Steroselective synthesis of maresin 1

Jørn E. Tungen, Marius Aursnes, Trond Vidar Hansen

PII: S0040-4039(15)00361-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.02.080
Reference: TETL 45950

To appear in: *Tetrahedron Letters*

Received Date: 24 November 2014
Revised Date: 2 February 2015
Accepted Date: 18 February 2015

Please cite this article as: Tungen, J.E., Aursnes, M., Hansen, T.V., Steroselective synthesis of maresin 1, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.02.080

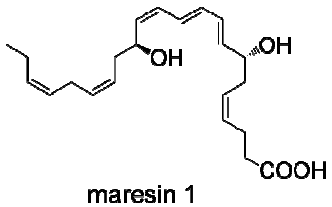
Graphical Abstract

.

Stereoselective synthesis of maresin 1

Jørn E. Tungen, Marius Aursnes, Trond Vidar Hansen

Leave this area blank for abstract info.



maresin 1
lipid mediator
potent anti-inflammatory and pro-resolving actions

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Steroselective synthesis of maresin 1

Jørn E. Tungen[a], Marius Aursnes[a], Trond Vidar Hansen[a,] *

[a]*School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1068 Blindern, N-0316 Oslo, Norway*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Maresin 1
Lipid mediator
Stereoselective synthesis
Nagao-Evans aldol
Pro-resolution

ABSTRACT

Maresin 1 is a potent anti-inflammatory and pro-resolving lipid mediator derived from docosahexaenoic acid. The total synthesis of maresin 1 is achieved in 10 steps and in 7% overall yield. The Evans-Nagao aldol reaction between (2*E*,4*E*)-5-bromopenta-2,4-dienal and different chiral auxiliaries is investigated. The reported synthesis is efficient and highly stereoselective, affording multi-milligram quantities of this biologically interesting lipid mediator.

The acute inflammatory response is a protective mechanism that starts within seconds to minutes following the injury of tissues. Ideally, this process should be self-limited and lead to complete resolution.[1] Unresolved inflammatory processes may lead to a wide range of human diseases.[1] Recent efforts by the Serhan group have shown that the resolution of inflammation is an active process regulated by distinct families of di- and trihydroxy-containing products derived from polyunsaturated fatty acids (PUFAs).[2,3]

Figure 1. Examples of SPMs.

These autacoid natural products are termed specialized pro-resolving mediators (SPM) and resolve inflammation, protect organs, stimulate resolution and induce tissue regeneration.[2,3] Several SPMs have entered clinical trials development programs.[3] Different families of SPMs are the resolvins,[4,5] the protectins[4-10] and the maresins,[9,11] with specific members of each family depicted in Figure 1. SPMs derived from the dietary ω-3 PUFA docosahexaenoic acid (DHA), such as maresin 1 (**1**), have attracted significant attention from chemists and pharmacologists.[3] Serhan and co-workers reported in 2013 that **1** is biosynthesized from DHA through a lipoxygenase-mediated pathway (Scheme 1).[12]

Scheme 1. Biosynthesis of maresin 1 (**1**).

12-Lipoxygenase (12-LO) converts DHA into the corresponding 14*S*-hydroperoxide intermediate, which is rapidly transformed into the 13,14-epoxide, followed by enzymatic hydrolysis to give maresin 1 (**1**). This DHA-derived natural product has been reported to exhibit several interesting biological effects *in vitro* and *in vivo*. For example, maresin 1 (**1**) regulates inflammation resolution,[11] tissue regeneration,[13] and relieves lung injury in mice.[14] Due to our interest in the synthesis and biological evaluations of PUFAs[15] and SPMs,[10,16] we wanted to develop a stereoselective and efficient total synthesis of the polyunsaturated oxygenated lipid **1**. Maresin 1 (**1**) has been the subject of total synthesis programs,[17] but room for improvements still exist.

