Tetrahedron Letters 55 (2014) 2738–2741

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of maresin 1 and (7*S*)-isomer

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ARTICLE INFO

Article history:
Received 30 December 2013
Revised 9 March 2014
Accepted 13 March 2014
Available online 20 March 2014

Keywords:
Maresin 1
Stereoselective synthesis
Suzuki–Miyaura coupling
Lipid mediator
Docosahexaenoic acid

ABSTRACT

Maresin 1 (with the 7*R* carbon) and (7*S*)-maresin 1 were synthesized stereoselectively. The conjugated triene system was constructed by Pd-catalyzed coupling of the *trans cis*-dienylborane (the C10–C22 part) with the *trans* vinyl iodide corresponding to the C1–C9 part. The stereogenic centers at C7 and C14 were created by Ru-catalyzed asymmetric reduction of ketone and asymmetric epoxidation/kinetic resolution of the racemic alcohol, respectively.

Maresin 1 is a metabolite of DHA by macrophage[1] and is a potent mediator that inhibits PMN infiltration, stimulates macrophage phagocytosis of apoptotic cells, and controls pain. These properties are similar to resolvins E1 and E2.[2,3] The structure including the olefin geometry and the absolute configuration of the chiral carbons has been determined as depicted in Figure 1 (**1a**).[2] Previously, two syntheses of maresin 1 have been reported. Asymmetric addition of alkyne to aldehyde and Julia–Kocienski olefination were the key reactions in constructing the C14 chiral carbon and the conjugated triene unit; however, these reactions suffer from low stereoselectivity.[4a] Sonogashira coupling gave the dehydro-derivative of the conjugated triene, and the acetylene part was reduced to cis olefin by using Zn(Cu/Ag) followed by HPLC separation.[4b] Although the full structure, including the chiral carbons, is unambiguously determined, the 7*S* isomer shows comparable activity in blocking neutrophil infiltration in the acute peritonitis model, suggesting that further study is necessary to establish the biochemical properties of maresin 1.[4a] However, availability is limited to the abovementioned syntheses and commercial supply is extremely expensive.[5] Therefore, we investigated the synthesis of maresin 1 (**1a**) and its (7*S*)-isomer (**1b**) and described the results herein.

Based on a successful strategy for the synthesis of the resolvins,[6] we envisaged a Suzuki–Miyaura coupling[7] of vinylborane **2** with iodide (*R*)-**3** for the synthesis of **1a** as delineated in Scheme 1. Borane **2** was in turn conceived to be synthesized from the *cis* olefin aldehyde **4** by Wittig reaction followed by Sonogashira coupling

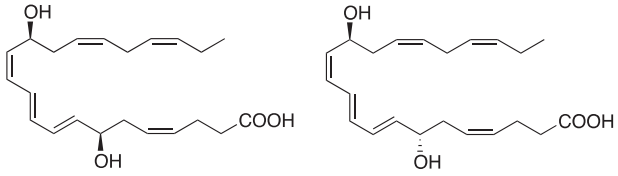

Figure 1. Structures of Maresin 1 and (7*S*)-maresin 1.

with an acetylene (an ethyne equivalent) and subsequent hydroboration. For the synthesis of **4**, two methods consisting of the Stork–Wittig reaction of **5** and Peterson elimination of the dibromide derived from aldehyde **6** were planned. The use of (*S*)-**3** should furnish the (7*S*)-isomer **1b**.

Results of the Stork–Wittig[8] approach to iodide **4a** (X = I, R = TBDPS) are summarized in Scheme 2. Methyl ester **8** was synthesized from malic acid according to the procedure reported in the literature[9] and converted to aldehyde **5** (R = TBDPS) by reduction with DIBAL followed by TPAP-catalyzed oxidation of the resulting alcohol in 80% yield. The key Stork–Wittig reaction was initiated by adding the aldehyde to the ylide prepared from $[Ph_3PCH_2I]^+I^-$ and KHMDS in THF/HMPA at −100 °C and the reaction temperature was gradually raised to 0 °C to afford **9**, which afforded iodide **4a** upon deprotection of the TBS group followed by oxidation. The cis selectivity of this iodide synthesized several times was ca. 90% on average and 94% at maximum.[10] The *trans* isomer was not separated by routine chromatography at this stage

