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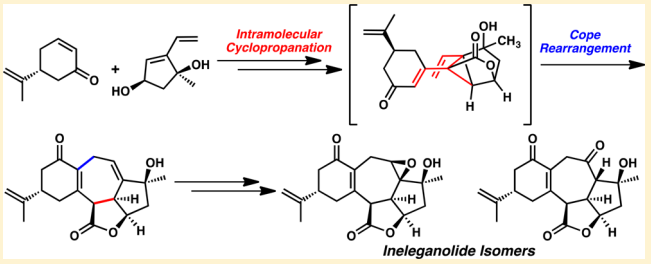
Development of a Unified Enantioselective, Convergent Synthetic Approach Toward the Furanobutenolide-Derived Polycyclic Norcembranoid Diterpenes: Asymmetric Formation of the Polycyclic Norditerpenoid Carbocyclic Core by Tandem Annulation Cascade

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

Supporting Information

ABSTRACT: An enantioselective and diastereoselective approach toward the synthesis of the tetracyclic scaffold of the furanobutenolide-derived polycyclic norditerpenoids is described. Focusing on synthetic efforts toward ineleganolide, the synthetic approach utilizes a palladium-catalyzed enantioselective allylic alkylation for the construction of the requisite chiral tertiary ether. A diastereoselective cyclopropanation−Cope rearrangement cascade enabled the convergent assembly of the ineleganolide [6,7,5,5]-tetracyclic scaffold. Investigation of substrates for this critical tandem annulation process is discussed along with synthetic manipulations of the [6,7,5,5]-tetracyclic scaffold and the attempted interconversion of the [6,7,5,5]-tetracyclic scaffold of ineleganolide to the isomeric [7,6,5,5]-core of scabrolide A and its naturally occurring isomers. Computational evaluation of ground-state energies of late-stage synthetic intermediates was used to guide synthetic development and aid in the investigation of the conformational rigidity of these highly constrained and compact polycyclic structures.



INTRODUCTION

Natural products derived from flora and fauna throughout the world have been successfully applied to the treatment of human ailments for centuries.[1] Modern synthetic chemistry has enabled the isolation, identification, and manufacturing of many of the most promising biologically active natural products for therapeutic application against a breadth of diseases including cancer,[1b,c,2] malaria,[1b,3] bacterial infection,[1b,c,4] and neurological diseases.[1b,2a,5] Despite these successes, the need for more effective therapeutics for a variety of intractable ailments remains constant.[1c,6] Toward this end, the furanobutenolide-derived norcembranoid diterpenes remain a largely unexplored class of biologically active natural products.[7] Included within this natural product family is the compact and highly oxygenated antileukemic ineleganolide (**1**)[8] as well as the closely related norcembranoid diterpenes horiolide (**2**),[9] kavaranolide (**3**),[10] sinulochmodin C (**4**),[11] scabrolide B (**5**),[12] scabrolide A (**6**),[12] and yonarolide (**7**, Figure 1).[13] The total synthesis of any member of these polycyclic furanobutenolide-derived norcembranoids has not been accomplished to date, although the syntheses of select members have been investigated[14] and the biomimetic semisynthesis of ineleganolide (**1**) and sinulochmodin C (**4**) has been disclosed.[15]

It has been proposed that ineleganolide (**1**) and sinulochmodin C (**4**) are the biosynthetic precursors to the other related polycyclic [6,7]- and [7,6]-fused norcembranoid diterpenes, respectively.[7a,b,10] Ineleganolide (**1**) is believed to undergo a retro-oxa-Michael addition followed by a retroaldol cyclization to furnish intermediate triketone **8** (Scheme 1). Although ketone **8** has not been isolated, it is the postulated biosynthetic precursor of horiolide (**2**), undergoing an

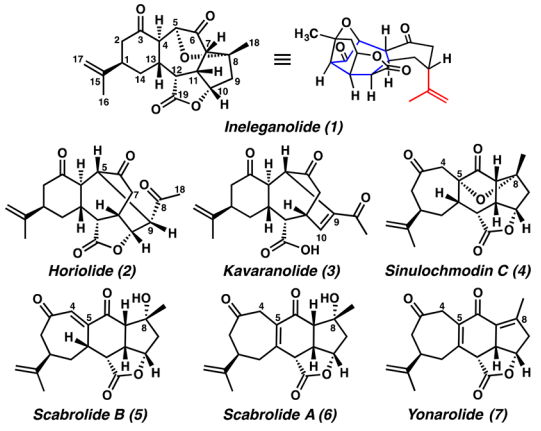


Figure 1. Furanobutenolide-derived polycyclic norcembranoid diterpenes.

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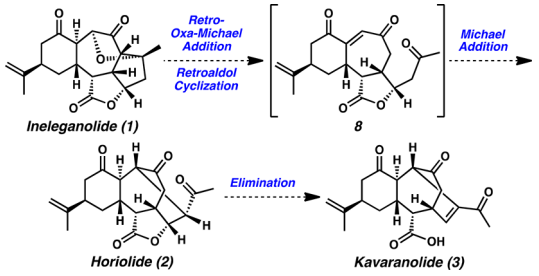
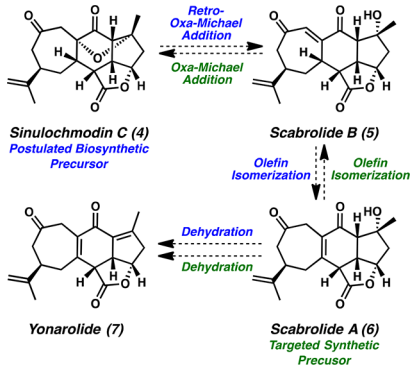
Scheme 1. Postulated Biosynthetic Advancement of Ineleganolide (1) to Kavaranolide (3)



intramolecular Michael addition with the vinylogous diketone moiety to construct the transannular C−C bond. Horiolide (**2**) would then undergo a β-elimination from the methyl ketone moiety to furnish kavaranolide (**3**).

Sinulochmodin C (**4**), a constitutional isomer of ineleganolide (**1**), is the postulated biosynthetic precursor to each of the other related [7,6]-fused norcembranoid diterpenes furnishing scabrolide B (**5**) after undergoing a retro-oxa-Michael addition (Scheme 2). Olefin isomerization of vinylogous diketone **5**

Scheme 2. Postulated Biosynthetic (Blue) and Proposed Synthetic (Green) Relationships between Polycyclic Furanobutenolide-Derived [7,6]-Norcembranoids



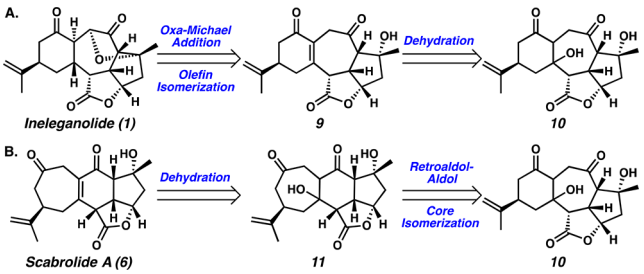
would furnish the tetrasubstituted enone scabrolide A (**6**). Finally, dehydration of tertiary alcohol **6** would afford dienone yonarolide (**7**).

We were drawn to the unique furanobutenolide-derived scaffold of these norcembranoid diterpenes and the challenge of designing a convergent synthetic pathway toward complex late-stage polycyclic intermediates from which divergent access to each of these six closely related natural products could be achieved. The synthesis would require careful design by strategies including oxidation state manipulation, substrate-controlled diastereoselective transformations, and intramolecular rearrangements to provide enantioselective synthetic access to these highly oxygenated, cycloheptanone-derived polycycles. Successful development of such a synthetic route would enable the thorough exploration of the biological activity of these largely untested members of the known antitumor and antileukemic norcembranoid diterpene natural product family. Ineleganolide (**1**) and scabrolide A (**6**) were targeted as the intermediates through which the remaining polycyclic furanobutenolide-derived norcembranoid diterpenes could be accessed.[16]

RESULTS AND DISCUSSION

Synthetic access to furanobutenolide-derived norcembranoid diterpenes **2**−**5** and **7** could be achieved through either ineleganolide (**1**) or scabrolide A (**6**) in a divergent fashion from a common, late-stage synthetic intermediate **10** (Scheme 3). Retrosynthetically, completion of the asymmetric total

Scheme 3. Retrosynthetic Analysis of Ineleganolide (1) and Scabrolide A (6)

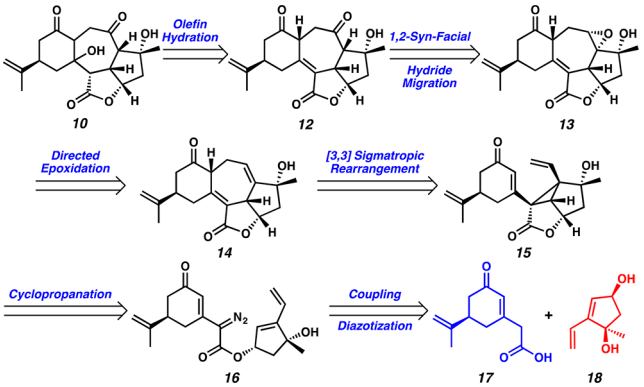


synthesis of ineleganolide (**1**) would be achieved by the olefin isomerization of enone **9** followed by intramolecular oxa-Michael addition (Scheme 3A). Unsaturated diketone **9** could by synthesized after the selective dehydration of common intermediate diol **10**.

Scabrolide A (**6**) would be accessed by dehydration of diol **11** (Scheme 3B). Synthesis of [7,6,5,5]-tetracyclic diol **11** would require a carbocyclic core isomerization from common intermediate diol **10**. We envision accomplishing this transformation directly from [6,7,5,5]-tetracyclic diol **10** by tandem retroaldol−aldol cyclization inspired by the biosynthetic formation of the polycyclic furanobutenolide-derived norcembranoids (i.e., **1**−**7**) from a common macrocyclic precursor through sequential intramolecular anionic cyclizations.[7a,b,15]

These divergent syntheses from [6,7,5,5]-tetracyclic diol **10** would be enabled by the concise, convergent enantioselective synthesis of the [6,7,5,5]-tetracyclic scaffold of ineleganolide (Scheme 4). Access to diol **10** would be achieved by selective

Scheme 4. Retrosynthetic Analysis of Tetracyclic Diol 10



olefin hydration of α,β-unsaturated lactone **12**. Diketone **12** would be constructed by the isomerization of epoxide **13** via *syn*-facial 1,2-hydride shift. Hydroxyl-directed epoxidation of allylic alcohol **14** would provide pentacycle **13** in diastereoselective fashion. Formation of the central cycloheptadiene within tetracycle **14** would be accomplished by the Cope rearrangement of divinylcyclopropane **15**, which would be synthesized by the intramolecular cyclopropanation of α-

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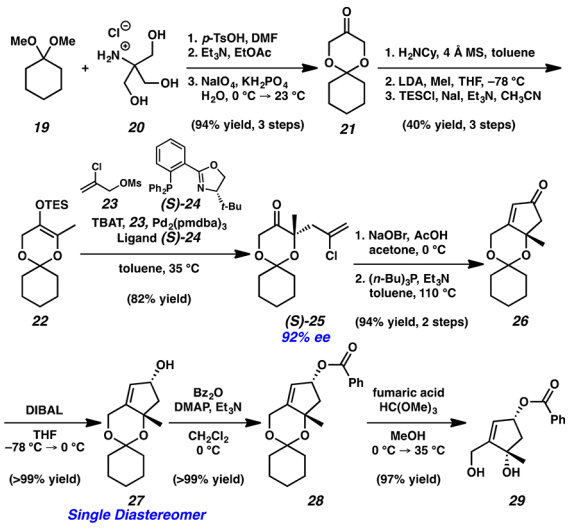
diazoester **16**.[17] Cyclization precursor **16** would be assembled in a convergent fashion by the coupling of carboxylic acid **17** and *cis*-1,3-cyclopentenediol **18**. Acid **17** would be rapidly constructed from (*S*)-(+)-carvone. Consequently, our initial synthetic efforts focused on the construction of enantioenriched *cis*-1,3-cyclopentenediol **18**.

Enantioselective synthesis of the targeted polycyclic norcembranoid diterpene natural products would require the construction of the common *cis*-1,3-cyclopentenediol building block **18** in enantioenriched form. Aside from the peripheral isopropenyl stereocenter, all chiral information contained within each natural product will be relayed from the two stereocenters in this highly oxygenated cyclopentene (**18**). Thus, an enantioselective sequence to this crucial building block is a compulsory feature of our route.

Previously, our group has disclosed first-generation pursuits toward ineleganolide[18] as well as the development of the enantioselective synthesis of a functionalized hydroxymethyl-*cis*-1,3-cyclopentenediol synthetic building block.[19] The construction of this carbocycle began with transketalization of dimethylketal **19** with tris(hydroxymethyl)amine hydrochloride salt (**20**) followed by a free-basing procedure and oxidative cleavage of the resultant amino alcohol provided ketodioxanone **21** in 94% yield over three steps (Scheme 5).[19a] Ketone **21** was

Scheme 5. Synthesis of Hydroxymethyl-*cis*-1,3-cyclopentenediol Building Block

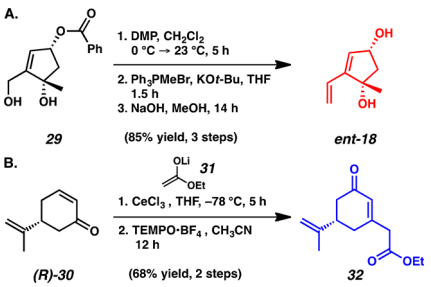


then alkylated over two steps through the cyclohexylimine intermediate. Alkylation of the intermediate imine rather than direct methylation of ketone **21** was critical to achieve a high yield by not only eliminating the undesired α,α'-dimethylation of the substrate, but also minimizing aldol dimerization.[20] Formation of fully substituted enol ether **22** was achieved under soft enolization conditions using sodium iodide paired with triethylsilyl chloride (TESCl). Spirocyclic enol ether **22** was the targeted substrate for the critical intermolecular asymmetric palladium-catalyzed allylic alkylation that would form the requisite chiral tertiary center. Using 2-chloroallyl mesylate (**23**) as the optimal external electrophile and employing (*S*)-*t*-BuPHOX ((*S*)-**24**), the more readily available enantiomer of the chiral ligand, chloroallyl ketone (*S*)-**25**, was furnished in 82% yield and 92% ee.[21] For the purposes of synthetic development, chloroallyl ketone (*S*)-**25** was used as an intermediate in the opposite enantiomeric series from the naturally occurring furanobutenolide-derived norcembranoid diterpenes. The synthesis of the enantiomerically matched norcembranoid diterpenes may be subsequently achieved using either (*R*)-*t*-BuPHOX ((*R*)-**24**)[22] or PHOX ligands derived from (*R*)-valine, which have been shown to be comparably effective for the enantioselective formation of ketone (*R*)-**25**.[23]

Transformation of chloroallyl ketone (*S*)-**25** through an experimentally intriguing oxidative α-bromoketone formation[24] and subsequent intramolecular Wittig olefination provided cyclopentenone **26** in 94% yield over two steps. Reduction of enone **26** at cryogenic temperature with diisobutylaluminum hydride (DIBAL) provided allylic alcohol **27** as a single diastereomer in quantitative yield. Benzoylation of secondary alcohol **27** then delivered allylic ester **28** in excellent yield as well. Cleavage of the cyclohexyl ketal moiety within ester **28** revealed primary alcohol **29** in 97% yield as the hydroxymethyl-*cis*-1,3-cyclopentenediol building block.

Hydroxymethylcyclopentene **29** could then be advanced toward the furanobutenolide-derived norcembranoid diterpene scaffolds beginning with oxidation of the primary alcohol with Dess–Martin periodinane (DMP, Scheme 6A). Methylenation

Scheme 6. Completion of Coupling Partners

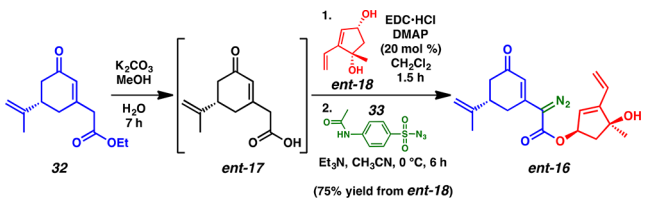


of the intermediate aldehyde and ultimate saponification of the benzoyl ester revealed the requisite diol fragment common to our strategy to the targeted norcembranoids (***ent*-18**) in 85% yield over three steps.

