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Total synthesis and structure–antifouling activity relationship of scabrolide F†

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An efficient synthetic strategy for scabrolide F (**7**), a norcembranolide diterpene that was isolated from the Taiwanese soft coral *Sinularia scabra*, has only recently been reported by our group. Herein, we report details of the first total synthesis of **7**. The tetrahydrofuran domain of **7** was stereoselectively constructed *via* the 5-*endo*-*tet* cyclization of a hydroxy vinyl epoxide. The reaction of alkyl iodide **30** with dithiane **38**, followed by the introduction of an alkene moiety, afforded allylation precursor **41**. The coupling of alkyl iodide **42** and allylic stannane **43** was examined as a model experiment of allylation. Because the desired allylated product **44** was not obtained, an alternative synthetic route toward **7** was investigated instead. In the second synthetic approach, fragment–coupling between alkyl iodide **56** and aldehyde **58**, macrolactonization, and transannular ring-closing metathesis were used as the key steps to achieve the first total synthesis of **7**. We hope that this synthetic strategy provides access to the total synthesis of other macrocyclic norcembranolides. We also evaluated the antifouling activity and toxicity of **7** and its synthetic intermediates toward the cypris larvae of the barnacle *Amphibalanus amphitrite*. This study is the first to report the antifouling activity of norcembranolides as well as the biological activity of **7**.

Introduction

Marine organisms produce many secondary metabolites with diverse chemical structures and biological activities.[1] These marine natural products are regarded as potential lead compounds in drug discovery and development.[2] 5-*epi*-Sinuleptolide (**1**, Fig. 1) was isolated from *Sinularia leptoclados* as the first example of a norcembranolide diterpene in 1978.[3] Since then, a number of reports on macrocyclic and polycyclic norcembranolide diterpenes isolated from the soft corals of the genus *Sinularia* have been published.[4] Norcembranoids exhibit various biological activities,[4] and cembranoids are suggested to act as chemical defense substances against predators.[5] The originally proposed relative configuration of **1**, which was not named in the isolation paper, was determined using spectroscopic methods and X-ray crystallography.[3] Fenical and Clardy's research group reported the isolation and structural determination of **1** and its C11 stereoisomer in 1985, which revised the C11 stereochemistry of natural product **1**.[6] The natural product sinuleptolide (**3**), which is the C5 stereoisomer of **1**, was isolated and structurally elucidated by Umeyama *et al.* in 1993.[7] Therefore, the name 5-*epi*-sinuleptolide is used for natural product **1**. 5-*epi*-Sinuleptolide acetate (**2**) was obtained by both the derivatization of natural product **1** [8] and isolation from a natural source.[9]

Sheu *et al.* elucidated the absolute configurations of **1** and **3** by applying a modified Mosher method in 2005.[10] The relative stereostructures of 10-*epi*-gyrosanolide E (**4**)[6,11] and scabrolides D (**5**),[12] E (**6**),[13] and F (**7**)[13] were clarified using spectroscopic analysis, X-ray crystallography, and comparison of their NMR data with those of **1** and **3**. The relative configurations of scabrolide A (**8**)[12,14] and yonarolide (**9**),[14,15] which are representative polycyclic norcembranolides, were assigned based on a detailed 2D NMR analysis to be a [5,6,7] fused carbocyclic system linked to a γ-lactone moiety. Ineleganolide (**10**) has a highly fused and oxygenated structure including a [5,7,6] carbon skeleton, which was determined using spectroscopic and X-ray diffraction analyses.[14,16] Among these norcembranolide diterpenoids, 5-*epi*-sinuleptolide (**1**) has been reported to show selective cytotoxicity against pancreatic cancer cells[17] as well as decreased extracellular matrix expression during biofilm formation.[18] 5-*epi*-Sinuleptolide acetate (**2**) is moderately cytotoxic toward human tumor cell lines,[9] and induces not only apoptosis in HL60 human leukemia cells by inhibiting Hsp90

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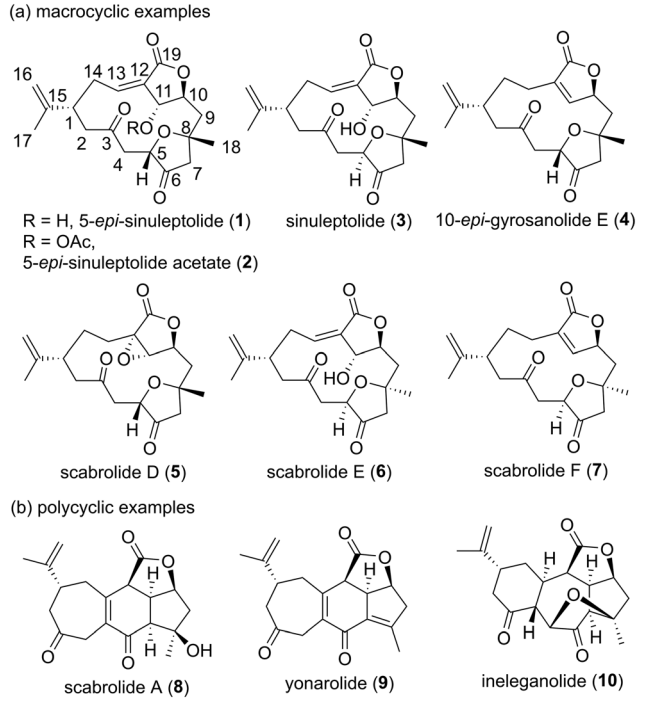


