**Synthesis of new artemisinin derivatives homodimers by Self-Cross Metathesis Reaction**

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**General experimental:**

Dichloromethane (CH₂Cl₂) was distilled from calcium hydride and all reactions were carried out with dry, freshly distilled solvents, under anhydrous conditions (argon atmosphere). All reactions were monitored by thin-layer chromatography using precoated aluminum-backed plates (Merck Kieselgel HF254) and are visualized by UV light and/or vaporisation of an acidic solution of vanillin and heating. Merck Kieselgel (70-200 µm) silica gel was used for flash chromatography.

Infra-red spectra were recorded on a Bruker vector 22 spectrophotometer. NMR spectra were recorded in CDCl₃ on Bruker AC200 and ARX400 spectrometers. Chemical shift are reported in ppm related to Me₄Si and CFCl₃ (for ¹⁹F NMR) as internal standards. In the ¹³C NMR data, reported signal multiplicities are related to C-F coupling. For the determination of fine coupling constants on acquisition of 16K data points, a Lorentz-Gauss transformation of the FID and a zero filling to 64K were performed in order to obtain a minimum of resolution of 0.2 Hz/pt (¹H) or 0.5 Hz/pt (¹³C). Complete assignments of signals resulted from a complete assignments of the spectrum through HMQC, HMBC experiments performed on a multinuclear probehead equipped with a Z-gradient coil. In NMR data numbering of atoms are presented according to the usual numbering in artemisinin as indicated in the text.

Elemental analysis were performed at the analytical laboratories of the Faculté de Pharmacie Paris XI.

Artemisinin is extracted and purified as the Institute of Natural Products (CNST, Hanoi, Vietnam)
• Preparation of compounds 4-11  
  S2-S9
• \(^1\text{H},\, ^{13}\text{C}\) and \(^{19}\text{F}\) NMR spectra for compounds 5, 7 and 11  
  S9-S16

*We thank Mrs Michèle Ourévitch for the NMR spectra.*
Preparation of the allylic ether artemisinin derivative 4.


**Self-cross metathesis of ether 4 : Access to dimers 5.**

A suspension of ethers 4 (100 mg, 0.31 mmol) and Grubbs catalyst 2 (25 mg, 0.031 mmol, 10%) in CH$_2$Cl$_2$ (620 µL, 0.3 M) was stirred at r.t. for 4 hours. The reaction mixture was then filtered on a pad of silica, and the filtrate was concentrated under reduced pressure. The residue was purified on a SiO$_2$ column (petroleum ether/ethyl acetate: 4/1 containing 0.1% of Et$_3$N) to afford a mixture of homodimers 5 (80 mg, 83%) as a colourless oil.

The major isomer is described:

(E)-(1S,4R,5R,8R,9R,12R,13S)-1,5,9-trimethyl-11,14,15,17-tetraoxatetracyclo[10.3.1.0$^{4,13}$,0$^{6,13}$]hexadec-10-yl]oxy)-3-hexenyl]oxy]-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0$^{4,13}$,0$^{6,13}$]hexadecane. $^{1}$H NMR δ 0.90 (d, $^3$J$_{H16-H9}$ = 7.5 Hz, 6 H, 2 CH$_3$-16), 0.92 (m, 2 H, 2 H-7), 0.94 (d, $^3$J$_{H15-H6}$ = 6 Hz, 6 H, 2 CH$_3$-15), 1.25 (m, 2 H, 2 H-5a), 1.30 (m, 2 H, H-6), 1.41 (s, 6 H, 2 CH$_3$-14), 1.47 (m, 6 H, 2 H-5, 2 H-8, 2 H-8a), 1.62 (m, 2 H, 2 H-7'), 1.80 (m, 4 H, 2 H-8', 2 H-8'), 2.00 (m, 2 H, 2 H-4eq), 2.36 (td, $^2$J$_{H4ax-H4eq}$ = $^3$J$_{H4ax-H5ax}$ = 14.5 Hz, $^3$J$_{H4ax-H5eq}$ = 4 Hz, 2 H, 2 H-4ax), 2.65 (m, 2 H, 2 H-9), 3.99 (dd, $^2$J$_{H17a-H17b}$ = 12 Hz, $^3$J$_{H17a-H18}$ = 1.5 Hz, 2 H, 2 H-17a), 4.30 (dd, $^2$J$_{H17b-H17a}$ = 12 Hz, $^3$J$_{H17b-H18}$ = 1.5 Hz, 2 H, 2 H-17b).
Hz, 2 H, 2 H-17b), 4.82 (d, $J_{H10-H9} = 3$ Hz, 2 H, 2 H-10β), 5.39 (s, 2 H, 2 H-12), 5.74 (t, $J_{H18-H17} = 1.5$ Hz, 2 H, 2 H-18); $^{13}$C NMR δ 13.0 (2 C-16), 20.3 (2 C-15), 24.5 and 24.7 (2 C-5, 2 C-8), 26.1 (2 C-14), 30.9 (2 C-9), 34.7 (2 C-7), 36.4 (2 C-4), 37.4 (2 C-6), 44.4 (2 C-8a), 52.6 (2 C-5a), 67.6 (2 C-17), 81.1 (2 C-12a), 87.9 (2 C-12), 101.1 (2 C-10), 104.0 (2 C-3), 128.4 (2 C-18). Anal. Calcd for C$_{34}$H$_{56}$O$_{10}$: C, 65.78; H, 8.44. Found : C, 66.02; H, 8.82.

