

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

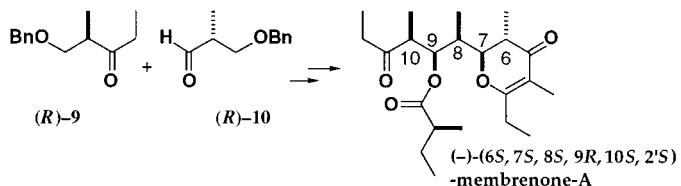
Rebecca A. Sampson and Michael V. Perkins*

School of Chemistry, Physics and Earth Sciences, The Flinders University of South Australia, G.P.O. Box 2100, S.A. 5001, Australia

mike.perkins@flinders.edu.au

Received February 5, 2002

ABSTRACT



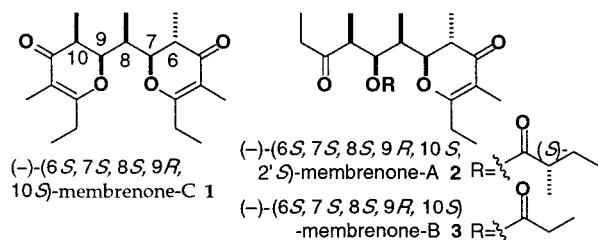
(-)-(6S,7S,8S,9R,10S,2'S)-Membrenone-A and (-)-(6S,7S,8S,9R,10S)-membrenone-B were prepared in 11 steps (3% and 2.4% overall yield, respectively). Key steps included a tin(II)-mediated aldol followed by a *syn* selective reduction, giving the C7–C9 stereocenters, a second chain extending aldol coupling, and a *p*-TsOH-promoted cyclization/dehydration giving the common γ -dihydropyrone precursor. We have thus established that synthetic (-)-(6S,7S,8S,9R,10S,2'S)-membrenone-A, (-)-(6S,7S,8S,9R,10S)-membrenone-B, and (-)-(6S,7S,8S,9R,10S)-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 (-)-(6S,7S,8S,9R,10S)-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 (-)-(6S,7S,8S,9R,10S)-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 (-)-(6S,7S,8S,9R,10S,2'S)-membrenone-A **2** and (-)-(6S,7S,8S,9R,10S)-membrenone-B **3** and revise the assignment² of the structure

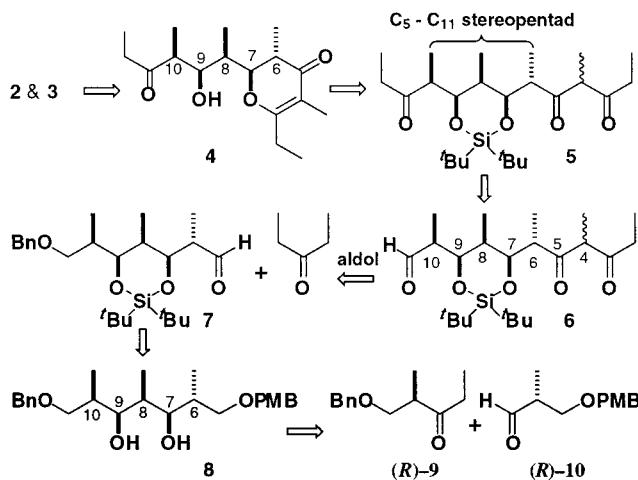
(1) Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, 34, 6791.

(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*,2*S*)-membrenone-B.

