Stereocontrolled Total Synthesis of (5*Z*,8*Z*,10*E*,12*R*,14*Z*)-12-Hydroxy-5,8,10,14-icosatetraenoic Acid [(12*R*)-HETE]

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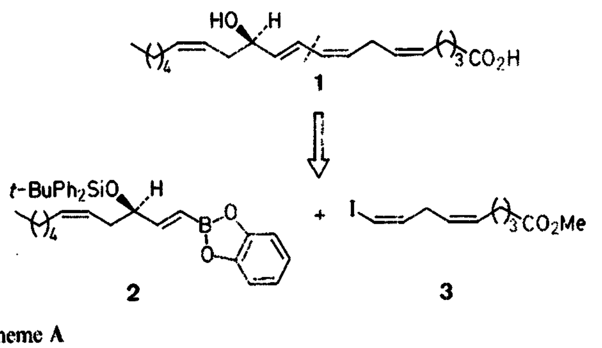
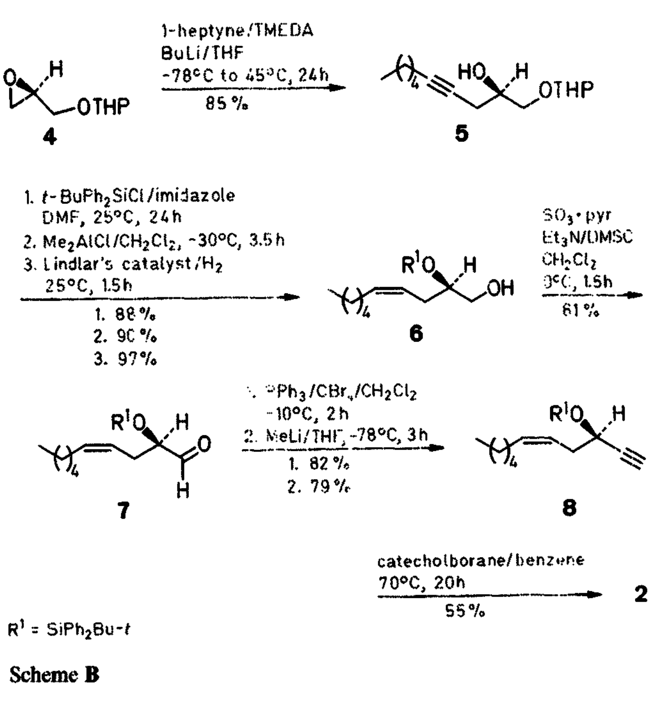
A stereocontrolled convergent synthesis of (12*R*)-HETE (**1**) by palladium(0)/thallium hydroxide mediated coupling of vinylborane **2** with the vinyl iodide **3** is reported.

(5*Z*,8*Z*,10*E*,12*R*,14*Z*)-12-Hydroxy-5,8,10,14-icosatetraenoic acid [(12*R*)-HETE, **1**] is an important and biologically active metabolite of arachidonic acid detected in several tissues.[1,2] In this communication we report a stereocontrolled total synthesis[3] of **1** via a palladium(0)/thallium hydroxide catalyzed reaction.[4]

A retrosynthetic analysis of (12*R*)-HETE (**1**) is shown in Scheme A. Thus, disconnection of the strategic bond C^9-C^{10} unravels the key intermediates **2** (vinylborane) and **3** (vinyl iodide) as subtargets for synthesis. Coupling of **2** and **3** by palladium(0)/thallium hydroxide catalysis[4] followed by deprotection was envisioned to lead to **1**.



