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

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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. 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, malaria, bacterial infection, and neurological diseases. Despite these successes, the need for more effective therapeutics for a variety of intractable ailments remains constant. Toward this end, the furanobutenolide-derived norcembranoid diterpenes remain a largely unexplored class of biologically active natural products. Included within this natural product family is the compact and highly oxygenated antileukemic ineleganolide (1) as well as the closely related norcembranoid diterpenes horiolide (2), kavaranolide (3), sinulochmodin C (4), scabrolide B (5), scabrolide A (6), and yonarolide (7, Figure 1). 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 and the biomimetic semisynthesis of ineleganolide (1) and sinulochmodin C (4) has been disclosed. 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

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Received: December 4, 2017
Published: February 21, 2018
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 would furnish the tetrasubstituted enone scabrolide A (6). Finally, dehydration of tertiary alcohol 6 would afford diene yonarolide (7).

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

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.

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

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 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 be 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 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. Hydroxy-directed epoxidation of allylic alcohol 14 would provide pentacyle 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-
diazoster. 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 as well as the development of the enantioselective synthesis of a functionalized hydroxymethyl-cis-1,3-cyclopentenediol synthetic building block. 18 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). 19 Ketone 21 was intermediate in the opposite enantiometric 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) 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 cyclopentene 26 in 94% yield over two steps. Reduction of enone 26 at cryogenic temperature with disobutylaluminum 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). Methylation 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. Diazocyclopropanation–Cope Rearrangement Precursor of the intermediate aldehyde 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

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

- **Reaction Conditions:**
  1. p-TsOH, DMF
  2. Et$_3$N, EtOH
  3. NaOAc, K$_2$CO$_3$, EtOH, 60°C, 23 h

- **Product:**
  - 21

- **Conversion:**
  - 94% yield (3 steps)

**Scheme 6. Completion of Coupling Partners**

- **A.**
  1. DMAP, CH$_2$Cl$_2$, 0 °C → 25 °C, 5 h
  2. Ph$_3$PMe$_3$, KO$_2$Bu, THF, 1.5 h
  3. NaOMe, MeOH, 14 h

- **B.**
  1. Cleavage, THF, −78 °C, 5 h
  2. TEMPO-Et$_3$, CH$_2$CN, 12 h

- **Product:**
  - 32

- **Conversion:**
  - 98% yield (2 steps)
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 % Rh₂OAc₆ 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 tetrасrystallinе 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-

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 diene 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 hetercycle 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 8. Construction of Tetracycle 34 by Tandem Cyclopropanation–Cope Rearrangement

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

Scheme 10. Advancement of Diene 34 and Formation of ent-Isomeleganolide 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,19 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

Figure 2. X-ray crystal structure of diene 34.
mediated by protic acid, aprotic base, and most commonly, Lewis acids. We hypothesized that epoxide 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 and vinylogous diketone (Scheme 11). Intramolecular

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The only isomerization observed for either epoxytetracycle 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 oxa-Michael addition of tertiary alcohol 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 and silyl ether derivative 37 proved largely unreactive or simply decomposed.

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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, 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 cyclopropanation 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 with DMP to the intermediate aldehyde followed by the 1,2-addition of a methyl substituent into the enal system provided secondary alcohol as a 1:1 mixture of diastereomers. This mixture of diastereomers proved inconsequential as the allylic oxidation of the diastereomeric mixture of alcohol 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). Alternatively, we reasoned that the formation of the enol ether from the methyl

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

Scheme 12. Isomerization of ent-Isoneleganolide A (36) to Trflate 39

Scheme 13. Alternative Retrosynthetic Disconnection of Divergent Intermediate 10

Scheme 14. Construction of Methyl Ketone 46

Scheme 15. Advancement of Silyl Ether 47
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 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. Diazoo 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 TBSTOTf and Et3N 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 Rh2(OAc)4−17 provided pyrazole 49 as the sole product in 38% yield over two steps (Scheme 17).33

