

Total Syntheses of Scabrolide A and Yonarolide

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ABSTRACT: The concise total syntheses of oxidized norcembranoid terpenoids (–)-scabrolide A and (–)-yonarolide have been accomplished in 10 and 11 steps, respectively. The carbocyclic skeleton was efficiently constructed from two chiral-pool-derived fragments, including a [5,5]-bicyclic lactone accessed through a powerful Ni-catalyzed pentannulation of functionalized cyclopentenone with methylenecyclopropane and subsequent fragmentation. Additional features included a Liebeskind–Srogl coupling, induction of a cyclization/elimination cascade by a zinc-amido base, and installation of a sensitive enedione motif by late-stage γ -oxidation.

As a rich source of cytotoxic terpenoids, soft corals of the Caribbean Sea have provided inspiration to synthetic chemists and chemical biologists in recent decades.¹ (–)-Yonarolide (**1**) and (–)-scabrolide A (**2**) (Figure 1a) are representative members of a class of norcembranoid diterpenoids first isolated in 1995 from *Simularia*.² Although poor isolation yields have precluded thorough evaluation of their biological activity, preliminary studies have indicated that **2** has anticancer and anti-inflammatory properties. Additionally, several close congeners are known to demonstrate cytotoxic effects.³ Interest in further exploration of their observed biological activity merits the development of an efficient synthetic strategy to access **1** and **2**. These compounds also possess noteworthy structural features, including a unique all-*cis* stereochemical arrangement surrounding the central cyclohexene core and a rich oxidative decoration of the carbon framework. Both **1** and **2** have resisted synthetic efforts for decades; only recently have the Stoltz and Fürstner laboratories disclosed their approaches leading to the first total syntheses of (–)-scabrolide A (**2**).⁴

Motivated by their topological complexity and demand for further biological studies, we sought to develop an efficient synthetic route to **1** and **2** featuring a [5,5]-bicyclic lactone, a conserved motif found in several members of the norcembranoid family.^{5,6} Herein, we report an annulation/fragmentation strategy that enables access to this core in only five steps from readily available material and its application to the total syntheses of (–)-yonarolide (**1**) and (–)-scabrolide A (**2**).

In our retrosynthetic analysis, it was readily apparent that (–)-yonarolide (**1**) could be derived from (–)-scabrolide A (**2**) through dehydration (Figure 1b). We envisioned installing the sensitive 1,4-dicarbonyl motif at the end of the synthesis through γ -oxidation of tetracycle **3**, which could be constructed from [5,5]-bicyclic lactone **4** and cycloheptenyl fragment **5**. Installation of proelectrophilic and pronucleophilic functional handles on **4** and **5** would be necessary for their convergent coupling. Bicyclic lactone **4** could be accessed via a [3 + 2]-annulation between Maimone's enone (**6**)⁷ and methylene

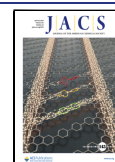
cyclopropane (MCP). Lastly, enones **6** and **7** could both be derived from readily available chiral pool materials.⁸

Our initial synthetic efforts focused on annulation strategies to access bicyclic lactone **4** from enone **6**. A annulation method reported by Noyori et al.⁹ and further developed by Binger et al. (Scheme 1a),¹⁰ which provides complementary regioselectivity to palladium-catalyzed trimethylenemethane (TMM) cycloaddition chemistry,¹¹ seemed well suited to this goal. It was reported that cyclopentenone (**8**) undergoes annulation with methylenecyclopropane (**9**) under nickel catalysis to deliver annulated product **10**. Although diastereoselectivity was a concern for our system, we were pleased to note that, (1) in cases of Lewis acid-mediated conjugate additions to protected γ -hydroxycyclopentenones, additions are known to occur on the more sterically encumbered face of the olefin¹² and that (2) the annulation strategy employs triethylborane as a Lewis acid. Therefore, we hypothesized that this annulation method could be successfully translated to functionalized cyclopentenone **6**.

