

Total Synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-Membrenone-A and (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)- Membrenone-B and Structural Assignment of Membrenone-C

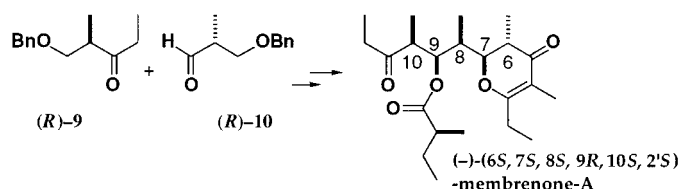
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ABSTRACT



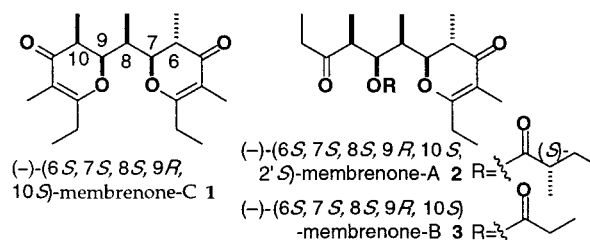
(–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-Membrenone-A and (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B were prepared in 11 steps (3% and 2.4% overall yield, respectively). Key steps included a tin(II)-mediated aldol followed by a *syn* selective reduction, giving the C7–C9 stereocenters, a second chain extending aldol coupling, and a *p*-TsOH-promoted cyclization/dehydration giving the common γ-dihydropyrone precursor. We have thus established that synthetic (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-membrenone-A, (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B, and (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-C are the *enantiomers* of the natural products.

Membrenone-A, membrenone-B, and membrenone-C are three structurally related γ-dihydropyrone-containing polypropionates, isolated from the skin of a Mediterranean mollusc by Ciavatta and co-workers.¹ In that paper the structures were assigned by extensive NMR analysis, but the relative and absolute configuration at C₈, C₉, and C₁₀ was not assigned.

We recently reported a short, enantiocontrolled synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-C **1**, exploiting a novel two directional chain extending *double* titanium aldol coupling.² In that paper we correctly assigned the relative configuration of membrenone-C but *incorrectly* assigned (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-C **1** as the absolute configuration of the natural product. This assignment² was based

on the sign of the reported¹ optical rotation, which we now believe is incorrect.

Assuming a common biosynthesis, membrenone-A and -B are proposed to have the same absolute configuration as structurally related membrenone-C.



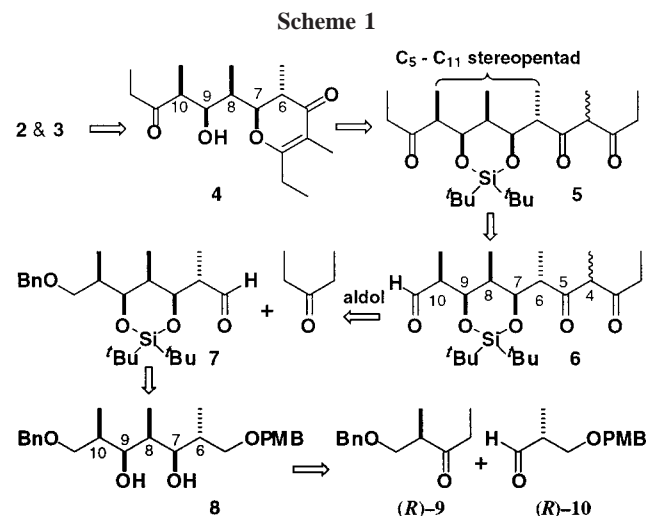
We now report the first total synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-membrenone-A **2** and (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B **3** and revise the assignment² of the structure

(1) Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, 34, 6791.

(2) Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, 3, 123.

