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Synthesis of γ- and δ-lactones from 1α-hydroxy-5,6-*trans*-vitamin D_3 by ring-closing metathesis route and their reduction with metal hydrides

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ARTICLE INFO

Article history:
Received 29 November 2006
Received in revised form
15 February 2007
Accepted 8 March 2007
Published on line 18 March 2007

Keywords:
Ring-closing metathesis
Hydride reduction
Vitamin D_3
Steroids

ABSTRACT

New synthetic pathway towards 19-functionalized derivatives of 1α-hydroxy-5,6-*trans*-vitamin D_3 was described. Ring-closing metathesis (RCM) of 1α-hydroxy-5,6-*trans*-vitamin D_3 1-ω-alkenoates was a key-step. Hydride reduction of resulting lactones led to the new vitamin D_3 analogues.

1. Introduction

Vitamin D_3 through its active metabolite, 1α,25-dihydroxy-vitamnin D_3, plays an important role in calcium and phosphorus homeostasis as well as differentiation and proliferation of various tumor cells [1]. Such a wide variety of biological activity of this compound encourages organic chemists, including our group, to synthesize new analogues as candidate therapeutic agents for the treatment of different diseases: cancer, psoriasis and osteoporosis [2–11].

Nowadays the discovery of olefin metathesis provides a new route for synthesis of the complex molecules [12,13]. Since the development of well-defined ruthenium and molybdenum alkylidene catalysts, this method has become a powerful tool in organic synthesis. It seems to be a method of choice for synthesis of vitamin D_3 analogues as new C–C double bonds may be formed under relatively mild conditions, which is especially important for these rather unstable compounds. One of the widely applied metathetic transformations is ring-closing metathesis (RCM), which allows cyclic compounds to be obtained from acyclic diene substrates [14,15]. Many classes of homo- and heterocyclic compounds, including unsaturated lactones of various ring size can be successfully synthesized *via* the RCM route.

2. Experimental

2.1. General remarks

Melting points were determined on a Kofler apparatus of the Boetius type. NMR spectra were recorded with a Bruker Avance DPX 200 or Bruker Avance II 400 spectrometer using $CDCl_3$ or C_6D_6 solutions with TMS as the internal standard (only

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0039-128X/$ – see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.steroids.2007.03.005

selected signals in the ^{1}H 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).

2.2. A representative procedure for esterification

A solution of 1α-hydroxy-3-TBS-vitamin D_3 (**1**) (80 mg, 15 mmol), 3-butenoic acid (0.015 ml, 0.17 mmol), *N*,*N*-dicyclohexylcarbodiimide (35 mg, 0.17 mmol) and 4-dimethylaminopyridine (2 mg) in DCM (2 ml) was stirred at room temperature until the reaction was completed (about 2 h). The *N*,*N*-dicyclohexyl urea was filtered off and the filtrate was washed with water, 5% acetic acid solution and again water, dried over magnesium sulfate and the solvent was evaporated to afford 3-butenoate **2b**.

The above method was also used for preparation of esters **2c–e**; acrylate **2a** was obtained by routine esterification with acryloyl chloride in DCM in presence of triethylamine.

2.2.1. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 2-propenoate* ***(2a)***

An oil; yield 41 mg (46%), eluted with hexane/AcOEt (98.5/1.5); IR ν_{max} (cm^{-1}): 1717, 1636, 1618, 1258, 1104; ^{1}H NMR δ (ppm): 6.53 (d, *J* = 11.5 Hz, 1H, 6-H), 6.41 (dd, *J* = 17.3, 1.7 Hz, 1H, 3′-H), 6.12 (dd, *J* = 17.3, 10.3 Hz, 1H, 2′-H), 5.87 (d, *J* = 11.5 Hz, 1H, 7-H), 5.81 (dd, *J* = 10.3, 1.7 Hz, 1H, 3′-H), 5.69 (m, 1H, 1β-H), 5.16 (brs, 1H, 19H), 4.96 (brs, 1H, 19-H), 4.17 (m, 1H, 3α-H), 2.86 (dd, *J* = 10.7, 2.9 Hz, 1H), 2.66 (dd, *J* = 3.6, 13.8 Hz), 0.94 (d, *J* = 5.9 Hz, 3H, 21-H), 0.89 (s, 9H, TBS), 0.88 (d, *J* = 5.4 Hz, 6H, 26-H and 27-H), 0.56 (s, 3H, 18-H), 0.1 (s, 6H, TBS); ^{13}C NMR δ (ppm): 165.3 (C), 147.5 (C), 144.9 (C), 133.4 (C), 130.6 (CH_2), 128.8 (CH), 122.7 (CH)116.0 (CH), 110.8 (CH_2), 73.0 (CH), 66.6 (CH), 56.6 (CH), 56.5 (CH), 46.0 (C), 40.5 (CH_2), 40.1 (CH_2), 39.5 (2× CH_2), 36.9 (CH_2), 36.1 (CH), 29.1 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.8 (3× CH_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), 18.1 (C), 12.1 (CH_3), −4.7 (2× CH_3); MS EI: 568 (M^+, 17), 496 (22), 75 (40); HRMS EI: calcd for $C_{36}H_{60}O_3Si$: 568.4312. Found: 568.4321.

