An Efficient Stereocontrolled Synthesis of Methyl (9*Z*,11*E*,13*S*)-13-Hydroxyoctadeca-9,11-dienoate (Methyl Coriolate)

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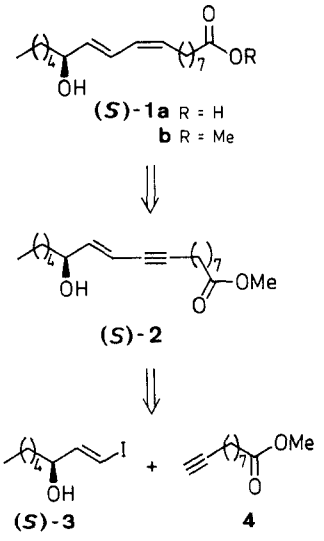
An efficient synthesis of methyl (13*S*)-coriolate (***S*)-1b** is accomplished by the palladium-catalyzed coupling of (1*E*,3*S*)-1-iodooct-1-en-3-ol **[(*S*)-3]** with methyl dec-9-ynoate **(4)** followed by selective reduction of the enyne **(*S*)-2**.

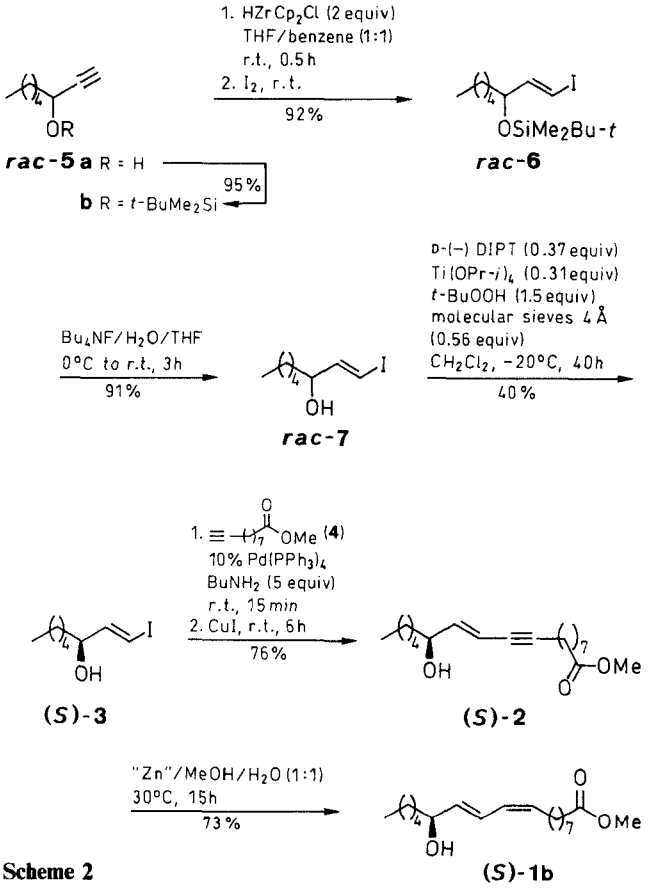
(9*Z*,11*E*,13*S*)-13-hydroxyoctadeca-9,11-dienoic acid, (13*S*)-HODE, **[(*S*)-1a]** is an important and biologically active metabolite of linoleic acid. It has been isolated from the resistant cultivar of rice plant[1] and has been shown to act as a self defence substance against rice blast disease. It is also present in sera of patients with Familial Mediterranean Fever[2] (FMF).

Several syntheses have been described.[3] We report herein a short stereocontrolled total synthesis of **(*S*)-1b** via a palladium–copper catalyzed reaction of the easily obtainable chiral alcohol **(*S*)-3** with methyl dec-9-ynoate **(4)** followed by selective reduction of the enyne **(*S*)-2** by activated zinc. A retrosynthetic analysis is shown in Scheme 1.