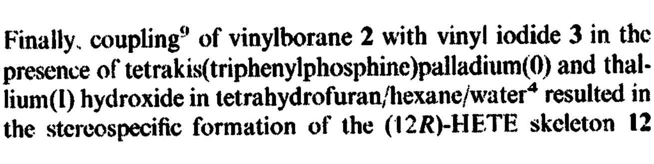
Scheme A



Scheme B

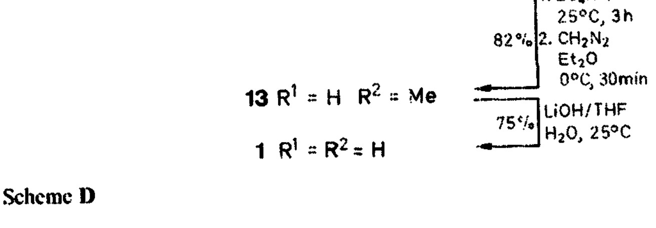
The construction of the vinylborane **2** is presented in Scheme B. Thus, regioselective opening of epoxide **4** with the anion derived from 1-heptyne and butyllithium resulted in the formation of acetylenic alcohol **5** in 85% yield. Silylation of **5** (88%) followed by selective removal of the tetrahydropyranyl protecting group was achieved by treatment with dimethylaluminum chloride[5] in dichloromethane at −30 °C leading to the corresponding primary alcohol (90%), which then underwent hydrogenation using Lindlar catalyst to give the olefinic compound **6** (97%). Oxidation by sulfur trioxide pyridine complex afforded the aldehyde **7** (81%). Conversion of **7** to the terminal acetylene **8** was accomplished by the Corey-Fuchs[6] procedure via the corresponding dibromoolefin (79% overall yield). Finally, addition[7] of catechol borane to **8** resulted in the formation of the rather sensitive vinylborane **2**, which was reacted further (*vide infra*) without isolation.

Construction of the other requisite key intermediate, vinyl iodide **3**, is shown in Scheme C. Bromination of alcohol **9**[8] followed by reaction with triphenylphosphine led to phosphonium salt **10** (95% yield). Condensation of the phosphorane derived from **10** and potassium bis(trimethylsilyl)amide with aldehyde **11** furnished stereoselectively the diene **3** (45%).



Scheme C

Finally, coupling[9] of vinylborane **2** with vinyl iodide **3** in the presence of tetrakis(triphenylphosphine)palladium(0) and thallium(I) hydroxide in tetrahydrofuran/hexane/water[4] resulted in the stereospecific formation of the (12*R*)-HETE skeleton **12**



Scheme D

(55%), from which (12*R*)-HETE methyl ester (**13**) and (12*R*)-HETE (**1**) were sequentially generated by fluoride-induced desilylation (82%) and saponification with lithium hydroxide (75%) (Scheme **D**).

The described synthesis provides a convenient route to (12*R*)-HETE (**1**) that could also deliver its enantiomer, (12*S*)-HETE,[10] by starting with the enantiomer of **4**.[11]

Petroleum ether used refers to boiling range 37–56 °C. ^{1}H-NMR were measured at 500 MHz.

(2*R*)-1-(Tetrahydro-2-pyranyloxy)-4-decyn-2-ol (5):

To a stirred solution of 1-heptyne (5.78 g, 60.2 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (6.99 g, 60.2 mmol) in THF (10 mL) at −30 °C is added a solution of BuLi (1.6 M in hexanes, 30.1 mL, 48.2 mmol) dropwise. After stirring for 5 min, the mixture is warmed to 0 °C and stirred at that temperature for 30 min. Cooling to −78 °C is followed by dropwise addition of epoxide **4** (3.80 g, 24.1 mmol) in THF (14 mL). The temperature is raised to 55 °C and stirring continued for 24 h (TLC monitoring). After cooling to 0 °C, water (24 mL) is added, and the mixture transferred to a separatory funnel, diluted with Et_2O (250 mL) and washed with brine (25 mL). The organic phase is dried ($MgSO_4$), concentrated and subjected to flash column chromatography (silica gel, 40% Et_2O in petroleum ether) furnishing **5** as a slightly yellow oil; yield: 5.03 g (85%); $R_f = 0.30$ (silica gel, 30% Et_2O in petroleum ether).

