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Total synthesis of the potent anti-inflammatory lipid mediator Protectin D1

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ABSTRACT

The total synthesis of the potent anti-inflammatory lipid mediator Protectin D1 derived from docosahexaenoic acid, has been achieved. The chiral hydroxy-groups at C10 and C17 were obtained via a chiral pool strategy from (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane and 3,4-*O*-isopropylidene-2-deoxy-D-ribose, respectively. Wittig reactions, Takai olefination, Pd^0/Cu^I Sonogashira coupling, and Zn(Cu/Ag) reduction completed the total synthesis of Protectin D1.

The health benefit of eicosapentaenoic and docosahexaenoic acids in inflammatory diseases is well documented.[1] We reported earlier that dietary enrichment with these ω-3 fatty acids in humans impairs in vitro neutrophil and monocyte leukotriene generation and neutrophil function.[2] These studies were later broadened to include auto-immune diseases such as rheumatoid arthritis and asthma.[3,4] The groundbreaking work by Serhan and collaborators revealed that the biologically active compounds in the resolution of inflammation were enzymatically formed di- and tri-hydroxylated products of eicosapentaenoic and docosahexaenoic acids, the Resolvins.[5–10]

In 2004, Serhan and collaborators discovered a novel docosanoid mediator of inflammation resolution in the brain named Neuroprotectin D1 (NPD1) also known as Protectin D1 (PD1).[11,12] The complete stereochemical structure of Protectin D1 was later on established as (4*Z*,7*Z*,10*R*,11*E*,13*E*,15*Z*,17*S*,19*Z*)-10,17-dihydroxy-4,7,11,13,15,19-docosahexaenoic acid.[13] This product is formed in vivo from docosahexaenoic acid via *S*-selective 17-lipoxygenation to the hydroperoxide intermediate that undergoes epoxide formation followed by enzymatic hydrolysis (Fig. 1). Protectin D1 is rapidly formed in response to oxidative stress in the brain and protects against resulting damage.[14] With respect to Alzheimer's disease pathogenesis, Protectin D1 regulates the β-amyloid secretion and improves neuronal survival.[15] Interestingly Alzheimer's patients are not capable to produce this neuroprotective lipid mediator; therefore Protectin D1 could be a lead molecule to be evaluated for the treatment of Alzheimer's disease and other neurological disorders.[16] The limited availability from natural sources requires its preparation by total synthesis to produce sufficient amounts for biological and pharmacological testings.

A strategy for the synthesis of Protectin D1 was first outlined by Petasis and collaborators.[13] A total synthesis of Protectin D1 was later reported by Ogawa and Kobayashi.[17] The key features of Kobayashi's strategy encompass the Suzuki coupling between the C13–C22 vinyl borane and the C1–C12 vinyl iodide. The chiral centers were obtained via a Sharpless kinetic resolution. The first total synthesis of the aspirin-triggered Protectin D1 (AT-PD1) was reported by Petasis and collaborators.[18,19] In their synthesis the chiral centers were derived from chiral glycidol derivatives via epoxide opening with acetylenes under Yamaguchi conditions. Recently Hansen and collaborators reported an interesting total synthesis of Protectin D1 using a stereocontrolled Evans-aldol reaction with Nagao's chiral auxiliary.[20] However the β-hydroxy-aldehyde key intermediate is extremely prone to elimination. Balas and collaborators prepared the 10*S*-epimer of Protectin D1 constructing first the conjugated triene system followed by Wittig reactions.[21] They observed, similar to Hansen, that their β-hydroxy-aldehyde intermediate easily eliminated the OTBS group during the final Wittig reaction.

As part of our continuing interest in the field of anti-inflammatory lipid mediators and in view of its promising biological profile we decided to undertake the total synthesis of Protectin D1.

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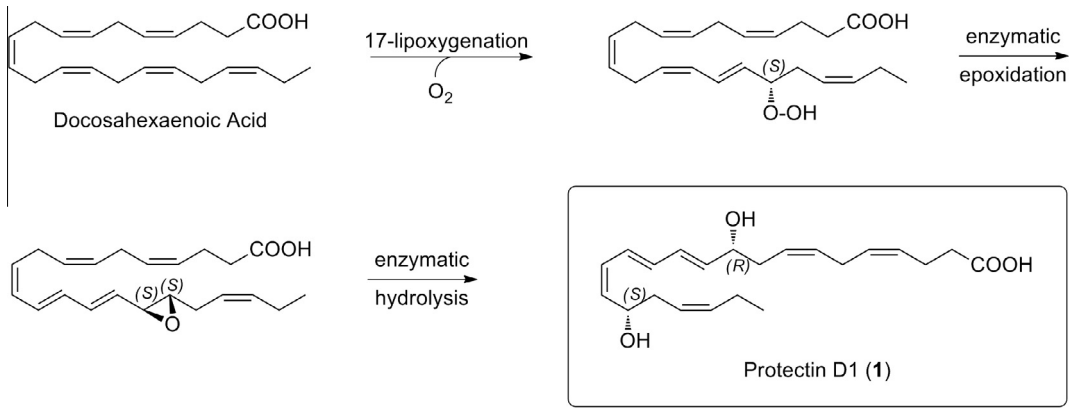