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http://dx.doi.org/10.1016/j.tetlet.2014.03.065
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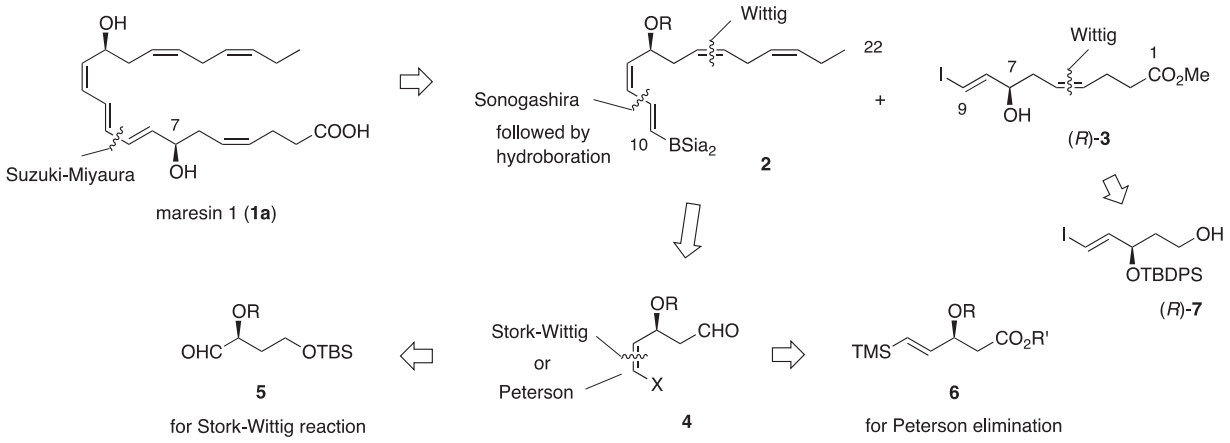
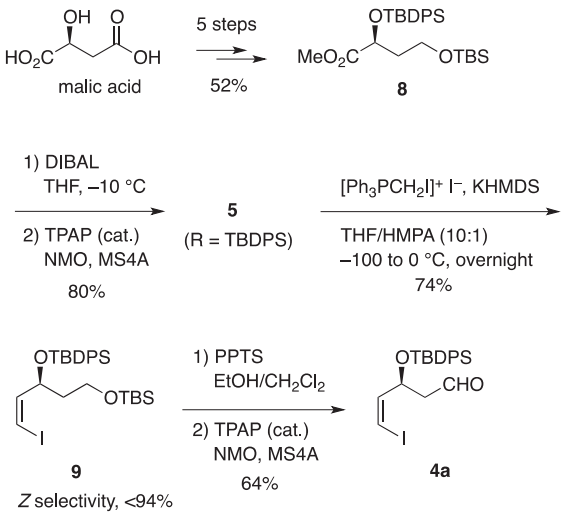


Scheme 1. Retrosynthetic analysis of maresin 1. Use of the enantiomer of (*R*)-**3** should produce (7*S*)-maresin 1 (**1b**).

