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First total synthesis of 7(*S*),16(*R*),17(*S*)-Resolvin D2, a potent anti-inflammatory lipid mediator

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Abstract—The first total synthesis of 7(*S*),16(*R*),17(*S*)-Resolvin D2, a lipid mediator derived from docosahexaenoic acid, has been achieved. The key features of our synthetic strategy encompass a Co-salen hydrolytic kinetic resolution of a terminal epoxide combined with a chiral pool strategy.

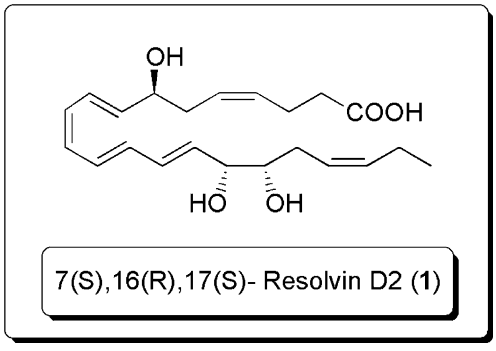

Figure 1.

Recently, Serhan and co-workers reported a new class of lipid mediators derived from docosahexaenoic acid that posses potent anti-inflammatory and immunoregulatory activities in the low pico to nanomolar range.[1–5] These new compounds are formed in vivo via cell–cell interaction and were named Resolvins (resolution phase interaction products).[6] Docosahexaenoic acid is highly enriched in brain, synapses and retina. Deficiencies of this ω-3 fatty acid are associated with Alzheimer disease, stroke, hyperactivity, schizophrenia and peroxisomal disorders.[7]

Serhan's work has established for the first time the molecular basis and the mechanism of ω-3 fatty acids immune protective action. Since from natural sources only tiny amounts are available they have to be prepared by total chemical synthesis in order to expedite

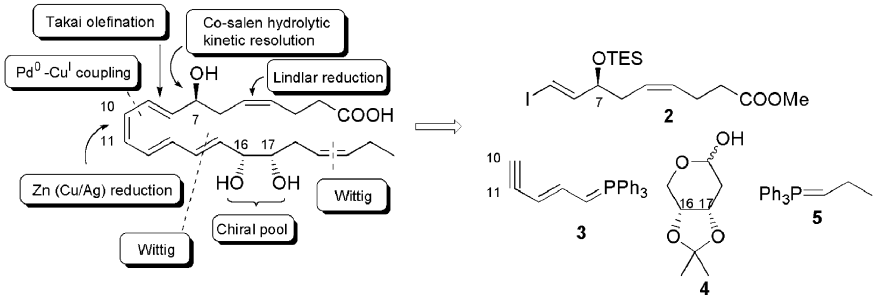

Figure 2.

Keywords: Resolvins; Hydrolytic kinetic resolution; Palladium catalyst; Takai reaction; Reduction.
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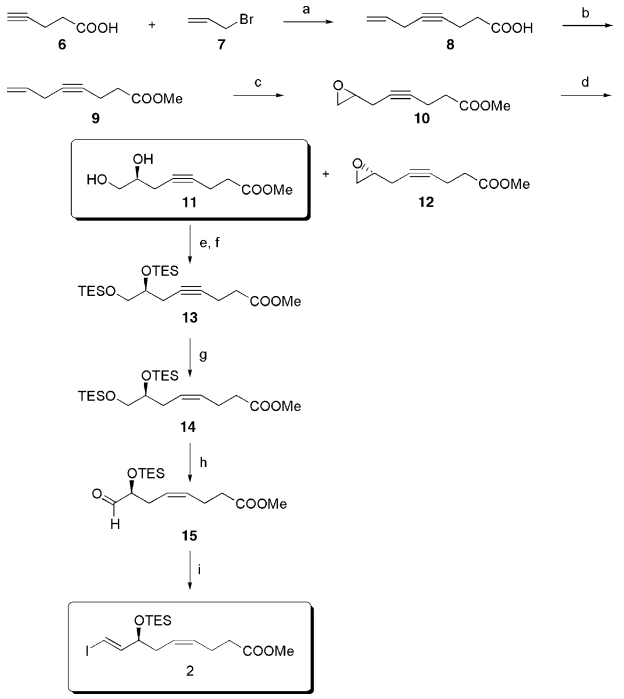


