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Total Synthesis of (−)- and (+)-Membrenone C

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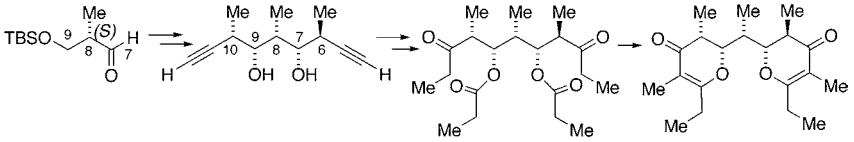
ABSTRACT



A synthesis of the polypropionate marine defense substance (+)-membrenone C and its enantiomer that starts from (*S*)-2-methyl-3-(*tert*-butyldimethylsilyloxy)propanal is described. Key steps include (1) additions of chiral allenylmetal reagents to effect both chain homologation and the concomitant introduction of four stereo centers, (2) a bis-intramolecular hydrosilylation–oxidation sequence to install *β*-hydroxy ketone subunits, and (3) a bis-intramolecular aldol reaction to construct the two dihydropyrone termini.

Opisthobranchs (marine nudibranchs) are small, usually brightly colored snail-like creatures that lack a protective shell. Their survival in the hostile marine environment is thought to depend on chemical defense compounds that render them unpalatable to potential predators. Three such compounds, membrenones A−C, were isolated in 1993 from the skin of the marine mollusc *Pleurobranchus membranaceus* (Montagu, 1815) (Figure 1).[1] The two-dimensional

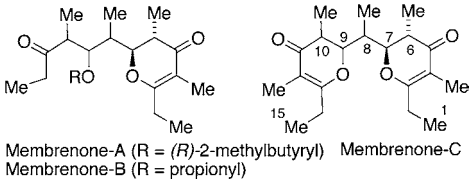
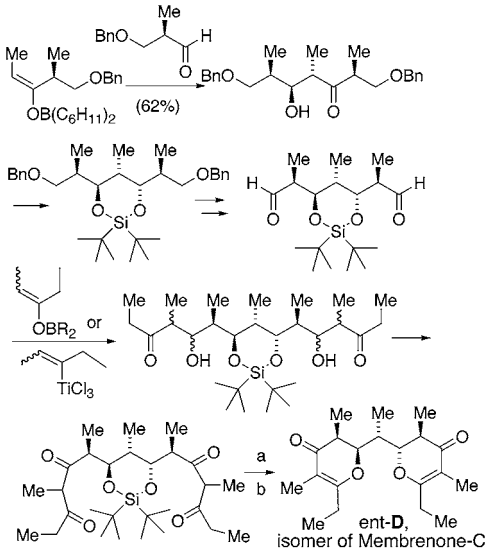


Figure 1. Partial structures for membrenones A−C.

structures of these three compounds were deduced from spectral data, but only the relative stereochemistry at C6 and C7 could be assigned.

Some years later, Perkins and Sampson reported a bidirectional synthesis of a *cis*,*anti*,*syn*,*trans*-bis-dihydropyrone (ent-**D**) that proved to be an isomer of membrenone C (Scheme 1).[2] This compound was one of four (Figure 2, **A**−**D**) with relative stereochemistry consistent with the reported NMR data (coupling constants for H6/H6 = 13.7

Scheme 1. Synthesis of an Isomer of Membrenone C[2]



[a] Conditions: (a) HF-pyridine; (b) TFA.

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

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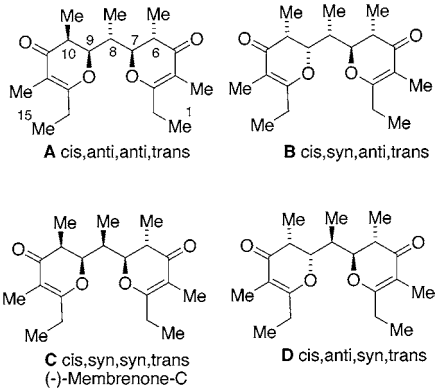


Figure 2. Structure possibilities for membrenone C.

Hz and H9/H10 = 2.6 Hz).[1] Subsequently, these authors prepared the other three isomers by analogous routes and found that the cis,syn,syn,trans isomer **C** exhibited spectral data in close agreement with that reported for membrenone C.[3] Although significantly lower in magnitude than the published value, the optical rotation of the synthetic material was of the same sign as that of natural membrenone C ($[\alpha]_D$ = −58[1] vs −28[3], respectively).

