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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Communication

Total Syntheses of Scabrolide B, Ineleganolide, and Related Norcembranoids

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Cite This: J. Am. Chem. Soc. 2025, 147, 130−135
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ABSTRACT: Concise total syntheses of several 5/7/6 norcembranoids, including ineleganolide, scabrolide B, sinuscalide C, and fragilolide A have been achieved through a fragment coupling/ring closure approach. The central seven-membered ring was forged through sequential Mukaiyama−Michael/aldol reactions using norcarvone and a decorated bicyclic lactone incorporating a latent electrophile. Subsequent manipulations installed the reactive enedione motif and delivered scabrolide B in 11 steps from a chiral pool-derived enone. Finally, ineleganolide, sinuscalide C, and fragilolide A were each accessed in one additional step.

Norcembranoid diterpenoids are marine natural products isolated from *Sinularia* soft corals that possess caged, polycyclic structures with diverse oxidation patterns (Figure 1a).[1,2] This family of natural products exhibits several different frameworks, including 5/7/6 and 5/6/7 carbotricyclic ring systems, as exemplified by ineleganolide (**1**),[3] scabrolide B (**2**),[4] sinuscalide C (**3**),[5] fragilolide A (**4**),[6] as well as scabrolide A (**5**)[7] and yonarolide (**6**).[8] Several norcembranoids have reported antileukemia, antithrombotic, and anti-inflammatory activity;[3−11] however, further investigations of bioactivity and its relationship to core structure have been hindered by low isolation yields and a lack of synthetic access to a diverse set of these natural products.[12,13] Nevertheless, over the last three decades, the scientific community has slowly started to breach the nexus of norcembranoid natural products and unravel the biosynthetic relationship between different congeners. Similarly, given the intricate structure and potential utility of the scaffold for further biological investigations,[14] these natural products have drawn significant attention from the synthetic community.[15−32]

