Pergamon

Tetrahedron Letters 39 (1998) 8367–8370

TETRAHEDRON LETTERS

Stereoselective Synthesis of an Isomer of Membrenone-C *via* an Aldol Based Two Directional Chain Extension

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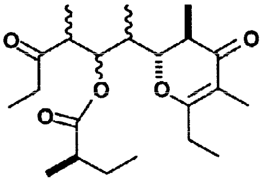
Received 22 July 1998; accepted 1 September 1998

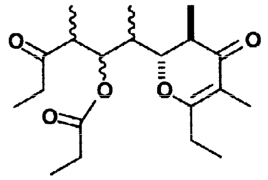
Abstract: An isomer of Membrenone-C was prepared in 8 steps (17% yield) with 93% overall ds starting from the ethyl ketone (*S*)-**10**. Key steps are the boron-mediated aldol followed by *anti* selective reduction, giving the C_6–C_{10} stereochemistry, the two direction chain extending *double* titanium aldol coupling, **16** + **20** → **19**, and the TFA promoted double cyclisation/dehydration giving an isomer of Membrenone-C, **21** → **4**. © 1998 Elsevier Science Ltd. All rights reserved.

In 1993 three new polypropionates, Membrenone-A, Membrenone-B and Membrenone-C, were 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 stereochemistry at C_8, C_9 and C_{10} was not assigned. The absolute configuration remains uncertain.

These natural products show the characteristics of polypropionate natural products possessing a linear carbon chain with alternating hydroxyl and methyl substituents and they also possess a somewhat unusual γ-dihydropyrone ring. Their biological role is uncertain and investigation has been limited by the small quantities that were isolated.[1] We now report a short, enantiocontrolled synthesis of an isomer of Membrenone-C, exploiting a novel two direction chain extending *double* titanium aldol coupling. Notably, this allows the first stereoselective synthesis of an isomer of Membrenone-C.



Membrenone-A



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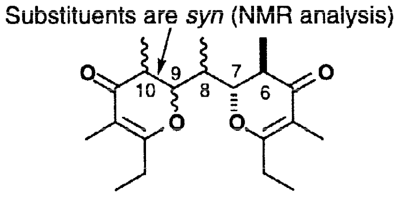
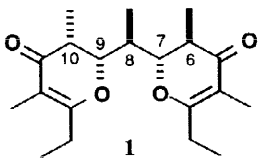


Membrenone-C

^{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 (ie *trans diequatorial* alkyl substituents) for one γ-dihydropyrone ring. The other dihydropyrone ring exhibited a small coupling ($J_{9\text{-}10}$ = 2.6 Hz) suggesting a *cis* orientation of the substituents at C_9 and C_{10}. Thus, since the relative stereochemistry from one dihydropyrone ring to the other is uncertain, and the stereochemistry of the C_8 methyl is unknown, 4 diastereomeric structures for Membrenone-C are possible (each a pair of enantiomers).[2]



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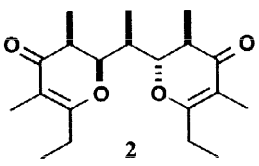

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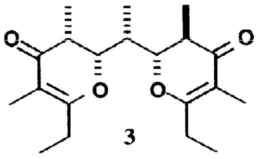

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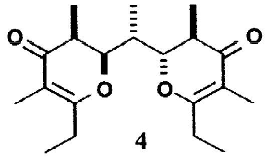

4

Modelling studies[3] on the low energy conformations of these four different isomers indicated that isomer 4 should exist in a conformation that would give the observed[1] couplings of H_7-H_8 (J = 2.7 Hz) and H_8-H_9 (J =10 Hz). Thus isomer **4** was chosen as the initial synthetic target.

