Total Synthesis of Scabrolide F

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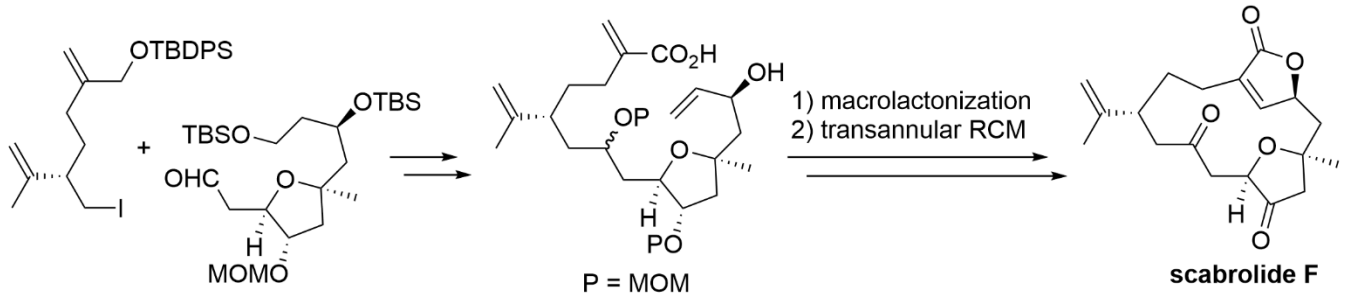
Supporting Information Placeholder



ABSTRACT: The first total synthesis of scabrolide F, a norcembranolide isolated from the soft coral *Sinularia scabra*, is described. Hydroxycarboxylic acid, which is the key synthetic intermediate, was synthesized in a convergent manner by fragment coupling. The obtained hydroxycarboxylic acid was subjected to macrolactonization and subsequent transannular ring-closing metathesis (RCM) to furnish scabrolide F. The synthetic protocol can be extended to the total synthesis of other norcembranolides.

Corals produce natural products with a wide variety of chemical structures and biological activities.[1] Macrocyclic and polycyclic norcembranolide diterpenes have been isolated from the soft corals of genus *Sinularia*, and several of them have been reported to exhibit biological and pharmacological activities.[2] From an ecological perspective, it has been suggested that cembranoid diterpenes are implicated in the defense of soft corals against predation.[1a,3] The first example of macrocyclic norcembranolide possessing a 14-membered carbon framework is 5-*epi*-sinuleptolide (**1**, Figure 1), which was isolated from *Sinularia leptoclados* in 1978.[4] The relative configuration of **1** was originally determined by NMR spectroscopy and X-ray crystallographic analysis. However, the stereochemistry at the C11 position of the original structure of **1** was revised to the opposite stereochemistry after its C11 epimer was isolated in 1985.[5] In 1993, Umeyama and co-workers isolated natural product **3**, the C5 epimer of **1**, and designated **3** as sinuleptolide;[6] hence, **1** was named 5-*epi*-sinuleptolide. The absolute configurations of **1** and **3** were elucidated using the modified Mosher method.[7] The relative stereochemistries of 10-*epi*-gyrosanolide E (**4**)[5,8] and scabrolides D (**5**),[9] E (**6**),[10] and F (**7**)[10] were assigned based on extensive spectroscopic analysis and by comparing their spectral data with those of the related natural products. Among these macrocyclic norcembranolide, **1** exhibits antibacterial activity by inhibiting the formation of a bacterial biofilm.[11] Compound **1** also exhibits cytotoxicity against pancreatic cancer cell lines.[12] Both **1** and **3** exert inhibitory effect on LPS-induced TNF-α production in a dose-dependent manner[13] and are cytotoxic to KB and Hepa59T/VGH cancer cells.[9,14] In addition, 5-*epi*-sinuleptolide acetate (**2**) shows moderate cytotoxicity toward human tumor cells.[15] Scabrolide E (**6**) is found to be cytotoxic against KB and Hepa59T/VGH cells, with ED_{50} values of 0.7 and 0.5 μg/mL, respectively.[10] To date, there are only two reports on the total synthesis of macrocyclic norcembranolides. Lee et al. accomplished the total synthesis of (+)-10-*epi*-gyrosanolide E (enantiomer of **4**), establishing that the absolute configuration of natural 10-*epi*-gyrosanolide E was same as that of **4**.[16] Theodorakis et al. achieved the total synthesis of (±)-scabrolide D (**5**), which led to the stereochemical revision of the epoxide moiety of this natural product.[17] Herein, we report the first total synthesis of scabrolide F (**7**), which involves fragment coupling, macrolactonization, and transannular ring-closing metathesis (RCM) as the key transformations.[18]