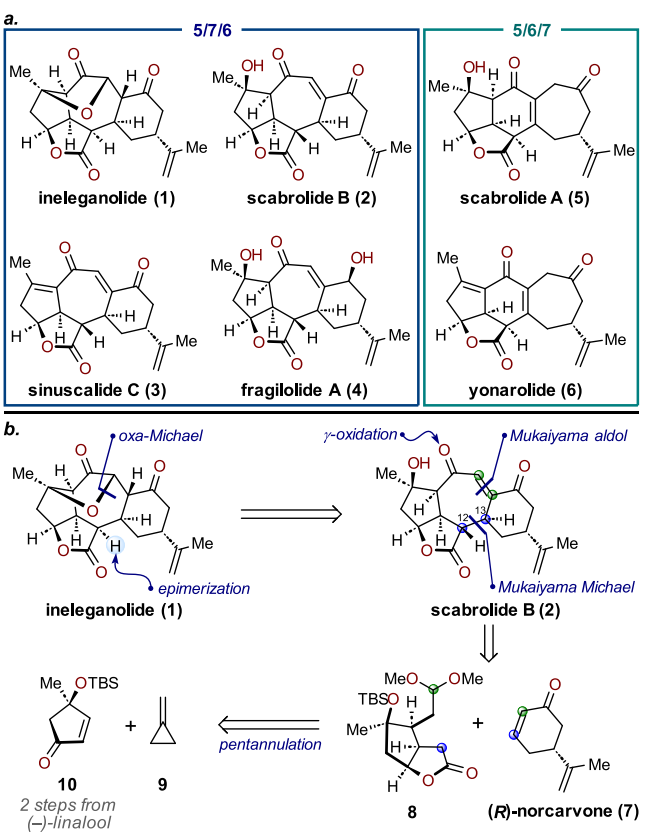


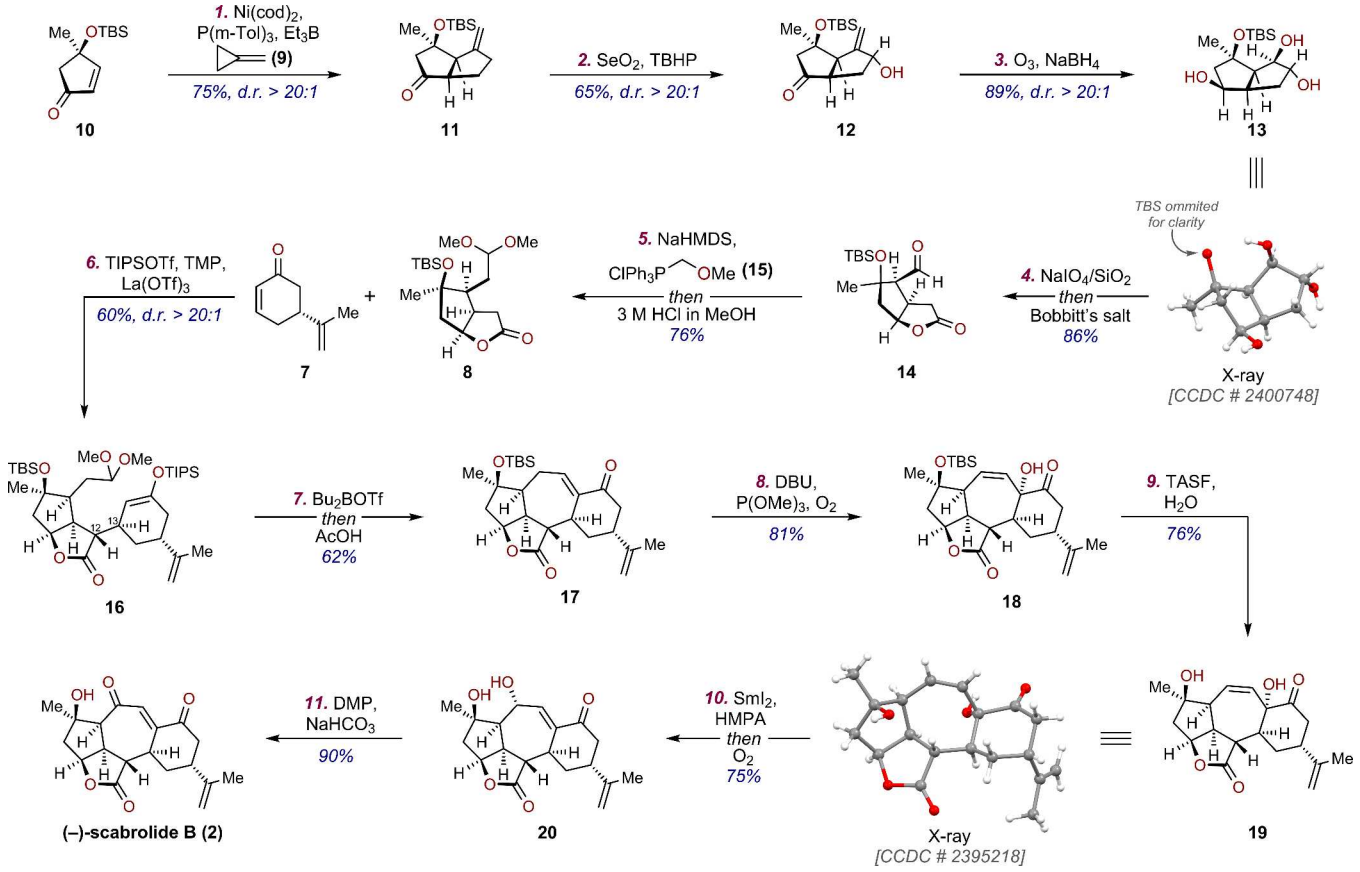
Figure 1. (a) Structures of representative norcembranoid diterpenoids. (b) Retrosynthetic analysis of ineleganolide (1) and scabrolide B (2).

Ineleganolide (**1**) is recognized as a flagship member of the norcembranoid family and possesses a challenging cupped, pentacyclic skeleton containing nine stereocenters, eight of which are contiguous, and a highly substituted central seven-membered ring. Several synthetic studies have been directed toward ineleganolide,[19−25] as well as a biomimetic semisynthesis by Pattenden.[26] The total synthesis of **1** has only recently been achieved by Wood,[27] Stoltz,[28,29] and Fürstner.[30] Moreover, a structural revision of scabrolide B (**2**) has recently been prompted by Fürstner's synthesis of its nominal structure.[31] Efforts by several isolation chemists have also contributed to the structural reassignment of **2** based on investigations of reisolated material. Although once previously published under the name of sinuscalide D,[5] this isolate was found to be spectroscopically identical to the original and reisolated scabrolide B.[4] Furthermore, during the course of our

Received: November 22, 2024
Revised: December 14, 2024
Accepted: December 17, 2024
Published: December 20, 2024

https://doi.org/10.1021/jacs.4c16629
J. Am. Chem. Soc. 2025, 147, 130−135

Scheme 1. Total Synthesis of (−)-Scabrolide B (2)



own investigations, Fürstner and co-workers disclosed their own strategy toward **2**, thus confirming the revision.