IR (neat): ν = 3440, 2928, 2860, 1458, 1380, 1352, 1260, 1205, 1130, 1042, 972, 910, 870, 815 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.82 (t, 1.5 H, J = 7.05 Hz, CH_3); 0.86 (t, 1.5 H, J = 7.05 Hz, CH_3); 1.20–1.47 (m, 7 H, CH_2 + OH); 1.54–1.79 (m, 7 H, CH_2 + OH); 2.07 (m, 1 $H_{propargyl}$); 2.11 (m, 1 $H_{propargyl}$); 2.33 (m, 1 $H_{propargyl}$); 2.40 (m, 1 $H_{propargyl}$); 3.47 (m, 1 H, OCH_2); 3.52 (m, 1 H, OCH_2); 3.74 (dd, 0.5 H, J = 3.63 Hz); 3.77 (dd, 0.5 H, J = 3.61 Hz); 3.80 (m, 0.5 H, OCH); 3.86 (m, 0.5 H, OCH); 4.48 (m, 0.5 H_{acetal}); 4.53 (m, 0.5 H_{acetal}).

HRMS: *m*/*z*, $C_{15}H_{28}O_3$ calc.: 254.1881; found: 255.1962 (M^+ + 1).

(2*R*,4*Z*)-2-(*tert*-Butyldiphenylsiloxy)-4-decen-1-ol (6):

(2R)-1-(Tetrahydro-2-pyranyloxy)-2-(tert-butyldiphenylsiloxy)-4-decene:

Alcohol **5** (5 g, 20.3 mmol), imidazole (3.04 g, 44.7 mmol) and *tert*-butyl chlorodiphenylsilane (8.38 g, 30.5 mmol) are dissolved in DMF (200 mL) and stirred under Ar at ambient temperature for 24 h. After 24 h (TLC monitoring) water (200 mL) is added and the product extracted with Et_2O (500 mL). The organic phase is dried ($MgSO_4$) and evaporated to dryness. The crude product is subjected to flash column chromatography (silica gel, 5% Et_2O in petroleum ether) to give the corresponding silyl ether as a yellow oil; yield: 8.79 g (88%); $R_f = 0.22$ (silica gel, 5% Et_2O in petroleum ether).

IR (neat): ν = 3078, 3052, 2940, 2860, 1962, 1900, 1828, 1597, 1471, 1430, 1392, 1368, 1265, 1205, 1115, 1038, 1000, 942, 910, 877, 824, 741, 705 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.86 (t, 1.5 H, J = 7.05 Hz, CH_3); 0.89 (t, 1.5 H, J = 7.05 Hz, CH_3); 1.05 (s, 4.5 H, $C(CH_3)_3$); 1.11 (s, 4.5 H, $C(CH_3)_3$); 1.23–1.49 (m, 6 H, CH_2), 1.53–1.79 (m, 6 H, CH_2); 2.02 (m, 1 $H_{propargyl}$); 2.11 (m, 1 $H_{propargyl}$); 2.28 (m, 1 $H_{propargyl}$); 2.38 (m, 1 $H_{propargyl}$); 3.39 (m, 1 H, CH_2OTHP + THP); 3.47 (m, 1 H, CH_2OTHP + THP); 3.72 (m, 1 H, CH_2OTHP + THP); 3.83 (m, 1 H, CH_2OTHP + THP); 3.99 (m, 0.5 H, CHOSi); 4.01 (m, 0.5 H, CHOSi); 4.48 (t, 0.5 H_{acetal}, J = 3.25 Hz); 4.54 (t, 0.5 H_{acetal}, J = 3.19 Hz); 7.31 (m, 3 H_{arom}); 7.38 (m, 3 H_{arom}); 7.69 (m, 2 H_{arom}); 7.78 (m, 2 H_{arom}).

HRMS: *m*/*z*, $C_{31}H_{44}O_3Si$ calc.: 492.3063; found: 510.3401 (M^+ + NH_4).