Fig. 1 Structures of selected norcembranolides **1–10**.

but also mitochondrial stress.[19] Sinuleptolide (**3**) exhibits antiproliferative activity against oral cancer Ca9–22 cells by inducing apoptosis, oxidative stress, and DNA damage.[20]

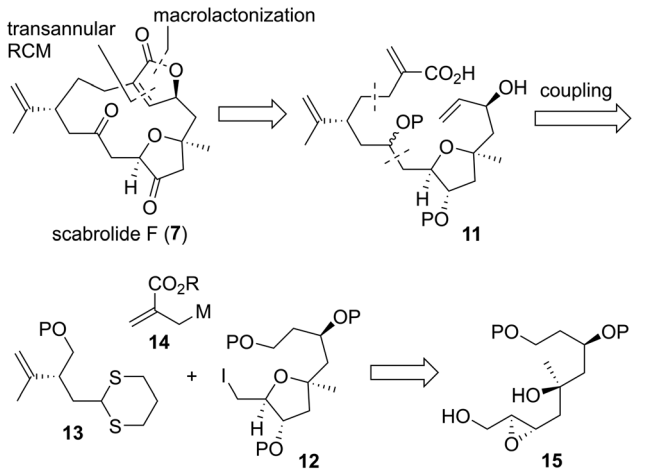
Compounds **1** and **3** have been reported to be dose-dependent inhibitors of TNF-α production;[21] they also inhibit the growth of KB and Hepa59T/VGH cancer cells with 50% effective dose (ED_{50}) values of 2.3–2.6 μg mL^{-1}.[12,22] Thao *et al.* reported the ability of scabrolide A (**8**) to inhibit IL-12 and IL-6 production with 50% inhibitory concentrations of 23.5 and 69.9 μM, respectively.[23] The same group found **1** to exhibit peroxy radical-scavenging activity and electron-donating capacity to reduce Cu(II) to Cu (I).[24] Yonarolide (**9**), a dehydration product of **8**,[4a,b] displays inhibitory activity on NF-κB transcriptional activation in HepG2 cells.[25] Ineleganolide (**10**) has been reported to inhibit the growth of P388 cells with an ED_{50} value of 3.82 μg mL^{-1}.[16] Polycyclic norcembranolides **8–10** have been proposed to be biosynthetically derived from macrocyclic norcembranolide **1** through transannular Michael addition and dehydration.[4a,b,26] Therefore, the development of a synthetic route toward macrocyclic norcembranolides would lead to a consistent supply of polycyclic norcembranolides by total synthesis.

Norcembranolides have attracted much attention from the natural product synthesis community owing to their structural complexity, wide range of biological activities, and biosynthetic relationships between macrocyclic and polycyclic norcembranoids. Two reports on the total synthesis of macrocyclic norcembranolide diterpenoids have been published. Theodorakis *et al.* completed the racemic total synthesis of **4** and **5** in 2011, which revised the C11,C12-epoxide stereochemistry of natural product **5**.[27,28] In the same year, Lee *et al.* achieved the enantioselective total synthesis of (+)-**4** (an enantiomer of **4**), which revealed the absolute configuration of natural (−)-10-*epi*-gyrosanolide E to be **4**.[29] Synthetic efforts toward polycyclic norcembranolides have culminated in recent reports of the enantioselective total synthesis of (−)-scabrolide A (**8**) by the groups of Stoltz,[30a,b] Fürstner,[31] Sarlah,[32] and Zhang;[33] (−)-yonarolide (**9**) by the groups of Stoltz[30b] and Sarlah;[32] and (+)-ineleganolide (**10**) by the groups of Wood[34] and Stoltz.[30c] In our work on the chemical synthesis and biological evaluation of cembranolides[35] and norcembranolides, we reported the first total synthesis of (−)-scabrolide F (**7**) as a communication in 2022.[36] However, we did not discuss our complete synthetic approaches to obtain this compound or investigate its biological properties. Herein, we disclose the full details of our first and second synthetic approaches toward **7**, and describe the antifouling activity and toxicity of **7** and its synthetic intermediates toward the cypris larvae of the barnacle *Amphibalanus amphitrite*. Our successful synthetic strategy toward **7**, which includes fragment–coupling, macrolactonization, and transannular ring-closing metathesis (RCM) as key steps, can be useful in the total synthesis of other macrocyclic norcembranolides. To the best of our knowledge, this study is the first to report the biological activity of **7** and the antifouling activity of norcembranolides.

Results and discussion

Retrosynthetic analysis

Macrocyclic norcembranolides have a 14-membered carbon framework and butenolide or butenolide-related structures, as shown in Fig. 1. Initially, we analyzed the retrosynthesis of **7** (Scheme 1), which would be applicable to other macrocyclic norcembranolides. Hydroxycarboxylic acid **11** was designed as the key synthetic intermediate to reach **7**. We investigated two possible transformations from **11** to **7**, namely, macrolactonization[37]/transannular RCM[38] and RCM/lactonization sequences. We selected the former because this sequence

