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Efficient and Scalable Total Synthesis of Calcitroic Acid and its ^{13}C-Labeled Derivative

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ABSTRACT

Calcitroic acid, the deactivated form of the physiological active vitamin D_3 metabolite calcitrol, and its ^{13}C labeled derivative has been synthesized starting from the commercially available Inhoffen-Lythgoe diol in 11 steps with an overall yield of 21%. The key steps in the synthesis were the formation of the C1-homologated nitrile with KCN and K^{13}CN as well as the Horner-Wittig reaction with the ring A phosphine oxide reagent.

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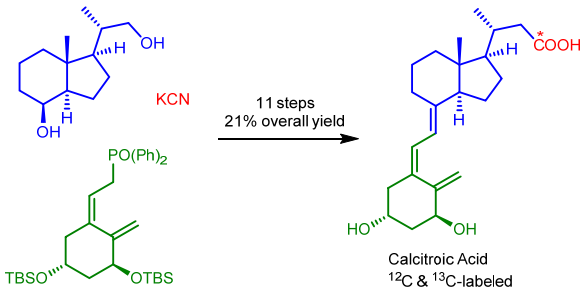


Calcitroic acid and its ^{13}C labeled derivative has been synthesized from Inhoffen-Lythgoe diol in 11 steps with an overall yield of 21%.

INTRODUCTION

To form the physiological active form, vitamin D_3 undergoes two hydroxylations – one in the liver at C25 and a subsequent one in the kidney at C1 to produce 1α,25-dihydroxy vitamin D_3, also called calcitriol (Fig. 1). Calcitriol regulates many biological functions like calcium homeostasis and bone mineralization, proliferation and differentiation of various types of cells, and immune modulation. Its interesting biological mode of action led to intense research and application in the field of bone disorder, as well as autoimmune disorders, cancer or psoriasis.[1]

Deactivation of calcitriol starts by hydroxylation on C24 and by further metabolic degradation, the inactive water soluble calcitroic acid (**1**) is formed, which is excreted via the liver into the bile.[2] For supporting analytical studies on the fate of vitamin D_3 and calcitriol in the body, there was a need for calcitroic acid (**1**) and a ^{13}C-labeled derivative as reference materials.

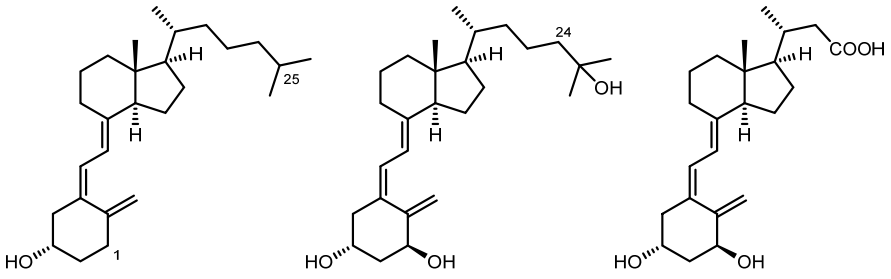
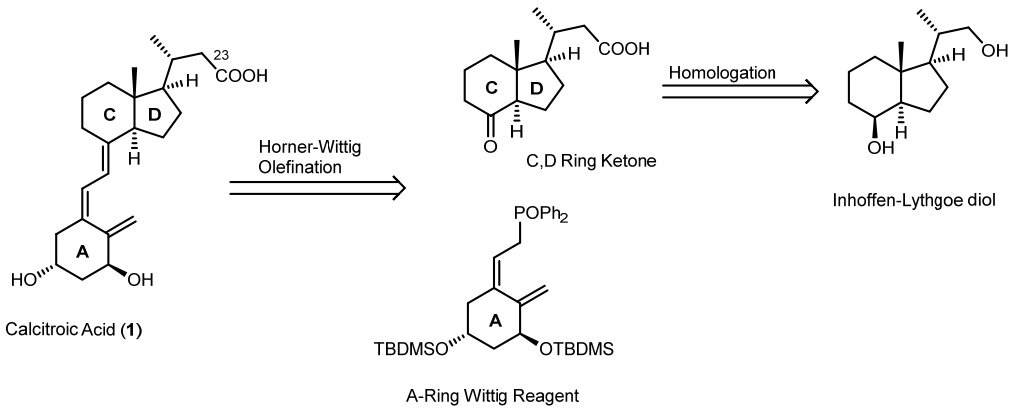


