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The Total Synthesis of (–)-Scabrolide A

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Supporting Information Placeholder

ABSTRACT: The first total synthesis of the norcembranoid diterpenoid scabrolide A is disclosed. The route begins with the synthesis of two chiral pool-derived fragments, which undergo a convergent coupling to expediently introduce all 19 carbon atoms of the natural product. An intramolecular Diels–Alder reaction and an enone-olefin cycloaddition/fragmentation sequence are then employed to construct the fused [5–6–7] linear carbocyclic core of the molecule and to complete the total synthesis.

The furanobutenolide-derived polycyclic norcembranoid diterpenoids comprise a family of complex and structurally diverse C_{19} marine natural products isolated from the *Sinularia* soft corals.[1] Biosynthetically, these isomeric compounds are believed to arise from the macrocyclic furanobutenolide norcembranoids following a divergent series of intramolecular cyclizations which give rise to the diverse set of fused ring systems characterizing this natural product class (Figure 1A). Specifically, members of this family typically feature complex, polycyclic carbon frameworks decorated with abundant and synthetically challenging oxygenation patterns and stereochemical arrays. Consequently, despite intense interest from the synthetic community over the past two decades, the polycyclic C_{19} norcembranoid diterpenoids have thus far evaded all total synthesis efforts, highlighting their difficulty as synthetic targets.[1,2,3,4]

Scabrolide A (1), a flagship member of this natural product family, was first isolated by Sheu and coworkers from the soft coral *Sinularia scabra* in 2002 alongside four other novel norcembranoids (scabrolides B–D) and four known norcembranoids, including closely related inelganolide (2).[6] Since its initial isolation, **1** has been demonstrated to inhibit IL-6 and IL-12 production in vitro, suggesting its potential as an anti-inflammatory agent.[7] Structurally, scabrolide A is characterized by a fused [5–6–7] carbocyclic framework featuring six

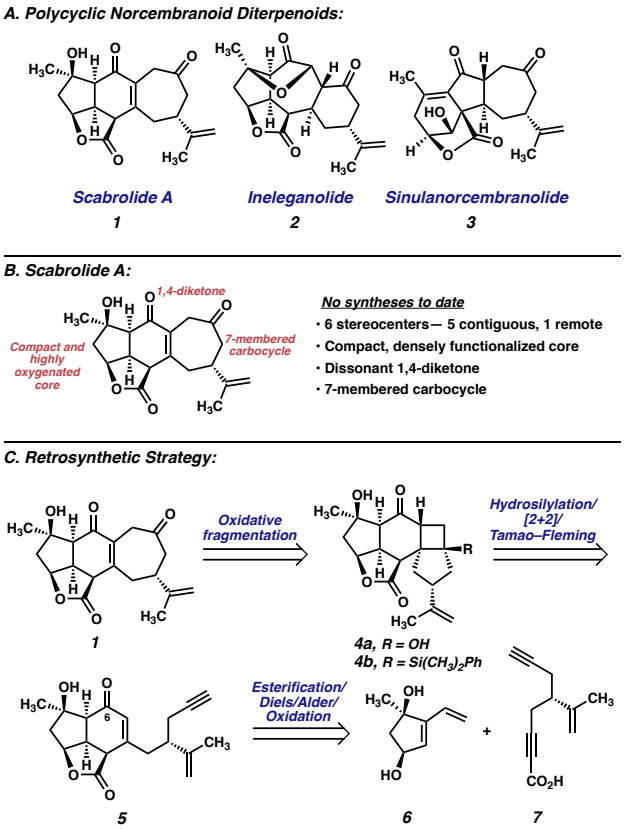
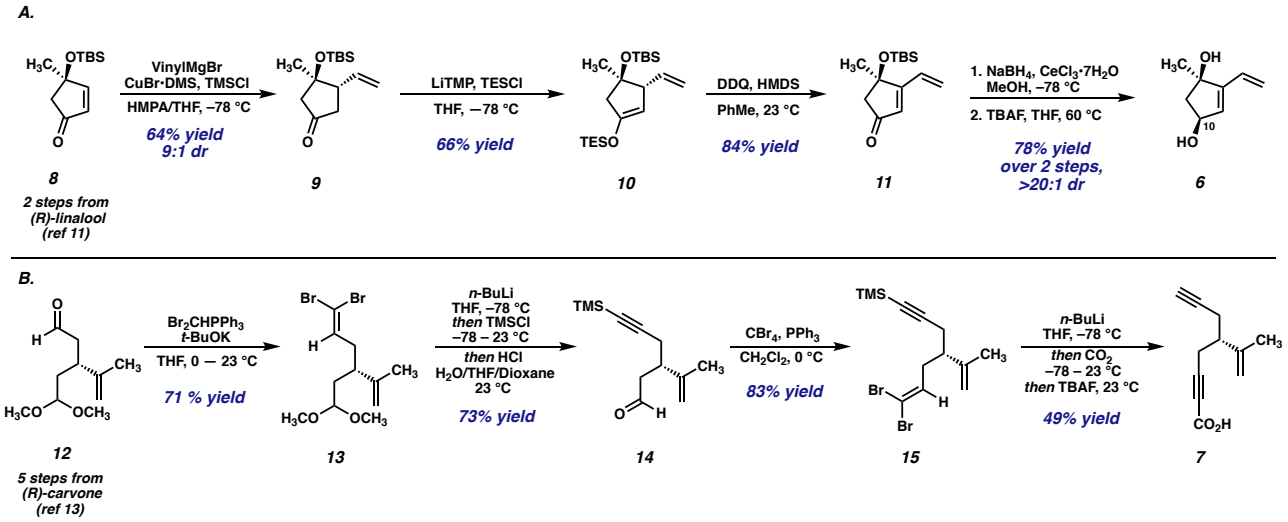