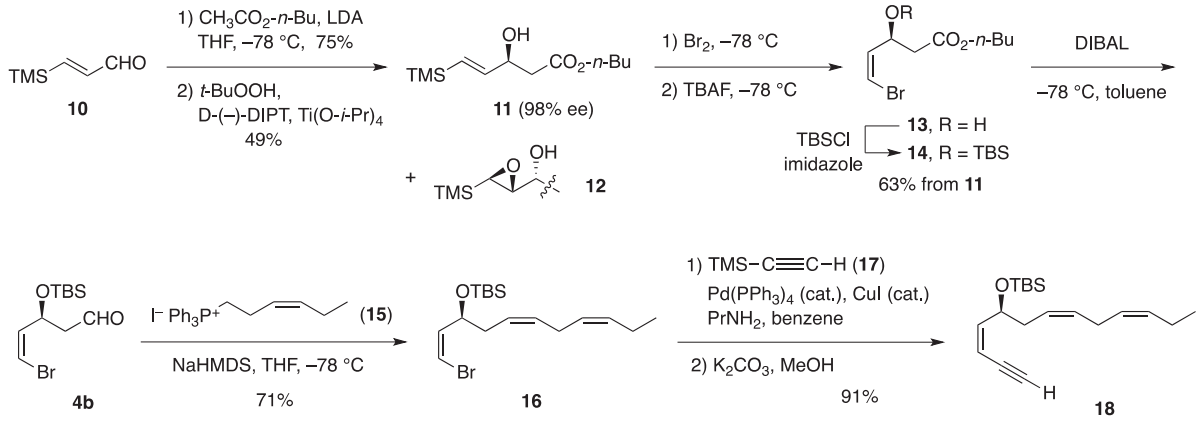


Scheme 2. Synthesis of iodide **4a** through Stork–Wittig reaction.

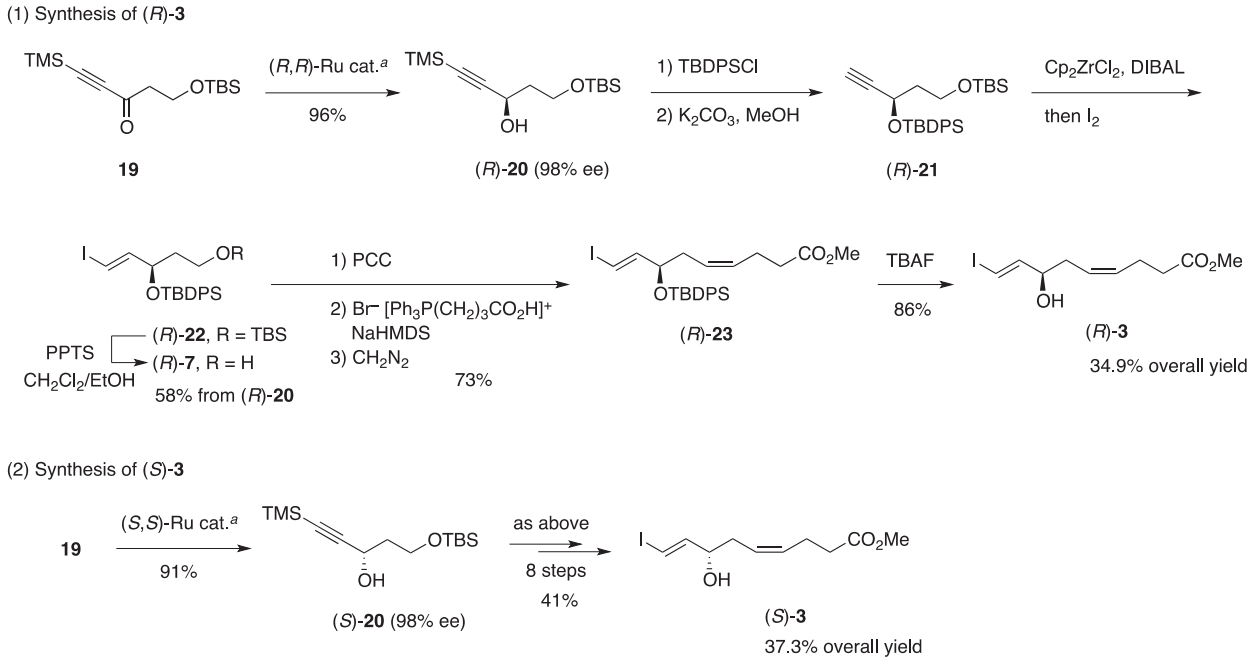
or at later stages of the conversion, leading to the borane intermediate **2** (scheme not shown). Therefore, we investigated a second route through **6**.