Given their intricate structures and underexplored biological activities, we sought to develop a concise synthesis of several ineleganane diterpenoids. Accordingly, we anticipated that a robust route to scabrolide B (**2**) would enable unified access to ineleganolide (**1**), sinuscalide C (**3**), and fragilolide A (**4**) through a single strategy.

Our group has previously disclosed the total synthesis of norcembranoids (−)-scabrolide A (**5**) and yonarolide (**6**), both of which contain a 5/6/7 carbocyclic core (Figure 1a).[32] We recognized the value of our caged lactone-containing 5/5 bicycle toward additional norcembranoids, including a 5/7/6 scaffold. Intrigued by the idea of providing a unified synthesis of multiple ineleganes, we envisioned late-stage conversion of scabrolide B (**2**) to ineleganolide (**1**) by epimerization of the C12 α-lactone proton and formation of the tetrahydrofuran ring through an oxa-Michael reaction (Figure 1b). From a strategic perspective, the construction of scabrolide B (**2**) could be traced back to a convergent fragment union and cyclization between ambiphilic (*R*)-norcarvone (**7**) and acetal lactone **8**. We envisioned a sequential Mukaiyama−Michael and Mukaiyama aldol sequence, which would properly establish the challenging C12−C13 bond and forge a seven-membered ring. Finally, the requisite bicyclic acetal **8** could be traced back to a nickel-catalyzed annulation between Maimone's enone (**10**)[33] and methylenecyclopropane (**9**).

We began our synthetic effort with a [3 + 2] annulation between (−)-linalool-derived cyclopentenone **10** and methylenecyclopropane (MCP, **9**) to deliver **11** with excellent diastereoselectivity (Scheme 1).[32,34,35] Sharpless allylic oxidation[36] provided allylic alcohol **12**, which was exposed to reductive ozonolysis conditions to furnish triol **13** as a single diastereomer. The stereochemical outcome of the reduction was confirmed by X-ray diffraction analysis and indicated approach of the hydrides from the less hindered convex face of the bicycle. Sodium periodate supported on silica gel[37] then cleanly affected cleavage of the diol before subsequent same-pot oxidation of an intermediate lactol to lactone **14** was carried out by the action of Bobbitt's salt.[38] After surveying a variety of conditions, we found that this oxoammonium salt outperformed more conventional reagents for this type of transformation (see the Supporting Information for details). The remaining task to access the desired coupling partner **8** required one-carbon homologation with concomitant installation of a competent electrophile for the envisaged Mukaiyama aldol ring closure. Ideally, this latent electrophile should remain unreactive under the fragment union conditions. We anticipated a dimethyl acetal would serve a dual purpose as a protecting group for the electrophilic and enolizable aldehyde and as a masked electrophile that could be activated with the proper Lewis acid in a subsequent cyclization step. To access the desired acetal, we first exposed aldehyde **14** to the Wittig reagent derived from phosphonium salt **15** and NaHMDS, followed by treatment of this reaction mixture with anhydrous HCl in methanol. This facilitated the complete conversion of an intermediate methyl vinyl ether (not shown) to dimethyl acetal **8**. With the lactone acetal in hand, the stage was then set to explore its coupling with (*R*)-norcarvone (**7**). Previous work from the Vanderwal group had shown that Mukaiyama−Michael addition to (*S*)-norcarvone was most effective under lanthanum catalyzed conditions.[23] Similarly, we found that *in*

https://doi.org/10.1021/jacs.4c16629
J. Am. Chem. Soc. 2025, 147, 130−135

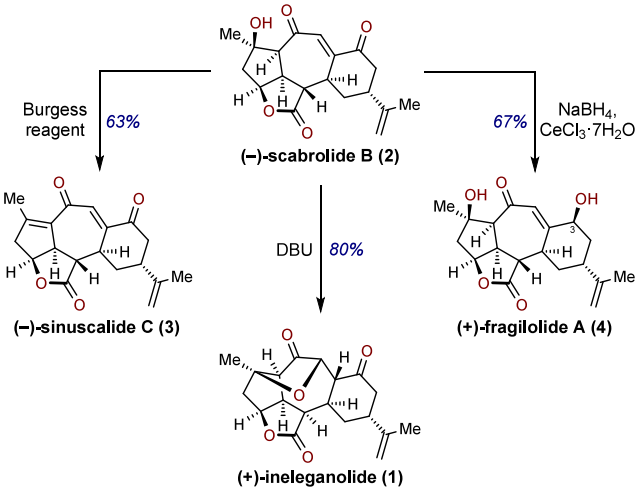
situ generation of the silyl ketene acetal derived from lactone **8** via soft enolization, followed by addition of $La(OTf)_3$ (20 mol %) and (*R*)-norcarvone (**7**), delivered silyl enol ether **16**. This product was isolated as a single diastereomer wherein the silyl ketene acetal nucleophile approached from the face opposite the isopropenyl group while **7** approached the bicycle from the convex face to set the desired stereochemistry at C12 and C13. The importance of precise orchestration of cyclization steps was exemplified by the unilateral failure of our early approaches relying on formation of the C12−C13 bond in an intramolecular fashion, similar to our approach toward scabrolide A (see the Supporting Information for details).