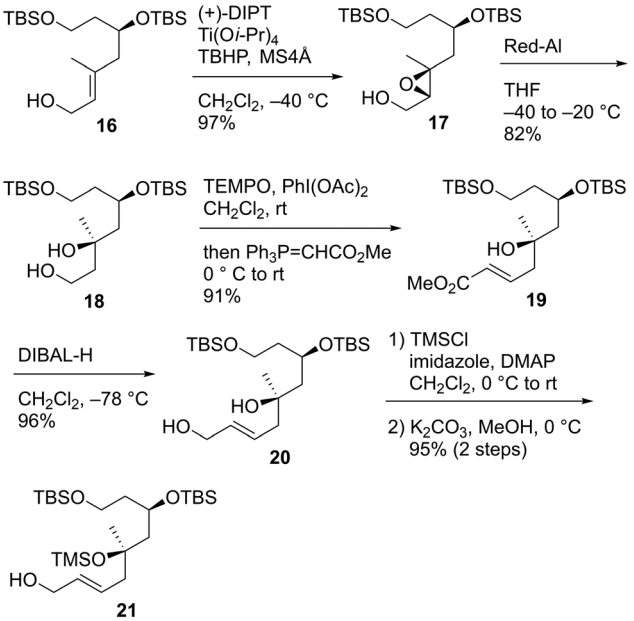


Scheme 1 First generation retrosynthetic analysis of scabrolide F (**7**).

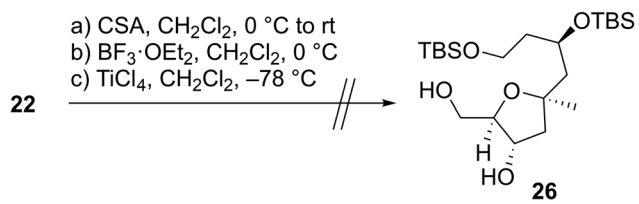
could control the alkene geometry of the RCM product.[39] We planned to synthesize **11** by connecting alkyl iodide **12**, dithiane **13**, and allylic metal reagent **14**. 2,5-*cis*-Disubstituted-3-oxygenated tetrahydrofuran **12**[40] could be obtained *via* the 5-*endo-tet* cyclization of epoxy diol **15**.

Synthesis of the tetrahydrofuran fragment

We first examined the stereoselective synthesis of the tetrahydrofuran fragment. The treatment of the known allylic alcohol **16**, which was prepared from L-aspartic acid in an optically pure form,[41] with (+)-diisopropyl tartrate (DIPT)/Ti(O*i*-Pr)$_4$/*tert*-butyl hydroperoxide (TBHP)/molecular sieves (MS) 4Å (ref. 42) gave epoxy alcohol **17** in 97% yield as a single diastereomer (Scheme 2).[43] The obtained epoxide **17** was subjected to regioselective reductive ring-opening with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[44] to afford 1,3-diol **18**. The oxidation of **18** with 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO)/PhI(OAc)$_2$ [45] and Wittig olefination of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ were carried out in a one-pot operation to provide α,β-unsaturated ester **19**. The reduction of **19** with diisobutylaluminum hydride (DIBAL-H), protection of the resulting diol **20** as the bis-trimethylsilyl (TMS) ether, and selective removal of the primary TMS group afforded allylic alcohol **21**. We then optimized the reaction conditions in the diastereoselective epoxidation of allylic alcohols **20** and **21** (Table 1). When we applied Sharpless epoxidation conditions[42] with (+)-diethyl tartrate (DET) to **20**, the desired epoxy diol **22** was produced as a single diastereomer;[43] however, the chemical yield of **22** was 22%, and the starting material **20** was recovered in 73% yield (entry 1). Changing the starting material from tertiary alcohol **20** to tertiary TMS ether **21** under the same conditions quantitatively provided the desired epoxy alcohol **24** as the sole product (entry 2). When we treated diol **20** with *meta*-chloroperoxybenzoic acid (*m*CPBA) under substrate-directed conditions, we fortunately observed the quantitative formation of **22** as a single diastereomer (entry 3).[46] The *m*CPBA-mediated epoxidation of tertiary TMS ether **21** afforded a diastereomeric mixture of **24** and **25** in a 1 : 1.2 ratio and 86% combined yield (entry 4). A comparison of the results obtained in entries 3 and 4 revealed that the tertiary alcohol moiety was essential for high diastereoselectivity during *m*CPBA epoxidation. With cyclization precursor **22** in hand, we attempted the 5-*endo-tet* cyclization of **22** (Scheme 3). The

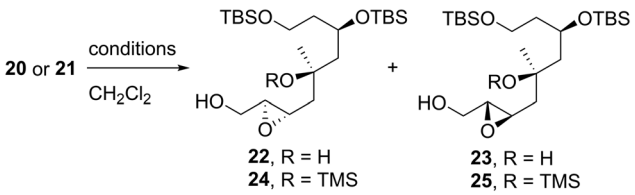


Scheme 2 Synthesis of epoxidation precursors **20** and **21**.



Scheme 3 Unsuccessful attempt for the 5-*endo-tet* cyclization of epoxy diol **22**.