**Preparation of the 10-CF$_3$ allylic ether artemisinin derivative 6.**

![Diagram of 10-CF$_3$ allylic ether artemisinin derivative 6.]


**Self-cross metathesis of ether 6: Access to dimer 7.**

(E)-1S,4R,5R,8R,12R,13S)-9-[[(-4-[[1S,4R,5R,8R,12R,13S]-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0$^{4,13}$,0$^{8,13}$]hexadec-9-en-9-yl]methoxy)-2-butenyloxy]methyl]-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0$^{4,13}$,0$^{8,13}$]hexadec-9-ene (7):

![Diagram of dimer 7.]

To a suspension of allylic ether 6 (80 mg, 0.21 mmol, 2 equiv) and Grubbs catalyst 3 (17 mg, 0.021 mmol, 10%) in CH$_2$Cl$_2$ (700 µL, 0.3 M) was stirred at r.t. for 24 hours. The reaction mixture was then filtered on a pad of silica and the filtrate was concentrated under reduced
pressure. The residue was purified on a SiO2 column (petroleum ether / ethyle acetate : 4/1 containing 0.1% of Et3N) to afford a mixture of a 100:0 mixture of E/Z homodimer 7 (53 mg, 69%), as a colourless oil; [α]25D = +1 (c 1; MeOH); 19F NMR δ -64.3 (d, 3JF-H16 = 1.5 Hz, 6 F, 2 CF3); 1H NMR δ 0.99 (d, 3JH15-H6 = 6 Hz, 6 H, 2 CH3-15), 1.20 (m, 4 H, 2 H-7ax, 2 H-8), 1.40 (m, 2 H, 2 H-6), 1.42 (s, 6 H, 2 CH3-14), 1.50 (m, 4 H, 2 H-5, 2 H-5a), 1.68 (qd, 2JH7ax-H7eq = 13 Hz, 3JH7eq-H8ax = 3JH7eq-H6 = 3 Hz, 2 H, 2 H-7eq), 1.95 (m, 2 H, 2 H-5'), 2.03 (m, 2 H, 2 H-4), 2.08 (m, 2 H, 2 H-8'), 2.24 (dd, 3JH8a-H8ax = 13 Hz, 3JH8a-H8eq = 4.5 Hz, 2 H, 2 H-8a), 2.40 (m, 2 H, 2 H-4'), 3.83 (dd, 2JH17a-H17b = 12.5 Hz, 3JH17a-H18 = 3 Hz, 2 H-17a), 3.99 (dd, 2JH17b-H17a = 12.5 Hz, 3JH17b-H18 = 2.5 Hz, 2 H-17b), 4.15 (d, 2JH16-F = 1.5 Hz, 4 H, 2 CH2-16), 5.72 (s, 2 H, 2 H-12), 5.77 (t, 3JH18-H17 = 2.5 Hz, 2 H-18); 13C NMR δ 19.9 (2 C-15), 24.3 (2 C-5), 25.4 (2 C-14), 28.9 (2 C-8), 33.8 (2 C-7), 35.9 (2 C-4), 37.4 (2 C-6), 50.3 (2 C-5a), 64.7 (2 C-16), 68.8 (2 C-17), 77.7 (2 C-12a), 90.9 (2 C-12), 104.9 (2 C-3), 112.7 (2 C-9), 120.4 (q, 1JC-F = 270 Hz, 2 CF3), 129.2 (2 C-18), 137.8 (q, 2JC-F = 34 Hz, 2 C-10). Anal. Calcd for C36H46F6O10: C, 57.40; H, 6.16. Found : C, 57.61; H, 6.25.

