ChemPubSoc Europe

DOI: 10.1002/ejoc.201701258

EurJOC European Journal of Organic Chemistry

Full Paper

Precursor Synthesis

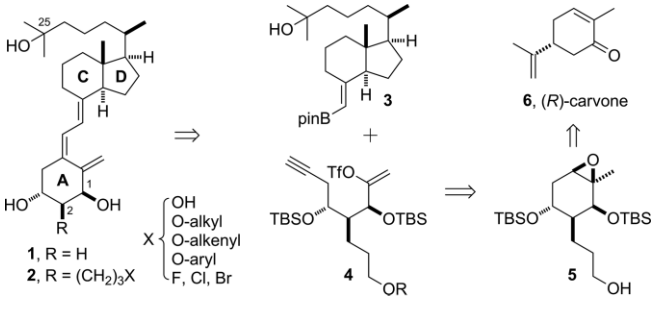
Synthesis of A-Ring Precursors of 1α,25-Dihydroxyvitamin D_3 Analogues Functionalized at C-2

Rita Sigüeiro*[a]

Abstract: A flexible approach to an A-ring building block for new 1α,25-dihydroxyvitamin D analogues functionalized at C-2 as potential clinical candidates is described. The synthesis of alcohol **5** starts from (*R*)-carvone, and uses a Criegee rearrangement to selectively degrade the isopropenyl side-chain as one of the key steps.

Introduction

1α,25-Dihydroxyvitamin D_3 [1α,25$(OH)_2D_3$, 1,25D, calcitriol, **1**; Scheme 1], the biologically active form of vitamin D_3, regulates mineral metabolism and mediates important biological functions, such as cell differentiation, cell proliferation, and immunomodulation.[1,2] The discovery of the VDR in more than 30 tissues including skin, brain, heart, pancreas, kidney, intestine, colon, prostate, ovary, and breast led to the study of the possible use of 1,25D in the treatment of metabolic bone diseases, psoriasis, cancers and immune disorders.[6,7] The solution of the crystal structure of 1,25D in complex with VDR (LBD)[8] opens up the possibility of rational design of 1,25D analogues and mimics as potential therapeutic agents.[9] The availability of space around the A-ring[10] in the binding pocket that could be used for the introduction of different substituents has led to the design and synthesis of various biologically active 1,25D analogues functionalized at C-2.[11] Among these compounds, 1α,25-dihydroxy-2β-(3-hydroxy-propoxy)vitamin D_3 (ED-71, eldecalcitol) has recently been commercialized by the Chugai Pharmaceutical Co. for the treatment of osteoporosis.[11b]



Scheme 1. Structure of target building block **5**, and retrosynthetic analysis of potential 1,25D analogues **2** functionalized at C-2 via intermediates **3** and **4**. TBS = *tert*-butyldimethylsilyl.

[a] *Departamento de Química Orgánica, Laboratorio de Investigación Ignacio Ribas, Universidad de Santiago de Compostela, Avda. Ciencias s/n, 15782 Santiago de Compostela, Spain*
E-mail: rita.sigueiro@usc.es

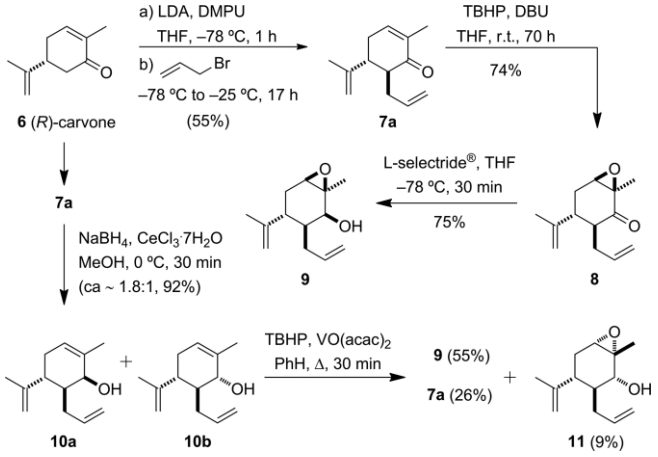
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201701258.

Most known vitamin D analogues modified at C-2 have been synthesized by convergent strategies such as the Wittig–Horner approach or Pd-catalysed processes,[11a] and the corresponding A-ring building blocks have been prepared using the Diels–Alder reaction, Heck-type cyclization, or fluoride-mediated elimination of allyl sulfones.[11f,11g,12] We have recently developed an efficient convergent approach to vitamin D metabolites and analogues featuring a highly stereoselective intramolecular cyclization of an enol triflate (A-ring or lower fragment) followed by an in-situ Suzuki–Miyaura coupling of the resulting palladium intermediate with an alkenyl boronic ester (CD-side-chain upper fragment).[13] This paper describes a further potential application of this strategy: a synthetic approach to A-ring alcohol **5** as a versatile building block for the synthesis of new analogues of 1,25D functionalized at C-2 (Scheme 1).

Results and Discussion

(*R*)-Carvone (**6**) was the starting point for the synthesis of target alcohol **5** (Scheme 2).[14,11a,12] Treatment of (*R*)-carvone with lithium diisopropylamide (LDA) in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) followed by the addition of allyl bromide provided, after flash chromatography, the desired alkylated product **7a** (55 %) together with its epimer and recovered starting material.[15] The structure of **7a** was proposed on the basis of a comparison of its spectroscopic data (^1H and ^{13}C NMR, COSY, and HMQC) with those of (*R*)-carvone. The stereoselective formation of epoxide **8** was best accomplished in 74 % yield by the reaction of **7a** with *tert*-butylhydroperoxide (TBHP) in the presence of DBU (1,5-diazabicyclo[5.4.0]undecane).[16] Epoxide **8** was then reduced with L-Selectride in THF to give alcohol **9** in 75 % yield. The stereochemistry of the hydroxy group was assigned by NOE analysis.

An alternative route to alcohol **9** was also explored. The stereoselective reduction of (*R*)-carvone was best accomplished under Luche reaction conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH)[17] to give a mixture of allylic alcohols **10a** and **10b** (ca. 1.8:1; 92 %).[18] This was then subjected to Sharpless hydroxy-group-directed epoxidation with *tert*-butyl hydroperoxide and vanadyl acetylacetonate in toluene to give, after flash chromatography,



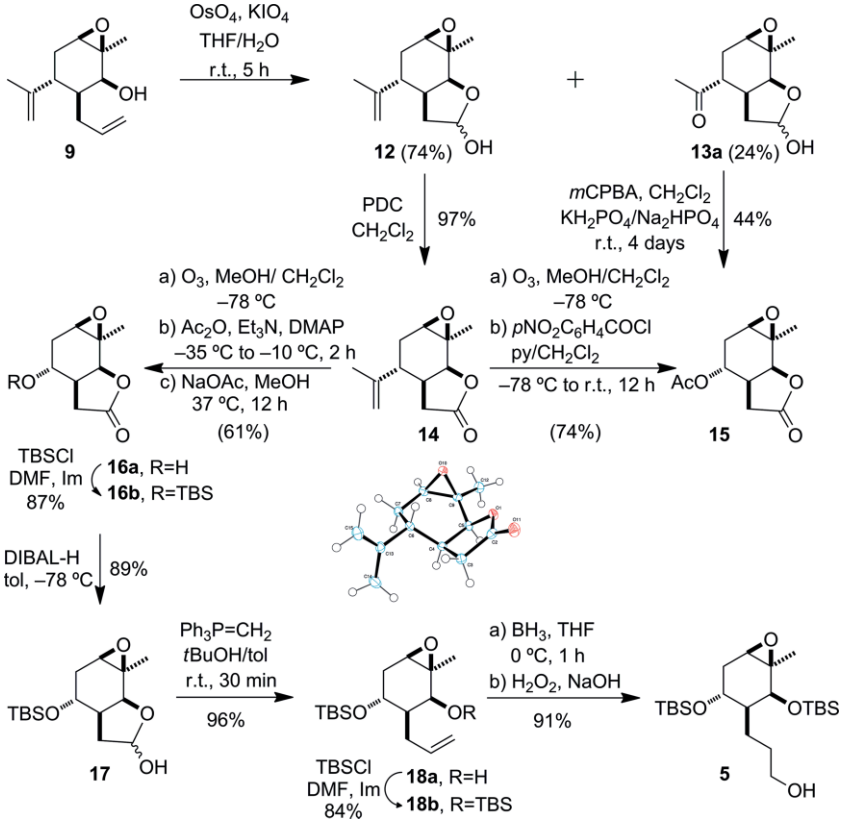
Scheme 2. Synthesis of alcohol **9** from (*R*)-carvone. DBU = 1,5-diazabicyclo[5.4.0]undecane; DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone; TBHP = *tert*-butylhydroperoxide; acac = acetoacetate.

the desired epoxide **9** (55 %) together with epoxide **11** (9 %) and starting ketone **7a** (26 %); this could be recycled through the first route to give additional amounts of **9** (65 % combined overall yield).