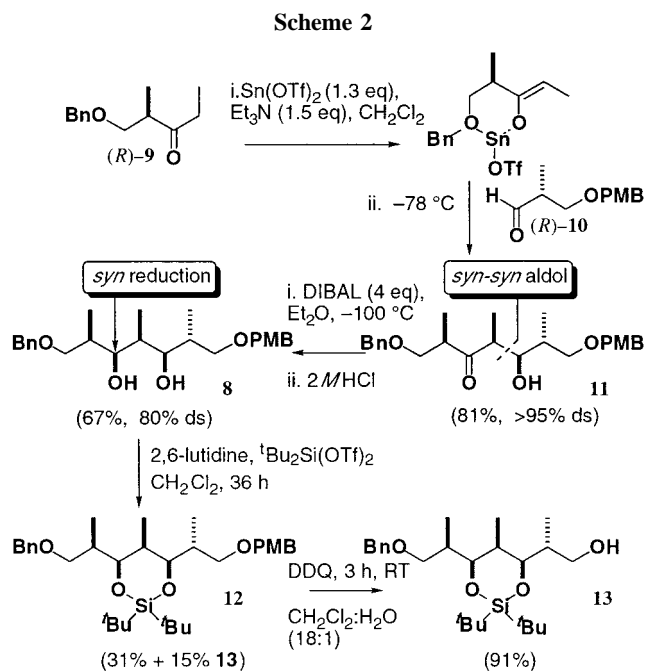
of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-C **1** to be the *enantiomer* of the natural product.

Scheme 1 outlines our general strategy for the synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-membrenone-A and (–)-



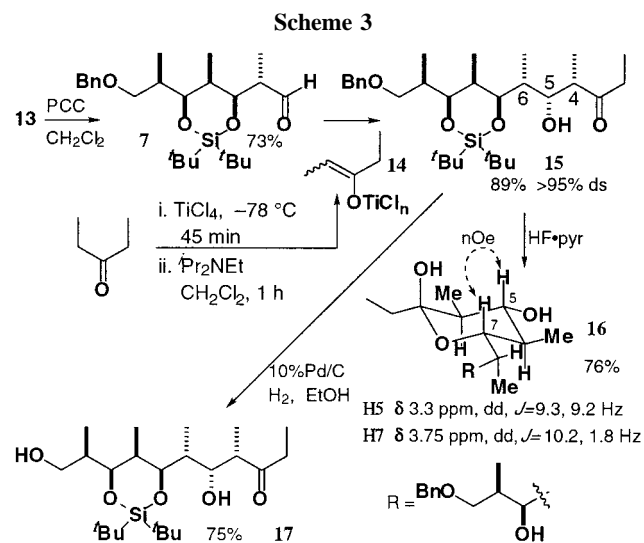
(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B based on the common γ -dihydropyrone intermediate **4**, where acylation using the appropriate acid equivalent would give access to either (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2′*S*)-membrenone-A **2** or (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B **3**. The γ -dihydropyrone **4** was envisaged to result from the deprotection and subsequent cyclization of triene **5**. The construction of the triene was based on a disconnection between the C₁₁–C₁₂ bond via a Grignard addition to aldehyde **6** followed by oxidation of the resulting secondary alcohol. Formation of **6** is by an aldol disconnection of the C₄–C₅ bond leaving aldehyde **7**. Aldehyde **7** is available from the differentially protected diol **8**. The sequence of five contiguous stereogenic centers, C₆ to C₁₀ in **8**, was amenable to the general protocol developed by Paterson³ for the synthesis of such stereopentads.

The synthesis of the required stereopentad for **4** is shown in Scheme 2. The tin enolate⁴ was prepared by precomplexation of Sn(OTf)₂ and Et₃N at –50 °C for 10 min followed by the addition of ketone (*R*)-**9** at –60 to –70 °C and stirring for 2 h. Subsequent addition of the chiral aldehyde (*R*)-**10** at –78 °C gave the *syn-syn* aldol product **11** with >95% ds. Reduction to the *syn* 1,3-diol **8** (containing five contiguous stereocenters) was achieved in 80% ds using DIBAL.⁵ Protection of the diol as the di-*tert*-butylsilylene⁶ gave a mixture of **12** and the primary alcohol **13** resulting from partial hydrolysis of the PMB-ether. Removal of the PMB-



ether in the presence of the benzyl ether protecting group was achieved using DDQ⁷ to give the known primary alcohol **13**.^{3g} The C₅–C₁₁ segment **13** was obtained in 23.2% yield in four steps from (*R*)-**9** and (*R*)-**10**.