**Preparation of the 10-CF3 alcohol artemisinin derivative 8.**

![Chemical structure](https://example.com/structure.png)


**Preparation of the 10-CF3 aldehyde artemisinin derivative 9.**

(1S,4R,5R,8R,12R,13S)-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo [10.3.1.04,13.08,13]hexadec-9-ene-9-carbaldehyde (9).
A suspension of allylic alcohol 8 (970 mg, 2.8 mmol) and MnO₂ (4.8 g, 56 mmol, 20 equiv) in CHCl₃ (50 mL) was stirred at rt for 24 h. After filtration on celite, the filtrate was concentrated under reduced pressure. The residue was purified on a SiO₂ column (petroleum ether – ethyle acetate 4:1) to afford the aldehyde 9 (868 mg, 89%) as a white solid; m.p. = 96°C (ether); [α]²⁵D = +153 (c 0.52; MeOH); IR νCO 1645 cm⁻¹; ¹⁹F NMR δ -62.4 (d, JF-H₁₆ = 1 Hz, 3 F, CF₃); ¹H NMR δ 1.00 (d, JH₁₅-H₆ = 6 Hz, 3 H, CH₃-15), 1.12 (qd, JH₈ax-H₈eq = 3JH₈ax-H₇ax = 3JH₆ax-H₈a = 13 Hz, 1H, H-8ax), 1.24 (qd, JH₇ax-H₇eq = 3JH₇ax-H₆ = 3JH₇ax-H₈ax = 13 Hz, 1H, H-7ax), 1.39 (m, 2 H, H-5, H-6), 1.44 (s, 3 H, CH₃-14), 1.56 (m, 1 H, H-5a), 1.67 (dq, JH₇eq-H₇ax = 13 Hz, JH₇eq-H₈eq = 3JH₇eq-H₈ax = 3JH₇eq-H₆ = 3 Hz, 1 H, H-7eq), 1.99 (m, 1 H, H-5'), H₈eq), 2.07 (dt, JH₄eq-H₄ax = 14 Hz, JH₆ax-H₅ax = 3JH₆ax-H₅ax = 3JH₆ax-H₈ax = 4 Hz, H-8eq), 2.44 (td, JH₄ax-H₄eq = 3JH₄ax-H₅ax = 14 Hz, JH₄ax-H₅eq = 4 Hz, 1 H, H-4ax), 2.76 (dd, JH₈ax-H₈a = 13 Hz, JH₈ax-H₈a = 4 Hz, 1 H, H-8a), 5.86 (s, 1 H, H-12), 9.95 (d, JH₆-H₆ = 1 Hz, 1 H, H-16); ¹³C NMR δ 19.9 (C-15), 24.3 (C-5), 25.2 (C-14), 29.7 (C-8), 33.6 (C-7), 35.6 (C-4), 37.6 (C-6), 38.0 (C-8a), 50.2 (C-5a), 77.1 (C-12a), 93.5 (C-12), 105.8 (C-3), 118.0 (C-9), 119.2 (q, J₃C-F = 277 Hz, CF₃), 152.9 (q, J₂C-F = 37.5 Hz, C-10), 187.0 (d, J₁C-F = 4.5 Hz, C-16); Anal. Calcd for C₁₆H₁₉F₃O₅: C, 55.17; H, 5.50. Found: C, 55.23; H, 5.59.

**Preparation of the 10-CF₃ aldehyde artemisinin derivative 10.**

1-[(1S,4R,5R,8R,12R,13S)-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxa tetracyclo[10.3.1.0⁴¹³.0⁸¹³]hexadec-9-en-9-yl]-3-buten-1-ol (10).