Synthesis of the complementary coupling partner required for the synthesis of the enantiomeric norcembranoids began with (*R*)-(−)-desmethylcarvone ((*R*)-**30**), which is available by a known procedure from (*R*)-(−)-carvone.[25] Cerium-mediated 1,2-addition of the preformed lithium enolate of ethyl acetate (**31**) into enone (*R*)-**30** followed by a 1,3-oxidative allylic transposition[26] provided ester **32** in 68% yield over two steps (Scheme 6B).

Saponification of ethyl ester **32** provided acid coupling partner ***ent*-17** (Scheme 7). Coupling of crude acid ***ent*-17** and diol ***ent*-18** was accomplished using EDC·HCl with catalytic DMAP, requiring nearly a 2-fold excess of acid ***ent*-17** to drive the reaction to completion relative to diol ***ent*-18**. Diazo

Scheme 7. Fragment Coupling and Synthesis of Cyclopropanation–Cope Rearrangement Precursor



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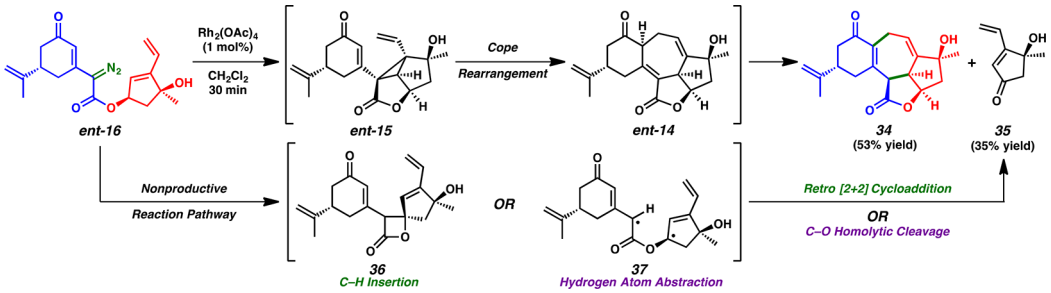
Scheme 8. Construction of Tetracycle 34 by Tandem Cyclopropanation−Cope Rearrangement



transfer onto the intermediate ester product using *p*-ABSA (**33**) furnished α-diazoester ***ent*-16** in 75% yield from diol ***ent*-18**.

With α-diazoester ***ent*-16** in hand, we began investigating the potential to accomplish a chemoselective intramolecular cyclopropanation. Employment of copper catalysis, which had previously proven effective for an analogous transformation on a model system, was ineffective, requiring high catalyst loading (>25 mol %) and low yield (<10%).[18] Alternative exposure of diazo ***ent*-16** to 1 mol % Rh_2OAc_4 in dichloromethane at ambient temperature enabled the desired chemoselective cyclopropanation in tandem with a Cope rearrangement, furnishing cycloheptadiene **34** in 53% yield (Scheme 8).[17] Proceeding through cyclopropane ***ent*-15**, cycloheptadiene **34** was isolated after in situ olefin isomerization from the unsaturated lactone ***ent*-14** to the corresponding tetrasubstituted enone. We were pleased to find diene **34** was a crystalline solid, and in addition to the general proof of structure, its relative configuration was unambiguously established by single-crystal X-ray diffraction (Figure 2), confirming the stereo-

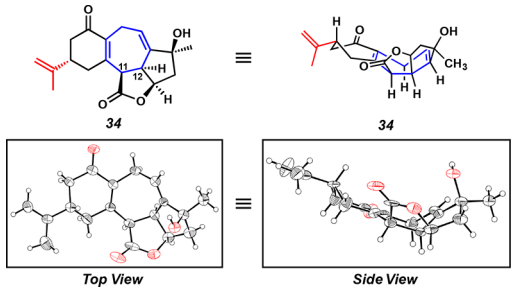


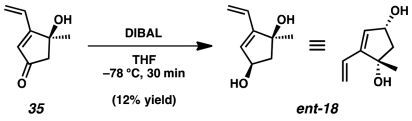
Figure 2. X-ray crystal structure of diene **34**.

centers at C(11) and C(12) were set as required for the furanobutenolide-derived norcembranoid diterpene natural products and revealing the *creased* conformation of the central cycloheptadiene.

The only other product observed from this transformation is extended enone **35**, which was isolated in 35% yield. Despite efforts to optimize this transformation further, screening a variety of rhodium catalysts as well as reaction conditions, we were never able to improve the ratio between desired tetracycle **34** and cyclopentenone byproduct **35**.[27] We hypothesize that the nonproductive reaction pathway proceeds from the metal carbenoid of α-diazoester ***ent*-16** through C−H insertion at or hydrogen abstraction from the allylic position of the cyclopentene fragment to furnish either intermediate β-lactone **36** or separated diradical **37**, respectively. Ultimately, retro-ketene (2 + 2)-cycloaddition from heterocycle **36** or radical recombination by homolytic cleavage of the ester C−O single bond within diradical **37** would furnish cyclopentenone **35**.

Enone byproduct **35** could be recycled through a diastereoselective 1,2-reduction with DIBAL at low temperature to provide *cis*-1,3-cyclopentenediol ***ent*-18**, albeit in low yield (Scheme 9). The unsatisfactory yield of this trans-

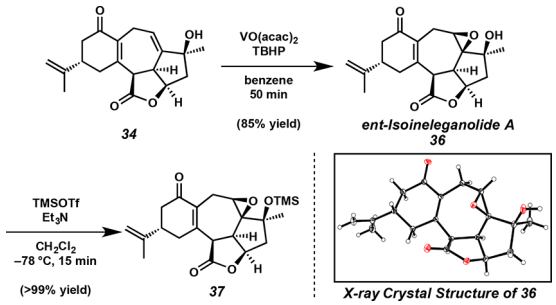
Scheme 9. Diastereoselective 1,2-Reduction of Enone Byproduct 35



formation is likely due to coordination of the product to the byproduct aluminum salts, preventing extraction of diol ***ent*-18** from the aqueous layer during purification. Other hydride sources such as $NaBH_4$ and L-Selectride failed to accomplish the reduction of enone **35** in a stereoselective fashion.

Nevertheless, we were pleased to have efficient and convergent synthetic access to the tetracyclic core of the furanobutenolide-derived norcembranoid diterpenes and began advancing toward the targeted natural products. Hydroxyl-directed epoxidation of allylic alcohol **34** was accomplished in 85% yield using catalytic $VO(acac)_2$ (Scheme 10). Epoxytetra-

Scheme 10. Advancement of Diene 34 and Formation of *ent*-Isoineleganolide A (36)



cycle **36** was found to be a crystalline white solid, and the relative configuration was unambiguously established by single-crystal X-ray diffraction, confirming the success of the diastereoselective and chemoselective directed epoxidation. Considering examples of successful epoxide-ketone rearrangements in the presence of free hydroxyl groups are extremely rare in the literature,[28] conditions for the protection of tertiary alcohol **36** were developed, affording silyl ether **37** in excellent yield at low temperature.

With two substrates in hand (**36** and **37**), we began screening reaction conditions known to effect epoxide−ketone rearrangements in the literature including reaction manifolds

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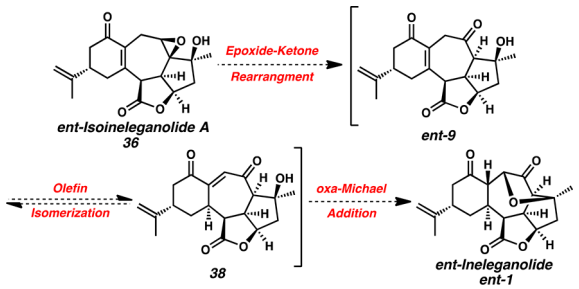
mediated by protic acid, aprotic base, and most commonly, Lewis acids.[28,29] We hypothesized that epoxide **36** would undergo a *syn*-facial 1,2-hydride shift to not only furnish the necessary 1,4-diketone pattern required for the norcembranoid diterpenes but would result in an equilibrium mixture of enone ***ent*-9** and vinylogous diketone **38** (Scheme 11). Intramolecular

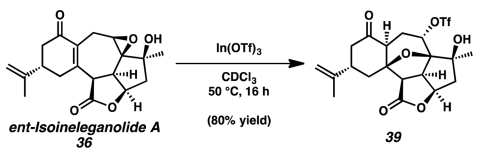
Scheme 11. Intended Completion of *ent*-Ineleganolide (*ent*-1)



oxa-Michael addition of tertiary alcohol **38** to the vinylogous diketone system would then form the expected thermodynamically favored natural product ***ent*-1**, driving the equilibrium mixture toward vinylogous diketone and thus *ent*-ineleganolide (***ent*-1**). Unfortunately, even under the most commonly employed conditions in the literature using magnesium(II)-, aluminum(III)-, and boron-based Lewis acids, both epoxide **36** and silyl ether derivative **37** proved largely unreactive or simply decomposed.[30]

The only isomerization observed for either epoxytetracycle **36** or silyl ether **37** was the isomerization of *ent*-isoineleganolide A (**36**) to triflate **39** using stoichiometric indium(III) triflate (Scheme 12). Although examples of stable

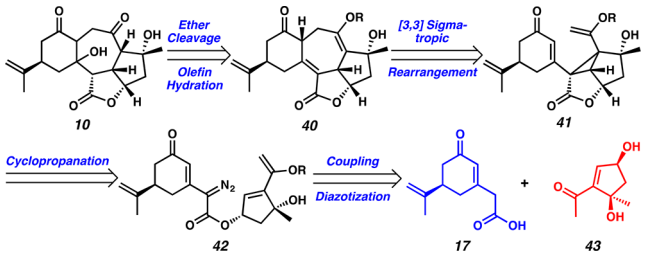
Scheme 12. Isomerization of *ent*-Isoineleganolide A (36) to Triflate 39



alkyl triflates are sparing, the strain release of the fused epoxide provides the necessary energetic driving force for the smooth formation of triflate **39**, which is further stabilized by α-oxygenation that discourages ionization.[31] Although triflate **39** is a fascinating structure that is as complex as any member of the furanobutenolide-derived norcembranoid diterpene natural products, we did not envision triflate **39** as immediately useful for completion of the asymmetric synthesis for either *ent*-ineleganolide or the remaining members of the norcembranoid diterpene natural product family.

In light of the difficulty encountered installing the transannular 1,4-dicarbonyl oxidation pattern that characterizes the norcembranoid diterpene natural product family from epoxytetracycle **36**, we reevaluated our synthetic strategy. Access to planned divergent intermediate **10** would be achieved by deprotection of enol ether **40** followed by olefin hydration of the unsaturated lactone moiety (Scheme 13). Construction of tetracyclic core **40** would be accomplished through an analogous Cope rearrangement from cyclopropane **41** that would be formed in turn after the intramolecular cyclo-

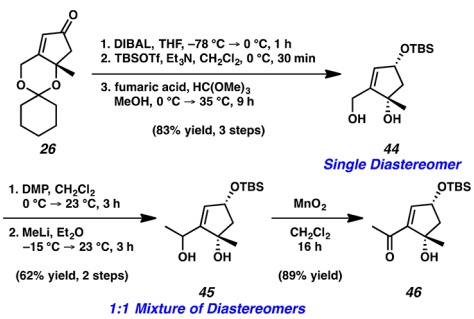
Scheme 13. Alternative Retrosynthetic Disconnection of Divergent Intermediate 10



propanation of α-diazoester **42**. Cyclization precursor **42** would be assembled by the coupling carboxylic acid **17** with methyl ketone **43**.

Having previously established synthetic access to acid ***ent*-17**, we turned our attention to the modification of the *cis*-1,3-cyclopentenediol synthetic route toward the complementary methyl ketone (***ent*-43**). Diastereoselective reduction of cyclopentenone **26**, silylation of the intermediate alcohol using TBSOTf, and removal of the cyclohexyl ketal under fumaric acid-mediated transketalization conditions furnished silyl ether **44** in 83% yield over three steps as a single diastereomer (Scheme 14). Oxidation of primary alcohol **44**

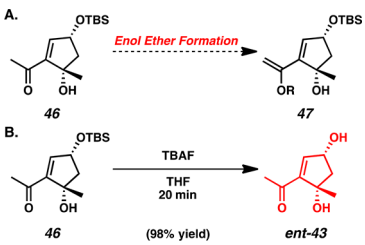
Scheme 14. Construction of Methyl Ketone 46



with DMP to the intermediate aldehyde followed by the 1,2-addition of a methyl substituent into the enal system provided secondary alcohol **45** as a 1:1 mixture of diastereomers. This mixture of diastereomers proved inconsequential as the allylic oxidation of the diastereomeric mixture of alcohol **45** delivered methyl ketone **46** in 89% yield.

Next, the methyl ketone needed to be converted into the corresponding enol ether for use in the desired Cope rearrangement. Unfortunately, all attempts to form a stable enol ether that would be orthogonal to the deprotection conditions needed for the requisite removal of the secondary TBS ether were unsuccessful (Scheme 15A).[32] Alternatively, we reasoned that the formation of the enol ether from the methyl

Scheme 15. Advancement of Silyl Ether 47



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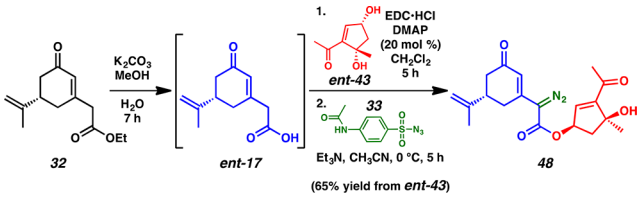
ketone moiety could be accomplished at a later stage. Thus, enone **46** was advanced by deprotection of the silyl ether using TBAF at ambient temperature to afford diol ***ent*-43** in 98% yield (Scheme 15B).

Saponification of ethyl ester **32** again revealed coupling partner ***ent*-17** (Scheme 16). Esterification of crude acid ***ent*-17**

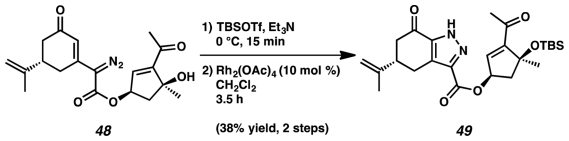
Scheme 16. Fragment Coupling with Methyl Ketone Diol *ent*-43



with diol ***ent*-43** was accomplished using catalytic DMAP in the presence of EDC·HCl, again requiring a 2-fold excess of acid ***ent*-17** to drive the reaction to completion relative to diol ***ent*-43**. Diazo transfer onto the intermediate ester product using *p*-ABSA (**33**) furnished α-diazoester **48** in 65% yield from ketodiol ***ent*-43**.