Scheme 1

The key synthon **(*S*)-3** was prepared from commercially available oct-1-yn-3-ol **(*rac*-5a)** (Scheme 2). Protection of the alcohol function by a *tert*-butyldimethylsilyl group, hydrozirconation with Schwartz's reagent[4,5] iodolysis and deprotection gave the iodo alcohol ***rac*-7** in 79% overall yield. The Sharpless kinetic resolution of ***rac*-7** using *tert*-butyl hydroperoxide, titanium(IV) isopropoxide



Scheme 2

and diisopropyl (−)-D-tartrate[6] [D-(−)DIPT] afforded **(*S*)-3** (97% ee)[7] in 40% yield.

The ester **4** was prepared from dec-9-yn-1-ol[8] by oxidation with Jones's reagent (CrO_3/H_2SO_4/acetone, 0 °C to 20 °C, 2 hours, 84%) followed by esterification[9] with methyl iodide (MeI/DMF, 20 °C, 24 hours, 75%).

Finally, coupling of the chiral vinyl iodide **(*S*)-3** with the acetylenic ester **4** in the presence of tetrakis(triphenylphosphine)palladium, copper(I) iodide and butylamine in benzene[10,11] furnished **(*S*)-2** (76%) from which the methyl ester HODE **(*S*)-1b** was generated by reduction with activated zinc[12] in 73% yield.[3]

The ester **(*S*)-1b** was characterized by its spectroscopic properties[13] by a comparison with an authentic sample.[14] The saponification leading to coriolic acid **(*S*)-1a** has already been described.[3]

In conclusion, a short synthesis of (13*S*)-HODE has been realized by coupling two easily obtainable synthons **(*S*)-3** and **4**. This strategy appears to be an efficient route to the chiral (*E*, *Z*) dienol structure which is characteristic of the basic structure of many polyunsaturated fatty acid metabolites.

^{1}H NMR spectra were recorded on Bruker VM 250 instrument. Mass spectra were determined on a Nermag R 10/10 instrument in the NH_3 chemical ionization mode. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter at r.t. IR spectra were recorded on a Perkin-Elmer Model 599 spectrophotometer. Analytical TLC was performed on 0.25 mm precoated silica gel plates purchased from E. Merck. Products were purified using the flash chromatography technique on silica gel 60 (230–400 mesh ASTM, 0.040–0.063 mm) purchased from E. Merck. Commercial grade reagents and solvents were used as supplied with the following exceptions: CH_2Cl_2, piperidine, Et_3N benzene and hexamethylphosphoric triamide (HMPT) distilled over CaH_2; pentane over P_2O_5; Et_2O and tetrahydrofuran over sodium benzophenone ketyl. Dec-9-en-1-ol and ***rac*-5a** were purchased from Aldrich Chemicals Zinc dust was purchased from E. Merck (ref: 8789). Reactions sensitive to O_2 or moisture were conducted under an Ar atmosphere.

3-(*tert*-Butyldimethylsiloxy)oct-1-yne (*rac*-5b):
To a stirred solution of oct-1-yn-3-ol (***rac*-5a**; 6.3 g, 50 mmol) in DMF (20 mL), were added at 0 °C *t*-BuMe$_2$SiCl (9.2 g, 62.5 mmol) and imidazole (10 g, 147 mmol).[15] After 24 h at r.t., the mixture was hydrolyzed with H_2O (60 mL) and extracted with pentane (3 × 50 mL). The organic layer was washed with H_2O (3 × 100 mL), dried ($MgSO_4$). The crude product ***rac*-5b** was distilled: bp 80 °C (0.07 Torr; yield: 11.48 g (95%).

IR (neat): ν = 3310, 2970, 2940, 2870, 1260, 1080 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 4.30 (td, 1 H, J = 7, 2 Hz, H-3); 2.35 (d, 1 H, J = 2 Hz, H-1); 1.92–1.00 (m, 8 H, H-4 to H-7); 0.90 (m, 12 H, H-8, $(CH_3)_3C$); 0.30 (s, 3 H, CH_3Si); 0.1 (s, 3 H, CH_3Si).