With the fragment coupling achieved, we investigated the key Mukaiyama aldol cyclization to close the seven-membered ring and secure the full skeleton of ineleganane-type diterpenoids. This transformation proved challenging as a variety of Lewis acids, including $SnCl_4$, $TiCl_4$, TMSOTf, $BF_3{\cdot}Et_2O$, and $Sc(OTf)_3$, only provided hydrolysis byproducts. In all cases, even after extended reaction time productive reactivity was not observed. Gratifyingly, we found that treatment of **16** with stoichiometric Bu_2BOTf at −78 °C resulted in rapid formation of the central ring, and *β*-elimination of the resultant methyl ether (not shown) with acetic acid provided enone **17**.[39] Bu_2BOTf was singularly able to accomplish this transformation, and this represents, to our knowledge, the first example of its use in an aldol reaction between a silyl enol ether and an acetal. Although there is one example of using a related reagent, 9BBN−OTf, in an intermolecular context,[40] this type of aldol chemistry has not seen further use in synthesis. It is unclear why this boron Lewis acid is uniquely effective, but we postulate that the silyl enol ether undergoes rapid exchange with Bu_2BOTf[41] and boron enolate formation enables concurrent generation and trapping of the reactive oxocarbenium preceding any deleterious pathways.

With a full 5/7/6 carbocyclic skeleton in place, the final step to complete scabrolide B (**2**) was a challenging *γ*-oxidation. In accordance with Fürstner,[30] all methods for allylic oxidation failed and attempts to form a dienol acetate, methyl or silyl dienol ether for Rubottom oxidation resulted exclusively in the formation of cross-conjugated products. Ultimately, we found that our previously employed aerobic oxidation conditions,[32] utilizing DBU and trimethylphosphite,[42] were suitable to deliver *α*-oxidation product **18** in high yield. Deprotection of the tertiary TBS group at this stage was critical due to the sensitivity of the enone and enedione motifs in downstream intermediates to a variety of deprotection conditions. Treatment of deconjugated enone **18** with TASF and water at 80 °C affected silyl deprotection to afford tertiary alcohol **19**.[43] Single crystal X-ray diffraction analysis of **19** confirmed the stereochemistry at C12 and C13, as well as that of the newly formed tertiary alcohol. Unfortunately, oxidative or redox-neutral transposition of this alcohol to install oxidation at the *γ*-position failed under the standard conditions surveyed. Attempts to translate our previously employed oxidative transposition[32] to this system led to only recovered starting material or decomposition after extended reaction times. Fortuitously, we found that reduction of **19** with SmI_2 led to *α*-elimination of the tertiary hydroxyl group[44,45] and the resulting samarium dienolate could be directly oxidized with O_2 to deliver formal transposition product **20**. During these experiments, we also detected trace amounts of scabrolide B (**2**), presumably arising through hydroperoxide fragmentation.[46] However, all attempts to provide reproducible and high-yielding fragmentation to **2** failed. During these studies, we also observed that oxidation of the Sm(III)-enolate with molecular oxygen was relatively slow. An extended exposure (12 h) of the samarium dienolate to an atmosphere of oxygen was required to form alcohol **20** without a detectable protonation/deoxygenation byproduct after aqueous workup. We suspect that hydroperoxide is rapidly reduced under the reaction conditions, and without accumulation of the hydroperoxide intermediate we could not manipulate it further toward fragmentation. Similar reactivity is precedented in other systems, where reactions of Sm(III) enolates with oxygen produce alcohols, even in the absence of additional reductants.[46,47] While the exact nature of the reduction is not well understood, several pathways have been proposed to explain the O−O bond cleavage under apparently oxidative conditions.[48]