Fig. 1 Vitamin D_3, calcitriol and calcitroic acid (1)

As of today, there are three total syntheses of calcitroic acid (**1**) reported - the first one published by De Luca *et al*. in 1981.[3] In this work, and in the one by Whalley *et al*. in 1985,[4] the total syntheses of calcitroic acid (**1**) start from steroid derivatives and introduce in a linear synthesis the 1α-hydroxy function, do a C1-homologation of the side chain, and forms the calcitriol skeleton by photochemical ring opening. In a similar approach, Caverley[5] synthesized calcitroic acid (**1**) via a seleno-acetal containing vitamin D synthon.

As all these syntheses take at least 15 to 18 steps, have a low yield and produce only very small amounts of the desired calcitroic acid (**1**), there is a need for a concise and scalable synthesis of calcitroic acid (**1**) and a ^{13}C-labeled derivative.

Our retrosynthetic approach is based on a convergent synthesis via Horner-Wittig olefination of an A-ring Wittig reagent and a C,D-ring carbonyl compound (Scheme 1).[6] The advantage of this approach is that the A-ring Wittig reagent[7] is commercially available as diphenylphosphine oxide whereas the C,D-ring ketone can be prepared from the Inhoffen-Lythgoe diol **2**, which itself is commercially available or is easily prepared from vitamin D by ozonolysis.[8]



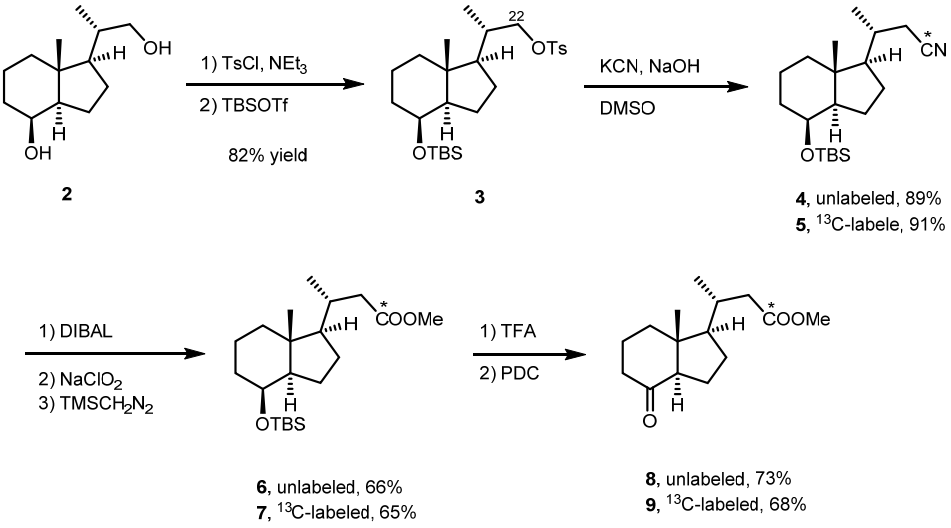
Scheme 1 Retrosynthetic Analysis of Calcitroic Acid (**1**)

RESULTS & DISCUSSION

Starting from the commercially available Inhoffen-Lythgoe diol **2** we first transformed the primary alcohol into a tosylate[9,10] followed by protecting the secondary hydroxyl group in the 7-position as a *tert*-butyldimethylsilyl ether[8] **3** (Scheme 2). Next, by a simple nucleophilic substitution reaction with cyanide the C1-homologated nitrile **4** was prepared,[10,11] while by using ^{13}C-labeled NaCN the corresponding ^{13}C-labeled derivative **5** in position C23 (based on steroidal numbering) as obtained. The overall yield for these three reactions was 74%, independent whether ^{13}CN was used or not.

