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Total synthesis of natural (+)-membrenone C and its 7-epimer☆

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Dedicated to Professor S. Chandrasekaran, IISc, Bangalore on his 60th birthday

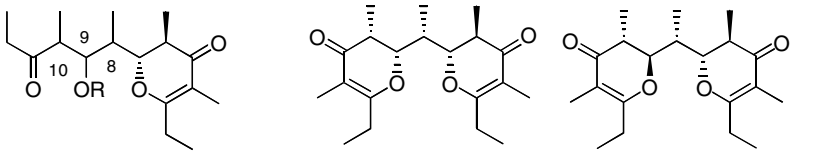
Abstract—Highly stereoselective asymmetric total syntheses of the polypropionate marine defense substance (+)-membrenone C and its 7-epimer have been achieved. Highlights of the strategy include the utilization of a desymmetrization technique to create five contiguous chiral centres from a single bicyclic precursor.

During the course of our ongoing programme of synthesis of biologically potent natural products we selected (+)-membrenone C, the polypropionate marine defense natural product as a synthetic target. Membrenone C was first isolated along with membrenone A and membrenone B from a Mediterranean mollusc *Pleurobranchus membranaceus* by Ciavatta et al.[1] Membrenones A–C were found to afford protection for the mollusc from potential predators in the hostile marine environment. Ciavatta and co-workers assigned structures to the membrenones by extensive NMR analysis, the relative and absolute stereochemistry of the natural products was confirmed by synthesis.[2,3]

The exceptional bioactivity and extreme scarcity of the natural material together with the novel structure prompted us to attempt the total synthesis of (+)-membrenone C **1**. It was envisioned that (+)-membrenone C could be obtained from tetraketone **3** as shown in Scheme 1. The construction of **3** was to be based on a disconnection between the C4–C5 and C11–C12 bonds via double aldol reactions as reported by Perkins and co-workers.[3] The dialdehyde could be derived from a single bicyclic precursor **6** which in turn is easily synthesized, and was earlier used by our group towards the synthesis of rifamycin S,[4] discodermolide,[5] scytophycin C[6] and prelactone B.[7]

The required lactone[5,6] **7** was prepared from **6** by a protocol we had developed and utilized for a number of syntheses wherein we had exploited a desymmetrization technique to create six stereogenic centres at once.

Alkylation of the lactone **7** with LHMDS/MeI afforded compound **5**[4] as the only product which on reductive opening with LAH furnished the triol **8** (Scheme 2). The triol **8** on dibenzyl ether protection followed by PMB[8] ether deprotection afforded diol **9**. Protection of the diol as its di-*tert*-butyl silyl ether **10** was achieved by using di-*tert*-butyl silyl bis[trifluoromethanesulfonate]



membrenone A (R=(*R*)-2-methylbutyryl)
membrenone B (R=propionyl)