We were attracted to the novel structure and potential bioactivity of membrenone C and felt that it could be readily assembled through application of allenylmetal and intramolecular hydrosilylation reactions.[4,5] The overall plan was a simple one starting from a chiral aldehyde derived from (*S*)-2-methyl-3-hydroxypropionic acid (Figure 3).[6]

Various practical considerations led us to employ the allenylstannane (*P*)-**1** and the allenylindium reagent (*M*)-**7**, rather than the methylated homologues **E** and **F** depicted in Figure 3, for the allenylmetal additions to aldehyde **2** and subsequently **6** (Scheme 2). The BF_3·OEt_2-promoted reaction of (*P*)-**1** led to the syn,syn adduct **3** in >95:5 dr and in 82% yield. Silylation of the secondary alcohol and hydrolysis of the primary OTBS ether afforded alcohol **5**. The derived aldehyde **6** was subjected to propargylation by the allenylindium reagent (*M*)-**7** prepared from the mesylate of (*S*)-4-trimethylsilyl-3-butyn-2-ol, this alcohol being readily obtained through lipase resolution of commercially available racemic 4-TMS-3-butyn-2-ol.[7] The propargylic adduct **8** of 96:4 dr was obtained in 97% yield. Removal of the silyl groups with TBAF and resilylation of the diol **9** with TESOTf afforded the diyne **10** in 98% overall yield. The terminal alkynyl methyl groups were introduced by methylation of the lithiated diyne in quantitative yield. Desilylation was effected in 98% yield to afford the diol **12**.

Treatment of diol **12** with tetramethyldisilazane afforded the bis-silyl ether **13**. Subjecting this silane to H_2PtCl_6 in

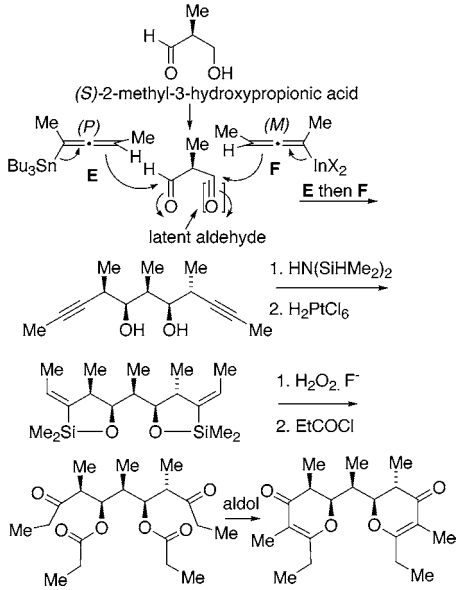
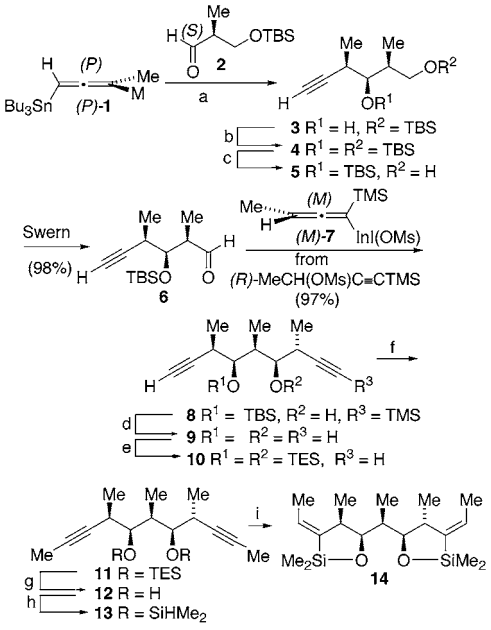


Figure 3. Synthetic plan for (−)-membrenone C.

THF at 55 °C, as previously reported,[5] led to a mixture of compounds. However, by increasing the temperature to 75 °C, we were able to isolate the bis-cyclic siloxane **14** in quantitative yield.

Initial attempts at direct oxidation of the siloxane **14** to the diketone met with several problems. The siloxane is quite

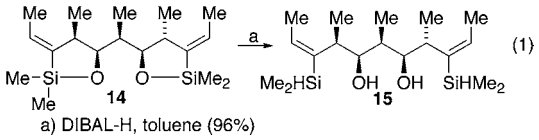
Scheme 2[a]



[a] Conditions: (a) BF_3·OEt_2, CH_2Cl_2, −78 °C (82%); (b) TESOTf, 2,6-lutidine (87%); (c) PPTS, EtOH (92%); (d) TBAF, THF (98%); (e) TESOTf, 2,6-lutidine (100%); (f) BuLi, THF and then $(MeO)_2SO_4$ (100%); (g) TBAF, THF (98%); (h) $(Me_2SiH)_2NH$, 85 °C (100%); (i) H_2PtCl_6, THF, 75 °C (100%).