With α-diazoester **48** in hand, we sought to form the enol ether from the methyl ketone moiety and subsequently accomplish a tandem cyclopropanation−Cope rearrangement. Exposure of diazoester **48** to a variety of base-mediated silyl enol ether forming conditions generated light-sensitive, neon orange intermediates that quickly decomposed in the presence of silica or as neat crude oils. Exposure of diazoester **48** to TBSOTf and Et_3N at 0 °C in the dark followed by immediate filtration through Florisil and dilution of the crude oil with dichloromethane and the addition of catalytic $Rh_2(OAc)_4$ provided pyrazole **49** as the sole product in 38% yield over two steps (Scheme 17).[33]

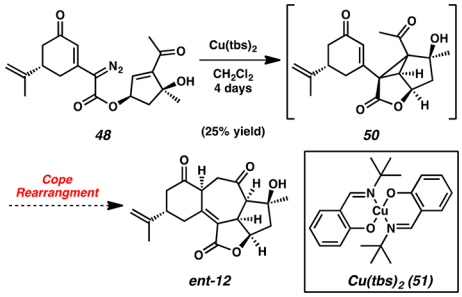
Scheme 17. Formation of Pyrazole 49



Without success in accomplishing the tandem cyclopropanation−Cope rearrangement, we began exploring the potential to synthesize the central cycloheptenone in a stepwise fashion. Intramolecular cyclopropanation of α-diazoester **48** onto the olefin of the enone system to access cyclopropane **50** proved challenging (Scheme 18). While rhodium(II) dimers including $Rh_2(OAc)_4$ and $Rh_2(CF_3CO_2)_4$ were ineffective catalysts for the desired intramolecular cyclization, we were pleased to find that $Cu(tbs)_2$ (**51**) was able to catalyze the desired transformation, albeit in low yield over an extended reaction period.[34]

With cyclopropane **50** in hand, we next needed to induce the Cope rearrangement to access ***ent*-12**. Unfortunately, formation of the silyl enol ether of methyl ketone **50** was unsuccessful as the TMS, TES, or TBS enol ethers using reaction conditions mediated by either weak ($(i\text{-}Pr)_2NEt$, Et_3N) or strong (LDA, LHMDS) bases. Additionally, the anionic 2-oxa-Cope rearrangement failed to proceed after subjecting cyclopropane **50** to LDA or LHMDS at −78 °C and warming to ambient

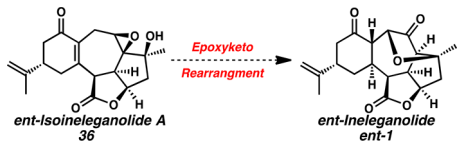
Scheme 18. Attempted Stepwise Formation of [7,6,5,5]-Fused Tetracycle *ent*-12 from Diazoester 49



temperature, only resulting in decomposition of the cyclopropane starting material.[17a,35] Without a method to construct the desired [6,7,5,5]-tetracyclic core of the norcembranoid diterpenes employing substrates derived from *cis*-1,3-cyclopentenediol analog ***ent*-43**, we returned to the initial route to explore alternative methods for the advancement of previously isolated epoxytetracycle **36** toward the polycyclic furanobutenolide-derived norcembranoid diterpene natural products.

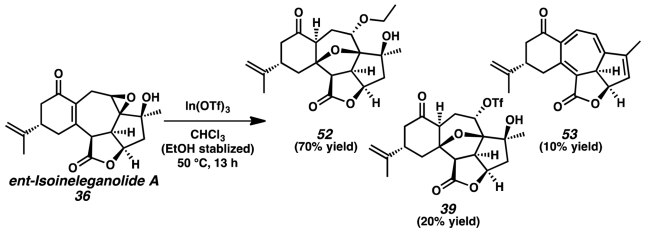
Although all attempts to effect the *syn*-facial 1,2-hydride shift within *ent*-isoineleganolide A (**36**) to provide *ent*-ineleganolide (***ent*-1**) or any 1,4-diketone product had failed (Scheme 19), we

Scheme 19. Originally Anticipated Completion of *ent*-Ineleganolide (*ent*-1)



sought to more thoroughly explore the reactivity of epoxide **36**. Having encountered the productive rearrangement of epoxytetracycle **36** to triflate **39** (see Scheme 12), the reactivity of epoxide **36** in the presence of indium(III) triflate on larger scale was investigated. To our surprise, simply switching the solvent from unstabilized $CDCl_3$ to $CHCl_3$, stabilized with 0.75% EtOH, caused triflate **39** to become a minor product (Scheme 20). Instead, ether **52** became the major product and was

Scheme 20. Reactivity of *ent*-Isoineleganolide A (37) with $In(OTf)_3$ in Stabilized $CHCl_3$



isolated in 70% yield,[36] with cycloheptatriene **53** as a third, minor product. Given the apparent propensity of the epoxide moiety within *ent*-isoineleganolide A (**36**) to undergo nucleophilic opening at the least hindered position, the potential to exploit this reactivity for the synthesis of the targeted norcembranoids was explored.

We quickly discovered that halogenated Lewis acids in nonpolar solvent systems containing a small amount to Lewis

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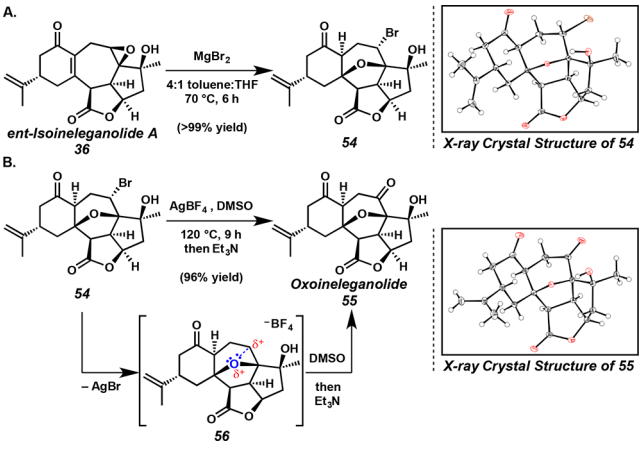
basic cosolvent could facilitate the opening of epoxide **36** with their halogen counterions.[37] Under optimized conditions, in a 4:1 mixture of toluene to THF, magnesium(II) bromide could be used to accomplish the formation of bromide **54** in quantitative yield (Scheme 21A). Bromide **54** proved to be a

Scheme 21. Formation of Requisite 1,4-Diketone Oxidation Pattern



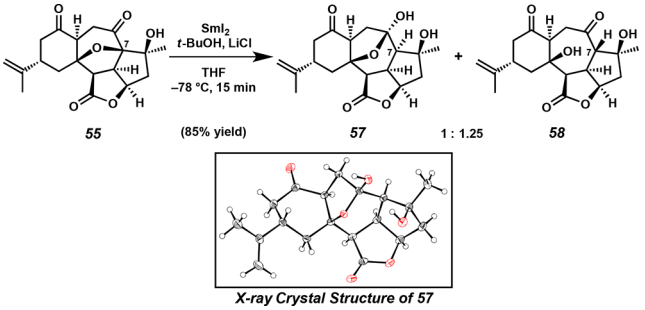
crystalline white solid whose relative and absolute configuration was unambiguously established by single-crystal X-ray diffraction, proving not only the stereochemical result of the expected S_n2 opening of the epoxide, but also the concomitant intramolecular oxa-Michael addition and construction of the transannular ether bridge.

Installation of the requisite 1,4-diketone oxidation pattern from bromide **54** would depend on the ability to oxidize the newly installed secondary halide. Toward this end, the Kornblum oxidation is most routinely used for the oxidation of a halide to the ketone oxidation state. This transformation, however, is largely limited to the oxidation of primary or benzylic halides to the corresponding aldehydes or benzylic ketones.[38] Fortunately, initial attempts to oxidize bromide **54** proved fruitful.[39] Optimized reaction conditions employing $AgBF_4$ in DMSO at 120 °C for 9 h provided ketopyran **55** in 96% yield (Scheme 21B). The isolation of ketopyran **55** in such high yield exemplifies the thermodynamic stability of the product, being formed under harsh, Lewis acidic conditions in the presence of a nucleophilic solvent. The stereochemical assignment of ketopyran **55** was unambiguously confirmed by single-crystal X-ray diffraction.

We hypothesize that the oxidation of secondary bromide **54** to ketopyran **55** is facilitated by the fused heterocyclic ring structure of the transannular ether. The reaction proceeds initially by abstraction of the halide by the silver(I) salt to generate intermediate carbocation **56**. The rigid conformation of pentacycle **56** positions the furyl oxygen bridge appropriately to allow for the donation of electron density into the vacant p-orbital of the secondary carbocation. The stabilization of cation **56** by distribution of the positive charge largely prevents nonproductive reaction pathways and decomposition, allowing the nucleophilic addition of DMSO to occur smoothly and, after the addition of Et_3N, the formation of the desired product in excellent yield. This hypothesis is supported by the failed Kornblum oxidation of the reduced substrate in which the vicinal hydroxyl group to the bromide cannot form the transannular ether bridge.[14a,40]

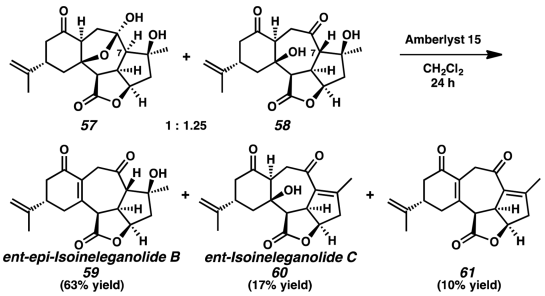
With the assembly of the desired 1,4-diketone skeleton complete (cf. **55**), the selective reductive opening of the furan bridge at the α-alkoxyketone bond was needed (Scheme 22).

Scheme 22. Chemoselective α-Alkoxyketone Reduction



The selective reduction of carbonyls oxidized at the α-position to the corresponding α-saturated carbonyl is routinely accomplished under single-electron-transfer conditions. We hypothesized that the rapid equilibration of the intermediate C(7) radical or intermediacy of an enolate would allow for the formation of the thermodynamically favorable *cis*-fused [7,5]-ring juncture. Chemoselective reduction of the ketopyran **55** was observed after exposure to freshly formed samarium(II) iodide in the presence of lithium chloride as an additive (Scheme 22).[41] The use of LiCl as an additive was essential for the high yield of this transformation, as the use of either H_2O or HMPA as an additive or the use of SmI_2 without an additive routinely furnished a complex mixture of products, including dehydrated forms of the desired intermediate. Under the optimized conditions employing lithium chloride, cleavage of the α-alkoxyketone afforded a nearly inseparable mixture of two compounds in an approximately 1.25:1 ratio. Initially, the identity of the minor component of the mixture was established by single-crystal X-ray diffraction as cyclic hemiketal **57**, which contained the desired α-stereochemical configuration of the newly formed C(7) methine. In addition, treatment of the mixture with Amberlyst 15 afforded a single stereoisomer of the desired enone product (i.e., **59**, Scheme 23) under acidic

Scheme 23. Selective Dehydration of Reduction Mixture



conditions in 63% yield. The extended reaction period required to accomplish the complete consumption of the starting material results in the formation of undesired enone *ent*-isoineleganolide C (**60**) and bisenone **61** as minor products.

The unambiguous assignment of hemiketal **57** paired with the formation of a single stereoisomer of enone **59** led to the assertion that both components of the SmI_2-reduction mixture (**57**, **58**) bore the correct α-stereochemistry at C(7) and were present as an equilibrium mixture by NMR analysis.[14a]

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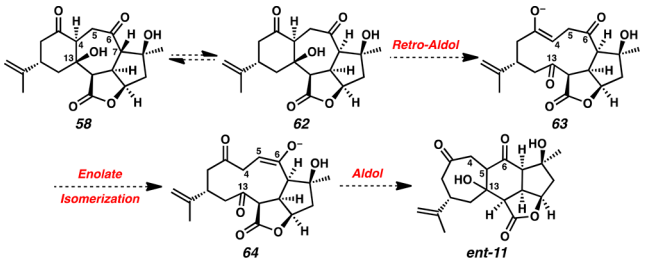
However, we have recently determined the X-ray structure of enone **59** and found that it bears the opposite β-stereochemistry at C(7) and clearly arose from the hydroxyketone component of the mixture (**58**). We present the ^{1}H NMR spectra of each component of the original mixture and the enone **59**. It is remarkable that the hydroxyketone **58** eliminates cleanly to enone **59**, while the hemiketal **57** fails to afford the isomeric enone product. Indeed, pure hydroxyketone **58** was readily converted completely to hemiketal **57** by treatment with 0.01 M potassium hydroxide in aqueous acetonitrile at room temperature over 30 min. The fact that this isomerization is so facile under weakly basic conditions may be attributed to the proximity of the hydroxyl group to the ketone α-proton in **58**. However, no such isomerization was observed under the acidic conditions of the subsequent elimination reaction.

With the successful samarium diiodide reduction products representing both hydroxyketone **58** and the isomeric hydroxyketone **62** (in its hemiketal form of **57**), we were encouraged to attempt the key aldol-based core isomerization to the scabrolide A ring system (Scheme 24 and Scheme 3B).

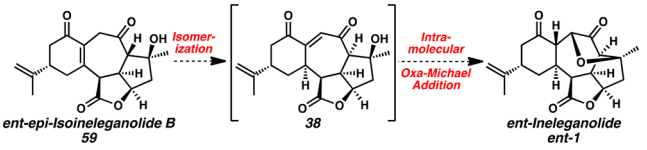
Scheme 24. Planned Core Isomerization of 57:58 Diol Mixture



Hemiketal **57** additionally represents a single stereoisomeric form of the desired retron **10** in the enantiomeric series (see Scheme 3) for the planned isomerization to access the [7,6,5,5]-tetracyclic norcembranoid diterpenes. Exposure of diol **58** to an appropriate base would induce a retroaldol from the isomeric hydroxyketone **62** to provide enolate **63**, which after isomerization to C(5)−C(6) enolate **64**, could undergo an aldol reaction to bond C(5) and C(13) to complete [7,6,5,5]-tetracycle ***ent*-11** (Scheme 24). Unfortunately, subjection of the mixture of hemiketal **57** and hydroxyketone **58** to amine base (e.g., Et_3N, $(i\text{-}Pr)_2NEt$) in protic and aprotic solvent failed to induce any reactivity. Alternatively, the use of hydroxide bases (e.g., NaOH, KOH) in H_2O or H_2O/MeOH blends resulted in the saponification of the lactone moiety.[42] Although the use of stronger bases (NaH, LHMDS, KHMDS) in THF at low temperature generally failed to induce any productive reactivity, the exposure of the diol mixture (**57**, **58**) to excess LDA at −78 °C effected the isomerization of configuration at C(4) and C(13), likely through the intended retroaldol−aldol pathway.[43] Although formation of [7,6,5,5]-diol ***ent*-11** has not yet been observed, we are optimistic that synthetic access to the [7,6,5,5]-norcembranoid diterpenes may still be achieved by this retroaldol−aldol core isomerization pathway.

With access to enone **59** established, we hypothesized that under olefin isomerization conditions, *ent-epi*-isoineleganolide B (**59**) could proceed through vinylogous diketone **38** after concomitant epimerization of configuration at C(7) and then undergo a spontaneous intramolecular oxa-Michael addition to complete the total synthesis of *ent*-ineleganolide (***ent*-1**, Scheme 25). Unfortunately, *ent-epi*-isoineleganolide B (**59**) proved to

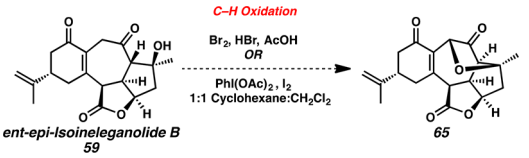
Scheme 25. Intended Completion of *ent*-Ineleganolide (*ent*-1) through Vinylogous Diketone 38



be a somewhat unstable, intractable intermediate. Exposure of enone **59** to protic acid-, protic base-, aprotic base-, and an assortment of transition metal-mediated as well as thermal olefin isomerization conditions failed to provide a single isolable product.[44]

Additionally, redox advancement of *ent-epi*-isoineleganolide B (**59**) proved unfortunately futile. Direct formation of the requisite dihydrofuranone ring by C−H oxidation through α-bromination[45] or under Suárez conditions[46] was complicated by the reactivity of the cyclohexenone system and the isopropenyl moiety and was ultimately unsuccessful (Scheme 26). Additionally, cyclohexenone **59** was unreactive to the

Scheme 26. Attempted Functionalization of *ent*-Isoineleganolide B (*ent*-9) by C−H Oxidation



conjugate reduction by the nucleophilic addition of hydride through transition metal catalysis and the 1,4-reduction could not be accomplished chemoselectively using samarium(II) iodide. Comparatively, the isomerization of enone **59** could not be facilitated by the 1,2-reduction of the cyclohexenone system as the selective reduction of the enone carbonyl could not be achieved in the presence of the cycloheptanone moiety.[47]

The empirical evidence surrounding *ent-epi*-isoineleganolide B (**59**) and the obstinate nature of productive reactivity suggested the barrier for isomerization of the enone system to the dihydrofuranone ring is a more complex transformation than simply assessing the thermodynamic equilibrium between a tetrasubstituted enone and trisubstituted vinylogous diketone (see Scheme 25). In order to assess the potential to accomplish the synthesis of *ent*-ineleganolide (***ent*-1**) from enone **59**, we turned to computational chemistry in order to evaluate the energy landscape of the proposed transformation. Supposing the ability to accomplish the epimerization of configuration at C(7), we focused to assessing the energy landscape of the isomerization from *ent*-isoineleganolide B (***ent*-9**) to *ent*-ineleganolide (***ent*-1**). On the basis of the conformation of *ent*-isoineleganolide A (**36**, Scheme 27A) and other intermediates, the conformation of *ent*-isoineleganolide B (***ent*-9**) would be analogously bisected across the central cycloheptenone (Scheme 27B). By continued analogy to the conformation of *ent*-isoineleganolide A (**36**), the cyclohexenone ring of *ent*-isoineleganolide B (***ent*-9**) would be in its most thermodynamically stable position when it has adopted a

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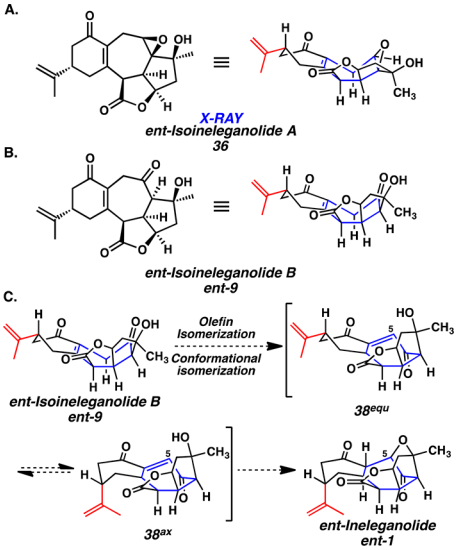
Scheme 27. Consideration of Three-Dimensional Structures of Late-Stage Intermediates



conformation in which the isopropenyl group is in the equatorial position.