(+)-membrenone C
1

(+)-7-epi-membrenone C
2

Keywords: (+)-Membrenone C and its 7-epimer; Desymmetrization technique.
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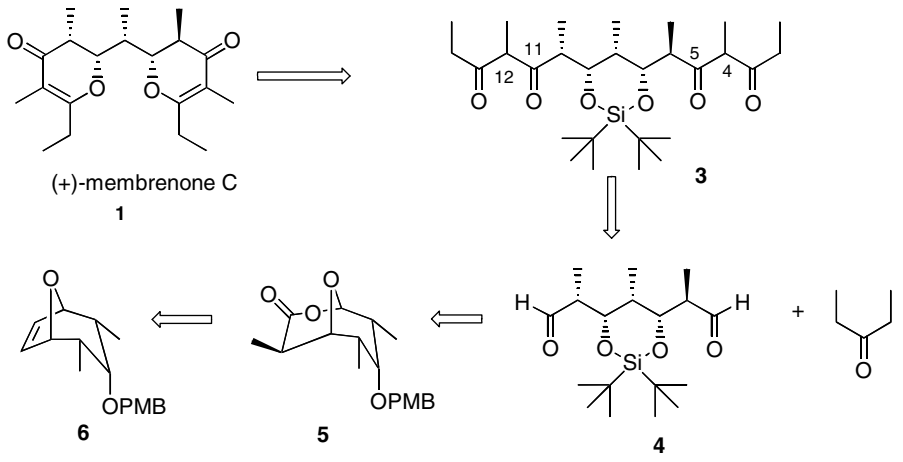
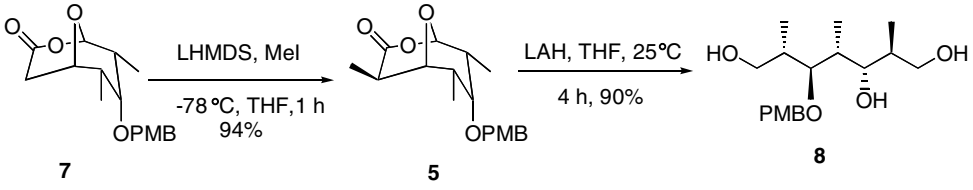
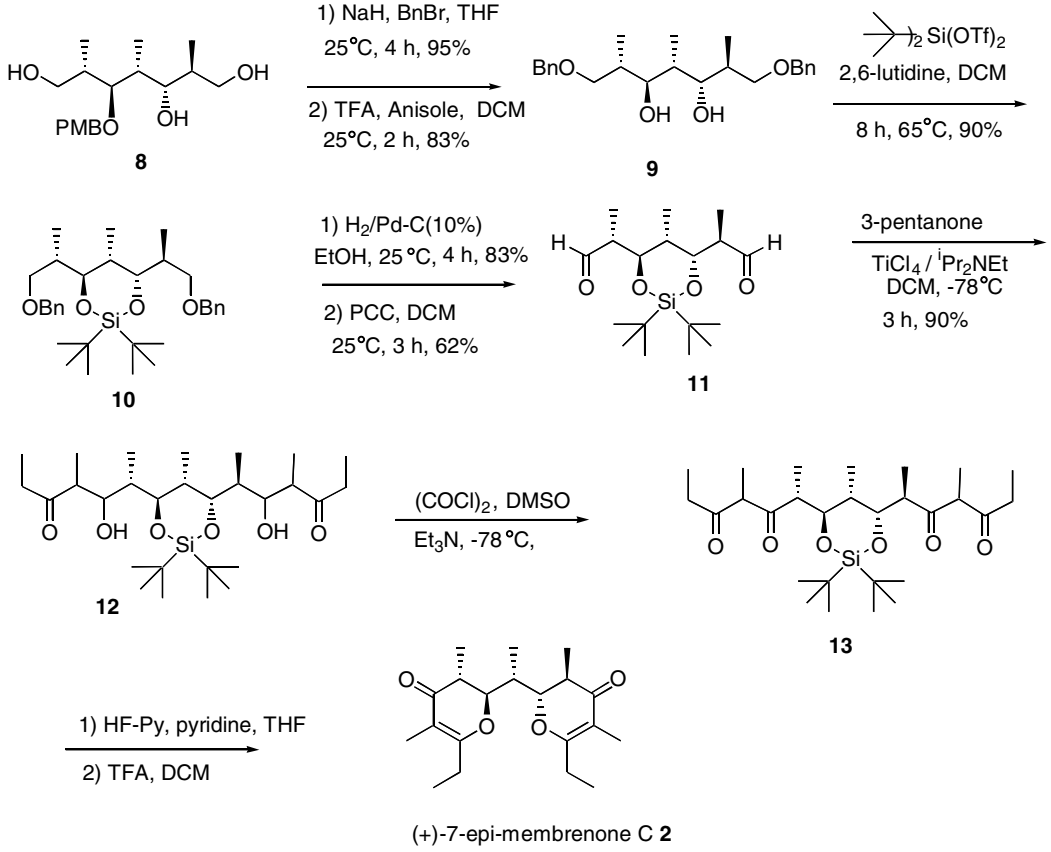


Scheme 1. Retrosynthetic strategy for (+)-membrenone C.