Figure 1. Biosynthesis of Protectin D1.

In this Letter, we wish to report a different synthetic strategy toward the total synthesis of Protectin D1 (**1**). As shown in the retrosynthetic approach (Fig. 2) Protectin D1 (**1**) has been prepared from the two key intermediates **2** and **3**. The chiral center at C10 was obtained from commercial (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6**) and 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**4**) was used as the source of chirality for C17. Wittig reactions, Takai olefination, Sonogashira coupling, and Zn(Cu/Ag) reduction provided Protectin D1 (**1**).

The phosphonium salt **5**, a key intermediate in our synthesis of compound **3**, was previously reported in the literature.[22] Herein we report two short alternative routes toward **5** as outlined in Scheme 1. γ-Butyrolactone (**7**) was converted to the hydroxymethyl ester **8** by treatment with 2 equiv of triethylamine in methanol containing a small amount of water.[23,24] Without the addition of water no reaction occurred. Compound **8** was oxidized to aldehyde **9** using PCC in CH_2Cl_2 in the presence of NaOAc.[25] Wittig reaction of aldehyde **9** with the silyloxy-substituted ylide generated in situ from phosphonium salt **10** gave, after acidic work-up, the *Z*-alkene ester **14**.[26] In the second route commercial phosphonium salt **11** was transformed to the crystalline methyl ester **12** with 2,2-dimethoxypropane/CH_3OH/10% TMSCl in quantitative yield.[27] The phosphonium salt **12** was converted to its ylide with NaHMDS in THF and then reacted with aldehyde

