A Convergent Total Synthesis of (+)-Ineleganolide

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ABSTRACT: We report the total synthesis of the furanobutenolide-derived diterpenoid (+)-ineleganolide. The synthetic approach relies on a convergent strategy, based on the coupling of two enantioenriched fragments which are derived from (–)-linalool and (+)-norcarvone respectively. A high-yielding, one-step Michael addition and aldol cascade furnishes a pentacyclic framework as a single diastereomer, overcoming previous challenges in controlling stereochemistry. The endgame features an O_2 facilitated C-H oxidation and a samarium diiodide induced semi-pinacol rearrangement to furnish the highly rigid central seven membered ring.

The cembranoid and norcembranoid diterpenoids represent a large family of natural products isolated from soft coral species.[1] Due to their unique, highly complex structures, the furanobutenolide-derived diterpenoids have received considerable attention from synthetic chemists over the past decades, giving rise to new reaction development in synthetic chemistry.[2] They have furthermore served as a proving ground in retrosynthetic planning and in delivering useful amounts of material for potential further investigations into their bioactivity.[3] A subclass of these molecules contain a macrocyclic structure, as represented by the neurotoxin lophotoxin (**2**), which functions as an irreversible inhibitor of the nicotinic acetylcholine receptor (Figure 1).[4,5] Biosynthetically, these macrocycles are suggested to engage in further modifications to give rise to more dense polycyclic structures. A showcase example of these architectures is reflected in bielschowskysin (**3**), showing promising cytotoxicity against non-small cell lung cancer and renal cancer.[6] Another flagship member of this class, ineleganolide (**1**), was isolated from the Formosan soft coral *Sinularia inelegans* by Duh and co-workers in 1999.[7] Showing preliminary cytotoxicity against P-380 leukeumia cell lines, further insights into its bioactivity remain undisclosed. Structurally, ineleganolide contains a highly rigid oxidized framework, bearing a key central seven-membered ring, a remote isopropenyl group, and a bridging β-keto tetrahydrofuran moiety. Due to its unique and challenging framework, synthesizing ineleganolide had remained an unsolved challenge over the past two decades, including efforts by the groups of Vanderwal,[8] Nicolaou,[9] Gaich,[10] Romo,[11] Moeller[12] and our group.[13] Only recently in 2022, Wood and co-workers showcased the first total synthesis of ineleganolide.[14] After elegantly constructing a macrocyclic precursor, they were able to form the last bond through a transannular Michael addition, similar to that disclosed by Pattenden and co-workers in their 2011 biomimetic semisynthesis of **1**,[15] giving rise to sinulochmodin C in 34.5% yield and ineleganolide in 11.5% yield respectively.

In our own research, issues surrounding the central 7-membered ring and constructing the ether bridge at a late-stage had halted previous efforts.[16,17] This sparked the idea of constructing the central seven membered ring at a later stage, and instead having the tetrahydrofuran motif introduced early. Therefore, we envisioned disconnecting through the C4–C5 bond as the final step, constructing the seven-membered ring last. Inspired by our previous research and specifically that of Vanderwal and co-workers', we planned our route back to the precursor **4**, to set the stereochemistry at C12 through a Michael addition.[18] As a vinylogous β-keto ester, we envisioned that the lowered acidity of the C12 proton would thereby provide an epimerizable handle. Disconnecting **4** through an esterification, we were left with two fragments, carboxylic acid **6** and alcohol **5**. We were able to derive these from (–)-linalool and (+)-norcarvone respectively, resulting in an overall convergent and stereospecific synthesis.