^{13}C NMR ($CDCl_3$): δ = 85.7 (C-2); 71.8 (C-1); 62.7 (C-3); 38.5 (C-4); 31.4 (C-6); 25.6 [$(\underline{C}H_3)_3C$]; 24.8 (C-5); 22.7 (C-7); 18.2 [$(CH_3)_3\underline{C}$]; 13.9 (C-8); −4.6 (CH_3Si); −5.1 (CH_3Si).

MS: m/z = 169; 240 (M^+, 100%).

$C_{14}H_{28}OSi$	calc.	C 69.93	H 11.73
(240.4)	found	70.08	11.85

(1*E*)-3-(*tert*-Butyldimethylsiloxy)-1-iodooct-1-ene (*rac*-6):
To a stirred solution of ether ***rac*-5b** (0.232 g, 0.966 mmol) in benzene/THF (1:1), was added one equivalent of Schwartz's reagent (zirconocene chloride hydride)[16] (0.250 g, 0.966 mmol). After stirring for 15 min, the resulting solution became clear, and a second equivalent of reagent was added. After 15 min, crystallized I_2 (0.254 g, 1 mmol) was introduced until a violet persistent coloration. The mixture was diluted with pentane (50 mL), filtered through a short column of silica gel, evaporated to dryness furnishing ***rac*-6**; yield: 0.325 g (92%).

^{1}H NMR ($CDCl_3$/TMS): δ = 6.48 (dd, 1 H, J = 14.50, 5.80 Hz, H-2); 6.16 (d, 1 H, J = 14.50 Hz, H-1); 4.05 (q, 1 H, J = 5.80 Hz, H-3); 1.42 (m, 2 H, H-4); 1.33–1.21 (m, 6 H, H-5 to H-7); 0.91–0.82 (m, 12 H, H-8 $(CH_3)_3C$); 0.03–0.00 (2 m, 6 H, 2 CH_3Si).

^{13}C NMR ($CDCl_3$): δ = 149.4 (C-2); 75.5 (C-1); 75.2 (C-3); 37.6 (C-4); 31.8 (C-6); 25.9 [$(\underline{C}H_3)_3C$]; 24.6 (C-5); 22.7 (C-7); 18.2 [$(CH_3)_3\underline{C}$]; 14.1 (C-8); −4.5 (CH_3Si); −4.8 (CH_3Si).

$C_{14}H_{29}OSiI$	calc.	C 45.64	H 7.93
(368.3)	found	45.48	8.11

1-Iodooct-1-en-3-ol (*rac*-7):
To a solution of iodo ether ***rac*-6** (0.325 g) in THF (10 mL) at 0 °C, was added crystallized $Bu_4NF \cdot H_2O$ (0.2666 g, 1.02 mmol). After stirring for 3 h at r.t., the mixture was hydrolyzed by H_2O (5 mL), extracted with Et_2O (3 × 20 mL). The organic phase was washed with H_2O (3 × 10 mL), dried ($MgSO_4$) and evaporated to dryness. The crude ***rac*-7** was subjected to flash column chromatography (silica gel, CH_2Cl_2) to afford the iodo alcohol ***rac*-7**; yield: 0.206 g (91%).

^{1}H NMR ($CDCl_3$/TMS): δ = 6.50 (dd, 1 H, J = 14.60, 6.30 Hz, H-2); 6.26 (dd, 1 H, J = 14.60, 1.09 Hz, H-1); 4.00 (qd, 1 H, J = 6.28, 1.05 Hz, H-3); 2.22 (s, 1 H, OH); 1.51 to 1.40 (m, 2 H, H-4); 1.35 to 1.18 (m, 6 H, H-5 to H-7); 0.83 (t, 3 H, J = 6.67 Hz, H-8).

^{13}C NMR ($CDCl_3$): δ = 148.4 (C-2); 77.1 (C-1); 74.3 (C-3); 36.3 (C-4); 31.5 (C-6); 24.7 (C-5); 22.4 (C-7); 14.0 (C-8).

MS: m/z = 245 (M^+).