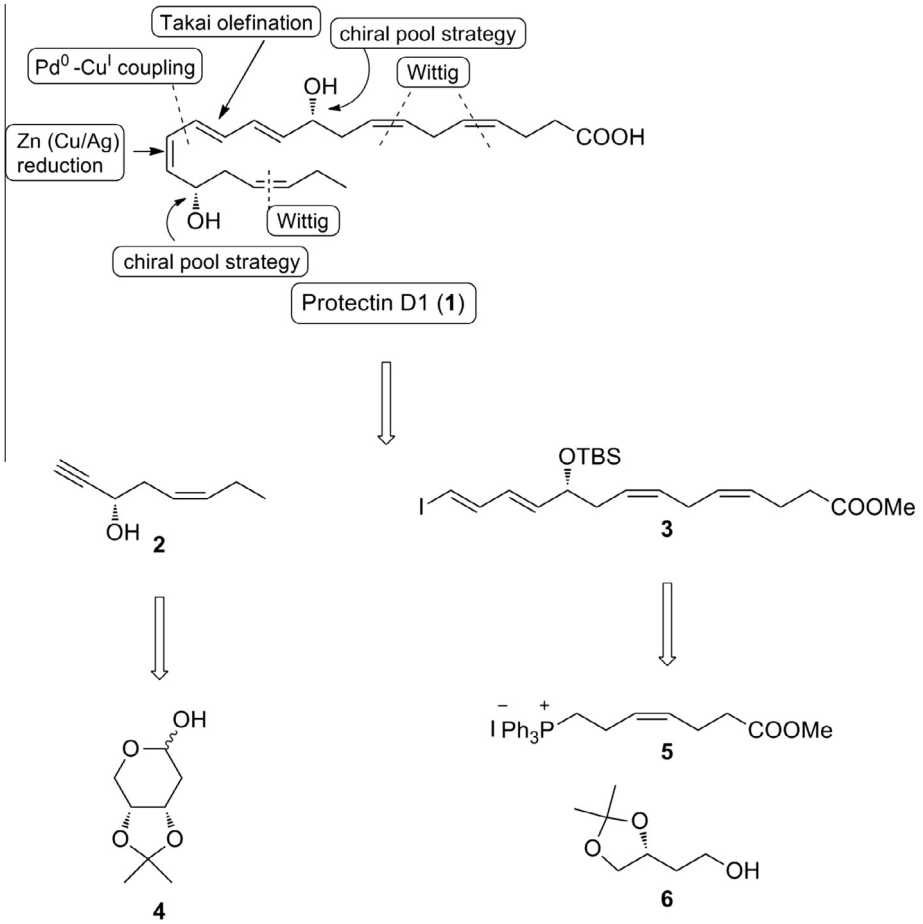
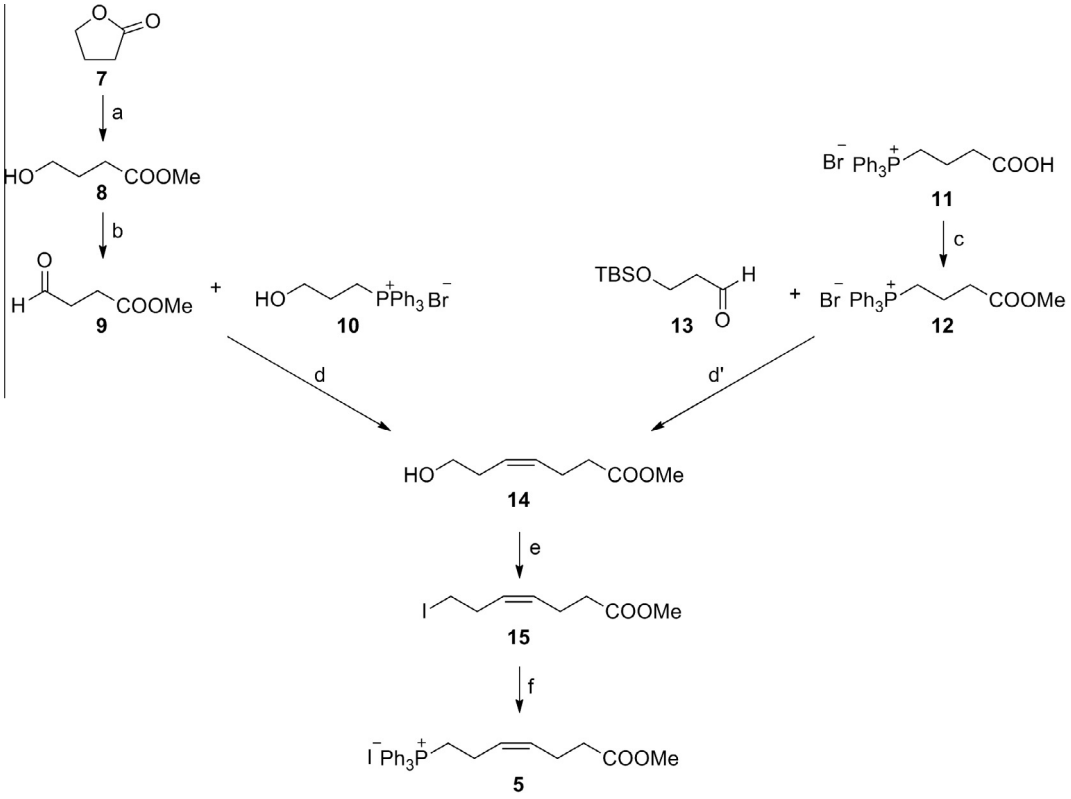
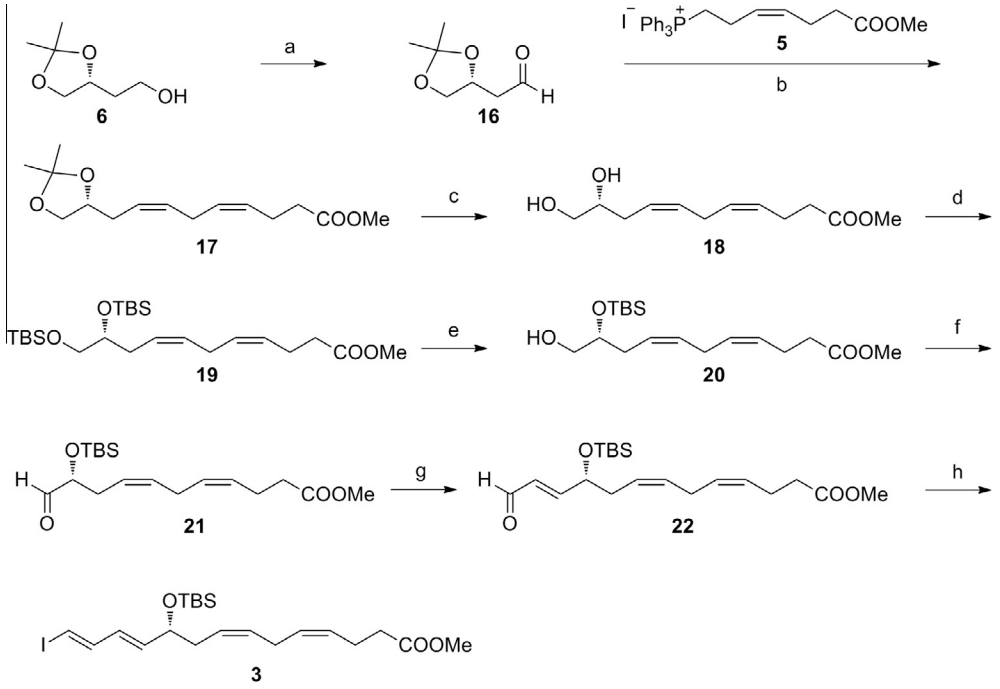


