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Total Synthesis of Norcembrenolide B and Scabrolide D

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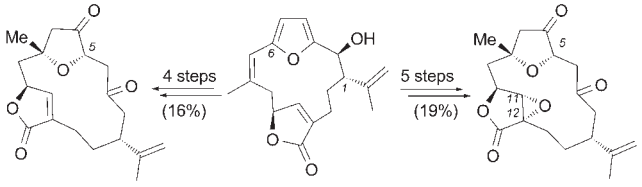
ABSTRACT



8: norcembrenolide B **6:** norbipinnatin J **9:** norcembrenolide C (scabrolide D)

An efficient stereoselective synthesis of norcembrenolide B (8) and scabrolide D (9) is reported. The strategy is inspired by biogenetic relationships of related cembrenoids. Central to this approach is the construction of norbipinnatin J which upon selective C2 deoxygenation and C8 oxygenation produces norrubifolide and norcoralloidolide A. A sequence of site-selective oxidations and skeletal reorganizations then yields, in a divergent manner, compounds 8 and 9. The studies allow revision of the proposed structure of scabrolide D (9), which is identical to norcembrenolide C.

Gorgonian octocorals and soft corals, particularly those of the genus *Sinularia*, have been recognized as a rich source of natural products containing the 14-membered cembrane skeleton (Figure 1).[1] Proposed to be utilized by the corals as a chemical defense against predation, these natural products display an intriguing array of biological and pharmacological activities.[2] For example, members of the bipinnatin subfamily have been evaluated as active-site-directed inhibitors of nicotinic acetylcholine receptors.[2b] Various norcembrenolides were found to exhibit low micromolar cytotoxicities against several cancer cell lines.[3] More recently, sinuleptolide (**7**) and scabrolide D (**9**) were shown to inhibit LPS-induced TNF-α production in a dose-dependent manner.[4]

Norcembrenolides A (**7**),[5] B (**8**), and C (**9**) were isolated by Fenical et al. from several *Sinularia* species collected in Palau.[6] Certain members of this family were also isolated by Sheu et al. from the Taiwanese soft coral *S. scabra* and were named scabrolides.[3a,7] From a biosynthetic standpoint, these compounds are proposed to derive from the furanocembrenoids, in which a furan (C3−C6) and a butenolide C10−C20) are embedded in the 14-membered cembrane macrocycle (see structure of rubifolide, **1**).[8] Oxidations of the carbocyclic framework of **1** are proposed

(1) (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298–317. (b) Lakshmi, V.; Kumar, R. *Nat. Prod. Res.* **2009**, *23*, 801–850. (c) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 429–440. (d) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

(2) (a) Kamel, H. N.; Slattery, M. *Pharmac. Biol.* **2005**, *43*, 253–269. (b) Abramson, S. N.; Fenical, W.; Taylor, P. *Drug Dev. Res.* **1991**, *24*, 297–312. (c) Su, J.-H.; Wen, Z.-H. *Mar. Drugs* **2011**, *9*, 944–951.

(3) (a) Ahmed, A. F.; Su, J.-H.; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2004**, *67*, 2079–2082. (b) Ahmed, A. F.; Shiue, R.-T.; Wang, G.-H.; Dai, C.-F.; Kuo, Y.-H.; Sheu, J.-H. *Tetrahedron* **2003**, *59*, 7337–7344.

(4) (a) Takaki, H.; Koganemaru, R.; Iwakawa, Y.; Higuchi, R.; Miyamoto, T. *Biol. Pharm. Bull.* **2003**, *26*, 380–382. (b) Cheng, S.-Y.; Chuang, C.-T.; Wen, Z.-H.; Wang, S.-K.; Chiou, S.-F.; Hsu, C.-H.; Dai, C.-F.; Duh, C.-Y. *Biorg. Med. Chem.* **2010**, *18*, 3379–3386.

