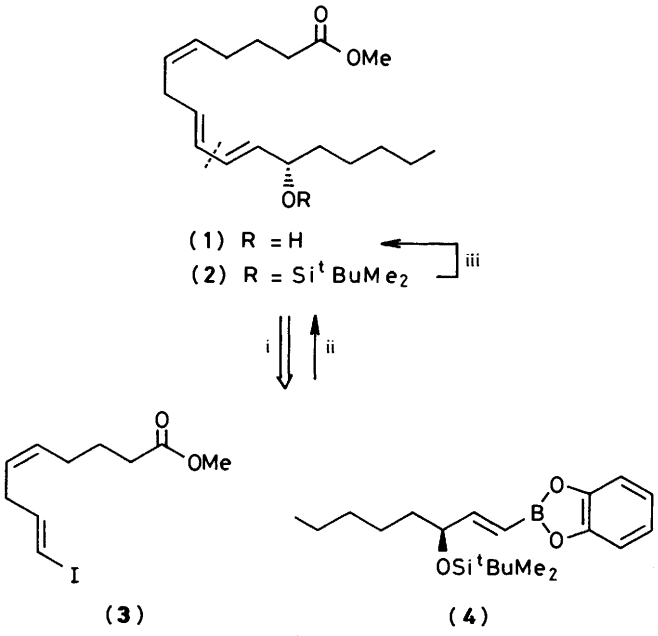
Stereocontrolled Total Synthesis of Methyl 12(*S*)-Hydroxy-5*Z*,8*E*,10*E*-heptadecatrienoate

K. C. Nicolaou,* N. A. Stylianides, and J. Y. Ramphal
Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

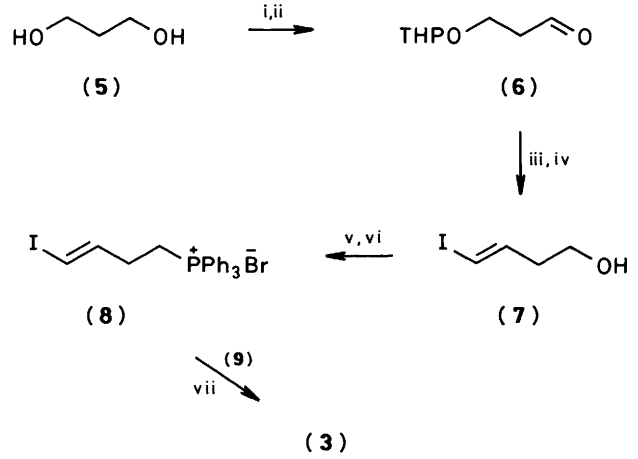
A short and stereocontrolled synthesis of methyl (12*S*,5*Z*,8*E*,10*E*)-12-hydroxyheptadeca-5,8,10-trienoate (**1**), based on a Pd^0–TlOH catalysed coupling reaction of the vinyl iodide (**3**) and the vinylborane (**4**) is described.

(12*S*,5*Z*,8*E*,10*E*)-12-Hydroxyheptadeca-5,8,10-trienoic acid (HHT) is a major metabolite of arachidonic acid (AA) formed by incubation of AA with washed human platelets in the presence of oxygen.[1,2] Here we report the first stereocontrolled total synthesis of HHT methyl ester (**1**) (see Scheme 1) *via* a Pd^0–TlOH catalysed coupling reaction of a vinyl iodide and a vinylborane according to Kishi's procedure.[3]



Scheme 1. *Reagents:* i, Retrosynthetic analysis; ii, TlOH (4.4 equiv.), $Pd(Ph_3P)_4$ (0.4 equiv.), H_2O–THF–hexane, (1:1:1), 25 °C, 15 min, 45%; iii, Bu_4NF (1.2 equiv.), THF, 0 °C, 2 h, 85%.

Retrosynthetic analysis of (**1**) led to disconnection of the C(9)–C(10) bond, revealing the fragments (**3**) and (**4**) (Scheme 1) as potential precursors for the synthesis of (**1**). The construction of the intermediate (**3**) is presented in Scheme 2. Thus, standard manipulation of propane-1,3-diol (**5**) led to the aldehyde (**6**) which was treated with CHI_3–$CrCl_2$[4] to furnish, after deprotection, the vinyl iodide (**7**)† in 65% overall yield (*trans-cis* isomers *ca.* 5:1, mixture carried through the sequence and separated at the product stage). Bromination of (**7**) (with CBr_4–PPh_3) followed by phosphonium salt formation led to compound (**8**) in 85% overall yield. Finally, condensation of the ylide derived from (**8**) and $KN(SiMe_3)_2$ with the aldehyde (**9**)‡ gave the requisite vinyl iodide (**3**)§ in 90% yield.