As delineated in Scheme 3, synthesis of **4b** (X = Br, R = TBS) began with the addition of enolate derived from CH_3CO_2-*n*-Bu to aldehyde **10**[11] according to a previously reported method.[12] The resulting racemic alcohol was subjected to kinetic resolution/asymmetric epoxidation to afford a mixture of **11** (98% ee)[13] and the epoxide **12**. These products were separated easily by routine chromatography on silica gel. Bromination of alcohol **11** (equivalent to **6**) at −78 °C followed by Peterson elimination with TBAF afforded *cis* bromide **13**. The ^{1}H NMR signals corresponding to the trans isomer were not observed at the expected region. The alcohol part of **13** was protected as TBS ether in 63% yield from **11** (3 steps), and DIBAL reduction of the ether **14** at −78 °C afforded aldehyde **4b** cleanly. Further transformation of **4b** to the intermediate **18**, which is the precursor of the vinylborane **2**, is summarized in Scheme 3. Aldehyde **4b** was subjected to the Wittig reaction with the ylide derived from **15**[14] and NaHMDS in THF to afford **16** in 71% yield. Sonogashira coupling of **16** with TMS-acetylene (**17**) under standard conditions followed by desilylation produced enyne **18**, which was shown to be highly clean by ^{1}H and ^{13}C NMR spectroscopy, proving exclusive formation of the *cis* olefin at C16.

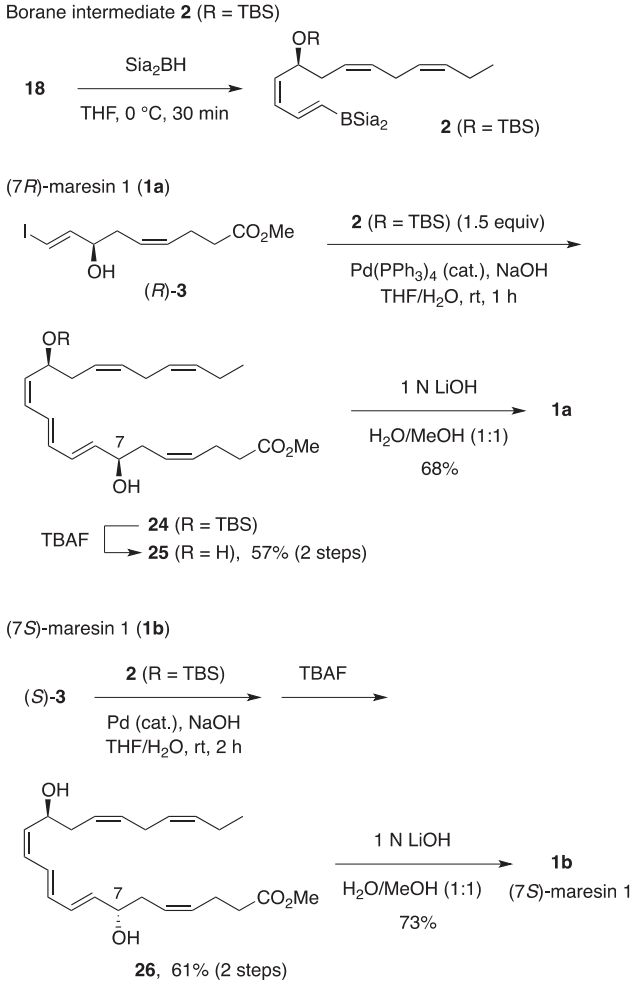
Synthesis of the C1–C9 intermediate (*R*)-**3** was accomplished by the method delineated in Scheme 4. Ketone **19** was prepared from propane-1,3-diol in four steps and subjected to the Ru-catalyzed asymmetric reduction in *i*-PrOH.[15] The alcohol (*R*)-**20** (98% ee)[13] obtained in 96% yield was transformed to (*R*)-**21** in two steps as indicated. Hydrozirconation of (*R*)-**21** with $Cp_2Zr(H)Cl$ generated in situ from Cp_2ZrCl_2 and DIBAL[16] followed by iodination of the resulting vinylzirconium species with I_2 produced vinyliodide (*R*)-**22**, which upon deprotection of the TBS group under slightly acidic conditions afforded the intermediary alcohol (*R*)-**7** in 58% from (*R*)-**20**. Oxidation of (*R*)-**7** was followed by Wittig reaction of the resulting aldehyde with the ylide derived from $Br^-[Ph_3P(CH_2)_3CO_2H]^+$ and afforded (*R*)-**23** in 73% yield after methylation with CH_2N_2. Finally,



Scheme 3. Synthesis of bromide **4b** through Peterson elimination, and further transformation to **18**, the precursor of **2**.



