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Total synthesis of the antiinflammatory and proresolving protectin D1

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ABSTRACT

Stereoselective total synthesis of protectin D1 was completed through construction of the *Z*,*E*,*E*-triene structure by using the Suzuki coupling between the vinyl borane (C13–C22) and the vinyl iodide (C1–C12). The *Z*-enyne, the acetylene precursor of the vinyl borane was synthesized from optically active γ-TMS allylic alcohol in a straightforward way. On the other hand, the vinyl iodide was prepared by using Wittig reaction between the C8–C12 aldehyde possessing the requisite iodo-olefin moiety and the C1–C7 phosphonium iodide.

Highly unsaturated fatty acids such as EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) are metabolized to polyhydroxylated linear acids that show antiinflammatory and proresolving activities.[1] Since these properties promise pharmaceutical application, biological aspects of these metabolites has extensively been studied. To support these studies we have established synthesis of resolvin E1, in which the chemically highly unstable conjugated *Z*,*E*,*E*-triene unit is constructed by using the Suzuki coupling.[2] Protectin D1 (**1**) and maresin 1 (**2**), metabolites of DHA, (Fig. 1) also show as high antiinflammatory and proresolving activities as RvE1.[3,4] Previously, synthesis of PD1 (**1**) was announced briefly by Serhan,[3a] who constructed the unstable conjugated triene unit by Sonogashira coupling followed by hydrogenation of the resulting dienylacetylene, though the efficiency in stereoselectivity and yield is not mentioned. We envisioned that Suzuki coupling between vinyl borane **3** and vinyl iodide **4a** or **4b** would furnish the conjugated triene structure of **1** by analogy with the structural similarity to RvE1 (Scheme 1),[2] though construction of the highly functionalized compound **4** was not established. Consequently, we investigated first construction of **4** and then synthesis of PD1.

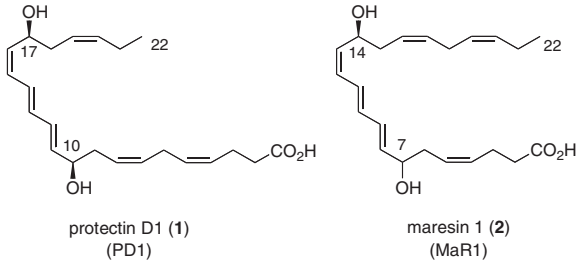
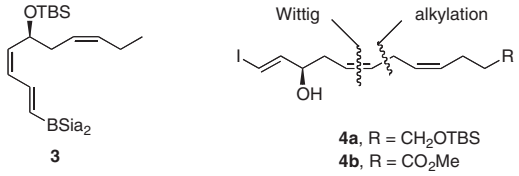


Figure 1. DHA-derived resolving mediators with the *Z*,*E*,*E*-conjugated triene unit.



Scheme 1. Key to protectin D1.

Scheme 1 shows two possible approaches to **4** via Wittig reaction or alkylation. Among them the alkylation was investigated first by using the racemic acetylenic alcohol **5**[5] and propargylic bromide **6** (Scheme 2). As summarized in Table 1, the standard conditions (EtMgBr for deprotonation and CuCl for alkylation) was not suited to **5**, which was recovered unreacted (entry 1). Use of *i*-PrMgBr, probably more basic, was ineffective as well (entry 2). After several unsuccessful attempts, conditions reported recently[6] gave the desired product **7** in 80% yield (entry 3), whereas further investigation with Bu_4NI instead of NaI afforded **7** in better yield (entry 4). Epoxidation of **7** with *t*-BuOOH[7] catalyzed by $Ti(OPr)_4$ gave epoxide **8** as a stereoisomeric mixture in a 4:3 ratio by ^1H NMR spectroscopy. Epoxide **8** was then subjected to reaction with Bu_3SnLi in THF at 0 °C and the crude product was treated with NIS. Unfortunately, the ^1H NMR spectrum disclosed little signals