The first reported total synthesis of maresin 1 (**1**) by Inoue and co-workers was based on a BF_3-mediated opening of (*S*)-glycidol and a stereoselective alkyne addition to an aldehyde.[17a] The product of the latter required a lipase-catalyzed hydrolysis for enhancing the enantiomeric excess to 97% ee. The chemically sensitive *E*,*E*,*Z*-triene in **1** was constructed using a Julia-Kocienski coupling reaction affording a 3:2 ratio of isomers that were separated by HPLC. This 17-step protocol established the absolute configuration of **1**.[17a] Rodriguez and Spur[17b] employed a Jacobsen hydrolytic kinetic resolution and 2-deoxy-D-ribose for establishing the absolute configuration at C-7 and C-14, respectively, in their total synthesis of maresin 1 (**1**). Purification by HPLC was required as part of the 14-step protocol. Kobayashi and co-workers have reported a 16-step protocol, starting from propan-1,3-diol, for the synthesis of **1**. A Sharpless asymmetric epoxidation reaction under kinetic resolution conditions and a Noyori asymmetric reduction were utilized for establishing the chirality at the two secondary alcohols. The Noyori reduction

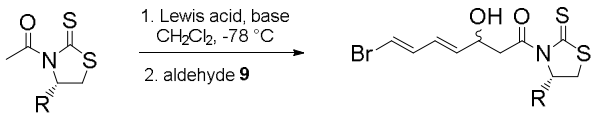
* Corresponding author. Tel.: +47-22-855-470; fax: +47-228 5-947; e-mail: t.v.hansen@farmasi.uio.no

gave 90-94% ee of a key intermediate. Again, purification by HPLC was required.[17c]

We have employed the Evans-Nagao aldol reaction[18,19] in the total synthesis of some SPMs.[16] However, this reaction was previously not studied extensively. Herein, we report further studies of this aldol condensation and its application in a stereoselective synthesis of the biologically interesting natural product **1**.

First, (*S*)-(-)-α-hydroxy-γ-butyrolactone (**6**) was efficiently converted into terminal alkyne **7** using a recently reported protocol.[16c] Overall, compound **7** was synthesized in seven steps and in 35% yield from **6** (Scheme 2). Next pyridinium-1-sulfonate (**8**) was converted into (2*E*,4*E*)-5-bromopenta-2,4-dienal (**9**) following literature procedures.[20,21] This aldehyde was then investigated in the Evans-Nagao aldol reaction using different auxiliaries **10a-f**.[22,23] The results are compiled in Table 1.

Table 1. Investigations of the Evans-Nagao aldol reaction using auxiliaries **10a-f**.



10a-f **11a-f**

Entry	R	Lewis-acid	Base	dr[a] (*R*:*S*)	Yield (%)[b]
1	**a**: Me	$TiCl_4$	(*i*-Pr)$_2$NEt	7.9:1	88
2	**b**: *i*-Pr	$TiCl_4$	(*i*-Pr)$_2$NEt	15.3:1	86
3	**c**: *t*-Bu	$TiCl_4$	(*i*-Pr)$_2$NEt	2.8:1	78
4	**d**: *i*-Bu	$TiCl_4$	(*i*-Pr)$_2$NEt	7.0:1	65
5	**e**: Ph	$TiCl_4$	(*i*-Pr)$_2$NEt	4.5:1	54
6	**f**: Bn	$TiCl_4$	(*i*-Pr)$_2$NEt	9.8:1	79
7	**b**: *i*-Pr	$TiCl_4$	(-)-sparteine	1.8:1	48
8	**b**: *i*-Pr	$PhBCl_2$	(-)-sparteine	3.2:1	43
9	**b**: *i*-Pr	$Sn(OTf)_2$	NEP[c]	10.6:1	67

[a]Determined by HPLC analysis. [b] Isolated yield. [c]1-*N*-Ethylpiperidine

The best diastereomeric ratio was observed with the *iso*-propyl-substituted thiazolidinethione **10b** in the presence of $TiCl_4$/(*i*-Pr)$_2$NEt in CH_2Cl_2 at -78 °C (entries 1-6). Substituting (*i*-Pr)$_2$NEt with (-)-sparteine resulted in a significant loss of diastereoselectivity (entry 7). Using the conditions reported by Sammakia and co-workers[24] ($PhBCl_2$/(-)-sparteine, entry 8) yielded a disappointing 3.2:1 dr of the desired isomer of **11b** in 43% yield. Employing $Sn(OTf)_2$ in the presence of 1-*N*-ethylpiperidine[25] gave a 10.6:1 mixture of diastereomers of **11b** in 67% yield (entry 9).

