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

Robert A. Craig, Russell C Smith, Jennifer L. Roizen, Amanda C Jones, Scott C Virgil, and Brian M. Stoltz

J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.9b00635 • Publication Date (Web): 08 May 2019

Just Accepted

“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.
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

Robert A. Craig, II, Russell C. Smith, Jennifer L. Roizen Amanda C. Jones, Scott C. Virgil, and Brian M. Stoltz*

Warren and Katherine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

ABSTRACT: Late-stage synthetic efforts to advance the enatio- and diastereoselectively constructed [6,7,5,5]-fused tetracyclic scaffold toward the polycyclic noriditerpenoid 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 cancer1 to bacterial infection6,12,2 and neurological diseases.1,2,3 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).7,8 Since the initial isolation and assignment of the structure in 1999 from the namesake soft coral Sinularia inelegans,6 ineleganolide (1) has been isolated from a number of other species belonging to the same genus along with the isomeric natural products horiolide (2)1 and kavaranolide (3).6c

Ineleganolide (1) poses a number of formidable synthetic challenges,5,9 highlighted by nine stereogenic centers distribut-
Scheme 1. Enantioselective Formation of the [6,7,5,5]-Tetracyclic Core of ent-Ineleganolide (ent-1)

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

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

Scheme 4. Conjugate Reduction of Diene 5

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). 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).

Late-stage synthetic efforts toward ent-ineleganolide (ent-1) began with the sequential reduction-oxidation strategy from tetracyclic diene 5. Retrosynthetically, access to ent-ineneleganolide (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-isoseineneleganolide B (6, see Scheme 1), endoene 7 would be synthesized by the oxidation of saturated 1,4-diketone 8. Alternatively, ent-ineneleganolide (ent-1) could be formed directly from 2H-ent-ineneleganolide (8) through intramolecular oxida-

tive annihilation by C–H functionalization. 2H-ent-ineneleganolide (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.

The conjugate reduction of the tetrsubstituted 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 (SmI2) 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, i- BuOH, LiCl, or fewer equivalents of H2O prevented the complete consumption of starting material. Contrastingly, the addition of HMPA or the use of additional equivalents of H2O resulted in diminished yield of tetracycle 12 through erosion of diastereoselectivity paired with over-reduction of the desired keto product (12).

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-ineneleganolide (ent-1, see Scheme 3).

Similar to our experiences with a related epoxide,11 advancement of epoxide 11 to 2H-ent-ineneleganolide (8) through an epoxide rearrangement proved unfruitful under a variety of Lewis acidic conditions (Scheme 5). Thus, alternative access to 2H-ent-ineneleganolide (8) was sought employing the method used successfully applied to the oxidized analogs, beginning
from ent-isoeleganolide A (13, Scheme 6A). 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 oxo-Michael addition. Subsequent installation of a ketone at C(6) was achieved under optimized Kornblum oxidation conditions to furnish ketopyran 9 in 96% yield. The efficiency of this transformation was ascribed to the ability of the transannular etheral oxygen to stabilize the intermediate carbocation.

**Scheme 5. Unsuccessful Epoxide Rearrangement of Epoxide 11**

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 2H-ent-isoeleganolide (8), we began to pursue a reductive epoxide opening strategy employing Cp2TiCl, which is generated in situ from Cp2TiCl2 and a suitable reductant. Initial exploration of this reductive epoxide opening proved immediately successful (Scheme 7). The use of H2O as an additive results in the formation of the Cp2TiCl2 aquo complex and thereby provides a sacrificial hydrogen atom donor. Subsequent oxidation under optimized conditions using Dess–Martin periodinane (DMAP) in 1,2-dichloroethane at elevated temperature provided 2H-ent-isoeleganolide (8) in 33% yield over two steps with the transactonized ketone 16 isolated in identical yield. The structures of both 2H-ent-isoeleganolide (8) and lactone 16 were unambiguously determined by single crystal X-ray diffraction, confirming the desired relative configuration at C(7).

In order to explore the conformational constraints of 2H-ent-isoeleganolide (8), knowing the propensity of tetracyclic intermediates to adopt conformations distinct from that of isoeleganolide, we explored the in vacuo ground state energies (DFT/B3LYP/6-311+G**) of four different conformational isomers: 8ax and 8eq and 8Aax and 8Aeq (Figure 2).

The two conformations in which the cyclohexanone ring adopts a chair conformation, placing the isopropenyl substituent in the axial position (8ax and 8Aax) 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-isoeleganolide (ent-8eq) as determined on initial isolation by single crystal X-ray diffraction. The difference in energy between 8ax and 8Aax and the corresponding equatorial conformations, 8eq and 8Aeq, respectively, was calculated to be no more than 1.0 kcal/mol. Complimentary, the X-ray crystal structure of the isolated 2H-ent-isoeleganolide shows 8eq 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 8eq and one of the conformational isomers 8Aax or 8Aeq en route the completion of the asymmetric total synthesis of ent-isoeleganolide (ent-1).