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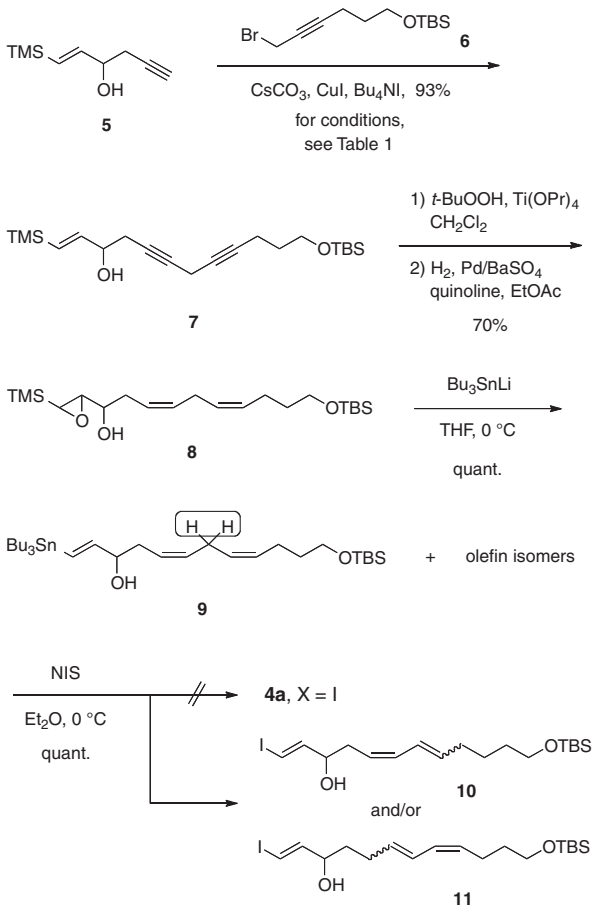
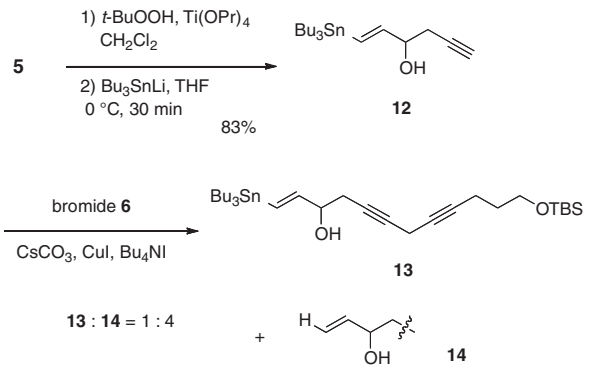


Scheme 2. Attempted synthesis of iodide **4a**.

for the two protons corresponding to the C6 methylene unit of the key intermediate **4a**, indicating contamination of the conjugated-olefins **10** and **11**, which were formed probably by deprotonation of the methylene proton of **8** and/or **9** by highly basic Bu_3SnLi.

To circumvent the above side reaction, epoxidation of **5** was followed by reaction with Bu_3SnLi to produce stannane **12** uneventfully (Scheme 3). However, the alkylation of **12** with bromide **6**

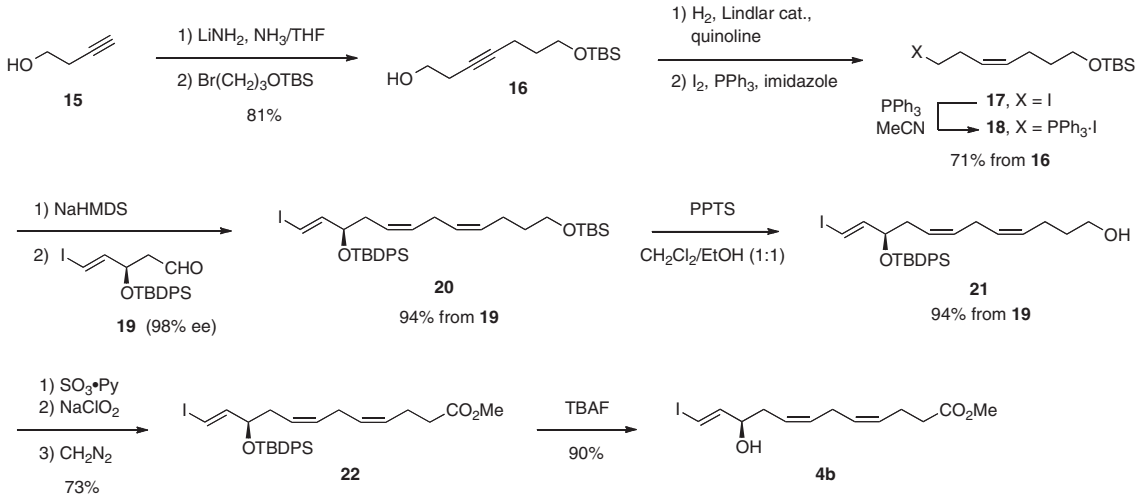


Scheme 3. Attempted synthesis of stannane **13**.

under the conditions for the preparation of **7** (Table 1, entry 3) gave a mixture of **13** and **14** in a 1:4 ratio by ^1H NMR spectroscopy.