Considering the three-dimensional conformation of *ent*-isoineleganolide B (***ent*-9**) in comparison to the conformation of *ent*-ineleganolide (***ent*-1**), observed by single-crystal X-ray diffraction during the initial isolation,[8] we need to not only effect the isomerization of the olefin from the enone system into a vinylogous diketone but also accomplish the conformational isomerization of the central cycloheptenone ring. This conformational isomerization would induce the proximity between C(5) and the tertiary hydroxyl group required for intramolecular oxa-Michael addition. Ultimate equilibration of the cyclohexanone ring into the chair conformation, placing the isopropenyl group in the axial position, would furnish *ent*-ineleganolide (***ent*-1**) in its observed, solid-state conformation.

In order to quantitatively assess the energy landscape of the intermediates along the proposed isomerization route toward *ent*-ineleganolide (***ent*-1**) from *ent*-isoineleganolide B (***ent*-9**), we performed a series of DFT ground-state energy computations in vacuo using the 6-311+G** basis set.[48] All ground-state energies were compared to the calculated ground-state energy of ineleganolide in its preferred conformation (***ent*-1^{ax}**), as determined on its initial isolation by single-crystal X-ray diffraction and confirmed herein by calculation of the ground state energies of the two cyclohexanone conformers (i.e., ***ent*-1^{ax}** vs ***ent*-1^{equ}**, Figure 3). The two conformers of *ent*-isoineleganolide B in its isolated form, ***ent*-9^{equ}** and ***ent*-9^{ax}**, were calculated to be higher in energy than the natural product (***ent*-1^{ax}**) by 0.8 and 2.1 kcal, respectively. This result implies that the most thermodynamically favorable conformation of *ent*-isoineleganolide B (***ent*-9**) is indeed closely related to the structure of *ent*-isoineleganolide A (**36**, see Scheme 27A vs Scheme 27B). This places the isopropenyl group of the cyclohexanone ring in the equatorial position in comparison to *ent*-ineleganolide (***ent*-1**), which finds increased thermodynamic stability with the saturated cyclohexanone moiety in the chair conformation, although the isopropenyl substituent is forced into the axial position.

Conformational isomerization of the central cycloheptenone within *ent*-isoineleganolide B provides two enones, ***ent*-9A^{equ}**

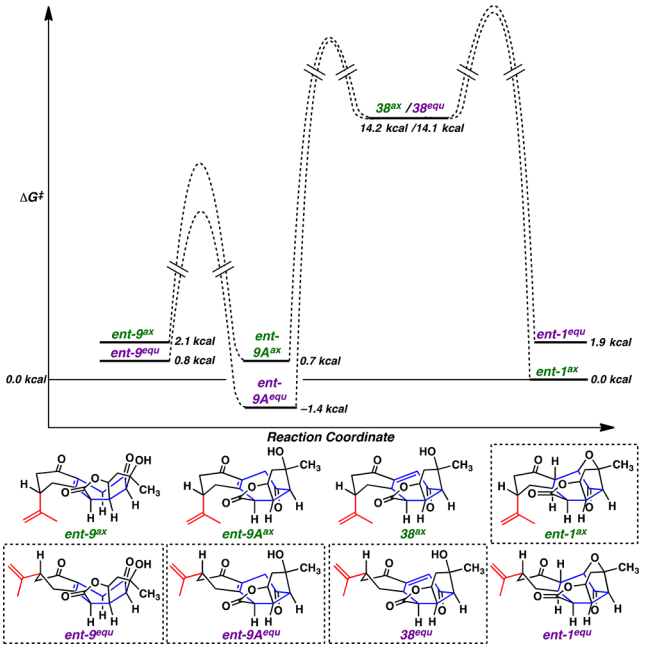


Figure 3. Free energy diagram based on computed ground-state energies.

and ***ent*-9A^{ax}**, that are both lower in energy than *ent*-isoineleganolide B in its isolated conformation. In fact, ***ent*-9A^{equ}** was calculated to be the most thermodynamically stable compound within the set of isomers evaluated. This conformational isomer closely resembles that of *ent*-ineleganolide (***ent*-1**) and would be correctly positioned for the construction of the dihydrofuranone ring by oxa-Michael addition after olefin isomerization

In order to convert *ent*-isoineleganolide B (***ent*-9**) to *ent*-ineleganolide (***ent*-1**), we would need to accomplish an olefin isomerization, proceeding through vinylogous diketone **38**. Computation of the ground-state energies of the two conformational isomers of conjugated diketone **38^{equ}** and **38^{ax}** revealed that this intermediate is significantly higher in energy than either *ent*-isoineleganolide B (***ent*-9**) or *ent*-ineleganolide (***ent*-1**). The energy gap between vinylogous diketone **38** and the highest energy conformation of *ent*-isoineleganolide B is calculated to be 12.0 kcal/mol. Considering the activation energy for this isomerization will make the energy cost even larger, decomposition of the substrate would likely occur before the direct conversion of *ent*-isoineleganolide B (***ent*-9**) to *ent*-ineleganolide (***ent*-1**) by olefin isomerization through vinylogous diketone **38**. Indeed, the lack of empirical evidence for the isolation of or equilibration to either ***ent*-9A^{equ}** or ***ent*-9A^{ax}** throughout our synthetic explorations and propensity of the isolated *ent-epi*-isoineleganolide B (**59**) to undergo decomposition rather than productive isomerization, epimerization, or oxidation implies that the energy barrier to interconvert between the conformational isomers of *ent*-isoineleganolide B (***ent*-9**) is greater than the energy required for the decomposition of the substrate.

CONCLUSIONS

The convergent, enantio- and diastereoselective de novo synthesis of the [6,7,5,5]-core of ineleganolide presented herein represents the first synthetic method that allows access to the complete carbocyclic scaffold of any member of the

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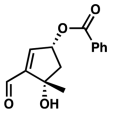
polycyclic furanobutenolide-derived norcembranoid diterpenes. The synthetic strategy was designed to convergently build the [6,7,5,5]-tetracycle of ineleganolide (**1**) and then accomplish divergent access to the isomerized carbon skeletons of horiolide (**2**), kavaranolide (**3**), sinulochmodin C (**4**), scabrolide B (**5**), scabrolide A (**6**), and yonarolide (**7**). The assembly of this tetracyclic scaffold was accomplished using two independent fragments. The western carboxylic acid fragment was derived from (*R*)-(−)-carvone and contained the requisite enantioenriched remote stereocenter possessing the isopropenyl group that characteristically decorates the norcembranoid diterpenes. The complementary eastern diol was constructed using a palladium-catalyzed asymmetric allylic alkylation to enantioselectively form a fully substituted tertiary ether center. A tandem intramolecular cyclopropanation−Cope cyclization cascade enabled the formation of the central cycloheptane ring. Synthetic advancement facilitated the construction of the first synthetic isomers and analogues of ineleganolide. Although the synthesis of the furanobutenolide-derived norcembranoid diterpene natural products themselves remains elusive, efforts toward that end continue, guided by computational evaluation, and are focused on the development of alternative synthetic pathways to complete the asymmetric total synthesis of ineleganolide (**1**).

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)[49] and stirred with a Teflon-coated magnetic stirring bar. Commercially available reagents were used as received. Et_3N was distilled from calcium hydride immediately prior to use. MeOH was distilled from magnesium methoxide immediately prior to use. Purified H_2O was obtained using a Barnstead NANOpure Infinity UV/UF system. Molecular sieves (4Å) were oven-dried at 120 °C for a minimum of 24 h and cooled in a desiccator to ambient temperature immediately prior to use. Hydroxymethyl-*cis*-1,3-cyclopentenediol **29**,[18] TEMPO·BF_4,[26] (*R*)-desmethylcarvone ((***R*****)-30**),[25] *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, **33**),[50] and Cu(tbs)$_2$, **51**)[34] 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. ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 600 (600 and 151 MHz, respectively), Varian Inova 500 (500 and 126 MHz, respectively), or Bruker AV III HD spectrometer equipped with a Prodigy liquid nitrogen temperature cryoprobe (400 and 101 MHz, respectively) or a Varian Mercury 300 spectrometer (300 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). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Infrared (IR) spectra were recorded on a PerkinElmer Paragon 1000 spectrometer and are reported as 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 (Multi-Mode: 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.



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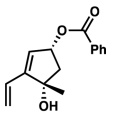
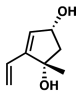


67

Diene ***67***. To a pale yellow solution of diol **29** (241 mg, 0.97 mmol, 1.00 equiv) in CH_2Cl_2 (49 mL) at 0 °C (ice/H_2O bath) was added Dess−Martin periodinane (DMP, 823 mg, 1.94 mmol, 2.00 equiv) as a solid in one portion. After 3 h, the off-white heterogeneous reaction mixture was removed from the bath and allowed to warm to ambient temperature (ca. 23 °C). After an additional 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 $Na_2S_2O_3$ (100 mL) in one portion. The biphasic mixture was allowed to stir for 10 min and subsequently poured into saturated $NaHCO_3$ (70 mL). The organics were separated, and the aqueous layer was extracted with Et_2O (3 × 70 mL). The combined organic layers were washed with brine (50 mL), dried quickly over $MgSO_4$, filtered, and concentrated in vacuo to provide crude aldehyde **66**, which was immediately used without further purification.

To a round-bottom flask in a N_2-filled glovebox were charged Ph_3PMeBr (1.040 g, 2.91 mmol, 3.00 equiv) and KO-*t*-Bu (294 mg, 2.62 mmol, 2.70 equiv) as solids followed by THF (97 mL). The bright yellow reaction mixture was then sealed with a rubber septum, removed from the glovebox, and placed under an argon atmosphere with stirring. After 2 h, a solution of crude aldehyde **66** in THF (3.00 mL) was added dropwise, causing the reaction mixture to become dark orange-brown. After 1.5 h, the consumption of starting material was complete as determined by TLC (3:7 EtOAc/hexanes eluent). The reaction was poured onto a mixture of H_2O (90 mL) and Et_2O (30 mL). The organics were separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude dark brown residue was purified by silica gel column chromatography (40% Et_2O in hexanes eluent) to afford diene **67** (236 mg, >99% yield) as a pale yellow oil: R_f = 0.30 (2:3 Et_2O/hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 8.04−7.99 (m, 2H), 7.56−7.51 (m, 1H), 7.41 (dddd, *J* = 7.6, 6.8, 1.5, 0.9 Hz, 2H), 6.35 (ddt, *J* = 17.8, 11.3, 0.7 Hz, 1H), 5.92 (d, *J* = 2.3 Hz, 1H), 5.80 (ddt, *J* = 17.8, 1.5, 0.6 Hz, 1H), 5.75−5.70 (m, 1H), 5.31 (ddd, *J* = 11.4, 1.6, 0.7 Hz, 1H), 2.73 (dd, *J* = 14.0, 7.3 Hz, 1H), 2.26 (dq, *J* = 6.6, 3.9, 3.0 Hz, 1H), 2.16 (ddd, *J* = 14.0, 4.7, 0.7 Hz, 1H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.5, 151.2, 133.1, 130.3, 129.7, 129.1, 128.4, 127.0, 119.2, 81.1, 76.0, 49.3, 26.9; IR (neat film, NaCl) 3447, 2973, 1714, 1451, 1355, 1315, 1271, 1177, 1111, 1070, 1026, 954, 858, 712 cm^{-1}; HRMS (APCI) *m*/*z* calc'd for $C_{15}H_{15}O_2$ $[M - OH]^+$ 227.1067, found 227.1064; $[\alpha]_D^{25.0}$ +126.9 (*c* 3.850, $CHCl_3$).



***ent*-18**

Diol ***ent*-18**. To a pale yellow solution of diene **67** (2.04 g, 8.33 mmol, 1.00 equiv) in distilled MeOH (167 mL) was added NaOH (16.7 mmol, 2.00 equiv) as a 0.50 M solution in distilled MeOH quickly dropwise over 5 min. After 14 h, the consumption of starting material was complete as determined by TLC (2:3 Et_2O/hexanes eluent). The reaction was then concentrated to less than one-half of the original volume (ca. 70 mL) and then poured onto H_2O (150 mL). This homogeneous aqueous mixture was then extracted with 1:1 $CHCl_3$/*i*-PrOH (5 × 200 mL). The combined organic layers were dried over Na_2SO_4 for 1 h, filtered, and concentrated in vacuo. The crude off-white solid was then adsorbed onto Celite (6.0 g) and purified by silica gel column chromatography (75% EtOAc in hexanes eluent) to afford diol ***ent*-18** (1.11 g, 85% yield) as an amorphous

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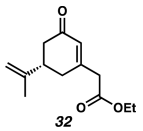
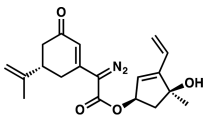
white solid: R_f = 0.13 (1:5 EtOAc/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (dd, J = 17.8, 11.3, 1H), 5.82 (d, J = 2.1, 1H), 5.73 (dd, J = 17.9, 1.7, 1H), 5.26 (dd, J = 11.2, 1.7, 1H), 4.65 (dd, J = 11.5, 5.1, 1H), 2.54 (dd, J = 13.6, 6.8, 1H), 1.85 (app dd, J = 13.6, 4.8, 2H), 1.68 (d, J = 6.6, 1H), 1.40 (s, 3H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 149.5, 131.3, 129.5, 118.6, 81.3, 73.0, 53.1, 26.8; IR (neat film, NaCl) 3287, 3252, 2968, 2930, 2873, 1587, 1481, 1445, 1370, 1341, 1316, 1124, 1088, 1056, 1032, 987, 945, 926 cm^{-1}; HRMS (EI+) m/z calcd for $C_8H_{12}O_2$ $[M^{\bullet}]^+$ 140.0837, found 140.0859; $[\alpha]_D^{25.0}$ +73.4 (c 0.600, MeOH).