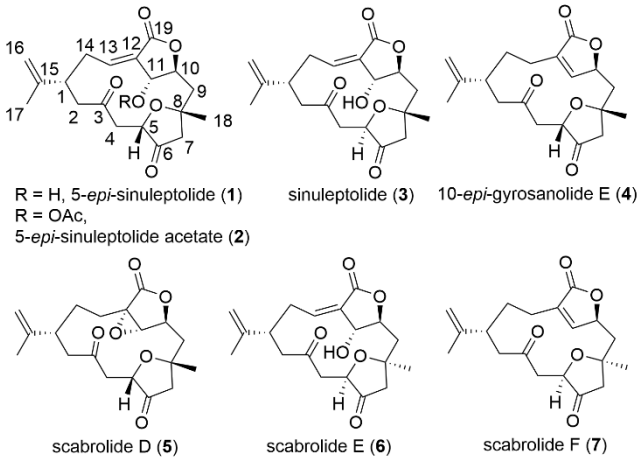
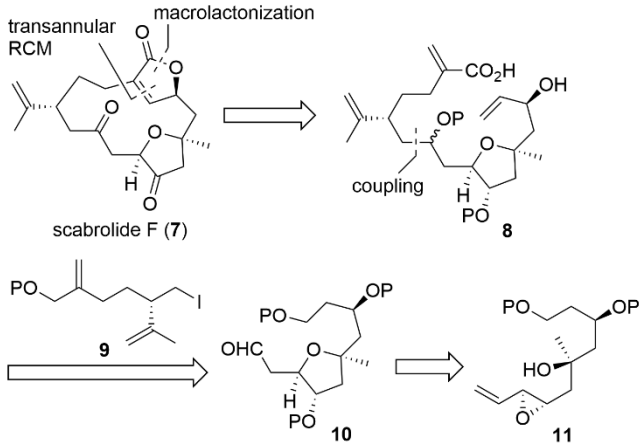


Figure 1. Structures of macrocyclic norcembranolides **1**–**7**.

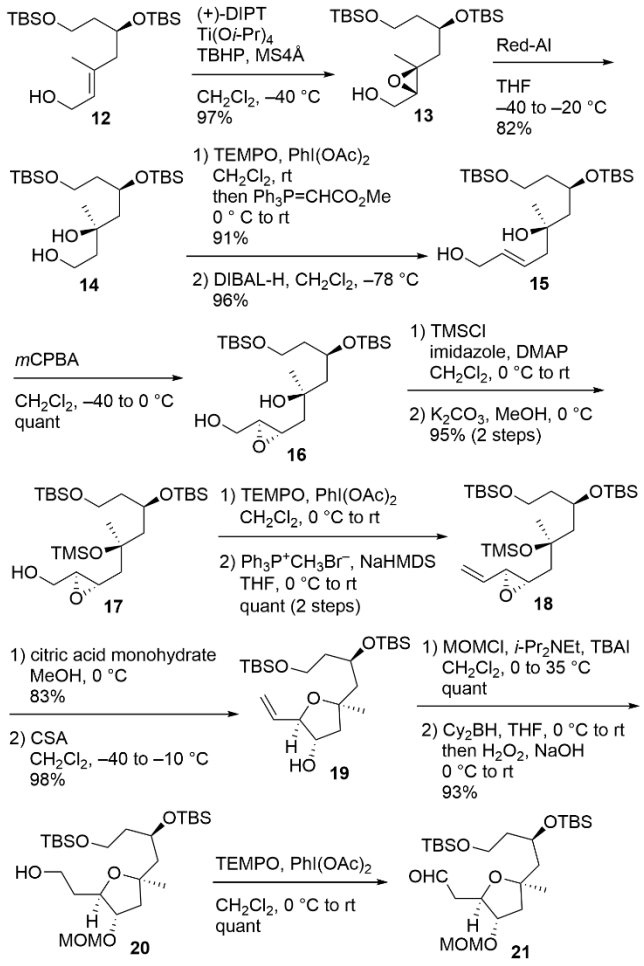
In the retrosynthetic analysis, we envisioned that the 14-membered carbon skeleton and the butenolide moiety of scabrolide F (**7**) could be constructed by macrolactonization[19]