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 Rh2(OAc)4 and Rh2(CF3CO2)4 were ineffective catalysts for the desired intramolecular cyclization, we were pleased to find that Cu(tbs)(OTf)(51) was able to catalyze the desired transformation, albeit in low yield over an extended reaction period.54

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-Pr)3NEt, Et3N) 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 temperature, only resulting in decomposition of the cyclopropane starting material.17c Without a method to construct the desired [7,6,5,5]-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-isoinseleganolide A (36) to provide ent-isoinseleganolide (ent-1) or any 1,4-diketone product had failed (Scheme 19), we 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 CDCl3 to CHCl3 stabilized with 0.75% EtOH, caused triflate 39 to become a minor product (Scheme 20). Instead, ether 52 became the major product and was isolated in 70% yield,36 with cycloheptatriene 53 as a third, minor product. Given the apparent propensity of the epoxide moiety within ent-isoinseleganolide 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
basic cosolvent could facilitate the opening of epoxide 36 with their halogen counterparts. 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 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 $\text{S}_{2}$ opening of the epoxide, but also the concomitant 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. Fortunately, initial attempts to oxidize bromide 54 proved fruitful. 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$_3$N, 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.

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). The use of LiCl as an additive was essential for the high yield of this transformation, as the use of either H$_2$O 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 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-isoleineganolidé 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.
However, we have recently determined the X-ray structure of enone 59 and found that it bears the opposite $\beta$-stereoisomer 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 $\alpha$-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 norcencrobianoid 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]-tetracyclic ent-11 (Scheme 24). Unfortunately, subjection of the mixture of hemiketal 57 and hydroxyketone 58 to amine base (e.g., Et$_3$N, (i-Pr)$_2$NEt) in protic and aprotic solvent failed to induce any reactivity. Alternatively, the use of hydroxide bases (e.g., NaOH, KOH) in H$_2$O or H$_2$O/MeOH blends resulted in the saponification of the lactone moiety. 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 $-78^\circ$C effected the isomerization of configuration at C(4) and C(13), likely associated to 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]-norcencrobianoid 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 vinyllogous 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-inoeleaganolide (ent-1, Scheme 25). Unfortunately, ent-epi-isoineleganolide B (59) proved to 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 dihydrofuraneone ring by C–H oxidation through $\alpha$-bromination or under Suárez conditions was complicated by the reactivity of the cyclohexenone system and the isopropanyl moiety and was ultimately unsuccessful (Scheme 26). Additionally, cyclohexenone 59 was unreactive to the conjugate reduction by the nuclophilic 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.37

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 dihydrofuraneone ring is a more complex transformation than simply assessing the thermodynamic equilibrium between a tetrastubstituted enone and trisubstituted vinyllogous diketone (see Scheme 25). In order to assess the potential to accomplish the synthesis of ent-inoeleanogolide (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 C–H Oxidation.

### Scheme 25. Intended Completion of ent-Inoeleaganolide (ent-1) through Vinyllogous Diketone 38

### Scheme 26. Attempted Functionalization of ent-Isoineleganolide B (ent-9) by C–H Oxidation
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.\(^{38}\) 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\(^{ax}\) and ent-9\(^{equ}\), 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\(^{ax}\) and ent-9A\(^{equ}\), 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 diketones 38\(^{ax}\) and 38\(^{equ}\) 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\(^{ax}\) or ent-9A\(^{equ}\) 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
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), simulochinom 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 enantiomerically enriched remote stereocenter possessing the isopropanol 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, degassed solvents (distilled or passed over a column of activated alumina)\(^{30}\) and stirred with a Teflon-coated magnetic stirring bar. Commercially available reagents were used as received. Et$_3$N was immediately prior to use. Hydroxymethylamine hydrochloride (HCl) (minimum of 24 h and cooled in a desiccator to ambient temperature °C) was used. Reactions requiring external heat were performed at ambient temperature (23 °C). Solvents were dried glassware under an argon or nitrogen atmosphere using dry, degassed solvents. The solvent mixtures were distilled from magnesium methoxide immediately prior to use. Purification of organic compounds was accomplished using a 100 mm path length cell at 589 nm.