With alcohol **9** in hand, the synthesis of the target A-ring building block **5** (Scheme 3) was undertaken. Oxidative cleavage of the double bond in alcohol **9** using catalytic OsO_4 and KIO_4 (1 equiv.) in THF/H_2O gave a mixture of lactols **12** (74 %) and **13** (24 %). Lactols **12** were oxidized with pyridinium dichromate in CH_2Cl_2 to give lactone **14** in 97 % yield. X-ray analysis of compound **14** confirmed the relative configuration of the five stereogenic centres of the molecule.[19]

At this stage, the degradation of the isopropenyl side-chain by Criegee rearrangement[20] was achieved. Ozonolysis of **14** in MeOH/CH_2Cl_2 followed by removal of the excess O_3 and acylation of the resulting α-methoxy hydroperoxide with *p*-nitrobenzoyl chloride in pyridine/CH_2Cl_2 provided acetate **15** in 74 % yield. The structural identity of **15** was established by comparison with the compound obtained by Baeyer–Villiger oxidation (*m*CPBA, CH_2Cl_2, KH_2PO_4/Na_2HPO_4) of **13a**. Problems associated with the selective hydrolysis of the acetate group with NaOMe/MeOH led us to study the Criegee rearrangement of **14** to give the desired alcohol **16a** directly. After several experiments, the Hoffmann La Roche reaction conditions (O_3, MeOH/CH_2Cl_2; Ac_2O, Et_3N, DMAP; NaOAc, MeOH)[21] provided alcohol **16a** in 61 % yield.

Protection (TBSCl, imidazole, DMF) and reduction of the resulting lactone **16b** with diisobutylaluminum hydride in toluene gave a mixture of lactols **17** (74 % yield over two steps), which, upon Wittig reaction with $Ph_3P{=}CH_2$ (generated from Ph_3PCH_3I and KO*t*Bu in toluene), resulted in the formation of alkene **18a** (96 %). Protection of **18a** (TBSCl, imidazole, DMF) and hydroboration–oxidation (BH_3, THF; H_2O_2, NaOH) of the resulting diprotected alkene **18b** gave the desired alcohol **5** (75 % over 2 steps; 13.6 % overall yield over 10 steps).



Scheme 3. Synthesis of building block **5**, and X-ray crystal structure of lactone **14**. DIBAL-H = diisobutylaluminum hydride; PDC = pyridinium dichromate; *m*CPBA = *m*-chloroperbenzoic acid; TBS = *tert*-butyldimethylsilyl; tol = toluene; DMAP = 4-dimethylaminopyridine.

Conclusions

A flexible route to 1α,25-dihydroxyvitamin D A-ring building block **5** has been developed [11 steps, 7.5 % overall yield from (*R*)-carvone]. This compound represents a precursor for the synthesis of new vitamin D analogues functionalized at C-2 for the screening of clinical candidates. Key features of the synthetic approach are the formation of lactone **14** from epoxy alcohol **9**, and the Criegee rearrangement to degrade the (*R*)-carvone isopropenyl side-chain.

Experimental Section

General Remarks: Reagents were purchased from Sigma–Aldrich or Acros Organics and used without further purification, unless otherwise stated. All reactions involving oxygen- or moisture-sensitive compounds were carried out under a dry argon atmosphere using oven-dried or flame-dried glassware and standard syringe/septum techniques. Liquid reagents or solutions of reagents were added by syringe or cannula. All dry solvents were distilled under argon immediately before use: tetrahydrofuran (THF), Et_2O, benzene, and toluene were distilled from Na/benzophenone; CH_2Cl_2 and Ac_2O were distilled from P_2O_5; pyridine, iPr_2NH, and Et_3N were distilled from CaH_2; MeOH was distilled from Mg/I_2; DMF (ACS reagent), DBU, and DMPU were dried with activated molecular sieves (4 Å). Solutions of *n*-butyllithium in hexanes were titrated with *N*-benzylbenzamide before use. Reaction temperatures refer to external bath temperatures. Acetone/dry-ice baths were used for reactions at low temperature. Alternatively, acetone baths were cooled with a CRYOCOOL immersion cooler equipped with a temperature regulator. Silicone baths with a contact thermometer were used for high-temperature reactions. Ozonolysis reactions were carried out using a Trailigaz ozonizer model LABO-5LOX. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-backed Merck silica gel 60 plates (0.2 mm thickness). TLC plates were visualized first with ultraviolet light (254 nm), and then by immersion in solutions of ceric ammonium molybdate or *p*-anisaldehyde followed by heating with a heat gun. Organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated using a rotary evaporator at aspirator pressure (20–30 Torr). Flash column chromatography was carried out with Merck silica gel 60 (230–400 mesh). *tert*-Butyl methyl ether (TBME) and Et_2O were used as received for extractions. EtOAc, hexanes, and CH_2Cl_2 used for extractions or chromatography were previously distilled. NMR spectra were measured as solutions in $CDCl_3$ or CD_3OD with Bruker DPX-250 (250 MHz), Varian Inova 400 (400 MHz), and Bruker DRX-500 (500 MHz) spectrometers. Chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane (δ = 0.0 ppm), and the residual solvent signal was used as an internal standard: δ = 7.26 ppm (^{1}H, $CHCl_3$) and δ = 77.0 ppm (^{13}C, t, $CDCl_3$); δ = 3.31 ppm (q, 1 H, CD_3OH) and δ = 79.0 ppm (^{13}C, hept, CD_3OD). Coupling constants (*J*) are reported in Hz. Distortionless enhancement by polarization transfer (DEPT-135) was used to assign carbon types. Low- (MS) and High-resolution mass spectra (HRMS) were measured with a Micromass Autospec instrument (CI) or with a Bruker Microtof instrument (ESI-TOF). IR spectra were recorded on a silicon disc with a Varian FTIR 670 spectrometer. Elemental analysis was carried out with a Fisons element analyser, model EA 1108. X-ray diffraction was carried out with a Bruker APPEX-II single-crystal diffractometer. Melting points were measured in open capillary tubes. Optical rotations were measured with a Jasco DIP-370 polarimeter in a 1 dm cell. $[\alpha]$ and *c* are given in deg cm^3 g^{-1} dm^{-1} and g cm^{-3}, respectively. Yields refer to chromatographically purified compounds, unless otherwise stated. Compound names and signals in the NMR spectra have been numbered using IUPAC numbering according to the Chemdraw program.