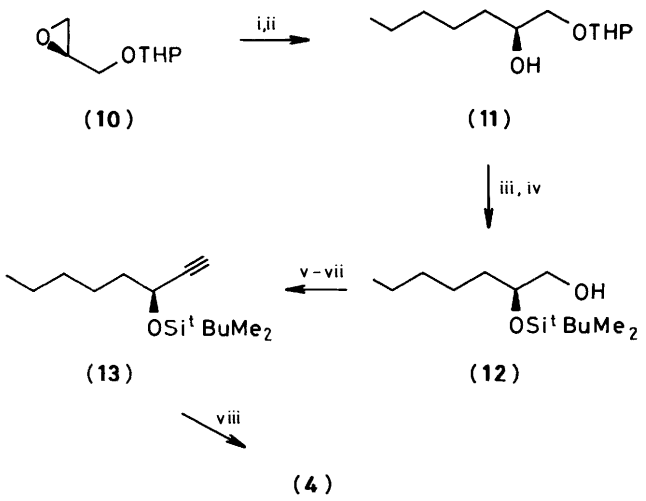
Scheme 2. *Reagents:* i, DHP (1.0 equiv.), pTSA (0.1 equiv.), CH_2Cl_2, 0 °C, 3 h, 70%; ii, SO_3-pyr (3.0 equiv.), Et_3N (5.0 equiv.), DMSO–CH_2Cl_2 (1:1), 0 °C, 1 h, 90%; iii, $CrCl_2$ (5.0 equiv.), CHI_3 (2.0 equiv.), THF, 0 °C, 1 h, 65%; iv, MeOH, Dowex-50, 25 °C, 3 h, 95%; v, Ph_3P (1.2 equiv.), CBr_4 (1.3 equiv.), CH_2Cl_2, −30 °C, 1 h, 85%; vi, Ph_3P (2.0 equiv.), CH_3CN, reflux, 12 h, 100%; vii, $KN(SiMe_3)_2$ (1.2 equiv.), THF, −78 °C, 0.5 h, 90%.

The vinylborane (**4**) was constructed as shown in Scheme 3. Regioselective opening of the epoxide (**10**) with the lithio derivative of but-1-yne followed by hydrogenation led to the hydroxy compound (**11**) in 75% overall yield. Protecting group

† New compounds exhibited satisfactory spectroscopic and analytical and/or exact mass data.

‡ This aldehyde (**9**) was obtained from δ-valerolacetone by the two-step sequence: i, MeOH, cat. H_2SO_4, reflux, 12 h (95%); ii, SO_3-pyr–Et_3N, DMSO–CH_2Cl_2 (1:1), 0 °C, 1 h (95%).

§ Selected physical properties of compound (**3**): colourless oil, R_F 0.29, 10% diethyl ether in light petroleum (b.p. 35—65 °C); δ_H(250 MHz, $CDCl_3$. signals for *trans* isomer) δ 6.48 (dt, *J* 14.36 and 6.54 Hz, 1, H, 7-H), 6.03 (dt, *J* 14.36 and 1.54 Hz, 1 H, 8-H), 5.43 (m, 2 H, 5-H and 6-H), 6.67 (s, 3 H, COO*Me*), 2.78 (t, *J* 6.45 Hz, 2 H, 6-H), 2.31 (t, *J* 7.42 Hz, 2 H, 2-H), 2.06 (m, 2 H, 4-H), and 1.70 (m, 2 H, 3-H) [Found: $(M + NH_4)^+$ 312.040. Calc. for $C_{10}H_{19}INO_2$: $(M + NH_4)$†, 312.046].



Scheme 3. *Reagents:* i, But-1-yne (5.0 equiv.), TMEDA (1.5 equiv), BuLi (2.0 equiv.), −78 ⟶ 45 °C, 24 h, 75%; ii, 10% Pd–C, H_2, EtOAc, 25 °C, 2 h, 100%; iii, ^{t}BuMe$_2$SiCl, imid., DMF, 25 °C, 3 h, 85%; iv, Me_2AlCl (2.0 equiv.), CH_2Cl_2, −30 °C, 4 h, 95%; v, SO_3-pyr (3.0 equiv.), Et_3N (5.0 equiv.), DMSO–CH_2Cl_2 (1:1), 0 °C, 3 h, 90%; vi, Ph_3P (3.8 equiv.), CBr_4 (2.2 equiv.), CH_2Cl_2, −10 °C, 15 min, 84%; vii, MeLi (2.1 equiv.), THF, −78 °C, 0.5 h, 85%; viii, catecholborane (2.0 equiv.), benzene, reflux, 24 h, 100%.

manipulation (silyl group on, THP group off[5]) furnished the primary alcohol (**12**) in 80% overall yield. Oxidation of (**12**) (SO_3-pyr–Et_3N, 90%) followed by acetylene formation *via* the Corey–Fuchs procedure[6] gave compound (**13**) in 72% yield. Finally, addition of catecholborane to (**13**) (benzene, reflux) gave a solution of the vinylborane (**4**), which was used without purification in the next step (essentially quantitative yield assumed).