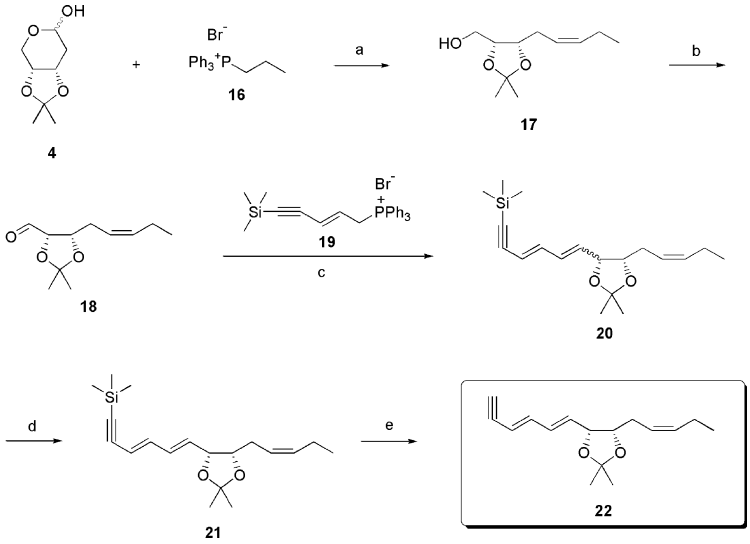
Scheme 1. Reagents and conditions: (a) MeMgBr, CuBr·Me_2S, THF, 0 °C to rt; (b) 10% TMSCl, MeOH, 2,2-dimethoxypropane, rt; (c) MCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C to rt; (d) (*R*,*R*)-(salen)Co(III)(OAc) catalyst, Et_2O/H_2O, 0 °C to rt; (e) flash chromatography separation; (f) TESCl, imidazole, Et_3N, DMF, 0 °C to rt; (g) Lindlar cat., Et_3N, hexane; (h) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C to rt; (i) $CrCl_2$, CHI_3, THF, 0 °C.

continuing biological and pharmacological investigations. These natural products could be novel lead structures for the development of drugs that inhibit PMN infiltration at the side of inflammation and to circumvent side effects of current anti-inflammatory drugs.[8,9]

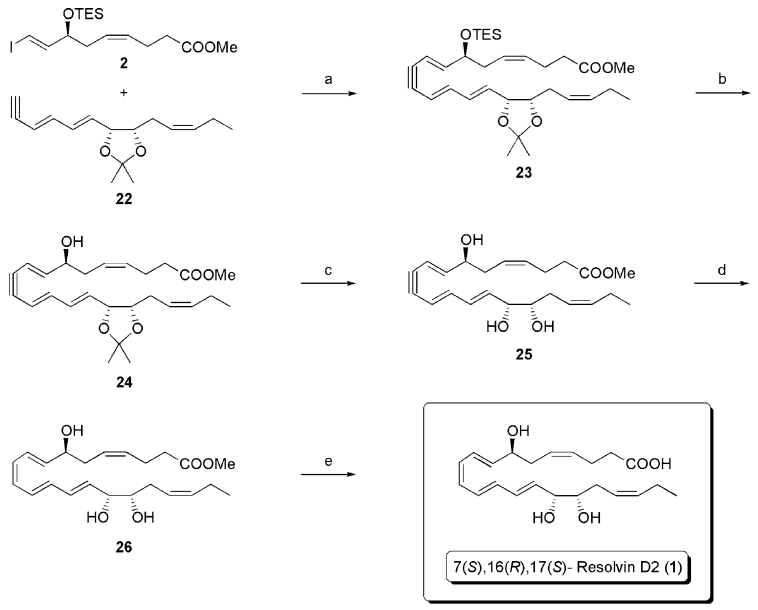
In this communication we wish to report the first total synthesis of 7(*S*),16(*R*),17(*S*)-Resolvin D2 (Fig. 1). As shown in the retrosynthetic scheme (Fig. 2), the chiral centre at C-7 was obtained via a Jacobsen hydrolytic kinetic resolution of a terminal epoxide whereas the centres at C-16 and C-17 arise from a chiral pool strategy.

The C_1–C_9 fragment was obtained from commercial pentynoic acid (**6**) as outlined in Scheme 1. Alkylation of the di-magnesium complex of pentynoic acid with allyl bromide (**7**) in THF, in the presence of a catalytic amount of CuBr–Me_2S,[10] afforded crude oct-7-en-4-ynoic acid (**8**) that was in situ esterified with 2,2-dimethoxypropane/MeOH/10% TMSCl[11] to give **9**. Epoxidation with 3-chloroperoxybenzoic acid in the presence of $NaHCO_3$ in CH_2Cl_2 at 0 °C furnished epoxide **10**. Jacobsen's hydrolytic kinetic resolution with H_2O in the presence of 5% (*R*,*R*)-salen-Co catalyst in Et_2O furnished the diol **11** with >94% ee as determined by chiral HPLC of the dibenzoate derivative.[12,13] Employing the (*S*,*S*)-salen-Co catalyst the enantiomer was obtained with >95% ee. Diol **11** was converted into the di-TES-ether **13** with 4 equiv TESCl/imidazole/Et_3N/DMF in 84% yield.[14] Lindlar reduction in hexane cleanly produced the *cis*-alkene **14** in quantitative yield. Chemoselective oxidation of the primary TES-ether using Swern reagent produced the aldehyde **15** in 54% yield.[15] The C_1–C_9 fragment (**2**) was obtained from **15** by Takai olefination $CrCl_2/CHI_3$/THF 0 °C in 50%.[16,17]