(*5R*,*6S*)-6-Allyl-2-methyl-5-(prop-1-en-2-yl)-cyclohex-2-en-1-one (7a): A solution of lithium diisopropylamide was prepared by the slow addition of *n*BuLi (2.44 M solution in hexanes; 3.6 mL, 8.8 mmol, 1.2 equiv.) to neat iPr_2NH (1.1 mL, 8 mmol, 1.1 equiv.) at −78 °C. The cooling bath was removed, and the white slurry was stirred at room temperature for 15 min. The suspension was cooled to −78 °C, and THF (12 mL) was added. After 15 min, 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 4 mL, 31.5 mmol, 4.7 equiv.) was added, and the reaction mixture was stirred for 15 min. Then, a solution of (*R*)-carvone (**6**; 1 g, 6.7 mmol, 1 equiv.) in THF (5 mL) was added by cannula. The resulting mixture was stirred for 1 h. Freshly, distilled allyl bromide (distilled from CaH_2; 0.72 mL, 7.9 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred for 14 h at −78 °C, and then for 3 h at −25 °C. The reaction was quenched with sat. aq. NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with brine (30 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3 × 21 cm, hexanes) to give **7a** (0.7 g, 55 %) as a colourless oil, and also recovered starting material **6** (0.216 g, conversion 71 %). Data for **7a**: R_f = 0.40 (5 % EtOAc/hexanes). $[\alpha]_D^{25}$ = +62.4 (*c* = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.62 (m, 1 H, 3-H), 5.75 (ddt, *J* = 17.1, 10.1, 7.0 Hz, 1 H, 2′-H), 4.98 (dm, *J* = 17.1 Hz, 1 H, 3′-H$_Z$), 4.94 (dm, *J* = 10.3 Hz, 1 H, 3′-H$_E$), 4.81 (dq, *J* = 3.0, 1.5 Hz, 1 H, 1″-H$_E$), 4.75 (d, *J* = 1.5 Hz, 1 H, 1″-H$_Z$), 2.65 (ddd, *J* = 11.4, 9.6, 5.2 Hz, 1 H, 5-H), 2.49 (dtd, *J* = 13.2, 7.0, 6.4 Hz, 1 H, 1′-H), 2.43–2.32 (m, 2 H, 6-H and 4-H), 2.27 (dtd, *J* = 18.0, 5.2, 1.5 Hz, 1 H, 4-H), 2.18 (ddd, *J* = 13.2, 7.1, 6.1 Hz, 1 H, 1′-H), 1.73 (br. s, 3 H, Me-C-2), 1.67 (s, 3 H, Me-3′) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 200.4 (C=O, C-1), 145.1 (=C, C-2″), 143.1 (=CH, C-3′), 135.9 (=CH, C-2′), 135.0 (=C, C-2), 116.5 (=CH_2, C-3′), 113.4 (=CH_2, C-1″), 48.7 (CH, C-6), 46.6 (CH, C-5), 31.6 (CH_2, C-1′), 30.5 (CH_2, C-4), 18.8 (CH_3, Me-C-2), 15.9 (CH_3, C-3″) ppm. IR (film): $\tilde{\nu}$ = 1713 (C=O), 1671 (C=C), 1644 (C=C) cm^{-1}. MS (CI$^+$): *m*/*z* (%) = 191.1 (100) [M + H]$^+$, 163.1 (19) [M − (CH=CH_2)]$^+$, 149.1 (48) [M − *i*Pr]$^+$, 109.1 (61) [M − 2*i*Pr]$^+$. HRMS (CI$^+$): calcd. for $C_{13}H_{19}O$ [M + H]$^+$ 191.1436; found 191.1430.

(1*R*,3*S*,4*R*,6*R*)-3-Allyl-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo-[4.1.0]heptan-2-one (8): Dry 1,5-diazabicycle[5.4.0]undecane (DBU; 2.4 mL, 15.8 mmol, 3 equiv.) and *tert*-butyl hydroperoxide (TBHP; 5 M solution in decane; 31.5 mL, 15.8 mmol, 3 equiv.) were successively added dropwise to a solution of enone **7a** (1 g, 5.3 mmol, 1 equiv.) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 12 h. Additional amounts of TBHP (1 mL, 5.3 mmol, 1 equiv.) and DBU (0.8 mL, 5.3 mmol, 1 equiv.) were then added. After a further 12 h, additional TBHP (1 mL, 5.3 mmol, 1 equiv.) and DBU (0.8 mL, 5.3 mmol, 1 equiv.) were again added. This process was repeated five times. The reaction was then quenched with sat. aq. NH_4Cl (20 mL). The mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (40 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3 × 20 cm, 1 % EtOAc/hexanes) to give epoxide **8** (0.797 g, 74 %) as a yellowish oil. R_f = 0.35 (6 % EtOAc/hexanes). $[\alpha]_D^{25}$ = +159.6 (*c* = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 (m, 1 H, 2′-H), 4.88 (dm, *J* = 15.6 Hz, 1 H, 3′-H$_Z$), 4.87 (d, *J* = 10.3 Hz, 1 H, 3′-H$_E$), 4.75 (m, 1 H, 1″-H$_E$), 4.70 (*J* = 1.8 Hz, 1 H, 1″-H$_Z$), 3.30 (d, *J* = 3.3 Hz, 1 H, 6-H), 2.63 (td, *J* = 11.7, 4.4 Hz, 1 H, 4-H), 2.50 (m, 1 H, 1′-H), 2.12 (dt, *J* = 14.8, 3.7 Hz, 1 H, 5-H), 2.06 (m, 1 H, 1′-H), 1.99 (ddd, *J* = 11.4, 5.4, 4 Hz, 1 H, 3-H), 1.87 (dd, *J* = 14.8, 11.1 Hz, 1 H, 5-H), 1.55

(d, J = 1.5 Hz, 3 H, Me-3''), 1.30 (s, 3 H, Me-C-1) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 206.8 (C=O, C-2), 144.4 (=C, C-2''), 134.6 (=CH, C-2'), 116.8 (=CH_2, C-3'), 113.4 (=CH_2, C-1''), 60.5 (CH, C-6), 58.8 (C, C-1), 48.7 (CH, C-3), 38.9 (CH, C-4), 32.4 (CH_2, C-1'), 28.8 (CH_2, C-5), 18.8 (CH_3, C-3''), 15.9 (CH_3, Me-C-1) ppm. IR (film): $\tilde{\nu}$ = 1704 (C=O), 1642 (C=C), 1613 (C=C) cm^{-1}. MS (CI^+): m/z (%) = 207.1 (2) [M + H]$^+$, 165.1 (4) [M – C_3H_5]$^+$, 125.1 (6) [M – 2C_3H_5 – H_2O]$^+$, 97.1 (14) [M – 2C_3H_5 – OMe]$^+$, 19.1 (100). HRMS (CI^+): calcd. for $C_{13}H_{19}O_2$ [M + H]$^+$ 207.1385; found 207.1379.