**Scheme 7. Sequential Reductive Epoxide Opening and Carbinol Oxidation**

Toward this end, completion of the total synthesis would require the oxidation of 2H-ent-isoeleganolide (8) in order to install the final requisite C–O bond and construct the characteristic bridging dihydrofuranone found within isoeleganolide (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, I2, hv) and a series of modified Suárez oxidation conditions, which
used mixed cyclohexane and dichloromethane solvent systems and exclude light. Additionally, we attempted the oxidation of C(5) using lead(IV) acetate and light as well as with functionalized hypervalent iodine reagents such as PhI(OH)(OTs). 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 2H-ent-ineleganolide (8), proceeding through vinylogous diketone 7, which we hypothesized would undergo a spontaneous intramolecular oxametallacycle at C(5) or by “thermodynamic” enolization 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), hypervalent iodine reagents (e.g., IBX), or various selenides (e.g., (PhSeO)2O, PhSeCl then H2O2) failed to yield any trace of intermediate 7 or ent-ineleganolide (ent-1), typically resulting in selective functionalization at C(2). Similar nonproductive reactivity was observed when attempting the C(4)–C(5) oxidation by a Saegusa–Ito oxidation. 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 2H-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). 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 transactonization, 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 12. Chemoselective Reduction of ent-Isoineleganolide A (13)

![Scheme 12](image)

Scheme 13. Attempted Epoxide Rearrangement

![Scheme 13](image)

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

![Scheme 14](image)

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-isoinolegalendiole 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-isolegalendiole (ent-1) continued.

Scheme 15. Assessment of Configurational Stability of Unsaturated Lactone Moiety

![Scheme 15](image)

In order to advance toward ent-isolegalendiole (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 translaconized alcohol 36 as the sole product in 60% yield (Scheme 17A). Subsequent oxidation failed to induce the desired retrotranslaconization, furnishing ketone 37 as the only isolable product without any trace of desired cycloheptane 38. Transannular lactone 37 was not immediately useful for continued advancement toward ent-isolegalendiole (ent-1).

Scheme 16. Attempted Reductive Opening of Epoxide 24

![Scheme 16](image)

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

![Scheme 17](image)

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

ACS Paragon Plus Environment
Interestingly, under these reducing and Lewis acidic conditions, the reduction of the \( \alpha,\beta \)-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\(_3\)N, desired enol ether 41 could be constructed, albeit with undesired concomitant hydration of the \( \alpha,\beta \)-unsaturated lactone (Scheme 18). Unfortunately, we were unable to advance further toward ent-inleineganolide (ent-I) at this stage as the oxidation of this enol ether 41 could not be accomplished.

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 tetracyclic 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.

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 \( \alpha,\beta \)-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-inleineganolide (ent-I) forced another reevaluation of the synthetic strategy.

As such, development of an alternative pathway to avoid the problematic translastionization 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 disobutylaluminum hydride (DIBAL) at low temperature to afford either allylic alcohol 45 or epoxycalcohol 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-inleineganolide (ent-I) 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-butylidimethylsilyl chloride (TBSCI) 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. Yet again, an intermediate was produced that was not useful for the progression toward ent-inleineganolide (ent-I) as opening of the acetal under acidic or oxidative conditions could not be achieved. Oxidative reactions using SO\(_4\)·pyridine in DMSO, DMP in wet CH\(_2\)Cl\(_2\), 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-inleineganolide (ent-I, cf. Scheme 2B).

Alternative completion of the asymmetric total synthesis of ent-inleineganolide (ent-I) was envisioned after dehydration of keto furan 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 endione 53 was envisioned through the selective reductive opening of dihydropy-
ranone 54. Access to dihydropyranoone 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). 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 polysaturated diketone 56 could not be avoided, which was isolated in 44% yield.

**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 SmI2 considering that this reagent is known to accomplish related transformations and has been used previously for the α-alkoxyketone cleavage of saturated 1,4-diketone 9. The use of SmI2 in the absence of an additive or with H2O, 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 SmI2 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 dihydropyranoone 55, but inspired by access to dihydropyranoone 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-isoinoengineolide 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 reformulation of starting material 13. Although the formation of the analogous trisopropylsilyl (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-Isoinoengineolide 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**

Comparedly, 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-isoinoengineolide 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. We did not believe γ-bromide 63 was useful for progression toward
ent-ineleganolide \((\text{ent-1})\), thus alternative oxidative procedures were explored.

\textbf{Scheme 28. Construction of }\alpha\text{-Bromolactone 63}

During that investigation, we were gratified to find C(4)–C(5) oxidation of \(\text{ent-}2\text{hineleganolide }\text{(13)}\) 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 \(\text{ent-dehydroisoineleganolide }\text{(65)}\) in 60% yield. Unfortunately, this transformation was plagued by routinely low yields on increased scale, but afforded enough material to continue synthetic explorations.

\textbf{Scheme 29. Oxidation of }\text{ent-}2\text{hineleganolide A (13)}\text{ to Cycloheptadiene 65}

\(\text{ent-Dehydroisoineleganolide }\text{(65)}\) was characterized by unique spectroscopic features, including an unexpected \(^{13}\text{C}\) NMR spectrum. For example, consider \(\text{ent-}2\text{hineleganolide A (13)}\) and the \(^{13}\text{C}\) 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 epoxy carbon C6 of \(\text{ent-dehydroisoineleganolide }\text{(65)}\) is within the expected range at 52.1 ppm, the tertiary epoxy carbon C7 is found at 94.9 ppm. We hoped that the spectral data associated with \(\text{ent-dehydroisoineleganolide }\text{(65)}\) was indicative of a reactivity profile that could be exploited.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Compound} & \textbf{Carbon} & \textbf{\(^{13}\text{C}\) ppm in CDCl3} \\
\hline
\text{13} & C6 & 54.4 \\
\text{65} & C6 & 52.1 \\
\text{13} & C7 & 70.2 \\
\text{65} & C7 & 94.9 \\
\hline
\end{tabular}
\caption{Comparison of \(^{13}\text{C}\) NMR Shifts of Enone 13 and Diene 65.}
\end{table}