(2R)-2-(tert-Butyldiphenylsiloxy)-4-decen-1-ol:

The silyl ether obtained above (8.65 g, 17.6 mmol) is dissolved in CH_2Cl_2 (60 mL) at −30 °C, and added to a solution of Me_2AlCl (1 M in CH_2Cl_2, 35.2 mL, 35.2 mmol) dropwise. After stirring for 3.5 h at −30 °C, the mixture is warmed to r.t. and stirred for 3.5 h (TLC monitoring). After cooling to −20 °C, sat. $NaHCO_3$ solution (40 mL) is added dropwise, the mixture diluted with Et_2O (250 mL), and stirred at ambient temperature for 4 h. The organic layer is diluted further with Et_2O (250 mL), washed with H_2O (40 mL), and brine (40 mL). The organic phase is dried ($MgSO_4$), concentrated and subjected to flash column chromatography (silica gel, 20% Et_2O in petroleum ether) to afford the corresponding primary alcohol as a colorless oil; yield: 6.46 g (90%); $R_f = 0.29$ (silica gel, 20% Et_2O in petroleum ether); $[\alpha]_D^{20}$ −24.88° (c = 2.13, $CHCl_3$).

IR (neat): ν = 3470, 3075, 2938, 2860, 1962, 1895, 1828, 1592, 1470, 1430, 1392, 1364, 1122, 1048, 880, 828, 821, 740, 705 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.87 (t, 3 H, J = 7.04 Hz, CH_3); 1.07 (s, 9 H, t-C_4H_9); 1.25–1.44 (m, 6 H, CH_2), 1.85 (t, 1 H, J = 6.06 Hz, OH); 2.05 (m, 2 $H_{propargyl}$); 2.30 (m, 1 $H_{propargyl}$); 2.42 (m, 1 $H_{propargyl}$); 3.64 (t, 2 H, J = 5.04, CH_2O); 3.89 (m, 1 H, CHOSi); 7.37 (m, 6 H_{arom}); 7.68 (m, 4 H_{arom}).

HRMS: *m*/*z*, $C_{26}H_{36}O_2Si$ calc.: 408.2481; found: 426.2826 (M^+ + NH_4).

(2R,4Z)-2-(tert-Butyldiphenylsiloxy)-4-decen-1-ol:

The above alcohol (6.46 g, 15.8 mmol) is dissolved in hexane (160 mL) and stirred under a H_2 atmosphere for 1.5 h (TLC monitoring) in the presence of Lindlar catalyst (1.94 g). Filtration through a celite pad followed by concentration and flash column chromatography (silica gel, 10% Et_2O in petroleum ether) gives **6** as colorless oil; yield: 6.28 g (97%); $R_f = 0.46$ (silica gel, 20% Et_2O in petroleum ether); $[\alpha]_D^{20}$ −33.84° (c = 3.57, $CHCl_3$).

IR (neat): ν = 3480, 3080, 3062, 3010, 2940, 1965, 1898, 1828, 1595, 1478, 1432, 1398, 1370, 1270, 1192, 1115, 978, 829, 742, 708 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.72 (t, 3 H, J = 7.23 Hz); 0.94 (s, 9 H, t-C_4H_9); 1.01–1.15 (m, 6 H, CH_2); 1.67 (m, 3 H, 2 H_{allyl} + OH); 2.14 (m, 1 H_{allyl}); 3.05 (m, 1 H_{allyl}); 3.38 (m, 2 H, CH_2O); 3.65 (m, 1 H, CHOSi); 5.07 (m, 1 H_{olefin}); 5.21 (m, 1 H_{olefin}); 7.25 (m, 6 H_{arom}); 7.55 (m, 4 H_{arom}).

HRMS: *m*/*z*, $C_{26}H_{38}O_2Si$ calc.: 410.2643; found: 428.2980 (M^+ + NH_4).

(2*R*,4*Z*)-2-(*tert*-Butyldiphenylsiloxy)-4-decenal (7):

Alcohol **6** (6.28 g, 15.3 mmol) and Et_3N (7.73 g, 76.6 mmol) are dissolved in DMSO and CH_2Cl_2 (1:1, 78 mL) and stirred at 0 °C. SO_3 · Pyridine complex (12.18 g, 76.6 mmol) is added and stirring is continued at 0 °C for 1.5 h (TLC monitoring). The mixture is diluted with Et_2O (400 mL), and washed with H_2O (100 mL), and brine (50 mL) before drying ($MgSO_4$) and evaporation. Flash column chromatography (silica gel, 5% Et_2O in petroleum ether) gives pure **7** as a slightly yellow oil; yield: 5.06 g (81%); $R_f = 0.52$ (silica gel, 5% Et_2O in petroleum ether); $[\alpha]_D^{20}$ −15.04° (c = 2.44, $CHCl_3$).

