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Synthesis of Optically Active Maresin 2 and Maresin $2_{n\text{-}3\ DPA}$

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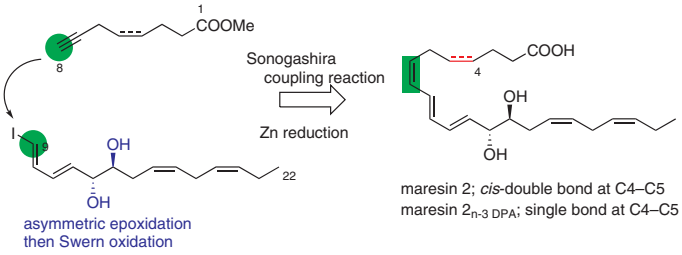

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Abstract Maresins are among the most potent antiinflammatory lipid metabolites. We report stereoselective syntheses of maresin 2 and maresin $2_{n\text{-}3\ DPA}$. The *anti*-diol was constructed through epoxide ring opening of an optically active β,γ-epoxy aldehyde, synthesized in situ by Swern oxidation of the corresponding alcohol. Finally, the target compounds were synthesized through a Sonogashira coupling of a C9–C22 iodide and methyl (*Z*)-oct-4-en-7-ynoate or methyl oct-7-ynoate, respectively.

Key words maresins, asymmetric synthesis, trienes, Swern oxidation

Resolvins and protectins, metabolized from polyunsaturated fatty acids, are specialized pro-resolving mediators (SPMs).[1] SPMs have been reported to actively promote the resolution of inflammation. In 2014, Serhan isolated maresin 2 from human macrophages as a metabolite derived from docosahexaenoic acid (Figure 1).[2] This compound shows a strong antiinflammatory effect at 1 ng per mouse in a mouse peritonitis model.[2] Maresin $2_{n\text{-}3\ DPA}$, possessing a single bond at the C4–C5 position of maresin 2, also shows an antiinflammatory effect.[3] Several SPMs are undergoing initial clinical trials, and maresin 1 has recently been reported to possess wound-healing activity.[4] Consequently, maresin 2 and maresin $2_{n\text{-}3\ DPA}$ are also of interest as candidates for drug-discovery research. However, maresins are available only in minute amounts from natural sources. In addition, commercially available maresin 2 is expensive, making it difficult to obtain sufficient amounts. The groups of Spur and Hansen have reported syntheses of these compounds through the chiral-pool method with 2-deoxy-D-ribose as a starting material.[5] However, drug-discovery research requires a flexible synthetic method that can efficiently supply the desired chiral centers. We have previously synthesized various lipid mediators by constructing chiral centers by asymmetric reactions.[6] Here, we report stereoselective syntheses of maresin 2 and maresin $2_{n\text{-}3\ DPA}$ by using asymmetric reactions.

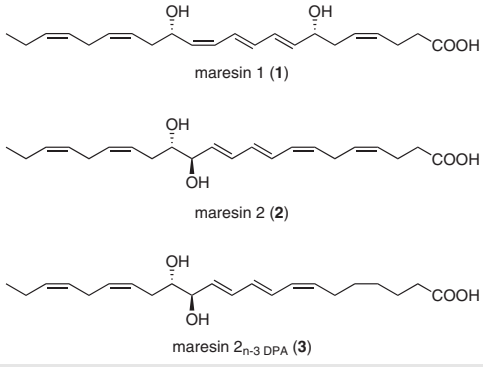

Figure 1 Structures of maresins

Scheme 1 outlines our retrosynthetic analysis of maresin 2 (**2**). We planned to construct the triene of **2** by connecting two components, the terminal alkyne **4** and the iodoalkene **5**, by a Sonogashira coupling reaction, followed by acetylene reduction.[6] The internal *cis*-olefin **4** would be obtained from γ-butyrolactone by a Wittig reaction. The vicinal diol at C13–C14 would be constructed stereoselectively by a Sharpless asymmetric epoxidation, followed by an epoxide ring opening of the β,γ-epoxy aldehyde.