Any further advancement toward \(\text{ent-}2\text{hineleganolide }\text{(ent-1)}\) would now require the opening of the epoxide moiety. Unfortunately, \(\text{ent-dehydroisoineleganolide }\text{(65)}\) 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 \(\text{(67)}\) were unfruitful. In fact, the only productive reactivity observed during this screen was the production of cyclohepta-

\textbf{Scheme 30. Formation of }\text{ent-Didehydroisoineleganolide (66)}

\textbf{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 \(\text{ineleganolide }\text{(1)}\) 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 \(\text{ineleganolide }\text{core}(\text{red})\) through a diastereoselective reduction followed by a key cyclopropanation-Cope rearrangement cascade.\(^{10,11,33}\)

\textbf{Scheme 31. Asymmetric Allylic Alkylation Stereoselectively Determines All Remaining Chiral Information}

Although the synthesis of neither \(\text{ineleganolide }\text{(1)}\) 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 \(\text{ineleganolide }\text{(1)}\). These natural product-like \(\text{ineleganoloides}\) 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 \(\text{ineleganolide }\text{analogues}(\text{Figure }4).^{10,11}\) 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 Methods.

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), being stirred with a Teflon®-coated magnetic stirring bar. Commercially available reagents were used as received unless otherwise noted. Et3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Reagent grade acetonitrile was obtained from Sigma-Aldrich and used as received. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Dienes,5,6 ent-Isoneleganolides A (13),8 ent-oxoineleganolide (9),47 were prepared by known methods. Reactions requiring external heat were modulated to the specified temperatures using an IAMag 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. Silicic acid SiliaFlash P60 Academic Silica gel (particle size 40-63 nm) was used for flash chromatography.1 H and 13C 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 CHCl3 (in CDCl3, δ 7.26 and δ 77.16, respectively) or CD3H in (in CD2N2, δ 7.16 and δ 128.06, respectively). Data for 1H NMR spectra are reported as follows: chemical shift (6 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.

(2aR,2a'S,4S,6aR,9S,10aS,10bS)-4-hydroxy-4-methyl-7-(prop-1-en-2-yl)decahydrobenzo[6,7]azuleno[1,8-bc]furan-1,7(2aH)-dione (12).

Preparation of a 0.07 M Stock Solution SmI2

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/H2O bath) with stirring. Diodooctane (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 SmI2.

Reduction of Diene 5

Each Schlenk tube was cooled to −78 °C (i-PrOH/dry ice bath) followed by the addition of H2O (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/H2O 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:CH2Cl2 eluent). The dark blue reaction mixture was quenched by the addition of hexanes (10.0 mL) and H2O (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 vacuum. 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: Rf = 0.21 (1:4 Acetone-Hexanes eluent); 1H NMR (CDCl3, 500 MHz) δ 6.32–6.24 (m, 1H), 4.93–4.86 (m, 1H), 7.44–7.40 (m, 1H), 4.63 (dt, J = 1.8, 0.9 Hz, 1H), 3.37 (dd, 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 (tm, J = 11.4, 3.8 Hz, 1H), 2.08 (dd, J = 15.7, 4.3 Hz, 1H), 2.02 (s, 1H), 1.83 (d, 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); 13C{1H} NMR (CDCl3, 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, 33.2, 30.0, 26.9, 22.5, 11 (Neat Film, NaCl) 3479, 2965, 1670, 1699, 1444, 1372, 1224, 1138, 992, 900, 754 cm–1; HRMS (FAB+): m/z calc’d for C19H25O4 [M–H]–: 315.1596, found 315.1600; [α]25D = −17.7° (c 0.400, CHCl3).
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, this dark green solution was added tert-butyl hydroperoxide (TBHP, 36 mL, 0.018 mmol, 1.10 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 became 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; Rf = 0.15 (1:4 Acetone:Hexanes eluent); 1H NMR (CDCl₃, 600 MHz) δ 4.87 (s, 1H), 4.79–4.73 (m, 1H), 4.63–4.57 (m, 1H), 3.34 (d, J = 6.0, 4.4 Hz, 1H), 2.97 (dd, 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 (s, 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); 13C{1H} NMR (CDCl₃, 126 MHz) δ 210.3, 173.8, 147.6, 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, CHCl₃) ν = 2923, 2853, 1761, 1719, 1668, 1600, 1526, 1461, 1364, 1259, 1131, 985, 893, 758 cm⁻¹; HRMS (FAB+) m/z Calcd for C₁₁H₁₈O₂Br [M+Br]⁺: 260.0176; Found: 260.0178 (50% yield). 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 (t-PrOH/dry ice bath) followed by the addition of H₂O₂ (108 µL, 6.00 mmol, 76.9 equiv). After stirring for 5 minutes, Cp₂TiCl (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/H₂O 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 NaHCO₃ (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 CH₂Cl₂ 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 (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:CH₂Cl₂ eluent). The reaction vessel was then 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 Na₂SO₃ (3.0 mL) and saturated NaHCO₃ (3.0 mL). After stirring to 10 minutes, the reaction mixture was diluted with H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organics were then dried over MgSO₄, filtered, and concentrated in vacuo. The crude brown solid was purified by silica gel column chromatography (25% acetone in hexanes eluent) to furnish 2H-ent-ineleganolide (8) (4 mg, 50% yield) and diketone 16 (4 mg, 50% yield), both as crystalline white solids.
heptane into a solution of 2H-ent-ingenolide (8) in EtOAc; mp: 218–220 °C; Rf = 0.23 (3:7 Acetone:Hexanes eluent); 1H NMR (CDCl3, 500 MHz) δ 4.96–4.92 (m, 1H), 4.80 (dd, 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 (dd, J = 14.7, 6.1, 1.0 Hz, 1H), 2.51–2.37 (m, 3H), 2.42–2.15 (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). 13C NMR (CDCl3, 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, 1218, 1262, 1160, 1081, 1030, 1003, 800, 758 cm–1; HRMS (FAB+) m/z calc’d for C18H28O3 [M+H]+: 333.1702, found 333.1714; [α]D 25.0 –32.6° (c 0.150, CHCl3).