(1*S*,2*S*,3*S*,4*R*,6*R*)-3-Allyl-1-methyl-4-(prop-1-en-2-yl)-7-oxabicyclo[4.1.0]heptan-2-ol (9):[22] L-Selectride® (1 M solution in THF; 10.5 mL, 10.5 mmol, 1.5 equiv.) was added dropwise to a solution of ketone **8** (1.45 g, 7.0 mmol, 1 equiv.) in THF (20 mL) at –78 °C. After 30 min, the reaction was quenched by the slow addition of MeOH (5 mL) and H_2O (5 mL). Solutions of NaOH (10 % aq.; 5 mL) and H_2O_2 (30 % aq. v/v; 7 mL) were successively and slowly added. The mixture was allowed to reach room temperature over 12 h. Sat. aq. NH_4Cl (15 mL) was added. The mixture was extracted with Et_2O (3 × 30 mL). The combined organic phases were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3 × 12 cm, 4 % EtOAc/hexanes) to give **9** (1.09 g, 75 %) as a colourless oil. R_f = 0.20 (8 % EtOAc/hexanes). $[\alpha]_D^{25}$ = –49.8 (c = 3.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (m, 1 H, 2'-H), 5.02 (d, J = 17.2 Hz, 1 H, 3'-H_Z), 4.96 (d, J = 10.1 Hz, 1 H, 3'-H_E), 4.72 (br. s, 1 H, 1''-H_E), 4.70 (s, 1 H, 1''-H_Z), 3.83 (br. s, 1 H, 2-H), 3.21 (t, J = 2.0 Hz, 1 H, 6-H), 2.10 (s, 1 H, OH), 2.06–1.97 (m, 3 H, 5-H, 4-H and 1'-H), 1.85 (m, 1 H, 1'-H), 1.75 (tm, J = 13.5 Hz, 1 H, 5-H), 1.56 (dq, J = 1.3, 0.8 Hz, 3 H, Me-3''), 1.38 (s, 3 H, Me-C-1), 1.19 (m, 1 H, 3-H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 145.4 (=C, C-2''), 137.0 (=CH, C-2'), 116.1 (=CH_2, C-3'), 113.2 (=CH_2, C-1''), 67.9 (CH, C-2), 62.5 (CH, C-6), 60.6 (C, C-1), 42.0 (CH, C-3), 36.6 (CH, C-4), 31.8 (CH_2, C-1'), 30.8 (CH_2, C-5), 22.0 (CH_3, Me-C-1), 18.1 (CH_3, C-3'') ppm. IR (film): $\tilde{\nu}$ = 3314 (O–H), 1661 (C=C) cm^{-1}. MS (CI^+): m/z (%) = 209.2 (24) [M + H]$^+$, 191.2 (53) [M – OH]$^+$, 175.1 (16) [M – H_2O – Me]$^+$, 151.1 (19) [M – C_3H_5 – OH]$^+$, 111.1 (17) [M – 2C_3H_5 – H_2O]$^+$. HRMS (CI^+): calcd. for $C_{13}H_{21}O_2$ [M + H]$^+$ 209.1542; found 209.1545.

(1a*R*,3*R*,3a*S*,6a*S*,6b*R*)-6b-Methyl-3-(prop-1-en-2-yl)octahydrooxireno[2,3-*g*]benzofuran-5-ol (12): OsO_4 (4 % solution in water; 10 drops) was added to a suspension of **9** (1.0 g, 4.8 mmol, 1 equiv.) in THF/H_2O (1:1; 40 mL). The mixture was stirred for 5 min, and then KIO_4 (1.1 g, 4.8 mmol, 1 equiv.) was added. After 5 h, the mixture was filtered through a pad of Celite, and the solids were washed with EtOAc. The combined organic phase was washed with sat. aq. $Na_2S_2O_3$ (30 mL), dried, filtered and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2 × 14 cm, 20 % EtOAc/hexanes) to give lactols **12** (0.742 g, 74 %; equilibrium mixture **12*R*** and **12*S***, 3:1) as a white solid, and ketone **13**[23] (0.245 g, 24 %; equilibrium mixture **13*R*** and **13*S***, 2:1) as a yellowish solid.

Data for **12**: M.p. 83–89 °C (EtOAc). R_f = 0.20 (30 % EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$; **12*R***, major compound): δ = 5.57 (t, J = 2.5 Hz, 1 H, 5-H), 4.72 (br. s, 1 H, 1'-H), 4.70 (br. s, 1 H, 1'-H), 4.42 (d, J = 7.0 Hz, 1 H, 6-Ha), 3.73 (s, 1 H, OH), 3.12 (d, J = 3.0 Hz, 1 H, 1-Ha), 2.18–1.88 (m, 4 H), 1.79–1.63 (m, 2 H), 1.60 (s, 3 H, Me-3'), 1.42 (s, 3 H, Me-C-6b) ppm; (**12*S***, minor compound) δ = 5.36 (t, J = 5.8 Hz, 1 H, 5-H), 4.77 (s, 1 H, 1'-H), 4.76 (s, 1 H, 1'-H), 4.32 (d, J = 7.9 Hz, 1 H, 6-Ha), 3.64 (d, J = 6.8 Hz, 1 H, OH), 3.25 (d, J = 3.3 Hz, 1 H, 1-Ha), 2.54 (m, 1 H), 2.29 (m, 1 H), 2.18–1.88 (m, 3 H), 1.79–1.63 (m, 1 H), 1.61 (s, 3 H, Me-3'), 1.44 (s, 3 H, Me-C-6b) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$; **12*R***, major compound): δ = 145.8 (C, C-2'), 112.2 (=CH_2, C-1'), 97.0 (CH, C-5), 77.5 (CH, C-6a), 59.8 (CH, C-1a), 56.5 (C, C-6b), 41.0 (CH, C-3), 38.4 (CH_2, C-4), 37.3 (CH, C-3a), 29.4 (CH_2, C-2), 21.8 (CH_3, C-3'), 19.0 (CH_3, Me-C-6b) ppm; (**12*S***, minor compound) δ = 146.0 (=C, C-2'), 112.6 (=CH_2, C-1'), 97.9 (CH, C-5), 80.4 (CH, C-6a), 62.0 (CH, C-1a), 57.2 (C, C-6b), 40.7 (CH, C-3), 37.1 (CH, C-3a), 33.0 (CH_2, C-4), 28.9 (CH_2, C-2), 21.8 (CH_3, C-3'), 19.2 (CH_3, Me-C-6b) ppm. IR (film): $\tilde{\nu}$ = 3378 (O–H), 1642 (C=C) cm^{-1}. MS (CI^+): m/z (%) = 211.2 (3) [M + H]$^+$, 193.1 (75) [M – OH]$^+$, 175.0 (88) [M – OH – H_2O]$^+$, 151.0 (25) [M – C_3H_5 – H_2O]$^+$, 106.7 (100). HRMS (CI^+): calcd. for $C_{12}H_{19}O_3$ [M + H]$^+$ 211.1334; found 211.1331.

Data for **13**:[23] M.p. 85.6–91.4 °C (EtOAc).

(1a*R*,3*R*,3a*S*,6a*S*,6b*R*)-6b-Methyl-3-(prop-1-en-2-yl)hexahydrooxireno[2,3-*g*]benzofuran-5(1a*H*)-one (14): Pyridinium dichromate (PDC; 5.9 g, 15.7 mmol, 1 equiv.) was added to a solution of lactols **12** (1.1 g, 5.24 mmol, 1 equiv.) in dry CH_2Cl_2 (30 mL). The mixture was stirred in the dark at room temperature for 12 h. The resulting black mixture was diluted with Et_2O (50 mL), and filtered through a pad of Celite/silica gel. The solids were washed with Et_2O (3 × 20 mL). The solution was concentrated in vacuo, and the resulting oil was purified by flash chromatography (SiO_2, 2 × 8 cm, 20 % EtOAc/hexanes) to give lactone **14** (1.06 g, 97 %) as a white solid. M.p. 155–156 °C (EtOAc). R_f = 0.50 (50 % EtOAc/hexanes). $[\alpha]_D^{25}$ = +75.6 (c = 3.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (d, J = 1.5 Hz, 1 H, 1'-H_E), 4.74 (d, J = 6.7 Hz, 1 H, 6-Ha), 4.68 (br. s, 1 H, 1'-H_Z), 3.16 (d, J = 2.5 Hz, 1 H, 1-Ha), 2.54 (dd, J = 17.9, 8.5 Hz, 1 H, 4-H), 2.33–2.18 (m, 3 H, 3-H, 3-Ha and 4-H), 2.05 (dt, J = 14.7, 2.6 Hz, 1 H, 2-H), 1.71 (dd, J = 14.7, 11.2 Hz, 1 H, 2-H), 1.56 (d, J = 0.7 Hz, 3 H, Me-3'), 1.42 (s, 3 H, Me-C-6b) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 175.8 (C=O, C-5), 144.3 (=C, C-2'), 113.5 (=CH_2, C-1'), 80.3 (CH, C-6a), 59.6 (CH, C-1a), 55.1 (C, C-6b), 38.7 (CH, C-3a), 35.3 (CH, C-3), 32.8 (CH_2, C-4), 28.6 (CH, C-2), 21.6 (CH_3, Me-C-6), 18.8 (CH_3, C-3') ppm. IR (film): $\tilde{\nu}$ = 1769 (C=O lactone), 1640 (C=C) cm^{-1}. MS (CI^+): m/z (%) = 209.1 (96) [M + H]$^+$, 193.1 (23) [M – Me]$^+$, 192.1 (47) [M – H_2O]$^+$, 191.1 (97) [M – OH]$^+$, 167.0 (64) [M – C_3H_5]$^+$, 150.0 (60) [M – $C_2H_2O_2$]$^+$, 106.7 (100). HRMS (CI^+): calcd. for $C_{12}H_{17}O_3$ [M + H]$^+$ 209.1178; found 209.1173.