(5) Norcembrenolide A (**7**), later named sinuleptolide, was initially isolated from the Australian soft-coral *Sinularia leptoclados*: Bowden, B. F.; Coll, J. C.; Mitchell, S. J.; Mulder, J.; Stokie, G. J. *Aust. J. Chem.* **1978**, *31*, 2049–2056. For the revision of its structure, see: Shoji, N.; Umeyama, A.; Arihara, S. *J. Nat. Prod.* **1993**, *56*, 1651–1653.

(6) Sato, A.; Fenical, W.; Qi-tai, Z.; Clardy, J. *Tetrahedron* **1985**, *41*, 4303–4308.

(7) Sheu, J.-H.; Ahmed, A. F.; Shiue, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.

(8) Williams, D.; Andersen, R. J.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 332–335.

(9) D'Ambrosio, M.; Fabbri, D.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 63–70.

(10) (a) Rodriguez, A. D.; Shi, J.-G. *J. Org. Chem.* **1998**, *63*, 420–421. (b) Rodriguez, A. D.; Shi, J.-G.; Huang, S. D. *J. Nat. Prod.* **1999**, *62*, 1228–1237.

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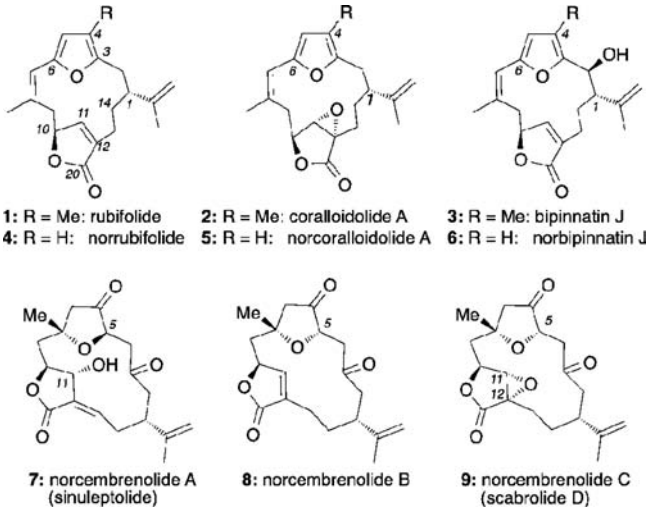
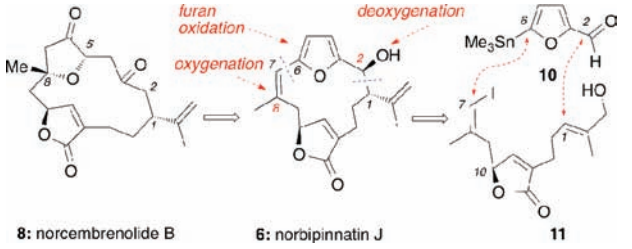


Figure 1. Chemical structures of selected cembrenoids.

to give access to oxygenated furanocembrenoids like **2**[9] and **3**.[10] Further oxidation at the furan ring followed by oxidative decarboxylation of the C4 methyl group could account for the formation of norcembrenolides.[1d]

Inspired by the combination of interesting chemical structures and unexplored bioactivities and guided by the proposed biosynthesis, we sought to develop a divergent synthesis toward this family of compounds.[11] Here we describe the first synthesis of norcembrenolides B (**8**) and C (**9**). Our results also revise the proposed structure of scabrolide D, which is in fact identical to that of norcembrenolide C.

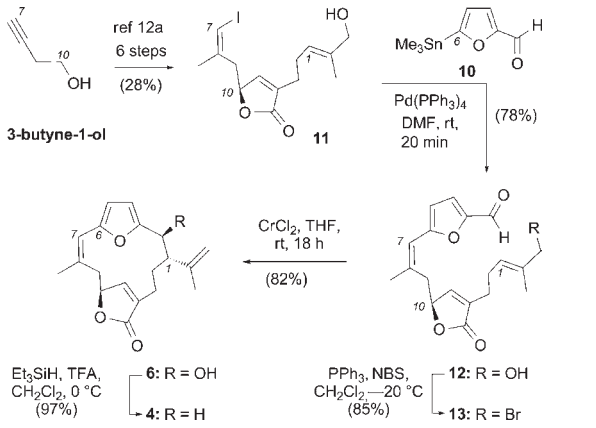
Scheme 1. Retrosynthetic Analysis of Norcembrenolide B (**8**)