IR (neat): ν = 3078, 3050, 3010, 2980, 2960, 2860, 2720, 1965, 1900, 1828, 1740, 1590, 1472, 1430, 1395, 1390, 1363, 1112, 957, 827, 740, 707 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.85 (t, 3 H, J = 3.69 Hz, CH_3); 1.09 (s, 9 H, t-C_4H_9); 1.26 (m, 6 H, CH_2); 1.89 (m, 2 H_{allyl}); 2.33 (m, 1 H_{allyl}); 2.41 (m, 1 H_{allyl}); 4.03 (m, 1 H, CHOSi); 5.35 (m, 1 H_{olefin}); 5.45 (m, 1 H_{olefin}); 7.36 (m, 6 H_{arom}); 7.63 (m, 4 H_{arom}); 9.53 (d, 1 H, J = 1.59 Hz, CHO).

HRMS: *m*/*z*, $C_{26}H_{36}O_2Si$ calc.: 408.2497; found: 426.2835 (M^+ + NH_4).

(3*R*,5*Z*)-3-(*tert*-Butyldiphenylsiloxy)-5-undecen-1-yne (8):

(3R,5Z)-3-(tert-Butyldiphenylsiloxy)-1,1-dibromo-1,5-undecadiene: To a stirred solution of CBr_4 (9.03 g, 27.3 mmol) in CH_2Cl_2 (10 mL) at −20 °C is added dropwise a solution of Ph_3P (12.34 g, 47.1 mmol) in CH_2Cl_2 (10 mL). After stirring for 30 min the aldehyde **7** (5.06 g, 12.4 mmol) is added dropwise in CH_2Cl_2 (11 mL). The mixture is allowed to reach r.t. over a period of 3 h at which time the reaction is complete (TLC monitoring). Concentration, followed by flash column chromatography (silica gel, 5% Et_2O in petroleum ether) affords the corresponding dibromoolefin as a colorless oil; yield: 5.87 g (82%); $R_f = 0.26$ (silica gel, petroleum ether); $[\alpha]_D^{20}$ +2.44° (c = 3.36, $CHCl_3$).

IR (neat) ν = 3078, 3057, 3020, 2962, 2938, 2860, 1960, 1895, 1822, 1622, 1595, 1477, 1430, 1392, 1366, 1288, 1117, 1077, 1005, 943, 825, 740, 703 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 0.87 (t, 3 H, J = 6.89 Hz, CH_3); 1.06 (s, 9 H, t-C_4H_9); 1.18–1.32 (m, 6 H, CH_2); 1.91 (q, 2 H_{allyl}, J = 6.97 Hz); 2.23–2.36 (m, 2 H_{allyl}); 4.36 (q, 1 H, J = 6.21 Hz, CHOSi); 5.37 (m, 1 H_{olefin}); 5.44 (m, 1 H_{olefin}); 6.39 (d, 1 H_{olefin}, J = 8.14 Hz); 7.30 (M, 6 H_{arom}); 7.66 (m, 4 H_{arom}).

HRMS: *m*/*z*, $C_{27}H_{36}Br_2O$ calc.: 562.0903; found: 580.1246 (M^+ + NH_4).

(3R,5Z)-3-(tert-Butyldiphenylsiloxy)-5-undecen-1-yne:
To the above dibromoolefin (5.87 g, 10.2 mmol) in CH_2Cl_2 (50 mL) at -78 °C is added dropwise a solution of MeLi (1.4 M in Et_2O 15.2 mL, 21.3 mmol). After stirring for 3 h at -78 °C (TLC monitoring) the mixture is allowed to reach 0 °C and quenched with successive additions of water (20 mL) and Et_2O (350 mL). The organic phase is washed with sat. NH_4Cl solution (20 mL), dried ($MgSO_4$) and concentrated. Flash column chromatography (silica gel, 1 % Et_2O in petroleum ether gives pure **8** as a slightly yellow oil; yield: 3.35 g (79 %); $R_f = 0.38$ (silica gel, 1 % Et_2O in petroleum ether); $[\alpha]_D^{20}$ 12.41° ($c = 0.83$, $CHCl_3$).