2.2.2. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 3-butenoate* ***(2b)***

An oil; yield 77 mg (85%), eluted with hexane/AcOEt (98/2); ^{1}H NMR δ (ppm): 6.53 (d, *J* = 11.5 Hz, 1H, 6-H), 5.94 (m, 1H, 3′-H), 5.89 (d, *J* = 11.5 Hz, 1H, 7-H), 5.64 (m, 1H, 1β-H), 5.19 (dd, *J* = 6.2, 1.1 Hz, 2H, 4′-H) 5.18 (brs, 1H, 19-H), 4.94 (brs, 1H, 19-H), 4.16 (m, 1H, 3α-H), 3.09 (dm, *J* = 6.8 Hz, 2H, 2′-H), 0.93 (d, *J* = 5.9 Hz, 3H, 21-H), 0.89 (s, 9-H, TBS), 0.88 (d, *J* = 5.3 Hz, 6H, 26-H and 27-H), 0.56 (s, 3H, 18-H), 0.08 (s, 6H, TBS); ^{13}C NMR δ (ppm): 170.5 (C), 147.5 (C), 144.9 (C), 133.4 (C), 130.4 (CH), 122.6 (CH), 118.5 (CH_2), 116.0 (CH), 110.9 (CH_2), 73.1 (CH), 66.6 (CH), 56.7 (CH), 56.5 (CH), 46.0 (C), 40.5 (CH_2), 40.1 (CH_2), 39.52 (CH_2), 39.46 (CH_2), 37.0 (CH_2, CH), 36.1 (CH_2), 29.1 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.8 (3× CH_3), 23.9 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.2 (CH_2), 18.8 (CH_3), 18.1 (C), 12.1 (CH_3), −4.7 (CH_3), −4.8 (CH_3); MS EI: 582 (M^+, 63), 496 (25), 75 (100); HRMS EI: calcd for $C_{37}H_{62}O_3Si$: 582.4468. Found: 582.4476.

2.2.3. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 4-pentenoate* ***(2c)***

An oil; yield 69 mg (75%), eluted with hexane/AcOEt (98/2); ^{1}H NMR δ (ppm): 6.51 (d, *J* = 11.5 Hz, 1H, 6-H), 5.87 (d, *J* = 11.5 Hz, 1H, 7-H), 5.78 (m, 1H, 4′-H), 5.62 (m, 1H, 1β-H), 5.15 (brs 1H, 19-H), 5.05 (m, 2H, 5′-H), 4.94 (bs, 1H, 19-H), 4.14 (m, 1H, 3α-H), 0.93 (d, *J* = 5.8 Hz, 3H, 21-H), 0.89 (s, 9H, TBS), 0.86 (d, *J* = 5.8 Hz, 6H, 26-H and 27-H), 0.56 (s, 3H, 18-H), 0.08 (s, 6H, TBS).

2.2.4. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 5-hexenoate* ***(2d)***

An oil; yield 80 mg (84%), eluted with hexane/AcOEt (98/2); ^{1}H NMR δ (ppm): 6.51 (d, *J* = 11.5 Hz, 1H, 6-H), 5.87 (d, *J* = 11.5 Hz, 1H, 7-H), 5.79 (m, 1H, 5′-H), 5.61 (m, 1H, 1β-H), 5.15 (brs 1H, 19-H), 5.00 (m, 2H, 6′-H) 4.94 (bs, 1H, 19-H), 4.14 (m, 1H, 3α-H), 0.94 (d, *J* = 6.0 Hz, 3H, 21-H), 0.89 (s, 9H, TBS), 0.88 (d, *J* = 5.7 Hz, 6H, 26-H and 27-H), 0.56 (s, 3H, 18-H), 0.08 (s, 6H, TBS).

2.2.5. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-trien-1α-yl 10-undecenoate* ***(2e)***

An oil; yield 86 mg (81%), eluted with hexane/AcOEt (98/2); ^{1}H NMR δ (ppm): 6.51 (d, *J* = 11.5 Hz, 1H, 6-H), 5.75–5.90 (m, 2H, 7-H and 10′-H), 5.61 (m, 1H, 1β-H), 5.14 (brs 1H, 19-H), 5.04–4.92 (m, 3H, 19-H and 11′-H) 4.14 (m, 1H, 3α-H), 0.94 (d, *J* = 5.9 Hz, 3H, 21-H), 0.89 (s, 9H, TBS), 0.88 (d, *J* = 5.8 Hz, 6H, 26-H and 27-H), 0.56 (s, 3H, 18-H), 0.08 (s, 6H, TBS).

2.3. A representative procedure for metathesis

To a solution of Hoveyda second-generation catalyst (11 mg, 10 mol%) in dry toluene (20 ml) in an oven-dried Schlenk flask, a solution of 1α-hydroxy-3-TBS-vitamin D_3 ester **2a** (100 mg, 0.18 mmol) in dry toluene (300 ml) was added dropwise during 2 h. The reaction mixture was stirred at 80 °C for 4 h under argon. Then the mixture was concentrated *in vacuo* and lactone **4a** was purified by silica gel column chromatography.

2.3.1. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-9,10-secocholesta-5,7,10(19)-triene-19,1α-carbolactone* ***(4a)***

An amorphous solid; yield 38 mg (40%) eluted with hexane/AcOEt (94/6); IR ν_{max} (cm^{-1}): 1739, 1615, 1257, 1062; ^{1}H NMR δ (ppm): 6.83 (d, *J* = 11.2 Hz, 1H, 6-H), 5.86 (d, *J* = 11.2 Hz, 1H, 7-H), 5.83 (brs, 1H, 19-H), 5.25 (dd, *J* = 11.7, 6.1 Hz, 1H, 1β-H), 4.41 (m, 1H, 3α-H), 2.90 (m, 2H), 0.94 (d, *J* = 5.4 Hz, 3H, 21-H), 0.88 (d, *J* = 6.7 Hz, 6H, 26-H and 27-H), 0.86 (s, 9H, TBS), 0.54 (s, 3H, 18-H), 0.10 (s, 3H, TBS), 0.09 (s, 3H, TBS); ^{13}C NMR δ (ppm): 173.8 (C), 170.9 (C), 150.2 (C), 127.0 (CH), 125.6 (C), 115.1 (CH), 109.8 (CH), 78.9 (CH), 66.6 (CH), 56.7 (CH), 56.6 (CH), 46.6 (C), 40.3 (CH_2), 39.5 (CH_2), 38.4 (CH_2), 36.1 (CH, CH_2), 35.3 (CH_2), 29.4 (CH_2), 28.0 (CH), 27.6 (CH_2), 25.6 (3× CH_3), 23.9 (2× CH_2), 22.8 (CH_3), 22.5 (CH_3), 22.2 (CH_2), 18.9 (C), 17.9 (CH_3), 11.9 (CH_3), −4.9 (2× CH_3); MS EI: 540 (M^+, 100), 483 (10); HRMS EI: calcd for $C_{34}H_{56}O_3Si$: 540.3999. Found: 540.4006.