Figure 1. (A) Representative members of the C_{19} polycyclic norcembranoids. (B) Key structural elements of scabrolide A. (C) Retrosynthetic analysis of scabrolide A.

stereogenic centers, five of which are contiguously situated about the compact and densely functionalized western region of the molecule (Scheme 1B). The eastern portion possesses a synthetically challenging cycloheptenone with its ketone positioned in a dissonant 1,4-relationship to the central ring ketone, and a distal stereocenter in the form of an isopropenyl substituent. Owing to the scarcity of this natural product from biogenic sources, its challenging structural complexity from a synthetic perspective, and the exciting biological activity displayed by it, and its closely related congeners, we were



Scheme 1. (A) preparation of dihydroxyvinylcyclopentene **6.** (B) Preparation of ynoic acid **7.**

motivated to pursue a total synthesis of this important target.

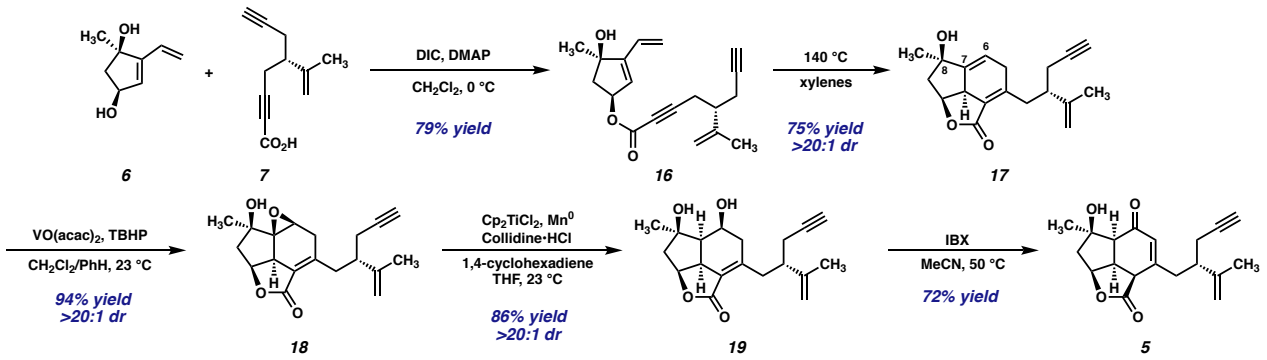
After evaluating several potential strategies, we developed a retrosynthetic analysis of scabrolide A (Figure 1C) hinging upon the late-stage construction of the cycloheptenone ring, which we envisioned as arising from an oxidative fragmentation of a cyclobutanol such as **4a**. We hypothesized that the inherent strain of the four-membered ring might provide a thermodynamic driving force for the formation of the otherwise synthetically challenging 7-membered carbocycle.[8] We imagined that the requisite cyclobutane could be furnished by an intramolecular enone-olefin [2+2] cycloaddition[9] and thus identified enone **5** as a suitable intermediate to interrogate this strategy. Specifically, we planned to employ a hydrosilylation of the terminal alkyne present in **5** to deliver the tethered olefin required for this key transformation. The cycloaddtion would deliver tertiary silane **4b**, which could be converted to **4a** by a Tamao–Fleming oxidation. We envisaged access to enone **5** via an intramolecular Diels–Alder reaction, which would forge the central 6-membered carbocycle of the natural product in a stereocontrolled fashion, followed by oxidative manipulations to install the required oxygenation at C(6) (scabrolide A numbering throughout). Thus, the diene and dienophile for this key step were identified as dihydroxyvinylcyclopentene **6** and ynoic acid **7**, which would be merged through a convergent esterification to set the stage for this cycloaddition.