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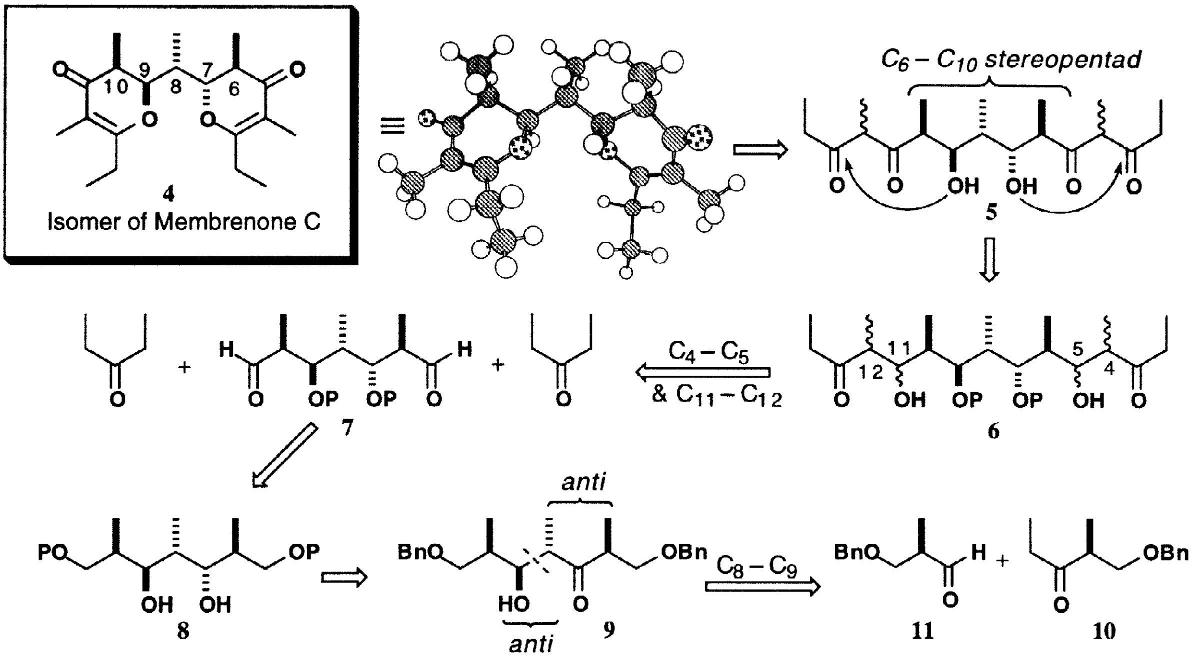
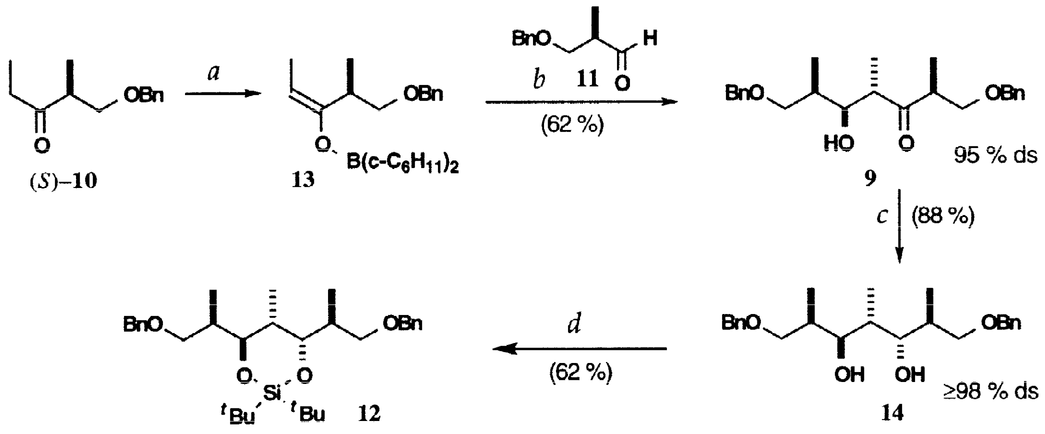
PII: S0040-4039(98)01846-2