IR (neat): $\nu = 3318, 3080, 3058, 3021, 2939, 2464, 2120, 1965, 1890, 1835, 1595, 1477, 1432, 1399, 1347, 1125, 946, 827, 742, 705\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.85$ (t, 3 H, $J = 7.8$ Hz, CH_3); 1.07 (s, 9 H, t-C_4H_9); 1.11–1.50 (m, 6 H, CH_2); 1.87 (m, 2 H_{allyl}); 2.29 (d, 1 H, $J = 1.82$ Hz, C≡CH); 2.39 (t, 2 H_{allyl}, $J = 6.59$ Hz); 4.31 (m, 1 H, CHOSi); 5.41 (m, 2 H_{olefin}); 7.35 (m, 6 H_{arom}); 7.72 (m, 4 H_{arom}).

HRMS: m/z, $C_{27}H_{36}OSi$ calc.: 404.2543; found: 422.2883 ($M^+ + NH_4$).

(4-Iodo-3-butenyl)triphenylphosphonium Bromide (10):

1-Bromo-4-iodo-3-butene:
To a stirred solution of alcohol **9** (2.65 g, 13.4 mmol) and CBr_4 (5.76 g, 17.4 mmol) in CH_2Cl_2 (90 mL) at -30 °C is added Ph_3P (4.90 g, 18.7 mmol). The mixture is allowed to reach 0 °C and stirred at 0 °C for 2 h (TLC monitoring). Concentration followed by flash column chromatography (silica gel, petroleum ether) affords the expected bromide; yield: 3.03 g (87 %); $R_f = 0.65$ (silica gel, petroleum ether).

IR (neat): $\nu = 3079, 2977, 1619, 1442, 1328, 1290, 1268, 1218, 1172, 938, 805, 707, 659, 630\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.71$ (q, 2 H_{allyl}, $J = 6.79$); 3.41 (t, 2 H, $J = 6.88$ Hz, CH_2Br); 6.27 (dd, 1 H_{olefin}, $J = 7.39, 6.69$ Hz); 6.39 (d, 1 H_{olefin}, $J = 7.47$).

HRMS: $m/z = C_4H_6BrI$ calc.: 259.8703; found: 260.8782 ($M^+ + 1$).

(4-Iodo-3-butenyl)triphenylphosphonium Bromide:

The above bromide (3 g, 11.5 mmol) and Ph_3P (4.53 g, 17.3 mmol) in CH_3CN (23 mL) are heated at reflux for 24 h (TLC monitoring) at which time the reaction is complete. Concentration followed by repeated washings with petroleum ether and drying under reduced pressure (P_2O_5) furnishes the phosphonium salt **10** as an off white powder; yield: 5.7 g (95 %); mp 175–177 °C (CH_3CN/petroleum ether).

IR ($CHCl_3$): $\nu = 3058, 2960, 2877, 2000, 1920, 1825, 1611, 1592, 1490, 1440, 1277, 1191, 1115, 997, 800, 730\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 2.50$ (m, 2 H_{allyl}); 4.04 (m, 2 H, CH_2P); 6.22 (d, 1 H_{olefin}, $J = 7.84$ Hz); 6.81 (dt, 1 H_{olefin}, $J = 6.94, 7.02$ Hz); 7.68 (m, 6 H_{arom}); 7.78 (m, 3 H_{arom}); 7.88 (m, 6 H_{arom}).

HRMS: m/z; $C_{22}H_{21}BrIP$ calc.: 521.962; found: 443.0426 ($M^+ - Br$).