Diketone 16: Colorless, translucent X-ray quality crystals that were obtained by slow diffusion of 1% benzene in heptane into a solution of diketone 16 in EtOAc, mp: 230–232 °C; Rf = 0.14 (3:7 Acetone:Hexanes eluent); 1H NMR (CDCl3, 600 MHz) δ 5.28 (dd, 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 (dd, 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 (dt, 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). 13C NMR (CDCl3, 126 MHz) δ 211.5, 208.9, 179.4, 146.3, 114.3, 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 C23H36O5Si [(M+H]+): 479.2838, found 479.2834; [α]D 25.0 +7.8° (c 0.100, CHCl3).

(2S,2aR,3aR,4aR,5S,7S,8aS,9bS,10aR)-5-((tert-butyldimethylsilyloxy)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)dodecahydrobenzo[6,7]oxireno[2,3':3,4']azulenol[1,8-bc]furan-9(2H)-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 i-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 became pale yellow and the consumption of starting material was complete as determined by TLC (3:7 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: Rf = 0.19 (3:17 Acetone:Hexanes eluent); 1H NMR (CDCl3, 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 (dd, 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 (dd, J = 14.3, 7.8, 2.1 Hz, 1H), 1.35–1.30 (m, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H), 13C NMR (CDCl3, 101 MHz) δ 174.3, 149.7, 108.3, 79.0, 77.4, 75.4, 73.6, 71.5, 55.4, 48.4, 44.5, 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 C23H36O5Si [(M+H]+): 447.2567, found 447.2572; [α]D 25.0 +19.9° (c 0.200, CHCl3).
Preparation of 0.50 M Solution of Titanocene Monochloride (Cp2TiCl)

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) in THF (1.5 mL) was sparged with argon for 1 h, the reaction mixture was then cooled to –78 °C (–0.06 (s, 3H); 13C{1H} NMR (CDCl3, 101 MHz) δ 4.92 (d, J = 1.6 Hz, 1H), 4.67 (q, J = 4.3 Hz, 1H), 3.72 (q, J = 2.8 Hz, 1H), 3.29 (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 (dd, 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); 31C(C1H) NMR (CDCl3, 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, 39.65, 35.81, 34.91, 34.69, 27.47, 25.95, 23.23, 18.18, –3.84, –4.81.; IR (Neat Film, NaCl) 3391, 2927, 1764, 1371, 1250, 1142, 1056, 887, 841 cm–1; HRMS (FAB+) m/z calc’d for C19H25O5Si [M+H]+: 405.2088, found 405.2087; 1H NMR (CDCl3, 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); 13C(C1H) NMR (CDCl3, 126 MHz) δ 173.8, 148.8, 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; 11 (Neat Film, NaCl) 3441, 2930, 1771, 1645, 1373, 1234, 1140, 986, 890, 757 cm–1; HRMS (FAB+) m/z calc’d for C6H10O3 [M+H]+: 333.1702, found 333.1695; [α]D25 +0.5° (c 0.500, CHCl3).

Epoxide Opening with Cp2TiCl

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 (–PrOH/dry ice bath) was added 1,2a,4,5,6,7,8,8b,10a-decahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-decahydrobenzo[6,7]furan-2,3,4,18a,19a,20a-decaydrobenzeno[6,7]oxireno[2',3':3a,4]azuleno[1,8-bc]furan-9(2H)-one (25). To a stirred solution of allylic alcohol 24 (11 mg, 0.033 mmol, 1.00 equiv) in CH2Cl2 (0.7 mL) at –78 °C (–PrOH/dry ice bath) was added EtN (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 NaHCO3 (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%) to furnish diol 19 (4 mg, 66% yield) as an amorphous white solid: Rf = 0.42 (1:1 EtOAc:CH2Cl2 eluent); 1H NMR (CDCl3, 400 MHz) δ 4.92 (d, J = 8.7 Hz, 1H), 4.69 (d, 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), 3.29 (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 (dd, 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); 31C(C1H) NMR (CDCl3, 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, 39.65, 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 C25H43O5Si [M+H]+: 451.2880, found 451.2890; [α]D25 +0.5° (c 0.200, CHCl3).