The expected coupling of (**3**) and (**4**) proceeded stereospecifically to afford the HHT skeleton (**2**) in 45% yield (Scheme 1) under the Kishi conditions[3] [$Pd(PPh_3)_4$–TlOH, THF–H_2O–hexane (1:1:1)].* Fluoride-induced desilylation of (**2**) then gave the targeted HHT methyl ester (**1**) (85%).

Experimental

Preparation of Methyl (12S,5Z,8E,10E)-12-*Hydroxyheptadeca*-5,8,10-*trienoate* (**1**).—To a round bottom flask (200 ml) equipped with a magnetic stirrer was added compound (**4**) (200 mg, 0.55 mmol) in THF (5 ml), followed by hexane (55 ml). The solution was degassed by bubbling Ar through it for 15 min, after which a degassed solution of 10% aqueous TlOEt (6.1 ml, 2.44 mmol) was added with vigorous stirring over 3 min at room temperature. A solution of (**3**) (179 mg, 0.61 mmol) in THF (5 ml) was then added followed by the immediate addition of $Pd(PPh_3)_4$ (244 mg, 0.21 mmol) in THF (8 ml). The reaction mixture was stirred for 0.5 h (t.l.c. monitoring) after which it was transferred to a separating funnel, diluted with diethyl ether (150 ml), and washed with saturated brine (15 ml). The organic phase was dried ($MgSO_4$), filtered through a Celite pad, concentrated, and subjected to flash column chromatography [silica, 20% benzene in light petroleum (b.p. 35—65 °C)], to furnish (**2**) as a colourless oil (102 mg, 45%). Compound (**2**) (50 mg, 0.12 mmol) was azeotropically dried with benzene and dissolved in dry THF (2.4 ml). The magnetically stirred solution was treated at 25 °C with tetrabutylammonium fluoride (1M solution in THF; 0.147 ml, 0.15 mmol). Stirring was continued at ambient temperature for 3 h while the reaction was monitored by t.l.c. The solution was then diluted with diethyl ether (100 ml) and washed with pH 6 phosphate buffer (1 ml). The organic layer was separated and washed with saturated brine (1 ml), dried ($MgSO_4$), and concentrated. Diethyl ether (25 ml) was added, and the solution was cooled to 0 °C and treated with diazomethane to give, after concentration, the crude product which was purified by flash column chromatography [silica, 30% diethyl ether in light petroleum (b.p. 35—65 °C)], to furnish pure (**1**) as a colourless oil (29 mg, 85%), R_F 0.24 [silica, 40% diethyl ether in light petroleum (b.p. 35—65 °C)]; δ_H(500 MHz, $CDCl_3$) δ 6.17 (dd, *J* 15.11 and 10.36 Hz, 1 H, 10-H), 6.04 (dd, *J* 15.05 and 10.52 Hz, 1 H, 9-H), 5.66 (dt, *J* 15.16 and 6.48 Hz, 1 H), 5.60 (dd, *J* 15.17 and 7.04 Hz, 1 H, 11-H), 5.42 (m, 2 H, 5-H and 6-H), 4.1 (m, 1 H, 12-H), 3.66 (s, 3 H, COO*Me*), 2.81 (m, 2 H, 7-H), 2.36 (t, *J* 7.51 Hz, 2 H, 2-H), and 2.1—0.85 (m, 16 H, CH_2, and Me); $\lambda_{max.}$(MeOH) 240 nm; $[\alpha]_D^{25}$ +7.5° (*c* 0.2, $CHCl_3$) (Found: M^+ 294.224. Calc. for $C_{18}H_{30}O_3$: *M*, 294.219).

Acknowledgements

This work was financially supported by Smith Kline & French (U.S.A.), Glaxo, Inc. (U.S.A.), Hoffmann-La Roche (U.S.A.), and the National Institutes of Health.

References

1 M. Hamberg, J. Svennson, and B. Samuelsson, *Proc. Natl. Acad. Sci, USA*, 1974, **71**, 3824.
2 P. Sirois, S. Roy, G. Beraldin, P. Vallerand, and P. Borgeat, *Prostaglandins*, 1982, **24**, 405 and references cited therein.
3 J. Uenishi, J. M. Bean, R. W. Armstrong, and Y. Kishi, *J. Am. Chem. Soc.*, 1978, **109**, 4757.
4 K. Takai, K. Nitta, and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.
5 Y. Ogawa and M. Shibasaki, *Tetrahedron Lett.*, 1984, 663.
6 E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.

Received 27*th April* 1989;
(*Accepted* 3*rd July* 1989) *Paper* 9/02814E

* We thank Professor Y. Kishi, Harvard University for experimental conditions regarding this coupling reaction.