### Optical Rotations.

Optical rotations were measured on a JASCO P-2000 polarimeter using a 100 mm path length cell at 589 nm.

### Diene 67.

To a pale yellow solution of diol 29 (241 mg, 0.97 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (49 mL) at 0 °C (ice/H$_2$O bath) was added Dess–Martin periodinane (DMP, 923 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$_2$S$_2$O$_3$ (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$_2$O (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.

### Diol ent-18.

To a round-bottom flask in a N$_2$-filled glovebox were charged Ph$_3$PMeBr (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$_2$O (90 mL) and Et$_2$O (30 mL). The organics were separated, and the aqueous layer was extracted with Et$_2$O (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo.

### Conclusion.

The Journal of Organic Chemistry

DOI: 10.1021/acs.joc.7b02825

J. Org. Chem., XXXX, XXX, XXX–XXX

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white solid: \( R_1 = 0.13 \) (1:5 EtOAc/CH₂Cl₂); \(^{1} \)H NMR (300 MHz, CDCl₃) \( \delta 6.30 \) (dd, \( J = 17.8, 11.3, 1H \)), 5.82 (dd, \( J = 2.1, 1H \)), 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, \( J = 13.6, 2.1, 2H \)), 1.68 (dd, \( J = 6.6, 1H \)), 1.40 (s, 3H); \(^{13} \)C NMR (76 MHz, CDCl₃) \( \delta 149.5 \), 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, 1435, 1370, 1316, 1131, 1088, 1056, 1032, 987, 945, 926 cm⁻¹; HRMS (EI+) m/z calcd for \( \text{C}_{9} \text{H}_{19} \text{O}_3 \text{Na}^+ 140.0837 \), found 140.0859; \(^{[2]} \)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 \( \text{H}_2\text{O} \) (31 mL) was added \( \text{K}_2\text{CO}_3 \) (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-EtO/Hexanes eluent). The reaction mixture was cooled to 0 °C (ice/H₂O 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 \( \text{H}_2\text{O} \) (100 mL). The organics were separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organics were dried over \( \text{Na}_2\text{SO}_4 \) 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 \( \text{CH}_2\text{Cl}_2 \) (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/H₂O 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/hexane eluent). The reaction was quenched by the addition of 0.50 N HCl (80 mL) quickly dropwise with vigorous stirring. After 10 min, the heterogeneous solution was poured onto a mixture of EtOAc (100 mL) and \( \text{H}_2\text{O} \) (40 mL). The organics were separated and washed with 0.50 N HCl (20 mL) followed by 5 wt % \( \text{K}_2\text{CO}_3 \) (3 × 30 mL), brine (30 mL), and saturated \( \text{NH}_4\text{Cl} \) (30 mL). The organics were then dried over \( \text{MgSO}_4 \) 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 \( \text{K}_2\text{CO}_3 \) washes were cooled to 0 °C (ice/H₂O 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 \( \text{Na}_2\text{SO}_4 \) filtered, and concentrated in vacuo, providing a recovered portion (60 mg) of excess carboxylic acid ent-17.

