), 4.14 (td, *J* = 6.3, 3.0 Hz, 1H), 3.55 (s, 1H), 3.16 (d, *J* = 5.3 Hz, 1H), 3.06 (d, *J* = 1.6 Hz, 1H), 2.98 (ddd, *J* = 12.3, 5.0, 1.6 Hz, 1H), 2.84–2.71 (m, 1H), 2.60–2.47 (m, 1H), 2.35–2.15 (m, 5H), 2.06–1.91 (m, 2H), 1.74–1.70 (m, 3H), 1.67 (dd, *J* = 14.0, 3.7 Hz, 1H), 1.44 (td, *J* = 13.3, 12.8, 10.2 Hz, 1H), 1.34 (s, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 173.3, 148.2, 132.7, 129.4, 109.7, 81.4, 76.0, 74.0, 71.6, 51.5, 49.6, 48.4, 47.7, 39.7, 38.1, 37.6, 36.8, 27.4, 26.1, 20.6, 18.3, -4.0, -4.7; IR (Neat Film, NaCl) 3365, 2927, 2855, 1733, 1454, 1386, 1259, 1081, 1060, 876, 836, 775 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{41}O_5Si$ $[M+H]^+$: 449.2723, found 449.2735; $[\alpha]_D^{25.0}$ +31.3° (*c* 0.100, $CHCl_3$).



37

(1*S*,3a*R*,4*R*,6*S*,8*S*,10*R*,10a*S*)-8-((*tert*-butyldimethylsilyl)oxy)-1-hydroxy-1-methyl-6-(prop-1-en-2-yl)-1,3a,4,5,6,7,8,9,10,10a-decahydro-10,4-(epoxymethano)benzo[*f*]azulene-3,12(2*H*)-dione (37). To a stirred solution of diol **36** (10 mg, 0.022 mmol, 1.00 equiv) in wet CH_2Cl_2 (2.0 mL) at 0 °C (ice/H_2O bath) was added Dess–Martin periodinane (DMP, 30 mg, 0.071 mmol, 3.23 equiv) was a solid in a single portion. After 3 h, the white suspension was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After an additional 10 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (3 mL) with vigorous stirring. After 15 minutes, the reaction was diluted with CH_2Cl_2 (10 mL) and poured onto saturated aqueous $NaHCO_3$ (3 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (4 x 2 mL). The combined organics were concentrated in vacuo. The crude golden solid was purified by silica gel column chromatography (15% EtOAc in hexanes eluent) to provide ketone **37** (6 mg, 60% yield) as an amorphous white solid: R_f = 0.27 (3:17 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.25 (ddd, *J* = 5.0, 2.3, 0.8 Hz, 1H), 4.75 (p, *J* = 1.5 Hz, 1H), 4.72 (dd, *J* = 1.7, 0.9 Hz, 1H), 4.19–4.11 (m, 1H), 3.26 (d, *J* = 2.0 Hz, 1H), 3.22 (ddt, *J* = 10.8, 2.0, 0.9 Hz, 1H), 2.86 (dd, *J* = 18.5, 2.6 Hz, 1H), 2.69–2.38 (m, 4H), 2.33–2.16 (m, 3H), 2.04–1.95 (m, 1H), 1.72 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.48 (s, 3H), 1.47–1.38 (m, 1H), 0.92 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 212.0, 169.9, 147.8, 133.3, 129.3, 109.9, 75.1, 74.0, 71.6, 53.3, 52.9, 47.8, 47.4, 39.6, 37.5, 37.5, 36.7, 29.1, 26.1, 20.5, 18.3, –3.9, –4.7; IR (Neat Film, NaCl) 3447, 2927, 2856, 1750, 1378, 1257, 1185, 1063, 872, 836, 777 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_5Si$ $[M+H]^+$: 447.2567, found 447.2551; $[\alpha]_D^{25.0}$ +35.4° (*c* 0.300, $CHCl_3$).



39

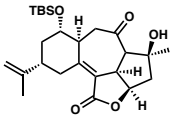
(2a*R*,2a^1*R*,4*S*,5*R*,6a*S*,7*S*,9*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4,5-dihydroxy-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,4a,5,6,6a,7,8,9,10-dodecahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1-one (39).

Preparation of 0.50 M Solution of Titanocene Monochloride (Cp_2TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with zinc(0) dust (647 mg, 9.90 mmol, 3.00 equiv) and titanocene dichloride (Cp_2TiCl_2, 822 mg, 3.30 mmol, 1.00 equiv). The flask was then evacuated and back filled with argon (3 x 5 minute cycles). To the reaction vessel was then added THF (6.6 mL) that had previously been sparged with argon for 60 minutes and stirring commenced. After 1.5 h, the bright red reaction mixture had become dark green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp_2TiCl.

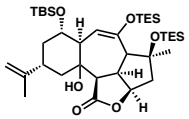
Epoxide Opening with Cp_2TiCl

A stirred solution of epoxide **31** (12 mg, 0.027 mmol, 1.00 equiv) in THF (2.0 mL) was sparged with argon for 1 h, resulting in a reaction volume of 0.8 mL. The homogeneous, off-white reaction mixture was then cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (27 μL, 1.50 mmol, 55.6 equiv). After stirring for 5 minutes, Cp_2TiCl (0.38 mmol, 0.50 M in THF, 14.1 equiv) was added dropwise over 3 minutes. After 2 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 2.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature. After an additional 12.5 h, the consumption of starting material was complete as determined by TLC (3:17 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH_2PO_4 (0.25 mL) and brine (0.25 mL), sparged with compressed air for 5 minutes, and allowed to stir for an additional 15 minutes. The reaction mixture was then filtered through a Celite® plug, washing with 50% acetone in hexanes eluent. The combined organics were concentrated in vacuo and purified *twice* by silica gel column chromatography (25% EtOAc in CH_2Cl_2 eluent) to furnish diol **39** (5 mg, 42% yield) as an amorphous white solid: R_f = 0.19 (1:4 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.89 (ddd, *J* = 8.3, 6.3, 2.2 Hz, 1H), 4.77–4.73 (m, 1H), 4.69 (q, *J* = 1.5 Hz, 1H), 4.53 (q, *J* = 4.2 Hz, 1H), 3.89 (ddd, *J* = 9.4, 7.6, 4.2 Hz, 1H), 3.86–3.80 (m, 1H), 3.79–3.69 (m, 1H), 3.44–3.34 (m, 1H), 2.76 (ddt, *J* = 19.1, 10.6, 5.3 Hz, 1H), 2.73–2.68 (m, 1H), 2.60 (dt, *J* = 8.7, 7.0 Hz, 1H), 2.42 (ddt, *J* = 14.7, 11.9, 4.4 Hz, 1H), 2.20 (dd, *J* = 14.6, 2.1 Hz, 1H), 2.17–1.92 (m, 6H), 1.71 (dd, *J* = 1.4, 0.7 Hz, 3H), 1.43 (s, 3H), 1.37 (ddd, *J* = 13.2, 11.2, 9.2 Hz, 1H), 0.90 (s, 9H), 0.09 (app d, *J* = 0.9 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 169.8, 158.2, 148.9, 122.7, 109.7, 81.7, 78.6, 74.6, 68.3, 52.8, 48.4, 47.4, 44.3, 38.8, 37.7, 34.2, 29.6, 26.9, 26.0, 20.1, 18.1, –3.9, –4.5; IR (Neat Film, NaCl) 3359, 2928, 2856, 1727, 1661, 1463, 1360, 1311, 1257, 1230, 1110, 1073, 1034, 887, 836, 775 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{41}O_5Si$ $[M+H]^+$: 449.2723, found 449.2721; $[\alpha]_D^{25.0}$ +46.4° (*c* 0.250, $CHCl_3$).