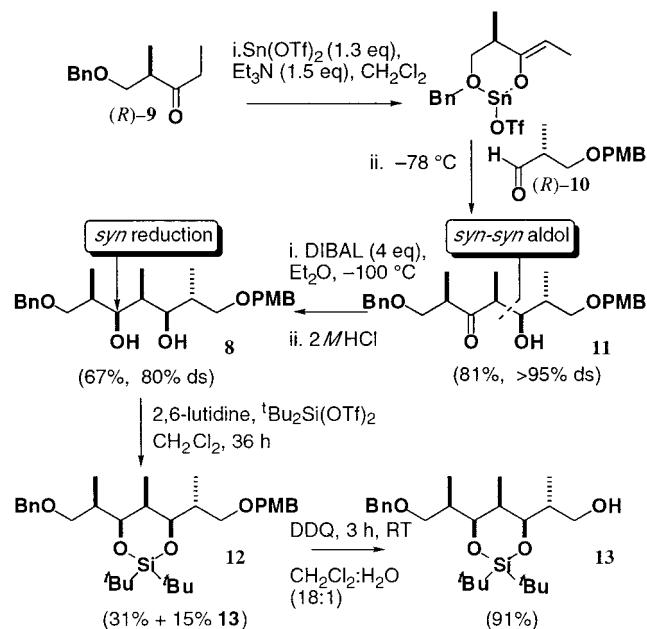
Scheme 1



(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 trione **5**. The construction of the trione 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 $^{\circ}$ C for 10 min followed by the addition of ketone **(R)**-**9** at -60 to -70 $^{\circ}$ C and stirring for 2 h. Subsequent addition of the chiral aldehyde **(R)**-**10** at -78 $^{\circ}$ 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*-butylsilyl enol ether⁶ gave a mixture of **12** and the primary alcohol **13** resulting from partial hydrolysis of the PMB-ether. Removal of the PMB-

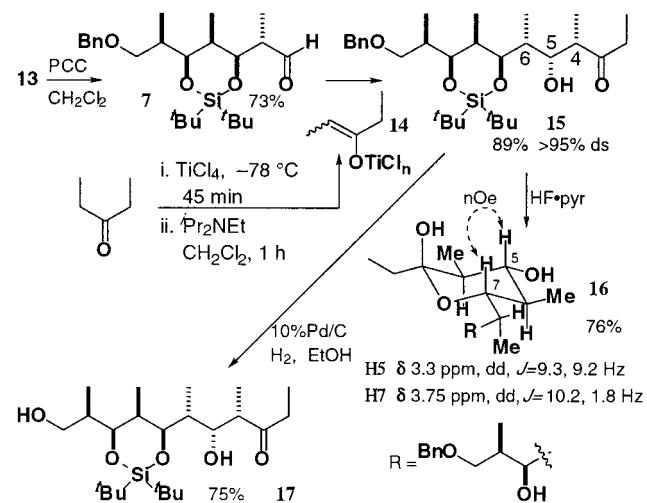
Scheme 2



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 debenzylation is shown in Scheme 3. Oxidation (PCC) of **13** gave the aldehyde **7**, which

Scheme 3

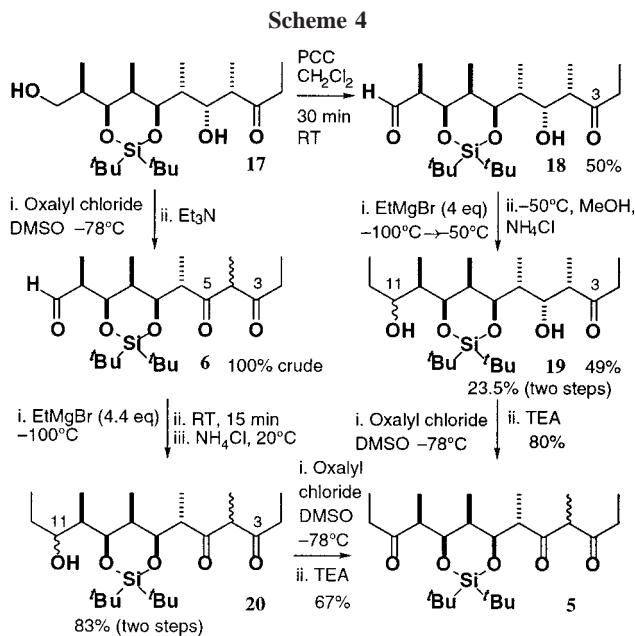


was used immediately in the subsequent aldol employing the Ti(IV)⁸ enolate **14** of diethyl ketone. This reaction gave predominantly one isomer (>95% ds) **15** in 89% yield. This

(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 (–)-(6S,7S,8S,9R,10S)-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



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.

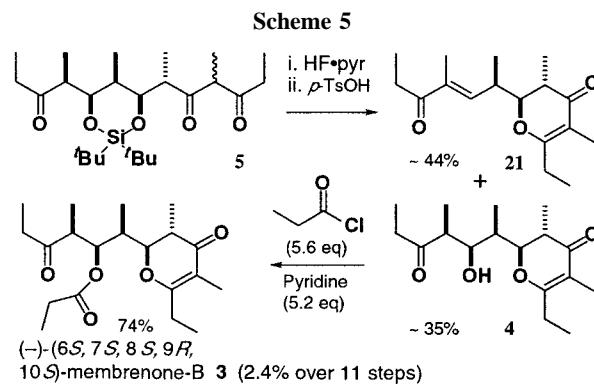
(7) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, 23, 885. (b) Horita, H.; Yoshioka, T.; Tanaka, T.; Oikawa, Y. *Tetrahedron* **1986**, 42, 3021.