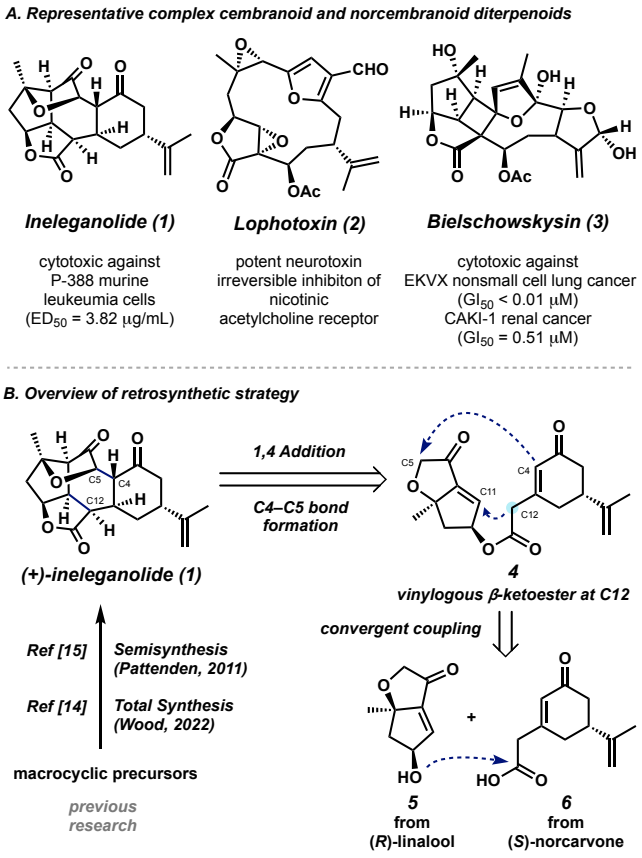
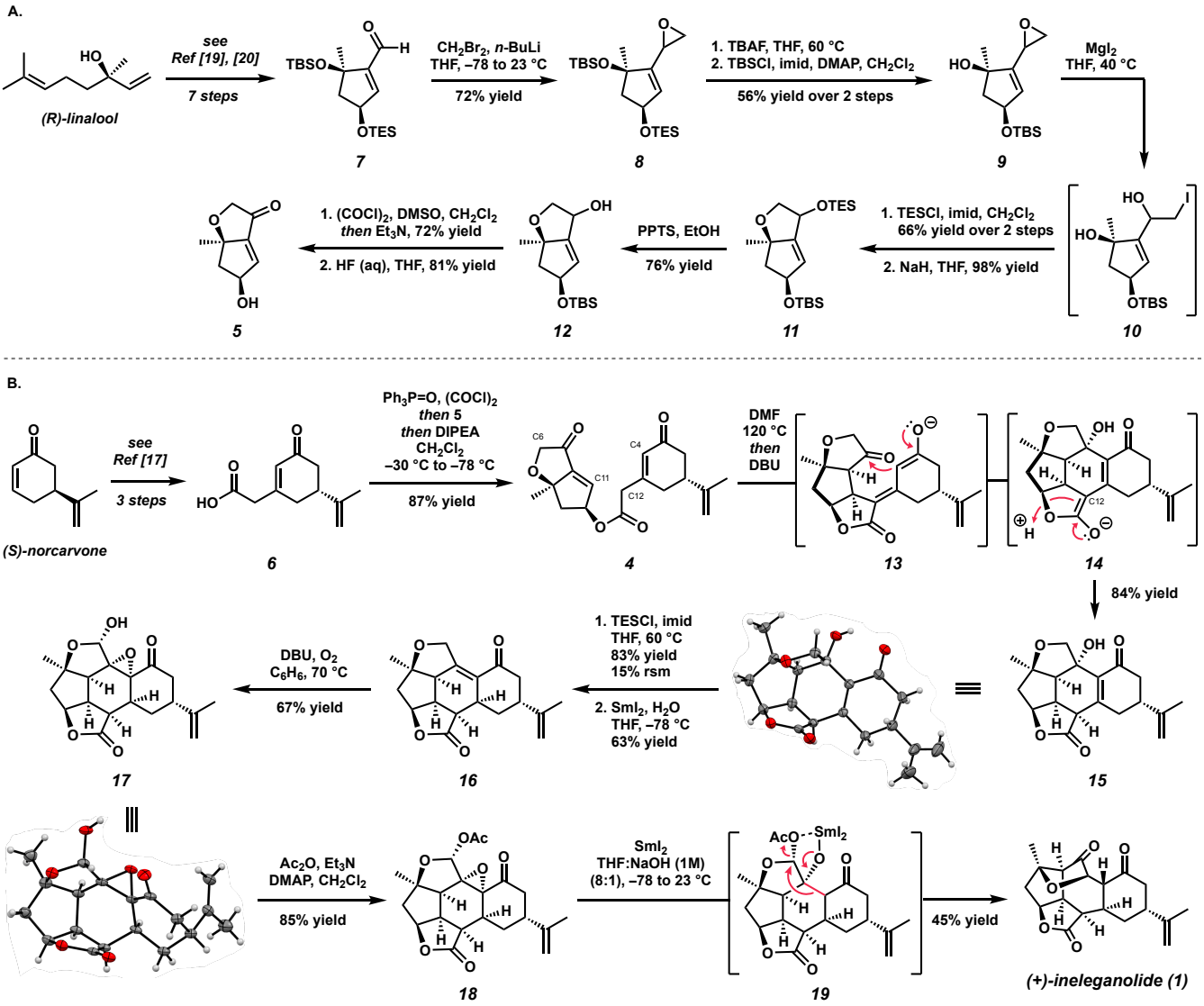