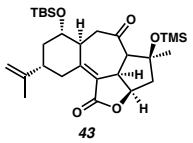
40

(2a*R*,2a^1*R*,4*S*,6a*S*,7*S*,9*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)-2a^1,3,4,4a,6,6a,7,8,9,10-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,5(2a*H*)-dione (40). To a stirred solution of diol **39** (49 mg, 0.11 mmol, 1.00 equiv) in wet CH_2Cl_2 (2.2 mL) at 0 °C (ice/H_2O bath) was added Dess–Martin periodinane (DMP, 140 mg, 0.33 mmol, 3.00 equiv) was a solid in a single portion. After 30 minutes, the white suspension was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After 2 h, additional DMP (140 mg, 0.33 mmol, 3.00 equiv) was added in a single portion. After an additional 10.5 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (4 mL) with vigorous stirring. After 15 minutes, the reaction was diluted with CH_2Cl_2 (10 mL) and poured onto saturated aqueous $NaHCO_3$ (4 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (4 x 2 mL). The combined organics were concentrated in vacuo. The crude golden brown solid was purified by silica gel column chromatography (8% EtOAc in hexanes eluent) to provide ketone **40** (10 mg, 23% yield) as an amorphous white solid: R_f = 0.27 (1:19 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.94 (ddd, *J* = 8.2, 7.4, 0.9 Hz, 1H), 4.76–4.70 (m, 2H), 4.37 (ddd, *J* = 14.4, 3.9, 2.0 Hz, 1H), 4.17 (tt, *J* = 8.5, 2.8 Hz, 1H), 3.73 (ddd, *J* = 10.6, 9.2, 4.5 Hz, 1H), 3.13 (dd, *J* = 12.2, 6.8 Hz, 1H), 3.08 (d, *J* = 8.9 Hz, 1H), 2.82 (dd, *J* = 12.2, 3.8 Hz, 1H), 2.68 (ddt, *J* = 9.9, 6.6, 3.2 Hz, 1H), 2.58 (d, *J* = 2.4 Hz, 1H), 2.28 (d, *J* = 15.2 Hz, 1H), 2.11–1.95 (m, 2H), 1.87 (ddd, *J* = 15.2, 7.4, 2.5 Hz, 1H), 1.81–1.70 (m, 4H), 1.51–1.40 (m, 4H), 0.91 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 209.3, 169.7, 153.6, 148.1, 123.9, 109.6, 78.5, 73.1, 67.6, 50.5, 47.3, 43.8, 40.5, 40.4, 40.0, 32.3, 29.9, 27.2, 26.1, 20.8, 18.2, –3.9, –4.5; IR (Neat Film, NaCl) 3542, 2929, 2857, 1733, 1634, 1456, 1362, 1256, 1182, 1147, 1090, 1033, 891, 838, 777 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_5Si$ $[M+H]^+$: 447.2567, found 447.2553; $[\alpha]_D^{25.0}$ +94.3° (*c* 0.750, $CHCl_3$).



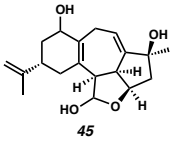
41

(2a*R*,2a^1*R*,4*S*,6a*R*,7*S*,9*R*,10b*R*)-7-((*tert*-butyldimethylsilyl)oxy)-10a-hydroxy-4-methyl-9-(prop-1-en-2-yl)-4,5-bis((triethylsilyl)oxy)-2a,2a^1,3,4,4a,6a,7,8,9,10,10a,10b-dodecahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1-one (41). To a stirred solution of ketone **40** (13 mg, 0.029 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C (ice/H_2O bath) was added Et_3N (0.20 mL, 1.45 mmol, 50.0 equiv) dropwise. After 5 minutes, TESOTf (66 mL, 0.29 mmol, 10.0 equiv) was added slowly dropwise. After an additional 20 minutes, the consumption of starting material was complete as determined by TLC (1:19 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL) and immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then filtered through a silica gel plug, eluting with 10% EtOAc in hexanes. The combined organics were concentrated in vacuo. The crude tan solid was purified by silica gel column chromatography (5% EtOAc in hexanes eluent) to provide enol ether **41** (11 mg, 55% yield) as an amorphous white solid: R_f = 0.50 (1:9 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.48 (t, *J* = 2.5 Hz, 1H), 4.91 (td, *J* = 8.3, 6.0 Hz, 1H), 4.72 (q, *J* = 1.2 Hz, 2H), 3.61 (ddd, *J* = 11.6, 8.3, 3.4 Hz, 1H), 3.13–3.04 (m, 1H), 2.68–2.53 (m, 3H), 2.45–2.33 (m, 2H), 2.26 (ddd, *J* = 13.1, 8.1, 1.3 Hz, 1H), 1.97–1.87 (m, 1H), 1.66 (t, *J* = 1.1 Hz, 3H), 1.60–1.46 (m, 4H), 1.15 (d, *J* = 1.2 Hz, 3H), 0.95 (td, *J* = 8.0, 5.4 Hz, 18H), 0.92 (s, 9H), 0.68–0.57 (m, 12H), 0.10 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 174.7, 147.8, 138.3, 124.2, 110.7, 88.6, 82.3, 80.2, 74.9, 59.6, 56.4, 48.1, 47.4, 47.0, 45.0, 44.2, 38.1, 29.9, 25.9, 20.2, 18.2, 7.4, 7.2, 6.9, 6.8, –4.0, –4.5; IR (Neat Film, NaCl) 2954, 2876, 1767, 1463, 1373, 1353, 1332, 1251, 1157, 1116, 1090, 1028, 871, 836, 775, 743 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{37}H_{69}O_6Si_3$ $[M+H]^+$: 693.4402, found 693.4422; $[\alpha]_D^{25.0}$ +34.9° (*c* 0.250, $CHCl_3$).



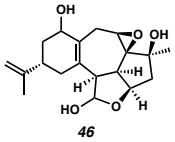
43

(2a*R*,2a^1*R*,4*S*,6a*S*,7*S*,9*S*)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-9-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)-2a^1,3,4,4a,6,6a,7,8,9,10-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,5(2a*H*)-dione (43). To a stirred solution of ketone **40** (4 mg, 0.009 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) at 0 °C (ice/H_2O bath) was added Et_3N (126 ml, 0.90 mmol, 100.0 equiv) dropwise. After 5 minutes, TMSOTf (20 mL, 0.11 mmol, 12.2 equiv) was added slowly dropwise. After an additional 5 minutes, the consumption of starting material was complete as determined by TLC (1:19 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1.5 mL) and immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). The reaction was diluted with Et_2O (2 mL) and poured onto H_2O (3 mL). The organics were separated and the aqueous was extracted with Et_2O (3 x 2 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (18% EtOAc in hexanes eluent) to provide bis-silyl ether **43** (4 mg, >99% yield) as an amorphous white solid: R_f = 0.28 (1:4 EtOAc:Hexanes eluent); ^{1}H NMR (C_6D_6, 400 MHz) δ 5.05–4.97 (m, 1H), 4.94 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.84 (p, *J* = 1.5 Hz, 1H), 4.18 (t, *J* = 7.8 Hz, 1H), 3.73 (ddd, *J* = 10.7, 9.6, 4.4 Hz, 1H), 3.13 (tt, *J* = 8.1, 2.9 Hz, 1H), 2.86 (dd, *J* = 11.5, 3.6 Hz, 1H), 2.62 (dd, *J* = 11.5, 5.4 Hz, 1H), 2.41 (ddt, *J* = 9.0, 6.0, 3.3 Hz, 1H), 2.28–2.16 (m, 2H), 1.90 (d, *J* = 14.9 Hz, 1H), 1.83 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.70 (d, *J* = 8.0 Hz, 1H), 1.68–1.49 (m, 2H), 1.39 (s, 3H), 1.08 (s, 9H), 1.03 (dd, *J* = 14.9, 7.6 Hz, 1H), 0.40 (s, 3H), 0.20 (s, 3H), 0.15 (s, 9H) ; ^{13}C{^{1}H} NMR (C_6D_6, 101 MHz) δ 204.9, 169.9, 150.1, 148.5, 124.5, 109.5, 81.3, 76.5, 73.3, 68.3, 50.9, 48.5, 43.6, 41.2, 41.2, 40.3, 33.3, 26.4, 26.0, 21.1, 18.5, 2.4, –4.1, –4.3; IR (Neat Film, NaCl) 2928, 2856, 1738, 1716, 1635, 1455, 1362, 1251, 1184, 1149, 1093, 1017, 886, 837, 778 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{28}H_{47}O_5Si_2$ $[M+H]^+$: 519.2962, found 519.2954; $[\alpha]_D^{25.0}$ +61.8° (*c* 0.200, benzene).