ACS Paragon Plus Environment
Unsaturated Lactone 31: R<sub>f</sub> = 0.29 (3:17 Acetone:Hexanes eluent); H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.80 (dd, J<sub>1</sub> = 7.5, 2.5 Hz, 1H), 4.75 (dt, J<sub>2</sub> = 1.8, 0.9 Hz, 1H), 4.73 (s, 1H), 4.16–4.07 (m, 1H), 3.88 (dd, J<sub>1</sub> = 10.1, 9.0, 4.3 Hz, 1H), 3.81 (dt, J<sub>1</sub> = 9.3, 2.5 Hz, 1H), 3.37 (dd, J<sub>1</sub> = 5.4, 2.0, 0.7 Hz, 1H), 2.61–2.51 (m, 2H), 2.41 (dd, J<sub>1</sub> = 9.3, 4.7, 2.4 Hz, 1H), 2.38–2.32 (m, 1H), 2.14 (tt, J<sub>1</sub> = 11.7, 4.1 Hz, 1H), 2.08–1.97 (m, 2H), 1.97–1.90 (m, 1H), 1.86 (dd, J<sub>1</sub> = 13.7, 11.1, 2.5 Hz, 1H), 1.74 (dd, J<sub>1</sub> = 1.5, 0.8 Hz, 3H), 1.43 (d, J<sub>1</sub> = 12.5, 10.2 Hz, 1H), 1.32 (d, J<sub>1</sub> = 0.9 Hz, 3H), 0.93 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); 3<sup>13</sup>C{1H} NMR (CDCl<sub>3</sub>, 100 MHz) δ 150.7, 142.8, 120.0, 51.3, 49.5, 44.5, 38.6, 28.8, 27.7, 20.8, 7.2, 6.6; IR (Neat Film, NaCl) 2951, 2937, 2857, 1742, 1645, 1455, 1360, 1259, 1176, 1078, 1053, 957, 918, 898, 837, 775 cm<sup>–1</sup>; HRMS (FAB+) m/z calecd for C<sub>25</sub>H<sub>39</sub>O<sub>5</sub>Si [M+H]<sup>+</sup>: 447.2567, found 447.2577; [α]<sup>D</sup> = 26.1° +56.1° (c = 0.600, CHCl<sub>3</sub>).
To a stirred solution of unsaturated lactone 32 (3 mg, 0.099 mmol, 1.00 equiv) in wet CH₂Cl₂ (1.3 mL) at 0 °C (ice/H₂O bath) was added a 0.50 M stock solution of Cp₂TiCl in THF (6.6 mL) that had previously been sparged 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 1 h, resulting in a bright red reaction mixture. After stirring for 5 minutes, the reaction was diluted with CH₂Cl₂ (5 mL) and poured onto saturated aqueous NaHCO₃ (2 mL). The organics were separated and the aqueous was extracted with CH₂Cl₂ (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-isoeisoneleganolide A (13, 2 mg, 66% yield) as a crystalline white solid: characterization match those reported previously.⁵

Preparation of 0.50 M Solution of Titanocene Monochloride (Cp₂TiCl)

Into a thoroughly flame-dried Schlenk tube under an overpressure of argon was charged with zinc(0) dust (647 mg, 9.90 mmol, 1.00 equiv) in THF (2.0 mL) was sparged with argon for 1 h, resulting in a white solid. 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 Cp₂TiCl.

Epoxide Opening with Cp₂TiCl

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 volume of 0.8 mL. The homogeneous, off-white reaction mixture was then cooled to −78 °C (−PrOH/dry ice bath) followed by the addition of H₂O (27 µL, 1.50 mmol, 55.6 equiv). After stirring for 5 minutes, Cp₂TiCl (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/H₂O 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 (3:1 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated aqueous Na₂SO₃ (2 mL) and poured onto saturated aqueous NaHCO₃ (2 mL). The combined organics were separated and the aqueous was extracted with CH₂Cl₂ (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-isoeisoneleganolide A (13, 2 mg, 66% yield) as a crystalline white solid: characterization match those reported previously.⁵
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 (Cp₂TiCl₂, 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 Cp₂TiCl₂.

Epoxide Opening with Cp₂TiCl₂

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 (isopropanol/dry ice bath) followed by the addition of H₂O₂ (27 µL, 1.50 mmol, 55.6 equiv). After stirring for 5 minutes, Cp₂TiCl₂ (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/H₂O 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 (3:1 Acetone:Hexanes eluent). The reaction was quenched by the addition of saturated NaH₂PO₄ (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 CH₂Cl₂ eluent) to furnish diol 39 (5 mg, 42% yield) as an amorphous white solid: Rf = 0.19 (1:4 EtOAc:CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 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 = 15.1, 10.6, 5.3 Hz, 1H), 2.73–2.68 (m, 1H), 2.60 (dt, J = 7.8, 7.0 Hz, 1H), 2.42 (dtt, J = 14.7, 11.9, 4.4 Hz, 1H), 2.20 (dd, J = 14.6, 2.1 Hz, 1H), 2.17–2.12 (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); ¹³C [¹H] NMR (CDCl₃, 101 MHz) δ 169.8, 158.0, 148.9, 122.7, 109.7, 81.7, 78.8, 74.6, 67.1, 56.6, 57.0, 48.4, 47.8, 47.4, 44.7, 43.9, 38.8, 37.7, 34.2, 29.6, 26.9, 26.0, 20.1, 18.1, 3.9–3.4, −0.5; IR (Neat Film, NaCl) 3542, 2929, 2856, 2886, 1767, 1661, 1435, 1362, 1361, 1125, 1270, 1110, 1033, 837, 836, 775 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₅H₄₀O₅Si [M+Na⁺]: 497.2627, found 497.2623; [α]D⁰ = 35.0° + 46.4° (c 0.250, CHCl₃).