The Evans-Nagao aldol reaction between **9** and **10b** using $TiCl_4$/(*i*-Pr)$_2$NEt in CH_2Cl_2 at -78 °C resulted in a 15.3:1 mixture of isomers of **11b** that was purified by silica gel chromatography. This afforded **11b** as a single stereoisomer in 86% yield. Protection of **11b** (TBSOTf, 2,6-lutidine in CH_2Cl_2 at -78 °C) gave a near quantitative yield of **12**. The thiazolidinethione was smoothly converted into the aldehyde **13** using DIBAL-H. Aldehyde **13** was immediately reacted with the ylide generated from (4-ethoxy-4-oxobutyl)triphenylphosphonium bromide (**14**) and NaHMDS in THF/HMPA at -78 °C. This *Z*-selective Wittig-reaction[26] afforded vinylic bromide ester **15** in 60% yield from **12** after purification by silica gel chromatography (Scheme 2). Only one stereoisomer of **15** was observed based on HPLC and ^{1}H-NMR analyses. Other efforts towards improving the yield or the *Z*-selectivity were unsuccessful.[26]

Next, in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI, alkyne **7** and vinylic bromide ester **15** were coupled via a Sonogashira reaction at ambient temperature. This afforded the bis-hydroxyl protected methyl ester **16** in 76% yield. With the whole carbon skeleton in place, manipulation of the protecting groups and the oxidation level were required to complete the total synthesis of maresin 1 (**1**). First, the two TBS groups were removed without difficulty in the presence of five equivalents of TBAF in THF. This produced the diol ester **17** in 87% yield. The internal alkyne in **17** was reduced using a modified Lindlar hydrogenation procedure.[27] This provided the ethyl ester **18**, with the sensitive *E*,*E*,*Z*-triene moiety in place, in 62% yield with excellent selectivity. Overall, less than 5% of over-reduced products were detected. Finally, mild basic hydrolysis of ethyl ester **18** resulted in an 81% yield of **1** after work-up and chromatography (Scheme 3).

HPLC analysis showed that synthetic maresin 1 (**1**) displayed identical retention times with maresin 1 (**1**) obtained from Cayman Chemical Company (see Supplementary Material). The UV spectrum of **1** showed characteristic absorbance peaks (λ_{max}^{MeOH}) at 262, 271 and 282 nm in full agreement with the literature.[11] Furthermore, IR, HRMS, ^{1}H and ^{13}C NMR data, see Supplementary Material, were in accordance with those published.[17]

In summary, the potent anti-inflammatory and pro-resolving lipid mediator maresin 1 (**1**) has been prepared efficiently and stereoselectively in 10 steps for the longest linear sequence, and in 7% non-optimized overall yield from commercially available salt **8**. Our synthesis of maresin (**1**) compares well with those previously published affording multi-milligram quantities of this potent lipid mediator. It is noteworthy that none of the steps required purification by HPLC. Moreover, synthetic material **1** displayed identical chromatographic properties and spectroscopic analyses with authentic **1**. Based on the total synthesis presented herein, analogs of **1** will be prepared in the future. Such analogs are expected to be important for the future development of new anti-inflammatory remedies exhibiting pro-resolving actions.[28]

Acknowledgments

The School of Pharmacy, University of Oslo and The Norwegian Research Council (KOSK II) are gratefully acknowledged for Ph.D. scholarships to J.E.T. and M.A., respectively.