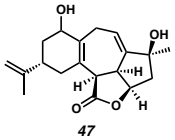
45

(2a*R*,2a^1*S*,4*S*,9*S*,10b*R*)-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,6,7,8,9,10,10b-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,4,7-triol (45).[38] To a stirred solution of diene **5** (5 mg, 0.016 mmol, 1.00 equiv) in CH_2Cl_2 (0.70 mL) at –78 °C (*i*-PrOH/dry ice bath) was added DIBAL (48 mL, 1.00 M in CH_2Cl_2, 3.00 equiv) slowly dropwise. After 5.5 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous NH_4Cl (0.5 mL) and saturated aqueous Rochelle salt (0.5 mL) and immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After stirring for 1 h, the reaction was diluted with CH_2Cl_2 (2.0 mL) and poured onto H_2O (3.0 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (4 x 1.5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude off-white solid was purified by silica gel column chromatography (50% EtOAc in hexanes eluent) to provide lactol **45** (11 mg, 55% yield) as an amorphous white solid: R_f = 0.21 (1:1 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (ddd, *J* = 8.6, 4.5, 3.0 Hz, 1H), 5.55 (d, *J* = 5.2 Hz, 1H), 4.77 (p, *J* = 1.7 Hz, 1H), 4.73 (dt, *J* = 2.0, 1.0 Hz, 1H), 4.61 (t, *J* = 4.7 Hz, 1H), 4.28–4.17 (m, 1H), 3.66–3.58 (m, 1H), 3.06 (d, *J* = 17.5 Hz, 1H), 3.01–2.93 (m, 1H), 2.83 (dd, *J* = 17.2, 8.6 Hz, 1H), 2.40 (d, *J* = 15.1 Hz, 1H), 2.37–2.20 (m, 2H), 2.16 (dddd, *J* = 12.6, 6.1, 2.9, 1.8 Hz, 1H), 2.02–1.92 (m, 2H), 1.76 (t, *J* = 1.1 Hz, 3H), 1.65–1.59 (m, 1H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 151.6, 149.0, 134.05, 129.7, 126.9, 109.8, 100.7, 85.1, 79.0, 72.9, 52.1, 48.8, 47.7, 38.8, 37.9, 36.2, 27.9, 27.3, 21.0; IR (Neat Film, NaCl) 3316, 2923, 1658, 1442, 1373, 1260, 1107, 1023, 925, 888, 806, 754 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{26}O_4$ $[M\bullet]^+$: 318.1831, found 318.1780; $[\alpha]_D^{25.0}$ +27.1° (*c* 0.200, $CHCl_3$).



46

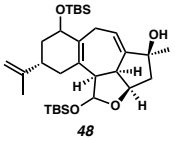
(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,8b*R*,10a*R*)-2-methyl-7-(prop-1-en-2-yl)-1,2,2a^1,3a,4,5,6,7,8,8b,9,10a-dodecahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-2,5,9-triol (46).[39] To a stirred solution of *ent*-isoineleganolide A (**13**, 5 mg, 0.015 mmol, 1.00 equiv) in toluene (0.70 mL) at –78 °C (*i*-PrOH/dry ice bath) was added DIBAL (45 mL, 1.00 M in toluene, 3.00 equiv) slowly dropwise. After 1.5 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous NH_4Cl (0.5 mL) and saturated aqueous Rochelle salt (0.5 mL) and immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After stirring for 1 h, the reaction was diluted with CH_2Cl_2 (2.0 mL) and poured onto H_2O (3.0 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (4 x 1.5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude off-white solid was purified by silica gel column chromatography (EtOAc eluent) to provide lactol **46** (2 mg, 40% yield) as an amorphous white solid: R_f = 0.23 (EtOAc eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.47 (dd, *J* = 12.1, 5.6 Hz, 1H), 5.39 (d, *J* = 12.1 Hz, 1H), 4.82–4.77 (m, 1H), 4.72 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.58–4.51 (m, 1H), 4.22–4.13 (m, 1H), 3.55 (dd, *J* = 5.5, 1.1 Hz, 1H), 3.19 (ddd, *J* = 7.7, 6.2, 3.8 Hz, 1H), 3.14–3.05 (m, 1H), 3.01–2.92 (m, 2H), 2.47 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.37 (s, 1H), 2.36–2.23 (m, 2H), 2.21–2.13 (m, 2H), 1.91 (ddt, *J* = 14.1, 10.3, 5.1 Hz, 1H), 1.78 (s, 3H), 1.55–1.43 (m, 1H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 148.7, 129.7, 128.1, 109.9, 99.4, 80.3, 76.0, 73.9, 71.4, 57.6, 53.2, 48.9, 43.4, 38.5, 38.0, 36.6, 27.8, 25.7, 21.0; IR (Neat Film, NaCl) 3388, 2925, 1660, 1445, 1260, 1098, 1027, 888, 800, 759 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{26}O_5$ $[M\bullet]^+$: 334.1780, found 334.2023; $[\alpha]_D^{25.0}$ +36.2° (*c* 0.250, $CHCl_3$).



47

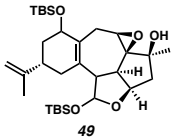
(2a*R*,2a^1*S*,4*S*,9*S*,10b*R*)-4,7-dihydroxy-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,6,7,8,9,10,10b-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1-one (47). To a stirred solution of diene **5** (35 mg, 0.11 mmol, 1.00 equiv) in CH_2Cl_2 (4.5

mL) at –78 °C (*i*-PrOH/dry ice bath) was added DIBAL (121 mL, 1.00 M in toluene, 1.10 equiv) slowly dropwise. After 2 h, the reaction was quenched before the complete consumption of starting material, as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent), by the addition of saturated aqueous NH_4Cl (6.0 mL) and saturated aqueous Rochelle salt (6.0 mL) and immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After stirring for 1 h, the reaction was diluted with CH_2Cl_2 (10 mL) and poured onto H_2O (30 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (4 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude off-white solid was purified by silica gel column chromatography (60% EtOAc in hexanes eluent) to provide allylic alcohol **47** (4 mg, 11% yield) as an amorphous white solid: R_f = 0.28 (1:1 EtOAc:CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.22 (dt, *J* = 8.2, 3.3 Hz, 1H), 4.83–4.69 (m, 3H), 4.20 (q, *J* = 7.0, 6.5 Hz, 1H), 3.73 (dq, *J* = 6.0, 2.9 Hz, 1H), 3.36 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.27–3.14 (m, 1H), 2.95–2.78 (m, 2H), 2.43 (d, *J* = 15.4 Hz, 1H), 2.40–2.31 (m, 1H), 2.25–2.14 (m, 1H), 2.02 (dd, *J* = 15.5, 4.1 Hz, 1H), 1.97 (s, 1H), 1.87 (ddt, *J* = 14.2, 10.6, 3.2 Hz, 1H), 1.77 (s, 3H), 1.53 (dd, *J* = 12.2, 9.4 Hz, 1H), 1.41 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 174.7, 148.7, 148.3, 133.2, 128.0, 127.1, 109.6, 82.3, 78.6, 73.0, 49.1, 47.8, 46.0, 38.7, 38.1, 37.0, 28.9, 28.4, 21.1; IR (Neat Film, NaCl) 3379, 2925, 2855, 1761, 1442, 1373, 1283, 1225, 1151, 1102, 1048, 987, 963, 890, 849, 805, 756 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{25}O_4$ $[M+H]^+$: 317.1753, found 317.1759; $[\alpha]_D^{25.0}$ +62.5° (*c* 0.200, $CHCl_3$).