Table 1 Diastereoselective epoxidation of allylic alcohols **20** and **21**

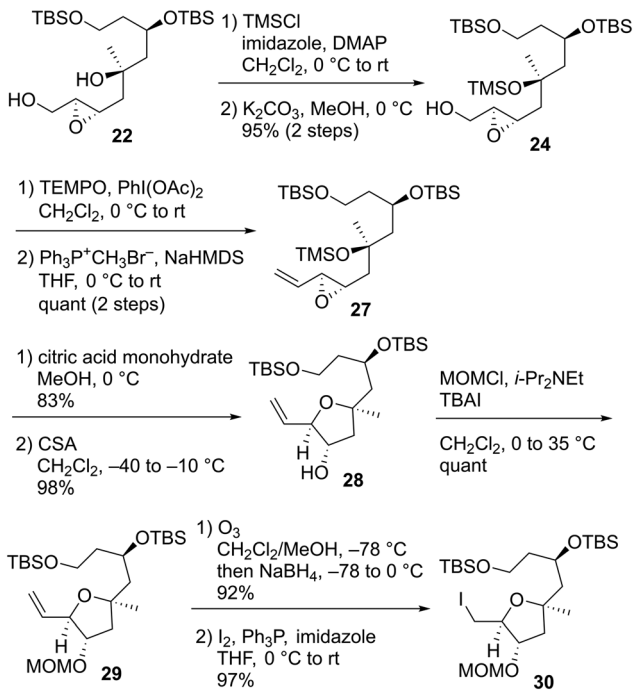


Entry	Allylic alcohol	Conditions	Yield[a]	Diastereomeric ratio[b]
1[c]	**20**	(+)-DET, Ti(O*i*-Pr)$_4$, TBHP, MS4Å, −40 to −20 °C	22%	**22** : **23** > 20 : 1
2	**21**	(+)-DET, Ti(O*i*-Pr)$_4$, TBHP, MS4Å, −40 to −20 °C	quant	**24** : **25** > 20 : 1
3	**20**	*m*CPBA, −40 to 0 °C	quant	**22** : **23** > 20 : 1
4	**21**	*m*CPBA, −40 to 0 °C	86%	**24** : **25** = 1 : 1.2

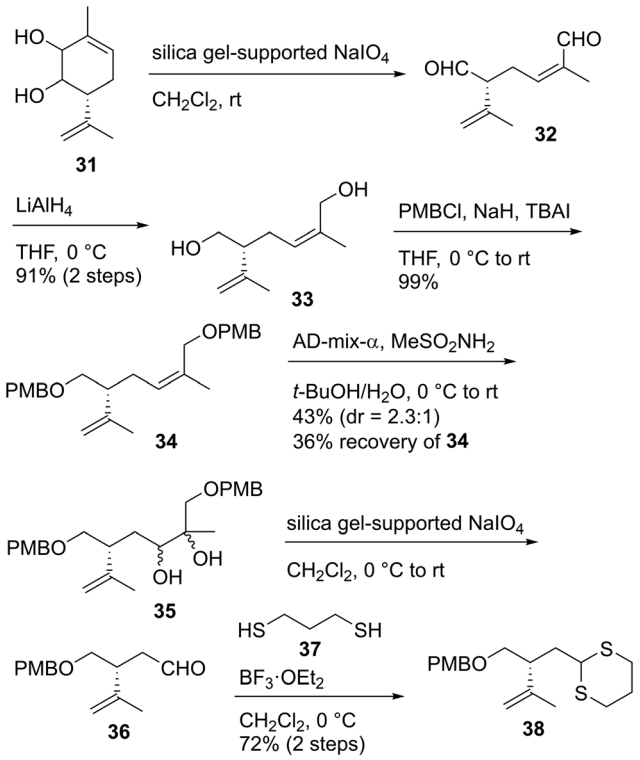
[a] Isolated yield. [b] Based on ^{1}H NMR analysis. [c] 73% Recovery of starting material **20**.

treatment of **22** with camphorsulfonic acid (CSA)[47c] as a Brønsted acid gave a complex mixture without the desired product **26**. The use of $BF_3{\cdot}OEt_2$ (OEt = diethyl ether)[47a,c] and $TiCl_4$ [47b] as Lewis acids did not produce tetrahydrofuran **26**. Given these unsuccessful results, we changed the cyclization precursor from epoxy diol **22** to the corresponding hydroxy vinyl epoxide[48] to promote 5-*endo-tet* cyclization.

The synthetic route toward tetrahydrofuran **30** is described in Scheme 4. The silylation of diol **22** with trimethylsilyl chloride (TMSCl), followed by the reaction of the resulting bis-TMS ether with K_2CO_3 in methanol (MeOH), gave alcohol **24** in 95% yield in two steps; this product was also stereoselectively obtained by the Sharpless epoxidation of **21**, as shown in Table 1. Epoxy alcohol **24** was subjected to TEMPO oxidation[45] and Wittig methylenation to quantitatively afford vinyl epoxide **27** in two steps. The TMS protecting group of tris-silyl ether **27** was selectively removed using citric acid monohydrate in MeOH to give the tertiary alcohol. The 5-*endo-tet*-cyclization of the obtained hydroxy vinyl epoxide[48] proceeded smoothly with CSA at temperatures ranging from −40 to −10 °C to produce tetrahydrofuran **28** in 98% yield. The resulting hydroxy group of **28** was protected with methoxymethyl chloride (MOMCl)/*N*,*N*-diisopropylethylamine (*i*-Pr_2NEt)/tetra-*n*-butylammonium iodide (TBAI) to yield **29**, which was subjected to ozonolysis/reduction and the subsequent iodination of the obtained alcohol with I_2/triphenylphosphine (Ph_3P)/imidazole to afford alkyl iodide **30**.



Scheme 4 Synthesis of tetrahydrofuran **30**.