(1*E*,3*S*)-1-Iodooct-1-en-3-ol [(*S*)-3]:
To a solution of iodo alcohol ***rac*-7** (1 g, 3.937 mmol) in CH_2Cl_2 (10 mL) stored on 4Å activated molecular sieves during 30 min, was added 4Å activated molecular sieves (m = 0.56 g, 0.56 equiv weight). The solution was cooled to −15 °C, D-(−)DIPT (0.345 g, 1.47 mmol), Ti(OPr-i)$_4$ (n = 0.350 g, 1.23 mmol) were added; after 30 min, *t*-BuOOH (1.96 mL, 3 M in 2,2,4-trimethylpentane) was slowly introduced in the stirred solution at −20 °C. After 40 h at −20 °C, the solution was warmed to 0 °C and hydrolyzed with H_2O (20 × n = 7 g). After 1 h, 30% aq NaOH (7 mL) saturated by NaCl was added. The resulting suspension was filtered through a pad of Celite, washed by CH_2Cl_2 (3 × 10 mL), the organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The crude product was chromatographed over silica gel (CH_2Cl_2) to furnish **(*S*)-3**; yield: 0.40 g (40%); $[\alpha]_D^{20}$ + 10° (c = 2.20, $CHCl_3$). The ee was confirmed to be 97%.[7]

Methyl (11*E*,13*S*)-13-Hydroxyoctadec-11-en-9-ynoate [(*S*)-2]:
To a stirred solution of chiral iodo alcohol **(*S*)-3** (0.400 g, 1.57 mmol) in anhydr. benzene (10 mL) under inert atmosphere at r.t., $Pd(PPh_3)_4$ (0.181 g, 0.157 mmol), acetylenic ester **4** (0.315 g, 1.71 mmol) and $BuNH_2$ (0.573 g, 7.85 mmol) were added. After 15 min, CuI (0.030 g, 0.157 mmol) was introduced and stirring was continued for 6 h (TLC monitoring). The mixture was quenched with sat. aq NH_4Cl (5 mL); the organic layer was diluted with Et_2O (30 mL), washed with brine (3 × 15 mL) and dried ($MgSO_4$). The crude product was purified by flash column chromatography (silica gel, Et_2O 30% in pentane) to afford compound **(*S*)-2**; yield: 0.220 g (76%); $[\alpha]_D^{20}$ + 7° (c = 1.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 5.97 (dd, 1 H, J = 15.8, 6.4 Hz, H-12); 5.60 (dq, 1 H, J = 15.8, 2.1 Hz, H-11); 4.05 (q, 1 H, J = 6.2 Hz, H-13); 3.6 (s, 3 H, OCH_3); 2.24 (t, 2 H, J = 7.5 Hz, H-2); 2.22 (dt, 2 H, J = 6.7, 2.1 Hz, H-8); 1.78 n(s, 1 H, OH); 1.62–1.17 (complex, 18 H, H-3 to H-7 and H-14 to H-17); 0.81 (t, 3 H, J = 6.6 Hz, H-18).

^{13}C NMR ($CDCl_3$): δ = 174.1 (C-1); 144.2 (C-12); 110.0 (C-11); 90.6 (C-9); 78.4 (C-10); 72.0 (c-13); 51.2 (OCH_3); 36.7 (C-14); 33.8 (C-2); 31.5 (C-16); 28.7, 28.5, 28.4, 28.35 (C-4 to C-7); 24.8, 24.6 (C-15, C-3); 22.4 (C-17); 19.0 (C-8); 13.8 C-18).

Methyl (9*Z*,11*E*,13*S*)-13-Hydroxyoctadeca-9,11-dienoate [(*S*)-1b]: To a suspension of activated zinc dust[12] (2 g) was added a solution of enyne **(*S*)-2** (0.220 g, 0.714 mmol) in MeOH (1 mL). The mixture was stirred at 30 °C during 15 h and filtered over a pad of Celite, washed with pentane (3 × 5 mL). The combined solutions were concentrated to 1/3 of the original volume and pentane/Et_2O (1:1) was added (10 mL). The organic layer was washed with brine, dried ($MgSO_4$), evaporated and flash column chromatography (silica gel, Et_2O 30% in pentane) furnished methyl ester (13*S*)-HODE; yield: 0.160 g (73%); $[\alpha]_D^{20}$ + 6.3° (*c* = 1.3, $CHCl_3$); Lit.[3] $[\alpha]_D^{25}$ + 6.5° (*c* = 0.7, $CHCl_3$), $[\alpha]_D^{20}$ + 7° (*c* = 0.98, $CHCl_3$).