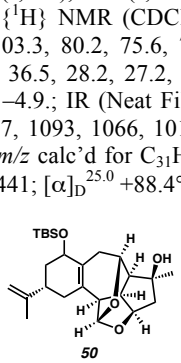
48

(2a*R*,2a^1*S*,4*S*,9*S*,10b*R*)-1,7-bis((*tert*-butyldimethylsilyl)oxy)-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,6,7,8,9,10,10b-decahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-4-ol (48). To a stirred solution of lactol **45** (11 mg, 0.035 mmol, 1.00 equiv) in CH_2Cl_2 (2.0 mL) were added imidazole (181 mg, 2.66 mmol, 76.0 equiv) and DMAP (26 mg, 0.21 mmol, 6.00 equiv) sequentially, each as a solid in a single portion. After 2 minutes, to the colorless homogeneous solution was added TBSCl (80 mg, 0.53 mmol, 15.1 equiv) as a solid in one portion. After 16 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:CH_2Cl_2 eluent). The reaction mixture was diluted with hexanes (6.0 mL) and the white suspension was filtered over Celite®, washing with 30% EtOAc in hexanes eluent. The combined organics were concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (5% EtOAc in hexanes eluent) to afford bis-silyl ether **48** (17 mg, 89% yield) as an amorphous white solid: R_f = 0.43 (1:19 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.13 (dt, *J* = 8.5, 3.4 Hz, 1H), 5.27 (d, *J* = 5.4 Hz, 1H), 4.71 (q, *J* = 1.7 Hz, 1H), 4.69 (d, *J* = 1.7 Hz, 1H), 4.66 (t, *J* = 3.2 Hz, 1H), 4.27 (d, *J* = 8.8 Hz, 1H), 3.47–3.34 (m, 2H), 3.05–2.92 (m, 1H), 2.80 (t, *J* = 6.1 Hz, 1H), 2.66 (dd, *J* = 18.5, 8.5 Hz, 1H), 2.28 (d, *J* = 17.6 Hz, 1H), 2.22–2.11 (m, 2H), 2.03 (ddt, *J* = 11.3, 6.4, 2.4 Hz, 1H), 1.89–1.76 (m, 2H), 1.74–1.66 (m, 3H), 1.52–1.39 (m, 1H), 1.35 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.06 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 150.8, 148.8, 132.5, 129.7, 126.7, 109.3, 104.0, 83.7, 78.6, 74.2, 55.8, 50.5, 46.3, 39.6, 38.7, 36.3, 28.2, 26.2, 25.9, 25.8, 20.5, 18.4, 17.9, –3.4, –3.6, –4.7, –4.9; IR (Neat Film, NaCl) 2928, 2856, 1461, 1256, 1103, 1066, 1026, 1002, 885, 837, 778 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{53}O_4Si_2$ $[(M+H)–H_2]^+$: 545.3482, found 545.3474; $[\alpha]_D^{25.0}$ +94.6° (*c* 0.200, $CHCl_3$).



49

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,8b*R*,10a*R*)-5,9-bis((*tert*-butyldimethylsilyl)oxy)-2-methyl-7-(prop-1-en-2-yl)-1,2,2a^1,3a,4,5,6,7,8,8b,9,10a-dodecahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-2-ol (49). To a colorless stirred solution of bis-silyl ether **48** (20 mg, 0.036 mmol, 1.00 equiv) in a vial open to air in benzene (2.0 mL) was added $VO(acac)_2$ (1.0 mg, 0.0036 mmol, 0.01 equiv). After 5 minutes, to this dark green solution was added *t*-butyl hydroperoxide (TBHP, 20 mL, 0.10 mmol, 2.78 equiv) as a 5 M solution in decane dropwise causing the reaction to immediately become deep ruby red. After 1 h, the reaction had lost all red color and become pale yellow and the consumption of starting material was complete as determined by TLC (1:19 EtOAc:Hexanes eluent). The reaction was concentrated in vacuo and the crude tan solid was purified by silica gel column chromatography (10% EtOAc in hexanes eluent) to afford epoxide **49** (18 mg, 90% yield) as an amorphous white solid: R_f = 0.17 (1:19 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.27 (d, *J* = 5.0 Hz, 1H), 4.71 (t, *J* = 1.6 Hz, 1H), 4.68 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.53 (td, *J* = 4.0, 2.0 Hz, 1H), 4.23 (t, *J* = 8.0 Hz, 1H), 3.22–3.17 (m, 1H), 2.96 (dd, *J* = 6.0, 3.6 Hz, 1H), 2.82–2.65 (m, 3H), 2.62 (s, 1H), 2.43 (d, *J* = 17.0 Hz, 1H), 2.25–2.09 (m, 3H), 2.02 (ddt, *J* = 11.3, 6.4, 2.2 Hz, 1H), 1.79–1.71 (m, 1H), 1.70 (t, *J* = 1.1 Hz, 3H), 1.39 (ddd, *J* = 13.1, 12.1, 10.0 Hz, 1H), 1.28 (s, 3H), 0.92 (s, 9H), 0.87 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 148.8, 130.4, 126.1, 109.3, 103.3, 80.2, 75.6, 75.2, 71.0, 57.6, 54.8, 46.7, 46.6, 39.1, 38.7, 36.5, 28.2, 27.2, 26.2, 25.9, 20.5, 18.4, 17.9, –3.5, –3.6, –4.7, –4.9.; IR (Neat Film, NaCl) 3441, 2955, 2928, 2856, 1471, 1257, 1093, 1066, 1018, 957, 878, 833, 776 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{31}H_{53}O_5Si_2$ $[(M+H)–H_2]^+$: 561.3432, found 561.3441; $[\alpha]_D^{25.0}$ +88.4° (*c* 0.150, $CHCl_3$).



50

(1*S*,2a*R*,2a^1*R*,4*S*,4a*S*,5*R*,9*S*,10b*R*)-7-((*tert*-butyldimethylsilyl)oxy)-4-methyl-9-(prop-1-en-2-yl)-2a,2a^1,3,4,4a,5,6,7,8,9,10,10b-dodecahydro-1*H*-1,5-epoxybenzo[6,7]azuleno[1,8-*bc*]furan-4-ol (50).

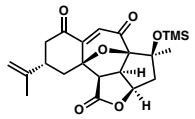
Preparation of 0.50 M Solution of Titanocene Monochloride (Cp_2TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with manganese(0) dust (543 mg, 9.90 mmol, 3.00 equiv) and titanocene dichloride (Cp_2TiCl_2, 822 mg, 3.30 mmol, 1.00 equiv). The flask was then evacuated and back filled with argon (3 x 5 minute cycles). To the reaction vessel was then added THF (6.6 mL) that had previously been sparged with argon for 60 minutes and stirring commenced. After 1.5 h, the bright red reaction mixture had become yellow-green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp_2TiCl.

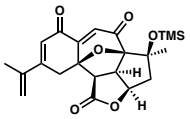
Epoxide Opening with Cp_2TiCl

A stirred solution of epoxide **49** (18 mg, 0.042 mmol, 1.00 equiv) in THF (3.0 mL) was sparged with argon for 1 h, result-

ing in a reaction volume of 2.0 mL. The homogeneous, off-white reaction mixture was then cooled to –78 °C (*i*-PrOH/dry ice bath) followed by the addition of H_2O (63 µL, 3.50 mmol, 83.3 equiv). After stirring for 5 minutes, Cp_2TiCl (0.88 mmol, 0.50 M in THF, 21.0 equiv) was added dropwise over 3 minutes. After 2.5 h, the reaction vessel was warmed to 0 °C (ice/H_2O bath). After an additional 5.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature. After an additional 42 h, the consumption of starting material was complete as determined by TLC (3:17 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH_2PO_4 (0.25 mL) and brine (0.25 mL), sparged with compressed air for 5 minutes, and allowed to stir for an additional 15 minutes. The reaction mixture was then filtered through a Celite® plug, washing with 50% acetone in hexanes eluent. The combined organics were concentrated in vacuo and immediately purified by silica gel column chromatography (8% acetone in hexanes eluent) to furnish acetal **50** (16 mg, 89% yield) as an amorphous white solid: R_f = 0.22 (3:17 Acetone:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.46 (dd, *J* = 3.7, 1.0 Hz, 1H), 4.80–4.69 (m, 2H), 4.44 (ddd, *J* = 6.0, 1.9, 0.8 Hz, 1H), 4.27–4.15 (m, 2H), 3.27 (d, *J* = 1.3 Hz, 1H), 3.14 (dt, *J* = 9.9, 3.3 Hz, 1H), 2.65–2.56 (m, 1H), 2.50–2.41 (m, 1H), 2.39 (d, *J* = 9.9 Hz, 1H), 2.35–2.27 (m, 2H), 2.24 (dd, *J* = 14.9, 1.1 Hz, 1H), 2.17 (dddd, *J* = 16.1, 11.3, 5.5, 2.3 Hz, 1H), 1.98 (dddt, *J* = 13.4, 7.5, 4.7, 2.3 Hz, 2H), 1.87 (ddd, *J* = 14.5, 3.2, 1.1 Hz, 1H), 1.73 (t, *J* = 1.1 Hz, 3H), 1.48 (ddd, *J* = 13.1, 12.3, 10.2 Hz, 1H), 1.33 (d, *J* = 1.1 Hz, 3H), 0.91 (s, 9H), 0.09 (app s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 148.7, 133.6, 126.9, 109.5, 103.6, 84.9, 82.1, 72.4, 65.8, 54.3, 51.0, 50.0, 48.3, 40.2, 39.8, 39.5, 37.8, 29.9, 26.1, 20.5, 18.4, –3.9, –4.6; IR (Neat Film, NaCl) 3440, 2928, 2856, 1463, 1367, 1258, 1211, 1068, 1046, 958, 869, 836, 776 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{39}O_4Si$ [(M+H)–H_2]$^+$: 431.2618, found 431.2622; $[\alpha]_D^{25.0}$ +44.3° (*c* 0.150, $CHCl_3$).