The chain extending aldol and debenzoylation is shown in Scheme 3. Oxidation (PCC) of **13** gave the aldehyde **7**, which



was used immediately in the subsequent aldol employing the Ti(IV)⁸ enolate **14** of diethyl ketone. This reaction gave predominantly one isomer (>95% ds) **15** in 89% yield. This

(3) (a) Paterson, I. *Pure Appl. Chem.* **1992**, *64*, 1821–30. (b) Paterson, I.; Perkins, M. V. *Tetrahedron Lett.* **1992**, *33*, 801. (c) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (d) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811. (e) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (f) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (g) Paterson, I.; Schlappbach, A. *Synlett* **1995**, 498.

(4) Paterson, I.; Tillyer, R. D. *Tetrahedron Lett.* **1992**, *33*, 4233.

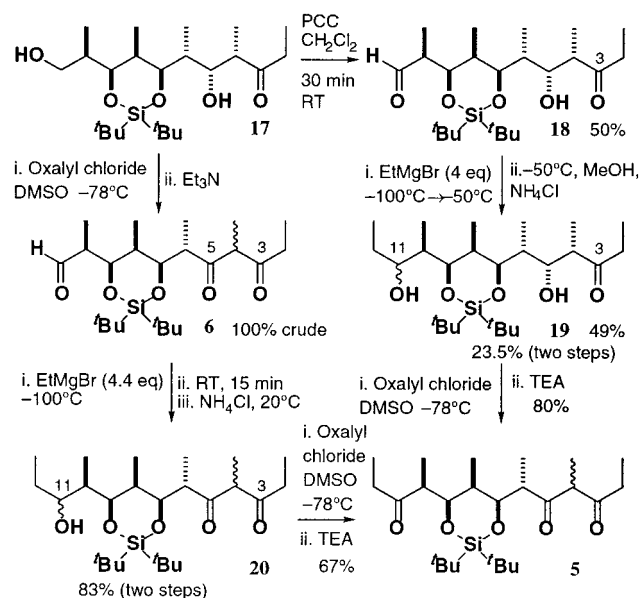
(5) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009.

(6) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871. (c) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

high selectivity shows significant substrate control for the aldehyde **7**. Although the new C₄–C₅ stereocenters produced in the formation of **15** are not present in the final product, the configuration of these two stereocenters was determined by treatment with HF-pyridine and subsequent cyclization to give the thermodynamically favorable hemiacetal **16**. Evidence for the structure of hemiacetal **16** was provided by NMR analysis. A NOE correlation between H₅ and H₇ confirmed the stereochemistry, thus revealing unexpected Felkin selectivity of aldehyde **7** to give the 6,5-*syn*-5,4-*syn*-aldol adduct **15**. The terminal benzyl ether was removed from **15** by catalytic hydrogenolysis to give the diol **17** for continuation of the synthesis.

In the initial synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B **3**, selective oxidation of the primary C₁₁ alcohol of diol **17** (while preserving the secondary C₅ alcohol) was achieved employing PCC to give the unstable aldehyde **18** in modest yield (Scheme 4). The immediate chemoselective

Scheme 4



addition of EtMgBr⁹ to the C₁₁ aldehydic carbonyl group in **18** was attempted at –100 °C to minimize the addition of the Grignard reagent to the C₃ ketone. Quenching at –50 °C with MeOH/NH₄Cl produced a single alcohol product **19** in >95% ds; however, the configuration of the C₁₁ stereocenter remains uncertain. Controlling the temperature of this addition reaction was critical, and substantial amounts of a double addition product were observed when the mixture was allowed to warm to above –50 °C before quenching.

(7) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885. (b) Horita, H.; Yoshioka, T.; Tanaka, T.; Oikawa, Y. *Tetrahedron* **1986**, 42, 3021.

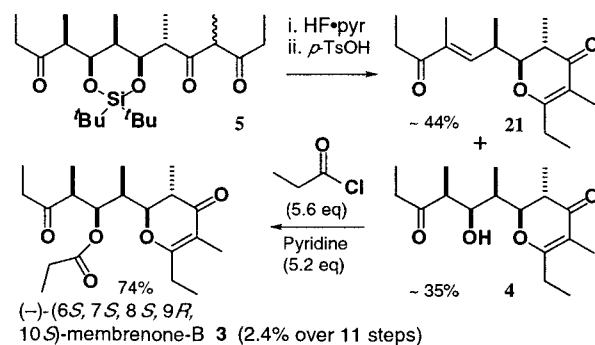
(8) (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novak, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, 112, 866. (b) Evans, D. A.; Urf, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, 112, 8215. (c) Evans, D. A.; Riegler, D. L.; Bilodeau, M. T.; Urf, F. *J. Am. Chem. Soc.* **1991**, 113, 1047.