Next we studied the transformation of the nitrile **4** into the corresponding carboxylic acid or methyl ester. All attempts to do a direct hydrolysis of nitrile **4** under acidic conditions[12] (HCl in MeOH) were not successful and resulted in the cleavage of the silyl ether and elimination of water in the 7-position. Under basic conditions[13] (KOH in MeOH), a mixture of acid and primary amide was obtained (by LC-MS). The use of nitrilase for the mild enzymatic hydrolysis failed due to the low solubility of the nitrile **4** in the aqueous

buffer system.[14] So we decided to first reduce the nitrile **4** to the aldehyde followed by oxidation to the corresponding carboxylic acid.

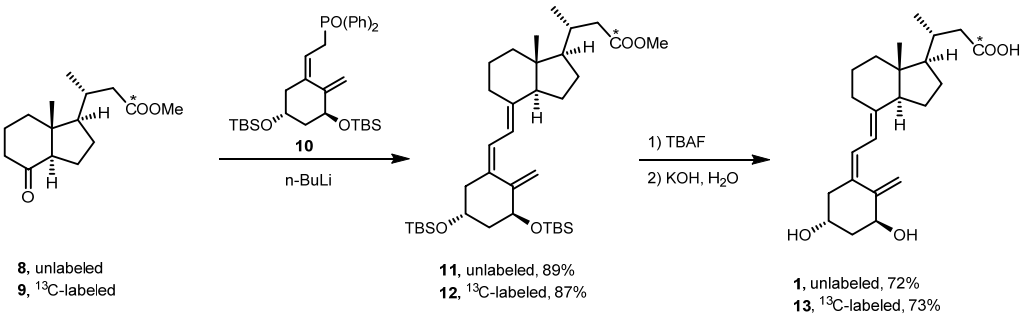


Scheme 2 Synthesis of C,D-ring ketone intermediate **8** and **9**

Therefore, the nitrile **4** was reduced by DIBAL to form the aldehyde.[10,11] It is important to do the hydrolysis of the aluminum/imine intermediate long enough otherwise the yield drops dramatically. Oxidation of the aldehyde was accomplished by the method of Pinnick and Lindgren[15] in quantitative yield and the carboxylic acid was directly transformed into the methyl ester **6** by using TMS-diazomethane in methanol.[16] Again, we observed no difference in the isolated yields for this 3-step sequence for the ^{13}C-labled ester **7**. Deprotection of the TBS group was accomplished by treatment with TFA[17] and after oxidation with PDC,[18] the C,D-ring ketone **8** was obtained with a 73% yield, respectively the ^{13}C-labeled C,D-ring ketone **9** with a 68% yield, over two steps.

As shown in Scheme 3, the Horner-Wittig reaction of the phosphine oxide reagent **10** and the C,D-ring ketone **8**, respectively ^{13}C-labeled ketone **9**, yields the calcitroic acid skeleton. After some optimization, the yield for this step was 89%. The products **11** and **12** are stable and can be easily purified by chromatography.[18,19] All attempts to reduce the equivalents of the expensive Horner-Wittig reagent **10** were not successful. Using less than 2 equivalents, only a complex mixture of products was obtained.

Finally, deprotection of the TBS group with TBAF[18] and hydrolysis of the methyl ester under basic conditions furnished the calcitroic acid **1** and its ^{13}C-derivative **13** with a 73% yield as an amorphous solid.[3] Its analytical data corresponds with the literature values,[3,4] while for the ^{13}C-derivative **13,** the typical ^{13}C-coupling could be observed in the ^{1}H and ^{13}C NMR spectra.