Scheme 1

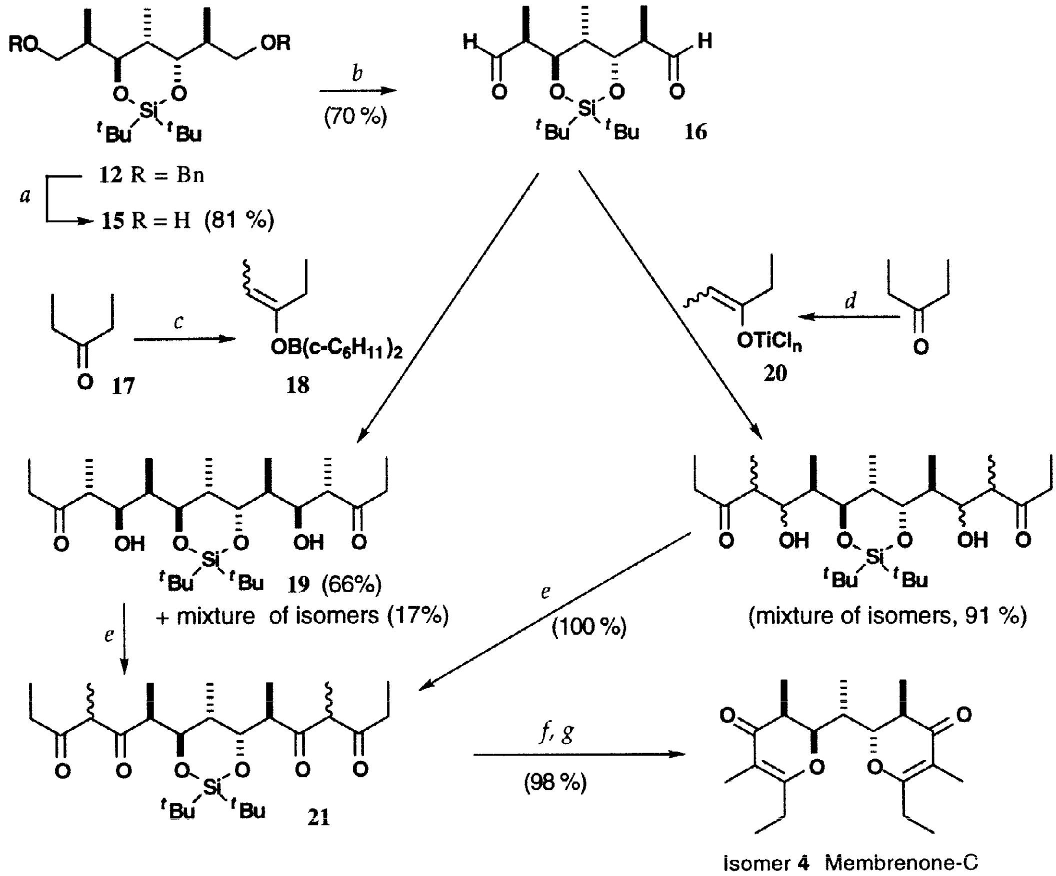
Scheme 1 outlines our strategy for the synthesis of isomer **4** of Membrenone-C *via* **5** and **6**, based on a double aldol-type disconnection of the C_4–C_5 and C_{11}–C_{12} bonds. The sequence of five contiguous stereogenic centres linking C_6 and C_{10} should be amenable to the general protocol developed by Paterson[4] for the synthesis of such stereopentads. In this case, the appropriate precursor is the product of *anti* reduction of the *anti-anti* aldol adduct **9** derived from the ethyl ketone (*S*)-**10** and aldehyde (*R*)-**11**.