2-[(1E,3R,5Z)-3-(*tert*-Butyldiphenylsiloxy)-1,5-undecaen-1-yl]-1,3,2-benzodioxaborole (2):

To a magnetically stirred solution of acetylene **8** (263 mg, 0.65 mmol) in benzene (9 mL) is added at r.t. a solution of catechol borane (1 M in THF, 3.2 mL, 3.2 mmol). The temperature is raised to 70 °C and stirring continued for 20 h (TLC monitoring). The mixture is cooled to 25 °C diluted with Et_2O (100 mL) and washed with H_2O (5 mL). Drying ($MgSO_4$) followed by concentration gives the vinyl borane **2** as a brownish waxy solid (187 mg, 55 %), which is used directly for the next step; yield: 187 mg (55 %); $R_f = 0.39$ (silica gel, 50 % Et_2O in petroleum ether).

HRMS: m/z, $C_{33}H_{41}BO_3Si$ calc.: 524.2923; found: 542.3264 ($M^+ + NH_4$).

Methyl (5Z,8Z)-9-Iodo-5,8-nonadienoate (3)

To a cold (-78 °C) magnetically stirred solution of phosphonium salt **10** (1.31 g, 2.51 mmol) in THF (4 mL) is added dropwise a solution of $KN(SiMe_3)_2$ (0.5 M in toluene, 5.3 mL, 2.65 mmol) dropwise. After stirring for 30 min, the aldehyde **11** (391 mg, 3.01 mmol) is added dropwise in THF (4 mL). The mixture is stirred for 1 h at -78 °C (TLC monitoring) and the reaction mixture allowed to reach 0 °C and the stirring continued for 15 min (TLC monitoring). The mixture is quenched with H_2O (10 mL) and transferred to a separatory funnel, where it was diluted with Et_2O (200 mL) and washed with brine (10 mL). The organic phase is dried ($MgSO_4$), concentrated and subjected to flash column chromatography (silica gel, 10 % Et_2O in petroleum ether) furnishing **3** as a slightly yellow oil; yield: 332 mg (45 %); $R_f = 0.42$ (silica gel, 10 % Et_2O in petroleum ether).

IR (neat): $\nu = 3072, 3018, 2940, 2860, 1742, 1608, 1438, 1370, 1313, 1235, 1172, 1090, 1020, 887, 690\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 1.69$ (t, 3 H, $J = 7.43$ Hz, CH_3); 2.11 (q, 2 H_{allyl}, $J = 7$ Hz); 2.29 (t, 2 H, $J = 7.55$, CH_2CO); 2.85 (t, 2 $H_{bisallyl}$), $J = 5.58$ Hz); 3.65 (s, 3 H, OCH_3); 5.41 (m, 2 H_{olefin}); 6.11 (m, 1 H_{olefin}); 6.20 (d, 1 H_{olefin}), $J = 7.27$ Hz).

HRMS: m/z, $C_{10}H_{15}IO_2$ calc.: 294.0125; found: 295.0203 ($M^+ + 1$).

Methyl (5Z,8Z,10E,12R,14Z)-12(*tert*-Butyldiphenylsiloxy),5,8,10,14-icosatetraenoate (12):

To a 250 mL round-bottom flask equipped with a magnetic stirrer is added **2** (285 mg, 0.65 mmol in 5 mL THF) followed by addition of hexane (82 mL). The solution is degassed by bubbling Ar for 15 min before adding a degassed solution of 10 % aq. TlOH (6.17 mL, 2.79 mmol) with vigorous stirring over a period of 3 min at r.t. A THF solution (1 mL) of **3** (137 mg, 0.46 mmol) is then added, followed by the immediate addition of Pd $(PPh_3)_4$ (133 mg, 0.12 mmol) in THF (2 mL). The reaction mixture is stirred for 0.5 h (TLC monitoring) and then transferred to a separatory funnel, diluted with Et_2O (150 mL) and washed with brine (15 mL). The organic phase is dried ($MgSO_4$) and filtered through a celite pad, concentrated, and subjected to flash column chromatography (silica gel, 10 % Et_2O in petroleum ether) furnishing **12** as a colorless oil; yield: 53 mg (55 %). $R_f = 0.52$ (silica gel 10 % Et_2O in petroleum ether); $[\alpha]_D^{20}$ +16.51° ($c = 0.10$, $CHCl_3$).