The C_{10}–C_{22} fragment was obtained in five steps from 3,4-*O*-isopropylidene-2-deoxy-D-ribose,[18] as outlined in Scheme 2. Wittig reaction with 2.5 equiv of phosphorane **5**, generated in situ from the phosphonium bromide **16** in THF and $NaN(TMS)_2$, produced the *cis*-alkene **17**,[19] containing 5–20% of the unwanted *trans*-isomer as identified by ^{13}C NMR (*cis*-isomer 124.0, 134.4 ppm, *trans*-isomer 124.4, 135.2 ppm). However, if the reaction was carried out in Et_2O at −78 °C followed by slowly warming up to 0 °C, **17** was produced without detectable amounts of the *trans*-isomer. Oxidation of **17** with PCC[20] in the presence of sodium acetate in CH_2Cl_2



Scheme 2. Reagents and conditions: (a) $NaN(TMS)_2$, Et_2O, −78 to 0 °C; (b) PCC, NaOAc, CH_2Cl_2; (c) BuLi, THF, −78 to 0 °C; (d) I_2, benzene, rt; (e) KF, 18-crown-6, DMF, rt.



Scheme 3. Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, *n*-$PrNH_2$, benzene, rt; (b) pyridinium, *p*-toluenesulfonate, CH_3OH, rt; (c) 1 N HCl, CH_3OH/H_2O, rt; (d) Zn(Cu/Ag), aq CH_3OH, 40 °C; (e) 1 N LiOH, THF, 0 °C, then EtOAc, satd NaH_2PO_4.

gave the isopropylidene aldehyde **18** in 70% yield after chromatography. Wittig reaction of **18** with 1.6 equiv of [2(*E*)-5-trimethylsilyl-2-penten-4-ynyl] triphenylphosphonium bromide/*n*-Bu–Li[21,22] in THF at −78 °C produced **20** as a mixture of *cis*- and *trans*-isomers. However, **20** could be easily isomerized with a catalytic amount of iodide in benzene to give the *trans*,*trans*-enyne **21**. Cleavage of the terminal TMS-group was achieved with KF and 5% 18-crown-6 in DMF in 83% isolated yield.[23]

Coupling of **2** with **22** in the presence of Pd^0/Cu^I,[21] furnished the Resolvin precursor **23** that was, without purification converted to **24** with pyridinium *p*-toluenesulfonate in MeOH. Removal of the isopropylidene group was best achieved with 1 N HCl in $MeOH/H_2O$ at room temperature for 15 min to give **25**. Stereospecific (*Z*)-reduction of the conjugate trienyne **25** to the tetraene **26** was carried out with fresh prepared Zn(Cu/Ag)[24] in 1:1 CH_3OH/H_2O at 40 °C for 5 h in 70% yield after HPLC purification. Mild alkaline hydrolysis of 7(*S*),16(*R*),17(*S*)-Resolvin D2 methyl ester (**26**) with 1 N LiOH in THF at 0 °C followed by acidification with NaH_2PO_4 in the presence of EtOAc gave 7(*S*),16(*R*),17(*S*)-Resolvin D2 (**1**) (Scheme 3).

In conclusion, a concise total synthesis of 7(*S*),16(*R*),17(*S*)-Resolvin D2 has been achieved,[25] making this novel lipid mediator available for further biological and pharmacological testing. The synthesis of other Resolvins, Docosatrienes and Neuroprotectins will be reported in due course.