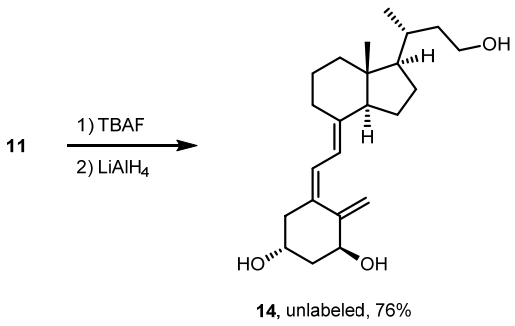
8, unlabeled
9, ^{13}C-labeled

11, unlabeled, 89%
12, ^{13}C-labeled, 87%

1, unlabeled, 72%
13, ^{13}C-labeled, 73%

Scheme 3 Synthesis of calcitroic acid (**1**) and ^{13}C-labeled calcitroic acid **13**

Additionally, alcohol **14**, a metabolic precursor to calcitroic acid (**1**) was prepared by reduction with $LiAlH_4$ from the bis-silylated ester **11** (76% yield over two steps, Scheme 4). The analytical data (NMR, MS) corresponds with literature[5] but we observed a fast decomposition within hours of the alcohol **14**.



14, unlabeled, 76%

Scheme 4 Synthesis of alcohol metabolite **14**

CONCLUSION

In conclusion, we developed a new scalable and facile synthesis of calcitroic acid (**1**) and its ^{13}C-labeled derivative **13** in 11 steps with an overall yield of 21%, starting from commercially available materials. In a highly efficient and concise protocol we homologated the Inhoffen-Lythgoe diol (C,D-ring) with KCN or K^{13}CN followed by a Wittig reaction using the A-ring phosphine oxide as the key steps. The easy availability of calcitroic acid (**1**) and its ^{13}C-labeled derivative **13** as disclosed in our work, will stimulates medical & pharmaceutical research on the metabolism and fate of vitamin D in the body.

EXPERIMENTAL SECTION

General. Inhoffen Lythgoe Diol **2** and A-ring phosphine oxide **10** were provided by Syncom BV. All reactions involving oxygen- or moisture-sensitive compound were carried out under a dry argon atmosphere. Reaction temperatures refer to external bath temperatures. Column chromatography was performed with Fluka silica gel (pore size 60 Å, 230-400 mesh particle size) packed in glass columns. Reactions were monitored by thin layer chromatography (TLC) using aluminum Merck 60 UV_{254} silica gel plates (0.2 mm thickness). Visualization was performed by ultraviolet light or by $KMnO_4$ stain, followed by gentle heating. NMR spectra were recorded at 300 MHz (for ^1H NMR) or 75 MHz (for ^{13}C NMR) in $CDCl_3$. Chemical shifts are reported as δ (ppm) downfield from tetramethylsilane (δ = 0.00) using residual solvent signal as an internal standard: δ singlet 7.26 (^1H), triplet 77.0 (^{13}C). IR spectra were obtained on neat samples (ATR spectroscopy). High-resolution mass spectra were recorded on an ESI-TOF MS spectrometer. Optical rotations were obtained at a wavelength of 589 nm using a 1.0 dm cell.

***O*-Silylated C,D-Ring Tosylate 3.** DMAP (2.27 g, 18.6 mmol) and *para*-toluenesulfonyl chloride (1.82 g, 9.56 mmol) was added to a solution of Inhoffen Lythgoe Diol **2** (1.97 g, 9.28 mmol) in DCM (30 mL). The mixture was stirred for 21 h at room temperature. The reaction mixture was treated with HCl 1 M (25 ml) and extracted with DCM (3 x 80 mL). The organic layers were washed with H_2O (25 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by chromatographic filtration (EtOAc : cyclohexane 1 : 9 → 2.5 : 7.5) to yield the C,D-ring tosylate (3.05 g, 90%) as a colorless oil: R_f 0.40 (EtOAc : cyclohexane 2.5 : 7.5). To a solution of C,D-ring tosylate (3.05 g,