The first step in our synthesis of maresin 2 (**2**) involved the preparation of enyne **4** (Scheme 2). Phosphonium salt **9** was synthesized from but-3-yn-1-ol (**8**) by a previously reported procedure.[7] The ring-opening reaction of γ-butyrolactone (**10**) with Et_3N/MeOH generated the corresponding alcohol, which was then oxidized with sulfur trioxide/pyridine (SO_3·py) to yield aldehyde **11**. Wittig reaction of **11**

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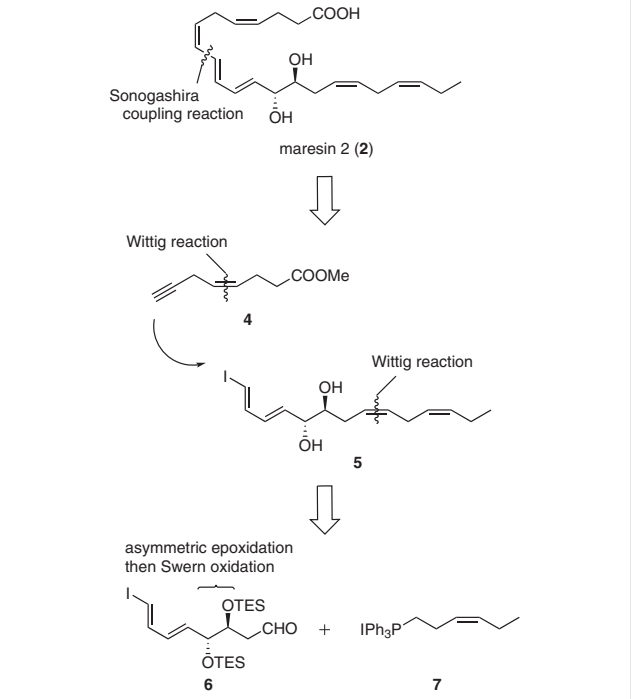
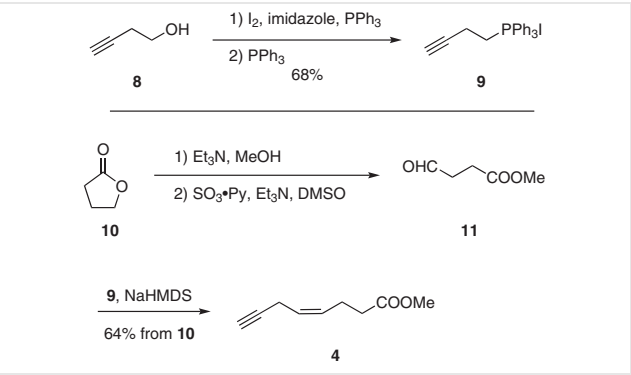


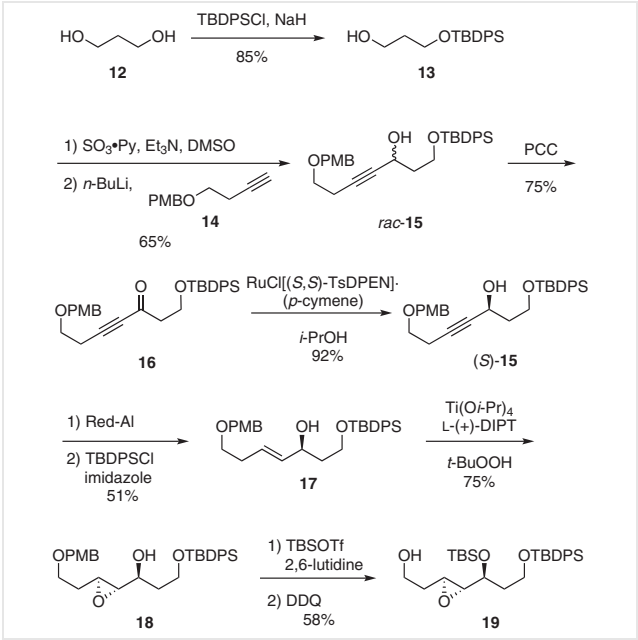
Scheme 1 Retrosynthetic analysis of maresin 2 (**2**)

with phosphonium salt **9** in the presence of NaHMDS afforded the terminal alkyne **4**[8] in 64% yield over the three steps.