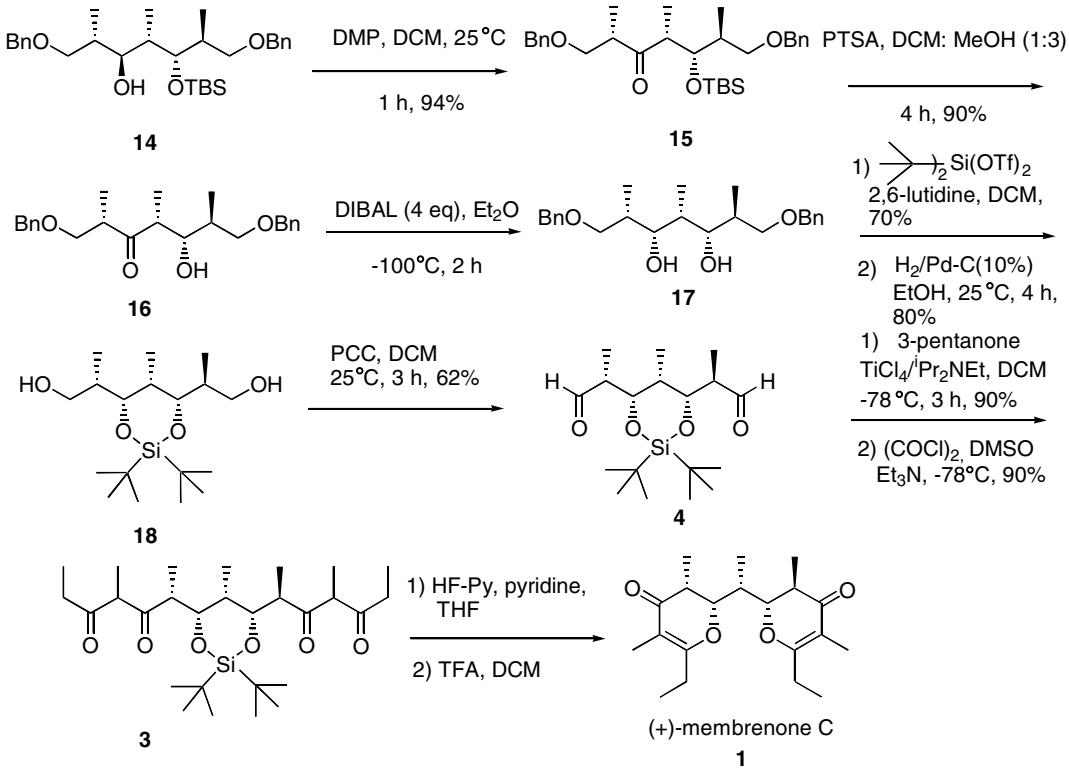


Scheme 2.

and 2,6-lutidine. Debenzylation of **10** using a catalytic amount of Pd/C and H_2 afforded a diol which on PCC oxidation gave dialdehyde **11**. Next, the bidirectional chain extending double aldol reaction was



Scheme 3.



Scheme 4.

achieved by reacting with the Ti(IV) enolate of 3-pentanone in DCM at −78 °C, as previously reported by Perkins et al. and Evans et al.[9,10] to yield compound **12** with high diastereoselectivity (Scheme 3). Since the four stereocentres produced in the formation of **12** are not present in the final product, we proceeded with the diastereomeric mixture.

Swern oxidation of **12** gave a quantitative yield of tetraketone **13**. Since the tetraketone was very sensitive having readily epimerisable centres, we proceeded with the crude product. The di-*tert*-butyl silyl group of **13** was removed by treatment with HF·Py buffered with excess pyridine, to give a mixture of diols and hemiacetals. Rapid acid catalyzed cyclization/dehydration gave a single product **2** in 52% overall yield in three steps from **12** (Scheme 3). The synthetic material exhibited the desired spectral properties of (+)-7-*epi*-membrenone C and a specific rotation of $[\alpha]_D^{25}$ +110.6 (*c* 1.81, $CHCl_3$).