55



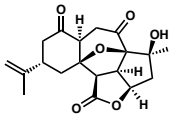
56

(2a*R*,2a^1*R*,4*S*,4a*R*,9*S*,10a*R*,10b*R*)-4-methyl-9-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)-2a^1,3,4,9,10,10b-hexahydro-5*H*-4a,10a-epoxybenzo[6,7]azuleno[1,8-*bc*]furan-1,5,7(2a*H*,8*H*)-trione (55) and (2a*R*,2a^1*R*,4*S*,4a*R*,10a*R*,10b*R*)-4-methyl-9-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)-2a^1,3,4,10b-tetrahydro-5*H*-4a,10a-epoxybenzo[6,7]azuleno[1,8-*bc*]furan-1,5,7(2a*H*,10*H*)-trione (56). To a stirred solution of ketopyran **9** (15 mg, 0.043 mmol, 1.00 equiv) in CH_2Cl_2 (0.4 mL) at 0 °C (ice/H_2O bath) was added Et_3N (0.12 mL, 0.87 mmol, 20.0 equiv) dropwise. After 2 minutes, TMSOTf (24 mL, 0.13 mmol, 3.00 equiv) was added slowly dropwise. After 1.5 h, TMSOTf (24 mL, 0.13 mmol, 3.00 equiv) was added slowly dropwise. After an additional 1.5 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1.5 mL) and the biphasic mixture was immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was diluted with Et_2O (2 mL) and poured onto H_2O (3 mL). The organics were separated and the aqueous was extracted with Et_2O (5 x 2 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude amorphous white solid was carried on without further purification.

To a stirred solution of the crude white solid in DMSO (1.5 mL) was added $Pd(OAc)_2$ (30 mg, 0.13 mmol, 3.11 equiv) as a solid in single portion. After 7 h, the consumption of starting material was complete as determined by TLC (3:3 EtOAc:Hexanes eluent). The dark brown reaction mixture was diluted with H_2O (8 mL) and the aqueous was extracted with CH_2Cl_2 (5 x 10 mL) followed by EtOAc (2 x 5 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude brown solid was purified by semi-preparative HPLC (Agilent ZORBAX RX-SIL silica gel column, 5 mm mesh, 9.4 mm x 250 mm, mobile phase: 20% EtOAc in hexanes, flow rate: 7.00 mL/min) to provide vinylogous diketone **55** (retention time 9.9 minutes, 10 mg, 56% yield) as an amorphous white solid and polyunsaturated diketone **56** (retention time 11.4 minutes, 8 mg, 44% yield) as an amorphous white solid.

Vinylogous Diketone 55. R_f = 0.37 (3:7 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.26 (q, *J* = 0.7 Hz, 1H), 4.93 (dddd, *J* = 9.4, 8.3, 6.8, 1.5 Hz, 1H), 4.89 (s, 1H), 4.84–4.82 (m, 1H), 3.35 (td, *J* = 8.8, 1.5 Hz, 1H), 3.15 (dd, *J* = 8.8, 1.5 Hz, 1H), 2.77–2.61 (m, 3H), 2.49–2.38 (m, 2H), 2.31 (ddd, *J* = 12.6, 7.7, 1.4 Hz, 1H), 2.19 (dtd, *J* = 15.1, 2.6, 1.6 Hz, 1H), 1.81 (m, 3H), 1.66 (s, 3H), 0.11 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz) δ 199.8, 194.3, 173.4, 156.2, 145.2, 127.7, 111.6, 96.7, 86.1, 81.2, 77.8, 54.0, 49.9, 47.1, 44.9, 37.8, 35.3, 27.1, 20.9, 2.4; IR (Neat Film, NaCl) 2960, 2928, 1765, 1702, 1252, 1193, 1069, 1046, 869, 841 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{29}O_6Si$ [M+H]$^+$: 417.1733, found 417.1741; $[\alpha]_D^{25.0}$ –16.9 ° (*c* 0.100, $CHCl_3$).

Polyunsaturated Diketone 56. R_f = 0.37 (3:7 EtOAc:Hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.64 (d, *J* = 0.7 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 5.75 (s, 1H), 5.57 (dd, *J* = 1.9, 1.0 Hz, 1H), 4.93 (tdd, *J* = 9.5, 8.6, 7.7, 3.4 Hz, 1H), 3.45–3.36 (m, 2H), 3.26 (dd, *J* = 8.8, 0.6 Hz, 1H), 3.01 (dd, *J* = 17.0, 2.6 Hz, 1H), 2.48–2.38 (m, 1H), 2.37–2.30 (m, 1H), 2.08 (d, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.2 Hz, 3H), 0.16–0.08 (m, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 193.8, 185.0, 173.2, 157.2, 151.4, 141.1, 127.0, 124.9, 122.9, 95.6, 86.5, 80.8, 78.0, 52.8, 50.2, 47.2, 30.3, 26.8, 20.6, 2.4; IR (Neat Film, NaCl) 2959, 1770, 1702, 1660, 1611, 1378, 1252, 1179, 1066, 1036, 870, 842, 759 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{22}H_{27}O_6Si$ [M+H]$^+$: 415.1577, found 415.1588; $[\alpha]_D^{25.0}$ +70.9° (*c* 0.100, $CHCl_3$).



9

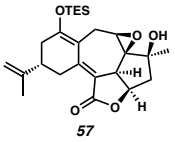
(2a*R*,2a^1*R*,4*S*,4a*R*,6a*S*,9*S*,10a*S*,10b*R*)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)octahydro-5*H*-4a,10a-epoxybenzo[6,7]azuleno[1,8-*bc*]furan-1,5,7(2a*H*,8*H*)-trione (9).

Preparation of a 0.07 M Stock Solution SmI_2

Into a Schlenk tube was added freshly filed samarium metal (150 mg, 1.00 mmol, 1.41 equiv). The reaction vessel was then thoroughly flame-dried, backfilled with argon, and allowed to cool to ambient temperature (ca. 23 °C). To the reaction vessel was then added THF (10.0 mL) that had previously been sparged with argon for 60 minutes and cooled to 0 °C (ice/H_2O bath) with stirring. EtI_2 (200 mg, 0.71 mmol, 1.00 equiv) was then added in separate 100 mg portions 30 minutes apart. After the addition of the second portion, the Schlenk tube was removed from the cooling bath, allowed to warm to ambient temperature, and the pale yellow solution was stirred overnight (ca. 14 h) causing the reaction to become deep blue, indicating to formation of SmI_2.

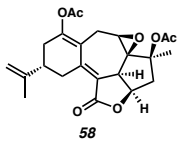
*Reduction of Vinlyogous Diketone **55***

A stirred solution of vinylogous diketone **55** (4 mg, 0.0010 mmol, 1.00 equiv) in THF (1.5 mL) was sparged to 1.5 h, leaving a reaction volume of 0.25 mL. The resultant colorless reaction mixture was then cool to –78 °C (*i*-PrOH/dry ice bath) at which time SmI_2 (0.010 mmol, 0.07 M in THF, 10.0 equiv) was added dropwise. After 20 minutes, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). To the reaction mixture was then added TBAF (0.01 mmol, 1.0 M in THF, 10.0 equiv). After 10 minutes, the reaction was quenched by addition of H_2O (50 mL), removed from the cooling bath, and allowed to warm to ambient temperature. The dark yellow reaction mixture was then filtered through a pad of silica gel (50% EtOAc in CH_2Cl_2 eluent), and concentrated in vacuo. The crude dark gold solid was purified by silica gel column chromatography (20% EtOAc in CH_2Cl_2 eluent) to afford ketopyran **9** (3 mg, 75% yield) as a crystalline white solid: characterization data match those reported previously.[8]