Next, the Wittig approach delineated in Scheme 1 was investigated starting with alkylation of **15** with $Br(CH_2)_3OTBS$ using $LiNH_2$ in NH_3/THF to afford acetylene alcohol **16** in 81% yield (Scheme 4). Hydrogenation of acetylene **16** to the cis olefin with Lindlar catalyst (Aldrich) in EtOAc was fast and competitive with further reduction of the cis olefin. Fortunately, addition of quinoline to the mixture successfully prevented over reduction. The alcohol was then converted to phosphonium salt **18** through iodide **17** in good yield. The phosphonium salt **18** was treated with NaHMDS to prepare the corresponding anion, which was subjected to Wittig reaction with aldehyde **19**[8] to afford olefin **20** in 94% yield. The reaction proceeded stereoselectively and cleanly. The ^1H NMR spectrum clearly showed high stereoselectivity (>95%) for the cis olefin and no abstraction of the methylene protons between the cis olefins. The TBS group was removed selectively and the resulting alcohol **21** was oxidatively converted to the methyl ester **22** by the standard three-step conversion. Finally, desilylation of the TBDPS group with TBAF furnished alcohol **4b** in 90% yield.

Acetylene **28**, the precursor of the vinylborane **3**, was synthesized by applying the methodology developed for synthesis of RvE1 (Scheme 5). In brief, alkylation of the EE ether derived from acetylene alcohol **5** with EtBr followed by hydrolysis of the EE group afforded racemic alcohol *rac*-**23**, which was subjected to asymmetric epoxidation[9] using $Ti(OPr)_4$/D-(−)-DIPT as a catalyst to afford, after chromatography, (*S*)-**23** and **24** in 48% and 46%

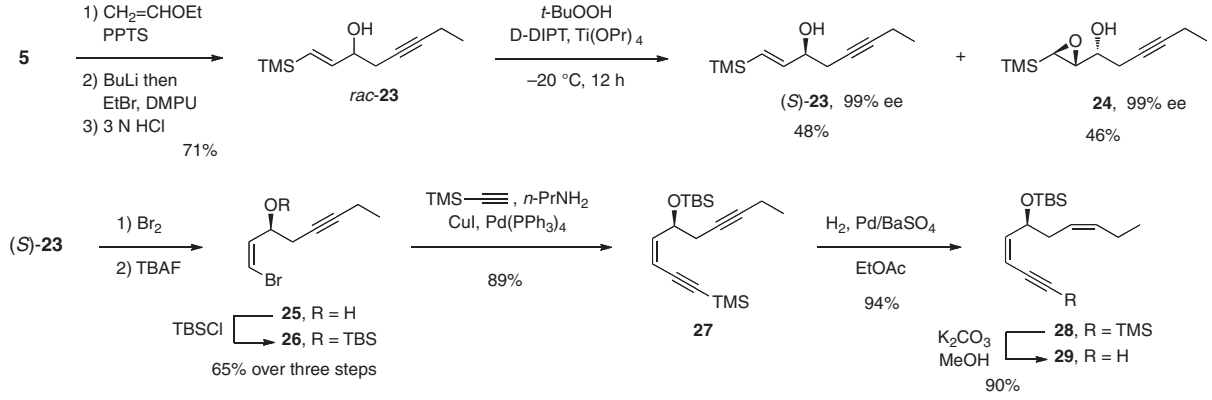


Scheme 4. Synthesis of **4b**.