To a solution of crude diester (269 mg, 0.85 mmol, 1.00 equiv) in \( \text{CH}_2\text{CN} \) (8.5 mL) in the dark was added \( p \)-acetoaminobenzensulfonyl 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/H₂O bath). Et₃N (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/CH₂Cl₂ eluent). The reaction was quenched by the addition of EtOAc (20 mL) 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 CH₂Cl₂ eluent) to afford \( \alpha \)-diazoester ent-16 (218 mg, 75% yield from diol ent-18) as a dark yellow oil: \( R_1 = 0.26 \) (1:4 EtOAc/CH₂Cl₂ eluent); \(^{1} \)H NMR (300 MHz, CDCl₃) \( \delta 6.39 \) (dd, \( J = 2.0, 1H \)), 6.32 (dd, \( J = 17.8, 11.4, 1H \)), 5.82 (s, 1H), 5.78 (s, 1H), 5.62 (dd, \( J = 7.2, 4.8, 2.2, 1H \)), 5.34 (dd, \( J = 11.4, 1.6, 1H \)), 4.86 (t, \( J = 1.4, 1H \)), 4.80 (s, 1H), 2.78–2.71 (m, 1H), 2.70–2.64 (m, 2H), 2.53 (dd, \( J = 16.1, 3.7, 1.4, 2H \)), 2.43 (dd, \( J = 17.4, 10.9, 2.2, 1H \)), 2.34 (dd, \( J = 16.3, 13.0, 1H \)), 2.05 (dd, \( J = 14.0, 4.8, 1H \)), 1.78 (s, 3H), 1.45 (s, 3H); \(^{13} \)C NMR (75 MHz, CDCl₃) \( \delta 197.2 \), 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, 1725, 1649, 1455, 1379, 1328, 1250, 1222, 1106, 1061, 952, 893, 744 cm⁻¹; HRMS (FAB+) m/z calcd for \( \text{C}_{9} \text{H}_{18} \text{O}_3 \text{Na}^+ [\text{M} + \text{H}]^+ 343.1659 \), found 343.1634; \([\alpha]_{D}^{25} +233.5 \) (c 5.470, CHCl₃).

Diene 34 and Enone 35. To a stirred solution of diazoester ent-16 (630 mg, 1.84 mmol, 1.00 equiv) in \( \text{CH}_2\text{Cl}_2 \) (184 mL) in a nitrogen-filled glovebox was added Rh₂OAc₄ (8 mg, 0.018 mmol, 0.01 equiv) at ambient temperature (ca. 30 °C). After 30 min, the consumption of