and subsequent transannular RCM[20] of hydroxycarboxylic acid **8** (Scheme 1).[21] The key synthetic intermediate **8** could be synthesized by the coupling between alkyl iodide **9** and aldehyde **10**. The tetrahydrofuran moiety of **10** could be formed via the 5-*endo*-*tet* cyclization of hydroxy vinyl epoxide **11**.[22–24] Our synthetic design not only provides an asymmetric route to scabrolide F (**7**) but is also expected to provide access to other macrocyclic norcembranolides.

Scheme 1. Retrosynthetic Analysis of Scabrolide F (7)

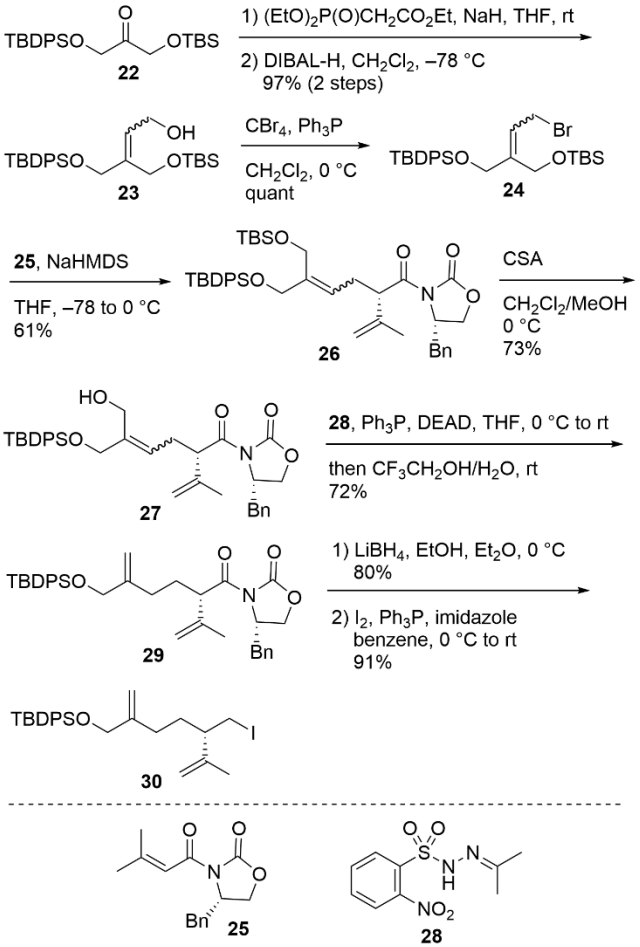


Scheme 2. Synthesis of Aldehyde 21



We initially investigated the stereoselective construction of the tetrahydrofuran ring. Sharpless asymmetric epoxidation[25] of optically pure allylic alcohol **12**[26] with (+)-DIPT afforded epoxy alcohol **13** as a single diastereomer (Scheme 2). Reductive epoxide-opening of **13** with Red-Al[27] produced 1,3-diol **14**.[28] Oxidation of **14** with TEMPO/PhI(OAc)$_2$[29] and subsequent treatment of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ in one-pot afforded the corresponding α,β-unsaturated ester, which was reduced to diol **15** with DIBAL-H. After extensive screening of the conditions for the stereoselective epoxidation of allylic alcohol **15**, it was demonstrated that the treatment of **15** with *m*CPBA at temperatures ranging from –40 to 0 °C quantitatively produced the desired epoxy diol **16** as a single diastereomer.