Application of ring closing metathesis to the synthesis of 19-functionalized derivatives of 1α-hydroxyvitamin D_3

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Supporting Information:

Melting points were determinated on a Kofler apparatus of the Boetius type. NMR spectra were recorded with a Bruker AC 200F spectrometer using $CDCl_3$ solutions with TMS as the internal standard (only selected signals in the ^1H NMR spectra are reported) Infrared spectra were recorded on a Nicolet series II Magna-IR 550 FT-IR spectrometer in chloroform solutions. Mass spectra were obtained at 70 eV with AMD-604 spectrometer. The reaction products were isolated by column chromatography performed on 70-230 mesh silica gel (J. T. Baker).

General procedure for esterification

A solution of carboxylic acid (1.1 eq), vitamin D_3 (or 1α-hydroxy vitamin D_3) (1 eq), *N*,*N*-dicyclohexylcarbodiimide (1.1 eq), and 4-dimethylaminopyridine (0.1 eq) in dichloromethane was stirred at room temperature until esterification was completed. The *N*,*N*-dicyclohexyl urea was filtered and the filtrate was washed with water, 5% acetic acid solution, and again water, dried over magnesium sulfate and solvent was evaporated to afford the corresponding ester.

General procedure for CM reaction

To the solution of vitamin D_3 (3 eq) and 20 mol % of Grubbs (or Hoveyda) second generation catalyst in dry dichloromethane (toluene) in oven-dried Schlenk flask alkene (1 eq) was added dropwise. The reaction mixture was stirred at 40°C (80°C) for 16 hours under argon atmosphere. Then the mixture was concentrated in vacuo and purified directly by silica gel chromatography.

General procedure for RCM reaction

To the solution (2 mM) of 20 mol % of Grubbs (or Hoveyda) second generation catalyst in dry toluene in oven-dried Schlenk flask, the solution (0.5 mM - 1.5 mM) of vitamin D_3 (or 1α-hydroxyvitamin D_3) ester in dry toluene was added dropwise during 2 hours. The reaction mixture was stirred 80^{o}C for 4 hours under argon. Then the mixture was concentrated *in vacuo* and purified by silica gel chromatography.

Selected spectral data:

(5*E*,7*E*)-(3S)-3β-*t*-butyldimethylsililoxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 3-butenoate (**7**). Yield 85%, eluted with hexane/ethyl acetate (98/2); ^{1}H NMR δ (ppm): 6.51 (d, *J* = 11.5 Hz, 1H), 5.94-5.84 (m, 2H), 5.62 (m, 1H), 5.15 (m, 3H), 4.94 (bs, 1H), 4.14 (m, 1H), 3.09 (d, *J* = 6.8 Hz, 1H), 0.93 (d, *J* = 5.9 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 5.3 Hz, 6H), 0.56 (s, 3H), 0.08 (s, 6H).

(5*E*,7*E*)-(3S)-3β-*t*-butyldimethylsililoxy-19a-homo-9,10-secocholesta-5,7,10(19)-triene-19a,1α-carbolactone (**8**). Yield 70% (achieved with Hoveyda catalyst), eluted with hexane/ethyl acetate (96/4); IR ν_{max} (cm^{-1}): 1728, 1258, 1069; ^{1}H NMR δ (ppm): 6.62 (d, *J* = 11.4 Hz, 1H), 5.84-5.79 (m, 2H), 5.31 (m, 1H), 4.32 (m, 1H), 3.20-3.11 (m, 2H), 0.93 (d, *J* = 5.8 Hz, 3H), 0,86 (d, *J* = 6.3 Hz, 6H), 0.84 (s, 9H), 0.54 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ (ppm): 169.6 (C), 145.8 (C), 139.4 (C), 130.5 (C), 123.2 (CH), 116.0 (CH), 112.5 (CH), 66.4 (CH), 56.6 (CH), 56.6 (CH), 46.2 (C), 40.5 (CH_2), 39.8 (CH_2),39.5 (2xCH_2), 36.1 (CH), 35.1 (CH_2), 30.8 (CH_2), 29.2 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.8 (CH), 25.7 (3xCH_3), 23.9 (CH_2), 23.7 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.2 (CH_2), 18.8 (CH_3), 18.0 (C), 12.0 (CH_3), -4.6 (CH_3), -4.9 (CH_3); MS EI: 554 (M^+, 17), 75 (100); HRMS EI: calcd for $C_{35}H_{58}O_3Si$: 554.4155. Found: 554.4145.