(2aR,2a¹R,4S,6aR,7S,9R,10bR)-7-((tert-butylidimethylsilyloxy)-4-hydroxy-4-methyl-9-(prop-1-en-2-yl)-4,5-bis(triethylsilyloxy)-2a,3a,4a,6a,7,8,9,10a,10b-dodecahydro-1H-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 CH₂Cl₂ (1.0 mL) at 0 °C (ice/H₂O bath) was added Et₂N (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 (1:9 EtOAc:CH₂Cl₂ eluent). The reaction was quenched by the addition of saturated aqueous NaHCO₃ (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: Rf = 0.50 (1.9 EtOAc:Hexanes eluent); ¹H NMR (CDCl₃, 400 MHz) δ 5.48 (td, 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 (dd, 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 (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); ¹³C [¹H] NMR (CDCl₃, 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, −0.4–0.5; IR (Neat Film, NaCl) 2954, 2929, 2857, 2781, 1736, 1643, 1538, 1362, 1361, 1125, 1147, 1090, 1033, 891, 838, 775 cm⁻¹; HRMS (FAB+) m/z calc'd for C₇₁H₄₃O₂Si [M+H⁺]: 1047.2844, found 1047.2842; [α]D⁰ = 25.0° + 34.9° (c 0.250, CHCl₃).
(2aR,2a'S,4S,6aS,7S,9S)-7-((tert-butylidimethylsilyloxy)-4-methyl-9-(prop-1-en-2-yl)-4-((trimethylsilyl)oxy)-2a,3,4,4a,6,7,8,9,10-decahydro-1H-benzo[6,7]azuleno[1,8-bc]furan-1,5(2aH)-dione (43). To a stirred solution of ketone 40 (4 mg, 0.009 mmol, 1.00 equiv) in CH2Cl2 (1.0 mL) at 0 °C (ice/H2O bath) was added Et3N (126 ml, 0.90 mmol, 100.0 equiv). 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 (1:1 EtOAc:CH2Cl2 eluent). The reaction was quenched by the addition of saturated aqueous NaHCO3 (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 EtO2 (2 mL) and poured onto H2O (3 mL). The organics were separated and the aqueous was extracted with EtO2 (3 x 2 mL). The combined organics were dried over MgSO4, 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: Rf = 0.28 (1:4 EtOAc:Hexanes).1H NMR (CDCl3, 400 MHz) δ 5.05–4.97 (m, 1H), 4.84 (p, J = 1.5 Hz, 1H), 4.18 (t, J = 7.8 Hz, 1H), 3.73 (dd, 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), 2.42 (d, 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) ; 13C{1H} NMR (CDCl3, 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, 40.2, 33.3, 26.4, 26.0, 21.1, 18.5, 2.41–4.13 (m, 1H), 4.72 (dt, J = 7.7, 6.2, 3.8 Hz, 1H), 3.14–3.05 (m, 1H), 3.01–2.92 (m, 2H), 2.47 (d, 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 (d, J = 14.1, 10.3, 5.1 Hz, 1H), 1.78 (s, 3H), 1.55–1.43 (m, 1H), 1.35 (s, 3H); HRMS (ES+) m/z calc'd for C22H28O5Si [M+H]+: 519.2962, found 519.2954; [α]D25.0 +61.8° (c 0.200, CHCl3).

(2S,2aS,2a'R,3aR,7S,8bR,10aR)-2-methyl-7-(prop-1-en-2-yl)-1,2a,3,4,5,6,7,8,8b,9,10-decahydrobenzo[6,7]xirenone[2,3':2a,3a:4']azuleno[1,8-bc]furan-2,5,9-triol (46). To a stirred solution of ent-isoeinonegadilactone 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:CH2Cl2 eluent). The reaction was quenched by the addition of saturated aqueous HCl (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 CH2Cl2 (2.0 mL) and poured onto H2O (3.0 mL). The organics were separated and the aqueous was extracted with CH2Cl2 (4 x 1.5 mL). The combined organics were dried over MgSO4, 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: Rf = 0.23 (EtOAc eluent); 1H NMR (CDCl3, 400 MHz) δ 5.47 (d, 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 (dd, J = 7.7, 6.2, 3.8 Hz, 1H), 3.14–3.05 (m, 1H), 3.01–2.92 (m, 2H), 2.47 (d, 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 (d, J = 14.1, 10.3, 5.1 Hz, 1H), 1.78 (s, 3H), 1.55–1.43 (m, 1H), 1.35 (s, 3H); 13C{1H} NMR (CDCl3, 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 C13H15O3Si [M+]+: 334.1780, found 334.2023; [α]D25.0 +36.2° (c 0.250, CHCl3).

(2R,2aR,S,4S,9S,10bR)-4,7-dihydroxy-4-methyl-9-(prop-1-en-2-yl)-2a,3,4,6,7,8,9,10,10b-decahydro-1H-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 CH2Cl2 (4.5
CH2Cl2 (4 x 20 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. The crude off-white solid was purified by silicone gel column chromatography (60% EtOAc in hexanes eluent) to provide allylic alcohol 47 (4 mg, 11% yield) as an amorphous white solid: Rf = 0.28 (1:1 EtOAc:CH2Cl2 eluent); 1H NMR (CDCl3, 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 (dtt, J = 14.0, 10.3, 3.2 Hz, 1H), 1.77 (s, 3H), 1.53 (dd, J = 12.2, 9.4 Hz, 1H), 1.41 (s, 3H); 13C{1H} NMR (CDCl3, 101 MHz) δ 174.7, 148.7, 148.3, 133.2, 128.0, 127.1, 109.6, 83.2, 73.0, 49.3, 41.7, 46.0, 38.7, 38.1, 37.0, 28.9, 28.4, 21.1; IR (Neat Film, NaCl) 2928, 2856, 1461, 1256, 1103, 1077, 1066, 1026, 1002, 885, 837, 778 cm⁻1; HRMS (FAB+) m/z calc’d for C19H22O2S: [M+H]+: 317.1575, found 317.1579; [α]D 25.0° +62.5° (c 0.200, CHCl3).