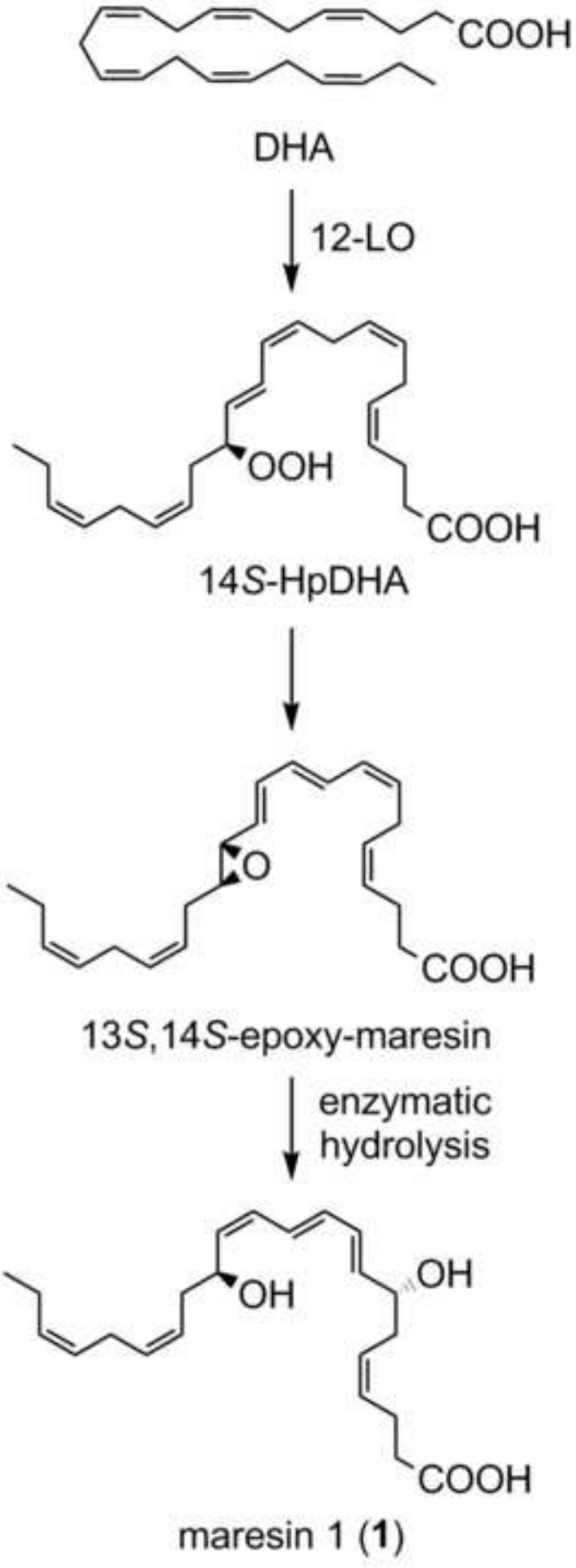
References and notes

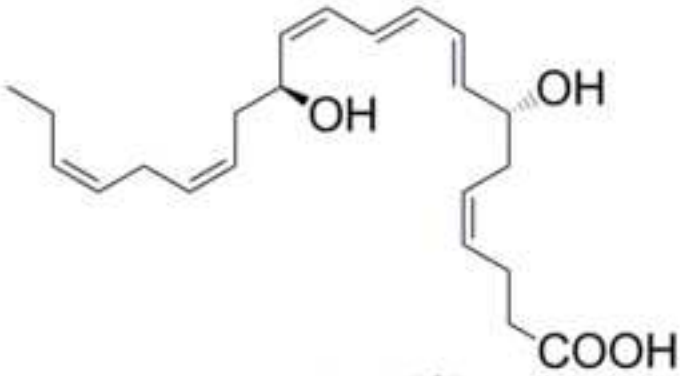
1. Tabas, I.; Glass, C. K. *Science* **2013**, *339*, 166–172.
2. Serhan, C. N.; Petasis, N. A. *Chem. Rev.* **2011**, *111*, 5922–5943, and references cited therein.
3. Serhan, C. N.; Chiang, N. *Curr. Opin. Pharmacol.* **2013**, *13*, 632–640.
4. Serhan C. N.; Clish, C. B.; Brannon, J.; Colgan, S. P.; Chiang, N.; Gronert, K. *J. Exp. Med.* **2000**, *192*, 1197–1204.
5. Serhan C. N.; Hong, S.; Gronert, K.; Colgan, S. P.; Devchand, P. R.; Mirick, G.; Moussignac, R. L. *J. Exp. Med.* **2002**, *196*, 1025–1037.
6. Hong, S.; Gronert, K.; Devchand, P. R.; Moussignac, R.-L.; Serhan, C. N. *J. Biol. Chem.* **2003**, *278*, 14677–14687.
7. Mukherjee, P. K.; Marcheselli, V. L.; Serhan, C. N.; Bazan, N. G. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 8491–8496.
8. Ariel, A.; Pin-Lan, L.; Wang, W.; Tang, W.-X.; Fredman, G.; Hong, S.; Gotlinger, K. H.; Serhan, C. N. *J. Biol. Chem.* **2005**, *280*, 43079–43086.
9. Dalli, J.; Colas, R. A.; Serhan, C. N. *Sci. Rep.* **2013**, *3*, 19409.
10. Aursnes, M.; Tungen, J. E.; Vik, A.; Collas, R.; Cheng, C.-Y.; Dalli, J.; Serhan, C. N.; Hansen, T. V. *J. Nat. Prod.* **2014**, *77*, 910–916.
11. Serhan, C. N.; Yang, R.; Martinod, K.; Kasuga, K.; Pillai, P. S.; Porter, T. F.; Oh, S. F.; Spite, M. *J. Exp. Med.* **2009**, *206*, 15–23.

