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Stereoselective Synthesis of Dihydropyrone-Containing Marine Natural Products. Total Synthesis and Structural Elucidation of (−)-Membrenone-C

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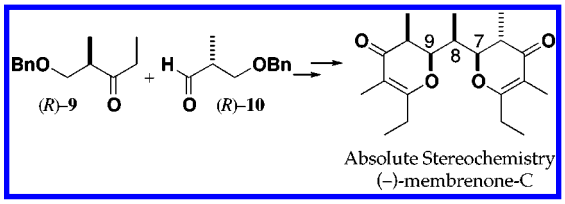
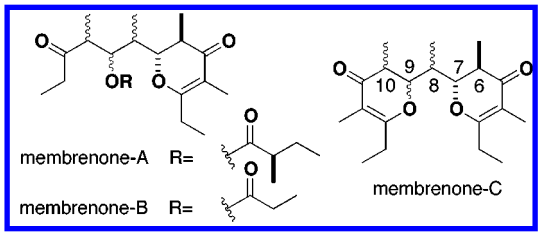
ABSTRACT



Three diastereomers of membrenone-C were separately prepared using a common two directional chain extending synthetic strategy. This has established the absolute and relative configuration of the natural product to be as shown in the foregoing graphic. Key steps in the synthesis of all the isomers are a stereoselective aldol coupling and reduction giving the C_7–C_9 stereocenters, a two direction chain extending *double* titanium aldol coupling, and the trifluoroacetic acid promoted double cyclization/dehydration giving the two dihydropyrone rings.

Membrenone-A, membrenone-B, and membrenone-C are three 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 C_8, C_9, and C_{10} was not assigned.

^{1}H NMR spectroscopic analysis reported in the original publication[1] (H_6−H_7, J = 13.7 Hz) suggested a pseudo *trans diaxial* relationship (i.e., *trans diequatorial* alkyl substituents) for one γ-dihydropyrone ring in membrenone-C. The other dihydropyrone ring exhibited a small coupling (J_{9-10} = 2.6 Hz) suggesting a *cis* orientation of the substituents at C_9 and C_{10}. Thus, since the relative configuration from one dihydropyrone ring to the other is uncertain, and the configuration of the C_8 methyl is unknown, four diastereomeric structures



for membrenone-C (**1**−**4**) were possible (each a pair of enantiomers).

We recently reported a short, enantiocontrolled synthesis of isomer **4** of membrenone-C, exploiting a novel two

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

(2) Perkins, M. V.; Sampson, R. A. *Tetrahedron Lett.* **1998**, *39*, 8367.

(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.; Schlapbach, A. *Synlett* **1995**, 498.

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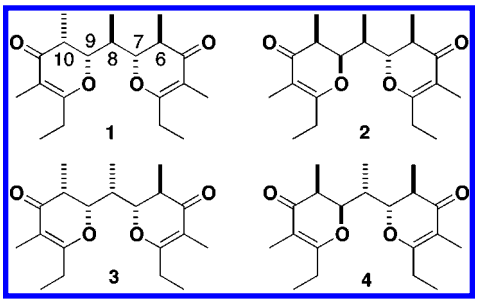
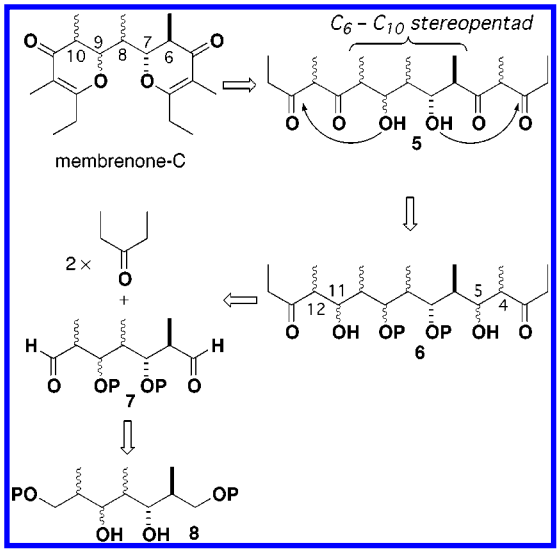
directional chain extending *double* titanium aldol coupling.[2] We now report extension of this method to the synthesis of the three possible remaining diastereoisomers of membrenone-C (**1**−**3**), which establishes the relative and absolute configuration of the natural product to be the *enantiomer* of isomer **3**.