Scheme 1 highlights the key elements of the strategy as applied to the synthesis of norcembrenolide B (**8**). A sequence of deoxygenation at the C2 center followed by a selective oxygenation at the C8 center and furan oxidation/cyclization would form **8** from norbipinnatin J (**6**). The central cembrane skeleton could be constructed from

(11) For related divergent strategies see: (a) Li, Y.; Pattenden, G. *Tetrahedron Lett*. **2011**, *52*, 3315–3319. (b) Kimbrough, T. J.; Roethle, P. A.; Mayer, P.; Trauner, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 2619–2621. (c) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett*. **2006**, *8*, 5901–5904. (d) Tang, B.; Bray, C. D.; Pattenden, G. *Org. Biomol. Chem*. **2009**, *7*, 4448–4457. (e) Tang, B.; Bray, C. D.; Pattenden, G. *Tetrahedron Lett*. **2006**, *47*, 6401–6404.

Scheme 2. Synthesis of Norbipinnatin J (**6**) and Norrubifolide (**4**)



aldehyde **10** and butenolide **11** using well established Stille and Kishi−Nozaki couplings.[12]

The synthesis began with 3-butyne-1-ol, containing the C7−C10 cembrane fragment (Scheme 2). A sequence of six steps, based on Trauner's strategy,[12a] afforded the racemic vinyl iodide **11** in 28% overall yield.[13] Coupling of **11** with furfural stannane **10** under Pd(0) conditions produced aldehyde **12** in 78% yield. In preparation for the Kishi−Nozaki coupling the allylic alcohol of **12** was first converted to allyl bromide **13** using Appel bromination[14] that upon treatment with $CrCl_2/NiCl_2$ produced norbipinnatin J (**6**) as the major diastereomer in 82% yield.[15] The relative stereochemistry of **6** was unambiguously confirmed via a single crystal X-ray analysis (Figure 2).[16] Deoxygenation of the C2 hydroxyl

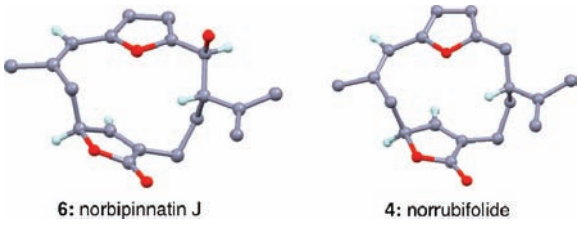


Figure 2. X-ray structures of compounds **6** and **4**.

(12) (a) Roethle, P. A.; Trauner, D. *Org. Lett*. **2006**, *8*, 345–347. (b) Huang, Q.; Rawal, V. H. *Org. Lett*. **2006**, *8*, 543–545.

(13) Detailed experimental procedures and data for all synthesis steps are shown in the Supporting Information.