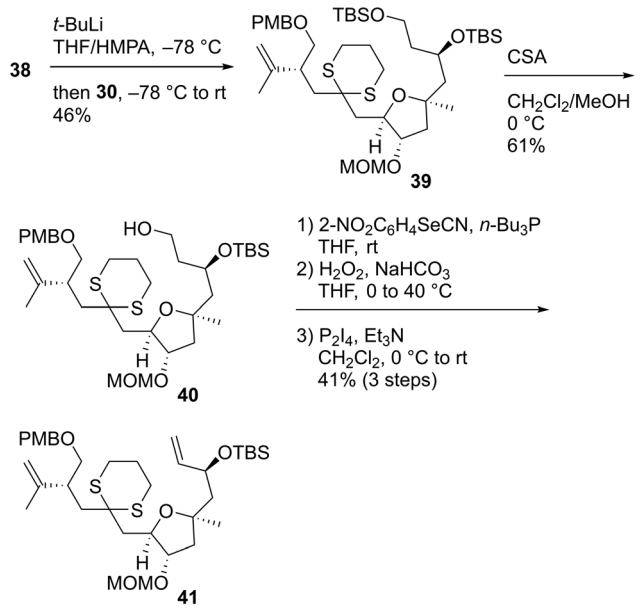


Scheme 5 Synthesis of dithiane **38**.

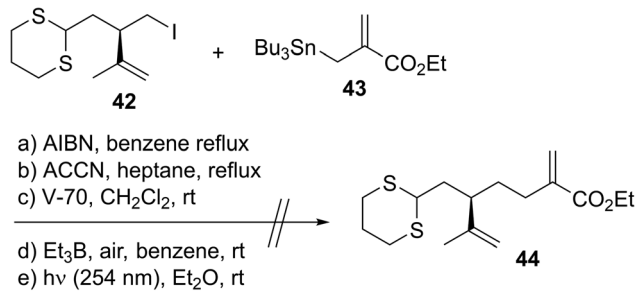
First synthetic approach

Having stereoselectively synthesized tetrahydrofuran fragment **30**, we investigated the enantioselective synthesis of dithiane **38**, which is the coupling partner of **30** (Scheme 5). The oxidative cleavage of 1,2-diol **31**, which was prepared from (*S*)-carvone in three steps,[49] was conducted with silica gel-supported $NaIO_4$ [50] to give the known dialdehyde **32**.[49] The unstable compound **32** was immediately reduced with $LiAlH_4$ to afford diol **33** in 91% yield in two steps. The protection of **33** with *p*-methoxybenzyl chloride (PMBCl)/NaH/TBAI provided bis-PMB ether **34** in 99% yield. The regioselective dihydroxylation of the trisubstituted alkene moiety of **34** possessing the disubstituted terminal alkene group was performed using AD-mix-α[51] to produce diol **35** as a 2.3 : 1 diastereomeric mixture in 43% yield, along with recovered **34** in 36% yield. When we extended the time or increased the temperature in this reaction, the formation of a byproduct in which the disubstituted alkene part was also dehydroxylated was observed. The use of AD-mix-β or OsO_4/*N*-methylmorpholine *N*-oxide (NMO) did not improve the chemical yield. Diol **35** was subjected to scission oxidation using silica gel-supported $NaIO_4$ [50] to yield aldehyde **36**, which was subsequently reacted with 1,3-propanedithiol (**37**)/$BF_3{\cdot}OEt_2$ to furnish dithiane **38**.

With both coupling precursors **30** and **38** in hand, we proceeded to connect these two compounds (Scheme 6). The deprotonation of dithiane **38** with *t*-BuLi in tetrahydrofuran (THF)/hexamethylphosphoric acid triamide (HMPA) was followed by a reaction with alkyl iodide **30** to produce the desired coupling product **39** in 46% yield.[52] The primary *tert*-butyldimethylsilyl (TBS) moiety of **39** was selectively removed using CSA in CH_2Cl_2/MeOH to afford alcohol **40**. The reaction of **40** with 2-$NO_2C_6H_4SeCN$/*n*-Bu_3P[53] and subsequent oxidation with

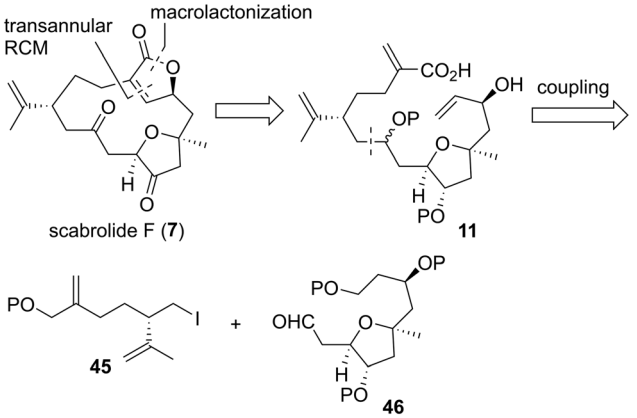


Scheme 6 Synthesis of dithiane **41**.



Scheme 7 Unsuccessful model study of allylation.