2.3.2. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-19a-homo-9,10-secocholesta-5,7,10(19)-triene-19a,1α-carbolactone (**4b**)*

An amorphous solid; yield 67 mg (70%), eluted with hexane/AcOEt (96/4); IR ν_{max} (cm^{-1}): 1728, 1258, 1069; ^1H NMR δ (ppm): 6.62 (d, J = 11.4 Hz, 1H, 6-H), 5.84–5.79 (m, 2H, 7-H and 19-H), 5.31 (m, 1H, 1β-H), 4.32 (m, 1H, 3α-H), 3.20–3.11 (m, 2H, 19a-H), 0.93 (d, J = 5.8 Hz, 3H, 21-H), 0.86 (d, J = 6.3 Hz, 6H, 26-H and 27-H), 0.84 (s, 9H, TBS), 0.54 (s, 3H, 18-H), 0.07 (s, 3H, TBS), 0.06 (s, 3H, TBS); ^{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 (2× CH_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 (3× CH_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), 162 (100); HRMS EI: calcd for $C_{35}H_{58}O_3Si$: 554.4155. Found: 554.4145.

2.3.3. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-19a,19b-dihomo-9,10-secocholesta-5,7,10(19)-triene-19b,1α-carbolactone (**4c**)*

An amorphous solid; yield 5 mg (5%), eluted with hexane/AcOEt (94/6); ^1H NMR δ (ppm): 6.62 (d, J = 12 Hz, 1H, 6-H), 5.82 (m, 2H, 7-H and 19-H), 5.31 (m, 1H, 1β-H), 4.32 (m, 1H, 3α-H), 3.21 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H, 21-H), 0.88 (d, J = 6.3 Hz, 6H, 26-H and 27-H), 0.84 (s, 9H, TBS), 0.54 (s, 3H, 18-H), 0.08 (s, 3H, TBS), 0.06 (s, 3H, TBS). MS EI: 568 (M^+, 3), 540 (17), 497 (5), 483 483 (4), 75 (100).

2.3.4. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-19a,19b,19c-trihomo-9,10-secocholesta-5,7,10(19)-triene-19c,1α-carbolactone (**4d**)*

An amorphous solid; yield 3 mg (3%), eluted with hexane/AcOEt (94/6); ^1H NMR δ (ppm): 6.62 (d, J = 11.2 Hz, 1H, 6-H), 5.82 (m, 2H, 7-H and 19-H), 5.31 (m, 1H, 1β-H), 4.32 (m, 1H, 3α-H), 3.17 (m, 2H), 0.93 (d, J = 6.6 Hz, 3H, 21-H), 0.89 (s, 9H, TBS), 0.88 (d, J = 5.9 Hz, 6H, 26-H and 27-H), 0.54 (s, 3H, 18-H), 0.08 (s, 3H, TBS), 0.06 (s, 3H, TBS).

2.4. LAH reduction of lactones

To a solution of lactone **4b** (22 mg, 0.04 mmol) in dry THF (5 ml) $LiAlH_4$ (2.5 mg) was added at room temperature under argon. The reaction mixture was stirred for 30 min and quenched carefully with water. The product **5** was extracted with DCM, the extract was washed with water, dried over magnesium sulfate, evaporated and purified by silica gel column chromatography.

Analogous LAH reduction of lactone **4a** was carried out at 0 °C.

2.4.1. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-19-hydroxyethyl-9,10-secocholesta-5,7-10(19)-trien-1α-ol (**5**)*

An amorphous solid; yield 22 mg (98%), eluted with hexane/AcOEt (70/30); IR ν_{max} (cm^{-1}): 3380, 1469, 1259, 1091; ^1H NMR δ (ppm): 6.46 (d, J = 11.4 Hz, 1H, 6-H), 5.89 (d, J = 11.4 Hz, 1H, 7-H), 5.66 (m, 1H, 19-H), 4.79 (t, J = 3.1 Hz, 1H, 1β-H), 4.11 (m, 1H, 3α-H), 3.77 (m, 1H, 19b-H), 3.65 (m, 1H, 19b-H), 0.93 (d, J = 7.7 Hz, 3H, 21-H), 0.91 (s, 9H, TBS), 0.88 (d, J = 6.8 Hz, 6H, 26-H and 27-H), 0.57 (s, 3H, 18-H), 0.10 (s, 3H, TBS), 0.09 (s, 3H, TBS); ^{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 (3× CH_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), 178 (100); HRMS EI: calcd for $C_{35}H_{62}O_3Si$: 558.4468. Found: 558.4481.