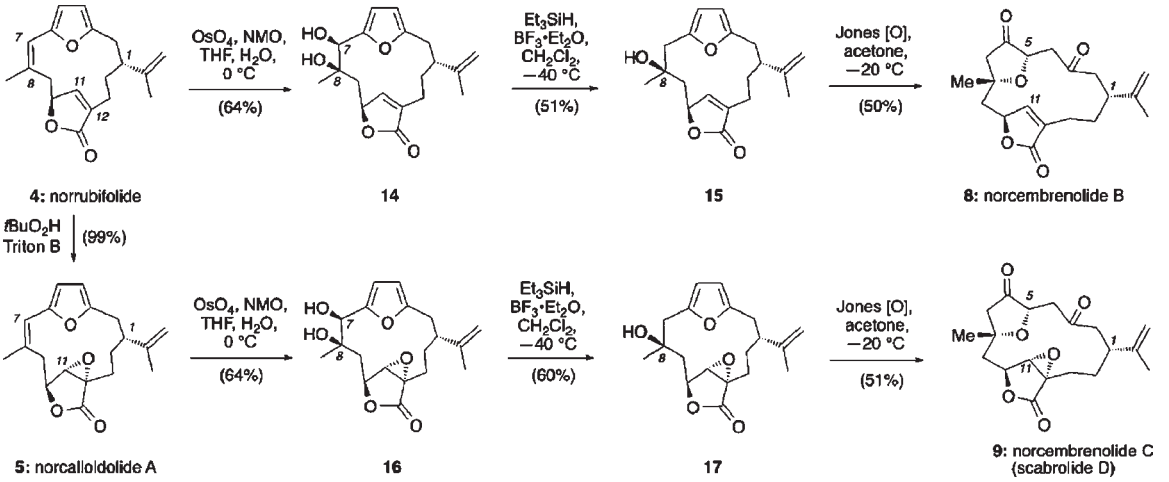
(14) Appel, R. *Angew. Chem., Int. Ed*. **1975**, *14*, 801–811.

(15) For the use of this reaction to the synthesis of related natural products, see: (a) Rayner, C. M.; Astles, P. C.; Paquette, L. A. *J. Am. Chem. Soc*. **1992**, *114*, 3926–3936. (b) Paquette, L. A.; Astles, P. C. *J. Org. Chem*. **1993**, *58*, 165–169.

(16) CCDC 831509 (**14**), 831510 (**8**), 831511 (**6**), 831512 (**5**), 831515 (**9**), and 831516 (**4**) contain the supplementary crystallographic data. This information can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/products/csd/request/. In the figures some hydrogen atoms have been omitted for clarity.

(17) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, *9*, 633–651.

Scheme 3. Synthesis of Norcembrenolide B (**8**) and Norcembrenolide C (Scabrolide D, **9**)



group was achieved using TFA/Et_3SiH[12a,17] to afford norrubifolide (**4**) in 97% yield.

Compound **4** represents a branching point of our strategy (Scheme 3). The X-ray of **4** shows a rigid structure that is amenable to regioselective functionalizations at both the C7−C8 and C11−C12 double bonds (Figure 2). The best way to achieve a selective oxygenation at C8 was found to be a dihydroxylation of the C7−C8 double bond, followed by deoxygenation of the C7 hydroxyl group. The dihydroxylation reaction proceeded best under Upjohn conditions[18] (OsO_4, NMO) and afforded diol **14** as a single isomer in 64% yield. As predicted, the hydroxyl groups were introduced from the sterically more accessible β-face of the cembrane ring (Figure 3). Deoxygenation under $Et_3SiH/BF_3{\bullet}Et_2O$ conditions[19] then produced compound **15** in 51% yield. Conversion of the furan to the β-keto-tetrahydrofuranone was accomplished utilizing the Jones reagent. It is believed that the transformation begins with an initial oxidation of the furan to an intermediate Z-ene-dione structure (Figure 4).[20] The tertiary alcohol, under acidic conditions, then quickly cyclizes in a 5-*exo*-trig fashion, producing norcembrenolide B (**8**) in 50% yield. The structure of **8** was confirmed via crystallographic studies (Figure 3).

Our synthesis diverges with a selective oxidation of **4** using anhydrous TBHP and catalytic Triton B[21] affording norcoralloidolide A (**5**) in 99% yield. As expected this epoxidation proceeded selectively from the α-face of the butenolide motif. The structure of **5** was unambiguously