Next, the iodoolefin **5** was prepared via the epoxy alcohol **19**. Propane-1,3-diol (**12**) was converted into the silyl ether **13** by a reported procedure (Scheme 3).[9] Oxidation of **13** by SO_3·py was followed by the addition of alkyne **14**[10] to the resulting aldehyde to give alcohol *rac*-**15** in 65% yield. Oxidation of *rac*-**15** followed by asymmetric transfer hydrogenation[11] produced the optically active alcohol (*S*)-**15** in 69% yield with 98% ee, as determined by ^{1}H NMR analysis of its α-methoxy-α-(trifluoromethyl)phenylacetic (MTPA) ester derivative. Treatment of (*S*)-**15** with Red-Al not only reduced the triple bond, but also promoted deprotection of the TBDPS group. As a result, the resulting primary hydroxy group was protected once again with TBDPSCl to give allylic alcohol **17**[8] in 51% yield. This was then converted into the epoxy alcohol **18** by a Sharpless asymmetric epoxidation[6c,12] in 75% yield with >99% ee, as determined by ^{1}H NMR analysis of the MTPA ester derivative. In this reaction, the enantiomeric purity was improved by kinetic resolution of **17** (98% ee). Protection of epoxy alcohol **18** followed by deprotection using DDQ afforded alcohol **19** in 58% yield.



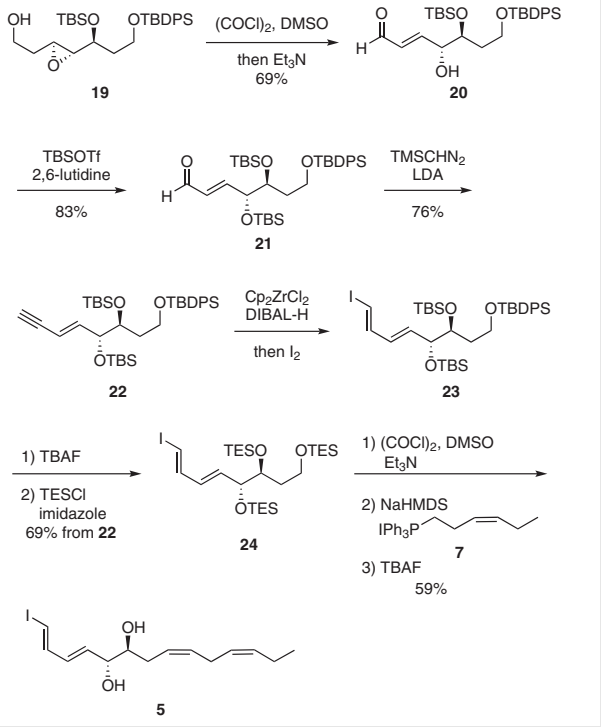
Scheme 2 Synthesis of terminal alkyne **4**



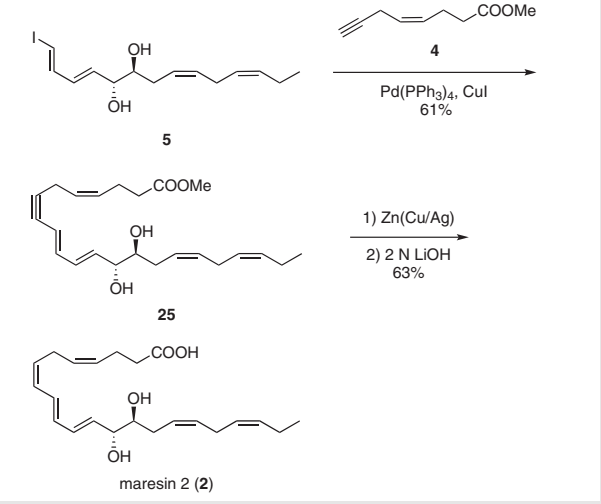
Scheme 3 Synthesis of epoxy alcohol **19**