2.4.2. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-19-hydroxymethyl-9,10-secocholesta-5,7-dien-1α-ol (**8**)*

A pale yellow amorphous solid; yield 20 mg (88%), eluted with hexane/AcOEt (70/30); IR ν_{max} (cm^{-1}): 3614, 1471, 1256, 1065; ^1H NMR δ (ppm): 6.27 (d, J = 11.3 Hz, 1H, 6-H), 5.88 (d, J = 11.3 Hz, 1H, 7-H), 4.17 (m, 1H, 1β-H), 4.00 (m, 1H, 3α-H), 3.75 (m, 2H, 19b-H), 0.95 (d, J = 6.4 Hz, 3H, 21-H), 0.90 (d, J = 6.2 Hz, 6H, 26-H and 27-H), 0.90 (s, 9H, TBS), 0.57 (s, 3H, 18-H), 0.09 (s, 3H, TBS), 0.08 (s, 3H, TBS); ^{13}C NMR δ (ppm): 142.7 (C), 135.3 (C), 121.4 (CH), 115.7 (CH), 69.0 (CH), 68.0 (CH), 61.7 (CH_2), 56.6 (CH), 56.4 (CH), 47.8 (CH), 45.7 (C), 40.7 (CH_2), 40.5 (CH_2), 39.5 (CH_2), 36.1 (CH, CH_2), 29.7 (2× CH_2), 29.0 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.9 (3× CH_3), 23.9 (CH_2), 23.5 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.2 (CH_2), 18.8 (CH_3), 18.1 (C), 12.1 (CH_3), −4.8 (CH_3), −4.9 (CH_3); MS EI: 546 (M^+, 20), 528 (31), 75 (100); HRMS EI: calcd for $C_{34}H_{62}O_3Si$: 546.44682. Found: 546.44693.

2.5. DIBAL-H reduction of lactones

To a stirred solution of lactone **4a** (30 mg, 0.05 mmol) in dry toluene (2 ml) cooled to −78 °C (dry ice–acetone bath) 1.7 M solution of DIBAL-H in toluene (0.12 ml) was added. The reaction mixture was maintained at −78 °C under argon 4 h, then poured to water, and extracted with ether. The organic extract was washed with water, dried over magnesium sulfate, evaporated and purified by silica gel column chromatography.

2.5.1. *(5E,7E)-(3S)-3β-t-butyldimethylsilyloxy-furo[2′3′:1,10]-19-nor-9,10-secocholesta-5,7-diene (**10**)*

A yellow foam; yield 11 mg (40%), eluted with hexane/AcOEt (99/1); IR ν_{max} (cm^{-1}): 1624, 1259, 1089, 838; ^1H NMR (C_6D_6) δ (ppm,): 7.27 (d, J = 1.9 Hz, 1H, 19a-H), 7.04 (d, J = 11.4 Hz, 1H, 6-H), 6.66 (d, J = 1.9 Hz, 1H, 19-H), 6.50 (d, J = 11.4 Hz, 1H, 7-H), 4.30 (m, 1H, 3α-H), 3.16–3.28 (m, 2H), 3.09 (d, J = 5.2 Hz, 1H), 2.95 (d, J = 7.8 Hz, 1H), 2.84 (m, 1H), 1.19 (d, J = 7.1 Hz, 3H, 21-H), 1.15 (d, J = 7.7 Hz, 6H, 26-H and 27-H), 1.13 (s, 9H, TBS), 0.86 (s, 3H, 18-H), 0.23 (s, 3H, TBS), 0.19 (s, 3H, TBS); ^{13}C NMR δ (ppm): 150.1 (C), 142.5 (CH), 142.0 (C), 125.7 (C), 120.0 (C), 117.0 (CH), 116.0 (CH), 105.8 (CH), 68.7 (CH), 56.7 (CH), 56.5 (CH), 45.9 (C), 40.6 (CH_2), 39.5 (CH_2), 36.2 (CH, CH_2), 35.4 (CH_2), 33.9 (CH_2), 29.0 (CH_2), 28.0 (CH), 27.7 (CH_2), 25.7 (3× CH_3), 23.9 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.2 (CH_2), 18.9 (CH_3), 18.1 (C), 12.0 (CH_3), −4.6 (2× CH_3); MS EI: 524 (M^+, 100), 509 (4), 481 (1), 167 (16); HRMS EI: calcd for $C_{34}H_{56}O_2Si$: 524.4050. Found: 524.4061.

Analogous DIBAL-H reduction of lactone **4b** afforded a diastereomeric mixture of lactols **7**, which could not be sepa-

rated into individual pure compounds, in the ratio 6:4 as arose from integration of the 19b-H signals at δ: 5.05 (m) and 5.42 (t, J = 4.6 Hz) in the ^{1}H NMR spectrum.

2.6. *Deprotection of compounds 5, 8 and 10*

To a stirred solution of TBS-ether **10** (18 mg, 0.03 mmol) in dry THF (1 ml), cooled to 0 °C, 1 M solution of TBAF in THF (0.11 ml) was added. The reaction mixture was removed from the cooling bath and stirred for about 30 min at room temperature to complete the reaction (TLC control). The reaction mixture was then poured into water and extracted with ether. The organic extract was washed with water, dried over magnesium sulfate, evaporated and purified by silica gel column chromatography.

Analogous deprotection reactions of compounds **5** and **8** were also performed.

2.6.1. *(5E,7E)-(3S)-19-hydroxyethyl-9,10-secocholesta-5,7-10(19)-triene-1α,3β-diol*

(6)

A foam; yield 4 mg (95%), eluted with hexane/AcOEt (10/90); ^{1}H NMR δ (ppm): 6.52 (d, J = 11.4 Hz, 1H, 6-H), 5.92 (d, J = 11.4 Hz, 1H, 7-H), 5.73 (t, J = 8.1 Hz, 1H, 19-H), 4.85 (t, J = 3.2 Hz, 1H, 1β-H), 4.18 (m, 1H, 3α-H), 3.82 (m, 1H, 19b-H), 3.67 (m, 1H, 19b-H), 3.18 (dm, J = 12.0 Hz, 1H), 2.73 (dm, J = 12.5 Hz, 1H), 0.95 (d, J = 6.3 Hz, 3H, 21-H), 0.90 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.89 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.58 (s, 3H, 18-H); ^{13}C NMR δ (ppm): 144.8 (C), 144.7 (C), 133.6 (C), 123.1 (CH), 122.5 (CH), 116.2 (CH), 65.8 (CH), 64.9 (CH), 61.5 (CH_2), 56.6 (CH), 56.5 (CH), 45.9 (C), 41.4 (CH_2), 40.5 (CH_2), 39.5 (CH_2), 37.5 (CH_2), 36.1 (CH_2, CH), 30.7 (CH_2), 29.7 (CH_2), 29.2 (CH), 28.0 (CH_2), 27.7 (CH_2), 23.9 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.3 (CH_2), 18.8 (CH_3), 12.1 (CH_3).