[Image 376x90 to 495x138]
starting material was complete as determined by TLC (1:4 EtOAc/CH₂Cl₂ eluent). The reaction mixture was then concentrated in vacuo, and the yellow solid was purified by silica gel column chromatography (20% EtOAc in CH₂Cl₂ eluent) to afford diene 34 (306 mg, 53% yield) as a crystalline pale yellow solid and cyclopentene 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 Et₂O: mp 150–153 °C; Rₛ = 0.38 (1:4 EtOAc/CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 500 MHz) δ 6.19 (dd, 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 (dd, 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 (dd, J = 16.5, 4.0, 1.7 Hz, 1H), 2.44 (dd, J = 15.5, 11.6 Hz, 2H), 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); ¹³C NMR (CDCl₃, 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 C₉H₁₆O₂ [M + H]⁺ 135.1596, found 135.1608 [© 0.18 (1:4 EtOAc/CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 (El⁺) m/z calcd for C₉H₁₆O₂ [M⁺]⁺ 138.0681, found 138.0674 [© 0.18 (1:4 EtOAc/CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 600 MHz) δ 6.43 (dd, 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 (dd, J = 17.5, 3.9, 1.9 Hz, 1H), 2.79 (td, J = 14.4, 3.9 Hz, 1H), 2.67 (dd, J = 16.6, 3.9, 1.9 Hz, 1H), 2.56–2.33 (m, 3H), 2.28 (d, 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); ¹³C NMR (CDCl₃, 126 MHz) δ 198.8, 172.1, 148.7, 146.6, 129.9, 110.6, 79.9, 75.0, 70.2, 54.5, 50.2, 45.8, 42.6, 39.8, 37.3, 26.8, 22.4, 20.9; IR (neat film, NaCl) 2962, 1770, 1665, 1380, 1262, 1101, 1024, 799 cm⁻¹; HRMS (FAB⁺) m/z calcd for C₉H₁₆O₂Si ([M + H]⁺) 401.1784, found 401.1798 [© 0.18 (1:4 EtOAc/CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 600 MHz) δ 6.51 (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 (dd, 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, 7.9 Hz, 1H), 2.27 (d, J = 12.9, 4.7 Hz, 1H), 2.11 (br s, 1H), 2.16 (dd, J = 13.5, 7.0 Hz, 1H), 2.02 (dd, J = 14.7, 3.5, 2.3 Hz, 1H), 1.76 (s, 3H), 1.71 (dd, J = 13.2, 10.1, 6.0 Hz, 1H), 1.35 (d, J = 12.2 Hz, 3H); ¹⁹F NMR (CDCl₃, 376 MHz) δ -74.8 ppm; ¹³C NMR (CDCl₃, 101 MHz) δ 208.4, 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 CF₃ group of dienedione 39 was not observed directly in the ¹³C NMR spectrum, but was observed at 118.3 ppm and correlated with the ¹F signal at -74.8 ppm in a ¹F–¹H HSQC experiment with ¹F detection at 376 MHz); (IR (neat film, NaCl) 3485, 2963, 1767, Article DOI: 10.1021/acs.jolc.7b02825 J. Org. Chem. XXXX, XXX, XXX–XXX
Allylic Alcohol 45. To a stirred solution of diol 44 (187 mg, 0.72 mmol, 1.00 equiv) in CH2Cl2 (36 mL) at 0 °C (ice/H2O 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 Na2S2O3 (50 mL) with vigorous stirring. After 10 min, the reaction was diluted with CH2Cl2 (50 mL) and poured onto saturated aqueous NaHCO3 (75 mL). The organics were separated, and the aqueous layer was extracted with CH2Cl2 (2 × 80 mL). The combined organics were dried quickly over MgSO4 (<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 Et2O (4.9 mL) at −15 °C (ice/Methanol bath) was added MeLi (1.92 mL, 1.5 M in Et2O, 4.00 equiv) quickly dropwise. After 1.5 h, an additional portion of MeLi (0.96 mL, 1.5 M in Et2O, 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 NH4Cl (15 mL, CAUTION: Vigorous gas evolution!) with vigorous stirring. The biphasic reaction mixture was diluted with Et2O (60 mL) and poured onto H2O (30 mL). The organics were separated, and the aqueous was extracted with Et2O (2 × 60 mL). The combined organics were washed with brine (20 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The crude golden oil was purified by silica gel column chromatography (60% EtO in hexanes eluant) 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.