(1a*R*,3*R*,3a*S*,6a*S*,6b*R*)-6b-Methyl-5-oxooctahydrooxireno-[2,3-*g*]benzofuran-3-yl Acetate (15): Ozone in oxygen (0.7 bar, 0.1 NL h^{-1}, 50 W) was bubbled through a solution of lactone **14** (1 g, 4.81 mmol, 1 equiv.) in dry MeOH (10 mL) and dry CH_2Cl_2 (50 mL) at –78 °C until the solution turned blue (20 min). The excess O_3 was removed by bubbling with argon for 30 min at –78 °C. The reaction mixture was allowed to reach room temperature under a slow flow of argon (40 min). Then, dry benzene (20 mL) was added and the mixture was concentrated in vacuo.

The residue was dissolved in dry CH_2Cl_2 (50 mL) and pyridine (5.5 mL), and the solution was cooled to –78 °C under argon. Then, freshly distilled *p*-nitrobenzoyl chloride (2.4 g, 12.9 mmol, 2.7 equiv., Kugelrohr) was added in one portion. The reaction mixture was allowed to reach room temperature slowly. After 12 h, the mixture was cooled to –78 °C and filtered through a cold filter plate, washing with CH_2Cl_2 (15 mL) precooled to –78 °C. The resulting solution was concentrated to dryness, and the residue was dissolved in $CHCl_3$/MeOH (3:1; 20 mL). The solution was washed with HCl (10 % aq.; 2 × 15 mL), and NaOH (3 M aq.; 2 × 15 mL), dried, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, 3 × 10 cm, 20 % EtOAc/hexanes) to give acetate **15** (0.810 g, 74 %) as a white solid. M.p. 124–126 °C (EtOAc). R_f = 0.62 (4 % MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +14.5 (c = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (m, 1 H, 3-H), 4.81 (d, J = 8.0 Hz, 1 H, 6-Ha), 3.21 (t, J = 2.1 Hz, 1 H, 1-Ha), 2.64 (m, 1 H, 3-Ha), 2.53 (ddd, J = 17.6, 9.4, 1.3 Hz, 1 H, 4-H), 2.46–2.31 (m, 2 H, 4-H and 3-H), 2.01 (d, J = 2.0 Hz, 3 H, Me-2'), 1.91 (ddt, J = 15.2, 7.3, 2.0 Hz, 1 H, 2-H), 1.46 (d, J = 2.2 Hz, 3 H, Me-C-6b) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ =

175.1 (C=O, C-5), 169.9 (C=O, C-1′), 79.9 (CH, C-6a), 69.0 (CH, C-3), 59.5 (CH, C-1a), 56.7 (C, C-6b), 37.7 (CH, C-3a), 31.4 (CH_2, C-4), 27.3 (CH_2, C-2), 20.9 (CH_3, C-2′), 20.3 (CH_3, Me-C-6b) ppm. IR (film): $\tilde{\nu}$ = 1775 (C=O lactone), 1732 (C=O acetate) cm^{-1}. MS (Cl^+): *m/z* (%) = 227.1 (25) $[M + H]^+$, 211.1 (5) $[M - Me]^+$, 193.1 (73) $[M - H_2O - Me]^+$, 193.1 (79) $[M - 2H_2O - Me]^+$, 167.0 (45) $[M - OAc]^+$, 148.9 (100) $[M - OAc - H_2O]^+$. $C_{11}H_{14}O_5$ (226.2263): calcd. C 58.40, H 6.24; found C 58.04, H 6.25.

(1a*R*,3*R*,3a*S*,6a*S*,6b*R*)-3-Hydroxy-6b-methylhexahydrooxireno[2,3-*g*]benzofuran-5(1a*H*)-one (16a): Ozone in oxygen (0.7 bar, 0.1 NL h^{-1}, 50 W) was bubbled through a solution of lactone **14** (0.5 g, 2.4 mmol, 1 equiv.) in dry MeOH (1 mL) and dry CH_2Cl_2 (10 mL) at –78 °C until the solution turned blue (10 min). The excess O_3 was removed by bubbling with argon for 30 min. The reaction mixture was allowed to reach room temperature (40 min) under a slow flow of argon.

The mixture was then cooled to –35 °C. After 10 min, Et_3N (4.6 mL, 33.6 mmol, 14 equiv.) and DMAP (60 mg, 0.48 mmol, 0.2 equiv.) were slowly added. Once the DMAP had dissolved, Ac_2O (freshly distilled from P_2O_5 under argon; 3.2 mL, 33.6 mmol, 14 equiv.) was added dropwise by syringe. The reaction mixture was allowed to reach –8 °C, and it was stirred at this temperature for 2 h. The reaction was quenched by the slow addition of MeOH (5 mL). The mixture was stirred at room temperature for 5 min, then it was diluted with EtOAc (30 mL), and successively washed with a solution of citric acid (10 % aq.; 2 × 30 mL) and sat. aq. $NaHCO_3$ (2 × 25 mL). The organic solution was dried, filtered, and concentrated in vacuo.

The residue was dissolved in dry MeOH (10 mL), and NaOAc (40 mg, 0.48 mmol, 0.2 equiv.) was added. The mixture was heated at 37 °C for 12 h, and then it was concentrated to half its volume. The suspension was diluted with EtOAc (30 mL), and the mixture was washed with sat. aq. NH_4Cl (25 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2.5 × 8 cm, 50 % EtOAc/hexanes) to give alcohol **16a** (0.265 g, 61 %) as a white solid. M.p. 135–136 °C. R_f = 0.25 (4 % MeOH/CH_2Cl_2). $[\alpha]_D^{25}$ = +1.31 (*c* = 1.8, $CHCl_3$). ^1H NMR (500 MHz, CD_3OD): δ = 4.96 (d, *J* = 7.7 Hz, 1 H, 6-Ha), 4.79 (br. s, 1 H, OH), 3.67 (td, *J* = 9.3, 4.6 Hz, 1 H, 3-H), 3.28 (dd, *J* = 2.8, 1.7 Hz, 1 H, 1-Ha), 2.72 (dd, *J* = 18.0, 9.4 Hz, 1 H, 4-H), 2.48 (dd, *J* = 18.0, 3.9 Hz, 1 H, 4-H), 2.40 (tdd, *J* = 9.4, 7.7, 3.9 Hz, 1 H, 3-Ha), 2.33 (ddd, *J* = 14.7, 4.5, 2.9 Hz, 1 H, 2-H), 1.82 (ddd, *J* = 14.7, 9.2, 1.7 Hz, 1 H, 2-H), 1.49 (s, 3 H, Me-C-6b) ppm. ^{13}C NMR (125.7 MHz, CD_3OD): δ = 178.7 (C=O, C-5), 83.1 (CH, C-6a), 66.4 (CH, C-3), 62.0 (CH, C-1a), 57.5 (C, C-6b), 42.0 (CH, C-3a), 32.9 (CH_2, C-4), 32.4 (CH_2, C-2), 21.4 (CH_3, Me-C-6b) ppm. IR (film): $\tilde{\nu}$ = 3311 (O–H), 1763 (C=O lactone) cm^{-1}. MS (Cl^+): *m/z* (%) = 185.1 (96) $[M + H]^+$, 186.1 (16) $[(M + 1) + H]^+$, 167.0 (95) $[M - OH]^+$, 153.0 (25) $[M - OH - Me]^+$, 138.9 (92) $[M - CO - H_2O]^+$, 124.8 (98) $[M - CO_2 - OH]^+$, 106.7 (100). $C_9H_{12}O_4$ (185.1910): calcd. C 58.69, H 6.57; found C 58.24, H 6.47.