Enal **20**,[8] containing a vicinal diol, was prepared in 69% yield by oxidation of epoxy alcohol **19** followed by cleavage of the epoxide ring (Scheme 4). Protection of **20** with TBSOTf in the presence of 2,6-lutidine gave the disilyl ether **21** in 83% yield; this was subsequently converted into enyne **22** (76% yield) by treatment with $TMSCHN_2$ and LDA.[13] The (*E*)-stereoselectivity of the olefin in **22** was >99%, as determined by ^{1}H NMR spectroscopy. Hydrozirconation of **22** with $Cp_2Zr(H)Cl$, generated in situ from Cp_2ZrCl_2 and DIBAL,[14] followed by iodination of the resulting vinylzirconium species with I_2 produced vinyl iodide **23**.[8] The TBS and TBDPS groups in **23** were then replaced by TES groups in a two-step reaction to produce **24**. Swern oxidation[15] of **24** occurred regioselectively at the terminal carbon to afford an aldehyde that, upon Wittig reaction with phosphonium salt **7**[5a] followed by desilylation, afforded iodoolefin **5**[8] in 59% yield over three steps.

In the last stage, the synthesis of maresin 2 (**2**) was completed, as shown in Scheme 5. Polyene **25** was synthesized in 61% yield by Sonogashira coupling of the alkyne **4** and iodoolefin **5**.[6] Finally, reduction of **25** by Zn(Cu/Ag),[6b,c,16] fol-



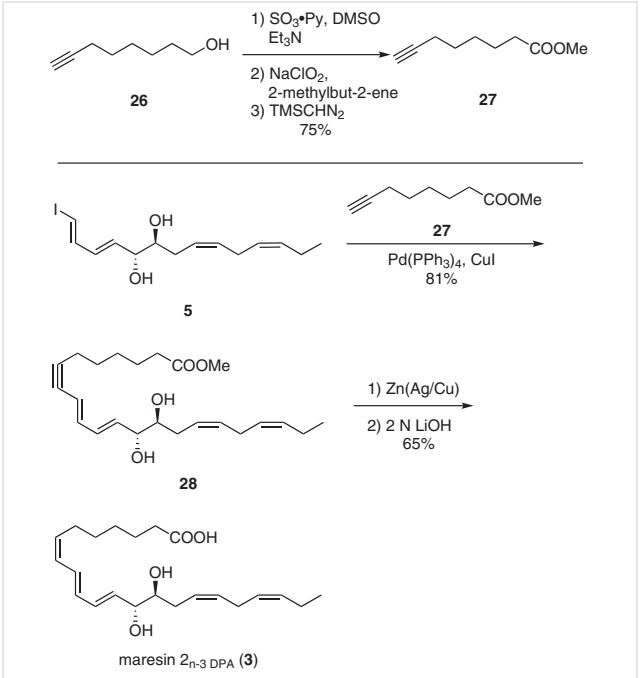
Scheme 4 Synthesis of iodoolefin **5**



Scheme 5 Synthesis of maresin 2 (**2**)

lowed by hydrolysis with aqueous LiOH afforded maresin 2 (**2**) in 63% yield.[17] The spectral data (NMR and UV) of **2** were in good agreement with those reported previously.[5b]

Next, maresin $2_{n\text{-}3\ DPA}$ (**3**) was synthesized according to the method shown in Scheme 6. Alkyne **28** was obtained by Sonogashira coupling of iodoolefin **5** with alkyne **27**, prepared from oct-7-yn-1-ol (**26**) in three steps. Maresin $2_{n\text{-}3\ DPA}$ (**3**) was then synthesized in a two-step reaction by using the same method as used for **2**. The spectral data (NMR and UV) and $[\alpha]_D$ of **3** were consistent with those reported previously.[5a]