12. Dalli, J.; Zhu, M.; Vlasenko, N. A.; Deng, B.; Haeggstrom, J. Z.; Petasis, N. A.; Serhan, Charles N. *FASEB J.* **2013**, *27*, 2573–2583.
13. Serhan, C. N.; Dalli, J.; Karamnov, S.; Choi, A.; Park, C. K.; Xu, Z. Z.; Ji, R. R.; Zhu, M.; Petasis, N. A. *FASEB J.* **2012,** *26,* 1755–1765.
14. Gong. J.; Wu, Z. Y.; Qi, H.; Chen, L.; Li, H. B.; Li, B.; Yao, C. Y.; Wang, Y. X.; Wu, J.; Yuan, S. Y.; Yao, S. L.; Shang, Y. *Br. J. Pharmacol*. **2014**, *171*, 3539–3550.
15. (a) Hansen, T. V.; Stenstrøm, Y. *Synth. Commun*. **2000**, *30*, 2549–2557. (b) Hansen, T. V.; Stenstrøm, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1407–1409. (c) Hansen, T. V.; Skattebøl. L. *Tetrahedron Lett*. **2004**, *45*, 2809–2811. (d) Anwar, H. F.; Hansen, T. V. *Org. Lett*. **2009**, *11*, 587–589. (e) Vik, A.; Hansen, T. V.; Holmeide, A. K.; Skattebøl, L. *Tetrahedron Lett.* **2010**, *51*, 2852–2854. (f) Yasser, M. A.; Hansen, T. V. *Pure Appl. Chem.* **2011**, *83*, 489–493. (g) Yasser, M. A.; Hansen, T. V. *Tetrahedron Lett.* **2011**, *52*, 1057–1059. (h) Vik, A.; Hansen, T. V. *Tetrahedron Lett*. **2011**, *52*, 1060–1061. (i) Jakobsen, M. G.; Vik, A.; Hansen, T. V. *Tetrahedron Lett*. **2012**, *53*, 5837–5839. (j) Yasser M. A.; Vik, A.; Hofer, T.; Hammer Andersen, J.; Hansen, T. V. *Chem. Phys. Lipids* **2013**, *170-171*, 41–45. (k) Jakobsen, M. G.; Vik, A.; Hansen, T. V. *Tetrahedron Lett*. **2014**, *55*, 2822–2824. (l) Tungen, J. E.; Aursnes, M.; Hansen, T. V. *Tetrahedron* **2014**, *70*, 3793-3797.
16. (a) Aursnes, M.; Tungen, J. E.; Vik, A.; Dalli, J.; Hansen, T. V. *Org. Biomol. Chem.* **2014**, *12*, 432-437. (b) Tungen, J. E.; Aursnes, M.; Vik, A.; Ramon, S.; Collas, R. A.; Dalli, J.; Serhan, C. N.; Hansen, T. V. *J. Nat. Prod.* **2014**, *77*, 2241–2247. (c) Tungen, J. E.; Aursnes, M.; Dalli, J.; Arnardottir, H.; Serhan, C. N.; Hansen, T. V. *Chem. Eur. J.* **2014**, *20*, 14575–14578.