Our synthetic efforts commenced with the preparation of dihydroxyvinylcyclopentene **6** (Scheme 1A). Although our group previously reported the preparation of this key building block by employing our Pd-catalyzed asymmetric allylic alkylation technology,[2e,10] in the course of this study we were able to streamline its synthesis significantly, as outlined in Scheme 1A. Beginning from known enone **8** (available from (*R*)-linalool in two steps),[11] a conjugate addition/dehydrogenation sequence[12] furnishes dienone **11**, which is then subjected to a diastereoselective Luche reduction, setting the stereochemistry of the secondary alcohol at C(10). Deprotection of the tertiary alcohol then delivers **6** in only 5 steps from enone **8** (seven steps from (*R*)-linalool) as opposed to the 15 steps previously required to access this fragment.

The synthesis of the nearly symmetric ynoic acid **7** is accomplished in four steps from monoprotected dialdehyde **12**, a known compound available in five steps from (*R*)-carvone (Scheme 1B).[13] A Corey–Fuchs homologation installs the terminal alkyne protected as a TMS–acetylene, followed by acid-mediated cleavage of the dimethyl acetal in the same pot. With the second aldehyde now revealed, another Corey–Fuchs sequence is employed to introduce the ynoic acid moiety by quenching of the resultant lithium acetylide with CO_2, and subsequent removal of the TMS group. This sequence proved highly robust, delivering ynoic acid **7** in multigram quantities in a single pass.

With the requisite coupling partners in hand, we focused our efforts on the convergent esterification of diol **6** and acid **7** (Scheme 2). After some experimentation, we discovered that this could be accomplished efficiently utilizing modified Steglich conditions,[14] furnishing ester **16** from an equimolar amount of each fragment in good yield. Having successfully merged **6** and **7**, and now in possession of an intermediate containing all 19 of the carbon atoms of scabrolide A, we turned our attention toward the key Diels–Alder cycloaddition. Gratifyingly, we found that this transformation proceeds smoothly under thermal conditions, and that simply heating ester **16** to 140 °C in xylenes delivers tricycle **17** in good yield, and as a single diastereomer.

Having constructed three of the four rings of scabrolide A, we next concentrated on the conversion



Scheme 2. Convergent esterification of **6** and **7**, and advancement to enone **5.**