Figure 2. Retrosynthetic approach to Protectin D1.



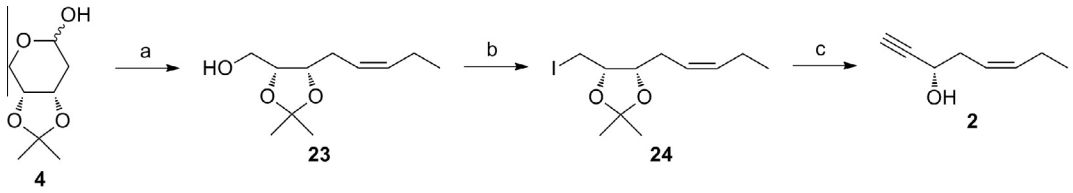
Scheme 1. Reagents and conditions: (a) Et_3N, CH_3OH, cat. H_2O, 85%; (b) PCC, NaOAc, CH_2Cl_2, 80%; (c) 2,2-dimethoxypropane, cat. TMSCl, CH_3OH, rt, 99%; (d) **10**, KHMDS, THF, 0 °C to rt, TMSCl, 0 °C, **9**, −78 °C to rt then 1 N HCl, 0 °C to rt, 45%; (d′) NaHMDS, THF, −78 °C to 0 °C then 1 N HCl, 0 °C to rt, 57%; (e) I_2, Ph_3P, imidazole, *i*-Pr_2EtN, CH_3CN, ether 75%; (f) Ph_3P, CH_3CN, 70 °C, 88%.



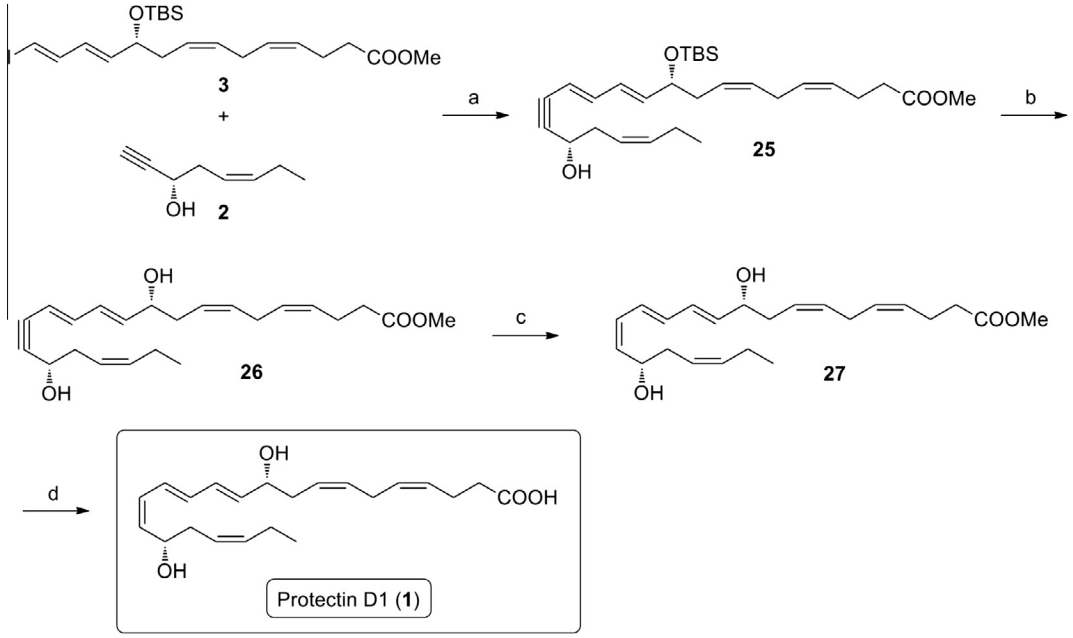
Scheme 2. Reagents and conditions: (a) Ref. 29; (b) NaHMDS, THF, −78 °C, 42%; (c) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C to rt, 92%; (d) TBSCl, imidazole, DMAP, DMF, 0 °C to rt, 81%; (e) HF·py, THF, 0 °C to rt, 60%; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 88%; (g) $Ph_3P{=}CH{-}CHO$, toluene, 90 °C, 89%; (h) $CrCl_2$, CHI_3, THF, 0 °C, 52%.