32

Ethyl Ester ***32***. To a flame-dried 250 mL round-bottom flask in a nitrogen-filled glovebox was charged anhydrous $CeCl_3$ (3.60 g, 14.6 mmol, 2.00 equiv). The flask was sealed with a rubber septum, removed from the glovebox, placed under vacuum, and heated in an oil bath to 140 °C with vigorous stirring.[51] After 12 h the flask was removed from the oil bath, allowed to cool to ambient temperature (ca. 23 °C), placed under an atmosphere of argon, and charged with THF (49 mL). After 3.5 h, the reaction was cooled to −78 °C (*i*-PrOH/dry ice bath). (*R*)-Desmethylcarvone ((***R***)-**30**, 994 mg, 7.30 mmol) was then added as a solution in THF (7.3 mL) and stirred for 1 h. Simultaneously, in a separate flask, to a solution of LDA (0.80 M in THF, 2.22 equiv) at −78 °C was added anhydrous EtOAc (1.47 mL, 15.0 mmol, 2.06 equiv) as a solution in THF (10.0 mL) dropwise, forming a solution of lithium enolate **31**. After 40 min, to the solution of enone (***R***)-**30** was added the solution of metal enolate **31** dropwise via cannula transfer with an overpressure of argon over 1 h. Exactly 3 h after the completion of addition, the reaction was quenched at temperature with saturated NH_4Cl (24 mL) and warmed slowly to ambient temperature (ca. 23 °C) overnight. The reaction mixture was then filtered through a Celite plug, washing with 100% Et_2O. To the resulting solvent mixture was added H_2O (80 mL), and the aqueous layer was then extracted with Et_2O (2 × 120 mL). The combined organic layers were washed with brine (60 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The resultant crude orange-brown oil (1.64 g, >99% yield) was carried on without further purification.

To a solution of intermediate allylic alcohol (408 mg, 1.82 mmol) in CH_3CN (18 mL) was added TEMPO·BF_4 (664 mg, 2.73 mmol, 1.5 equiv) as a solid in one portion with stirring. Consumption of starting material was complete after 12 h, as determined by TLC (3:2 Et_2O/hexanes eluent), and the reaction was diluted with Et_2O (125 mL), washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude orange-red oil was purified by silica gel column chromatography (40% Et_2O in hexanes eluent) to afford cyclohexenone ester **32** (275 mg, 68% yield) as an orange-tan oil: R_f = 0.26 (3:2 Et_2O/hexanes eluent); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (s, 1H), 4.79 (s, 1H), 4.75 (s, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.22 (s, 2H), 2.68 (ddd, J = 18.2, 9.5, 4.5 Hz, 1H), 2.49 (ddd, J = 16.3, 3.7, 1.1 Hz, 1H), 2.46−2.33 (m, 2H), 2.33−2.24 (m, 1H), 1.73 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.1, 169.2, 156.3, 146.0, 128.3, 110.8, 61.2, 43.2, 42.0, 41.7, 34.7, 20.4, 14.0; IR (neat film, NaCl) 2979, 1735, 1672, 1415, 1369, 1329, 1294, 1248, 1176, 1029, 891 cm^{-1}; HRMS (MM: ESI-APCI) m/z calcd for $C_{13}H_{19}O_3$ $[M + H]^+$ 223.1329, found 223.1326; $[\alpha]_D^{25.0}$ +40.3 (c 3.400, $CHCl_3$).



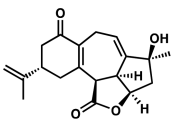
ent-16

*α-Diazoester ent-***16**. To a stirred solution of ethyl ester **32** (2.07 g, 9.32 mmol, 1.00 equiv) in MeOH (31 mL) and H_2O (31 mL) was added K_2CO_3 (5.16 g, 37.3 mmol, 4.00 equiv). After 7 h, the consumption of starting material was complete as determined by TLC (2:3 Et_2O/hexanes eluent). The reaction mixture was cooled to 0 °C (ice/H_2O bath) and the pH was adjusted to between 1 and 2 by the careful addition of aqueous 1 N HCl (CAUTION: Vigorous gas evolution!). The reaction mixture was then poured onto a mixture of EtOAc (200 mL) and H_2O (100 mL). The organics were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude dark orange oil of carboxylic acid ***ent*-17** (1.81 g, >99% yield) was carried on without further purification.

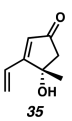
To a stirred solution of diol ***ent*-18** (119 mg, 0.85 mmol, 1.00 equiv) in CH_2Cl_2 (28 mL) were added a portion of crude carboxylic acid ***ent*-17** (330 mg, 1.70 mmol, 2.00 equiv) and EDC·HCl (326 mg, 1.70 mmol, 2.00 equiv). The orange reaction mixture was cooled to 0 °C (ice/H_2O bath), at which time DMAP (21 mg, 0.17 mmol, 0.20 equiv) was added in a single portion. After 30 min, the dark red-orange reaction mixture was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After 1 h, the consumption of starting material was complete as determined by TLC (3:1 EtOAc/hexanes eluent). The reaction was quenched by the addition of 0.50 N HCl (8.0 mL) quickly dropwise with vigorous stirring. After 10 min, the heterogeneous solution was poured onto a mixture of EtOAc (100 mL) and H_2O (40 mL). The organics were separated and washed with 0.50 N HCl (20 mL) followed by 5 wt % K_2CO_3 (3 × 30 mL), brine (30 mL), and saturated NH_4Cl (30 mL). The organics were then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude dark brown-orange oil of intermediate ester (269 mg, 0.85 mmol, >99% yield) was carried on without further purification.

Additionally, the combined K_2CO_3 washes were cooled to 0 °C (ice/H_2O bath), and the pH was adjusted to between 1 and 2 by the careful addition of aqueous 1 N HCl (CAUTION: Vigorous gas evolution!). The aqueous mixture was extracted with EtOAc (4 × 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo, providing a recovered portion (60 mg) of excess carboxylic acid ***ent*-17**.

To a solution of crude ester (269 mg, 0.85 mmol, 1.00 equiv) in CH_3CN (8.5 mL) in the dark was added *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, **33**, 226 mg, 0.94 mmol, 1.10 equiv) as a solid in one portion. The dark orange homogeneous reaction mixture was cooled to 0 °C (ice/H_2O bath). Et_3N (0.36 mL, 2.55 mmol, 3.00 equiv) was then added slowly dropwise. After 6 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 EtOAc (20 mL), removed from the cooling bath, and allowed warm to ambient temperature (ca. 23 °C). The reaction mixture was then concentrated in vacuo. The crude tan solid was the adsorbed onto Celite (2.0 g) and purified by silica gel column chromatography (20% EtOAc in CH_2Cl_2 eluent) to afford *α*-diazoester ***ent*-16** (218 mg, 75% yield from diol ***ent*-18**) as a dark yellow oil: R_f = 0.26 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.39 (d, J = 2.0 Hz, 1H), 6.32 (dd, J = 17.8, 11.4 Hz, 1H), 5.82 (s, 1H), 5.78 (s, 1H), 5.62 (ddd, J = 7.2, 4.8, 2.2 Hz, 1H), 5.34 (dd, J = 11.4, 1.6 Hz, 1H), 4.86 (t, J = 1.4 Hz, 1H), 4.80 (s, 1H), 2.78−2.71 (m, 1H), 2.70−2.64 (m, 2H), 2.53 (ddd, J = 16.1, 3.7, 1.4 Hz, 1H), 2.43 (ddd, J = 17.4, 10.9, 2.2 Hz, 1H), 2.34 (dd, J = 16.3, 13.0 Hz, 1H), 2.05 (dd, J = 14.0, 4.8 Hz, 1H), 1.78 (s, 3H), 1.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 197.2, 162.5, 151.7, 146.6, 145.9, 128.9, 126.0, 120.2, 119.6, 111.5, 80.8, 76.9, 67.3, 49.2, 41.8, 41.6, 31.7, 27.1, 20.5; IR (neat film, NaCl) 3406, 2971, 2102, 1708, 1645, 1579, 1377, 1328, 1250, 1222, 1140, 1061, 992, 952, 893, 744 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{19}H_{23}O_4N_2$ $[M + H]^+$ 343.1659, found 343.1634; $[\alpha]_D^{25.0}$ +233.5 (c 5.470, $CHCl_3$).



34



35

Diene ***34*** *and Enone* ***35***. To a stirred solution of diazoester ***ent*-16** (630 mg, 1.84 mmol, 1.00 equiv) in CH_2Cl_2 (184 mL) in a nitrogen-filled glovebox was added Rh_2OAc_4 (8 mg, 0.018 mmol, 0.01 equiv) at ambient temperature (ca. 30 °C). After 30 min, the consumption of

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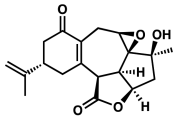
starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The reaction mixture was then concentrated in vacuo, and the yellow solid was purified by silica gel column chromatography (20% EtOAc in CH_2Cl_2 eluent) to afford diene **34** (306 mg, 53% yield) as a crystalline pale yellow solid and cyclopentenone **35** (89 mg, 35% yield) as an amorphous bright yellow solid.

Diene ***34***. Colorless, translucent X-ray quality crystals were obtained by slow diffusion of pentane into a solution of diene **34** in Et_2O: mp 150−153 °C: R_f = 0.38 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.19 (dt, J = 8.6, 3.5 Hz, 1H), 4.81 (dd, J = 4.5, 3.9 Hz, 1H), 4.76 (td, J = 1.4, 0.7 Hz, 1H), 4.67 (td, J = 1.3, 0.7 Hz, 1H), 3.83−3.77 (m, 1H), 3.63−3.52 (m, 2H), 3.32−3.21 (m, 1H), 2.74−2.64 (m, 2H), 2.61 (ddd, J = 16.5, 4.0, 1.7 Hz, 1H), 2.44 (d, J = 15.5 Hz, 1H), 2.29 (dd, J = 16.5, 12.6 Hz, 1H), 2.15−2.06 (m, 1H), 1.95 (dd, J = 15.4, 4.0 Hz, 1H), 1.71 (dt, J = 1.3, 0.6 Hz, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.2, 172.9, 149.2, 148.8, 146.3, 133.5, 128.1, 110.5, 82.2, 78.1, 49.6, 47.0, 45.9, 42.7, 40.0, 36.4, 27.8, 22.6, 20.8; IR (neat film, NaCl) 3435, 2923, 2853, 1761, 1661, 1443, 1377, 1263, 1148, 1106 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{19}H_{23}O_4$ $[M + H]^+$ 315.1596, found 315.1608; $[\alpha]_D^{25.0}$ +39.6 (c 0.680, $CHCl_3$).

Enone ***35***: R_f = 0.18 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.59 (dd, J = 17.7, 11.2 Hz, 1H), 6.10 (d, J = 17.7 Hz, 1H), 6.03 (s, 1H), 5.73 (d, J = 11.1 Hz, 1H), 2.62 (d, J = 2.3 Hz, 2H), 1.56 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.4, 174.7, 128.5, 127.7, 126.2, 77.1, 53.2, 27.4; IR (neat film, NaCl) 3400, 2970, 2927, 1687, 1599, 1408, 1373, 1261, 1233, 1195, 1064, 952, 864, 801 cm^{-1}; HRMS (EI+) m/z calcd for $C_8H_{10}O_2$ $[M^\bullet]^+$ 138.0681, found 138.0674; $[\alpha]_D^{25.0}$ +71.4 (c 0.900, $CHCl_3$).

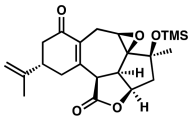
ent-18

*Diol ent-***18**. To a stirred solution of enone **35** (50 mg, 0.36 mmol, 1.00 equiv) in THF (5.0 mL) at −78 °C (*i*-PrOH/dry ice bath) was added DIBAL (540 μL, 1 M in THF, 1.50 equiv) slowly dropwise. After 30 min, 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 $Na_2SO_4{\cdot}(H_2O)_n$ (made by stirring anhydrous Na_2SO_4 with H_2O for 30 min prior to use). The reaction vessel was immediately removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C) with stirring. After 15 min, the reaction was filtered and concentrated in vacuo, and the crude white solid was purified by silica gel column chromatography (75% EtOAc in hexanes eluent) to afford diol ***ent*-18** (6 mg, 12% yield) as an amorphous white solid and as a single diastereomer: characterization data match those reported above.



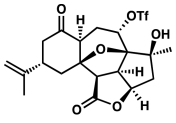
***ent*-Isoineleganolide A**
36

*ent-Isoineleganolide A (***36***)*. To a pale yellow stirred solution of diene **34** (100 mg, 0.32 mmol, 1.00 equiv) in a vial open to air in benzene (10.7 mL) was added $VO(acac)_2$ (0.9 mg, 0.0032 mmol, 0.01 equiv). After 5 min, to this dark green solution was added *tert*-butyl hydroperoxide (TBHP, 72 μL, 0.036 mmol, 1.10 equiv) as a 5 M solution in decane dropwise causing the reaction to immediately become deep ruby red. After 45 min, the reaction had lost all red color and become pale yellow. The consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The reaction was concentrated in vacuo and the crude tan solid was purified by silica gel column chromatography (25% EtOAc in CH_2Cl_2 eluent) to afford epoxide **36** (89 mg, 89% 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 **36** in EtOAc: mp 272−275 °C; R_f = 0.22 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.84−4.80 (m, 2H), 4.74 (s, 1H), 3.75 (dd, J = 19.1, 6.1 Hz, 1H), 3.50−3.46 (m, 1H), 3.42−3.35 (m, 2H), 3.26 (ddd, J = 17.3, 3.9, 2.0 Hz, 1H), 2.78 (ddt, J = 14.3, 10.7, 3.9 Hz, 1H), 2.66 (ddd, J = 16.6, 3.9, 1.9 Hz, 1H), 2.48 (dt, J = 19.1, 2.0 Hz, 1H), 2.41 (m, 1H), 2.36 (m, 1H), 2.27 (dd, J = 16.5, 13.4 Hz, 1H), 2.10 (ddd, J = 17.3, 11.0, 3.8 Hz, 1H), 1.76 (d, J = 1.3 Hz, 3H), 1.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.8, 172.1, 148.7, 146.4, 129.9, 110.6, 79.9, 75.0, 70.2, 54.4, 50.2, 45.8, 43.6, 42.6, 39.8, 37.3, 26.7, 22.4, 20.9; IR (neat film, NaCl) 3479, 2965, 1767, 1647, 1625, 1369, 1233, 1154, 1102, 992, 975, 907 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545, found 331.1540; $[\alpha]_D^{25.0}$ +161.3 (c 0.900, $CHCl_3$).



37

Silyl Ether ***37***. To a stirred solution of isoineleganolide A (**36**, 3 mg, 0.009 mmol, 1.00 equiv) in CH_2Cl_2 (0.25 mL) at −78 °C (*i*-PrOH/dry ice bath) was added Et_3N (50 μL, 0.36 mmol, 40.0 equiv) dropwise. After 5 min, TMSOTf (8 μL, 0.045 mmol, 5.00 equiv) was added slowly dropwise. After 15 min, 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 $NaHCO_3$ (50 μL), removed from the cooling bath, and allowed to warm to ambient temperature (ca. 23 °C). The reaction mixture was then filtered through a pad of SiO_2 (100% EtOAc eluent). The combined organics were then concentrated in vacuo to afford silyl ether **37** (3 mg, >99% yield) as an amorphous white solid: R_f = 0.50 (EtOAc eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.83 (qd, J = 4.0, 3.5, 1.5 Hz, 2H), 4.74 (d, J = 1.6 Hz, 1H), 3.76 (dd, J = 19.1, 6.2 Hz, 1H), 3.51−3.45 (m, 1H), 3.43−3.35 (m, 2H), 3.27 (ddd, J = 17.5, 3.9, 1.9 Hz, 1H), 2.79 (td, J = 14.4, 3.9 Hz, 1H), 2.67 (ddd, J = 16.6, 3.9, 1.9 Hz, 1H), 2.56−2.33 (m, 3H), 2.28 (dd, J = 16.6, 13.3 Hz, 1H), 2.14−2.05 (m, 1H), 1.77 (s, 3H), 1.36 (s, 3H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 198.8, 172.1, 148.7, 146.4, 129.9, 110.6, 79.9, 75.0, 70.2, 54.5, 50.2, 45.8, 43.7, 42.6, 39.8, 37.3, 26.8, 22.4, 20.9, 1.2; IR (neat film, NaCl) 2962, 1770, 1665, 1380, 1262, 1101, 1024, 799 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{22}H_{29}O_5Si$ $[(M + H) - H_2]^+$ 401.1784, found 401.1798; $[\alpha]_D^{25.0}$ +1.4 (c 0.150, $CHCl_3$).