(2) Perkins, M. V.; Sampson, R. A. *Tetrahedron Lett.* **1998**, *39*, 8367.
(3) Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2001**, *3*, 123.
(4) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.
(5) Marshall, J. A.; Yanik, M. M. *Org. Lett.* **2000**, *2*, 2173.
(6) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203.
(7) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M *Org. Lett.* **2001**, *3*, 3369.

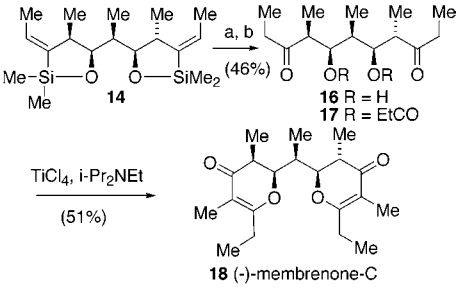
polar and required methanol as a cosolvent for the oxidation reaction. However, the oxidation product, diketo diol **16**, is readily soluble in water and methanol. Hence, product recovery was problematic. In addition, attempted purification of the diketone **16** by chromatography on silica gel led to partial epimerization. For these reasons, we explored an alternative plan whereby the siloxane would be cleaved with a hydride nucleophile and the liberated diol converted to the bis-propionic ester, which would then be subjected to oxidative removal of the vinylsilanes. We were able to effect the desired cleavage in high yield with DIBAL-H in toluene (eq 1), but the diol **15** proved to be difficult to acylate. No product was obtained after prolonged treatment with propionic anhydride or propionyl chloride with added Et_3N and DMAP. In a model system (see Supporting Information), the propionate could be obtained, but Tamao oxidation of the vinylsilane (H_2O_2, KF, THF−MeOH) caused cleavage of the propionic ester.[5,8]



(1)

We therefore revisited the direct oxidation of the cyclic siloxane **14** (Scheme 3). By carrying out an exhaustive

Scheme 3[a]



[a] Conditions: (a) MeOH−THF (2:1), $KHCO_3$, KF, H_2O_2; (b) $CH_3CH_2CO_2H$, DMAP, DCC, CH_2Cl_2.

extraction of the polar diketo diol **16** with ethyl acetate and directly acylating the crude diol with DCC and propionic acid, we were able to isolate the diketo dipropionate **17** in 46% overall yield. Interestingly, both propionic anhydride and propionyl chloride in the presence of Et_3N and DMAP were less effective acylating agents.

The final step of the (−)-membrenone C synthesis entailed a double aldol cyclization. Experiments with model systems were conducted by using LiHMDS, NaHMDS, and NaH as basic catalysts. None produced more than a trace of dihydropyrone. However, the use of $TiCl_4$[9] proved to be effective. Slow addition of $TiCl_4$ to diketo diester **17** at −78 °C in the

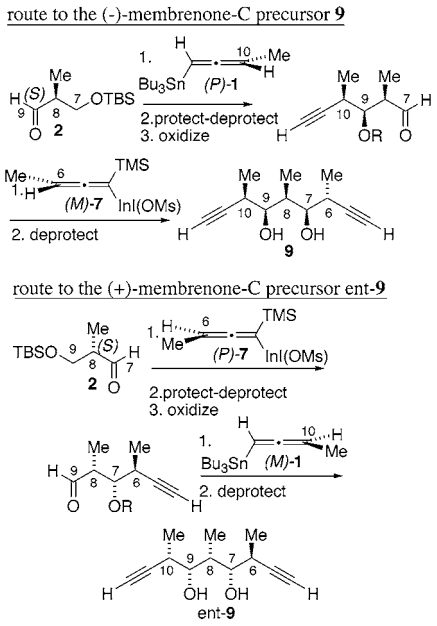


Figure 4. Plan for the synthesis of enantiomeric stereopentads.

presence of Hunig's base afforded (−)-membrenone C (**18**) in 51% yield. The spectral data and rotation closely matched the published data of Perkins and Sampson.[3]