17. (a) Sasaki, K.; Urab, D.; Arai, H.; Arita, M.; Inoue, M. *Chem. Asian J*. **2011**, *6*, 534-543. (b) Rodriguez, A. R.; Spur, B. W. *Tetrahedron Lett*. **2012**, *53*, 4169-4172. (c) Ogawa, N.; Tojo, T.; Kobayashi, Y. *Tetrahedron Lett*. **2014**, *55*, 2738-2741. (d) Zhu, M. Total Synthesis of Specialized Pro-Resolving Lipid Mediators and Their Analogs. Ph.D. Dissertation, University of Southern California, 2013.
18. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
19. Nagao, Y.; Dai, W. M.; Ochiai, M.; Tsukagoshi, S.; Fujita, E. *J. Org. Chem.* **1989**, *54*, 5211-5217.
20. (a) Detterbeck, R.; Guggisberg, A.; Popaj, K.; Hesse, M. *Helv. Chim. Acta* **2002**, *85*, 1742-1758. (b) Kojima, K.; Koyama, K.; Amemiya, S. *Tetrahedron* **1985**, *41*, 4449-4462.
21. (a) Becher, J. *Org. Synth*. **1979**, *59*, 79-82. (b) Soullez, D.; Ple, G.; Duhamel, L.; Duhamel, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, *11*, 1639-1646.
22. (a) Romea, P.; Urpí, F. In Modern Methods in Stereoselective Aldol Reactions, Ed.: Mahrwald, R. Wiley-VCH Verlag GmbH & Co., 2013; pp 42-47. (b) Crimmins, M. T. In Modern Methods in Stereoselective Aldol Reactions, Ed.: Mahrwald, R. Wiley-VCH Verlag GmbH & Co., 2013; pp 431-473.
23. (a) Romero-Ortega, M.; Colby, D. A.; Olivio, H. F.; *Tetrahedron Lett.* **2002**, *43*, 6439-6441. (b) Tello-Aburto, R.; Ochoa-Teran, A.; Olivo, H. F. *Tetrahedron Lett*. **2006**, *47*, 5915–5917.
24. Zhang, Y.; Phillips, A. J.; Sammakia, T. *Org. Lett.* **2004**, *6*, 23–25.
25. Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391-2393.
26. The *Z*:*E* ratio was determined to be >98:2 by HPLC and ^{1}H NMR-analyses prior to chromatographic purification. Altering the concentrations of the reagents or lowering the temperature did not effect the *Z*:*E* ratio, but diminished the yields.
27. Nicolaou, K. C.; Ladduwahetty, T.; Taffer, I. M.; Zipkin, R. E. *Synthesis* **1986**, 344-347.
28. Serhan. C. N. *Nature*, **2014**, *510*, 92-101.