Scheme 1 outlines our general strategy for the synthesis of isomers **1**−**3** of membrenone-C via **5** and **6**, based on a

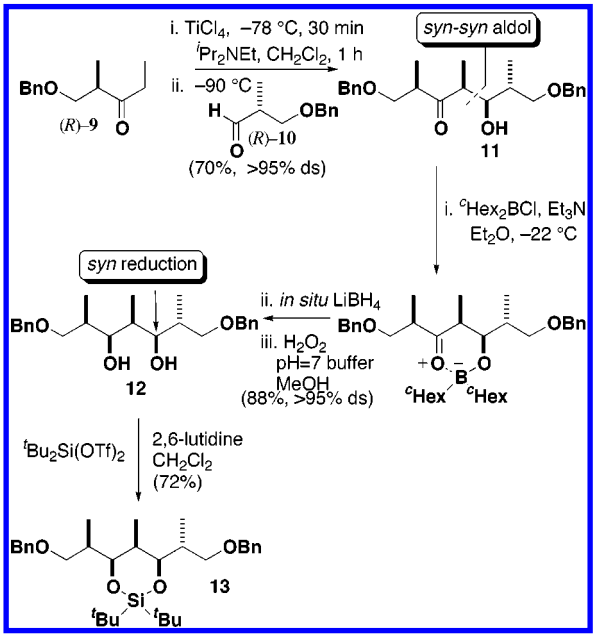
Scheme 1



double aldol-type disconnection of the C_4-C_5 and $C_{11}-C_{12}$ bonds. The sequence of five contiguous stereogenic centers in **7** and **8**, linking C_6 and C_{10}, were amenable to the general protocol developed by Paterson[3] for the synthesis of such stereopentads.

The synthesis of the required stereopentad for *ent*-**3** is shown in Scheme 2. Addition of the titanium enolate,[4]

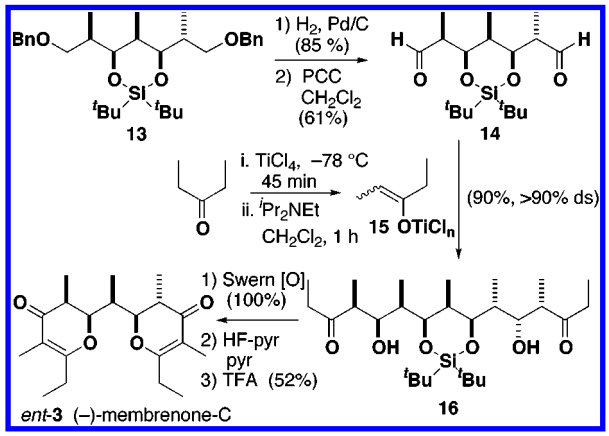
Scheme 2



obtained by precomplexation of (*R*)-**9** with $TiCl_4$ at −78 °C for 30 min followed by addition of diisopropylethlyamine, to chiral aldehyde (*R*)-**10** at −90 °C gave the *syn-syn* aldol isomer **11** with >95% ds. This selectivity is significantly higher than that reported[5] for the reaction of the Ti(IV) enolate of (*R*)-**9** with the achiral aldehyde methacrolein. Reduction to the *syn* 1,3-diol **12** was achieved in a modification of the procedure of Narasaka[6] where the alcohol was added to a $(^cC_6H_{11})_2BCl/Et_3N$ mixture at −23 °C to form a borinate complex, which was reduced with $LiBH_4$ in 88% yield and >95% ds. Protection of the diol as the di-*tert*-butylsilylene[7] gave the key intermediate **13**. Thus the C_5-C_{11} segment **13** was obtained in 44.3% yield in three steps from (*R*)-**9** and (*R*)-**10** with >90% ds, forming three new stereocenters and resulting in a total of five contiguous stereocenters.

The remainder of the synthesis is shown in Scheme 3.

Scheme 3



(4) (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.; Riegler, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.

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

(6) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Paterson, I.; Donghi, M.; Gerlach, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3315.