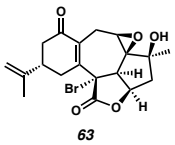
57

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,10a*R*)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-5-((triethylsilyl)oxy)-1,2a^1,3a,4,6,7,8,10a-octahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-9(2*H*)-one (57). To a stirred solution of *ent*-isoineleganolide A (**13**, 5 mg, 0.015 mmol, 1.00 equiv) in CH_2Cl_2 (0.5 mL) was added DMAP (7 mg, 0.057 mmol, 3.83 equiv) as a solid in one portion. After 2 minutes, the reaction mixture had become a completely homogenous pale yellow solution, and TESCl (25 mL, 0.15 mmol, 10.0 equiv) was added quickly dropwise. After 4 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). After 5 minutes, the white suspension was filtered through a pad of silica gel (20% EtOAc in CH_2Cl_2 eluent). The combined organics were concentrated in vacuo and the resultant crude white solid was purified by silica gel column chromatography (30% EtOAc in hexanes eluent) to provide intermediate enol ether **57** (1.5 mg, 50% yield) as an amorphous white solid: R_f = 0.24 (3:7 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.82–4.70 (m, 3H), 4.04–3.95 (m, 1H), 3.91–3.85 (m, 1H), 3.68 (dd, *J* = 16.0, 6.6 Hz, 1H), 3.49 (dd, *J* = 6.5, 0.7 Hz, 1H), 2.57 (dd, *J* = 12.9, 7.0 Hz, 1H), 2.51–2.24 (m, 6H), 1.97 (dd, *J* = 12.9, 8.2 Hz, 1H), 1.76 (dd, *J* = 1.5, 0.8 Hz, 3H), 1.31 (d, *J* = 1.0 Hz, 3H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.75 (qd, *J* = 7.9, 0.8 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 171.0, 160.7, 154.7, 147.2, 114.7, 110.5, 110.2, 73.8, 72.9, 71.5, 53.9, 48.8, 42.4, 39.9, 36.8, 30.7, 23.6, 23.0, 21.2, 6.8, 5.9; IR (Neat Film, NaCl) 3478, 2960, 1728, 1586, 1449, 1345, 1192, 1112, 1046, 961, 937, 889, 790, 764 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{25}H_{37}O_5Si$ $[M+H]^+$: 445.2410, found 445.2419; $[\alpha]_D^{25.0}$ +229.2° (*c* 0.100, $CHCl_3$).



58

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,10a*R*)-2-methyl-9-oxo-7-(prop-1-en-2-yl)-1,2,2a^1,3a,4,6,7,8,9,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-2,5-diyl diacetate (58). To a stirred solution of *ent*-isoineleganolide A (**13**, 10 mg, 0.030 mmol, 1.00 equiv) in CH_2Cl_2 (1.0 mL) was added DMAP (14 mg, 0.11 mmol, 3.67 equiv) as a solid in one portion. After 2 minutes, the reaction mixture had become a completely homogenous pale yellow solution, and Ac_2O (30 mL, 0.32 mmol, 10.7 equiv) was added quickly dropwise. After 2 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was diluted with CH_2Cl_2 (3 mL) and poured onto saturated aqueous $NaHCO_3$ (3 mL). The organics were separated and the aqueous was extracted with CH_2Cl_2 (2 x 5 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. The crude golden solid was purified by silica gel column chromatography (50% EtOAc with 0.5% Et_3N in hexanes eluent) to provide dienol acetate **58** (11 mg, 85% yield) as an amorphous white solid: R_f = 0.42 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.84 (ddd, *J* = 9.4, 7.9, 7.2 Hz, 1H), 4.80–4.76 (m, 2H), 3.96 (d, *J* = 13.0 Hz, 1H), 3.84 (d, *J* = 9.1 Hz, 1H), 3.71 (dd, *J* = 6.5, 0.7 Hz, 1H), 3.24 (dd, *J* = 16.1, 6.5 Hz, 1H), 3.01 (dd, *J* = 13.2, 7.2 Hz, 1H), 2.57–2.24 (m, 6H), 2.23 (s, 3H), 1.98 (s, 3H), 1.77–1.72 (m, 3H), 1.61 (d, *J* = 1.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 170.2, 170.0, 168.1, 156.0, 152.4, 146.7, 122.2, 115.1, 110.6, 80.9, 73.1, 69.7, 53.2, 46.3, 42.8, 39.7, 34.2, 30.5, 23.6, 21.9, 21.7, 21.1, 21.0; IR (Neat Film, NaCl) 2925, 1740, 1615, 1440, 1372, 1241, 1204, 1153, 1118, 1043, 968, 934, 899, 792, 754 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{23}H_{27}O_7$ $[M+H]^+$: 415.1757, found 415.1737; $[\alpha]_D^{25.0}$ +241.6° (*c* 0.100, $CHCl_3$).

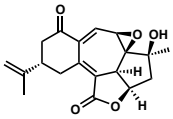


63

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,8b*S*,10a*R*)-8b-bromo-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,4,6,7,8,8b,10a-octahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-5,9(2*H*,3a*H*)-dione (63). To a stirred solution of *ent*-isoineleganolide A (**13**, 15 mg, 0.047 mmol, 1.00 equiv) in CH_2Cl_2 (3.0 mL) was added DMAP (25 mg, 0.20 mmol, 4.36 equiv) as a solid in one portion. After 2 minutes, the reaction mixture had become a completely homogenous pale yellow solution, and TBSCl (70 mg, 0.46 mmol, 9.79 equiv) was added as a solution in CH_2Cl_2 (0.7 mL) quickly dropwise over 2 minutes. After 2 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of Et_3N (0.30 mL, 2.15 mmol, 45.7 equiv) in hexanes (3.0 mL) with stirring. After 5 minutes, the white suspension was loaded directly onto a silica gel column and purified by silica gel column chromatography (30% EtOAc with 0.5% Et_3N in hexanes eluent, silica gel deactivated by wet loading with eluent prior to purification) to provide intermediate dienol ether **59** (20 mg, >99% yield), which was immediately carried on to the next transformation.

To a clear, colorless stirred solution of a portion of dienol ether **59** (5 mg, 0.011 mmol, 1.00 equiv) in CH_2Cl_2 (0.6 mL) at –78 °C (*i*-PrOH/dry ice bath) was added *N*-bromosuccinimide (NBS, 3.4 mg, 0.019 mmol, 1.73 equiv) as a solid in a single portion to provide a homogenous, colorless reaction mixture. After 2 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:Hexanes eluent). The reaction was quenched by the addition of saturated aqueous $Na_2S_2O_3$ (0.5 mL) and the reaction vessel was immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). The biphasic solution was then diluted with CH_2Cl_2 (4.0 mL) and poured onto saturated aqueous $NaHCO_3$ (3.0 mL). The organics were separated and the aqueous was extracted with

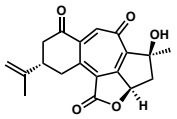
CH_2Cl_2 (3 x 2 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude white solid was purified by silica gel column chromatography (50% EtOAc in hexanes eluent) to afford α-bromolactone **63** (4 mg, 80% yield) as an amorphous white solid: R_f = 0.32 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.18 (ddd, *J* = 5.1, 4.2, 2.2 Hz, 1H), 4.88–4.83 (m, 1H), 4.77 (q, *J* = 1.0 Hz, 1H), 3.96 (dd, *J* = 17.3, 6.7 Hz, 1H), 3.68 (ddt, *J* = 16.8, 3.5, 1.9 Hz, 1H), 3.62 (d, *J* = 4.2 Hz, 1H), 3.36 (d, *J* = 6.6 Hz, 1H), 2.80–2.65 (m, 2H), 2.62–2.49 (m, 1H), 2.49–2.42 (m, 2H), 2.42–2.37 (m, 2H), 2.37–2.32 (m, 1H), 1.82 (s, 3H), 1.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 198.8, 169.3, 150.2, 146.4, 129.0, 110.8, 80.7, 75.1, 69.8, 62.1, 54.3, 52.4, 45.1, 43.1, 40.6, 35.6, 27.4, 21.1, 20.8; IR (Neat Film, NaCl) 3508, 2965, 1774, 1668, 1443, 1367, 1260, 1168, 1100, 973, 894, 789, 759 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{22}O_5{}^{81}Br$ $[M+H]^+$: 411.0630, found 411.0634; $[\alpha]_D^{25.0}$ +141.1° (*c* 0.200, $CHCl_3$).



ent-Dehydroisoineleganolide
65

(2*S*,2a*S*,2a^1*R*,3a*R*,7*S*,10a*R*)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a^1,6,7,8,10a-hexahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-*bc*]furan-5,9(2*H*,3a*H*)-dione (*ent*-Dehydroisoineleganolide, 65). To a stirred solution of *ent*-isoineleganolide A (**13**, 46 mg, 0.14 mmol, 1.00 equiv) in CH_2Cl_2 (6.0 mL) was added DMAP (85 mg, 0.70 mmol, 5.00 equiv) as a solid in one portion. After 2 minutes, the reaction mixture had become a completely homogenous pale yellow solution, and TBSCl (210 mg, 1.39 mmol, 10.0 equiv) was added as a solution in CH_2Cl_2 (2.1 mL) quickly dropwise over 2 minutes. After 2 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc:CH_2Cl_2 eluent). The reaction was quenched by the addition of Et_3N (0.97 mL, 7.0 mmol, 50.0 equiv) in hexanes (6.0 mL) with stirring. After 5 minutes, the white suspension was loaded directly onto a silica gel column and purified by silica gel column chromatography (30% EtOAc with 0.5% Et_3N in hexanes eluent, silica gel deactivated by wet loading with eluent prior to purification) to provide intermediate dienol ether **59** (62 mg, >99% yield), which was immediately carried on to the next transformation.