(25S,2aS,2a1R,3aR,7S,8bR,10aR)-5,9-bis((tert-butylidimethylsilyl)oxy)-2-methyl-7-(prop-1-en-2-yl) -1,2,2a,3a,4,5,6,7,8,8b,9,10a-dodecahydrobenzo[6,7]oxireno[2',3':3a,4]azuleno[1,8-bc]furane-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 (1:1 EtOAc:Hexanes eluent). The reaction was concentrated in vacuo and the crude tan solid was purified by silicone gel column chromatography (10% EtOAc in hexanes eluent) to afford epoxide 49 (18 mg, 90% yield) as an amorphous white solid: Rf = 0.17 (1:1 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 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 (dtt, 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 (dtt, 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); 13C{1H} NMR (CDCl3, 101 MHz) δ 148.8, 130.4, 126.1, 109.3, 103.3, 80.2, 75.6, 75.2, 71.0, 75.7, 54.8, 47.9, 46.7, 36.9, 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 C19H21SiO2S: [(M+H)-H2]+: 561.3432, found 561.3441; [α]D 25.0° +88.4° (c 0.150, CHCl3).

Preparation of 0.5 M Solution of Titanocene Monochloride (Cp2TiCl)

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 (Cp2TiCl, 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 (66 mL) that had previously been sparged for 60 minutes and stirred commencing. After 1.5 h, the bright red reaction mixture had become yellowish-green and stirring was halted. After 30 minutes, the supernatant was used as a 0.50 M stock solution of Cp2TiCl.

Epoxide Opening with Cp2TiCl

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 (ice/H2O bath) followed by the addition of H2O2 (63 μL, 3.50 mmol, 83.3 equiv). After stirring for 5 minutes, CH3TICl (0.88 mM, 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/H2O 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 (3:3 EtOAc:Hexanes eluent). The brown dark reaction mixture was diluted with H2O (8 mL) and the aqueous was extracted with CH2Cl2 (5 x 10 mL) followed by EtOAc (2 x 5 mL). The combined organics were dried over MgSO4, 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 polysaturated diketone 56 (retention time 11.4 minutes, 8 mg, 44% yield) as an amorphous white solid.

**Vinylogous Diketone 55.** Rf = 0.37 (3:7 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 600 MHz) δ 6.26 (q, J = 0.7 Hz, 1H), 4.93 (ddd, δ = 9.4, 8.3, 6.8, 1.5 Hz, 1H), 4.89 (s, 1H), 4.84–4.82 (m, 1H), 3.35 (td, δ = 8.8, 1.5 Hz, 1H), 3.15 (dd, δ = 8.8, 1.5 Hz, 1H), 2.77–2.61 (m, 3H), 2.49–2.38 (m, 2H), 2.31 (dd, δ = 12.6, 7.7, 1.4 Hz, 1H), 2.19 (dd, J = 15.1, 2.6, 1.6 Hz, 1H), 1.81 (m, 3H), 1.66 (s, 1H), 0.11 (s, 9H); 13C{1H} NMR (CDCl3, 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, 849, 841 cm–1; HRMS (FAB+) m/z calc'd for C25H30O5Si [M+H+] +: 417.1733, found 417.1741; [α]D25 0 +16.9° (c 0.100, CHCl3).

**Polysaturated Diketone 56.** Rf = 0.37 (3:7 EtOAc:Hexanes); 1H NMR (CDCl3, 400 MHz) δ 6.64 (d, δ = 0.7 Hz, 1H), 6.44 (d, J = 2.5 Hz, 1H), 5.75 (s, 1H), 5.57 (ddd, δ = 9.4, 1.0 Hz, 1H), 4.93 (ddd, δ = 9.5, 8.6, 7.7, 3.4 Hz, 1H), 3.45–3.36 (m, 2H), 3.26 (dd, δ = 8.8, 0.6 Hz, 1H), 3.01 (dd, δ = 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); 13C{1H} NMR (CDCl3, 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) 2975, 1770, 1702, 1660, 1611, 1378, 1252, 1179, 1066, 1036, 870, 842, 759 cm–1; HRMS (FAB+) m/z calc'd for C25H29O6Si [M+H+] +: 415.1577, found 415.1588; [α]D25 0 +70.9° (c 0.100, CHCl3).

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). After an additional 5.5 h, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature.

**Preparation of SmI2.** 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/H2O bath) with stirring. EtI2 (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 SmI2.