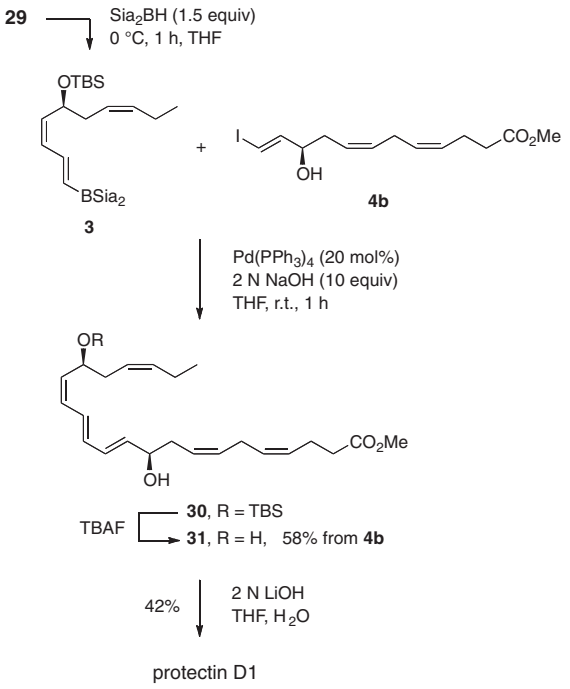
Table 1
Alkylation of **5** with **6**

Entry	Base (equiv)	CuX (equiv)	Additive (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	EtMgBr (2.2)	CuCl (0.1)	—	THF	Reflux	13	0
2	*i*-PrMgBr (2.2)	CuCl (0.1)	—	THF	Reflux	12	0
3	$CsCO_3$ (1.0)	CuI (1.0)	NaI (1.0)	DMF	rt	4	80[a]
4	$CsCO_3$ (1.0)	CuI (1.0)	Bu_4NI (1.0)	DMF	rt	21	93[b]

[a] NMR yield.
[b] Isolated yield.



Scheme 5. Synthesis of **29**, the precursor of **1**.



Scheme 6. Synthesis of protectin D1.

yields, respectively. High ee of 99% for each product was determined by ^{1}H NMR spectroscopy of the MTPA ester. Next, (*S*)-**23** was converted to cis olefin **25** stereoselectively by bromination at −78 °C followed by TBAF treatment.[10,11] The hydroxyl group of **25** was protected with TBSCl to produce TBS ether **26**, which upon Sonogashira reaction with TMS-acetylene produced acetylene **27** in good yield. Hydrogenation of **27** to cis olefin **28** was successful with $Pd/BaSO_4$ in EtOAc, whereas $Pd/BaSO_4$ deactivated with quinoline and Lindlar catalyst (Aldrich) used in Scheme 2 were found to proceed quite slowly. Finally, the TMS group was removed by K_2CO_3 in MeOH to afford the key intermediate **29** in 90% yield.

The final stage of the synthesis was summarized in Scheme 6, in which hydroboration of acetylene **29** with freshly prepared Sia_2BH (1.5 equiv) produced vinylborane **3**. Without isolation, **3** was subjected to Pd-catalyzed coupling with iodide **4b** in the presence of NaOH. The reaction completed within 1 h to afford alcohol **29**, which was treated with TBAF to afford diol **30** in 58%. Finally, hydrolysis with LiOH in aqueous THF afforded PD1. The ^{1}H NMR spectrum of PD1 synthesized was consistent with that reported in CD_3OD.[3a] The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were consistent with the structure.[12]

In summary, we established synthesis of the key intermediate **4b**, which was subjected to coupling reaction with **3** to afford PD1 stereoselectively. The synthesis in total was carried out without isomerization of the skipped diene moiety in 10-mg scale of **1**. The synthesis and the mild conditions would be applied to synthesis of other C22 metabolites.

Acknowledgment

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Supplementary data

Supplementary data (the ^{1}H NMR spectrum of protectin D1) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.152.

References and notes

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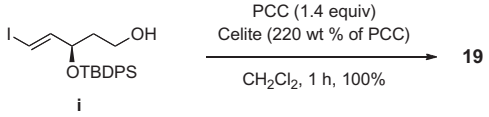
8. Prepared by PCC oxidation of the corresponding alcohol **i**, which was used for the synthesis of RvE1.[2]