Acknowledgements

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25. Satisfactory spectroscopic data were obtained for all compounds. Selected physical data: compound **11**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.9–3.8 (m, 1H), 3.8–3.7 (m, 1H), 3.7 (s, 3H), 3.6–3.5 (m, 1H), 2.6–2.4 (m, 4H), 2.4–2.3 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 172.72, 81.13, 76.79, 70.35, 65.53, 51.70, 33.59, 23.84, 14.73. Compound **2**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6 (dd, J = 14.4, 6.0 Hz, 1H), 6.2 (dd, J = 14.4, 1.2 Hz, 1H), 5.5–5.4 (m, 2H), 4.0–3.9 (m, 1H), 3.4 (s, 3H), 2.4–2.1 (m, 6H), 1.0 (t, J = 7.8 Hz, 9H), 0.6 (q, J = 7.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 173.18, 149.68, 130.98, 126.60, 76.67, 75.53, 51.31, 36.17, 34.33, 23.62, 7.25 (3C), 5.56 (3C). Compound **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.6–5.4 (m, 1H), 5.4–5.2 (m, 1H), 4.3–4.1 (m, 2H), 3.7–3.6 (m, 2H), 2.5–2.2 (m, 2H), 2.1–2.0 (m, 2H), 2.0 (br s, 1H), 1.5 (s, 3H), 1.4 (s, 3H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 134.40, 124.00, 108.20, 77.90, 76.87, 61.70, 28.03, 27.32, 25.32, 20.70, 13.86. Compound **21**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.6 (dd, J = 15.3, 11.1 Hz, 1H), 6.3 (dd, J = 15.3, 11.1 Hz, 1H), 5.8–5.7 (dd, J = 15.3, 7.8 Hz, 1H), 5.6 (d, J = 15.3 Hz, 1H), 5.5–5.4 (m, 1H), 5.4–5.2 (m, 1H), 4.6–4.5 (m, 1H), 4.2–4.1 (dt, J = 8.1, 6.3 Hz, 1H), 2.3–2.1 (m, 2H), 2.0 (m, 2H), 1.5 (s, 3H), 1.3 (s, 3H), 0.9 (t, J = 7.5 Hz, 3H), 0.2 (s, 9H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 141.65, 134.13, 132.12 (2C), 124.04, 112.05, 108.44, 104.15, 97.74, 78.59, 78.51, 28.67, 28.01, 25.42, 20.68, 13.91, 0.26 (3C). Compound **25**: ^{1}H NMR (d_6-benzene, 300 MHz): δ 6.7 (dd, J = 15.6, 11.1 Hz, 1H), 6.3–6.1 (m, 3H), 5.8 (dd, J = 15.6, 2.1 Hz, 1H), 5.7–5.6 (dd, J = 15.3, 6.3 Hz, 1H), 5.6–5.3 (m, 4H), 4.1–3.9 (m, 2H), 3.6–3.5 (m, 1H), 3.4 (s, 3H), 2.4–2.1 (m, 8H), 2.0 (m, 2H), 1.8–1.7 (br s, 1H), 1.7 (br s, 1H), 1.6 (br s, 1H), 0.9 (t, J = 7.5 Hz, 3H), 0.2 (s, 9H); ^{13}C NMR (d_6-benzene, 75.5 MHz): δ 173.47, 146.22, 141.56, 135.13, 135.07, 132.07, 131.64, 126.75, 125.48, 112.78, 110.59, 91.96, 90.53, 75.24, 74.66, 71.74, 51.38, 35.70, 34.06, 30.77, 23.40, 21.31, 14.60. HPLC/API–ES/MS (m/z): 411 $[M+Na^+]^+$. Compound **26**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.9–6.7 (m, 2H), 6.5–6.3 (m, 2H), 6.1–6.0 (m, 2H), 5.9–5.7 (m, 2H), 5.6–5.4 (m, 4H), 4.2 (m, 1H), 4.1–4.0 (m, 1H), 3.6 (s, 3H), 3.6–3.5 (m, 1H), 3.2–3.1 (br d, J = 4.8 Hz, 1H), 3.0 (br d, J = 4.8 Hz, 1H), 2.9–2.8 (br d, J = 5.1 Hz, 1H), 2.4–2.0 (m, 10H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 174.03, 138.75, 134.58, 134.02, 133.93, 132.28, 130.55, 129.87, 129.76, 128.47, 127.29, 126.12, 125.52, 75.30, 75.05, 71.86, 51.46, 35.67, 34.01, 30.84, 23.21, 20.85, 13.97. UV (EtOH) λ_{max} 289, 302, 316 nm. HPLC/API–ES/MS (m/z): 413 $[M+Na^+]^+$. Compound **1**: ^{1}H NMR (CD_3CN, 300 MHz): δ 6.9–6.7 (m, 2H), 6.5–6.3 (m, 2H), 6.1–6.0 (m, 2H), 5.9–5.7 (m, 2H), 5.6–5.4 (m, 4H), 4.3–4.1 (m, 1H), 4.1–4.0 (m, 1H), 3.6–3.5 (m, 1H), 2.5–2.0 (m, 8H), 1.0 (t, J = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75.5 MHz): δ 175.0, 139.81, 135.59, 135.03, 134.93, 133.30, 131.67, 130.90, 130.77, 129.50, 128.26, 127.15, 126.49, 76.29, 76.03, 72.88, 36.65, 31.84, 31.20, 24.13, 21.89, 15.04. UV (EtOH) λ_{max} 289, 302, 316 nm. HPLC/API–ES/MS (m/z): 399 $[M+Na^+]^+$.