(1a*R*,3*R*,3a*R*,6a*S*,6b*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6b-methylhexahydrooxireno[2,3-*g*]benzofuran-5(1a*H*)-one (16b): Imidazole (0.67 g, 9.78 mmol, 3 equiv.) and TBSCl (0.74 g, 4.89 mmol, 1.5 equiv.) were successively added to a solution of alcohol **16a** (0.6 g, 3.26 mmol, 1 equiv.) in dry DMF (10 mL). The reaction mixture was stirred for 12 h, and then ice was added. The resulting mixture was extracted with TBME (2 × 20 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (SiO_2, 2 × 10 cm, 10 % EtOAc/hexanes) to give **16b** (0.847 g, 87 %) as a white solid. M.p. 34.1–34.8 °C. R_f = 0.7 (40 % EtOAc/hexanes). $[\alpha]_D^{25}$ = –0.82 (*c* = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.77 (d, *J* = 7.3 Hz, 1 H, 6-Ha), 3.83 (dd, *J* = 11.7, 7.5 Hz, 1 H, 3-H), 3.17 (t, *J* = 2.3 Hz, 1 H, 1-Ha), 2.57–2.30 (m, 3 H, CH_2-4 and 3-H), 2.23 (ddd, *J* = 14.9, 4.2, 2.3 Hz, 1 H, 2-H), 1.79 (ddd, *J* = 14.9, 7.5, 2.3 Hz, 1 H, 2-H), 1.43 (s, 3 H, Me-C-6b), 0.82 (s, 9 H, Me_3CSi), 0.023 (s, 3 H, MeSi), 0.015 (s, 3 H, MeSi) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.9 (C=O, C-5), 80.7 (CH, C-6a), 66.6 (CH, C-3), 60.0 (CH, C-1a), 56.4 (C, C-6b), 41.1 (CH, C-3a), 37.1 (CH_2, C-4), 31.2 (CH_2, C-2), 25.5 (3 CH_3, Me_3CSi), 20.8 (CH_3, Me-C-6b), 17.7 (C, CSi), –4.5 (CH_3, MeSi), –5.0 (CH_3, MeSi) ppm. IR (film): $\tilde{\nu}$ = 1768 (C=O lactone) cm^{-1}. MS (ESI-TOF$^+$): *m/z* (%) = 321.1 (100) $[M + Na]^+$, 299.2 (9) $[M + H]^+$, 283.2 (3) $[M - Me]^+$, 253.2 (2) $[M - OH - CO]^+$, 239.1 (10) $[M - CO_2 - Me]^+$, 167.1 (12) $[M - OTBS]^+$, 149.1 (4) $[M - OTBS - H_2O]^+$ 121.0 (5), 105.0 (4). HRMS (ESI-TOF$^+$): calcd. for $C_{15}H_{27}O_4Si$ $[M + H]^+$ 299.1673; found 209.1674.

(1a*R*,3*R*,3a*R*,6a*S*,6b*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6b-methyloctahydrooxireno[2,3-*g*]benzofuran-5-ol (17): DIBAL-H (1 M solution in CH_2Cl_2; 1.5 mL, 1.51 mmol, 1.2 equiv.) was added to a solution of **16b** (0.375 g, 1.26 mmol, 1 equiv.) in dry toluene (10 mL) at –78 °C. The mixture was stirred for 30 min. The reaction was then quenched with sat. aq. NH_4Cl (10 mL). The mixture was allowed to reach room temperature, and then it was extracted with EtOAc (2 × 15 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3 × 8 cm, 15 % EtOAc/hexanes) to give **17** (0.336 g, 89 %, equilibrium mixture 5.6:1) as a colourless oil. R_f = 0.7 (50 % EtOAc/hexanes). ^1H NMR (250 MHz, $CDCl_3$; major compound): δ = 5.61 (d, *J* = 4.1 Hz, 1 H, 5-H), 4.48 (d, *J* = 8.1 Hz, 1 H, 6-Ha), 3.71 (br. s, 1 H, OH), 3.66 (td, *J* = 9.3, 4.6 Hz, 1 H, 3-H), 3.12 (d, *J* = 2.5 Hz, 1 H, 1-Ha), 2.53–1.61 (m, 5 H), 1.41 (br. s, 3 H, Me-C-6b), 0.83 (s, 9 H, Me_3CSi), 0.03 (s, 6 H, Me_2Si) ppm; (minor compound) δ = 5.41 (m, 1 H, 5-H), 4.38 (d, *J* = 7.6 Hz, 1 H, 6-Ha), 4.01 (td, *J* = 7.7, 4.9 Hz, 1 H, 3-H), 3.71 (br. s, 1 H, OH), 3.24 (m, 1 H, 1-Ha), 2.53–1.61 (m, 5 H), 1.44 (br. s, 3 H, Me-C-6b), 0.83 (s, 9 H, Me_3CSi), 0.01 (s, 6 H, Me_2Si) ppm. ^{13}C NMR (63 MHz, $CDCl_3$; major compound): δ = 97.5 (CH, C-5), 78.9 (CH, C-6a), 69.5 (CH, C-3), 60.5 (CH, C-1a), 57.1 (C, C-6b), 43.4 (CH, C-3a), 38.1 (CH_2, C-4), 32.8 (CH_2, C-2), 25.6 (3 CH_3, Me_3CSi), 21.1 (CH_3, Me-C-6b), 17.8 (C, CSi), –4.3 (CH_3, MeSi), –4.8 (CH_3, MeSi) ppm; (minor compound) δ = 98.5 (CH, C-5), 80.9 (CH, C-6a), 68.3 (CH, C-3), 62.3 (CH, C-1a), 57.8 (C, C-6b), 43.8 (CH, C-3a), 37.4 (CH_2, C-4), 31.9 (CH_2, C-2), 25.6 (3 CH_3, Me_3C-Si), 21.0 (CH_3, Me-C-6b), 17.8 (C, CSi), –4.4 (CH_3, MeSi), –4.8 (CH_3, MeSi) ppm. IR (film): $\tilde{\nu}$ = 3371 (O–H) cm^{-1}. MS (ESI-TOF$^+$): *m/z* (%) = 301.2 (90) $[M + H]^+$, 299.2 (18) $[(MH - OH)]^+$, 283.2 (7) $[M - OH]^+$, 283.2 (5) $[M - Me]^+$, 269.1 (20) $[M - CH_2OH]^+$, 255.1 (23) $[M - OH - CO]^+$, 185.0 (23) $[M - TBS]^+$, 137.0 (100) $[M - OTBS - Me - OH]^+$ 115.1 (36), 109.0 (39). HRMS (ESI-TOF$^+$): calcd. for $C_{15}H_{29}O_4Si$ $[M + H]^+$ 301.1835; found 301.1841.