Scheme 6 Synthesis of maresin $2_{n\text{-}3\ DPA}$ (**3**)

In conclusion, we have accomplished asymmetric syntheses of maresin 2 (**2**) and maresin $2_{n\text{-}3\ DPA}$ (**3**). Alkyne **4** was synthesized from γ-butyrolactone (**10**) and phosphonium salt **7** in three steps. Meanwhile, vicinal diol **20** was constructed by a Sharpless asymmetric epoxidation and a Swern oxidation. Diol **20** was then converted into iodoolefin **5** by a multistep reaction. Finally, reaction of **4** with **5** gave maresin 2 (**2**) in 22 steps from propane-1,3-diol (**12**) with a total yield of 0.79%. We also synthesized **3** by using the same approach as that described for **2** in 22 steps from **12**, with a total yield of 0.58%. The spectral data for **2** and **3** were consistent with those previously reported.[5]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1705959.

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(17) **Maresin 2 (2)**
$Cu(OAc)_2$ (101 mg, 0.55 mmol) and $AgNO_3$ (103 mg, 0.61 mmol) were added to a slurry of Zn (1.08 g, 16.5 mmol) in H_2O (1 mL), and the mixture was stirred for 1 h then filtered by using a Hirsch funnel. The remaining Zn solids were washed successively with H_2O (1 mL), MeOH (1 mL), acetone (1 mL), and Et_2O (1 mL). The activated Zn solids were transferred to 1:1 MeOH–H_2O (2 mL), and a solution of alkyne **25** (30.7 mg, 0.082 mmol) in MeOH (1 mL) was added to the suspension of activated Zn. The mixture was stirred for 11 h then filtered through a plug of cotton that was washed with EtOAc. The mixture was concentrated, and the residue was semi-purified by chromatography (silica gel), ready for the next reaction.
To an ice-cold solution of the resulting ester in MeOH (1 mL) and THF (1 mL) was added 2 N aq LiOH (0.82 mL, 1.64 mmol). After 5 h at 0 °C, citrate–phosphate buffer (pH 5.0, 40 mL) was added, and the resulting mixture was extracted with EtOAc (×7). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography (silica gel, hexane–EtOAc) to give maresin 2 (**2**) as a pale-yellow oil; yield: 18.5 mg (63% from **25**); R_f = 0.61 (hexane–EtOAc, 1:2); $[\alpha]_D^{24}$ +45.8 (*c* 0.37, MeOH).
IR (neat): 3454, 2064, 1727, 1652 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 0.86 (t, *J* = 7.4 Hz, 3 H), 1.97 (quin, *J* = 7.4 Hz, 2 H), 2.02–2.13 (m, 1 H), 2.20–2.33 (m, 5 H), 2.70 (t, *J* = 6.2 Hz, 2 H), 2.89 (t, *J* = 6.0 Hz, 2 H), 3.47 (dt, *J* = 8.4, 5.0 Hz, 1 H), 3.92 (dd, *J* = 7.0, 5.0 Hz, 1 H), 4.84 (s, 3 H, overlapped with the residue from CD_3OD), 5.15–5.43 (m, 7 H), 5.72 (dd, *J* = 14.8, 7.0 Hz, 1 H), 5.94 (t, *J* = 11.0 Hz, 1 H), 6.16 (dd, *J* = 14.8, 11.0 Hz, 1 H), 6.26 (dd, *J* = 14.8, 11.0 Hz, 1 H), 6.48 (dd, *J* = 14.8, 11.0 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 14.7, 21.5, 23.8, 26.6, 27.0, 31.8, 35.0, 75.8, 76.3, 127.1, 128.2, 129.1, 129.5, 129.7, 129.8, 131.0, 131.2, 132.7, 133.6, 133.7, 133.8, 177.1. HRMS (FD): *m/z* [M$^+$] calcd for $C_{22}H_{32}O_4$: 360.23006; found: 360.23029. UV (MeOH): λ_{max} = 262, 274, 282 nm.