The synthesis of (+)-membrenone C **1**, our target molecule was achieved directly from **8** which on di-*O*-benzyl protection of the primary alcohols followed by TBS protection of the secondary alcohol and deprotection of the PMB ether using DDQ in aqueous DCM[11] gave compound **14** in 90% overall yield in three steps. Dess–Martin oxidation (DMP)[12] of the secondary alcohol in **14** gave the ketone **15** which was subjected to desilylation using 2 equiv of PTSA in methanolic DCM[13] to afford the hydroxy-ketone **16**. Our subsequent task was the 1,3-*syn*-selective reduction of **16** which was achieved by using DIBAL-H in diethyl ether[14] at −100 °C to give the desired product **17** as the major diastereoisomer with high diastereoselectivity (>90% ds). The protection of diol **17** as the di-*tert*-butyl silylene[15] followed by debenzylation gave the diol **18** (Scheme 4). PCC oxidation of **18** gave the compound **4** which on double aldol chain extension followed by Swern oxidation gave compound **3**. Deprotection of the di-*tert*-butyl silylene group followed by cyclization/dehydration then gave **1** in 35% overall yield from **3** in two steps (Scheme 4).

The synthetic material exhibited spectral properties[16] and a specific rotation, $[\alpha]_D^{25}$ +23.6 (*c* 0.38, $CHCl_3$) {lit.[3] $[\alpha]_D$ +23.5 (*c* 0.63, $CHCl_3$)}, in agreement with those reported earlier by the Marshall group.[2]

In summary, the highly stereoselective synthesis of (+)-membrenone C and its 7-epimer illustrates the utility of the bicyclic precursor **6** and the desymmetrization approach control for the five required stereocentres. This is the first report of the total synthesis of (+)-7-*epi*-membrenone C.

Acknowledgements

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16. *Spectral data of compound* **1**: Low melting solid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.24 (dd, 1H, $J = 10.4$, 2.4 Hz), 3.90 (dd, 1H, $J = 13.6$, 2.4 Hz), 2.51 (m, 1H), 2.46–2.22 (m, 5H), 2.19 (m, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.19 (d, 3H, $J = 7.5$ Hz), 1.18 (t, 3H, $J = 8.0$ Hz), 1.11 (d, 3H, $J = 8.0$ Hz), 1.07 (t, 3H, $J = 7.2$ Hz), 1.02 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.0, 194.3, 173.5, 172.3, 108.4, 107.5, 83.2, 81.6, 80.8, 40.2, 39.8, 34.5, 25.3, 10.8, 10.7, 9.6, 9.4, 9.2, 9.1, 9.0; IR (Neat): 1721, 1662, 1615 cm^{-1}; FAB Mass: *m/z* 335 $[M+H]^+$, $[\alpha]_D^{25}$ +23.6 (*c* 0.38, $CHCl_3$); *Spectral data of compound* **2**: liquid, ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.22 (dd, 1H, $J = 8.6$, 4.3 Hz), 4.13 (dd, 1H, $J = 12.16$, 1.43 Hz), 2.48 (m, 1H), 2.42–2.34 (m, 5H), 2.18 (m, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.25 (d, 3H, $J = 7.2$ Hz), 1.16 (t, 3H, $J = 7.8$ Hz), 1.13 (t, 3H, $J = 7.2$ Hz), 1.01 (d, 3H, $J = 7.2$ Hz), 1.00 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 194.8, 172.6, 170.4, 108.2, 107.5, 84.3, 82.5, 80.8, 40.7, 40.0, 34.0, 25.4, 15.4, 10.9, 10.7, 9.5, 9.2, 9.1, 8.8; IR (Neat) : 1739, 1658, 1615 cm^{-1}; FAB Mass: *m/z* 335 $[M+H]^+$, HRMS calcd for $C_{20}H_{30}O_4$: 335.2222. Found: 335.2251. $[\alpha]_D^{25}$ +110.6 (*c* 1.81, $CHCl_3$).