2.6.2. *(5E,7E)-(3S)-19-hydroxymethyl-9,10-secocholesta-5,7-diene-1α,3β-diol*

(9)

An oil; yield 3 mg (89%), eluted with hexane/AcOEt (5/95); ^{1}H NMR δ (ppm): 6.34 (d, J = 11.3 Hz, 1H, 6-H), 5.88 (d, J = 11.3 Hz, 1H, 7-H), 4.14 (m, 1H, 1β-H), 4.06 (m, 1H, 3α-H), 3.75 (m, 2H, 19a-H), 0.93 (d, J = 6.3 Hz, 3H, 21-H), 0.88 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.87 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.56 (s, 3H, 18-H); ^{13}C NMR δ (ppm): 142.5 (C), 135.2 (C), 122.7 (CH), 115.1 (CH), 68.9 (CH), 67.5 (CH), 61.5 (CH_2), 56.6 (CH), 56.4 (CH), 53.4 (CH_2), 47.5 (CH), 45.7 (C), 40.5 (CH_2), 39.5 (CH_2), 36.1 (CH, CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.1 (CH_2), 28.0 (CH), 27.6 (CH_2), 23.9 (CH_2), 23.5 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.3 (CH_2), 18.8 (CH_3), 12.1 (CH_3).

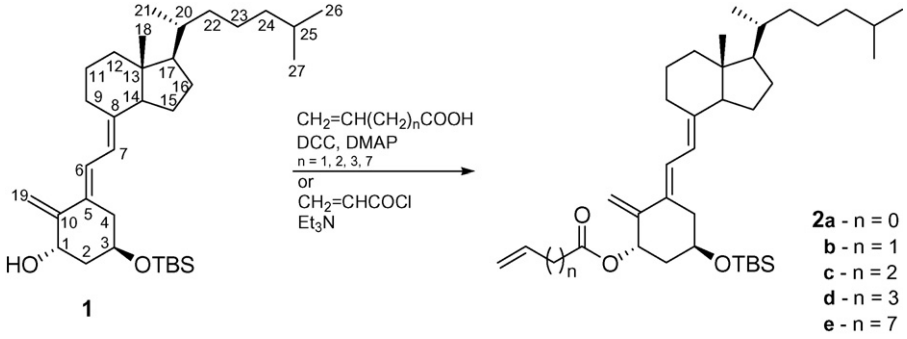
2.6.3. *(5E,7E)-(3S)-furo[2′3′:1,10]-19-nor-9,10-secocholesta-5,7-dien-3β-ol*

(11)

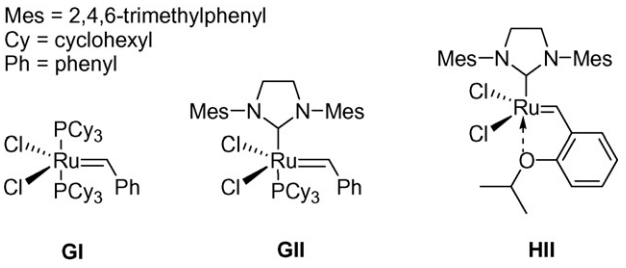
A yellow amorphous solid; yield 13 mg (93%), eluted with hexane/AcOEt (90/10); IR ν_{max} (cm^{-1}): 3611, 1624, 1034; ^{1}H NMR δ (ppm,): 7.30 (d, J = 2.0 Hz, 1H, 19a-H), 6.59 (d, J = 11.5 Hz, 1H, 6-H), 6.54 (d, J = 2.0 Hz, 1H, 19-H), 5.95 (d, J = 11.5 Hz, 1H, 7-H), 4.31 (m, 1H, 3α-H), 3.06 (dd, J = 16.4, 4.7 Hz, 1H), 2.89 (dm, J = 12.7 Hz, 1H), 2.74 (m, 3H), 0.94 (d, J = 6.4 Hz, 3H, 21-H), 0.89 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.88 (d, J = 6.6 Hz, 3H, 26-H/27-H), 0.58 (s, 3H, 18-H); ^{13}C NMR δ (ppm): 149.0 (C), 143.3 (C), 142.3 (CH), 124.1 (C), 120.4 (C), 118.7 (CH), 115.8 (CH), 105.8 (CH), 67.2 (CH), 56.6 (CH), 56.5 (CH), 46.0 (C), 40.5 (CH_2), 39.5 (CH_2), 36.1 (CH, CH_2), 34.0 (CH_2), 33.0 (CH_2), 29.0 (CH_2), 28.0 (CH), 27.7 (CH_2), 23.9 (CH_2), 23.6 (CH_2), 22.8 (CH_3), 22.6 (CH_3), 22.3 (CH_2), 18.8 (CH_3), 12.1 (CH_3); MS EI: 410 (M^+, 88), 367 (3), 57 (100); HRMS EI: calcd for $C_{28}H_{42}O_2$: 410.3185. Found: 410.3197.