39

Triflate ***39***. To a stirred solution of *ent*-isoineleganolide A (**36**, 5 mg, 0.015 mmol, 1.00 equiv) in $CDCl_3$ (0.60 mL) at ambient temperature (ca. 23 °C) was added $In(OTf)_3$ (20 mg, 0.036 mmol, 2.40 equiv) as a solid in one portion. The white suspension was stirred for 5 min and then introduced to a preheated 50 °C bath. After 12 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The reaction was directly purified by silica gel column chromatography (10% EtOAc in CH_2Cl_2 eluent) to provide triflate (**39**, 4 mg, 80% yield) as an amorphous white solid: R_f = 0.78 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 5.31 (dd, J = 10.2, 6.2 Hz, 1H), 4.93 (dt, J = 9.2, 7.5 Hz, 1H), 4.86 (br s, 1H), 4.82 (s, 1H), 3.58 (t, J = 9.1 Hz, 1H), 3.25 (d, J = 9.4 Hz, 1H), 3.14 (dd, J = 13.5, 6.5 Hz, 1H), 2.73 (d, J = 5.9 Hz, 1H), 2.73 (tt, J = 13.1, 3.7 Hz, 1H), 2.59 (ddd, J = 12.9, 3.8, 2.1 Hz, 1H), 2.40 (dd, J = 13.2, 7.9 Hz, 1H), 2.34 (t, J = 13.2 Hz, 1H), 2.27 (dd, J = 12.9, 14.7 Hz, 1H), 2.21 (br s, 1H), 2.16 (dd, J = 13.5, 7.0 Hz, 1H), 2.02 (ddd, J = 14.7, 3.5, 2.3 Hz, 1H), 1.76 (s, 3H), 1.71 (ddd, J = 13.2, 10.1, 6.0 Hz, 1H), 1.35 (d, J = 1.2 Hz, 3H); ^{19}F NMR ($CDCl_3$, 376 MHz) −74.8 ppm; ^{13}C NMR ($CDCl_3$, 101 MHz) δ 204.8, 174.6, 145.6, 111.6, 94.0, 89.6, 79.0, 77.4, 77.1, 54.9, 54.6, 48.1, 46.4, 45.4, 41.3, 36.3, 26.3, 24.3, 20.3, where signal for the CF_3 group of **39** was not observed directly in the ^{13}C NMR spectrum, but was observed at 118.3 ppm and correlated with the ^{19}F signal at −74.8 ppm in a ^{19}F−^{13}C HSQC experiment with ^{19}F detection at 376 MHz.); (IR (neat film, NaCl) 3485, 2963, 1767,

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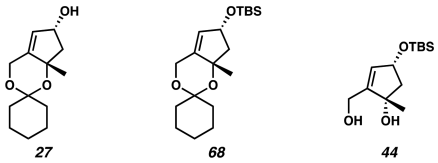
1721, 1410, 1260, 1243, 1209, 1142, 1034, 926, 798 cm^{-1}; HRMS (EI +) *m/z* calcd for $C_{20}H_{23}F_3O_8S$ $[M + H]^+$ 481.1138, found 481.1147; $[\alpha]_D^{25.0}$ +10.4 (*c* 0.100, $CHCl_3$).

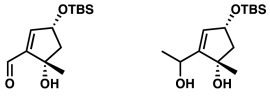


27 68 44

Diol **44**. To a pale yellow solution of cyclopentenone **26** (918 mg, 4.13 mmol, 1.00 equiv) in THF (41 mL) at −78 °C (*i*-PrOH/dry ice bath) was added a solution of DIBAL (1.47 mL, 8.26 mmol, 2.00 equiv) in THF (8.3 mL) slowly dropwise over 15 min. After 30 min, the golden reaction mixture was removed from the bath and allowed to warm slowly. After an additional 30 min, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/hexanes eluent), and the reaction mixture was cooled to 0 °C (ice/H_2O bath). The reaction was subsequently quenched with a 1:1 solution of saturated aqueous NH_4Cl and saturated aqueous Rochelle's salt (40 mL) dropwise, vigorously evolving gas on the first drops. The mixture was then diluted with CH_2Cl_2 (250 mL) and H_2O (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide crude allylic alcohol **27** (0.848 g, >99% yield), which was used without further purification.

To a stirred solution of crude allylic alcohol **27** (880 mg, 3.92 mmol, 1.00 equiv) in CH_2Cl_2 (39 mL) at 0 °C (ice/H_2O bath) was added Et_3N (1.09 mL, 7.84 mmol, 2.00 equiv). After 15 min, TBSOTf (0.99 mL, 4.31 mmol, 1.10 equiv) was added dropwise. After 30 min, the consumption of starting material was complete as determined by TLC (2:3 Et_2O/hexanes eluent). The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with H_2O (50 mL). The aqueous was extracted with CH_2Cl_2 (2 × 70 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford intermediate silyl ether alcohol **68** (1.33 g, >99% yield), which was used without further purification.

To a flask containing silyl ether **68** (1.33 g, 3.92 mmol, 1.00 equiv) were added MeOH (79 mL) and $HC(OMe)_3$ (3.86 mL, 35.3 mmol, 9.00 equiv). The reaction mixture was cooled to 0 °C (ice/H_2O bath) with stirring, at which time the addition of fumaric acid (1.14 g, 9.80 mmol, 2.50 equiv) was accomplished in one portion. After 10 min, the reaction was removed from the cold bath and immediately introduced to a preheated 35 °C oil bath. After 9 h, the consumption of starting material was complete as determined by TLC (2:3 Et_2O/hexanes eluent), and the reaction was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). The reaction mixture was diluted with EtOAc (150 mL) and poured onto saturated $NaHCO_3$ (125 mL). The organics were separated, and the aqueous layer was extracted with EtOAc (2 × 125 mL). The combined organic layers were washed with brine (100 mL), dried over $MgSO_4$ for 2 min, filtered, and concentrated in vacuo to generate a yellow oil. The crude residue was then purified by silica gel column chromatography (50% EtOAc in hexanes eluent) to afford diol **44** (841 mg, 83% yield) as a pale yellow oil: R_f = 0.27 (1:1 EtOAc/hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.60 (q, *J* = 1.7 Hz, 1H), 4.59 (ddt, *J* = 6.7, 4.7, 1.9 Hz, 1H), 4.30 (dt, *J* = 14.6, 1.7 Hz, 1H), 4.19 (dt, *J* = 15.0, 1.6 Hz, 1H), 3.67 (s, 2H), 2.38 (dd, *J* = 13.4, 6.9 Hz, 1H), 1.86 (dd, *J* = 13.4, 4.6 Hz, 1H), 1.26 (s, 3H), 0.86 (s, 9H), 0.05 (app d, *J* = 2.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 150.5, 129.2, 80.9, 73.6, 58.4, 52.4, 26.3, 26.0, 18.3, −4.6, −4.6; IR (neat film, NaCl) 3367, 2929, 2857, 1472, 1362, 1256, 1089, 1017, 939, 901, 835, 776 cm^{-1}; HRMS (FAB +) *m/z* calcd for $C_{13}H_{25}O_3Si$ $[(M + H) - H_2]^+$ 257.1573, found 257.1569; $[\alpha]_D^{25.0}$ +42.4 (*c* 10.550, $CHCl_3$).



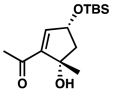
69 45

Allylic Alcohol **45**. To a stirred solution of diol **44** (187 mg, 0.72 mmol, 1.00 equiv) in CH_2Cl_2 (36 mL) at 0 °C (ice/H_2O bath) was added DMP (611 mg, 1.44 mmol, 2.00 equiv) as a solid in a single portion. After 30 min, the reaction vessel was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After an additional 2.5 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 $Na_2S_2O_3$ (50 mL) with vigorous stirring. After 10 min, the reaction was diluted with CH_2Cl_2 (50 mL) and poured onto saturated aqueous $NaHCO_3$ (75 mL). The organics were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 80 mL). The combined organics were dried quickly over $MgSO_4$ (<2 min), filtered, and concentrated in vacuo to afford crude aldehyde **69** (187 mg >99% yield), which was carried on without further purification.

To a stirred solution of crude aldehyde **69** (187 mg, 0.72 mmol, 1.00 equiv) in Et_2O (4.9 mL) at −15 °C (ice/MeOH bath) was added MeLi (1.92 mL, 1.5 M in Et_2O, 4.00 equiv) quickly dropwise. After 1.5 h, an additional portion of MeLi (0.96 mL, 1.5 M in Et_2O, 2.00 equiv) was added quickly dropwise, and the reaction vessel was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After an additional 1.5 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc/hexanes eluent). The reaction was quenched by the careful addition of saturated aqueous NH_4Cl (15 mL, CAUTION: Vigorous gas evolution!) with vigorous stirring. The biphasic reaction mixture was diluted with Et_2O (60 mL) and poured onto H_2O (30 mL). The organics were separated, and the aqueous was extracted with Et_2O (2 × 60 mL). The combined organics were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude golden oil was purified by silica gel column chromatography (60% Et_2O in hexanes eluent) to afford diol **45** (152 mg, 76% yield) as a pale yellow oil. For the purpose of characterization, a portion of each diastereomer was collected during purification.

Diol **45**, *diastereomer A:* R_f = 0.43 (3:1 Et_2O/hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.59 (dd, *J* = 2.1, 1.4 Hz, 1H), 4.58 (ddt, *J* = 6.6, 4.5, 1.9 Hz, 1H), 4.48 (qt, *J* = 6.4, 1.7 Hz, 1H), 3.64 (bs, 1H), 3.55 (bs, 1H), 2.38 (dd, *J* = 13.4, 6.8 Hz, 1H), 1.89 (dd, *J* = 13.4, 4.5 Hz, 1H), 1.36 (d, *J* = 6.4 Hz, 3H), 1.34 (s, 3H), 0.87 (s, 9H), 0.06 (app d, *J* = 1.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 152.6, 129.0, 81.9, 73.1, 63.7, 52.2, 26.5, 26.0, 21.8, 18.3, −4.5, −4.5; IR (neat film, NaCl) 3364, 2929, 2856, 1463, 1362, 1256, 1204, 1080, 1001, 940, 905, 835, 775 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{14}H_{27}O_3Si$ $[(M + H) - H_2]^+$ 271.1730, found 271.1728; $[\alpha]_D^{25.0}$ +54.9 (*c* 3.500, $CHCl_3$).

Diol **45**, *diastereomer B:* R_f = 0.35 (3:1 Et_2O/hexanes eluent); ^1H NMR ($CDCl_3$, 500 MHz) δ 5.63 (dd, *J* = 2.1, 1.2 Hz, 1H), 4.59 (dddd, *J* = 6.6, 4.3, 2.2, 1.2 Hz, 2H), 2.94−2.76 (m, 1H), 2.68 (s, 1H), 2.33 (dd, *J* = 13.2, 6.5 Hz, 1H), 1.86 (dd, *J* = 13.2, 4.1 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H), 1.39 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.3, 129.0, 81.5, 73.2, 65.4, 52.9, 26.7, 26.0, 24.1, 16.3, −4.6; IR (neat film, NaCl) 3370, 2929, 2857, 1472, 1362, 1257, 1206, 1085, 1004, 939, 905, 836, 775 cm^{-1}; HRMS (FAB+) *m/z* calcd for $C_{14}H_{27}O_3Si$ $[(M + H) - H_2]^+$ 271.1730, found 271.1735; $[\alpha]_D^{25.0}$ +61.4 (*c* 3.100 $CHCl_3$).



46

Methyl Ketone **46**. To a stirred solution of diol **45** (152 mg, 0.56 mmol, 1.00 equiv) as a 1:1 mixture of diastereomers in CH_2Cl_2 (3.8 mL) at ambient temperature (ca. 23 °C) was added MnO_2 (1.45 g, 16.7 mmol, 30.0 equiv) as a solid in a single portion. After 16 h, the consumption of starting material was complete as determined by TLC (1:1 EtOAc/hexanes eluent). The reaction mixture was then filtered through a Celite plug with washing with CH_2Cl_2. The combined organics were concentrated in vacuo to provide methyl ketone **46** (134 mg, 89% yield) as a spectroscopically pure dark yellow oil: R_f = 0.24 (1:9 EtOAc/hexanes eluent); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.53 (d,

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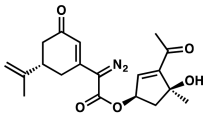
J = 1.9 Hz, 1H), 4.76 (td, J = 7.1, 1.9 Hz, 1H), 2.41 (dd, J = 12.6, 7.0 Hz, 1H), 2.34 (s, 3H), 2.05−1.96 (m, 1H), 1.41 (d, J = 1.0 Hz, 3H), 0.90 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 198.8, 147.1, 146.1, 80.0, 73.0, 51.1, 28.2, 27.5, 25.9, 18.3, −4.4, −4.6; IR (neat film, NaCl) 3534, 2929, 2857, 1667, 1472, 1362, 1275, 1259, 1094, 939, 914, 884, 836, 777 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{14}H_{25}O_3Si$ [(M + H) − H_2]$^+$ 269.1573, found 269.1584; $[\alpha]_D^{25.0}$ +114.7 (c 0.750, $CHCl_3$).

ent-43

*Methyl Ketone Diol ent-**43**.* To a golden yellow stirred solution of methyl ketone **46** (200 mg, 0.78 mmol, 1.00 equiv) in THF (3.8 mL) at ambient temperature (ca. 23 °C) was added TBAF (0.92 mL, 1 M in THF, 1.20 equiv) dropwise. After 20 min, the consumption of starting material was complete as determined by TLC (3:7 EtOAc/hexanes eluent). The orange-brown reaction mixture was then concentrated in vacuo and immediately purified by silica gel column chromatography (80% EtOAc in hexanes eluent) to furnish *cis*-1,3-cyclopentenediol ***ent*-43** (120 mg, 98% yield) as an amorphous white solid: R_f = 0.18 (3:1 EtOAc/hexanes eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.63 (d, J = 2.0 Hz, 1H), 4.75 (ddd, J = 7.2, 6.1, 2.1 Hz, 1H), 2.49 (dd, J = 13.4, 7.2 Hz, 1H), 2.35 (s, 3H), 1.96 (dd, J = 13.4, 6.1 Hz, 1H), 1.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 199.0, 148.1, 145.0, 80.6, 72.9, 50.4, 27.9, 27.6; IR (neat film, NaCl) 3386, 2968, 1667, 1372, 1316, 1275, 1231, 1107, 1071, 958 cm^{-1}; HRMS (ES+) m/z calcd for $C_8H_{11}O_2$ [M − OH]$^+$ 139.0759, found 139.0741; $[\alpha]_D^{25.0}$ +103.3 (c 0.650, $CHCl_3$).

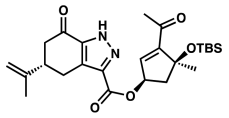


48

*Methyl Ketone α-Diazoester **48**.* To a stirred solution of ethyl ester **32** (2.07 g, 9.32 mmol, 1.00 equiv) in MeOH (31 mL) and H_2O (31 mL) was added K_2CO_3 (5.16 g, 37.3 mmol, 4.00 equiv). After 7 h, the consumption of starting material was complete as determined by TLC (2:3 Et_2O/hexanes eluent). The reaction mixture was cooled to 0 °C (ice/H_2O bath), and the pH was adjusted to between 1 and 2 by the careful addition of aqueous 1 N HCl (CAUTION: Vigorous gas evolution!). The reaction mixture was then poured onto a mixture of EtOAc (200 mL) and H_2O (100 mL). The organics were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude dark orange oil of carboxylic acid ***ent*-17** (1.81 g, >99% yield) was carried on without further purification.

To a stirred solution of diol ***ent*-43** (76 mg, 0.49 mmol, 1.00 equiv) in CH_2Cl_2 (16 mL) were added portions of crude carboxylic acid ***ent*-17** (190 mg, 0.98 mmol, 2.00 equiv) and EDC·HCl (188 mg, 0.98 mmol, 2.00 equiv). The orange reaction mixture was cooled to 0 °C (ice/H_2O bath), at which time DMAP (12 mg, 0.010 mmol, 0.20 equiv) was added in a single portion. After 30 min, the dark red-orange reaction mixture was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C). After 2.5 h, additional DMAP (12 mg, 0.010 mmol, 0.20 equiv) was added in a single portion. After an additional 2 h, the consumption of starting material was nearly complete as determined by TLC (1:1 EtOAc/hexanes eluent). The crude reaction mixture was concentrated in vacuo to approximately 25% of the original reaction volume and directly purified by silica gel column chromatography (50% → 70% → 90% EtOAc in hexanes eluent) to furnish a recovered portion of diol ***ent*-43** (11 mg, 14% yield) and the intermediate ester (125 mg, 77% yield), which was directly carried on to the next reaction.