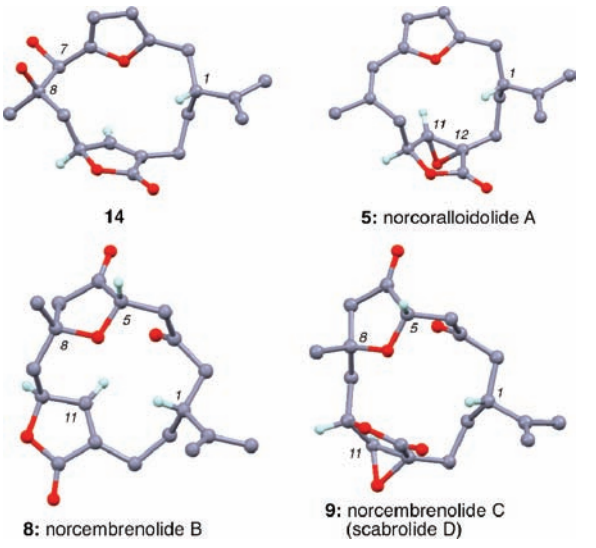


Figure 3. X-rays of compounds **14**, **5**, **8**, and **9**.

confirmed via a single crystal X-ray analysis (Figure 3). Further manipulation of **5** using the conditions described

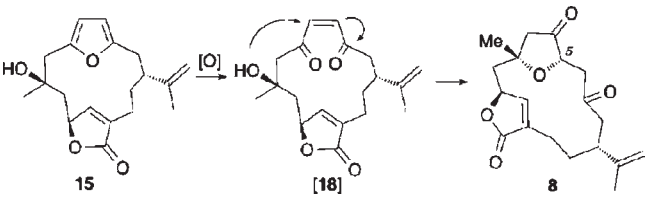


Figure 4. Conversion of **15** to **8** via the Jones oxidation.

(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron* **1976**, *17*, 1973–1976.

(19) Nomura, S.; Sakamaki, S.; Hongu, M.; Kawanishi, E.; Koga, Y.; Sakamoto, T.; Yamamoto, Y.; Ueta, K.; Kimata, H.; Nakayama, K.; Tsuda-Tsukimoto, M. *J. Med. Chem.* **2010**, *53*, 6355–6360.

(20) Hayes, S. J.; Knight, D. W.; Smith, A. W. T.; O'Halloran, M. J. *Tetrahedron Lett.* **2010**, *51*, 720–723.

(21) Yoshimitsu, T; Nojima, S; Hashimoto, M; Tsukamoto, K; Tanaka, T *Synthesis* **2009**, *17*, 2963–2969.

above gave rise to norcembrenolide C (**9**) in three steps and 17% overall yield.

Interestingly, the proposed structure of scabrolide D, as reported by Sheu et al.,[7] had a relative stereochemistry in which the epoxide moiety is on the same face as the lactone oxygen (see Figure 5). Spectroscopic (^{1}H and ^{13}C NMR) comparison of synthetic **9** taken in $CDCl_3$ with the data reported for scabrolide D[7] reveals that the structures are identical. Moreover, X-ray crystallographic analysis of synthetic **9** confirmed the structural identity of scabrolide D leading to the revision of its relative stereochemistry at the C11 and C12 centers, with the epoxide occurring on the opposite face in regard to the lactone oxygen. It was previously unrealized, but in fact, scabrolide D is identical to norcembrenolide C (**9**) which was studied in benzene-d_6 and was first reported by the Fenical group[6] several years earlier.

In conclusion, we present here a divergent strategy for the synthesis of norcembrenolides B (**8**) and C (**9**), two members of a family of structurally complex marine natural products with potent and largely unexplored biological properties. Our approach utilizes highly substrate-controlled modifications and allows an efficient, stereoselective and protecting-group-free access to this scaffold. Our results also establish that norcembrenolide C (**9**) is structurally identical to scabrolide D. The overall strategy paves the way for a methodical evaluation of the structure–activity relationship and chemical biology of this family of natural products.

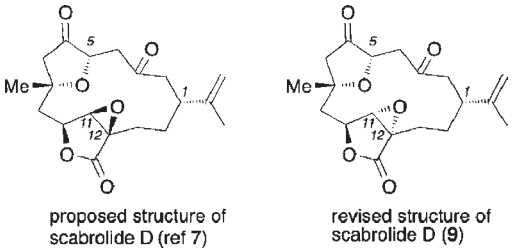


Figure 5. Proposed and revised structures of scabrolide D (**9**).

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Supporting Information Available. Detailed experimental procedures, spectral characterization, and copies of ^{1}H and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.