H_2O_2 gave the corresponding monosulfoxide to which the terminal alkene moiety was successfully introduced. The resulting dithiane monoxide was deoxygenated using P_2I_4/Et_3N,[54] and dithiane **41** was obtained in 41% yield in three steps. Our next task was to transform **41** to the macrolactonization precursor, which corresponds to compound **11** in Scheme 1. We conducted a model study of allylation using alkyl iodide **42**[55] and allylic stannane **43**,[56] as described in Scheme 7. Although we applied several radical reaction conditions, we did not obtain the desired product **44**. The use of 2,2′-azobisisobutyronitrile (AIBN)[56] as a radical initiator in benzene under reflux gave a complex mixture. When we used 1,1′-azobis(cyclohexanecarbonitrile) (ACCN)[57d] in heptane under reflux, the starting material **42** was consumed, but several byproducts with unidentified structures were formed. When we conducted the reaction using 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile) (V-70)[57c] at room temperature, compound **42** was recovered in 52% yield. The use of Et_3B/air[57a] at room temperature recovered **42** in 55% yield. The photoirradiation reaction at 254 nm (ref. 57*b*) yielded a complex mixture. These unsuccessful outcomes motivated us to change our synthetic plan toward **7**.



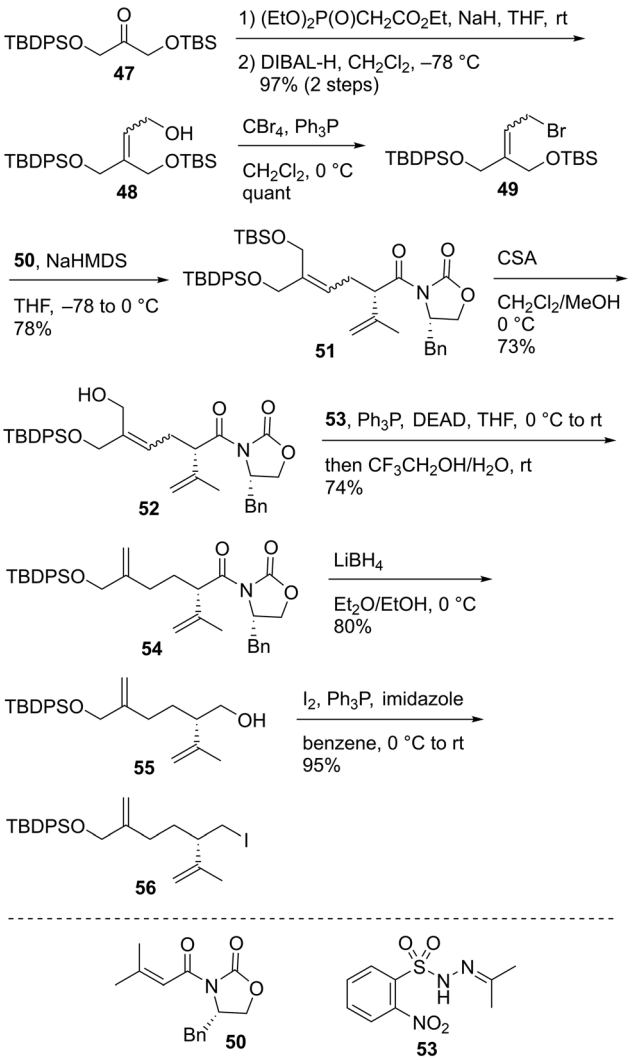
Scheme 8 Second generation retrosynthetic analysis of scabrolide F (**7**).

Second synthetic approach

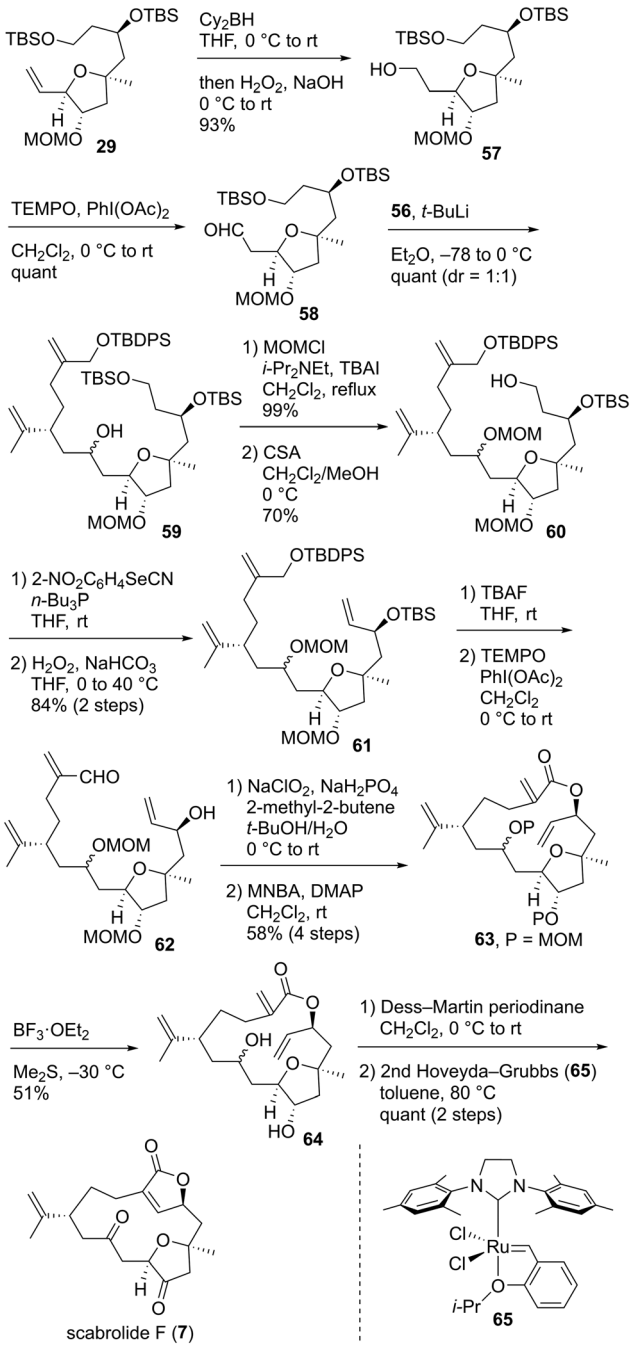
As in the case of the first retrosynthetic analysis, hydroxycarboxylic acid **11** was set as the key synthetic intermediate toward **7** in the second synthetic plan (Scheme 8). We planned to synthesize **11** in a convergent manner by fragment–coupling between alkyl iodide **45** and aldehyde **46**.