The synthesis of the C_5–C_{11} segment **12**, with the two hydroxyl groups at C_7 and C_9 protected as the cyclic di-*tert*-butylsilylene derivative,[5] is shown in **Scheme 2**. We anticipated that this silyl protecting group would be removed under mild conditions using buffered HF-pyridine,[6] liberating a diol precursor at a late stage in the synthesis, thus allowing double cyclisation/dehydration to occur, forming the two dihydropyrone rings in the isomer of Membrenone-C **4**. Addition of the *E*-enol dicyclohexyl borinate **13**, obtained by enolisation of (*S*)-**10** with $(c\text{-}C_6H_{11})_2BCl/Et_3N$, to chiral aldehyde (*R*)-**11** gave on oxidative work-up the expected[4] *anti-anti* aldol isomer **9** with 95% ds.[6] Reduction to the corresponding *anti* 1,3-diol **14** was achieved by stereoselective Evans *anti* reduction[7] in 88% yield. Protection of the diol as the di-*tert*-butylsilylene gave the key intermediate **12**. Thus the C_5–C_{11} segment **12** was obtained in 34% yield in three steps from (*S*)-**10** and (*R*)-**11** with 93% ds, forming three new stereocentres and resulting in a total of five contiguous stereocentres.



Scheme 2 (*a*) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, −22 °C, 2 h; (*b*) **11**, 2 h; H_2O_2, MeOH-pH7 buffer, 0 °C → RT 2h; (*c*) $Me_4NBH(OAc)_3$, MeCN, AcOH, −23 °C; (*d*) $^tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2, 20 °C, 5 h.

The remainder of the synthesis is shown in **Scheme 3**. Debenzylation (catalytic hydrogenolysis) of **12** and oxidation (PCC) gave the dialdehyde **16**. The two directional chain extending double aldol was first achieved by treating **16** with the enol dicyclohexyl borinate of diethylketone **17**. Addition of the dialdehyde **16** to 10 equivalents of the enolate **18** followed by oxidative removal of the boron gave one major product in 66% yield and a mixture of minor isomers (17%). The major product was tentatively assigned the structure **19** assuming it is produced by Cram-Felkin addition of the major *E*-enolate. While interesting, the selectivity of this reaction is not critical for the synthesis as the 4 stereocentres produced in this reaction are lost in the subsequent oxidation/dehydration to give the final product. A higher yielding and experimentally simpler but less selective two directional chain extending aldol, using the Ti(IV)[8] enolate **20** of diethylketone, produced an inseparable mixture of at least 4 isomers in 91% yield. Double Swern oxidation of either of the above double aldol products gave a quantitative yield of the tetraone **21** 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-pyr, buffered with excess pyridine, giving a mixture of diols and hemiacetals. Rapid acid catalysed cyclisation/dehydration was achieved by treatment with trifluoroacetic acid giving a single isomer. This product was identified as an isomer of Membrenone-C by analysis of the ^1H, ^{13}C NMR and mass spectral data.



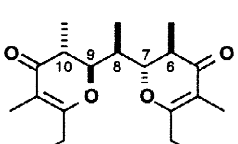
Scheme 3 (*a*) H_2, 10% Pd/C, EtOH, 20 °C, 5 h; (*b*) PCC, CH_2Cl_2, 20 °C, 3.5 h; (*c*) Diethylketone 11 equiv, $(c\text{-}C_6H_{11})_2BCl$ 10 equiv, Et_3N 10 equiv, Et_2O, −22 °C, 2 h; **16**, 3.5h; H_2O_2, MeOH-pH7 buffer (*d*) Diethylketone 10 equiv, $TiCl_4$ 9 equiv, CH_2Cl_2, −78 °C, 45 min; $^iPr_2NEt$ 9 equiv, 1 h; **16**, 2h, → −5 °C, 5 min; (*e*) $(COCl)_2$ 10 equiv, DMSO, CH_2Cl_2 20 equiv, −78 °C, 20 min, Et_3N, → −5 °C, 5 min; (*f*) HF-pyr/pyr, THF, 20 °C, 4 h; (*g*) TFA, 5 min.

In summary, a short and highly efficient stereoselective (>93% overall ds) synthesis of an **isomer** of Membrenone-C (8 steps in 17% yield from (*S*)-**10** and (*R*)-**11**) has been achieved. The two directional chain extending double aldol strategy exploiting the *pseudo* symmetry of the molecules has been shown to be efficient for the synthesis of these compounds and will be extended to the synthesis of the other isomers and thus the ultimate synthesis of Membrenone-C.