Methyl Ketone 46. To a stirred solution of diol 45 (132 mg, 0.56 mmol, 1.00 equiv) as a 1:1 mixture of diastereomers in CH2Cl2 (3.8 mL) at ambient temperature (ca. 23 °C) was added MnO2 (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 CH2Cl2. The combined organics were concentrated in vacuo to provide methyl ketone 46 (134 mg, 89% yield) as a spectroscopically pure dark yellow oil: Rf = 0.24 (1:9 EtOAc/hexanes eluent); 1H NMR (CDCl3, 400 MHz) δ 6.53 (d, 1H, meta, J = 2.1 Hz)
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Pyrazole 49. In the dark, to a stirred solution of diazoester 48 (20 mg, 0.056 mmol, 1.00 equiv) in CH2Cl2 (0.56 mL) at 0 °C (ice/H2O bath) was added Et3N (78 µL, 0.56 mmol, 1.00 equiv) dropwise. After 5 min, TBSOTf (64 µL, 0.50 mmol, 1.00 equiv) was added. After an additional 15 min, the consumption of starting material was complete as determined by TLC (1:4 EtOAc/CH2Cl2 eluent). The deep red reaction mixture was filtered through a Florisil plug, washed 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 CH2Cl2 (5.6 mL) was added Rh3OAc (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 H2O (10 mL). The organics were separated, and the aqueous was extracted with CH2Cl2 (3 × 25 mL). The combined organics were washed with brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The crude golden solid was purified by silica gel column chromatography (30% → 50% EtOAc in CH2Cl2 eluent) to afford pyrazole 49 (10 mg, 38% yield) as an amorphous white solid: Rf = 0.30 (1:4 EtOAc/CH2Cl2 eluent); 1H NMR (CDCl3, 600 MHz) δ 6.59 (d, J = 2.0 Hz, 1H), 5.79 (d (J, d = 6.6, 7.4 Hz, 1H), 4.89 (q, J = 1.4 Hz, 1H), 4.86 (q, J = 1.0 Hz, 1H), 3.32 (d, J = 16.3, 3.7, 1.3 Hz, 1H), 2.97–2.83 (m, 3H), 2.78–2.69 (m, 2H), 2.68–2.58 (m, 1H), 2.36 (s, 3H), 2.25 (s, 3H), 2.25 (d, J = 13.0, 6.6 Hz, 1H), 1.82 (s, 1.1 Hz, 1H), 1.59 (s, 3H, 0.83 Hz, 1H), 0.12 (s, 3H), 0.09 (s, 3H); 13C NMR (CDCl3, 126 MHz) δ 196.1, 189.2, 161.0, 152.4, 145.6, 136.6, 111.8, 81.5, 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, 1001, 906, 837, 776 cm⁻¹; HRMS (FAB+) m/z calc for C20H15O4N2Na [M + Na]⁺ 455.1211, found 455.1212; [α]D 26.6 +251.6 (c 0.135, CH2Cl2).52

Cyclopropane 50. To a stirred solution of diazoester 48 (14 mg, 0.039 mmol, 1.00 equiv) in CH2Cl2 (3.9 mL) in a nitrogen-filled...
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; [α]D 0.26 (1:19 EtOAc/CH2Cl2 eluent); 1H NMR (CDCl3, 600 MHz) δ 4.89 (d, 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); 13C NMR (CDCl3, 126 MHz) δ 205.7, 182.2, 145.7, 111.2, 96.3, 88.9, 80.8, 77.5, 55.5, 54.4, 48.6, 46.2, 45.4, 41.5, 41.1, 36.7, 32.3, 26.6, 20.2; IR (neat film, NaCl) 3408, 2970, 1767, 1716, 1443, 1354, 1271, 1203, 1173, 1073, 1016, 755 cm–1; HRMS (FAB+) m/z calcd for C13H20O7Br [M + H]+ 411.0807, found 411.0800, [α]D 25.0 +26.7 (c 1.150, CHCl3).

Ketopyran 55. A reaction vessel in a nitrogen-filled glovebox was charged with AgBF4 (3 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/CH2Cl2 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, Et2N (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 H2O (4 × 20 mL). The combined aqueous layers were then extracted with EtOAc (3 × 20 mL). The combined organics were dried over MgSO4, filtered, and concentrated in vacuo. The crude brown solid was purified by silica gel column chromatography (40% EtOAc in CH2Cl2 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; [α]D 0.40 (1:3 EtOAc/CH2Cl2 eluent); 1H NMR (CDCl3, 500 MHz) δ 4.89–4.84 (m, 2H), 4.83 (dd, J = 2.3, 12.0 Hz, 1H), 3.56 (s, J = 9.0 Hz, 1H), 3.44 (dd, 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 = 3.6, 2.6 Hz, 1H), 2.61 (dd, J = 13.0, 3.6, 2.1 Hz, 1H), 2.43–2.28 (m, 6H), 2.13 (ddd, J = 14.7, 3.6, 2.1 Hz, 1H), 1.77 (t, J = 7.4 Hz, 1H), 1.50 (d, J = 1.1 Hz, 3H); 13C NMR (CDCl3, 126 MHz) δ 204.9, 199.1, 174.8, 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) 3498, 2965, 2923, 1766, 1732, 1204, 1142, 1033, 974, 754 cm–1; HRMS (FAB+) m/z calcd for C19H24O7Br [M + H]+ 525.1346, found 525.1346, [α]D 25.0 –30.8 (c 0.800, CHCl3).