As we approached the final stages of the foregoing synthetic sequence, those investigators reported experiments that led to their reversal of the assigned configuration for natural membrenone C.[10] Although the configuration of their synthetic material was secure, their findings suggested to them that the initial investigators had mistakenly reported the sign of rotation for both membrenone B and C as minus rather than plus. Accordingly, the sign agreement between their synthetic material and the reported rotation for the natural material was not a valid confirmation of absolute configuration. As we hoped to evaluate the potential antitumor activity of membrenone C, we decided to prepare both enantiomers. Initially, we considered repeating our synthetic sequence with the (*R*)-enantiomer of aldehyde **2** and the enantiomeric allenylmetal reagents of Scheme 2. However, upon further reflection, we formulated a more interesting plan involving a reordering of the allenylmetal additions (Figure 4).

Thus, instead of forming the 9,10-syn bond first with the (*P*)-allenylstannane (*P*)-**1** followed by the 6,7-anti bond with the (*M*)-allenylindium (*M*)-**7** reagent, we decided to construct the 6,7-anti bond first and the 9,10-syn bond second by using the (*P*)-allenylindium and (*M*)-allenylstannane reagents (*P*)-**7** and (*M*)-**1**, respectively. In this way, the (*S*)-aldehyde **2** could be utilized as the starting material for both enantiomers. This alternative plan would also extend the scope of the allenylmetal reactions to additional aldehyde substrates.

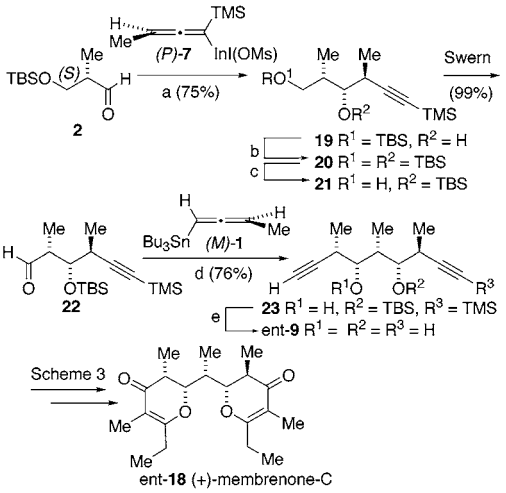
Accordingly, the (*P*)-allenylindium reagent (*P*)-**7**, derived from (*R*)-4-TMS-3-butyn-2-ol mesylate,[7] was added to the

(8) Tamao, K.; Kumada, M.; Maeda, K. *Tetrahedron Lett.* **1984**, *25*, 321. Review: Jones, G. R.; Landis, Y. *Tetrahedron* **1996**, *52*, 7599.

(9) Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1275.

(10) Sampson, R. A.; Perkins, M. V. *Org. Lett.* **2002**, *4*, 1655.

Scheme 4[a]



[a] Conditions: (a) (*R*)-TMSC≡CCH(OMs)Me, $Pd(OAc)_2$, PPh_3, InI, THF−HMPA (75%, dr = 99:1); (b) TBSOTf, $CHCl_2$, 2,6-lutidine (97%); (c) PPTS, EtOH (90%); (d) BF_3•OEt_2, CH_2Cl_2, −78 °C (76%, dr = 95:5); (e) TBAF, THF (100%).

(*S*)-aldehyde **2** affording the anti adduct **19** in 99:1 dr and in 75% yield (Scheme 4). Silylation and selective desilylation followed by Swern oxidation of the primary alcohol led to aldehyde **22**, which reacted with the (*M*)-allenylstannane (*M*)-**1** to give the homopropargylic alcohol **23** in 95:5 dr and in 76% yield. Desilylation with TBAF afforded diol ent-**9** quantitatively. This diol was identical to that prepared in Scheme 2 except for the optical rotation, which was opposite in sign but nearly equal in magnitude ($[\alpha]_D = -2.3$ for **9** and +2.1 for ent-**9**). The remaining steps of the synthesis were carried out as outlined in Scheme 3. The final product was, as expected, identical to the previous sample of (−)-membrenone C except for the optical rotation, which was equal in magnitude but of opposite sign ($[\alpha]_D = -22.6$ and +23.5).

The foregoing syntheses of (−)- and (+)-membrenone C reconfirm the relative stereochemistry as assigned by Perkins and Sampson,[3] but as samples of the natural material are no longer available, the absolute configuration remains unsubstantiated.

Acknowledgment. Support for this research was provided by grant R01 CA90383 from the National Cancer Institute.

Supporting Information Available: Experimental procedures for all compounds and selected ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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