UV (MeOH): $\lambda_{max} = 325, 229, 210$ nm.

IR (neat): $\nu = 3078, 3012, 2958, 2925, 2855, 1745, 1465, 1430, 1365, 1115, 1060, 828, 740, 705\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): 0.86 (t, 3 H, $J = 7.2$ Hz, CH_3); 1.07 (s, 9 H, t-C_4H_9); 1.20–1.90 (m, 8 H, CH_2); 2.06 (m, 4 H_{allyl}); 2.28 (m, 4 H, 2 H_{allyl}) + CH_2CO); 2.77 (t, 2 $H_{bisallyl}$, $J = 5.57$ Hz); 3.65 (s, 3 H, OCH_3); 4.22 (m, 1 H, CHOSi); 5.25–5.40 (m, 5 H_{olefin}); 5.63 (dd, 1 H_{olefin}, $J = 15.05, 6.39$ Hz); 5.88 (t, 1 H_{olefin}, $J = 9.82$ Hz); 6.21 (dd, 1 H_{olefin}, $J = 15.08, 10.62$ Hz); 7.31 (m, 6 H_{arom}); 7.68 (m, 4 H_{arom}).

HRMS: m/z, $C_{37}H_{52}O_3Si$ calc.: 572.8596; found: 573.8456 ($M^+ + 1$).

Methyl (5Z,8Z,10E,12R,14Z)-12-Hydroxy-5,8,10,14-icosatetraenoate (13):

Compound **12** (30 mg, 0.05 mmol) is azeotropically dried with benzene and dissolved in dry THF (1.0 mL). The magnetically stirred solution is treated at 25 °C with Bu_4NF (1 M solution in THF, 65 μL, 0.065 mmol). Stirring is continued at ambient temperature for 3 h while the reaction is monitored by TLC. The mixture is then diluted with Et_2O (100 mL) and washed with pH 6 phosphate buffer (1 mL). The organic layer is separated and washed with brine (1 mL), dried ($MgSO_4$), filtered and concentrated. Et_2O (25 mL) is added, followed by cooling to 0 °C and diazomethane treatment to give, after concentration, the crude product, which is subjected to flash column chromatography (silica gel, 30 % Et_2O in petroleum ether) furnishing pure **13** as a colorless oil; yield: 15 mg (90 %); $R_f = 0.40$ (silica gel, 30 % Et_2O in petroleum ether); $[\alpha]_D^{20}$ -1.25° ($c = 0.25$, $CHCl_3$).

IR (neat): $\nu = 3420, 3020, 2960, 2940, 2920, 2860, 1745, 1250\ cm^{-1}$.

UV (MeOH): $\lambda_{max} = 235$ nm.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 0.85$ (t, 3 H, $J = 7$ Hz, CH_3); 1.20–1.90 (m, 9 H, CH_2 + OH); 2.05 (m, 4 H_{allyl}); 2.30 (m, 4 H, CH_2CO + 2 H_{allyl}); 2.92 (t, 2 $H_{bisallyl}$, $J = 6$ Hz); 3.65 (s, 3 H, OCH_3); 4.21 (m, 1 H, C$\underline{H}$OH); 5.32–5.62 (m, 5 H_{olefin}); 5.72 (dd, 1 H_{olefin}, $J = 15.1, 6.8$ Hz); 5.98 (t, 1 H_{olefin}, $J = 10.8$ Hz); 6.55 (dd, 1 H_{olefin}, $J = 15.1, 10.8$ Hz).

HRMS: m/z, $C_{21}H_{34}O_3$ calc.: 334.2499; found: 334.2479 (M^+).

(5Z,8Z,10E,12R,14Z)-12-Hydroxy-5,8,10,14-icosatetraenoic Acid [(12R)-HETE, 1]:

Alkaline hydrolysis of the methyl ester **12** (15 mg, 0.04 mmol) with LiOH as previously described for its enantiomer[10] gives (12*R*)-HETE (**1**); yield: 10.7 g (75 %).

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