3. Results and discussion

The aim of this work was to elaborate a simple synthetic approach to the 19-functionalized vitamin D_3 derivatives. Cross metathesis (CM) of suitably protected vitamin D_3 (in 5,6-*cis* and 5,6-*trans* series) with various olefins failed. Therefore the synthesis of vitamin D_3 lactones *via* RCM approach was attempted. In our early studies vitamin D_3 long-chain esters with a terminal double bond were prepared and subjected to metathesis. However, instead of RCM, self metathesis (SM) of unsaturated esters was only observed, probably due to insufficient conformational flexibility of ring A [16]. Further attempts of RCM were carried out with 1α-hydroxy-vitamin D_3 esters containing unsaturated acyl unit at the position 1. This approach also completely failed – even RCM of 1α-OH-D_3 3-butenoate, which was expected to afford product of a six-membered ring closure, did not work. The most likely reason of this failure is the steric hindrance caused by the CD ring fragment of a steroid molecule. Inspection of the Dreiding stereomodels indicated that the C_{10}–C_{19} double bond in 1α-hydroxy-5,6-*trans*-vitamin D_3 derivatives is more accessible than in the 5,6-*cis* isomers. To check, if the steric hindrance is the main reason of the failure, the RCM reaction of 1α-hydroxy-5,6-*trans*-vitamin D_3 3-butenoate was performed and the desired six-membered lactone was obtained as the main product. The synthesis of the lactone and its further transformations to the 19-functionalized 1α-OH-D_3 derivatives was



Scheme 1



Scheme 2

described in our preliminary communication [16]. Now, we present results of our further study on metathesis of 1α-hydroxy-5,6-*trans*-D_3 ω-unsaturated esters with various sized acid chain (C_3, C_4, C_5, C_6, and C_{11}). Further reductive transformations of the γ- and δ-lactones obtained by the RCM methodology are also described in this paper.

Five 1α-hydroxy-3-TBS-5,6-*trans*-vitamin D_3 ω-alkenoates (compounds **2b–e**) were prepared in high yields by reaction of **1** with ω-alkenoic acids in presence of DCC and DMAP. Only in the case of 1α-hydroxy-3-TBS-5,6-*trans*-vitamin D_3 acrylate (**2a**), esterification was carried out using the acid chloride method (Scheme 1). All esters obtained were found to be rather unstable and were subjected to RCM reactions immediately without thorough purification.

In the first RCM experiments, acrylate **2a** and 3-butenoate **2b** reactions were studied that theoretically allow for a closure of a five or six-membered lactone ring, respectively. According to literature, synthesis of unsatured lactones through RCM has been accomplished using either Grubbs (first- or second-generation) or Hoveyda catalysts [14–19]. The synthesis of phosphonate or silicon analogues of 1α-hydroxy-5,6-*trans*-vitamin D_3 by a similar approach was achieved in presence of the second-generation Grubbs catalyst [20]. We decided to test all three commercially available metathesis promoters: Grubbs first-generation (GI), Grubbs second-generation (GII) and Hoveyda second-generation (HII) (Scheme 2).

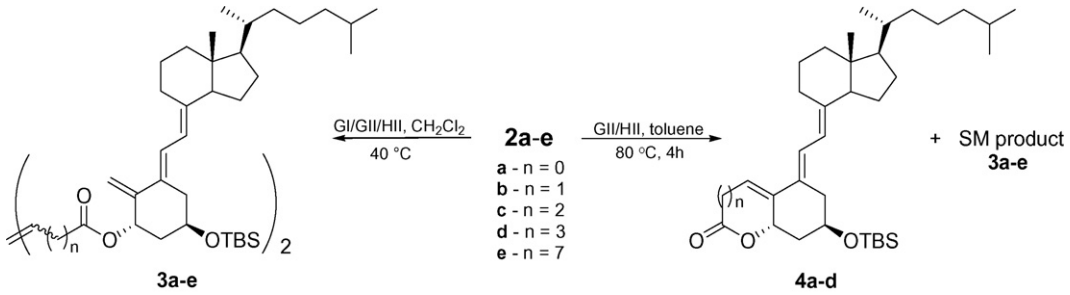
Bearing in mind the low stability of 1α-hydroxy-5,6-*trans*-vitamin D_3 esters (**2**), we carried out the first experiments under relatively mild conditions: 20 mol% of catalyst in dry and degassed dichloromethane at room temperature. It was assumed that such quantities of catalyst might be necessary because of possible chelation of the ruthenium complex by the triene moiety. However, no RCM reaction was observed for all three catalysts under these conditions. The only isolated products were dimers **3a** or **3b**, formed as a result of self metathesis. In the next experiments, the reaction temperature was raised to 40 °C without significant change of reaction course. Only the use of catalysts of the second generation (either Grubbs or Hoveyda) at 80 °C in dry and degassed toluene proved effective in the RCM products (**4a** or **4b**) formation (Scheme 3).

Such effect of temperature, mentioned above, was not reported earlier for similar compounds [20]. The influence of other reaction conditions on the reaction course, e.g. type of catalyst, dilution (tested concentration: 0.5–1.5 mM), mode of reagent addition, appeared to be much less important. For substrates **2a** and **2b**, a slightly better yield of RCM product was achieved with the second-generation Hoveyda (HII) promoter. It was found that 10 mol% of catalyst was the optimal load; higher amount of catalyst or its portionwise addition did not improve the yield. 5,6-*trans*-vitamin D_3 19,1-carbolactone (**4a**) was obtained in 40% yield in presence of HII catalyst. The lactone was accompanied by dimer **3a** (23%)—the SM reaction product. The remaining material was mainly the unreacted starting ester **2** (about 30%).