Figure 1. (A) Structures and bioactivity of representative furanobutenolide-derived diterpenoids. (B) Outline for the synthesis of (+)-ineleganolide.

To synthesize bicyclic enone **5**, we began from (*R*)-linalool (Scheme 1). Aldehyde **7** was readily available through previously developed chemistry, established by the Maimone group and our group respectively.[19,20] This route proved to be highly

scalable to access aldehyde **7** in sufficient quantities (>70 g prepared). We next focused our attention on building the essential β-keto tetrahydrofuran moiety present in bicycle **5**. This proved challenging, due to the highly strained nature of enone **5**. Initially, extensive efforts of an intramolecular cyclization of the tertiary alcohol onto an α-functionalized ketone showed no success. We envisioned that oxidizing to the ketone later, would alleviate the induced strain and allow for the intramolecular cyclization to occur. This idea proved to be successful, as the cyclization onto a β-functionalized secondary alcohol was possible. We converted aldehyde **7** to the corresponding epoxide **8**, using dibromomethane as the one carbon source. Removal of both silyl groups by treatment of **8** with TBAF, followed by selective silylation of the resulting secondary alcohol with TBSCl, revealed the tertiary alcohol **9**. Treatment of epoxide **9** with magnesium diiodide revealed the intermediary iodohydrin **10**. Protecting the insipient secondary alcohol as the corresponding silyl ether proved necessary, since cyclization in the presence of the unprotected secondary alcohol failed, even with excess amounts of base. Upon silylation, however, intramolecular substitution of the alkyl iodide by the tertiary alkoxide occurred at room temperature to afford bicycle **11** in excellent yield (98%). Selective deprotection of the triethyl silyl ether under mild acidic conditions gave alcohol **12**, which was oxidized to the enone under Swern conditions in 72% yield. Lastly, deprotection employing aqueous HF yielded **5** in 81% yield. Other deprotection conditions proved unsuccessful, due to the presumed high reactivity and instability of enone **5** as an electrophilic Michael acceptor.

Scheme 1: (A) Synthesis of bicyclic enone **5**; (B) Completed synthesis of (+)-ineleganolide **1**.