Scheme 4. Synthesis of the intermediates (*R*)- and (*S*)-**3**. (a) Ru cat. = Ru[(*R*,*R*)-TsDPEN](*p*-cymene) or the (*S*,*S*)-isomer.



Scheme 5. Final stage of maresins 1 synthesis.

deprotection of the TBDPS ether afforded alcohol (*R*)-**3** in good yield. The *Z* selectivity of this Wittig reaction was determined to be 95% by ^{1}H NMR spectroscopy, and the selectivity in the repeated reaction was ca. 90–95%. Fortunately, the purity was improved by preparative HPLC for the final stage of the synthesis.

As shown in Scheme 5, hydroboration of enyne **18** with freshly prepared Sia_2BH gave vinylborane **2** (R = TBS) in THF (0 °C, 30 min). The coupling reaction of iodide (*R*)-**3** (1 equiv) with **2** (1.5 equiv) was set up in the presence of $Pd(PPh_3)_4$ (10 mol %) and 2 N NaOH (10 equiv) in THF and H_2O (14:1) and conducted at rt for 1 h to prevent hydrolysis. The crude product **24** was passed through a short column of silica gel to eliminate most of the reagent residue.[17] Desilylation of **24** with TBAF afforded diol **25**, and the spectral data (^{1}H and ^{13}C NMR in $CDCl_3$ and in CD_3CN; UV)[18] were consistent with those previously reported.[4b] Finally, hydrolysis furnished maresin 1 (**1a**) in 68% yield. The spectral data (NMR and UV) and $[\alpha]_D$ were again consistent with those reported.[4a,b] Similarly, (7*S*)-maresin 1 (**1b**) was synthesized through **26** in an overall yield comparable to that of **1a**. Spectroscopic data and $[\alpha]_D$ are attached in the ref[18] and copies of the spectra are attached to the Supplementary material.

In summary, maresin 1 and (7*S*)-maresin 1 were synthesized in a highly stereoselective manner in 13.5% and 16.6% yields, respectively, over 12 steps from ketone **19**. The method presented herein complements those reported previously; these methods will be useful for the synthesis of structural analogues for biochemical studies, such as structure–activity relationships.

Acknowledgments

Plasticizer-free silica gel was kindly provided by Fuji Silysia, Japan. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supplementary data

Supplementary data (^{1}H NMR, ^{13}C-APT NMR, (and UV) of **18**, (*R*)-**20**, (*R*)-**3**, **25**, **1a**, **26**, **1b**) associated with this article can be

found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.065.