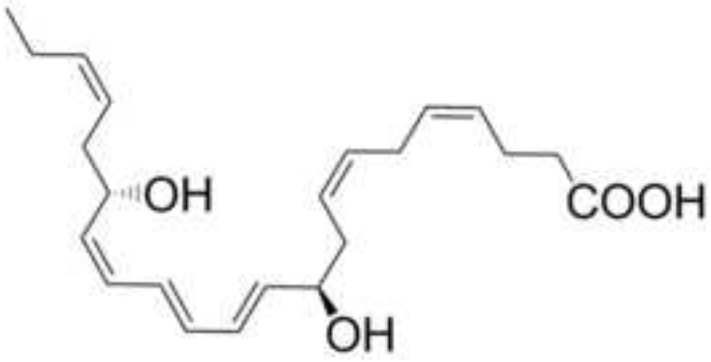
Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and characterization data (UV/VIS spectra, HPLC chromatograms and matching experiments) of maresin 1 (**1**) as well as experimental procedures, are available at **[to be inserted by editorial office]**.

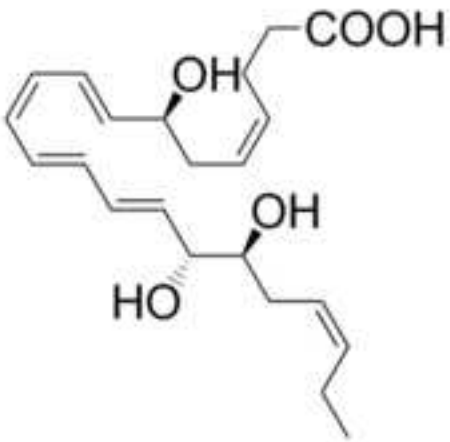




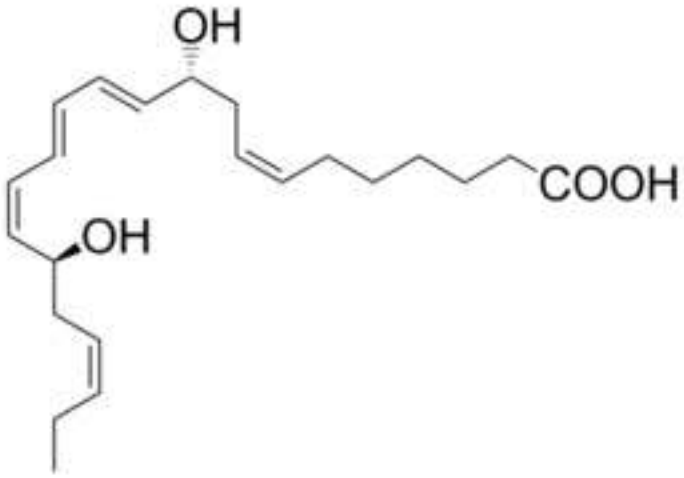
maresin 1 (**1**)



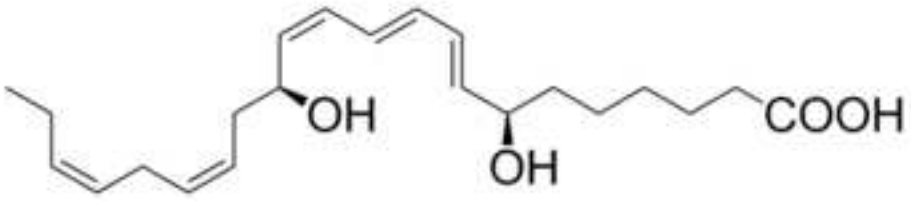
protectin D1 (**2**)