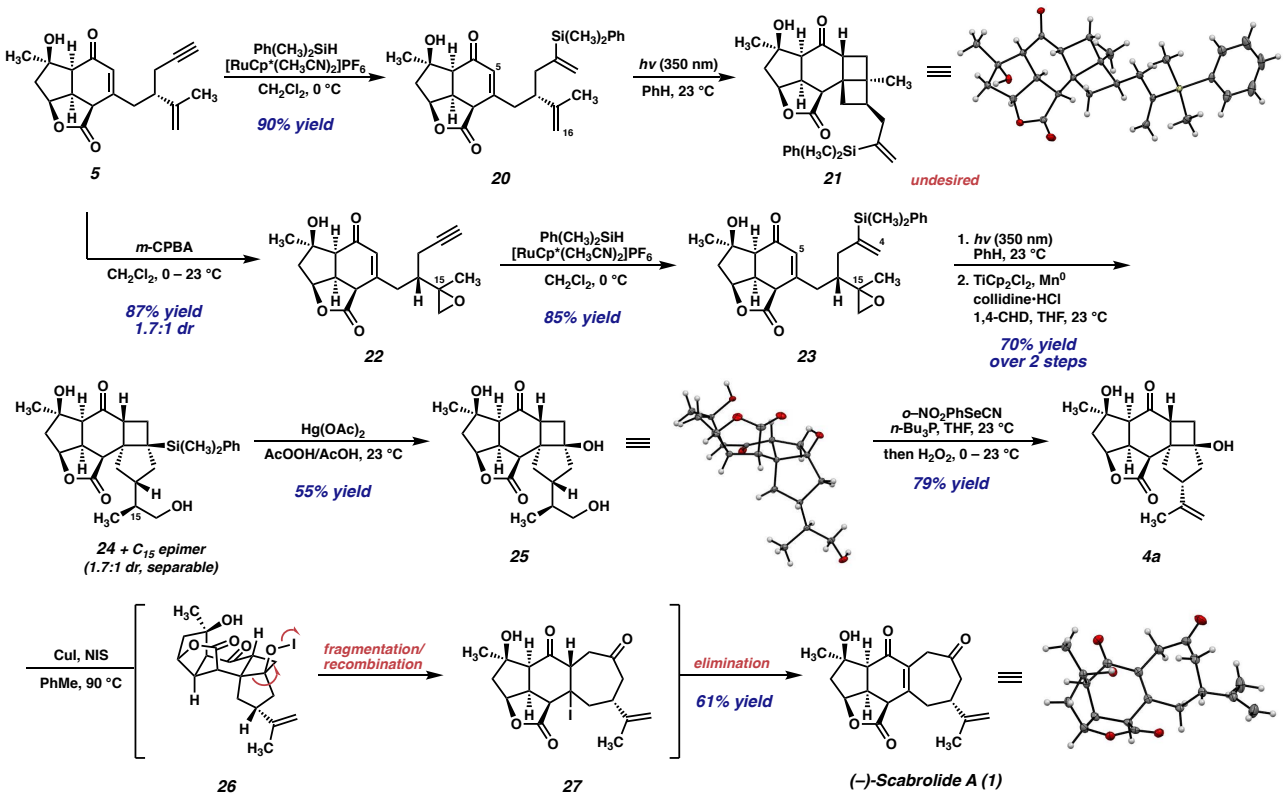
of Diels–Alder adduct **17** to the key intermediate **5**, requiring the net conversion of the $\Delta^{6,7}$ olefin to a carbonyl at C(6), and the migration of the remaining endocyclic olefin into conjugation. This sequence is efficiently initiated with a vanadium-catalyzed epoxidation, directed by the C(8) alcohol, which delivers epoxide **18** in excellent yield and as a single diastereomer. Initially, we hypothesized that epoxide **18** might be converted to enone **5** directly via a Meinwald rearrangement, however, attempts to perform this transformation proved fruitless on this and related systems. Fortunately, a Ti-catalyzed epoxide opening[15] can be employed to cleanly convert **18** to diol **19**. The oxidation of secondary alcohol **19** proved to be unexpectedly challenging, with stalwart conditions such as DMP, TPAP/NMO,[16] and CuOTf/ABNO/O_2[17] failing to effect this transformation in synthetically useful yields. However, upon treatment with IBX in MeCN at 50 °C, enone **5** is furnished in good yield following olefin migration, which occurs spontaneously during purification on silica.

With the western hemisphere of the natural product complete, we set our sights on the [2+2] photocycloaddition and the construction of the cycloheptenone ring. To this end, enone **5** was subjected to a Ru-catalyzed alkyne–selective hydrosilylation,[18] delivering vinyl silane **20** in good yield (Scheme 3). However, we were surprised to find that irradiation of **20** at 350 nm did not lead to formation of the expected fused [6–4–5] ring system (i.e. **4a**, Figure 1C), but instead furnished *cis*-fused [6–4–4] product **21**, the result of a [2+2] cycloaddition between the enone and the isopropenyl olefin. Although we were aware that the formation of undesired adducts such as **21** could compete with formation of the desired [6–4–5] ring system, we were reasonably confident at the outset of this study that these seemingly more strained intermediates would be formed to a lesser degree than **4a**. Thus we were surprised to find **21** as the predominant product of this reaction.

We attribute the conversion of **20** to **21** to an initial 1,6-cyclization between C(5) and C(16), followed by a collapse of the resultant 1,4-diradical to compound **21**. While this is an interesting exception to the "Rule of Fives" typically observed in enone-olefin cycloadditions,[19] examples do exist in which this type of reactivity is observed, especially in cases where the olefin is substituted at the internal position.[20] Furthermore, it is likely that the regiochemical preference for cyclization onto the isopropenyl olefin (as opposed to the silyl-substituted olefin) is a result of the steric encumbrance imposed by the bulky phenyldimethylsilyl group at the desired site of reactivity.