(1*S*,2*S*,3*R*,4*R*,6*R*)-3-Allyl-4-[(*tert*-butyldimethylsilyl)oxy]-1-methyl-7-oxabicyclo[4.1.0]heptan-2-ol (18a): A mixture of Ph_3PCH_3I (1.06 g, 2.96 mmol, 7 equiv.) and dry toluene (15 mL) was vigorously stirred for 5 min, and then KO*t*Bu (0.330 g) was added. The mixture was heated at 90 °C for 30 min. The oil bath was then removed, and the yellow suspension was allowed to reach room temperature. After 15 min, a solution of lactols **17** (0.127 mg, 0.422 mmol, 1 equiv.) in toluene (10 mL) was added by cannula. The mixture was stirred at room temperature for 35 min. The reaction was quenched with sat. aq. NH_4Cl (50 mL). The resulting mixture was extracted with hexanes (2 × 30 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1.5 × 10 cm, 10 % EtOAc/hexanes) to give **18a** (0.121 g, 96 %) as a yellowish foam. R_f = 0.7 (40 % EtOAc/hexanes). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.79 (dq, *J* = 17.2, 8.7 Hz, 1 H, 2′-H), 5.09 (d, *J* = 17.2 Hz, 1 H, 3′-H_Z), 5.02 (d, *J* = 10.0 Hz, 1 H, 3′-H_E), 3.92 (dd, *J* = 8.8, 4.2 Hz, 1 H, 2-H), 3.56

(dt, J = 9.3, 4.2 Hz, 1 H, 4-H), 3.21 (d, J = 0.9 Hz, 1 H, 6-H), 2.45–2.30 (m, 2 H), 2.20–1.88 (m, 2 H), 1.66 (dd, J = 14.8, 8.8 Hz, 1 H), 1.40 (s, 3 H, Me-C-1), 0.85 (s, 9 H, Me_3CSi), 0.02 (s, 3 H, MeSi), 0.01 (s, 3 H, MeSi) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 137.2 (=C, C-2′), 116.3 (=CH_2, C-3′), 69.4 (CH, C-2), 65.1 (CH, C-4), 63.2 (CH, C-6), 60.7 (C, C-1), 47.4 (CH, C-3), 34.9 (CH_2, C-1′), 30.3 (CH_2, C-5), 25.7 (3 CH_3, Me_3C-Si), 21.5 (CH_3, Me_3C-1), 17.9 (C, CSi), –4.5 (CH_3, MeSi), –4.9 (CH_3, MeSi) ppm. IR (film): $\tilde{\nu}$ = 3320 (O–H), 1641 (C=C) cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 321.2 (100) $[M + Na]^+$, 306.3 (10) $[(M - OH) + Na]^+$, 301.1 (61), 292.3 (14) $[(M - CH_2 - OH) + Na]^+$, 239.0 (22) $[M - C_3H_5 - H_2O]^+$, 224.2 (4) $[M - OH - tBu]^+$, 118.1 (4). HRMS (ESI-TOF$^+$): calcd. for $C_{16}H_{30}NaO_3Si$ $[M + Na]^+$ 321.1856; found 321.1856.

{[(1*R*,2*S*,3*S*,4*R*,6*R*)-3-Allyl-1-methyl-7-oxabicyclo[4.1.0]heptane-2,4-diyl]bis(oxy)}bis(*tert*-butyldimethylsilane) (18b): Imidazole (0.55 g, 0.8 mmol, 2 equiv.) and TBSCl (0.91 g, 0.6 mmol, 1.5 equiv.) were successively added to a solution of alcohol **18a** (0.120 g, 0.4 mmol, 1 equiv.) in dry DMF (2 mL). The reaction mixture was stirred at room temperature for 12 h, and then ice was added. The resulting mixture extracted with hexanes (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 1.5 × 10 cm; 5 % EtOAc/hexanes) to give **18b** (0.140 g, 84 %) as a colourless oil. R_f = 0.8 (20 % EtOAc/hexanes). $[\alpha]_D^{25}$ = –23.6 (c = 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.65 (dddd, J = 17.0, 9.6, 8.5, 5.7 Hz, 1 H, 2′-H), 4.99 (d, J = 17.0 Hz, 1 H, 3′-H_Z), 4.94 (d, J = 9.6 Hz, 1 H, 3′-H_E), 4.35 (d, J = 5.8 Hz, 1 H, 2-H), 3.89 (m, 1 H, 4-H), 2.98 (d, J = 4.5 Hz, 1 H, 6-H), 2.44 (ddd, J = 15.1, 5.8, 4.2 Hz, 1 H, 3-H), 2.23–2.04 (m, 2 H), 1.82–1.62 (m, 2 H), 1.32 (s, 3 H, Me-C-1), 0.94 (s, 9 H, Me_3CSi), 0.87 (s, 9 H, Me_3CSi), 0.12 (s, 3 H, MeSi), 0.08 (s, 3 H, MeSi), 0.02 (s, 6 H, 2 MeSi) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 138.6 (=C, C-2′), 115.3 (=CH_2, C-3′), 70.0 (CH, C-2), 68.2 (CH, C-4), 59.8 (CH, C-6), 59.0 (C, C-1), 46.4 (CH, C-3), 30.3 (CH_2, C-5), 29.6 (CH_2, C-1′), 25.9 (3 CH_3, Me_3CSi), 25.7 (3 CH_3, Me_3CSi), 20.9 (CH_3, Me-C-1), 18.3 (C, CSi), 17.9 (C, CSi), –4.4 (CH_3, MeSi), –4.7 (CH_3, MeSi) –4.9 (CH_3, MeSi), –5.0 (CH_3, MeSi) ppm. IR (film): $\tilde{\nu}$ = 1639 (C=C) cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 413.3 (38) $[M + H]^+$, 395.3 (50) $[M - OH]^+$, 281.2 (100) $[M - OTBS]^+$, 263.2 (18) $[M - OTBS - H_2O]^+$, 239.1 (4) $[M - C_3H_5 - H]^+$, 224.2 (3) $[M - OTBS - tBu]^+$. HRMS (ESI-TOF$^+$): calcd. for $C_{22}H_{45}O_3Si_2$ $[M + H]^+$ 413.2902; found 413.2900.

3-{(1*R*,2*S*,3*S*,4*R*,6*R*)-2,4-Bis[(*tert*-Butyldimethylsilyl)oxy]-1-methyl-7-oxabicyclo[4.1.0]heptan-3-yl}propan-1-ol (5): BH_3 (1 M solution in THF; 0.26 mL, 0.255 mmol, 1.5 equiv.) was added to a solution of **18b** (70 mg, 0.170 mmol, 1 equiv.) in dry THF (1.5 mL) at 0 °C. After 1 h, NaOH (3 M aq.; 1 mL) and H_2O_2 (30 % aq.; 2 mL) were successively added. The mixture was vigorously stirred for 3 h, and then it was extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (1.5 × 8 cm; 10 % EtOAc/hexanes) to give **5** (67 mg, 91 %) as a colourless oil. R_f = 0.2 (20 % EtOAc/hexanes). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.34 (d, J = 5.8 Hz, 1 H, 2-H), 3.91 (m, 1 H, 4-H), 3.56 (t, J = 5.0 Hz, 2 H, CH_2-1), 2.97 (d, J = 4.6 Hz, 1 H, 6′-H), 2.17 (dd, J = 15.1, 5.8 Hz, 1 H), 2.03 (br. s, 1 H, OH), 1.83–1.27 (m, 6 H), 1.31 (s, 3 H, Me-C-1′), 0.93 (s, 9 H, Me_3CSi), 0.88 (s, 9 H, Me_3CSi), 0.12 (s, 3 H, MeSi), 0.08 (s, 3 H, MeSi), 0.02 (s, 6 H, 2 MeSi) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 70.3 (CH, C-2′), 68.4 (CH, C-4′), 63.3 (CH_2, C-1), 59.7 (C, C-1′), 59.0 (CH, C-6′), 47.0 (CH, C-3′), 32.4 (CH_2, C-2), 30.6 (CH_2, C-5′), 25.9 (3 CH_3, Me_3CSi), 25.7 (3 CH_3, Me_3CSi), 21.0 (CH_2, C-3), 20.9 (CH_3, Me-C-1), 18.2 (C, CSi), 17.9 (C, CSi), –4.4 (CH_3, MeSi), –4.7 (CH_3, MeSi), –4.9 (CH_3, MeSi), –5.0 (CH_3, MeSi) ppm. IR (film): $\tilde{\nu}$ = 3432 (O–H) cm^{-1}. MS (ESI-TOF$^+$): m/z (%) = 453.3 (15) $[M + Na]^+$, 431.3 (3) $[M + H]^+$, 415.3 (100) $[M - OH]^+$, 282.2 (10) $[M - OH - OTBS]^+$, 225.2 (9) $[M - OH - OTBS - tBu]^+$. HRMS (ESI-TOF$^+$): calcd. for $C_{22}H_{45}NaO_3Si_2$ $[M + Na]^+$ 453.2832; found 453.2829.