By HPLC analysis[3] using a Baker dinitrobenzoylphenylglycine (covalent) chiral phase column (250 × 4.6 mm), eluting with hexane/*i*-PrOH (99.5:0.5) and a flow rate of 0.8 mL/min, **(*S*)-1b** had a retention time of 31.7 min (98%) and the enantiomer **(*R*)-1b**, 32.5 min (2%). The ee was thus 96%.

^{13}C NMR ($CDCl_3$): δ = 174.2 (C-1); 136.0 (C-12); 132.3 (C-9); 127.8 (C-10); 125.4 (C-11); 72.6 (C-13); 51.3 (OCH_3); 37.2 (C-14); 33.9 (C-2); 31.6 (C-16); 29.3 (C-4); 28.9 (C-6, C-7); 28.8 (C-5); 27.5 (C-8); 25.0 (C-3); 24.7 (C-17); 22.5 (C-15); 13.9 (C-18).

(1) Kato, T.; Yamaguchi, Y.; Hirano, T.; Yokoyama, T.; Uyahara, T.; Namai, T.; Yamanaka, S.; Harada, N. *Chem. Lett.* **1984**, 409.

(2) Aisen, P.S.; Haines, K.A.; Given, W.; Abramson, S.B.; Pras, M.; Serham, C.; Hamberg, M.; Samuelsson, G.; Weissmann, G. *Proc. Natl. Scad. Sci. USA* **1982**, 1232.

(3) For recent syntheses, see:
Tranchepain, I.; Leberre, F.; Duréault, A.; LeMerrer, Y.; Depezay, J.C. *Tetrahedron* **1989**, *45*, 2057.
deMontarby, L.; Tourbah, H.; Gree, R. *Bull. Soc. Chim. Fr.* **1989**, *3*, 419.
Bloch, R.; Perfetti, M.T. *Tetrahedron Lett.* **1990**, *31*, 2577.
Lumin, S.; Schwartzmann, M.L.; Falk, J.R. *Tetrahedron Lett.* **1991**, *32*, 2315.

(4) Hart, D.W.; Blackburn, T.F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(5) Avignon-Tropis, M.; Treilhou, M.; Pougny, J.R.; Frechard-Ortuno, I.; Linstrumelle, G. *Tetrahedron* **1991**, *47*, 7279.

(6) Kobayashi, Y.; Shimazaki, T.; Taguchi, H.; Sato, F. *J. Org. Chem.* **1990**, *55*, 5324.

(7) The enantiomeric excess was determined according to a new unpublished method studied by Dr. G. Cahiez (Université P. et M. Curie). We are grateful to Dr. Cahiez, for providing us with experimental details of the procedure prior to publication.

(8) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed., Elsevier: Amsterdam, **1988**; p 173.
Kobayashi, Y.; Okamoto, S.; Shimazaki, T.; Ochiai, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 3959.

(9) Corey, E.J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 3959.

(10) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 853.

(11) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315.
Ratovelomanana, V.; Linstrumelle, G. *Ibid* **1984**, *25*, 6001.

(12) Boland, W.; Sieler, C.; Schroer, N.; Feigel, M. *Helv. Chim. Acta* **1987**, *70*, 1025.

(13) Wolff, I.A.; Tallent, W.H.; Harris, J. *Tetrahedron Lett.* **1966**, 4329.

(14) We thank Dr. M. Delaforge and Dr. J.L. Boucher (Université René Descartes, Paris) for HPLC analyses of this product.

(15) Corey, E.J.; Niimura, K.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199.

(16) Buchwald, S.L.; LaMaire, S.J.; Nielsen, R.B.; Watson, B.T.; King, S.M. *Tetrahedron Lett.* **1987**, *28*, 3895.