[28,30] Protection of **16** as the tetrakis-silyl ether and selective removal of the primary TMS group gave alcohol **17**. The terminal alkene moiety was introduced by sequential TEMPO oxidation[29] and Wittig reaction to quantitatively yield vinyl epoxide **18** in two steps. After selective removal of the TMS group of **18** with citric acid monohydrate in MeOH, the resulting hydroxy vinyl epoxide underwent 5-*endo*-*tet* cyclization in the presence of CSA from –40 to –10 °C to furnish tetrahydrofuran **19** in 98% yield as the sole product.[24] Alcohol **19** was protected as the MOM ether and subsequently subjected to hydroboration/oxidation to produce primary alcohol **20**. Treatment of **20** with TEMPO/PhI(OAc)$_2$[29] quantitatively afforded aldehyde **21**.

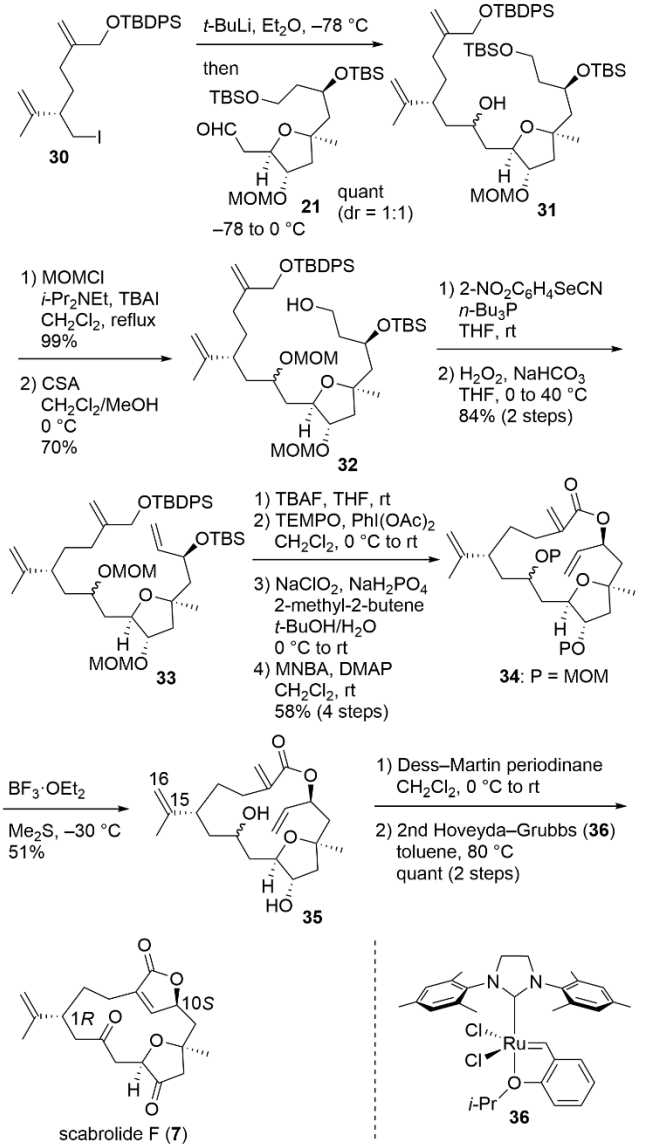
Scheme 3. Synthesis of Alkyl Iodide 30



After synthesizing the coupling precursor **21**, we examined the stereoselective synthesis of its coupling partner. Horner–Wadsworth–Emmons olefination of the known ketone **22**[31] with $(EtO)_2P(O)CH_2CO_2Et$/NaH, followed by reduction of the resulting α,β-unsaturated ester with DIBAL-H gave allylic alcohol **23** as a mixture of geometric isomers (Scheme 3). Treatment