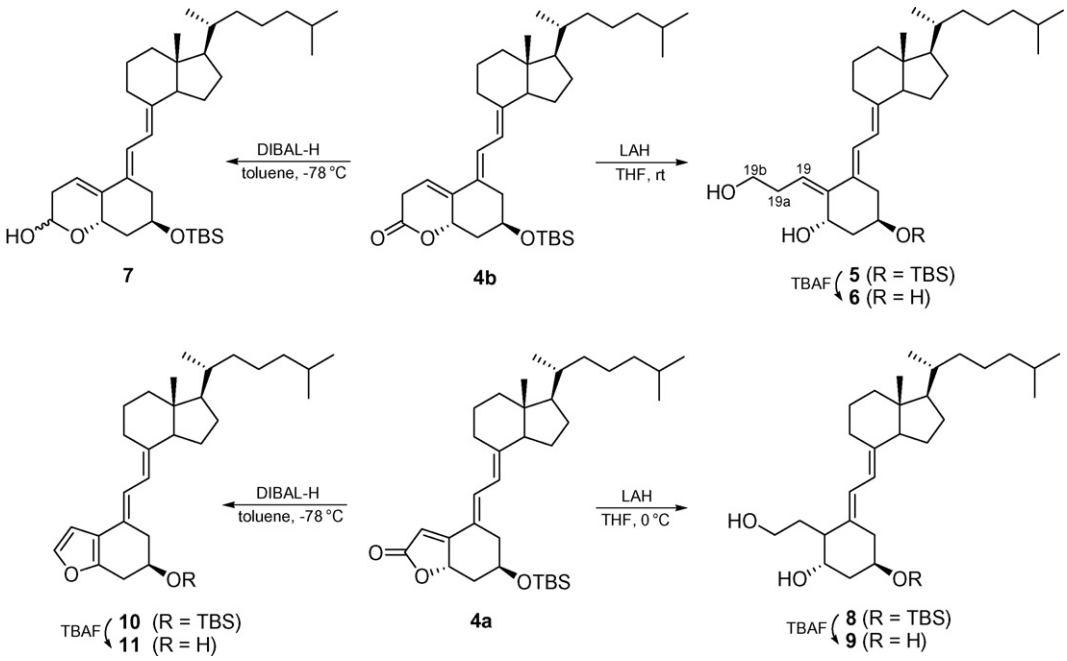
In an analogous reaction, 3-butenoate **2b** yielded 70% of the RCM product **4b** and the SM by-product **3b** (24%). Interestingly, no terminal olefin isomerization was observed during this reaction. This is quite surprising since in many reports, comparable systems were found to be prone to isomerization under metathetic conditions, especially, if the GII catalyst was used [21–24]. In some cases the isomerized substrate was obtained even as the main reaction product under conditions analogous to ours [25].

Other 1α-hydroxy-5,6-*trans*-vitamin D_3 esters (**2c–e**) were also subjected to metathesis under the same conditions (10 mol% of HII catalyst; dilution = 0.5 mM; 80 °C; toluene, 4–16 h). Although many successful applications of RCM to the synthesis of medium sized rings are known, in the case of **2c–e**, the major products were dimers **3c–e**, formed as a result of SM. The desired lactones **4** were obtained in very low yields (below 5%) or as in the case of attempted closure of a 12-membered ring, lactone **4e** was not observed at all. Also in the case of these substrates, no double bond isomerization was observed.

Further synthesis of 19-functionalized vitamins consisted of reduction of the obtained lactones (**4a**, **4b**) with metal hydrides. Reduction of δ-lactone **4b** with LAH afforded the desired unsaturated diol **5**. A similar reaction of γ-lactone **4a** proceeded with simultaneous reduction of the C_{10}–C_{19} double bond but the diene core remained intact and diol **8** was obtained. Reduction of γ-lactone **4a** with the more selective DIBAL-H yielded the furan derivative **10**. Furan ring formation during reduction of α,β-unsaturated γ-lactones is known in



Scheme 3



Scheme 4

literature [26,27] (Scheme 4). The presence of a rigid furan system in the molecule causes a change of A ring conformation, as is evident from the ^{1}H NMR spectrum showing a broadened 3α-H signal. This proves that the 3β-substituent assumes an equatorial position, favorable for biological activity of vitamin D analogues [28,29].

A similar reduction of δ-lactone **4b** with DIBAL-H afforded the mixture of diastereomeric lactols **7** in the ratio 6:4 (by integration of the 19b-H signals in the ^{1}H-NMR spectrum) that were rather difficult to separate. The mixture can be used for further transformations towards different 1α-hydroxyvitamin D_3 analogues.

In the final step, the 3β-hydroxyl group in compounds **5**, **8** and **10** was deprotected with TBAF in a standard manner to afford the corresponding alcohols **6**, **9** and **11**.

4. Conclusion

It was proved that the RCM strategy can be successfully applied to the synthesis of γ- and δ-lactones from 1α-hydroxy-5,6-*trans*-vitamin D_3 unsaturated esters. The synthesis of larger rings was of a low yield or failed. The subsequent reduction of the obtained RCM products afforded 19-functionalized derivatives of 1α-hydroxy-5,6-*trans*-vitamin D_3, which can be photochemically transformed into the 5,6-*cis* isomers (the 5,6-*cis* configuration occurs in natural vitamin D_3), as was proved previously by us [16].

Acknowledgment

This work was supported by the Polish State Committee for Scientific Research (Grant No. 3 T09A 013 27).