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17. Coupling of the TBDPS ether of (*S*)-**3**, that is, (*S*)-**23**, with **2** (R = TBS) gave a mixture of the coupling product and the reagent residue. Because these products were less polar with similar R_f values on TLC, separation of the products were partially successful.
18. *Methyl ester **25**:* To an ice-cold solution of enyne **18** (33.2 mg, 0.109 mmol) in THF (5 mL) was added freshly prepared Sia_2BH (0.50 M in THF, 0.29 mL, 0.145 mmol). The solution was stirred at 0 °C for 30 min, and aqueous 2 N NaOH (0.36 mL, 0.727 mmol) and a solution of iodide (*R*)-**3** (22.5 mg, 0.0727 mmol) in THF (1 mL) were added. Argon was bubbled into the reaction mixture for 15 min and then $Pd(PPh_3)_4$ (8.4 mg, 0.00727 mmol) was added. The mixture was stirred at room temperature for 1 h, and diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography on silica gel (Fiji Silysia, BW-200, hexane/EtOAc) to give triene **24**. To a solution of the above triene in THF (5 mL) was added TBAF (1.0 M in THF, 0.10 mL, 0.10 mmol). The mixture was stirred at room temperature for 7 h, and diluted with McIlvaine's phosphate buffer (pH 5.0). The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (Fiji Silysia, BW-200, Et_2O) to give alcohol **25** (15.9 mg, 57% over 2 steps); $[\alpha]_D^{20}$ −31 (*c* 0.23, $CHCl_3$); UV (EtOH) λ_{max} 262, 271, 282 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.6–1.9 (br s, 2H), 2.07 (quint, *J* = 7.5 Hz, 2H), 2.22–2.51 (m, 8H), 2.82 (t, *J* = 7 Hz, 2H), 3.67 (s, 3H), 4.24 (q, *J* = 6.5 Hz, 1H), 4.62 (dt, *J* = 8, 6.5 Hz, 1H), 5.24–5.62 (m, 7H), 5.79 (dd, *J* = 14, 6.5 Hz, 1H), 6.10 (t, *J* = 11 Hz, 1H), 6.24 (dd, *J* = 14, 11 Hz, 1H), 6.33 (dd, *J* = 14, 11 Hz, 1H), 6.51 (dd, *J* = 14, 12 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (+), 20.7 (−), 22.8 (−), 25.8 (−), 33.7 (−), 35.4 (−), 35.5 (−), 51.8 (+), 67.7 (+), 71.7 (+), 124.5 (+), 126.2 (+), 126.8 (+), 127.7 (+), 130.20 (+), 130.24 (+), 131.2 (+), 131.8 (+), 132.3 (+), 133.4 (+), 134.0 (+), 136.7 (+), 173.8 (−); ^{1}H NMR (300 MHz, CD_3CN) δ 0.90 (t, *J* = 7.5 Hz, 3H), 2.02 (quint, *J* = 7.5 Hz, 2H), 2.08–2.36 (m, 8H), 2.74 (t, *J* = 6.5 Hz, 2H), 2.86 (d, *J* = 4.5 Hz, 1H), 2.92 (d, *J* = 4.5 Hz, 1H), 3.56 (s, 3H), 4.06 (quint, *J* = 6 Hz, 1H), 4.43–4.55 (m, 1H), 5.20–5.46 (m, 7H), 5.70 (dd, *J* = 14, 6.5 Hz, 1H), 5.99 (t, *J* = 11 Hz, 1H), 6.13–6.28 (m, 2H), 6.40–6.58 (m, 1H); ^{13}C NMR (75 MHz, CD_3CN) δ 14.6 (+), 21.1 (−), 23.6 (−), 26.3 (−), 34.3 (−), 36.0 (−), 36.2 (−), 51.9 (+), 67.9 (+), 72.1 (+), 126.3 (+), 127.6 (+), 128.0 (+), 128.7 (+), 129.7 (+), 130.3 (+), 130.8 (+), 131.0 (+), 132.6 (+), 134.4 (+), 135.5 (+), 138.5 (+), 174.3 (−); HRMS (FAB) calcd for $C_{23}H_{34}O_4$ 374.2457 [M$^+$], found 374.2465.