of **23** with CBr_4/Ph_3P quantitatively produced allylic bromide **24**. Evans asymmetric alkylation[32] of chiral imide **25**[33] with **24** proceeded from –78 to 0 °C, affording the desired allylated product **26** in 61% yield. TBS ether **26** was selectively deprotected with CSA in CH_2Cl_2/MeOH to produce allylic alcohol **27**. Next, **27** was subjected to reductive allylic transposition reaction in accordance with the protocol reported by Movassaghi et al.[34] Thus, the reaction of allylic alcohol **27**, which is a geometric mixture, with *N*-isopropylidene-*N'*-2-nitrobenzenesulfonyl hydrazine **28**, followed by hydrolysis with CF_3CH_2OH/H_2O and subsequent sigmatropic loss of dinitrogen furnished diene **29** in 72% yield as the sole product. The oxazolidinone chiral auxiliary of **29** was reductively removed with $LiBH_4$, and the resulting alcohol reacted with I_2/Ph_3P/imidazole to give alkyl iodide **30**.

Scheme 4. Completion of the Total Synthesis



With the two coupling precursors **21** and **30** in hand, we next focused on the fragment coupling and completion of the total synthesis. Addition reaction of the anion, which was generated by lithium–iodine exchange between alkyl iodide **30** and *t*-BuLi, with aldehyde **21** led to the quantitative formation of alcohol **31** as a 1:1 diastereomeric mixture (Scheme 4). The resulting hydroxy group of **31** was protected as the MOM ether and selective deprotection of the primary TBS ether gave alcohol **32**. The monosubstituted terminal alkene was introduced using Grieco's protocol[35] to afford triene **33** in 84% yield in two steps. Selective removal of the TBDPS protecting group with TBAF and subsequent stepwise oxidation of the primary alcohol with $TEMPO/PhI(OAc)_2$[29] and $NaClO_2/NaH_2PO_4$/2-methyl-2-butene[36] produced the corresponding carboxylic acid. Shiina lactonization[19,37] with 2-methyl-6-nitrobenzoic anhydride (MNBA)/DMAP was successfully applied to the obtained hydroxycarboxylic acid to produce macrolactone **34** in 58% yield in four steps. The MOM protecting groups of **34** were removed using $BF_3{\cdot}OEt_2/Me_2S$[18,38] to furnish diol **35** in 51% yield. Diol **35** was treated with Dess–Martin periodinane[39] to give the diketone. Finally, transannular RCM[20] of the obtained triene was realized using second-generation Hoveyda–Grubbs catalyst (**36**)[40,41] in toluene at 80 °C, in which the C15/C16 disubstituted alkene domain was inert to the reaction conditions, to quantitatively afford scabrolide F (**7**) in two steps. The ^1H and ^{13}C NMR signals of synthetic scabrolide F (**7**) were assigned by the detailed analysis of its 2D NMR spectra. The NMR data of the synthesized product **7** were in excellent agreement with those of natural scabrolide F.[10,42] The specific rotation of synthesized **7**, $[\alpha]_D^{25}$ –5.1 (*c* 0.075, $CHCl_3$), was consistent with that reported for the natural product ($[\alpha]_D^{27}$ –6.3 (*c* 0.48, $CHCl_3$)).[10] Therefore, the absolute stereochemistry of the natural product was revealed to be that concluded for **7** obtained by this total synthesis.[43]

In conclusion, we accomplished the first total synthesis of scabrolide F (**7**), a macrocyclic norcembranolide. The synthetic route toward **7** involves fragment coupling between alkyl iodide and aldehyde, macrolactonization, and transannular RCM. This total synthesis clarifies that the absolute stereostructure of natural scabrolide F is that concluded for **7**. The synthetic scheme used in this work can be employed for the total synthesis of other norcembranolides.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

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

Experimental procedures and characterization data of all new compounds, stereochemical determination of the synthetic product **19**, comparison of the NMR data of natural scabrolide F and the synthetic product **7**, and NMR spectra of all new compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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DEDICATION

We dedicate this work to the memory of Prof. Daisuke Uemura, who sadly passed away on April 13, 2021.

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