(9) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, 52, 1811.

Because of low yields from the PCC oxidation of **17** and the subsequent chemoselective addition of EtMgBr (23.5% over two steps), an alternative pathway was attempted. Swern oxidation of **17** gave an assumed quantitative yield of the aldehyde-dione **6** as a 1:1 C₄ epimeric mixture. A chemoselective Grignard addition to the aldehydic carbonyl group of **6** in the presence of the C₃ and C₅ ketones gave a 3:2 mixture of epimeric alcohols **20** (83% yield over two steps) with >95% ds for the new C₁₁ stereocenter. The high diastereoselectivity for this reaction is again testament to the intrinsic π -facial selectivity of the aldehyde **6**. It appears the addition of excess Grignard reagent to the aldehyde **6** in the presence of a β -diketone moiety results in proton abstraction to give a resonance stabilized anion. This protects the β -diketone from addition of the organometallic reagent at room temperature, allowing complete addition of EtMgBr to the aldehyde. Finally, oxidation of both **19** and **20** under Swern conditions gave the protected trione **5** as a 3:2 mixture of C₅ epimers.

The synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B **3** is shown in Scheme 5. Removal of the di-*tert*-butylsilylene

Scheme 5

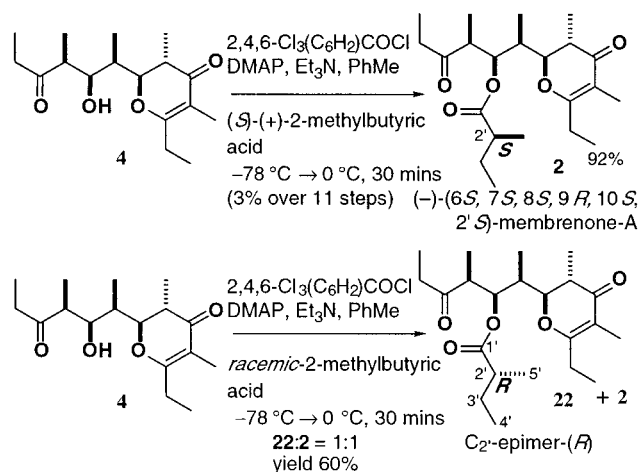


protecting group from **5** by treatment with HF-pyridine, buffered with excess pyridine, gave a complex mixture of compounds. However, acid catalysis (*p*-TsOH) assisted the cyclization/dehydration, giving a 1:1 mixture of two products, **21** and **4**. Thus formation of the γ -dihydropyrone ring was less efficient than we previously found in the two directional example,² as the neighboring β -hydroxyketone moiety was sensitive to the acidic conditions necessary for this conversion.

However, the two products **21** and **4** were separable, and acylation of the hydroxyl group of dihydropyrone **4** with propionyl chloride in the presence of pyridine gave a crystalline solid (76% yield, mp 63–65 °C) after purification. The ¹H and ¹³C NMR spectra were identical to that reported¹ for membrenone-B, confirming the relative configuration of the natural product to be that shown in **3**. Thus the total synthesis of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membrenone-B **3** was achieved in 2.4% yield over 11 steps.

Scheme 6 outlines the preparation of (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2'*S*)-membrenone-A. Acylation of **4** using a modified