The enantioselective synthesis of alkyl iodide **56** commenced from the known ketone **47** (Scheme 9).[58] The treatment of **47** with $(EtO)_2P(O)CH_2CO_2Et$/NaH and subsequent reduction of the resulting α,β-unsaturated ester using DIBAL-H afforded allylic alcohol **48** in 97% yield in two steps as a 1.5 : 1 mixture of geometric isomers. Compound **48** was reacted with CBr_4/Ph_3P to provide allylic bromide **49**. The obtained compound **49** was subjected to Evans asymmetric alkylation[59] using chiral imide **50**[60] to produce the allylated product **51** in 78% yield. The TBS protective group of bis-silyl ether **51** was selectively removed using CSA to give allylic alcohol **52**. The reductive transposition of allylic alcohol **52** was realized using the conditions reported by Movassaghi *et al.*[61] The reaction of **52** with *N*-isopropylidene-*N*′-2-nitrobenzenesulfonyl hydrazine (**53**)/Ph_3P/diethyl azodicarboxylate (DEAD) afforded the corresponding Mitsunobu adduct, which was subjected to hydrolysis using CF_3CH_2OH/H_2O with the subsequent sigmatropic release of N_2 to give diene **54** in 74% yield. Imide **54** was reduced to alcohol **55** using $LiBH_4$ in 80% yield, and the reaction of **55** with I_2/Ph_3P/imidazole furnished alkyl iodide **56** in 95% yield.

Having successfully prepared coupling precursor **56**, we focused on the connection of the fragments and their subsequent transformation toward the total synthesis of **7**. The hydroboration of alkene **29** and oxidative work-up afforded alcohol **57**, which was oxidized with TEMPO/$PhI(OAc)_2$[45] to give coupling precursor **58** (Scheme 10). Convergent fragment–coupling was achieved by the lithium–iodine exchange of alkyl iodide **56** with *t*-BuLi and reaction of the resulting anion with



Scheme 9 Synthesis of alkyl iodide **56**.



Scheme 10 Total synthesis of scabrolide F (**7**).

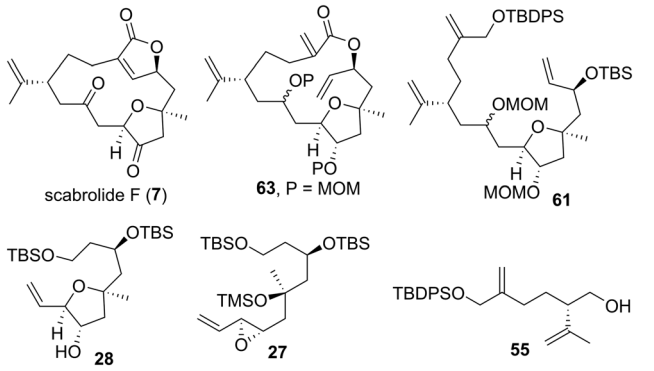
aldehyde **58**, quantitatively affording the desired alcohol **59** as a 1 : 1 diastereomeric mixture. Alcohol **59** was protected as the methoxymethyl (MOM) ether, and the primary TBS group was selectively removed to yield alcohol **60**. Dienol **60** was converted to triene **61** by the formation of the corresponding selenide[53] and subsequent oxidation in 84% yield in two steps. Bis-silyl ether **61** was treated with tetra-*n*-butylammonium fluoride (TBAF) to give the corresponding diol, which was subjected to TEMPO oxidation[45] to provide hydroxyaldehyde **62**. The Pinnick oxidation of **62** with $NaClO_2/NaH_2PO_4$/2-methyl-2-butene[62] afforded the hydroxycarboxylic acid, which was immediately treated with 2-methyl-6-nitrobenzoic anhydride (MNBA)/4-dimethylaminopyridine (DMAP)[63] to furnish macrolactone **63** in 58% yield in four steps. Bis-MOM ether **63** was deprotected using $BF_3{\cdot}OEt_2/Me_2S$[35a,c] to give diol **64** in 51% yield.[64] Prolonging the reaction time reduced the chemical yield of **64** owing to the formation of byproducts. Therefore, this reaction was stopped after 1 h and repeated three times. **64** was oxidized to the corresponding diketone using Dess–Martin periodinane.[65] Finally, the transannular RCM[38] of the triene proceeded smoothly in the presence of a second-generation Hoveyda–Grubbs catalyst (**65**)[66] in toluene at 80 °C, leading to the quantitative formation of scabrolide F (**7**) in two steps. After the completion of the total synthesis of **7**, we analyzed its 2D NMR spectra. The ^1H and ^{13}C NMR data of the synthesized **7** were nearly identical to those reported for the natural product.[13,67] The measured specific rotation of the synthetic product **7** was $[\alpha]_D^{25}$ −5.1 (*c* 0.075, $CHCl_3$), which was consistent with that of the natural product, $[\alpha]_D^{27}$ −6.3 (*c* 0.48,

$CHCl_3$).[13] Therefore, the absolute configuration of natural scabrolide F was elucidated to be that shown in **7**.