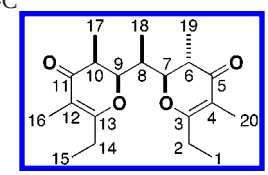
(7) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999. (b) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871. (c) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

Debenzylation (catalytic hydrogenolysis) of **13** and oxidation (PCC) gave the dialdehyde **14**. The two directional chain extending double aldol was achieved by treating **14** with the Ti(IV)[4] enolate **15** of diethyl ketone. This gave predominantly one isomer (>90% ds) **16** in 90% yield. This high selectivity shows significant substrate control for this isomer of the dialdehyde, which is not apparent in the reaction of any of the other isomeric dialdehydes with the highly reactive titanium enolates. The configuration of the four stereocenters produced in the formation of **16** is tentatively assigned as shown; however, they are not present in the final product and are removed in the subsequent steps. Double Swern oxidation of **16** gave a quantitative yield of the tetraone as a mixture of C_4 and C_{12} epimers (enol forms were also evident from NMR studies). The protecting group was removed by treatment with HF-pyridine, buffered with excess pyridine, giving a mixture of diols and hemiacetals. Rapid acid catalyzed cyclization/dehydration was achieved by treatment with trfluoroacetic acid, giving a single product *ent*-**3** as a crystalline solid (mp 98−100 °C) after purification.[8]

The ^{1}H and ^{13}C NMR reported[1] for the natural product and that obtained for *ent*-**3** are shown in Table 1. Comparison of these spectra confirms the relative configuration of the natural product to be that shown for *ent*-**3**.[9] The optical rotation obtained for the synthetic material $[\alpha_D^{20}] = -28.2$ (*c* 0.46, $CHCl_3$) was somewhat lower than that reported for the natural product $[\alpha_D^{20}] = -58.09$ (*c* 0.1, $CHCl_3$); however, the same signs of rotation confirms the assigned absolute configuration of the natural product.[10] Thus the total synthesis of (−)-membrenone-C was achieved in eight steps from (*R*)-**9** and (*R*)-**10** in an overall yield of 10.7%.

While we are confident the assigned configuration of the natural product is correct, we have also synthesized the remaining two possible isomers **1** and **2**. The synthesis of the isomer **1** is shown in Scheme 4.

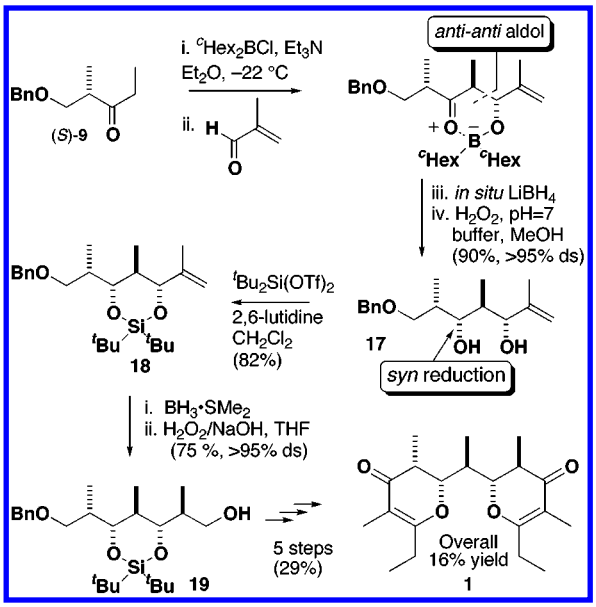
Table 1. Comparison of the ^{1}H and ^{13}C NMR Data for Synthetic Isomer *ent*-**3** and That Previously Reported[1] for (−)-Membrenone-C



	(−)-membrenone-C[a]		isomer *ent*-**3**[b]	
C	δ ^{13}C[c]	δ ^{1}H, m, ^3J (Hz)[c]	δ ^{13}C[c]	δ ^{1}H, m, ^3J (Hz)[c]
1	10.9	1.06, t, 7.6	10.92	1.06, t, 7.5
2	25.16	2.35, m	25.43[d]	2.36−2.22, m
3	172.5		172.48	
4	108.4		108.65	
5	194.51		194.57	
6	39.93	2.51, dq, 13.7, 6.9	39.91	2.51, dq, 13.8, 7.2
7	81.74	3.90, dd, 13.7, 2.1	80.93	3.89, dd, 13.8, 2.1
8	34.68	2.20, m	34.67	2.20, dqd, 10.2, 6.6, 2.1
9	83.05	4.25, dd, 10, 2.6	81.69	4.24, dd, 10.2, 3.0
10	40.25	2.40, m	40.43	2.40, m
11	197.41		197.11	
12	107.48		107.70	
13	173.81		173.73	
14	25.16	2.40, m	25.45[d]	2.46−2.32, m
15	10.8	1.17, t, 7.6	10.82	1.17, t, 7.5
16	9.11	1.74, s	9.10	1.73, s
17	9.77	1.02, d, 7.3	9.79	1.01, d, 7.2
18	9.11	1.19, d, 6.8	9.26	1.19, d, 6.6
19	9.33	1.09, d, 6.9	9.33	1.08, d, 7.2
20	9.11	1.71, s	9.11	1.70, s