*Maresin 1 (**1a**):* To a solution of **25** (7.6 mg, 0.0203 mmol) in MeOH (1 mL) was added aqueous 1 N LiOH (1.0 mL, 1.0 mmol). The mixture was stirred at room temperature for 2 h and diluted with McIlvaine's phosphate buffer (pH 5.0). The resulting mixture was extracted with Et_2O approximately 5 times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (Fiji Silysia, BW-200, Et_2O) to give maresin 1 (**1a**) (5.0 mg, 68%); $[\alpha]_D^{20}$ −25 (*c* 0.18, MeOH); cf. lit.[4a] $[\alpha]_D^{22}$ −31 (*c* 0.19, MeOH); UV (EtOH) λ_{max} 260, 271, 281 nm; ^{1}H NMR (300 MHz, CD_3OD) δ 0.96 (t, *J* = 7.5 Hz, 3H), 2.07 (quint, *J* = 7.5 Hz, 2H), 2.16–2.45 (m, 8H), 2.79 (t, *J* = 6.0 Hz, 2H), 4.07–4.18 (m, 1H), 4.51–4.62 (m, 1H), 5.22–5.54 (m, 7H), 5.74 (dd, *J* = 14, 6.5 Hz, 1H), 6.07 (t, *J* = 11 Hz, 1H), 6.17–6.36 (m, 2H), 6.44–6.60 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.7, 21.5, 24.0, 26.6, 34.9, 36.2, 36.5, 68.5, 73.0, 126.1, 127.5, 128.2, 128.9, 130.6, 131.1, 131.3, 131.4, 132.8, 134.8, 135.0, 138.0, 177.0; HRMS (FAB) calcd for $C_{22}H_{31}O_4$ 359.2222 [(M−H)$^+$], found 359.2222.
*Methyl ester **26**:* $[\alpha]_D^{22}$ −14 (*c* 0.19, $CHCl_3$); UV (EtOH) λ_{max} 262, 271, 282 nm; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3H), 1.5–1.7 (br s, 1H), 1.9–2.1 (br s, 1H), 2.07 (quint, *J* = 7.5 Hz, 2H), 2.16–2.50 (m, 8H), 2.82 (t, *J* = 7 Hz, 2H), 3.67 (s, 3H), 4.24 (q, *J* = 6 Hz, 1H), 4.62 (q, *J* = 7, 1H), 5.24–5.62 (m, 7H), 5.79 (dd, *J* = 14, 6 Hz, 1H), 6.10 (t, *J* = 11.5 Hz, 1H), 6.26 (dd, *J* = 14, 11 Hz, 1H), 6.32 (dd, *J* = 14, 11 Hz, 1H), 6.51 (dd, *J* = 14, 11 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (+), 20.7 (−), 22.8 (−), 25.8 (−), 33.7 (−), 35.4 (−), 35.5 (−), 51.8 (+), 67.7 (+), 71.7 (+), 124.5 (+), 126.2 (+), 126.8 (+), 127.7 (+), 130.20 (+), 130.24 (+), 131.2 (+), 131.8 (+), 132.3 (+), 133.4 (+), 134.0 (+), 136.7 (+), 173.8 (−); HRMS (FAB) calcd for $C_{23}H_{34}O_4$ 374.2457 [M$^+$], found 374.2459.
*(7S)-Maresin 1 (**1b**):* $[\alpha]_D^{20}$ −21 (*c* 0.18, MeOH); cf. lit.[4a] $[\alpha]_D^{22}$ −23 (*c* 0.18, MeOH); UV (EtOH) λ_{max} 260, 271, 281 nm; ^{1}H NMR (300 MHz, CD_3OD) δ 0.96 (t, *J* = 7.5 Hz, 3H), 2.07 (quint, *J* = 7.5 Hz, 2H), 2.15–2.47 (m, 8H), 2.79 (t, *J* = 6.0 Hz, 2H), 4.12 (q, *J* = 6.5 Hz, 1H), 4.51–4.63 (m, 1H), 5.15–5.56 (m, 7H), 5.74 (dd, *J* = 14, 6.5 Hz, 1H), 6.07 (t, *J* = 11 Hz, 1H), 6.16–6.37 (m, 2 H), 6.42–6.60 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 14.7 (+), 21.5 (−), 24.1 (−), 26.6 (−), 34.9 (−), 36.2 (−), 36.5 (−), 68.5 (+), 73.0 (+), 126.1 (+), 127.5 (+), 128.2 (+), 128.9 (+), 130.6 (+), 131.1 (+), 131.3 (+), 131.4 (+), 132.8 (+), 134.8 (+), 135.0 (+), 138.0 (+), 177.2 (−); HRMS (FAB) calcd for $C_{22}H_{31}O_4$ 359.2222 [(M−H)$^+$], found 359.2222.