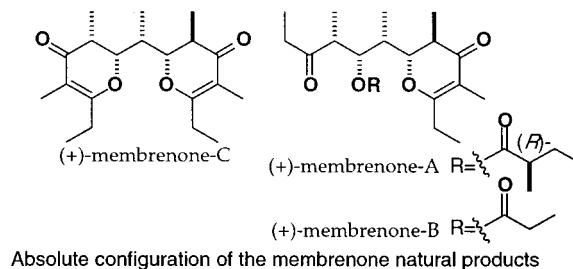
Scheme 6



Yonemitsu–Yamaguchi esterification procedure¹⁰ with (*S*)-(+)-2-methylbutyric acid gave a product (92%) whose ¹H and ¹³C NMR data were identical to that reported for (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2'*S*)-membranone-A (3% over 11 steps). The acylation of **4** was also performed using racemic 2-methylbutyric acid to give an inseparable 1:1 mixture of **2** and **22**. NMR analysis of the mixture showed **2** and **22** were similar; however, a distinct chemical shift difference in the ¹H NMR was observed for the 5' methyl group doublet for the C_{2'} epimers. The 5' methyl for **22** (C_{2'} = *R* configuration) occurred at $\delta = 1.142$ ppm, and the 5' methyl for **2** (C_{2'} = *S* configuration) occurred at $\delta = 1.132$ ppm in direct agreement with that reported for the natural product.¹ Thus it can be concluded that the relative configuration of natural membranone-A is that shown in **2**. In the original isolation the authors determined the absolute configuration of the acyl residue of (+)-membranone-A to be of the *R*-configuration. However, we have just shown acylation of **4** using (*S*)-(+)-2-methylbutyric acid gives a product with ¹H and ¹³C NMR data identical to those reported¹ for the natural membranone-A. The optical rotation obtained for the *synthetic* material was $[\alpha]_D^{20} = -23.7^\circ$ (*c* 0.51, CHCl₃), which is of the same magnitude as the natural product ($[\alpha]_D^{20} = +24.72^\circ$ (*c* 0.05, CHCl₃)),¹ but of the opposite sign. Furthermore the CD curve: $[\theta]_{300} +5661$ (max), $[\theta]_{260} -10654$ (max) of the *synthetic* material is opposite in sign to that reported¹ for the natural product. These three pieces of information show that **2** is the enantiomer of the natural product, (+)-membranone-A.

We now consider *synthetic* (–)-(6*S*,7*S*,8*S*,9*R*,10*S*)-membranone-B **3** with optical rotation $[\alpha]_D^{20} = -44.4^\circ$ (*c* 0.68

CHCl₃) and CD curve: $[\theta]_{300} +6613$ (max), $[\theta]_{267} -15438$ (max). Notably the optical rotation and CD curve are of the same sign as that observed for *synthetic* (–)-(6*S*,7*S*,8*S*,9*R*,10*S*,2'*S*)-membranone-A **2** with the same configuration of the C₆–C₁₀ stereopentad. The reported rotation¹ for the natural membranone-B was $[\alpha]_D^{20} = -24.77^\circ$ (*c* 0.2, CHCl₃), but this is not consistent (being of the opposite sign to natural membranone-A) with the nearly identical CD curves¹¹ reported for membranone-A and -B. Thus it appears that the sign of the rotation for membranone-B was *misreported*,^{1,12} and natural membranone-B should have a positive rotation, the same sign as that reported for membranone-A. Similarly it appears that the sign of rotation for membranone-C was reported incorrectly¹ (assuming all three natural products have the same absolute configuration). Thus we now believe our previous assignment^{2,13} of the absolute configuration of *natural* membranone-C (based on the reported¹ negative rotation) was incorrect. The absolute and relative configuration of the natural membranones is summarized below.



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Supporting Information Available: Copies of NMR spectra, experimental procedures, and data for key compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Membranone-A and -B were reported (ref 1) to have opposite signs of rotation but had almost identical CD curves. Reported values were membranone-A $[\alpha]_D^{20} = +24.72^\circ$ (*c* 0.05, CHCl₃), CD curve $[\theta]_{300} -2278$ (max), $[\theta]_{270} +6126$ (max); membranone-B $[\alpha]_D^{20} = -24.77^\circ$ (*c* 0.2, CHCl₃), CD curve $[\theta]_{302} -2354$ (max), $[\theta]_{269} +6230$ (max); membranone-C $[\alpha]_D^{20} = -58.09^\circ$ (*c* 0.1, CHCl₃), CD curve $[\theta]_{318} -166$ (max), $[\theta]_{270} +2023$ (max).

(12) Authentic samples of the membranones were not available for direct comparison of the $[\alpha]_D^{20}$ and CD curve.

(13) *Synthetic* (–)-*ent*-membranone-C was observed to have $[\alpha]_D^{20} = -28.2^\circ$ (*c* 0.46, CHCl₃) and CD curve $[\theta]_{322} +5550$ (max), $[\theta]_{263} -16232$ (max).

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