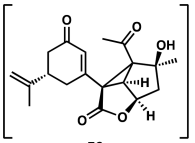
To a portion of intermediate ester (57 mg, 0.17 mmol, 1.00 equiv) in CH_3CN (1.7 mL) in the dark was added *p*-acetamidobenzenesulfonyl azide (*p*-ABSA, **33**, 46 mg, 0.19 mmol, 1.10 equiv) as a solid in one portion. The dark orange homogeneous reaction mixture was cooled to 0 °C (ice/H_2O bath). Et_3N (71 μL, 0.51 mmol, 3.00 equiv) was then added slowly dropwise. After 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 EtOAc (20 mL), removed from the cooling bath, and allowed warm to ambient temperature (ca. 23 °C). The reaction mixture was then concentrated in vacuo. The crude tan solid was then adsorbed onto Celite (1.0 g) and purified by silica gel column chromatography (20% EtOAc in CH_2Cl_2 eluent) to afford diazoester **48** (51 mg, 65% yield from diol ***ent*-43**) as a dark yellow oil: R_f = 0.17 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.63 (d, J = 2.0 Hz, 1H), 6.45 (d, J = 2.0 Hz, 1H), 5.80 (ddd, J = 7.6, 6.6, 2.0 Hz, 1H), 4.89 (p, J = 1.5 Hz, 1H), 4.85−4.81 (m, 1H), 3.50 (s, 1H), 2.78 (tt, J = 11.1, 4.2 Hz, 1H), 2.69 (ddd, J = 17.4, 4.2, 1.4 Hz, 1H), 2.62 (dd, J = 13.5, 7.5 Hz, 1H), 2.59−2.53 (m, 1H), 2.47 (ddd, J = 17.3, 10.9, 2.2 Hz, 1H), 2.46−2.36 (m, 4H), 2.17 (dd, J = 13.5, 6.6 Hz, 1H), 1.80 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 198.2, 197.1, 162.3, 150.1, 146.0, 145.9, 139.5, 120.6, 111.6, 80.2, 75.6, 67.2, 46.7, 41.9, 41.6, 31.7, 28.3, 27.7, 20.6; IR (neat film, NaCl) 3454, 2967, 2104, 1709, 1652, 1580, 1377, 1274, 1223, 1136, 1048, 893, 741 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{19}H_{23}O_5N_2$ [M + H]$^+$ 359.1607, found 359.1598; $[\alpha]_D^{25.0}$ +164.2 (c 0.500, $CHCl_3$).



49

*Pyrazole **49**.* In the dark, to a stirred solution of diazoester **48** (20 mg, 0.056 mmol, 1.00 equiv) in CH_2Cl_2 (0.56 mL) at 0 °C (ice/H_2O bath) was added Et_3N (78 μL, 0.56 mmol, 10.0 equiv) dropwise. After 5 min, TBSOTf (64 μL, 0.28 mmol, 5.00 equiv) was added dropwise. After an additional 15 min, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The deep red reaction mixture was filtered through a Florisil plug, washing with 100% EtOAc. The combined organics were concentrated in vacuo to afford a bright red oil that was immediately carried on to the next reaction.

In the dark, to a solution of the red oil in CH_2Cl_2 (5.6 mL) was added Rh_2OAc_4 (0.3 mg, 0.0006 mmol, 0.01 equiv) as a solid in one portion. After an additional 15 min, the consumption of starting material was complete as determined by IR spectroscopy (complete disappearance of diazo absorbance at ca. 2100 cm^{-1}). The reaction mixture was then poured onto H_2O (10 mL). The organics were separated, and the aqueous was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude golden solid was purified by silica gel column chromatography (30% → 50% EtOAc in CH_2Cl_2 eluent) to afford pyrazole **49** (10 mg, 38% yield) as an amorphous white solid: R_f = 0.30 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.59 (d, J = 2.0 Hz, 1H), 5.79 (ddd, J = 7.4, 6.6, 2.0 Hz, 1H), 4.89 (t, J = 1.4 Hz, 1H), 4.86 (q, J = 1.0 Hz, 1H), 3.32 (ddd, J = 16.3, 3.7, 1.3 Hz, 1H), 2.97−2.83 (m, 2H), 2.78−2.69 (m, 2H), 2.68−2.58 (m, 1H), 2.36 (s, 3H), 2.25 (dd, J = 13.0, 6.6 Hz, 1H), 1.82 (t, J = 1.1 Hz, 3H), 1.59 (s, 3H), 0.83 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 196.1, 189.2, 161.0, 152.4, 145.6, 136.6, 111.8, 81.8, 75.3, 49.9, 44.0, 43.5, 28.8, 28.5, 26.5, 25.7, 20.7, 18.0, −2.4, −2.5; IR (neat film, NaCl) 3207, 2928, 2856, 1688, 1464, 1367, 1259, 1167, 1101, 1006, 837, 776 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{25}H_{36}O_5N_2NaSi$ [M + Na]$^+$ 495.2286, found 495.2291; $[\alpha]_D^{25.0}$ +55.1 (c 0.135, $CHCl_3$).[52]



50

*Cyclopropane **50**.* To a stirred solution of diazoester **48** (14 mg, 0.039 mmol, 1.00 equiv) in CH_2Cl_2 (3.9 mL) in a nitrogen-filled

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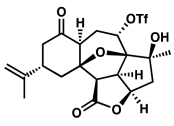
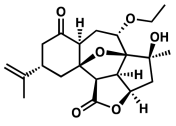
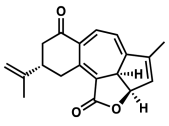
glovebox at ambient temperature (ca. 30 °C) was added $Cu(tbs)_2$ (**51**, 1.6 mg, 0.004 mmol, 0.10 equiv) as a solid in one portion. After 4 days, although the starting material was not fully consumed as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent), the reaction was removed from the glovebox and concentrated in vacuo to approximately 25% of the original reaction volume. The crude reaction solution was directly purified by silica gel column chromatography (50% EtOAc in CH_2Cl_2 eluent) to afford cyclopropane **50** (4 mg, 29% yield, R_f = 0.21 (1:1 EtOAc/CH_2Cl_2 eluent)) which was directly carried on, although the subsequent reactions were not successful.



39



52



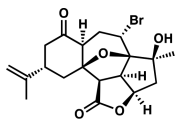
53

*Triflate **39**, Ethyl Ether **52**, and Cycloheptatriene **53**.* To a colorless stirred solution of *ent*-isoineleganolide A (**36**, 10 mg, 0.30 mmol, 1.00 equiv) in $CHCl_3$ (stabilized with 0.75% EtOH, 1.0 mL) at ambient temperature (ca. 23 °C) was added $In(OTf)_3$ (40 mg, 0.71 mmol, 2.37 equiv). The white suspension was stirred for 5 min and then introduced to a preheated 50 °C bath. After 13 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The reaction was directly purified by silica gel column chromatography (10% → 20% EtOAc in CH_2Cl_2 eluent) to provide triflate **39** (2 mg, 20% yield) as an amorphous white solid, ethyl ether **52** (7 mg, 70% yield) as an amorphous white solid, and cycloheptatriene **53** (1 mg, 10% yield) as an amorphous white solid.

*Triflate **39**.* Characterization data match those reported above.

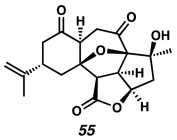
*Ethyl ether **52**:* R_f = 0.39 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.88–4.76 (m, 3H), 3.79–3.65 (m, 2H), 3.59–3.44 (m, 2H), 3.15 (d, J = 9.2 Hz, 1H), 2.91 (ddt, J = 13.3, 5.6, 1.1 Hz, 1H), 2.65 (tt, J = 13.2, 3.7 Hz, 1H), 2.60–2.49 (m, 2H), 2.36–2.18 (m, 4H), 2.17–2.09 (m, 1H), 1.98 (ddd, J = 14.5, 3.7, 2.1 Hz, 1H), 1.79–1.73 (m, 3H), 1.30 (d, J = 1.2 Hz, 3H), 1.17 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 206.7, 176.1, 146.2, 111.1, 95.5, 89.0, 79.6, 78.1, 69.3, 64.4, 55.4, 54.0, 48.5, 46.3, 45.7, 41.2, 36.8, 25.6, 24.7, 20.4, 15.7; IR (neat film, NaCl) 3490, 2965, 1767, 1717, 1447, 1357, 1262, 1178, 1107, 1025, 967, 895, 799, 758 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{21}H_{29}O_6$ $[M + H]^+$ 377.1964, found 377.1970; $[\alpha]_D^{25.0}$ +28.4 (c 0.200, $CHCl_3$).

*Cycloheptatriene **53**:* R_f = 0.94 (1:4 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, J = 6.7 Hz, 1H), 6.46 (ddd, J = 6.7, 1.8, 0.6 Hz, 1H), 6.36 (t, J = 1.8 Hz, 1H), 5.48 (ddd, J = 7.2, 2.3, 1.1 Hz, 1H), 4.84 (t, J = 1.4 Hz, 1H), 4.76 (q, J = 1.0 Hz, 1H), 3.33 (dq, J = 6.8, 2.3 Hz, 2H), 2.93 (dd, J = 7.5, 1.9 Hz, 1H), 2.76–2.69 (m, 1H), 2.67–2.58 (m, 2H), 2.01 (t, J = 1.3 Hz, 3H), 1.81 (dd, J = 1.5, 0.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 200.1, 166.1, 149.1, 146.2, 145.9, 143.5, 140.2, 138.1, 137.5, 117.4, 114.8, 111.3, 81.1, 44.8, 44.1, 38.7, 32.2, 21.1, 12.7; IR (neat film, NaCl) 2924, 2854, 1738, 1684, 1611, 1495, 1451, 1262, 1234, 1086, 1006, 827 cm^{-1}; HRMS (EI+) m/z calcd for $C_{19}H_{18}O_3$ $[M^\bullet]^+$ 294.1256, found 294.1260; $[\alpha]_D^{25.0}$ −84.6 (c 0.100, $CHCl_3$).



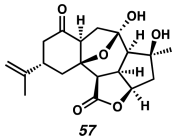
54

*Bromide **54**.* To a stirred colorless solution of *ent*-isoineleganolide A (**36**, 133 mg, 0.40 mmol, 1.00 equiv) in a mixture of toluene (27 mL) and THF (7 mL) in a nitrogen-filled glovebox was added $MgBr_2$ (370 mg, 2.01 mmol, 5.00 equiv) in a single portion. The reaction mixture was then sealed and heated to 70 °C. After 6 h, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH_2Cl_2 eluent). The golden yellow solution was removed from the glovebox and concentrated in vacuo to approximately 25% of the original reaction volume. The reaction was then filtered through a silica gel plug, eluting the product with 20% EtOAc in CH_2Cl_2 to afford spectroscopically pure bromide **54** (166 mg, >99% 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 bromide **54** in EtOAc: mp 150–153 °C; R_f = 0.26 (1:19 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.89 (dt, J = 9.1, 7.6 Hz, 1H), 4.84 (t, J = 1.5 Hz, 1H), 4.81 (s, 1H), 4.39 (dd, J = 11.3, 5.5 Hz, 1H), 3.74 (t, J = 9.2 Hz, 1H), 3.25 (d, J = 9.0 Hz, 1H), 3.08 (ddd, J = 14.1, 5.6, 1.4 Hz, 1H), 2.66 (tt, J = 13.2, 3.9 Hz, 1H), 2.56 (ddd, J = 13.2, 3.7, 2.0 Hz, 1H), 2.52 (d, J = 5.8 Hz, 1H), 2.36–2.27 (m, 2H), 2.22 (dd, J = 14.6, 12.9 Hz, 1H), 2.16–2.11 (m, 1H), 1.98–1.91 (m, 2H), 1.76 (d, J = 1.0 Hz, 3H), 1.49 (d, J = 1.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.7, 175.2, 145.7, 111.2, 96.3, 88.9, 80.8, 77.5, 55.5, 55.4, 48.4, 46.2, 45.4, 41.5, 41.1, 36.7, 32.3, 26.6, 20.2; IR (neat film, NaCl) 3508, 2970, 1767, 1716, 1443, 1354, 1271, 1203, 1173, 1073, 1016, 755 cm^{-1}; HRMS (FAB+) m/z calcd for $C_{19}H_{24}O_5{}^{79}Br$ $[M + H]^+$ 411.0807, found 411.0800; $[\alpha]_D^{25.0}$ +26.7 (c 1.150, $CHCl_3$).

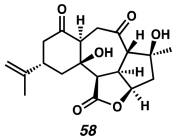


55

*Ketopyran **55**.* A reaction vessel in a nitrogen-filled glovebox was charged with $AgBF_4$ (43 mg, 0.22 mmol, 3.00 equiv) followed by bromide **54** (30 mg, 0.073 mmol, 1.00 equiv) as a solution in DMSO (1.5 mL) with stirring. The reaction vessel was sealed, and after 5 min the white suspension had become a completely homogeneous, pale yellow solution. The reaction vessel was removed from the glovebox and introduced to an argon atmosphere and a preheated 120 °C bath. After 9 h, the consumption of starting material was complete as determined by TLC (1:19 EtOAc/CH_2Cl_2 eluent). The dark brown, heterogeneous solution was removed from the heating bath and allowed to cool to ambient temperature (ca. 23 °C). Once the temperature had equilibrated, Et_3N (0.30 mL, 2.15 mmol, 29.5 equiv) was added quickly dropwise with vigorous stirring. After 2 h, the reaction was filtered through a Celite plug, washing with EtOAc. The combined organics were diluted with EtOAc (30 mL) and washed with H_2O (4 × 20 mL). The combined aqueous layers were then extracted with EtOAc (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude brown solid was purified by silica gel column chromatography (40% EtOAc in CH_2Cl_2 eluent) to furnish ketopyran **55** (24 mg, 96% yield) as a crystalline white solid. Colorless, translucent X-ray quality crystals were obtained by slow diffusion of 1% benzene in heptane into a solution of ketopyran **55** in EtOAc: mp 270–273 °C: R_f = 0.40 (1:3 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.89–4.84 (m, 2H), 4.83 (dd, J = 2.3, 1.2 Hz, 1H), 3.56 (t, J = 9.0 Hz, 1H), 3.44 (d, J = 9.1 Hz, 1H), 3.20 (d, J = 15.6 Hz, 1H), 3.07 (dt, J = 7.4, 1.0 Hz, 1H), 2.76 (tt, J = 13.2, 3.6 Hz, 1H), 2.61 (ddd, J = 13.0, 3.6, 2.1 Hz, 1H), 2.43–2.28 (m, 5H), 2.13 (ddd, J = 14.7, 3.6, 2.1 Hz, 1H), 1.77 (t, J = 1.0 Hz, 3H), 1.50 (d, J = 1.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 204.9, 199.1, 174.6, 145.8, 111.4, 95.2, 90.8, 78.1, 77.5, 57.4, 54.4, 51.2, 46.1, 45.5, 41.0, 36.6, 34.9, 24.6, 20.4; IR (neat film, NaCl) 3484, 2965, 2923, 1766, 1732, 1204, 1172, 1071, 1032, 947, 754 cm^{-1}; HRMS (EI+) m/z calcd for $C_{19}H_{22}O_6$ $[M^\bullet]^+$ 346.1416, found 346.1403; $[\alpha]_D^{25.0}$ −30.8 (c 0.800, $CHCl_3$).



57



58

*Diol Tetracycles **57** and **58**. 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 min and cooled to 0 °C (ice/H_2O bath) with stirring. 1,2-

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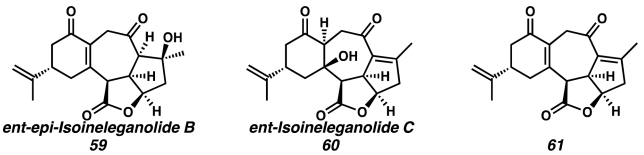
Diiodoethane (200 mg, 0.71 mmol, 1.00 equiv) was then added in separate 100 mg portions 30 min apart. After the addition of the second portion, the Schlenk tube was removed from the cooling bath and allowed to warm to ambient temperature (ca. 23 °C), and the pale yellow solution was stirred overnight (ca. 14 h), causing the reaction to become deep blue, indicating the formation of SmI_2.