Dial Tetracycles 57 and 58. Preparation of a 0.07 M Stock Solution SmI2. Into a Schlenk tube was added freshly filed samarium metal (150 mg, 1.00 mmol, 1.41 equiv). The reaction vessel was then thoroughly flame-dried, backfilled with argon, and allowed to cool to ambient temperature (ca. 23 °C). To the reaction vessel was then added THF (10.0 mL) that had previously been sparged with argon for 60 min and cooled to 0 °C (ice/H2O bath) with stirring. 1.2-
Diodooethane (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 SmI₂.

Reduction of Ketopyran 55. A reaction vessel in a nitrogen-filled glovebox was charged with LiCl (49 mg, 1.15 mmol, 18.9 equiv), sealed, removed from the glovebox, and introduced to an argon atmosphere. To the reaction vessel was added 1H NMR (CDCl₃, 500 MHz) data for compound 55: δ 7.0 Hz (1H), 1.17 (s, 3H), 1.77 (s, 3H), 1.71 (dd, J = 14.1, 12.3 Hz, 1H), 1.35 (s, 3H).

Hydroxyketone 58: Rᵢ = 0.32 (3:1 EtOAc/CH₂Cl₂ eluent); ¹H NMR (CDCl₃, 600 MHz) δ 4.84 (dd, J = 7.4, 2.9 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).

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ASSOCIATED CONTENT

Supporting Information The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02825.
Determination of (PDF) and 13C 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)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, and Caltech for financial support and Eli Lilly & Co. for assistance with biological activity screening. Additionally, we gratefully acknowledge Larry Henling and Dr. Michael Takase (Caltech) for X-ray crystallographic structural determination, Dr. Mona Shahgholi and Naseem Torian (Caltech) for mass spectrometry assistance, and Dr. David VanderVelde (Caltech) for NMR experimental assistance and helpful discussions. Additionally, Prof. Sarah Reisman, Dr. Jeffrey C. Holder, Dr. Corey M. Reeves, Prof. Hosea M. Nelson, Dr. Jonny R. Gordon, Dr. Pamela M. Tadross, and Beau P. Pritchett (Caltech) are thanked for helpful discussions. R.A.C. gratefully acknowledges the support of this work provided by a fellowship from the National Cancer Institute of the National Institutes of Health (NIH) under Award No. F31AI7435. J.L.R. thanks the California Tobacco-Related Disease Research Program of the University of California, Grant No. 14DT-0004 for a predoctoral fellowship. A.C.J. thanks the NIH for the support of this work provided by a postdoctoral fellowship (Award No. F32GM082000).

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(18) For full details of the synthetic program, see the paper preceding this article: Roizen, J. L.; Jones, A. C.; Smith, R. C.; Virgil, S. C.; Stoltz, B. M. Model Studies to Access the [6,7,5,5]-Core of Inelanogolide Using Tandem Translocation-Cope or Cyclopropanation-Cope Rearrangements as Key Steps. J. Org. Chem. 2017, 82, 13051–13067.


(47) The ketone moieties within enone 59 could be reduced with hydride sources (e.g., NaBH₄, Li(O-t-Bu)₃AlH), but the reaction could not be performed chemo- or diastereoselectively.


(51) Although we began with anhydrous CeCl₃, the drying procedure greatly increased the yield. It is likely the increased surface area of the CeCl₃ after grinding due to stirring during the drying procedure that facilitated the observed increase in yield.

(52) Only 20 lines appear in the ¹³C 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 ¹H−¹³C gradient HMBC experiments, and their approximate shifts are as follows: 146 and 140 ppm.