REFERENCES

[1] Holick MF, editor. Vitamin D: physiology, molecular biology and clinical applications. Totowa, NJ: Humana Press; 1999.
[2] Bouillon RM, Okamura WH, Norman AW. Structure-function relationships in the vitamin D endocrine system. Endocr Rev 1995;16:200–7.
[3] Muralidharan KR, De Lera AR, Isaeff SD, Norman AW, Okamura WH. Studies of vitamin D (calciferol) and its analogs. 45. Studies on the A-ring diastereomers of 1α,25-dihydroxyvitamin D3. J Org Chem 1993;58:1895–9.
[4] Perlman KL, Sicinski RR, Schnoes HK, DeLuca HF. 1α,25-Dihydroxy-19-nor-vitamin D_3, a novel vitamin D-related compound with potential therapeutic activity. Tetrahedron Lett 1990;31:1823–4.
[5] Kanzler S, Halkes S, van de Velde JP, Reischl W. A novel class of vitamin D analogs. Synthesis and preliminary biological evaluation. Bioorg Med Chem Lett 1996;6:1865–8.
[6] Kroszczyński W, Morzycka B, Morzycki JW. A never ending story of vitamin D. Wiadomości Chemiczne 2002;56:793–809.
[7] Yamada S, Nakayama K, Takayama H, Itai A, Iitaka Y. Studies of vitamin D oxidation. 3. Dye-sensitized photooxidation of vitamin D and chemical behavior of vitamin D 6,19-epidioxides. J Org Chem 1983;48:3477–83.
[8] Yamada S, Suzuki T, Takayama H, Miyamoto K, Matsunaga I, Nawata Y. Stereoselective synthesis of (5*E*)- and (5*Z*)-vitamin D_3 19-alkanoic acids via vitamin D_3-sulfur dioxide adducts. J Org Chem 1983;48:3483–8.
[9] Addo JK, Ray R. Synthesis and binding-analysis of 5*E*-[19-(2-bromoacetoxy)methyl]25-hydroxyvitamin D_3 and 5*E*-25-hydroxyvitamin D_3-19-methyl[(4-azido-2-nitro)phenyl]glycinate: novel C_{19}-modified affinity and photoaffinity analogs of 25-hydroxyvitamin D_3. Steroids 1998;63:218–23.
[10] Swamy N, Addo JK, Ray R. Development of an affinity-driven cross-linker: isolation of a vitamin D receptor associated factor. Bioorg Med Chem Lett 2000;10:361–4.

[11] Addo JK, Swamy N, Ray R. The C_{19} position of 25-hydroxyvitamin D_3 faces outward in the vitamin D sterol-binding pocket of vitamin D-binding protein. Bioorg Med Chem Lett 2002;12:279–81.
[12] Grubbs RH. Olefin metathesis. Tetrahedron 2004;60:7117–40.
[13] Connon SJ, Blechert S. Recent developments in olefin cross-metathesis. Angew Chem Int Ed Engl 2003;42:1900–23.
[14] Deiters A, Martin SF. Synthesis of oxygen- and nitrogen-containing heterocycles by ring-closing metathesis. Chem Rev 2004;104:2199–238.
[15] Armstrong SK. Ring closing diene metathesis in organic synthesis. J Chem Soc; Perkin Trans 1998;1:371–88.
[16] Wojtkielewicz A, Morzycki JW. Application of ring-closing metathesis to the synthesis of 19-functionalized derivatives of 1α-hydroxyvitamin D_3. Org Lett 2006;8:839–42.
[17] Chatterjee AK, Morgan JP, Scholl M, Grubbs RH. Synthesis of functionalized olefins by cross and ring-closing metatheses. J Am Chem Soc 2000;122:3783–4.
[18] Furstner A, Thiel OR, Ackermann L, Schanz H-J, Nolan SP. Ruthenium carbene complexes with N,N′-bis(mesityl)imidazol-2-ylidene ligands: RCM catalysts of extended scope. J Org Chem 2000;65:2204–7.
[19] Bassetti M, D′Annibale A, Fanfoni A, Minissi F. Synthesis of α,β-unsaturated 4,5-disubstituted γ-lactones via ring-closing metathesis catalyzed by the first-generation Grubbs' catalyst. Org Lett 2005;7:1805–8.
[20] Ahmed M, Atkinson CE, Barrett AGM, Malagu K, Procopiou PA. Synthesis of C-19-functionalized 1α-hydroxyvitamin D_2 analogues via ring-closing metathesis. Org Lett 2003;5:669–72.
[21] Formentin P, Gimeno N, Steinke JHG, Vilar R. Reactivity of Grubbs' catalysts with urea- and amide-substituted olefins. Metathesis and isomerization. J Org Chem 2005;70:8235–8.
[22] Schmidt B. In situ conversion of a Ru metathesis catalyst to an isomerization catalyst. J Chem Soc; Chem Commun 2004:742–3.
[23] Schmidt B. Catalysis at the interface of ruthenium-carbene and ruthenium-hydride chemistry: organometallic aspects and applications to organic synthesis. Eur J Org Chem 2004:1865–81.
[24] Alcaide B, Almendros P. Non metathetic behavior patterns of Grubb's carbine. Chem Eur J 2003;9:1258–62.
[25] de la Torre MC, Deometrio AM, Alvaro E, Gracia I, Sierra MA. Synthesis of α-onoceradiene-like terpene dimers by intermolecular metathesis processes. Org Lett 2006;8:593–6.
[26] Minuto H, Nagasaki T. Studies on sesquiterpenoids. Part XVII. Total synthesis of (±)-lindestrene. J Chem Soc (C) 1968:621–4.
[27] Minuto H, Nagasaki T. A new method for the synthesis of furan compounds. J Chem Soc (C) 1966:377–9.
[28] Peleg S, Posner GH. Vitamin D analogs as modulators of vitamin D receptor action. Curr Top Med Chem 2003;3:1555–72.
[29] Rochel N, Wurtz JM, Mitschler A, Klaholz B, Moras D. The crystal structure of the nuclear receptor for vitamin D bound to its natural ligand. Mol Cell 2000;5:173–9.