[a] Chemical shifts and coupling constants as reported in ref 1 (Bruker 500 AMX). [b] Varian Unity Inova 600 MHz NMR Spectrometer. Assigments assisted by ^{1}H−^{13}C HMBC, HSQC, and ^{1}H−^{1}H COSY. [c] Chemical shifts in ppm referenced to $\underline{C}HCl_3$ at 7.26 ppm and to $\underline{C}DCl_3$ at 77.0 ppm. [d] Tentative assignment and may be interchanged.

Scheme 4



Addition of methacrolein to the *E*-enol dicylohexylborinate of ketone (*S*)-**9** followed by in situ reduction of the intermediate boron aldolate gave diol **17**, which contains the C_7−C_9 stereocenters required for isomer **1**, with a diastereoselectivity greater than 95%. Protection as the di-*tert*-butylsilylene[7] gave **18**, which was selectively hydroborated with BH_3·SMe_2 (>95% ds)[3b−d] to give the key intermediate **19**. This compound was converted to isomer **1** of membrenone-C by the same debenzylation, double aldol, oxidation, and deprotection/cyclization/dehydration sequence used above.

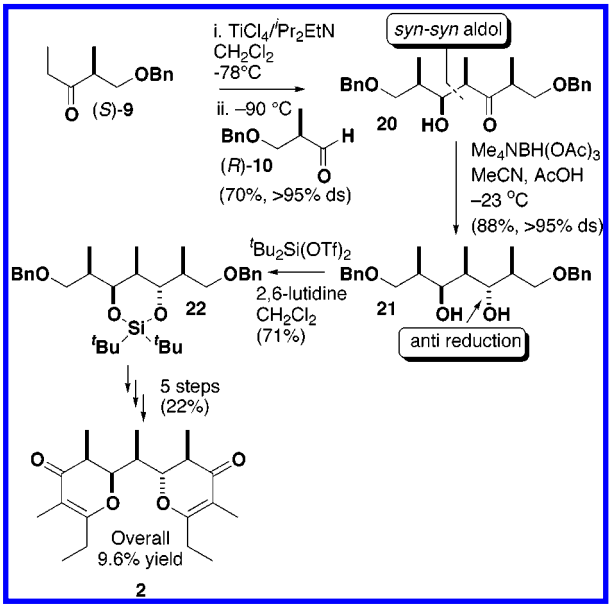
(8) The natural product was reported (ref 1) as an oil, presumably as a result of the small amount isolated (3 mg).

(9) All of the signals in the ^{1}H NMR spectrum match in chemical shift and coupling constants. All of the signals in the ^{13}C NMR spectrum match *except* for the signal reported (ref 1) at δ = 81.74 ppm, which was found to occur at δ = 80.93 ppm, and the signal at δ = 83.05 ppm, which was found to occur at δ = 81.69 ppm. We cannot explain this discrepancy, but the identity of all of the other signal confirms the stereochemical assignment.

(10) Synthetic membrenone-B, having the same absolute configuration as *ent*-**3**, was found to have an optical rotation of $[\alpha_D^{20}] = -44$ (*c* 0.68, $CHCl_3$) (Perkins, M. V.; Sampson, R. A. unpublished results) compared to the reported (ref 1) $[\alpha_D^{20}] = -24.77$ (*c* 0.2 $CHCl_3$).

(11) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

Scheme 5



The synthesis of the isomer **2** is shown in Scheme 5. In this case the Ti(IV)[4] enolate of (*S*)-**9** was treated with (*R*)-**10** to give the *syn-syn* aldol product **20** in 70% yield and >95% ds. Selective *anti* reduction[11] gave **21** in 88% yield, which was protected as the di-*tert*-butylsilylene[7] to give the key intermediate **22**. The debenzylation, aldol, oxidation, and deprotection/cyclization/dehydration sequence was again employed giving isomer **2** of membrenone-C.

Comparison of the ^{1}H and ^{13}C NMR reported[1] for the natural product and that obtained for isomers **1**, **2**, and **4**[2] shows significant differences both in the ^{1}H NMR chemical shifts and coupling constants and in the ^{13}C NMR chemical shifts, further confirming the stereochemical assignment of (−)-membrenone-C as that depicted in *ent*-**3**.

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

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