Faced with this issue of regioselectivity in the photocycloaddition, we opted to re-engineer our route accordingly. We reasoned that this problem might be circumvented if the more reactive isopropenyl olefin were to be masked as an epoxide, allowing for the [2+2] photocycloaddition to occur selectively at the desired position. Following the cycloaddition, we planned to remove this epoxide to regenerate the required isopropenyl group. Pursuing this strategy, we found that treatment of enone **5** with *m*-CPBA resulted in selective epoxidation of the isopropenyl olefin, delivering **22** as a mixture of epimers at C(15) in good yield. This mixture is then subjected to the same Ru-catalyzed hydrosilylation conditions, affording [2+2] substrate **23**, again as a mixture of diastereomers, with the isopropenyl unit now suitably masked.

To our delight, irradiation of **23** at 350 nm induces a smooth [2+2] photocycloaddition to produce the desired cycloadduct. Following reductive epoxide opening by Cp_2TiCl, a separable mixture of diol **24** and its C(15) epimer were isolated, each of which could be carried forward through the remainder of the synthesis (see SI for details). Next, the tertiary silane of **24** was converted to the corresponding alcohol via Hg-mediated Tamao–Fleming oxidation. The structure of triols **25** and C(15)-*epi*-**25** (not shown, see SI) were each unambiguously determined via X-ray diffraction, verifying the relative stereochemical configuration about the cyclobutane ring established in the [2+2] cycloaddition. Notably, each of these products possess a *trans*-fused [6–4] ring juncture, which is an



Scheme 3. Formation of unexpected cycloadduct **21** and completion of the total synthesis of scabrolide A (**1**).

uncommon stereochemical outcome of enone-olefin photocycloaddtitions, further highlighting the unique nature of substrates such as **20** and **23** in the context of this transformation. This observation can be explained by invoking a mechanism in which an initial 1,7-cyclization between C(4) and C(5) occurs from the convex (α-) face of the molecule, followed by collapse of the 1,4-diradical from the β-face, which prevents severe steric interactions between the bulky phenyldimethylsilyl substituent and the cyclohexanone ring. Similar stereochemical outcomes (i.e. preferential formation of *trans*-fused adducts) have been reported in analogous systems[21] presumably due to the presence of substitution at the internal position of the reacting olefin.

At this stage, two tasks remained: the elimination of the primary alcohol at C(16) to regenerate the masked isopropenyl group, and the oxidative cyclobutanol fragmentation to furnish the complete [5–6–7] carbocyclic core of the natural product. Although the optimal ordering of these events was at first unclear, extensive experimentation revealed that initial elimination of the hydroxyl group at this point proved to be the successful path forward. To this end, a Grieco dehydration[22] was employed, furnishing penultimate intermediate **4a.** Notably, in this elimination reaction, the two epimers generated during the isopropenyl olefin epoxidation converge to a single compound after ablation of the C(15) stereocenter, setting the stage for the oxidative cyclobutanol fragmentation as the final step of the synthesis.

After a brief survey of conditions, we were delighted to find that, upon treatment with NIS and CuI in toluene at 90 °C,[23] the cyclobutanol smoothly undergoes oxidative fragmentation, furnishing the cycloheptenone ring and completing the total synthesis of scabrolide A (**1**). As shown in Scheme 3, this transformation presumably proceeds through an in situ-generated hypoiodite (**26**), which then undergoes radical fragmentation and recombination to iodide **27**. The β-disposed iodide is then spontaneously eliminated (i.e. E1cB) to the requisite enone present in the natural product. All physical and spectroscopic data of the synthetic material were in good accordance with those reported for natural scabrolide A.[6,24] Additionally, the structure of our synthetic material was determined unambiguously by X-ray diffraction (Scheme 3).

In conclusion, we have disclosed the first total synthesis of the norcembranoid diterpenoid (–)-scabrolide A. To our knowledge, this report constitutes the first total synthesis of any member of the polycyclic C_{19} norcembranoid diterpenoid family, a class of natural products that have evaded synthetic efforts for the more than two decades since their initial isolation. The route exploits the convergent esterification and subsequent intramolecular Diels–Alder cycloaddition of two enantiopure fragments to introduce each of the 19 carbon atoms of the natural product. An initially unsuccessful [2+2] cycloaddition was enabled by an unconventional olefin protection strategy, which allows

for the correct regiochemical outcome of this key reaction. Finally, a late-stage oxidative cyclobutanol fragmentation was employed to furnish the cycloheptenone ring and complete the total synthesis. Efforts are currently ongoing to extend this synthetic strategy toward the synthesis of other norcembranoid diterpenoids, and progress will be reported in due course.

Supporting Information

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

Experimental procedures, spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, HRMS) (PDF)

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Author Contributions

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