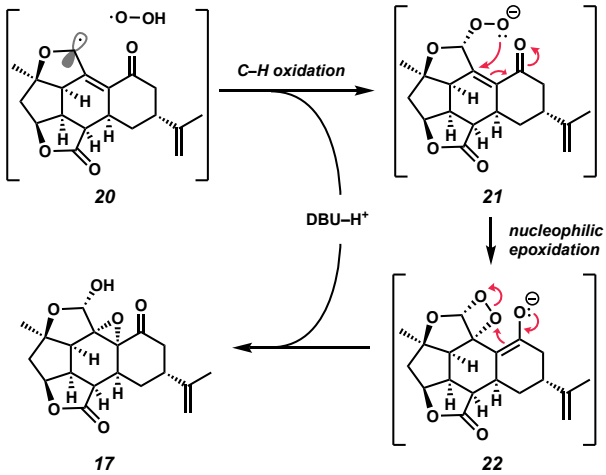


Carboxylic acid **6** could be accessed through a protocol previously employed by our group, utilizing (*S*)-norcarvone as enantioenriched starting material.[17] With acid **6** and alcohol **5** in hand, we turned to develop conditions for esterification. This proved challenging due to 1) the acidic α-proton of the acid **6** and 2) the instability of enone **5** toward amine base or nucleophiles (Et_3N, DIPEA, DMAP, pyridine, etc.), leading to decomposition within minutes. We eventually developed specific conditions to overcome these issues, activating the acid as the triphenylphosphonium salt at low temperatures,[21] which reacted with alcohol **5** within seconds upon addition of base, affording

ester **4** in 87% yield. Next, we investigated the intramolecular Michael addition. While evaluating conditions, ester **4** also appeared unstable to base and gave various side products upon reaction. To our surprise, treatment of ester **4** with DBU at 23 °C gave trace amounts of an unexpected pentacycle (**15**), the structure of which was determined by X-ray crystallography and resulted from not only Michael addition, but a subsequent aldol cyclization as well. We were able to optimize this process by preheating a solution of the ester **4** in DMF at high temperatures (i.e., 120 °C) and adding DBU in one portion. Under this protocol the reaction then proceeded within minutes to smoothly give **15** in 84% yield, suppressing previous side products. Mechanistically, we believe that a Michael addition occurs first to form the C12–C11 bond. The second proton at C12 (i.e., **14**) can be abstracted again to give the conjugated enolate **13**. The extended enolate can then undergo aldol addition at C4 with the neighboring ketone and isomerize to give rise to intermediate **14**. Being sp^2-hybridized, the enolate at C12 is preferentially protonated from the convex face, giving **15** as a single diastereomer. Overall, this Michael addition and aldol cascade forges two bonds and four stereocenters as a single diastereomer in high yield, crucially providing the correct stereochemistry at C12.

With this result in hand, we could envision a path toward ring expansion and completion of the natural product. To this end, protection of the tertiary alcohol as the silyl ether facilitated reduction of the tetrasubstituted enone under samarium diiode conditions and subsequent elimination to enone **16**.[17] While attempting an allylic oxidation at C5, we discovered that enone **16** undergoes a unique air oxidation under basic conditions producing the epoxide hemiacetal **17** (Scheme 2). We were surprised by this nearly unprecedented reaction[22] and speculate that the ability to form the highly stabilized captodative radical **20** on the γ-position of the enone facilitates a radical oxidation with O_2, initially producing a peroxide.

Scheme 2: Suggestive mechanism for the formation of **17**.



Under basic conditions, the peroxyanion **21** can then undergo intramolecular nucleophilic epoxidation with the enone to give intermediate **22**, which converts to the final product **17**. After optimization, **17** could be reliably obtained in 67% yield, being highly sensitive to the stirring rate and oxygen atmosphere. Having the correct oxidation pattern in place, we planned to construct the crucial C4–C5 bond through reductive opening of the epoxide and a subsequent semi-pinacol shift. We deemed the odds in our favor, predicting good anti-periplanar orbital overlap between the shifting carbon-carbon bond and hemi-acetal leaving group. Additionally, the ability to form a stabilized oxocarbenium ion could also be beneficial. Initial investigations showed that epoxide opening typically lead to elimination of the resulting tertiary alcohol.[23] Converting hemiacetal **17** to the acetate **18** provided the initial lead, as reductive opening of **18** with samarium diiode provided trace amounts of ineleganolide, indicating that the semipinacol rearrangement proceeded in the same pot as epoxide opening. We then extensively evaluated additives and temperatures and found that addition of an aqueous 1M sodium hydroxide solution as relatively high *p*H proton source significantly improved the yield. Although a number of mechanistic scenarios are possible, we deemed the existence of intermediate **19** to be crucial, with Samarium potentially engaging as a Lewis acid to promote the rearrangement.[24] The basicity of the proton source could provide improved conditions to protonate the initially forming samarium enolate without protonating the tertiary alcohol too rapidly and forcing elimination. Quickly warming up the reaction mixture from −78 °C to 23 °C gave (+)-ineleganolide **1** in 45% isolated yield. While the isolation paper initially provides an X-ray structure of ineleganolide, lower resolution prevented determination of absolute stereochemistry.[7] This led us to obtain a higher-resolution crystal structure, that further confirms the absolute stereochemistry of the naturally occurring enantiomer (+)-ineleganolide, in accordance with observations by Wood[14] and Pattenden[15] (Figure 2).