Antifouling activity and toxicity

Having completed the total synthesis of **7** and elucidation of the absolute configuration of natural scabrolide F, we examined the biological activity of the synthetic product **7**. We previously evaluated the antifouling activity of sarcophytonolides H and J, which are cembranolide diterpenes isolated from the soft coral *S. latum*, and found these compounds to be antifouling-active.[35b,c] Thus, we envisioned that **7**, a norcembranolide isolated from the same genus, would also exhibit the antifouling activity demonstrated by sarcophytonolides H and J. We first evaluated the antifouling activity and toxicity of $CuSO_4$ as a positive control against the cypris larvae of the barnacle *A. amphitrite* after a 96 h incubation period. In this study, antifouling activity and toxicity were represented by 50% effective concentration (EC_{50}) and 50% lethal concentration (LC_{50}) values, respectively. The EC_{50} (0.29 μg mL^{-1}) and LC_{50} (2.10 μg mL^{-1}) values of $CuSO_4$ were nearly equivalent to those reported in the literature (Table 2).[68] As expected, the synthetic product **7** inhibited the settlement of cypris larvae with an EC_{50} value of 9.46 μg mL^{-1}. Encouraged by this result, we assessed the antifouling activity of several synthetic intermediates of **7**. Transannular RCM precursor **63** exhibited approximately twice as high antifouling activity (EC_{50} = 4.51 μg mL^{-1}) as **7**, potentially proposing that the butenolide structure is not essential for exerting antifouling activity. Macrocyclization precursor **61** demonstrated a settlement-inhibitory effect, with an EC_{50} value of 5.74 μg mL^{-1}. Tetrahydrofuran **28** and epoxide **27** also exhibited antifouling activity regardless of the differences in their molecular skeleton (**28**: EC_{50} = 5.89 μg mL^{-1}, **27**: EC_{50} = 5.60 μg mL^{-1}). Interestingly, acyclic compound **55** showed higher antifouling activity (EC_{50} = 2.65 μg mL^{-1}) than the five other compounds. The relatively low solubility of **7** in water may explain why its antifouling effect is weaker than that of the five other compounds. Furthermore, we evaluated the toxicity of **7**, **63**, **61**, **28**, **27**, and **55**, and found these compounds to be nontoxic at a concentration of 50 μg mL^{-1} (LC_{50} > 50 μg mL^{-1}). Among the six compounds evaluated, **55**, which showed the highest antifouling activity without toxicity, is a candidate for the development of environmentally friendly antifouling agents.

Table 2 Antifouling activity (EC_{50}) and toxicity (LC_{50}) of $CuSO_4$, synthetic scabrolide F (**7**), and its synthetic intermediates[a]



Compound	EC_{50} (μg mL^{-1})	LC_{50} (μg mL^{-1})
$CuSO_4$	0.29	2.10
7	9.46	>50
63	4.51	>50
61	5.74	>50
28	5.89	>50
27	5.60	>50
55	2.65	>50

[a] Against the cypris larvae of the barnacle *Amphibalanus amphitrite*.

Conclusions

We performed the first total synthesis and evaluation of the antifouling activity of scabrolide F (**7**), a norcembranolide diterpene isolated from *S. scabra*. The 2,5-*cis*-disubstituted-3-oxygenated tetrahydrofuran moiety of **7** was constructed using the 5-*endo-tet* cyclization of a hydroxy vinyl epoxide. The coupling between alkyl iodide **30** and dithiane **38** and introduction of an alkene moiety afforded compound **41**. As our model study on allylation using alkyl iodide **42** and allylic stannane **43** was unsuccessful, we investigated an alternative synthetic approach toward **7** instead. In the revised synthetic route, convergent fragment–coupling between alkyl iodide **56** and aldehyde **58**, macrocyclization, and transannular RCM were successfully accomplished as key steps, leading to the first total synthesis of **7**. We then assayed the antifouling activity and toxicity of **7** and its key synthetic intermediates **63**, **61**, **28**, **27**, and **55** against the cypris larvae of *A. amphitrite*; these six compounds were found to be antifouling-active (EC_{50} = 2.65–9.46 μg mL^{-1}) and nontoxic (LC_{50} > 50 μg mL^{-1}). Among these six active compounds, acyclic compound **55**, which showed the most potent settlement-inhibitory activity without toxicity, was proposed as a candidate for the preparation of environmentally benign antifoulants. The synthetic route toward **7** proposed in this study can be useful in the total synthesis of other macrocyclic norcembranolides. Further synthetic and biological studies of other norcembranolides are underway in our laboratory.

Author contributions

H. T. conceived and directed the study. Y. S. and R. M. conducted the syntheses and collected the compound data. T. Y. collected and maintained the barnacles. H. T. evaluated the biological activities. All authors analyzed the collected data. H. T. prepared the manuscript.

Conflicts of interest

There are no conflicts to declare.

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