(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.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, 112, 8215. (c) Evans, D. A.; Riegle, D. L.; Bilodeau, M. T.; Urpí, 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 (–)-(6S,7S,8S,9R,10S)-membrenone-B **3** is shown in Scheme 5. Removal of the di-*tert*-butylsilylene

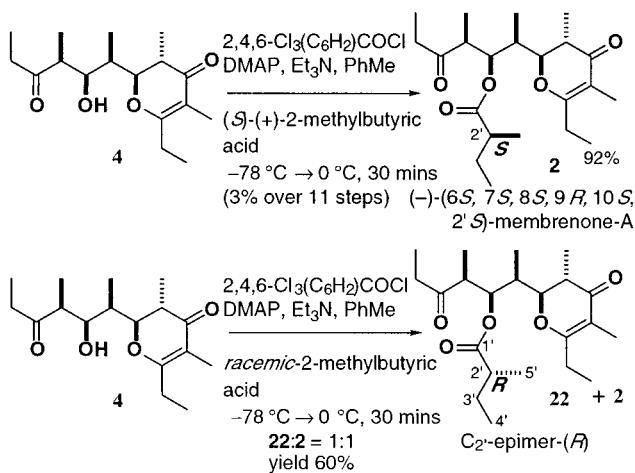


protecting group from **5** by treatment with HF-pyridine, buffered with excess pyridine, gave a complex mixture of compounds. However, acid catalysis (*p*-TsOH) assisted the cyclization/dehydration, giving a 1:1 mixture of two products, **21** and **4**. Thus formation of the γ -dihydropyrone ring was 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 (–)-(6S,7S,8S,9R,10S)-membrenone-B **3** was achieved in 2.4% yield over 11 steps.

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

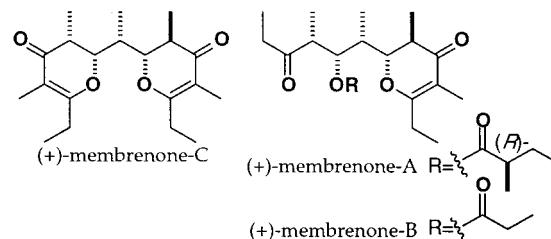
Scheme 6



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

(10) (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikotam, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *31*, 6367.

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 (–)-(6S,7S,8S,9R,10S,2'S)-membrnone-A **2** with the same configuration of the C₆–C₁₀ stereopentad. The reported rotation¹ for the natural membrnone-B was $[\alpha]_D^{20} = -24.77^\circ$ (*c* 0.2, CHCl₃), but this is not consistent (being of the opposite sign to natural membrnone-A) with the nearly identical CD curves¹¹ reported for membrnone-A and -B. Thus it appears that the sign of the rotation for membrnone-B was *misreported*,^{1,12} and natural membrnone-B should have a positive rotation, the same sign as that reported for membrnone-A. Similarly it appears that the sign of rotation for membrnone-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 membrnone-C (based on the reported¹ negative rotation) was incorrect. The absolute and relative configuration of the natural membrnones is summarized below.



Absolute configuration of the membrnone natural products

Acknowledgment. We thank the Australian Research Council (Large ARC grant A00000585 to M.V.P.) for support. Thanks also to Mr. Paul Gugger (Research School of Chemistry, Australian National University) for performing the CD spectral analysis.

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>.

OL025674O

(11) Membrnone-A and -B were reported (ref 1) to have opposite signs of rotation but had almost identical CD curves. Reported values were membrnone-A $[\alpha]_D^{20} = +24.72^\circ$ (*c* 0.05, CHCl₃), CD curve $[\theta]_{300} -2278$ (max), $[\theta]_{270} +6126$ (max); membrnone-B $[\alpha]_D^{20} = -24.77^\circ$ (*c* 0.2, CHCl₃), CD curve $[\theta]_{302} -2354$ (max), $[\theta]_{269} +6230$ (max); membrnone-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 membrnones were not available for direct comparison of the $[\alpha]_D^{20}$ and CD curve.

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