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 brown dark reaction mixture was diluted with H2O (8 mL) and the aqueous was extracted with CH2Cl2 (5 x 10 mL) followed by EtOAc (2 x 5 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. The crude amorphous white solid was carried on without further purification.
Reduction of Vinlyogous Diketone 55

A stirred solution of vinlyogous 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 cooled to -78 °C (i-PrOH/dry ice bath) at which time SmI2 (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:CH2Cl2 eluent). The reaction was diluted with CH2Cl2 (3 mL) and poured onto saturated aqueous NaHCO3 (3 mL). The organics were separated and the aqueous was extracted with CH2Cl2 (2 x 5 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. The white crude solid was purified by silica gel column chromatography (50% EtOAc in hexanes eluent) to provide dienol acetate 58 (11 mg, 85% yield) as an amorphous white solid: Rd = 0.42 (1:1 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 400 MHz) δ 4.84 (ddd, d 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, 4H), 2.23 (s, 3H), 1.98 (s, 3H), 1.77–1.72 (m, 3H), 1.61 (d, J = 1.0 Hz, 3H); 13C{1H} NMR (CDCl3, 100 MHz) δ 170.2, 170.0, 168.1, 156.0, 152.4, 146.7, 122.2, 112.5, 111.5, 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 (Nujol, NaCl) 2925, 1740, 1615, 1440, 1372, 1241, 1204, 1153, 1118, 1043, 989, 972, 754 cm⁻¹; HRMS (FAB+) m/z calculated for C23H28O3 [M+H+] : 415.1757, found 415.1737; [α]D25.0 +241.6° (c 0.100, CHCl3).

Reduction of Vinlyogous Diketone 55

To a stirred solution of ent-isoineleganolide A (13, 10 mg, 0.0030 mmol, 1.00 equiv) in CH2Cl2 (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 (1:4 EtOAc:CH2Cl2 eluent). The reaction was quenched by the addition of saturated aqueous Et3N (1.5 mL) as an amorphous white solid: Rd = 0.58 (1:1 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 400 MHz) δ 4.82–4.70 (m, 3H); 13C{1H} NMR (CDCl3, 101 MHz) δ 171.0, 160.7, 154.7, 147.2, 146.0, 145.7, 144.0, 137.2, 132.4, 131.7, 129.2, 123.6, 120.4, 110.6, 80.9, 73.1, 70.8, 53.2, 46.3, 42.8, 39.7, 34.2, 30.5, 23.6, 21.9, 21.7, 21.1, 21.0; IR (Nujol, NaCl) 2925, 1740, 1615, 1440, 1372, 1241, 1204, 1153, 1118, 1043, 989, 972, 754 cm⁻¹; HRMS (FAB+) m/z calculated for C23H28O3 [M+H+] : 415.1757, found 415.1737; [α]D25.0 +241.6° (c 0.100, CHCl3).
CH2Cl2 (3 x 2 mL). The combined organics were dried over MgSO4, 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: Rf = 0.32 (1:1 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 400 MHz) δ 5.18 (dd, 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 (dd, J = 16.8, 3.5, 1.9 Hz, 1H), 3.62 (dd, J = 4.2 Hz, 1H), 3.36 (dd, 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); 13C{1H} NMR (CDCl3, 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, 1775, 1692, 1603, 1441, 1332, 1261, 1202, 1090, 1046 cm–1; HRMS (FAB+) m/z calc’d for C17H19O5Br [M+H]+: 329.1389, found 329.1384; [α]D25.0 +22.9° (c 0.150, CHCl3).

(2S,3aR,7S,10aR)-2-hydroxy-2-methyl-7-(prop-1-en-2-yl)-1,2a,6,7,8,9,10a-hexahydrobenzo[6,7]oxireno[2',3':4,5]azonia[1,8-bc]furan-5,9(2H,3aH)-dione (ent-Dehydroisoineleganolide, 65). To a stirred solution of ent-isoineleganolide A (13 mg, 0.14 mmol, 1.0 equiv) in CH2Cl2 (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 TBSCI (210 mg, 1.39 mmol, 10.0 equiv) was added as a solution in CH2Cl2 (2.1 mL) quickly dropwise over 2 minutes. 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 Et3N (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% Et3N 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 of dienol ether 59 (62 mg, 0.14 mmol, 1.0 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 H2O (30 mL). The organics were separated and the aqueous was extracted with EtOAc (3 x 20 mL). The combined organics were washed with H2O (30 mL), dried over MgSO4, 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: Rf = 0.25 (1:1 EtOAc:Hexanes eluent); 1H NMR (CDCl3, 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); 13C{1H} NMR (CDCl3, 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, 1193, 1090, 1026, 798 cm–1; HRMS (FAB+) m/z calc’d for C19H19O5 [M+H]+: 329.1389, found 329.1373; [α]D25.0 +40.2° (c 0.075, CHCl3).

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

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

AUTHOR INFORMATION
Corresponding Author
* stoltz@caltech.edu

Notes
The authors declare no competing financial interests.

ACKNOWLEDGMENT

The Journal of Organic Chemistry
Page 20 of 24
The references are cited in the text as follows:


9. The biosynthetic speculations concerning the formation of ineleganolide (1) from a macrocyclic precursor natural product through a series of anionic intramolecular cyclizations were investigated and confirmed by the biomimetic semisynthesis, see: Li, Y.; Pattenden, G. Biomimetic Syntheses of Ineleganolide and Sinulchoclidin C from 5-Epispieuliopoletide via Sequences of Transanular Michael Reactions. *Tetrahedron* **2004**, *60*, 5751–5759.


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.


**Page 22 of 24**

**The Journal of Organic Chemistry**

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


24. The relative stereochemistry at carbonyl 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 1H NMR. The direction of epoxidation of the dihomallylic 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 1H 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 1H 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/CH2Cl2).

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


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


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 inegalenoloids 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.


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

38. 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