Reduction of Ketopyran ***55***. A reaction vessel in a nitrogen-filled glovebox was charged with LiCl (49 mg, 1.15 mmol, 19.8 equiv), sealed, removed from the glovebox, and introduced to an argon atmosphere. To the reaction vessel was added a solution of ketopyran **55** (20 mg, 0.058 mmol, 1.00 equiv) in THF (26 mL) followed by *t*-BuOH (15 μL, 0.16 mmol, 1.23 equiv). The white suspension was then sparged with argon for 1 h, reducing the reaction volume to 20 mL. The reaction solution was then cooled to −78 °C (*i*-PrOH/dry ice bath) at which time SmI_2 (2.00 mL, 0.07 M in THF, 1.08 equiv) was added slowly dropwise over 5 min, dropping the SmI_2 solution down the sides of the reaction flask. After 15 min, the consumption of starting material was complete as determined by TLC (1:3 EtOAc/CH_2Cl_2 eluent). The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 μL), immediately removed from the cooling bath, and allowed to warm to ambient temperature (23 °C). The yellow reaction mixture was filtered through a silica gel plug, eluting the product with 100% EtOAc. The organics were concentrated in vacuo and the crude pale yellow solid was purified by silica gel column chromatography (75% → 85% EtOAc in CH_2Cl_2 eluent) to provide a mixture of hemiketal **57** and hydroxyketone **58** (17 mg, 85% yield) as an amorphous white solid. Compounds **57** and **58** were initially characterized as an inseparable mixture. Colorless, translucent X-ray quality crystals of hemiketal **57** were obtained by slow diffusion of 1% benzene in heptane into a solution of hemiketal **57** and hydroxyketone **58** in EtOAc: mp 225−228 °C; R_f = 0.32 (3:1 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.92 (dd, *J* = 7.0, 5.1 Hz, 1.00 H), 4.84 (dt, *J* = 2.8, 1.4 Hz, 2.28 H), 4.82−4.76 (m, 3.44 H), 3.63 (s, 0.90 H), 3.38 (tdd, *J* = 10.4, 7.0, 0.7 Hz, 0.99 H), 3.30 (d, J = 13.6 Hz, 1.23 H), 3.24 (d, *J* = 8.2 Hz, 1.23 H), 3.22−3.09 (m, 3.42 H), 3.02−2.95 (m, 2.19 H), 2.86−2.80 (m, 2.48 H), 2.76−2.55 (m, 8.94 H), 2.46 (dd, *J* = 14.0, 10.1 Hz, 1.00 H), 2.39−2.22 (m, 5.58 H), 2.19 (d, *J* = 10.3 Hz, 0.99 H), 2.15−2.09 (m, 1.17 H), 1.90 (dd, *J* = 15.3, 12.4 Hz, 1.04 H), 1.82−1.75 (m, 7.77 H), 1.72 (dd, *J* = 14.3, 12.1 Hz, 1.14 H), 1.53 (s, 2.88 H), 1.35 (d, *J* = 1.0 Hz, 3.78 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 209.9, 209.1, 206.1, 174.8, 173.2, 146.5, 146.2, 111.0, 110.9, 105.6, 83.9, 81.2, 80.5, 79.3, 78.9, 75.0, 58.0, 54.4, 54.3, 52.2, 51.9, 47.6, 47.4, 46.4, 46.0, 45.6, 44.5, 42.7, 41.7, 41.1, 40.3, 38.2, 37.5, 36.1, 28.8, 24.8, 20.8, 20.7; IR (neat film, NaCl) 3358, 2921, 1752, 1711, 1689, 1358, 1261, 1182, 1098, 1026, 936, 896, 799, 756 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calcd for $C_{19}H_{23}O_6$ $[M - H]^-$ 347.1500, found 347.1509; $[\alpha]_D^{25.0}$ +3.1 (*c* 0.250, $CHCl_3$).

Subsequently, hemiketal **57** and hydroxyketone **58** were purified further for the purpose of characterization by preparative HPLC on SiO_2 (Agilent Zorbax RX-SIL, 9.4 × 250 mm, 5 μm particle size) with 40% EtOAc in CH_2Cl_2 as eluent to afford pure components hemiketal **57** and hydroxyketone **58**, each as white amorphous solids.

Hemiketal ***57***: R_f = 0.32 (3:1 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.91 (dd, *J* = 6.8, 5.0 Hz, 1H), 4.84 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.81 (br s, 1H), 3.57 (br s, 1H), 3.38 (td, *J* = 10.3, 7.0 Hz, 1H), 3.20 (dt, *J* = 15.3, 2.6 Hz, 1H), 3.00 (br s, 1H), 2.65 (d, *J* = 10.6 Hz, 1H), 2.66−2.60 (m, 2H), 2.58 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.45 (dd, *J* = 13.8, 10.3 Hz, 1H), 2.36 (d, *J* = 15.3 Hz, 1H), 2.34 (dd, *J* = 14.1, 6.5 Hz, 1H), 2.32 (t, *J* = 14.7 Hz, 1H), 2.19 (d, *J* = 10.6 Hz, 1H), 1.90 (dd, *J* = 15.3, 12.3 Hz, 1H), 1.79 (s, 3H), 1.78 (dd, *J* = 14.5, 5.3 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 209.8, 173.0, 146.3, 110.8, 105.4, 83.8, 81.0, 80.3, 54.3, 51.8, 47.4, 47.2, 45.4, 42.4, 40.9, 37.4, 35.9, 28.6, 20.5.

Hydroxyketone ***58***: R_f = 0.32 (3:1 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.84 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.79 (td, *J* = 7.6, 5.9, 3.5 Hz, 1H), 4.77 (br s, 1H), 3.29 (d, *J* = 13.5 Hz, 1H), 3.23 (d, *J* = 8.2 Hz, 1H), 3.16 (dd, *J* = 17.0, 9.4 Hz, 1H), 3.13 (dt, *J* = 14.7, 2.8 Hz, 1H), 2.98 (ddd, *J* = 13.5, 8.2, 5.9 Hz, 1H), 2.84 (dd, *J* = 17.0, 5.9 Hz, 1H), 2.80 (br s, 1H), 2.74−2.62 (m, 4H), 2.31 (dd, *J* = 14.7, 7.0 Hz, 1H), 2.26 (t, *J* = 14.1 Hz, 1H), 2.12 (dd, *J* = 14.7, 2.9 Hz, 1H), 1.77 (s, 3H), 1.71 (dd, *J* = 14.1, 12.3 Hz, 1H), 1.35 (s, 3H).



*ent-epi-Isoineleganolide B (****59****), ent-Isoineleganolide C (****60****), and Bisenone* ***61***. To a heterogeneous reaction mixture of hemiketal **57** and hydroxyketone **58** (30 mg, 0.086 mmol, 1.00 equiv) in CH_2Cl_2 (6.0 mL) was added Amberlyst 15 (75 mg, 2.5 equiv by weight to diol mixture **57** and **58**) as a solid in one portion. After 24 h, the consumption of starting material was complete as determined by TLC (3:1 EtOAc/CH_2Cl_2 eluent). The heterogeneous, light yellow reaction mixture was filtered, and the organics were concentrated in vacuo. The crude yellow solid was purified by silica gel column chromatography (30% EtOAc in CH_2Cl_2 eluent) to provide *ent-epi*-isoineleganolide B (**59**, 19 mg, 63% yield) as an amorphous yellow solid, isoineleganolide C (**60**, 5 mg, 17% yield) as an amorphous white solid, and bisenone **61** (3 mg, 10% yield) as an amorphous white solid. Colorless, translucent X-ray quality crystals of enone **59** were obtained by layer diffusion of a dichloromethane solution of enone **59** into diethyl ether at room temperature.

*ent-epi-Isoineleganolide B (****59****):* R_f = 0.27 (2:3 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 4.85 (q, *J* = 1.4 Hz, 1H), 4.80 (ddd, *J* = 7.0, 5.8, 2.8 Hz, 1H), 4.69 (br s, 1H), 4.21 (d, *J* = 15.3 Hz, 1H), 3.90 (ddt, *J* = 7.4, 2.6, 1.3 Hz, 1H), 3.71 (dddt, *J* = 18.0, 4.5, 2.7, 1.3 Hz, 1H), 3.31 (ddd, *J* = 13.5, 7.3, 5.6 Hz, 1H), 3.08 (dq, *J* = 15.3, 2.7 Hz, 1H), 2.87 (d, *J* = 12.9 Hz, 1H), 2.86 (s, 1H), 2.77 (tt, *J* = 9.0, 4.5 Hz, 1H), 2.71 (ddd, *J* = 16.4, 4.7, 1.2 Hz, 1H), 2.53 (ddd, *J* = 16.4, 9.4, 1.2 Hz, 1H), 2.45 (dddt, *J* = 18.2, 8.2, 2.4, 1.2, 1.2 Hz, 1H), 2.39 (dd, *J* = 15.3, 7.0 Hz, 1H), 2.24 (dd, *J* = 15.0, 2.1 Hz, 1H), 1.78 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 207.9, 196.5, 172.1, 149.7, 145.6, 128.2, 111.3, 79.5, 78.2, 59.8, 51.0, 46.2, 43.0, 42.4, 39.7, 39.5, 33.8, 25.2, 21.3; IR (neat film, NaCl) 3458, 2960, 2923, 2854, 1767, 1709, 1662, 1438, 1377, 1262, 1139, 1038 cm^{-1}; HRMS (FAB+) *m*/*z* calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545, found 331.1548; $[\alpha]_D^{25.0}$ −66.3 (*c* 0.275, $CHCl_3$).

*ent-Isoineleganolide C (****60****):* R_f = 0.73 (3:1 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.99 (t, *J* = 5.1 Hz, 1H), 4.83 (q, *J* = 1.5 Hz, 1H), 4.77 (s, 1H), 4.01 (bt, *J* = 7.0 Hz, 1H), 3.53 (dd, *J* = 14.3, 2.7 Hz, 1H), 3.22 (d, *J* = 8.6 Hz, 1H), 3.19 (t, J = 2.9 Hz, 1H), 2.95−2.77 (m, 3H), 2.77−2.64 (m, 2H), 2.54 (dd, *J* = 14.3, 10.9 Hz, 1H), 2.25 (t, *J* = 13.3 Hz, 1H), 2.19 (s, 3H) 2.17 (d, *J* = 2.7 Hz, 1H) 1.77 (s, 3H), 1.69 (app t, *J* = 13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 205.1, 195.1, 175.0, 151.2, 146.5, 131.3, 110.7, 79.0, 76.3, 53.5, 53.2, 49.2, 46.2, 45.7, 42.8, 38.7, 37.9, 20.9, 16.3; IR (neat film, NaCl) 3355, 2922, 1750, 1712, 1679, 1626, 1372, 1260, 1184, 1017, 801 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1540, found 331.1539; $[\alpha]_D^{25.0}$ +10.5 (*c* 0.200, $CHCl_3$).

Bisenone ***61***: R_f = 0.61 (2:3 EtOAc/CH_2Cl_2 eluent); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.98 (td, *J* = 4.5, 1.1 Hz, 1H), 4.84 (td, *J* = 1.4, 0.7 Hz, 1H), 4.72 (q, *J* = 1.0 Hz, 1H), 4.16−4.08 (m, 2H), 3.76 (ddt, *J* = 7.4, 2.5, 1.2 Hz, 1H), 3.62 (dd, *J* = 18.1, 3.5 Hz, 1H), 3.14 (ddt, *J* = 13.6, 3.3, 2.4 Hz, 1H), 2.92−2.88 (m, 2H), 2.79−2.68 (m, 2H), 2.49−2.41 (m, 1H), 2.28−2.20 (m, 4H), 1.78 (dt, *J* = 1.2, 0.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 196.4, 193.8, 172.1, 156.9, 149.0, 145.9, 131.4, 128.2, 110.8, 78.5, 50.4, 49.0, 45.7, 42.5, 39.8, 38.7, 34.3, 21.0, 16.7; IR (neat film, NaCl) 2924, 1767. 1674, 1622, 1435, 1377, 1259, 1158, 893, 754 cm^{-1}; HRMS (MM: ESI-APCI) *m*/*z* calcd for $C_{19}H_{21}O_4$ $[M + H]^+$ 313.1434, found 313.1437; $[\alpha]_D^{25.0}$ +41.1 (*c* 0.250, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

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Computational assessment and Cartesian coordinates (PDF)
^{1}H and ^{13}C NMR and IR spectra (PDF)
X-ray crystal structure analyses (PDF)
X-ray data for epoxide **36** (CIF)
X-ray data for diene **34**(CIF)
X-ray data for bromide **54** (CIF)
X-ray data for hemiketal **57** (CIF)
X-ray data for ketopyran **55** (CIF)
X-ray data for enone **59** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: stoltz@caltech.edu.

ORCID

Robert A. Craig II: 0000-0002-2435-1564
Jennifer L. Roizen: 0000-0002-6053-5512
Brian M. Stoltz: 0000-0001-9837-1528

Notes

The authors declare no competing financial interest.

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(30) A characteristic list of the conditions attempted to induce the desired epoxide isomerization: $H_2SO_4/CHCl_3$, $SiO_2/CHCl_3$, DBU/$CHCl_3$, KO*t*-Bu/THF, $Pd(CH_3CN)_2Cl_2$/benzene, $BF_3{\cdot}Et_2O/CHCl_3$, $In(OTf)_3/CHCl_3$, $Al(Oi\text{-}Pr)_3/CHCl_3$, $Ti(Oi\text{-}Pr)_4$/THF, $Zn(OTf)_2$/toluene, $Mg(OTf)_2$/toluene, $MgCl_2$/toluene, $MgBr_2$/toluene.

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(36) The stereochemical assignment of ethyl ether **52** was accomplished by comparison to the unambiguous assignment of bromide **54** by single-crystal X-ray analysis (vide infra).

(37) The Lewis acids that accomplished the opening of epoxide **36** with their halogen counterion include $BF_3{\cdot}Et_2O$, $YbCl_3$, $MgCl_2$, $MgBr_2$, and MgI_2.

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(39) The chloride analogue of bromide **54** failed to undergo oxidation, resulting in the quantitative recovery of starting material. Alternatively, the iodide analog underwent oxidation but provided ketopyran **55** in reduced yield.

(40) For full details, see part 3 of this series, published in sequence following this paper, entitled: 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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(42) Product formation assessed by ^1H NMR evaluation of the crude reaction product.

(43) Exposure of diol mixture **57**/**58** to LDA at low temperature induced an equilibrium between **58** and the isomeric hydroxyketone (**62**) along with the epimerization of configuration along the [6,7]-ring junction as determined by detailed NMR studies.

(44) A characteristic list of the conditions attempted to induce the desired olefin isomerization: DBU/CH_2Cl_2, $PdCl_2(CH_3CN)_2$/CH_2Cl_2, Grubbs Gen. II/MeOH, $RhCl_3{\cdot}H_2O$/EtOH, LiHMDS/THF.

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(47) The ketone moieties within enone **59** could be reduced with hydride sources (e.g., $NaBH_4$, $Li(Ot\text{-}Bu)_3AlH$), but the reaction could not be performed chemo- or diastereoselectively.

(48) 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, R. A., Jr.; 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, H. L., III; 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. *Phys. Chem. Chem. Phys.* **2006**, *8*, 3172−3191.

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(51) Although we began with anhydrous $CeCl_3$, the drying procedure greatly increased the yield. It is likely the increased surface area of the $CeCl_3$ after grinding due to stirring during the drying procedure that facilitated the observed increase in yield.

(52) Only 20 lines appear in the ^{13}C spectrum of pyrazole **49**. Two are lost due to the symmetry of the TBS group. The remaining three carbons belong to the pyrazole ring and are broadened by the adjacent nitrogen atoms. Two of these three carbons, however, can be identified by two-dimensional $^{1}H-^{13}C$ gradient HMBC experiments, and their approximate shifts are as follows: 146 and 140 ppm.

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