(5*E*,7*E*)-(3S)-3β-*t*-butyldimethylsililoxy-19-hydroxyethyl-9,10-secocholesta-5,7-10(19)-trien-1α-ol (**12**). Yield 98%, eluted with hexane/ethyl acetate (70/30); IR ν_{max} (cm^{-1}): 3380, 1259, 1091; ^{1}H NMR δ (ppm): 6.46 (d, *J* = 11.4 Hz, 1H), 5.89 (d, *J* = 11.4 Hz, 1H), 5.66 (t, *J* = 8.2 Hz, 1H), 4.79 (t, *J* = 3.1 Hz, 1H), 4.11 (m, 1H), 3.77 (m, 1H), 3.65 (m, 1H), 0.93 (d, *J* = 7.7 Hz, 3H), 0.91 (s, 9H), 0,88 (d, *J* = 6.8 Hz, 6H), 0.57 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR δ (ppm): 145.2 (C), 144.2 (C), 134.6 (C), 122.6 (CH), 122.1 (CH), 116.2 (CH), 66.5 (CH), 65.2 (CH), 61.5 (CH_2), 56.6 (CH), 56.5 (CH), 48.5 (C), 42.0 (CH_2), 40.5 (CH_2), 39.5 (CH_2), 38.2 (CH_2), 36.1 (CH, CH_2), 30.7 (CH_2), 29.1 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.9

(3xCH_3), 23.9 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.2 (CH_2), 18.8 (CH_3), 18.2 (C), 12.1 (CH_3), -4.6 (CH_3), -4.7 (CH_3); MS EI: 558 (M^+, 11), 540 (M^+-H_2O, 9), 178 (100); HRMS EI: calcd for $C_{35}H_{62}O_3Si$: 558.4468. Found: 558.4481.

(5*Z*,7*E*)-(3S)-3β-*t*-butyldimethylsililoxy-19-hydroxyethyl-9,10-secocholesta-5,7,10(19)-trien-1α-ol (**13**). Yield 50%, eluted with hexane/ethyl acetate (70/30); IR ν_{max} (cm^{-1}): 3611, 1257, 1069; ^{1}H NMR δ (ppm): 6.30 (d, *J* = 11.4 Hz, 1H), 5.91 (d, *J* = 11.4 Hz, 1H), 5.50 (t, *J* = 7.3 Hz, 1H), 4.39 (m, 1H), 4.15 (m, 1H), 3.85 (m, 1H), 3.69 (m, 1H), 0.96 (d, *J* = 5.9 Hz, 3H), 0.89 (s, 9H), 0.88 (d, *J* = 5.8 Hz, 6H), 0.58 (s, 3H), 0.09 (s, 6H); ^{13}C NMR δ (ppm): 146.6 (C), 144.2 (C), 130.4 (C), 125.4 (CH), 120.6 (CH), 115.8 (CH), 73.0 (CH), 67.2 (CH), 62.9 (CH_2), 56.6 (CH), 56.5 (CH), 45.9 (C), 43.7 (CH_2), 40.5 (CH_2), 39.5 (2xCH_2), 38.4 (CH_2), 36.1 (CH), 31.9 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.9 (3xCH_3), 23.9 (2xCH_2), 23.6 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.2 (CH_2), 18.8 (CH_3), 18.2 (C), 12.2 (CH_3), -4.7 (CH_3), -4.8 (CH_3); MS EI: 558 (M^+, 11), 540 (M^+-H_2O, 5), 178 (100). HRMS EI: calcd for $C_{35}H_{62}O_3Si$: 558.4468. Found: 558.4480.