Acknowledgment: We thank the Australian Research Council (Flinders University Small ARC grant to MVP) and Flinders University (Flinders University establishment grant to MVP) for support.

References and Notes

1. Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993**, *34*, 6791.
2. A further isomer **22** exists which could possibly sit in a conformation where in one dihydropyrone ring the two alkyl groups are pseudo *trans diaxial* ie. the two hydrogens are *trans diequatorial*, giving the small coupling. The related isomers **23** and **24** can be ruled out as they are *meso* and the natural product is optically active.



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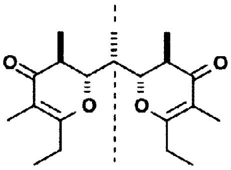

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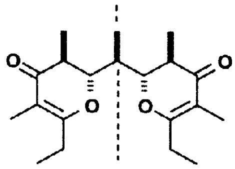

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3. The low energy conformation for the isomers was determined by PCMODEL. This conformation is staggered along the carbon chain with the largest alkyl groups *anti* and *syn* pentane interactions with groups other than hydrogen being avoided. However these modelling studies did not rule out low energy conformations of the other isomers **1-3** giving couplings for H_7-H_8 and H_8-H_9 similar to those observed for natural Membrenone-C.
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5. (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.
6. All new compounds gave spectroscopic data in agreement with the assigned structures. **9** had ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.35-7.27 (10H, m), 4.54-4.43 (4H, m), 4.00 (1H, ddd, *J* = 9.21, 7.05, 3.76 Hz), 3.67 (1H, t, *J* = 8.61 Hz), 3.53-3.51 (2H, m), 3.44 (1H, dd, *J* = 8.61, 5.01 Hz), 3.08 (1H, dqd, *J* = 8.61, 7.00, 5.01 Hz), 2.99 (1H, d, *J* = 3.87 Hz), 2.86 (1H, dq, *J* = 9.21, 7.05 Hz), 1.90 (1H, m), 1.05 (3H, d, *J* = 7.00 Hz), 1.01 (3H, d, *J* = 7.05 Hz), 0.95 (3H, d, *J* = 6.96 Hz); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 217.5, 138.2, 137.9, 128.4, 128.3, 127.6, 127.5, 74.8, 74.6, 73.4, 73.3, 72.4, 49.4, 46.0, 34.73, 13.5, 13.0, 9.7; **14** had ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.28 (10H, m), 4.56-4.47 (4H, m), 3.91 (1H, ddd, *J* = 9.42, 2.13, 1.38 Hz), 3.9 (1H, d, *J* = 1.38 Hz), 3.74 (1H, ddd, *J* = 7.68, 4.29, 3.81 Hz), 3.61-3.44 (4H, m), 3.27 (1H, d, *J* = 4.29 Hz), 2.04-1.89 (2H, m), 1.75-1.65 (1H, m), 1.03 (3H, d, *J* = 6.99 Hz), 0.88 (3H, d, *J* = 6.93 Hz), 0.72 (3H, d, *J* = 6.93 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.2, 137.6, 128.5, 128.3, 128.2, 127.8, 127.4, 127.6, 75.9, 75.8, 75.4, 73.6, 73.4, 36.9, 35.0, 35.7, 13.0, 10.98, 9.59; **12** had ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.26 (10H, m), 4.54-4.45 (4H, m,), 3.96 (1H, dd, *J* = 3.5, 2.1 Hz), 3.93 (1H, dd, *J* = 7.1, 3.5, Hz), 3.71 (1H, dd, *J* = 8.55, 3.27 Hz), 3.53 (1H, t, *J* = 9.0 Hz), 3.50 (1H, t, *J* = 8.55 Hz), 3.36 (1H, dd, *J* = 9.0, 5.85 Hz), 1.98-1.81 (3H, m), 1.03 (9H, s), 1.00 (9H, s), 0.98 (3H, d, *J* = 7.3 Hz), 0.95 (3H, d, *J* = 6.93 Hz), 0.93 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 138.9, 138.8, 128.3, 128.2, 127.6, 127.55, 127.4, 127.3, 77.9, 74.2, 73.2, 73.15, 73.05, 72.6, 40.0, 36.9, 36.8, 28.3, 27.8, 22.1, 21.8, 14.0, 13.4, 10.7; **15** had ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.09 (1H, dd, *J* = 9.8, 3.3 Hz), 4.06 (1H, dd, *J* = 4.2, 2.8 Hz), 3.72 (4H, m), 3.69 (1H, m), 3.57 (1H, m), 2.04-1.89 (2H, m), 1.74-1.67 (1H, m), 1.08 (9H, s), 1.07 (9H, s), 1.05 (3H, d, *J* = 7.29 Hz), 1.04 (3H, d, *J* = 6.93 Hz), 0.78 (3H, d, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 81.0, 80.0, 69.1, 67.2, 41.3, 37.4, 37.2, 28.1, 27.8, 22.2, 22.0, 13.7, 13.3, 9.7; **16** had ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.89 (1H, d, *J* = 3.15 Hz), 9.75 (1H, d, *J* = 1.08 Hz), 4.38 (1H, dd, *J* = 5.73, 4.02 Hz), 4.34 (1H, dd, *J* = 8.6, 4.42 Hz), 2.65 (1H, dqd, *J* = 8.55, 6.93, 3.15 Hz), 2.48 (1H, qdd, *J* = 6.96, 4.02, 1.08 Hz), 2.08 (1H, qdd, *J* = 7.35, 5.73, 4.42 Hz), 1.19 (3H, d, *J* = 6.93 Hz), 1.06 (3H, d, *J* = 7.35 Hz), 1.05 (3H, d, *J* = 6.96 Hz), 1.01 (9H, s), 1.00 (9H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 204.6, 203.9, 76.0, 75.4, 51.8, 49.1, 37.3, 27.7, 27.5, 21.9, 21.8, 13.4, 11.3, 7.4; **19** had ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.33 (1H, ddd, *J* = 6.75, 4.95, 1.68 Hz), 4.13 (1H, dd, *J* = 9.28, 3.37 Hz), 4.08 (1H, dd, *J* = 4.48, 1.92 Hz), 4.02 (1H, dd, *J* = 9.6, 0.5 Hz), 3.75 (1H, s), 2.80-2.68 (2H, m), 2.64-2.49 (4H, m), 2.46 (1H, d, *J* = 4.95 Hz), 1.97-1.89 (1H, m), 1.74-1.63 (1H, m), 1.62-1.51 (1H, m), 1.09-1.01 (33H, m), 0.93 (3H, d, *J* = 7.05 Hz), 0.80 (3H, d, *J* = 6.96); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 216.4, 215.4, 85.1, 79.1, 73.5, 71.0, 49.4, 48.7, 39.7, 38.3, 37.0, 36.9, 35.4, 28.2, 27.6, 22.1, 21.9, 13.9, 13.8, 13.45, 8.8, 7.6, 7.4, 4.6; Isomer of Membrenone-C **4** had R_f = 0.48 (10% Et_2O/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.37 (1H, dd, *J* = 14.05, 1.90 Hz), 4.34 (1H, dd, *J* = 10.47, 2.76 Hz), 2.55-2.23 (6H, m), 2.17(1H, dqd, *J* = 10.47, 7.05, 1.9 Hz), 1.73 (6H, s), 1.10 (3H, d, *J* = 6.87 Hz), 1.07 (3H, t, *J* = 7.51 Hz), 1.06 (3H, t, *J* = 7.59 Hz), 1.04 (3H, d, *J* = 7.35 Hz), 0.92 (3H, d, *J* = 7.05 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.53, 195.15, 172.94, 172.51, 108.31, 107.895, 79.95, 79.13, 40.85, 39.88, 34.73, 25.43, 25.26, 10.92, 10.88, 9.46, 9.3, 9.10, 9.10, 7.57; HRMS: Calc for $C_{20}H_{30}O_4$ (M^+) 334.2144 found 334.2145.
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