To a clear, colorless stirred solution to dienol ether **59** (62 mg, 0.14 mmol, 1.00 equiv) in DMSO (3.0 mL) was added $Pd(OAc)_2$ (35 mg, 0.016 mmol, 1.14 equiv) as a solid in a single portion. After 2 h, the golden yellow homogeneous reaction mixture had become dark brown and the consumption of starting material was complete as determined by TLC (3:7 EtOAc:Hexanes eluent). The reaction was then diluted with EtOAc (10 mL) and poured onto H_2O (30 mL). The organics were separated and the aqueous was extracted with EtOAc (3 x 20 mL). The combined organics were washed with H_2O (30 mL), dried over $MgSO_4$, filtered through a pad of silica gel (EtOAc eluent), and concentrated in vacuo. The crude brown solid was purified by silica gel column chromatography (55% EtOAc in hexanes eluent) to afford ent-dehydroisoineleganolide (**65**, 27 mg, 60% yield) as an amorphous white solid: R_f = 0.25 (1:1 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19 (d, *J* = 4.6 Hz, 1H), 4.98 (ddd, *J* = 8.4, 7.5, 6.8 Hz, 1H), 4.83 (h, *J* = 1.5 Hz, 1H), 4.72–4.65 (m, 1H), 3.72 (d, *J* = 4.6 Hz, 1H), 3.59–3.47 (m, 2H), 3.18–3.05 (m, 1H), 2.73–2.60 (m, 3H), 2.56–2.46 (m, 1H), 2.15 (d, *J* = 1.0 Hz, 1H), 1.87 (ddd, *J* = 13.7, 7.0, 1.2 Hz, 1H), 1.79 (dt, *J* = 1.2, 0.6 Hz, 3H), 1.41 (t, *J* = 1.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 197.5, 169.5, 146.3, 145.9, 140.5, 137.7, 119.6, 111.5, 94.9, 74.6, 74.5, 52.1, 47.1, 44.0, 43.7, 37.9, 31.7, 23.8, 21.3; IR (Neat Film, NaCl) 3459, 2923, 2852, 1742, 1706, 1634, 1449, 1377, 1259, 1173, 1090, 1026, 798 cm^{-1}; HRMS (FAB+) *m/z* calc'd for $C_{19}H_{21}O_5$ $[M+H]^+$: 329.1389, found 329.1373; $[\alpha]_D^{25.0}$ –40.2° (*c* 0.075, $CHCl_3$).



ent-Didehydroisoineleganolide
66

(2a*R*,4*S*,9*S*)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)-2a,3,4,8,9,10-hexahydro-1*H*-benzo[6,7]azuleno[1,8-*bc*]furan-1,5,7-trione (*ent*-Didehydroisoineleganolide, 66). To a reaction vessel in a nitrogen-filled glovebox was charged $Yb(OTf)_3$ (8 mg, 0.013 mmol, 1.08 equiv). The reaction vessel was sealed, removed from the glovebox, and introduced to an argon atmosphere. To the white solid was added *ent*-dehydroisoineleganolide (**65**, 4 mg, 0.012 mmol, 1.00 equiv) as a solution in toluene (1.0 mL) with stirring. The white suspension was then introduced to a preheated 50 °C bath. After 7 h, the reaction was further heated to 80 °C. After an additional 17 h, the reaction was heated to 100 °C. After 11 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc:Hexanes eluent). The golden yellow heterogeneous reaction mixture was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The reaction was then concentrated in vacuo. The crude golden brown solid was purified by silica gel column chromatography (40% EtOAc in hexanes eluent) to provide *ent*-didehydroisoineleganolide (**66**, 3 mg, 75% yield) as an amorphous white solid: R_f = 0.09 (3:7 EtOAc:Hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 5.54 (dd, *J* = 12.8, 5.5 Hz, 1H), 4.94–4.91 (m, 1H), 4.86 (dd, *J* = 1.8, 0.9 Hz, 1H), 3.95 (ddd, *J* = 18.4, 4.0, 2.0 Hz, 1H), 3.57 (s, 1H), 3.18 (dd, *J* = 18.5, 10.2 Hz, 1H), 2.99–2.80 (m, 3H), 2.72 (dd, *J* = 16.0, 11.7 Hz, 1H), 2.20 (t, *J* = 12.3 Hz, 1H), 1.89–1.79 (m, 3H), 1.59 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz) δ 197.4, 195.4, 168.1, 158.5, 151.0, 145.3, 135.9, 131.7, 124.6, 123.8, 112.2, 75.2, 73.8, 43.8, 42.6, 41.0, 30.4, 25.7, 20.8; IR (Neat Film, NaCl) 3366, 2923, 2853, 1775, 1692, 1603, 1441, 1332, 1261, 1202, 1090, 1046, 988, 891, 801 cm^{-1}; HRMS (ES+) *m/z* calc'd for $C_{19}H_{19}O_5$ $[M+H]^+$: 327.1232, found 327.1236; $[\alpha]_D^{25.0}$ +22.7° (*c* 0.150, $CHCl_3$).

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H NMR, ^{13}C NMR, and IR spectra (PDF)
Computational Procedures (PDF)
X-ray crystallographic data for epoxide **11** (CIF)
X-ray crystallographic data for 2*H*-*ent*-ineleganolide (**8**, CIF)
X-ray crystallographic data for diketone **16** (CIF)

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Notes

The authors declare no competing financial interests.

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12. In order to be consistent with the initial communication of this research program, epoxide **13** has been named *ent*-isoineleganolide A, enone **5** has been named *ent*-isoineleganolide B, and oxetane **70** has been named *ent*-isoineleganolide C. See references 8 and 9 for full details.

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15. 1,4-Cyclohexadiene was also screened as a hydrogen atom donor, but was not as effective as the Cp_2TiCl aquo complex. Mn^0 and Zn^0 were both screened as reductants.

16. Calculations were performed with Spartan '10 (Wavefunction, Inc., Irvine, CA). The in vacuo equilibrium geometry for each structure was calculated by a series of sequential calculations as follows: Hartree–Fock computation (equilibrium geometry, 3-21G basis set), DFT (equilibrium geometry, B3LYP/6-31G basis set), DFT (energy, B3LYP/6-311+G** basis set), DFT (equilibrium geometry, B3LYP/6-311+G** basis set). The error from these calculations is ±0.23 kcal/mol, thus all energy differences larger than 0.46 kcal/mol were considered significant. Except for molecular mechanics and semi-empirical models, the calculation methods used in Spartan have been documented in: Shao, Y.; Molnar, L. F.; Jung, Y.; Kussmann, J.; Ochsenfeld, C.; Brown, S. T.; Gilbert, A. T. B.; Slipchenko, L. V.; Levchenko, S. V.; O'Neill, D. P.; DiStasio, Jr., R. A.; Lochan, R. C.; Wang, T.; Beran, G. J. O.; Besley, N. A.; Herbert, J. M.; Lin, C. Y.; Van Voorhis, T.; Chien, S. H.; Sodt, A.; Steele, R. P.; Rassolov, V. A.; Maslen, P. E.; Korambath, P. P.; Adamson, R. D.; Austin, B.; Baker, J.; Byrd, E. F. C.; Dachsel, H.; Doerksen, R. J.; Dreuw, A.; Dunietz, B. D.; Dutoi, A. D.; Furlani, T. R.; Gwaltney, S. R.; Heyden, A.; Hirata, S.; Hsu, C-P.; Kedziora, G.; Khalliulin, R. Z.; Klunzinger, P. Lee, A. M.; Lee, M. S.; Liang, W. Z.; Lotan, I.; Nair, N.; Peters, B.; Proynov, E. I.; Pieniazek, P. A.; Rhee, Y. M.; Ritchie, J.; Rosta, E; Sherrill, C. D.; Simmonett, A. C.; Subotnik, J. E.; Woodcock, III, H. L.; Zhang, W.; Bell, A. T.; Chakraborty, A. K.; Chipman, D. M.; Keil, F. J.; Warshel, A.; Hehre, W. J.; Schaefer, H. F.; Kong, J.; Krylov, A. I.; Gill, P. M. W.; Head-Gordon M. Advances in Methods and Algorithms in a Modern Quantum Chemistry Program Package. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172–3191.