Nonetheless, we could cleanly perform this formal redox-neutral transposition reaction to deliver **20**, and oxidation of the *γ*-alcohol with DMP proceeded smoothly to furnish (−)-scabrolide B (**2**) in 11 steps and 4.0% overall yield from enone **10**. Additionally, the route is scalable and delivered over 80 mg of scabrolide B in total. With ample quantities of **2** in hand, we explored its conversion into ineleganolide (**1**). Recent work from the Fürstner laboratory showed that exposure of scabrolide B (**2**) to weakly basic Et_3N at elevated temperatures could affect its conversion to ineleganolide (**1**), but these conditions also enabled further reaction of **1** and resulted in low isolated yields.[30] On the other hand, we discovered that treatment of **2** with a stronger base at low temperatures cleanly performed the desired transformation of **2** to **1** (Scheme 2). Specifically, DBU in MeCN at 0 °C

Scheme 2. Conversion of (−)-Scabrolide B (2) to (+)-Ineleganolide (1), (−)-Sinuscalide C (3), and (+)-Fragilolide A (4)



afforded ineleganolide (**1**) in 80% yield (3.20% overall yield, 12 steps LLS from **10**), accomplishing both C12 epimerization and oxa-Michael addition to form the THF ring in a single operation. Under the reaction conditions, further rearranged products were not detected and conversion to **1** was not observed to be reversible. Furthermore, TBS-protected scabrolide B (not shown) does not undergo epimerization under the same conditions, nor do intermediates that lack the

https://doi.org/10.1021/jacs.4c16629
J. Am. Chem. Soc. 2025, 147, 130−135

enedione oxidation state. This suggests that oxa-Michael may precede epimerization, and C12 epimerization likely occurs through a *retro*-Michael/Michael mechanism rather than simple deprotonation/reprotonation.

Finally, (−)-scabrolide B (**2**) could be further transformed into several additional ineleganane natural products (Scheme 2), including (−)-sinuscalide C (**3**) and (+)-fragilolide A (**4**). Specifically, dehydration of the tertiary alcohol with Burgess reagent, as disclosed before by Fürstner and others in similar settings,[17,30,32] furnished (−)-sinuscalide C (**3**). On the other hand, the first total synthesis of (+)-fragilolide A (**4**) was achieved by chemoselective Luche reduction of the less hindered C3 ketone from the convex face. Key NOE cross-peaks between the C3 proton and both C13 and the isopropenyl methylene indicate that the hydride was delivered from the bottom face of **2**, consistent with spectroscopic data from the original isolation.

In conclusion, we have accomplished the synthesis of four ineleganane diterpenoids, namely (+)-ineleganolide (**1**), (−)-scabrolide B (**2**), (−)-sinuscalide C (**3**), and (+)-fragilolide A (**4**), in 11 or 12 steps from enone **10**. The salient features of our synthetic approach include MCP pentannulation, which enabled rapid and controlled access to highly decorated bicyclic fragment **8**. The key Mukaiyama−Michael and aldol reactions of lactone acetal **8** with norcarvone efficiently forged the central seven-membered ring, and we expect that the unique role of the Bu_2BOTf may prove useful in similarly challenging ring-closing strategies. The irreversible and complete conversion of (−)-scabrolide B (**2**) into (+)-ineleganolide (**1**) demonstrated a potential biogenetic linkage between these two metabolites. Moreover, by performing dehydration or chemoselective reduction, (−)-scabrolide B (**2**) was also readily converted to (−)-sinuscalide C (**3**) and (+)-fragilolide A (**4**). Importantly, in combination with our previous report, this approach complements and completes the collective synthesis of 5/6/7 and 5/7/6 families of norcembranoids, where the distinct fragment synthesis from a common intermediate and its late-stage union played a vital role in achieving synthetic efficiency. Overall, we expect that we will be able to leverage these syntheses of norcembranoid diterpenoids to thoroughly probe the biological role of these naturally occurring secondary metabolites.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c16629.

Experimental Section including characterization data, NMR spectra of new compounds, and supporting crystallographic information (PDF)

Accession Codes

Deposition Numbers 2395218 and 2400748 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by the University of Illinois (Seemon H. Pines Graduate Fellowship to Y.B.), Bristol-Myers Squibb (predoctoral fellowship to Y.B.), and the National Science Foundation (CHE-2154393). We thank the SCS NMR Lab, Dr. D. Olson, and Dr. L. Zhu (University of Illinois) for technical support and NMR spectroscopic assistance. We also thank Eric Pettipiece and Yianni Lysandrou for their assistance with X-ray crystallographic analysis, and F. Sun for their assistance with mass spectrometric analysis. We acknowledge Samantha Barlock for critical proofreading of this paper.

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