Allyl bromide (416 mg, 3.44 mmol, 4.0 equiv), Zn (169 mg, 2.58 mmol, 3.0 equiv) and TMSCl (22 µL, 0.17 mmol, 0.2 equiv) were added at 0°C to a solution of aldehyde 9 (300 mg,
0.86 mmol) in DMF (8 mL). After 5 minutes of stirring at 0°C and 1h at r.t., the reaction was diluted with ether, hydrolysed with a solution of HCl 1N and washed with brine. The organic layer was then dried (MgSO₄) and concentrated under reduced pressure. The residue was purified on a SiO₂ column (petroleum ether / ethyle acetate : 4/1 containing 0.1% of Et₃N) to afford the alcohol 10 (289 mg, 86%) as a colorless oil; IR νOH 3425 cm⁻¹; ¹⁹F NMR δ -63.7 (s, CF₃) (5%, minor isomer), -64.2 (s, CF₃) (95%, major isomer); ¹H NMR δ 0.98 (d, ³J_H15-H6 = 5.5 Hz, 3 H, CH₃-15), 1.20 (s, 1 H, H-7), 1.30 (qd, ²J_H8ax-H8eq = ³J_H8ax-H7ax = ³J_H8ax-H8a = 13 Hz, ³J_H8ax-H7eq = 3 Hz, 1 H, H-8ax), 1.39 (s, 3 H, CH₃-14), 1.50 (m, 3 H, H-5, H-5a, H-6), 1.66 (m, 1 H, H-7'), 1.82 (sl, 1 H, OH), 1.97 (m, 1 H, H-4, H-5'), 2.18 (m, 1 H, H-8eq), 2.30 (m, H-8a major isomer, CH₂-17), 2.37 (m, 1 H, H-4'), 2.54 (dd, ³J_H8a-H8ax = 13 Hz, ³J_H8a-H8eq = 4 Hz, H-8a minor isomer), 4.78 (t, ³J_H16-H17 = 7.5 Hz, 2 H, CH₂-16 minor isomer), 4.82 (t, ³J_{16,17} = 6 Hz, CH₂-16 major isomer), 5.08 (d, ³J_H18-H19 = 8.5 Hz, H-19 minor isomer), 5.15 (d, ³J_H18-H19a = 10 Hz, 1 H, H-19a), 5.16 (d, ³J_H18-H19b = 18 Hz, 1 H, H-19b), 5.75 (s, 1 H, H-12), 5.98 (tdd, ³J_H18-H19b = 18 Hz, ³J_H18-H19a = 10 Hz, ³J_H18-H17 = 6 Hz, 1 H, H-18); ¹³C NMR δ 19.9 (C-5), 24.4 (C-5), 25.3 (C-14), 30.1 (C-8), 34.0 (C-7), 36.0 (C-4), 37.8 (C-6), 40.9 (C-8a), 41.3 (C-17), 50.2 (C-5a), 67.7 (C-16), 77.3 (C-12a), 91.1 (C-12), 104.8 (C-3), 118.2 (C-9), 118.7 (C-19), 120.5 (q, ¹J_C-F = 275 Hz, CF₃), 134.1 (C-18), 137.0 (C-10); Anal. Calcd for C₁₉H₂₅F₃O₅: C, 58.46; H, 6.45. Found : C, 58.31; H, 6.60.

**Self-cross metathesis of ether 10: Access to dimers 11.**

To a suspension of alcohol 10 (108 mg, 0.28 mmol, 2 equiv) and Grubb’s catalyst 3 (24 mg, 0.028 mmol, 10%) in CH₂Cl₂ (930 µL, 0.3 M) was stirred at rt for 8h. The mixture was then filtered on a pad of silica and the filtrate was concentrated under reduced pressure. The residue was purified on a SiO₂ column (petroleum ether / ethyle acetate : 4/1 then 2/1, containing 0.1% of Et₃N) to afford a mixture of dimers 11 (53 mg, 50%), as a colorless oil. The major isomer is described:

(E)-1,6-bis[(1S,4R,5R,8R,12R,13S)-1,5-dimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo [10.3.1.0.4,13.08,13]hexadec-9-en-9-yl]-3-hexene-1,6-diol (11).
$^{19}$F NMR δ -64.3 (s, 6 F, 2 CF$_3$); $^1$H NMR δ 0.99 (d, $^3$J$_{H15-H6}$ = 5.5 Hz, 6 H, 2 CH$_3$-15), 1.20 (m, 2 H, 2 H-7), 1.30 (m, 2 H, 2 H-8), 1.39 (s, 6 H, 2 CH$_3$-14), 1.47 (m, 6 H, 2 H-5, 2 H-5a, 2 H-6), 1.65 (m, 2 H, 2 H-7'), 1.95 (m, 2 H, 2 H-5'), 2.00 (m, 4 H, 2 H-4, 2 OH), 2.18 (m, 2 H, 2 H-8'), 2.25 (m, 6 H, 2 H-8a, 2 CH$_2$-17), 2.38 (m, 2 H, 2 H-4'), 4.81 (dd, $J = 8$ Hz, $J = 5$ Hz, 2 H, 2 H-16), 5.56 (t, $^3$J$_{H18-H17}$ = 4 Hz, 2 H, 2 H-18), 5.74 (s, 2 H, 2 H-12); $^{13}$C NMR δ 19.9 (2 C-15), 24.4 (2 C-5), 25.3 (2 C-14), 30.1 (2 C-8), 34.0 (2 C-7), 36.0 (2 C-4), 37.8 (2 C-6), 40.0 (2 C-17), 40.8 (2 C-8a), 50.2 (2 C-5a), 67.8 (2 C-16), 77.4 (2 C-12a), 91.0 (2 C-12), 104.8 (2 C-3), 118.2 (2 C-9), 120.5 (q, $^1$J$_{C-F}$ = 274.5 Hz, 2 CF$_3$), 129.7 (2 C-18), 136.1 (q, $^2$J$_{C-F}$ = 35 Hz, 2 C-10).
mixture of dimers 5, $^1$H NMR
mixture of dimers 5. $^{13}$C NMR
dimer 7. $^{19}$F NMR
dimer 7. $^1$H NMR
dimer 7. $^{13}$C NMR
mixture of dimers 11. $^{19}$F NMR
mixture of dimers 11. $^1$H NMR
mixture of dimers $11$. $^{13}$C NMR