13 to give, after acidic work up, the *Z*-alkene ester **14**. Compound **14** was converted into iodide **15** by the method of Samuelsson[28] and transformed to the crystalline phosphonium salt **5** with PPh_3 in CH_3CN at 70 °C in 88% yield.

The synthesis of the C1–C14 key intermediate **3** from commercial (4*R*)-4-(2-hydroxyethyl)-2,2-dimethyl-1,3-dioxolane (**6**) is outlined in Scheme 2. The alcohol **6** was converted to the aldehyde **16** using the Swern reagent in good yield.[29] *Z*-selective Wittig



Scheme 3. Reagents and conditions: (a) $CH_3(CH_2)_2P^+Ph_3Br^-$, NaHMDS, ether, −78 °C to 0 °C, 60%; (b) I_2, Ph_3P, imidazole, toluene, 60 °C, 90%; (c) LDA, THF, −78 °C, 72%.



Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, piperidine, benzene, rt, 76%; (b) TBAF, THF, 0 °C to rt, 82%; (c) Zn(Cu/Ag), CH_3OH, H_2O, 40–45 °C, 47%; (d) 1 N LiOH, CH_3OH, H_2O, 0 °C, then satd NaH_2PO_4, 89%.

reaction between **16** and the ylide generated from the phosphonium salt **5** using NaHMDS produced **17**, no trace of the *E*-isomer was detected. The isopropylidene protective group was cleaved with $CuCl_2{\cdot}2H_2O$ in CH_3CN to give **18** in 92% isolated yield.[30] The free hydroxyl groups were silylated using TBSCl, imidazole, DMAP in DMF to give **19**. Attempts to convert **19** directly into **21** by selective oxidation using quinolinium fluorochromate resulted in the full recovery of **19**.[31] Therefore the primary TBS group of **19** was first selectively deprotected with excess HF·py in THF to give **20** which was then converted to the aldehyde **21** in 88% by Dess Martin oxidation in CH_2Cl_2.[32,33] Wittig homologation of the aldehyde **21** with (triphenylphosphoranylidene)acetaldehyde in toluene at 90 °C gave enal **22** that was converted to the key intermediate **3** by a modified Takai reaction.[34,35]

The C15–C22 fragment **2** was obtained in three steps from 3,4-*O*-isopropylidene-2-deoxy-D-ribose (**4**)[36] as outlined in Scheme 3. Wittig reaction of **4** with 2.5 equiv of phosphorane generated from *n*-propyl triphenylphosphonium bromide and NaHMDS in ether at −78 °C gave the *cis*-olefination product **23**.[37] Using the method of Samuelsson,[28] **23** was converted into the iodide **24** with triphenylphosphine, imidazole, and iodine in toluene at 60 °C in 90% yield.[38] The isopropylidene iodide **24** was converted directly into the key intermediate **2** using 7 equiv of LDA in THF at −78 °C.

The total synthesis of Protectin D1 was completed as shown in Scheme 4. Modified Sonogashira coupling[35,39] of **3** in the presence of $Pd(PPh_3)_4$,[40] CuI, and piperidine in benzene with a very slow addition of the acetylene **2** gave the TBS-mono-protected triple bond precursor of Protectin D1 methyl ester (**25**). Cleavage of the TBS protective group with TBAF in THF gave **26**.[18,20] Two approaches have been described in the literature for the selective *cis*-reduction of the triple bond in **26** to give Protectin D1 methyl ester (**27**): a modified Lindlar reduction[20] and the Boland reduction with Zn(Cu/Ag) alloy.[18] The modified Lindlar reduction was hampered in our hands by simultaneous over-reduction. We therefore employed the Boland reduction with freshly prepared Zn(Cu/Ag)[41,42] in CH_3OH/H_2O at 40–45 °C for 60 min to produce Protectin D1 methyl ester (**27**) along with Δ15-*trans*-Protectin D1 methyl ester in an average ratio of 65:35. The products could be easily separated by flash chromatography using triethylamine-deactivated silica.[43] When the reaction was performed in CD_3OD/D_2O the 15,16-dideuterio-Protectin D1 methyl ester was cleanly produced.