Indeed, when compound **6** was subjected to Binger et al.'s reported conditions,¹⁰ the annulation adduct **11** was obtained as a single diastereomer resulting from *syn*-addition relative to the sterically bulky *t*-butyldimethylsilyl ether (OTBS) group on the γ -carbon (Scheme 1b). Although these conditions provided irreproducible yields of adduct **11** in 40–60% yield, the desired compound could be reliably accessed in 75% yield after optimization (see the Supporting Information for full details). First, an alternative procedure for the synthesis of volatile MCP (**9**) was adopted for consistent titer and ease of operation (Scheme 1c).¹³ Second, use of P(*m*-Tol)₃ as a ligand improved the stability and reactivity of the active nickel catalyst. Additional experiments revealed the necessity of

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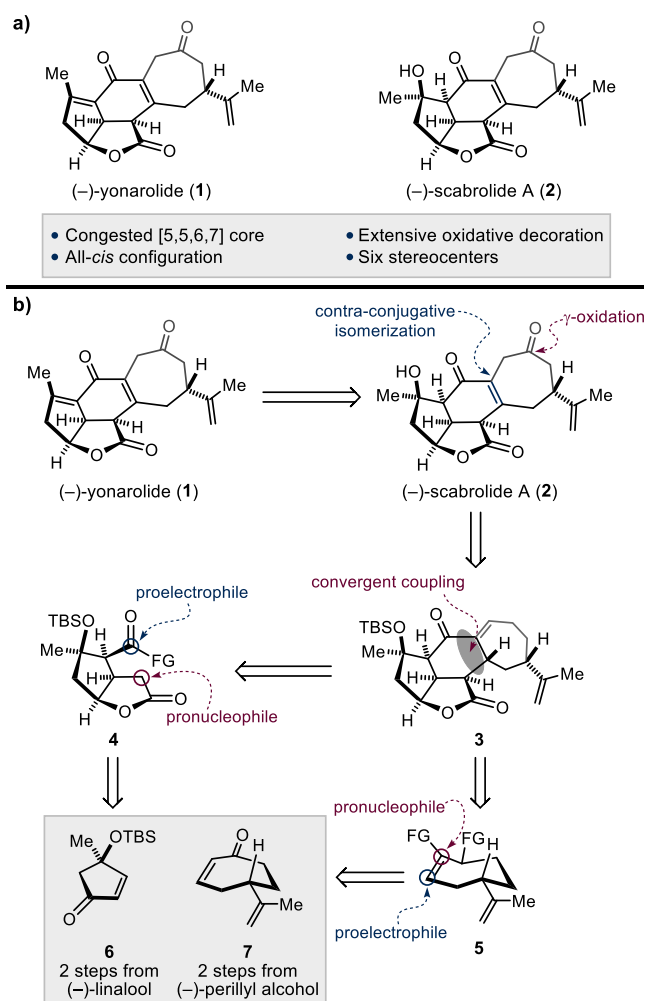


Figure 1. (a) Structures of (-)-yonarolide (1) and (-)-scabrolide A (2). (b) Retrosynthetic analysis.

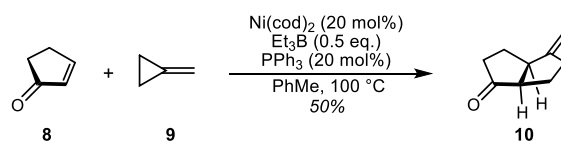
triethylborane as an additive for electrophile activation. Finally, catalyst loadings of the nickel source and triethylborane were lowered to 10 mol % without erosion of yield. The optimized protocol routinely afforded multigram quantities of bicycle 11.

Sharpless allylic oxidation¹⁴ of 11 followed by treatment with ruthenium tetroxide¹⁵ afforded diacid 12 (Scheme 2a). Reduction and careful acidification led to *in situ* lactonization. Finally, Steglich thioesterification¹⁶ afforded thioester 13 in multigram quantities. With scalable access to the western fragment achieved, we turned our attention to constructing the cycloheptenyl coupling partner from 7, which is available in 2 steps from commercial (*S*)-perillyl alcohol.¹⁷ Our intended coupling strategy required installation of both an allylic electrophile and a vinyl nucleophile in fragment 15. To this end, α -iodination¹⁸ followed by Luche reduction¹⁹ afforded alcohol 14, and subsequent etherification secured the appropriate allylic nucleofuge. Finally, sequential lithium–halogen exchange and trapping with tributyltin chloride provided vinyl stannane 15.