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22. Determined by ^{1}H NMR studies of the crude reaction product.

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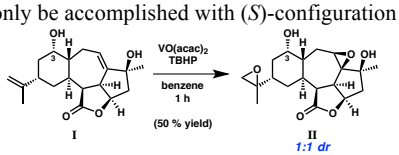
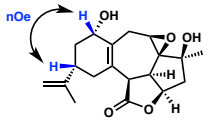
24. The relative stereochemistry at carbinol C(3) of tetracycle **17** was assigned by analogy to the relative stereochemistry of allylic alcohol **24** and by the observed oxidation of alcohol **I** to diepoxide **II** as an inseparable 1:1 mixture of diastereomers as determined by ^{1}H NMR. The directed epoxidation of the dihomoallylic isopropenyl group could only be accomplished with (*S*)-configuration at C(3).



25. The C(3) configuration of allylic alcohol **24** was determined by two-dimensional ^{1}H NOE studies and the positive NOE correlation between the methine protons at C(1) and C(3).



26. Reexposure of isolated silyl ethers **30** and **31** to the reaction conditions did not result in any detectable interconversion between the two products.

27. Under titanium(III)-mediated reductive epoxide opening conditions described in Scheme 16, diol **24** failed to furnish any expected product. Rather, dehydration of the secondary alcohol at C(3) was routinely observed under the acidic reaction conditions, as determined by crude ^{1}H NMR.

28. The relative stereochemistry the reduction product was assigned by analogy to ketones **8** and **16**, whose configurations were established unambiguously by single crystal X-ray diffraction.

29. Attempts to oxidize enol ether **41** focused on reaction conditions employing stoichiometric palladium(II) (e.g., $Pd(OAc)_2$/DMSO) and halogenation reagents (e.g., NBS/CH_2Cl_2).

30. In solution, the *s-trans* conformation of extended polyunsaturated diketone **56** is preferred and was determined by two-dimensional ^{1}H NOE studies and the positive NOE correlation between the C(16) methyl group and the vinyl proton at C(2).

31. (a) Szostak, M.; Spain, M.; Procter, D. J. Determination of the Effective Redox Potentials of SmI_2, $SmBr_2$, $SmCl_2$, and their Complexes with Water by Reduction of Aromatic Hydrocarbons. Reduction of Anthracene and Stilbene by Samarium(II) Iodide–Water Complex. *J. Org. Chem.* **2014**, *79*, 2522–2537. (b) Egger, J.; Bretscher, P.; Freigang, S.; Kopf, M.; Carreira, E. M. Synthesis of Epoxyisoprostanes: Effects in Teducing Secretion of Pro-inflammatory Cytokines IL-6 and IL-12. *Angew. Chem., Int. Ed.* **2013**, *52*, 5382–5385. (c) Shoji, M.; Uno, T.; Kakeya, H.; Onose, R.; Shiina, I.; Osada, H.; Hayashi, Y. Enantio- and Diastereoselective Total Synthesis of EI-1941−1, −2, and −3, Inhibitors of Interleukin-1β Converting Enzyme, and Biological Properties of Their Derivatives. *J. Org. Chem.* **2005**, *70*, 9905–9915. (d) Yamaguchi, J.; Kakeya, H.; Uno, T.; Shoji, M.; Osada, H.; Hayashi, Y. Determination by Asymmetric Total Synthesis of the Absolute Configuration of Lucilactaene, a Cell-Cycle Inhibitor in p53-Transfected Cancer Cells. *Angew. Chem., Int. Ed.* **2005**, *44*, 3110–3115. (e) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. A Mild and Efficient Synthesis of Oxindoles: Progress Towards the Synthesis of Welwitindolinone A Isonitrile. *Angew. Chem. Int. Ed.* **2004**, 43, 1270–1272. (f) Fuchs, J. R.; Mitchell, M. L.; Shabangi, M.; Flowers, R. A. The Effect of Lithium Bromide and Lithium Chloride on the Reactivity of SmI_2 in THF. *Tetrahedron Lett.* **1997**, *38*, 8157–8158. (g) Molander, G. A.; Hahn, G. Lanthanides in Organic Synthesis. 2. Reduction of Alpha-heterosubstituted Ketones. *J. Org. Chem.* **1986**, *51*, 1135–1138. (h) Molander, G. A.; Hahn, G. Lanthanides in Organic Synthesis. 4. Reduction of α,β-epoxy Ketones with Samarium Diiodide. A Route to Chiral, Nonracemic Aldols. *J. Org. Chem.* **1986**, *51*, 2596–2599.

32. The relative stereochemistry of α-bromolactone **63** was assigned by analogy to the unambiguous assignment of the relative stereochemistry of *ent*-isoineleganolide A (**13**) by single crystal X-ray diffraction, see references 8 and 9.

33. (a) Craig, R. A., II; Smith, R. C.; Pritchett, B. P.; Estipona, B. I.; Stoltz, B. M. Preparation of 1,5-Dioxaspiro[5.5]undecan-3-one. *Org. Synth.* **2016**, *93*, 210–227. (b) Craig, R. A., II; Roizen, J. L.; Smith, R. C.; Jones, A. C.; Stoltz, B. M. Enantioselective Synthesis of a Hydroxymethyl-cis-1,3-cyclopentenediol Building Block. *Org. Lett.* **2012**, *14*, 5716–5719.

34. Biological activity data generated through the Open Innovation Drug Discovery Program (OIDD) and screening data were supplied courtesy of Eli Lilly and Company—used with Lilly's permission. To learn more about the Lilly Open Innovation Drug Discovery program, please visit the program website at https://openinnovation.lilly.com (last accessed on 10-01-2018).

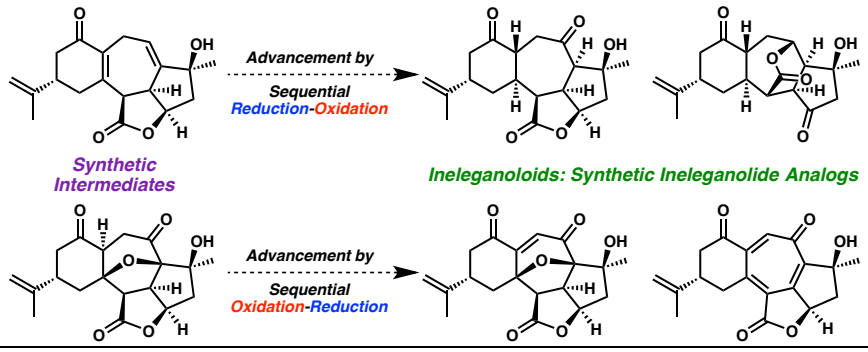
35. A selection of the ineleganoloids were screened against DU145 and A2038 cell viability assays in triplicate, revealing no significant activity. Special, personal thanks to Prof. David Horne and Prof. Sangkil Nam (City of Hope, Duarte, CA) for their assistance in performing these cell viability assays.

36. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. Safe and Convenient Procedure for Solvent Purification. *Organometallics* **1996**, *15*, 1518–1520.

37. DCE was neither distilled, dried, nor degassed prior to use.

38. No HRMS peak for the parent mass of lactol **45** could be observed, despite screening all instruments and ionization sources available to us. The acid required for most ionization methods is likely causing decomposition of the free lactol. The major mass peaks observed for this compound by ES+ were: 253.1585, 299.1633, 317.1746, 318.1780.

39. No HRMS peak for the parent mass of lactol **46** could be observed, despite screening all instruments and ionization sources available to us. The acid required for most ionization methods is likely causing decomposition of the free lactol. The major mass peaks observed for this compound by ES+ were: 281.1531, 282.1579, 322.1805, 334.2023, 335.2060.


Advancement by
Sequential
Reduction-Oxidation
Synthetic
Intermediates
Ineleganoloids: Synthetic Ineleganolide Analogs
Advancement by
Sequential
Oxidation-Reduction