Mild hydrolysis of the methyl ester **27** with 1 N LiOH in CH_3OH/H_2O at 0 °C under argon gave, after acidification with satd NaH_2PO_4 (pH 3) in the presence of ethyl acetate, Protectin D1 (**1**) in 89% yield. All spectroscopic data were in agreement with those reported in the literature.[18,20,44]

In summary, a concise total synthesis of Protectin D1 has been achieved,[44] making this anti-inflammatory lipid mediator from docosahexaenoic acid available for further biological and pharmacological testing. The synthesis of other specialized pro-resolving mediators (SPM) will be reported in due course.

Acknowledgments

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43. Flash chromatography purification: triethylamine-deactivated silica gel 60 (40–63 μm), 25–35% ethyl acetate in hexane.
44. *Satisfactory spectroscopic data were obtained for all compounds. Selected physical data:* Compound **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.6 (s, 3H), 3.7–3.6 (t, J = 6.2 Hz, 2H), 2.4 (t, J = 7.2 Hz, 2H), 1.9–1.8 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 174.29, 61.92, 51.58, 30.74, 27.71. Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.8 (s, 1H), 3.6 (s, 3H), 2.8–2.7 (t, J = 6.6 Hz, 2H), 2.6 (t, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 199.72, 172.63, 51.84, 38.54, 26.38. Compound **14**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.5–5.4 (m, 2H), 3.7–3.6 (s and m, 5H), 2.4–2.3 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.58, 130.54, 127.14, 62.09, 51.48, 33.82, 30.77, 22.77. Compound **15**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (m, 1H), 5.4–5.3 (m, 1H), 3.6 (s, 3H), 3.1 (t, J = 7.2 Hz, 2H), 2.7–2.6 (br q, J = 7.2 Hz, 2H), 2.4–2.3 (m, 4H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.31, 130.07, 129.43, 51.52, 33.81, 31.34, 22.97, 4.93. Compound **5**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.9–7.6 (m, 15H), 5.7–5.6 (m, 1H), 5.4–5.2 (m, 1H), 3.7–3.6 (m, 2H), 3.6 (s, 3H), 2.5–2.3 (m, 2H), 2.3–2.2 (br t, J = 6.7 Hz, 2H), 2.2–2.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.28, 135.13 (d, J = 3.1 Hz, 3C), 133.69 (d, J = 9.9 Hz, 6C), 130.54 (d, J = 12.5 Hz, 6C), 130.27, 127.45 (d, J = 15.4 Hz), 117.46 (d, J = 85.3 Hz, 3C), 51.47, 33.25, 23.18 (d, J = 48.7 Hz), 22.60, 20.38 (d, J = 3.1 Hz). Mp 114–115 °C. Compound **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.2 (m, 4H), 4.2–4.1 (m, 1H), 4.0 (dd, J = 7.8, 6.3 Hz , 1H), 3.7 (s, 3H), 3.6–3.5 (dd, J = 7.8, 6.9 Hz, 1H), 2.8 (m, 2H), 2.5–2.2 (m, 6H), 1.4–1.3 (2 s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.44, 130.52, 129.02, 128.07, 124.57, 108.94, 75.54, 69.02, 51.49, 33.98, 31.54, 26.88, 25.76, 25.63, 22.82. Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.3 (m, 4H), 3.8–3.7 (m, 2H), 3.7 (s, 3H), 3.5 (dd, J = 10.8, 6.6 Hz, 1H), 2.9–2.7 (m, 2H), 2.4–2.2 (m, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.69, 131.10, 129.02, 128.10, 124.98, 71.79, 66.22, 51.56, 33.96, 31.43, 25.74, 22.87. Compound **19**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.2 (m, 4H), 3.7–3.6 (m, 1H), 3.6 (s, 3H), 3.5–3.4 (dd, J = 9.9, 5.4 Hz, 1H ABsystem), 3.4 (dd, J = 9.9, 6.0 Hz, 1H ABsystem), 2.8–2.7 (m, 2H), 2.4–2.1 (m, 6H), 0.87 (s, 9H), 0.85 (s, 9H), 0.031 (s, 6H), 0.023 (s, 3H), 0.020 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.47, 129.58, 129.28, 127.71, 126.43, 73.21, 67.05, 51.45, 34.08, 32.28, 25.98 (3C), 25.90 (3C), 25.75, 22.84, 18.36, 18.14, −4.39, −4.65, −5.32, −5.37. Compound **20**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.3 (m, 4H), 3.8–3.7 (m, 1H), 3.6 (s, 3H), 3.6–3.5 (dd, J = 11.1, 3.9 Hz , 1H ABsystem), 3.5–3.4 (dd, J = 11.1, 5.4 Hz , 1H ABsystem), 2.8 (m, 2H), 2.4–2.2 (m, 6H), 0.88 (s, 9H), 0.073 (s, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.54, 130.03, 129.19, 127.99, 125.41, 72.72, 66.00, 51.50, 34.00, 32.03, 25.83 (3C), 25.72, 22.84, 18.08, −4.44, −4.66. Compound **22**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.5 (d, J = 7.8 Hz, 1H), 6.8 (dd, J = 15.6, 4.5 Hz, 1H), 6.3–6.2 (ddd, J = 15.6, 8.1, 1.5 Hz, 1H), 5.6–5.3 (m, 4H), 4.5–4.4 (m, 1H), 3.6 (s, 3H), 2.8–2.7 (m, 2H), 2.4–2.2 (m, 6H), 0.88 (s, 9H), 0.052 (s, 3H), 0.020 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 193.39, 173.42, 159.17, 130.92, 130.75, 128.88, 128.18, 124.35, 71.52, 51.50, 35.35, 33.93, 25.77 (4C), 22.82, 18.16, −4.73, −4.83. Compound **3**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.1–6.9 (dd, J = 14.1, 10.8 Hz, 1H), 6.3–6.2 (d, J = 14.1 Hz, 1H), 6.1–6.0 (br dd, J = 15.3, 10.8 Hz, 1H), 5.8–5.6 (dd, J = 15.3, 5.7 Hz, 1H), 5.4–5.2 (m, 4H), 4.2–4.0 (m, 1H), 3.6 (s, 3H), 2.8–2.7 (m, 2H), 2.4–2.2 (m, 6H), 0.87 (s, 9H), 0.024 (s, 3H), 0.002 (s, 3H). Compound **24**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 5.4–5.3 (dtt, J = 10.8, 7.2, 1.5 Hz, 1H), 4.4–4.3 (m, 1H), 4.2–4.1 (td, J = 7.2, 5.7 Hz, 1H), 3.2–3.1 (m, 2H), 2.3 (br t, J = 7.2 Hz, 2H), 2.1–2.0 (br quint, J = 7.5 Hz, 2H), 1.5 (s, 3H), 1.3 (s, 3H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 134.44, 123.63, 108.52, 78.30, 77.69, 28.36, 27.45, 25.68, 20.86, 14.00, 3.66. Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.7–5.5 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 5.5–5.3 (dtt, J = 10.8, 7.5, 1.5 Hz, 1H), 4.4–4.3 (m, 1H), 2.5–2.4 (m, 2H), 2.4 (d, J = 2.1 Hz, 1H), 2.1–2.0 (br quint, J = 7.5 Hz, 2H), 1.9 (d, J = 5.7 Hz, 1H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 136.13, 122.43, 84.56, 72.90, 61.88, 35.47, 20.79, 14.14. Compound **25**: ^{1}H NMR (C_6D_6, 300 MHz): δ 6.6 (dd, J = 15.6, 10.8 Hz, 1H), 6.2 (dd, J = 15.0, 10.8 Hz, 1H), 5.7–5.2 (m, 8H), 4.4–4.3 (br qd, J = 6.3, 1.8 Hz, 1H), 4.1 (br q, J = 6.3 Hz, 1H), 3.3 (s, 3H), 2.8–2.7 (m, 2H), 2.5–2.4 (br t, J = 6.3 Hz, 2H), 2.4–2.2 (m, 4H), 2.2–2.1 (t, J = 7.5 Hz, 2H), 2.0–1.8 (m, 2H), 1.5–1.4 (d, J = 6.3 Hz, 1H), 