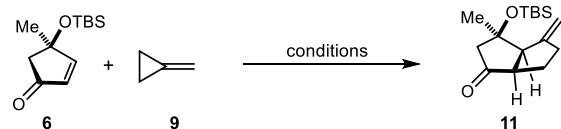
The stage was then set for the convergent assembly of the carbon skeleton. We hypothesized that formation of the C-6/C-7 linkage followed by base-mediated cyclization would provide the central ring with the requisite all-*cis* stereochemical configuration. Liebeskind–Srogl coupling²⁰ afforded tricycle 16 in 89% yield on gram scale. We then investigated C-12/C-

Scheme 1. Optimization of Ni-Catalyzed Annulation

a) Original report (Binger, 1988)



b) Application to enone 6



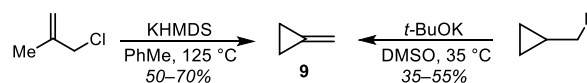
Initial conditions

Ni(cod)₂ (20 mol %), Et₃B (0.5 eq.), PPh₃ (20 mol %), PhMe, 100 °C
Yield: 40–60%, d.r. > 20:1, r.r. > 20:1

Optimized conditions (see SI for details)

Ni(cod)₂ (10 mol %), Et₃B (0.1 eq.), P(*m*-Tol)₃ (10 mol %), Et₂O, 75 °C
Yield: 75%, d.r. > 20:1, r.r. > 20:1

c) Improved synthesis of MCP (9)



Previous synthesis

- inconsistent titer of MCP
- irreproducible
- incomplete conversion

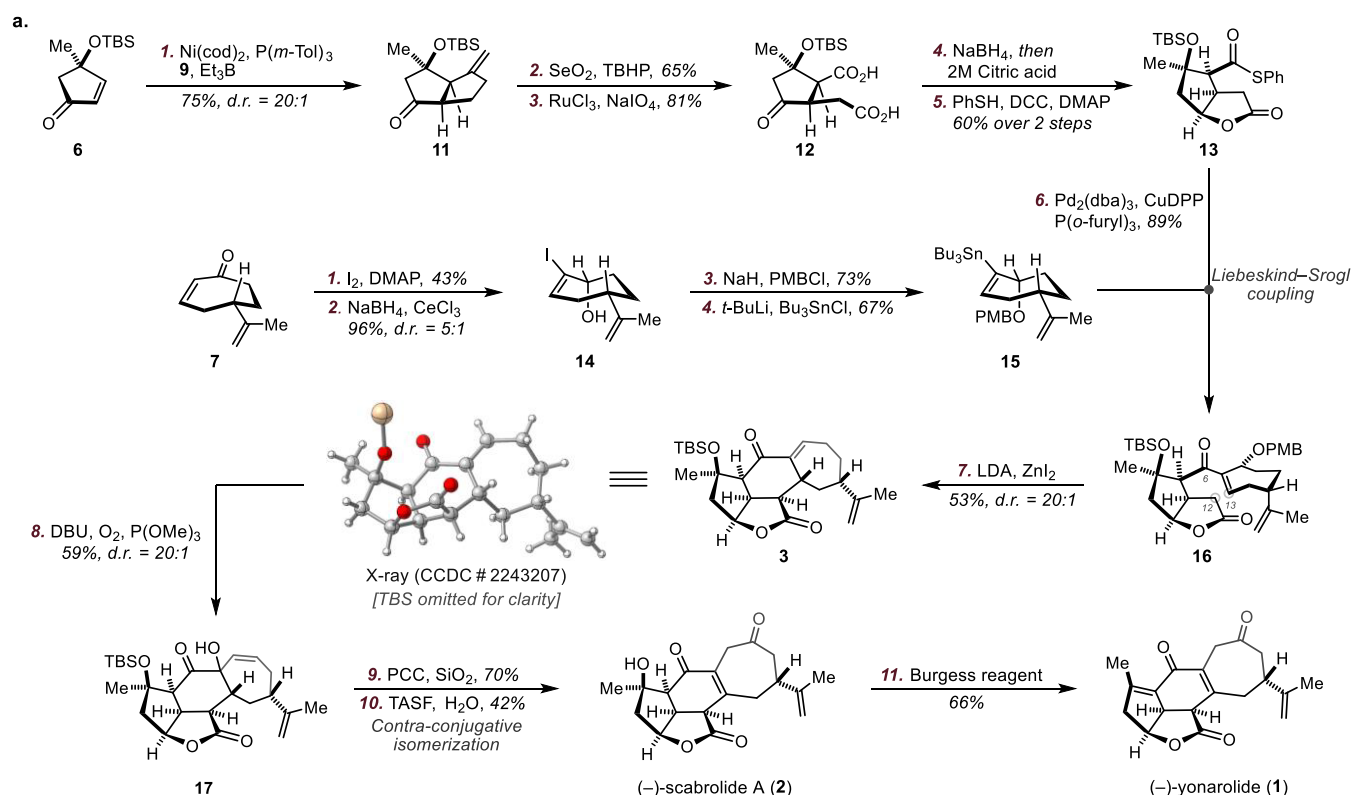
New synthesis

- consistent conversion
- scalable and practical (>10 g)