i

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10. Epoxide **24** can be converted to the cis bromo olefin **25** according to the established procedure.[11] However, **24** was not used in the present synthesis of PD1 simply due to completion of the synthesis with **25** derived from (*S*)-**23**.
11. Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 2033–2036.
12. *Alcohol* **i** (*precursor of* **19**): $[\alpha]_D^{23}$+66 (*c* 0.632, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 9 H), 1.05–2.04 (m, 2 H), 3.56–3.78 (m, 2 H), 4.35 (q, *J* = 6 Hz, 1 H), 5.98 (d, *J* = 15 Hz, 1 H), 6.51 (dd, *J* = 15, 7 Hz, 1 H), 7.35–7.51 (m, 6 H), 7.62–7.77 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (−), 27.0 (+), 39.1 (−), 59.1 (−), 74.4 (+), 77.7 (+), 127.7 (+), 127.8 (+), 129.9 (+), 130.0 (+), 133.1 (−), 133.3 (−), 135.8 (+), 136.0 (+), 147.4 (+). *Alcohol* **21**: $[\alpha]_D^{24}$+11 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 9 H), 1.48–1.72 (m, 2 H), 2.09 (q, *J* = 7 Hz, 1 H), 2.16–2.30 (m, 1 H), 2.62 (t, *J* = 7 Hz, 1 H), 3.63 (t, *J* = 6.5 Hz, 2 H), 4.06–4.16 (m, 1 H), 5.20–5.52 (m, 4 H), 5.97 (dd, *J* = 14, 1 Hz, 1 H), 6.47 (dd, *J* = 14, 6.5 Hz, 1 H), 7.32–7.47 (m, 3 H), 7.57–7.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (−), 25.7 (−), 27.0 (+), 29.8 (−), 32.5 (−), 35.3 (−), 62.6 (−), 75.7 (+), 124.3 (+), 127.67 (+), 127.69 (+), 128.4 (+), 129.5 (+), 129.9 (+), 130.6 (+), 135.9 (+), 136.0 (+), 147.8 (+). *Iodide* **4b**: $[\alpha]_D^{23}$+15 (*c* 0.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26–2.42 (m, 6 H), 2.70–2.92 (m, 2 H), 3.67 (s, 3 H), 4.15 (q, *J* = 6 Hz, 1 H), 5.31–5.48 (m, 3 H), 5.52–5.64 (m, 1 H), 6.38 (dd, *J* = 14.5, 1.5 Hz, 1 H), 6.60 (dd, *J* = 14.5, 6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9 (−), 25.9 (−), 34.0 (−), 34.8 (−), 51.7 (+), 73.9 (+), 77.4 (+), 124.2 (+), 128.2 (+), 129.0 (+), 131.9 (+), 147.8 (+), 173.8 (−). *Acetylene* **29**: $[\alpha]_D^{23}$+15 (*c* 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 0.96 (t, *J* = 7.5 Hz, 3 H), 1.90–2.14 (m, 2 H), 2.15–2.37 (m, 2 H), 3.08–3.13 (m, 1 H), 4.59–4.74 (m, 1 H), 5.31–5.58 (m, 3 H), 5.88–6.01 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.8 (+), −4.4 (+), 14.3 (+), 20.8 (−), 25.9 (+), 35.5 (−), 70.9 (+), 79.9 (−), 82.4 (−), 107.3 (+), 124.3 (+), 133.8 (+), 148.6 (+). PD1 (**1**): UV (MeOH) λ_{max} 270 with shoulders 261 (s), 281 (s) nm (lit. [3a] 271 with shoulders 262 (s), 282 (s) nm); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.5 Hz, 3 H), 1.92–2.12 (m, 2 H), 2.20–2.50 (m, 8 H), 2.70–2.82 (m, 1 H), 2.84–2.95 (m, 1 H), 4.16–4.28 (m, 1 H), 4.54–5.64 (m, 1 H), 5.22–5.48 (m, 5 H), 5.50–5.61 (m, 2 H), 5.70–5.83 (m, 1 H), 6.10 (dt, *J* = 4.5, 11 Hz, 1 H), 6.14–6.36 (m, 2 H), 6.52 (dd, *J* = 14.5, 11 Hz, 1 H); ^{1}H NMR (500 MHz, CD_3OD) δ 0.93 (t, *J* = 7.5 Hz, 3 H), 1.95–2.10 (m, 2 H), 2.10–2.42 (m, 8 H), 2.76–2.90 (m, 2 H), 4.02–4.18 (m, 1 H), 4.50–5.60 (m, 1 H), 5.29–5.57 (m, 6 H), 5.64–5.78 (m, 2 H), 6.07 (dd, *J* = 11, 11 Hz, 1 H), 6.18–6.34 (m, 2 H), 6.50 (dd, *J* = 13, 11.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 18.5, 23.9, 26.0, 29.2, 29.8, 35.4, 67.8, 71.8, 123.6, 124.9, 128.2, 128.9, 129.2, 130.3, 130.5, 131.5, 133.3, 133.9, 135.5, 136.8, 175.6; ^{13}C NMR (75 MHz, CD_3OD) δ 13.6, 20.7, 23.0, 25.7, 29.8, 34.3, 35.4, 67.5, 72.0, 124.3, 125.5, 128.3, 129.0, 129.1, 129.6, 130.0, 130.4, 133.7, 133.8, 134.0, 137.0, 176.5; HR-MS (FAB) calcd for $C_{22}H_{31}O_4$ [(M−H)$^+$] 359.2222, found 359.2222.