0.98 (s, 9H), 0.9–0.8 (t, J = 7.5 Hz, 3H), 0.068 (s, 3H), 0.043 (s, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ 172.69, 141.68, 139.65, 135.18, 130.14, 129.39, 128.95, (one carbon overlaps with C_6D_6 signal), 125.88, 123.73, 111.07, 93.65, 84.20, 73.10, 62.78, 50.95, 36.62, 36.14, 34.01, 26.16, 26.06 (3C), 23.14, 21.05, 18.41, 14.30, −4.27, −4.61. Compound **26**: ^{1}H NMR (C_6D_6, 300 MHz): δ 6.6 (dd, J = 15.6, 10.8 Hz, 1H), 6.2–6.1 (br dd, J = 15.3, 10.8 Hz, 1H), 5.6–5.2 (m, 8H), 4.4–4.3 (m, 1H), 3.9 (m, 1H), 3.3 (s, 3H), 2.8–2.7 (m, 2H), 2.5–2.4 (m, 2H), 2.3–2.2 (m, 2H), 2.2–2.0 (m, 4H), 2.0–1.8 (m, 2H), 0.9–0.8 (t, J = 7.5 Hz, 3H); ^{13}C NMR (C_6D_6, 75.5 MHz): δ 172.84, 141.74, 139.03, 135.20, 131.04, 129.24, 129.08, (one carbon overlaps with C_6D_6 signal), 125.39, 123.72, 111.10, 93.64, 84.21, 71.40, 62.79, 50.99, 36.13, 35.67, 33.96, 26.08, 23.11, 21.04, 14.30. Compound **27**: ^{1}H NMR (CD_3OD, 300 MHz): δ 6.5 (dd, J = 14.1, 11.1 Hz, 1H), 6.3–6.2 (m, 2H), 6.1 (t, J = 11.1 Hz, 1H), 5.8–5.7 (dd, J = 14.4, 6.3 Hz, 1H), 5.5–5.3 (m, 7H), 4.6–4.5 (m, 1H), 4.1 (q, J = 6.3 Hz, 1H), 3.6 (s, 3H), 2.9–2.7 (m, 2H), 2.5–2.1 (m, 8H), 2.1–2.0 (m, 2H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 175.46, 137.93, 134.94, 134.81, 134.77, 131.40, 130.92, 130.57, 130.31, 128.92 (2C), 126.50, 125.24, 72.98, 68.56, 52.14, 36.35, 36.30, 34.84, 26.68, 23.79, 21.68, 14.59; UV (EtOH) λ_{max} 262, 271, 282 nm; HPLC-UV: Zorbax SB-C18, 1.8 μm, 50 × 2.1 mm, 271 nm, H_2O/CH_3OH (0.1% formic acid) 50:50–30:70, 0.2 mL/min, t_R = 20.0 min; HPLC/MS (m/z): 397.2 $[M-Na]^+$. Δ15-*trans*-Protectin D1 methyl ester: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.3–6.1 (m, 4H), 5.8–5.7 (m, 2H), 5.6–5.3 (m, 6H), 4.3–4.1 (m, 2H), 3.6 (s, 3H), 2.9–2.7 (m, 2H), 2.4–2.2 (m, 8H), 2.1–2.0 (m, 2H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.65, 135.81, 135.68, 135.41, 132.27, 132.19, 131.17, 130.38, 130.31, 129.03, 128.02, 124.90, 123.54, 71.89, 71.85, 51.62, 35.36, 35.20, 33.93, 25.78, 22.79, 20.73, 14.21; UV (EtOH) λ_{max} 261, 270, 281 nm; HPLC-UV: Zorbax SB-C18, 1.8 μm, 50 × 2.1 mm, 271 nm, H_2O/CH_3OH (0.1% formic acid) 50:50–30:70, 0.2 mL/min, t_R = 18.4 min; HPLC/MS (m/z): 397.2 $[M-Na]^+$. Protectin D1 (**1**): ^{1}H NMR (CD_3OD, 300 MHz): δ 6.5 (dd, J = 14.1, 11.1 Hz, 1H), 6.4–6.2 (m, 2H), 6.1 (t, J = 11.1 Hz, 1H), 5.8–5.7 (dd, J = 14.4, 6.3 Hz, 1H), 5.5–5.3 (m, 7H), 4.6–4.5 (m, 1H), 4.2–4.1 (m, 1H), 2.9–2.7 (m, 2H), 2.4–2.1 (m, 8H), 2.1–2.0 (m, 2H), 1.0–0.9 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3OD, 75.5 MHz): δ 176.99, 137.95, 134.95, 134.81, 134.73, 131.39, 130.98, 130.58, 130.14, 129.17, 128.89, 126.48, 125.27, 72.98, 68.55, 36.37, 36.32, 35.00, 26.70, 23.88, 21.69, 14.58; UV (EtOH) λ_{max} 262, 271, 282 nm; HPLC-UV: Zorbax SB-C18, 1.8 μm, 50 × 2.1 mm, 271 nm, H_2O/CH_3OH (0.1% formic acid) 50:50–30:70, 0.2 mL/min, t_R = 16.6 min; HPLC/MS (m/z): 359.2 $[M-H]^-$.