13 cyclization through an addition/elimination sequence (see the Supporting Information for details). Initial screening of standard amide bases yielded trace conversion to 3 (Scheme 2b). We speculated that a metal additive could promote the desired coupling by chelating the central ketone at C-6 and the proximal PMB-ether, thereby enforcing a reactive conformation for cyclization. The addition of zinc and magnesium salts improved reactivity but provided inconsistent yields. Control experiments indicated that premixing zinc iodide with two equivalents of LDA was necessary, which suggests that a bis-amidozinc base may be operative under the reaction conditions.²¹ The developed protocol was reliable on gram scale and allowed access to tetracycle 3 in 53% yield as a single diastereomer. The stereochemistry at C-12 and C-13 was confirmed with X-ray crystallography.

With the carbon framework fully assembled, we next pursued oxidative decoration of the core. Initial attempts to install the 1,4-dicarbonyl with chromium oxidants²² and traditional allylic oxidation conditions²³ resulted in decomposition or trace conversion (see Scheme 2c and the Supporting Information for details). Therefore, we adopted a two-step oxidative sequence to access the desired enedione. While Rubottom oxidation produced intractable mixtures,²⁴ aerobic oxidation under mild basic conditions provided the α -hydroxy ketone 17 in 59% yield as a single diastereomer.²⁵ The accompanying olefin migration was likely driven by release of ring strain in the eastern hemisphere of the tetracyclic core. Though the stereochemistry of the hydroxyl group could not be assigned with NMR spectroscopy, it was rendered inconsequential by subsequent oxidative transposition. Standard chromium-mediated conditions and oxoammonium salts²⁶ provided the desired 1,4-dicarbonyl in variable yield (Scheme 2d). The observed variability was likely a consequence of product instability. Additional screening revealed that PCC adsorbed on SiO₂²⁷ reliably provided the desired enedione in 70% yield.

Scheme 2. Syntheses of Yonarolide (1) and (–)-Scabrolide A (2)



b. 7. Cyclization	c. 8. Oxidation	d. 9. Oxidative transposition	e. 10. Deprotection
(1) MHDS (M = Na, K) decomp.	(1) CrO ₃ , 3,5-DMP 10%	(1) PCC 26–55%	(1) TBAF, THF elimination
(2) LDA or LHMDS 5–10%	(2) Mn(OAc) ₃ , TBHP decomp.	(2) PCC, NaOAc 40%	(2) TBAF, AcOH no reaction
(3) LDA, ZnCl ₂ 30–40%	(3) Pd(OH) ₂ , TBHP decomp.	(3) PCC, SiO ₂ 70%	(3) TASF, DMF elimination
(4) LDA, ZnI ₂ 53%	(4) Rh ₂ (cap) ₄ , TBHP decomp.	(4) PDC 32%	(4) TASF, H ₂ O (1:2) 17%
(5) LDA, MgBr ₂ decomp.	(5) DBU, O ₂ , P(OMe) ₃ 59%	(5) Bobbitt's salt no reaction	(5) TASF, H ₂ O (1:10) 42%

The final deprotection proved to be challenging because the β -siloxy ether was prone to undergo elimination in both acidic and basic conditions (Scheme 2e). Ultimately, TASF/H₂O²⁸ afforded (–)-scabrolide A (2) in 42% yield through concurrent deprotection/isomerization. Spectroscopic analysis of our synthetic sample matched spectral data from the natural isolate, as well as data provided by Fürstner and Stoltz.⁴ Our synthetic strategy enabled preparation of (–)-scabrolide A (2) in batches >20 mg at a time. Furthermore, (–)-yonarolide (1) was obtained in 66% yield by treating (–)-scabrolide A (2) with Burgess reagent.²⁹

Efficient total syntheses of (–)-scabrolide A (2) and (–)-yonarolide (1) were achieved in 10 and 11 steps (longest linear sequence), respectively, from enone 6. Our synthetic strategy featured a powerful pentannulation with MCP to establish two key stereocenters in a single operation. This method, which has not seen prior use in total synthesis, is analogous to classical TMM-cycloaddition, but synergy between a Lewis acid and nickel catalyst achieved orthogonal regio- and diastereoselectivity. The carbon skeleton was constructed as a single diastereomer from a tandem cyclization/elimination cascade, and the desired natural products were accessed through subsequent chemoselective oxidations. We believe our reported strategy will contribute to future synthetic efforts toward the remaining members in the norcembranoids class of natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c02317>.

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

Accession Codes

CCDC 2243207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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