Acknowledgments

A postdoctoral fellowship (Axudas posdoutorais, plan I2C, mod B) from the Xunta de Galicia, USC-RIADIT (X-ray, NMR spectroscopy, and MS sections), and the input given to this work by Prof. Antonio Mouriño are gratefully acknowledged.

Keywords: Synthesis design · Natural products · Chiral pool · Asymmetric synthesis · Rearrangement

[1] D. Feldman, J. W. Pike, J. S. Adam (Eds.), *Vitamin D, 3rd ed.*, Elsevier Academic Press, San Diego, CA, **2011**.
[2] L. A. Plum, H. F. DeLuca, *Nat. Rev. Drug Discovery* **2010**, *9*, 941–955.
[3] M. J. Campbell, L. Adorini, *Expert Opin. Ther. Targets* **2006**, *10*, 735–748.
[4] J. W. Pike, M. B. Meyer, K. A. Bishop, *Rev. Endocr. Metab. Disord.* **2012**, *13*, 45–55.
[5] R. M. Evans, *Mol. Endocrinol.* **2005**, *19*, 1429–1438.
[6] G. Jones, S. A. Strugnell, H. F. DeLuca, *Physiol. Rev.* **1998**, *78*, 1193–1231.
[7] D. Feldman, A. V. Krishnan, S. Swami, E. Giovannucci, B. J. Feldman, *Nat. Rev. Cancer* **2014**, *14*, 342–357.
[8] N. Rochel, J. M. Wurtz, A. Mitschler, B. Klaholz, D. Moras, *Mol. Cell* **2000**, *5*, 173–179.
[9] a) S. Eduardo-Canosa, R. Fraga, R. Sigüeiro, M. Marco, N. Rochel, D. Moras, A. Mouriño, *J. Steroid Biochem. Mol. Biol.* **2010**, *121*, 7–12; b) C. Carlberg, F. Molnár, A. Mouriño, *Expert Opin. Ther. Pat.* **2012**, *22*, 417–435; c) S. Yamada, M. Makishima, *Trends Pharmacol. Sci.* **2014**, *35*, 324–337; d) M. A. Maestro, F. Molnár, A. Mouriño, C. Carlberg, *Expert Opin. Ther. Pat.* **2016**, *26*, 1291–1306.
[10] S. Hourai, T. Fujishima, A. Kittaka, Y. Suhara, H. Takayama, N. Rochel, D. Moras, *J. Med. Chem.* **2006**, *49*, 5199–5205.
[11] a) A. Glebocka, G. Chiellini, *Arch. Biochem. Biophys.* **2012**, *523*, 48–57; b) N. Kubodera, *Heterocycles* **2016**, *92*, 1013–1029; c) A. Kittaka, Y. Suhara, H. Takayanagi, T. Fujishima, M. Kurihara, H. Takayama, *Org. Lett.* **2000**, *2*, 2619–2622; d) Y. Suhara, K. Nihei, M. Kurihara, A. Kittaka, K. Yamaguchi, T. Fujishima, K. Konno, N. Miyata, H. Takayama, *J. Org. Chem.* **2001**, *66*, 8760–8771; e) S. Honzawa, K. Hirasaka, Y. Yamamoto, S. Peleg, T. Fujishima, M. Kurihara, N. Saito, S. Kishimoto, T. Sugiura, K. Waku, H. Takayama, A. Kittaka, *Tetrahedron* **2005**, *61*, 11253–11263; f) V. Sikervar, J. C. Fleet, P. L. Fuchs, *J. Org. Chem.* **2012**, *77*, 5132–5138; g) V. Sikervar, J. C. Fleet, P. L. Fuchs, *Chem. Commun.* **2012**, *48*, 9077–9079; h) D. R. Laplace, M. V. Overschelde, P. J. De Clercq, A. Verstuyf, J. M. Winne, *Eur. J. Org. Chem.* **2013**, 728–735; i) M. Matsuo, A. Hasegawa, M. Takano, H. Saito, S. Kakuda, T. Chida, K. Takagi, E. Ochiai, K. Horie, Y. Harada, M. Takimoto-Kamimura, K. Takenouchi, D. Sawada, A. Kittaka, *ACS Med. Chem. Lett.* **2013**, *4*, 671–674; j) H. Saito, K. Takagi, K. Horie, S. Kakuda, M. Takimoto-Kamimura, E. Ochiai, T. Chida, Y. Harada, K. Takenouchi, A. Kittaka, *J. Steroid Biochem. Mol. Biol.* **2013**, *136*, 3–8; k) I. K. Sibilska, R. R. Sicinski, J. T. Ochalek, L. A. Plum, H. F. DeLuca, *J. Med. Chem.* **2014**, *57*, 8319–8331; l) H. Saitoh, H. Watanabe, S. Kakuda, M. Takimoto-Kamimura, K. Takagi, A. Takeuchi, K. Takenouchi, *J. Steroid Biochem. Mol. Biol.* **2015**, *148*, 27–30; m) I. K. Sibilska, M. Szybinski, R. R. Sicinski, L. A. Plum, H. F. DeLuca, *J. Med. Chem.* **2015**, *58*, 9653–9662; n) A. Flores, I. Massarelli, J. B. Thoden, L. A. Plum, H. F. DeLuca, *J. Med. Chem.* **2015**, *58*, 9731–9741; o) D. Sawada, E. Ochiai, A. Takeuchi, S. Kakuda, M. Kamimura-Takimoto, F. Kawagoe, A. Kittaka, *J. Steroid Biochem. Mol. Biol.* **2016**, https://doi.org/10.1016/j.jsbmb.2016.09.007.
[12] For reviews, see: Y. Z. Yin, J. P. Li, C. Liu, L. Q. Tang, Z. P. Liu, *Curr. Org. Synth.* **2011**, *8*, 374–392.
[13] P. Gogoi, R. Sigüeiro, S. Eduardo, A. Mouriño, *Chem. Eur. J.* **2010**, *16*, 1432–1435.
[14] For previous uses of (*R*)- or (*S*)-carvone for the synthesis of A-ring building blocks of vitamin D, see: a) Y. Chen, T. Ju, *Org. Lett.* **2011**, *13*, 86–89; b) See also refs.[11a,12]

[15] Alkylation attempts using other bases [LDA or NaHMDS (sodium hexamethyldisilazide)] in THF or Et_2O at different temperatures gave mixtures of products, including the dialkylated compound, which were difficult to separate by flash chromatography.
[16] The classical method using H_2O_2 and LiOH gave a mixture of products, with a low yield of the desired epoxide **8** (22 %).
[17] J. L. Luche, *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
[18] The use of other reducing agents (DIBAL-H, THF; L-Selectride, THF; $NaBH_4/ZnCl_2$, Et_2O; $NaBH_4/CeCl_3$, MeOH, pyridine) gave the desired product in a lower yield (<50 %) with similar stereoselectivity.
[19] CCDC 1571570 (for **14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
[20] a) R. Criegee, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745–752; *Angew. Chem.* **1975**, *87*, 765–771; b) S. L. Schreiber, W. F. Liew, *Tetrahedron Lett.* **1983**, *24*, 2363–2366.
[21] A. R. Daniewski, L. M. Garafalo, S. D. Hutching, M. M. Kabat, W. Liu, M. Okade, R. Radinov, *J. Org. Chem.* **2002**, *67*, 1580–1587.
[22] For experimental procedures to obtain alcohol **9** by an alternative route (Luche–Sharpless), see the Supporting Information.
[23] For the characterization of this compound, see the Supporting Information.

Received: September 7, 2017