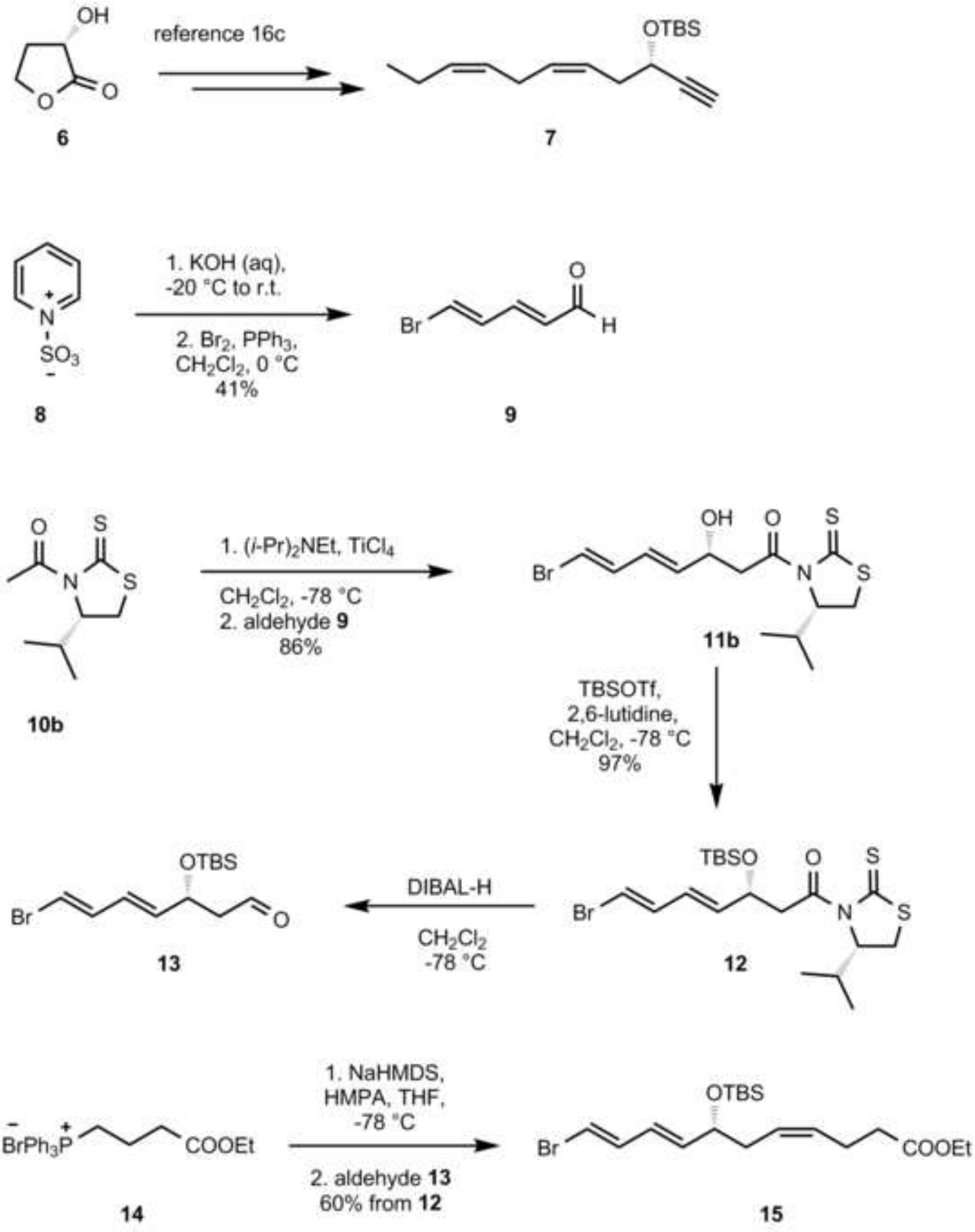
resolvin D2 (**3**)



$PD1_{n\text{-}3\ DPA}$ (**4**)



$MaR1_{n\text{-}3\ DPA}$ (**5**)


OH
O
O
6
reference 16c
OTBS
7
1. KOH (aq),
-20 °C to r.t.
2. Br2, PPh3,
CH2Cl2, 0 °C
41%
N
SO3
8
O
Br
H
9
O
S
N
S
10b
1. (i-Pr)2NEt, TiCl4
CH2Cl2, -78 °C
2. aldehyde 9
86%
OH
O
S
Br
N
S
11b
TBSOTf,
2,6-lutidine,
CH2Cl2, -78 °C
97%
TBSO
O
S
Br
N
S
12
DIBAL-H
CH2Cl2
-78 °C
OTBS
Br
O
13
1. NaHMDS,
HMPA, THF,
-78 °C
2. aldehyde 13
60% from 12
BrPh3P
COOEt
14
OTBS
Br
COOEt
15