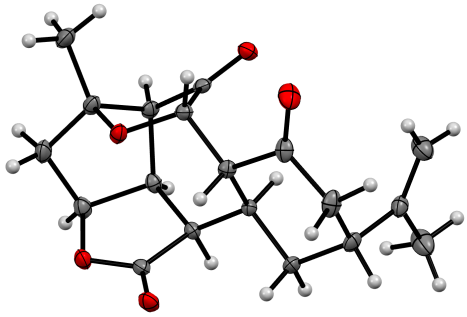


Figure 2. X-ray diffraction structure of (+)-ineleganolide.

In conclusion, we have completed the total synthesis of (+)-ineleganolide in an overall longest linear sequence of 23 steps from (–)-linalool. We based our convergent strategy on the union of two fragments, providing a concise endgame with only seven total steps from our coupling partners **5** and **6**. We were able to access a highly strained enone **5**, and develop underutilized esterification conditions for sensitive substrates, employing triphenyl phosphine oxide and oxalyl chloride as activating reagents. Furthermore, we realized an exceptional Michael addition and aldol cascade, constructing a crucial pentacyclic intermediate as a single diastereomer (i.e., **4**→**15**). In the later stage, we discovered a unique air oxidation and epoxidation sequence to install the needed oxidation pattern (i.e., **16**→**17**). Reductive opening of acetoxy epoxide **18** with samarium diiode induced a semi-pinacol shift in the same pot to furnish (+)-ineleganolide (**1**) in good yield. Future efforts will be directed toward shortening the overall step-count, particularly in developing a more concise route to enone **5**. However, our present sequence proved to be scalable and reliable. Additionally, we envision that the developed chemistry can be utilized in solving future problems in the synthesis of related compounds and enable further investigations into the bioactivity of the cembranoid and norcembranoid diterpenoids, specifically (+)-ineleganolide.

ASSOCIATED CONTENT

Supporting Information

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

brief description (file type, i.e., PDF)

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Notes

The authors declare no competing financial interest.

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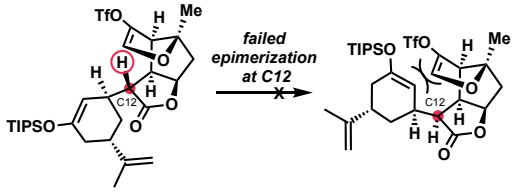

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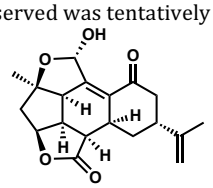

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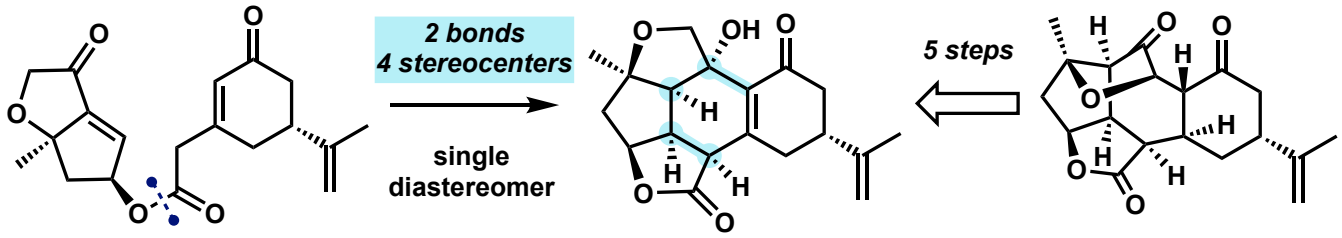
2 bonds
4 stereocenters
single
diastereomer
5 steps
convergent coupling
(+)-ineleganolide