8.32 mmol) in dry DCM (100 mL), 2,6-lutidine (1.07 g, 10.0 mmol) was added followed by a solution of tert-butyldimethylsilyl trifluoromethanesulfonate (3.08 g, 11.7 mmol) in dry DCM (15 mL) at 0 °C. After stirring 1.5 h at 0 °C, the mixture was quenched with H_2O (80 mL) and the water phase was extracted with DCM (80 mL). The organic layers were washed with H_2O (80 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 5 : 95) to yield **3** (3.62 g, 91%) as a slightly yellow oil: R_f 0.40 (EtOAc : cyclohexane 5 : 95); ^{1}H-NMR (300 MHz, $CDCl_3$) δ -0.03 (s, 3H), 0.00 (s, 3H), 0.87 (s, 3H), 0.87 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.03-1.25 (m, 4H), 1.26-1.42 (m, 3H), 1.43-1.57 (m, 1H), 1.58-1.71 (m, 3H), 1.72-1.81 (m, 1H), 1.83-1.92 (m, 1H), 2.45 (s, 3H), 3.79 (dd, *J* = 9.2, 6.3 Hz, 1H), 3.91-4.02 (m, 2H) 7.31-7.38 (m, 2H), 7.75-7.82 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.7, 16.8, 17.6, 18.0, 21.6, 23.0, 25.8, 26.5, 34.3, 35.8, 40.3, 42.1, 52.4, 52.7, 69.2, 75.7, 127.9, 129.8, 133.2, 144.6.

O-Silylated C,D-Ring Nitrile 4. Sodium hydroxide (0.58 g, 14.6 mmol) and potassium cyanide (0.95 g, 14.6 mmol) were added to a solution of **3** (3.51, 7.30 mmol) in DMSO (100 mL) and heated to 90 °C for 5 h. A solution of NaCl (2% in H_2O, 200 mL) was added to the reaction mixture and extracted with cyclohexane (4 x 100 mL). The organic layers were washed with a solution of NaCl (2% in H_2O, 2 x 100 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **4** (2.31 g, 89%) as a colorless oil: R_f 0.35 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.93 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.15-1.27 (m, 3H), 1.28-1.33 (m, 1H), 1.34-1.46 (m, 3H), 1.52-1.68 (m, 2H), 1.69-1.86 (m, 3H), 1.87-1.96 (m, 1H), 2.23 (dd, *J* = 16.7, 6.9 Hz, 1H), 2.34 (dd, *J* = 16.7, 3.9 Hz, 1H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz,

$CDCl_3$) δ -5.2, -4.8, 13.9, 17.5, 18.0, 19.3, 22.9, 24.7, 25.8, 27.2, 33.1, 34.2, 40.3, 42.2, 52.9, 55.4, 69.2, 119.0; IR (neat) 772, 834, 1020, 1083, 1164, 1251, 2245, 2856, 2929 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{20}H_{37}NOSiNa$ 358.2537 $[M + Na]^+$, found 358.2539; $[\alpha]_D^{20}$ + 53.0 (*c* 2.0, $CHCl_3$).

[23-^{13}C] O-Silylated C,D-Ring Nitrile 5. Sodium hydroxide (1.86 g, 46.6 mmol) and potassium cyanide-^{13}C (3.08 g, 46.6 mmol) were added to a solution of **3** (11.18, 23.3 mmol) in DMSO (300 mL) and heated to 90 °C for 5 h. A solution of NaCl (2% in H_2O, 600 mL) was added to the reaction mixture and extracted with cyclohexane (4 x 300 mL). The organic layers were washed with a solution of NaCl (2% in H_2O, 2 x 300 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **5** (7.10 g, 91%) as a colorless oil: R_f 0.35 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.93 (s, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.15-1.27 (m, 3H), 1.28-1.33 (m, 1H), 1.34-1.46 (m, 3H), 1.51-1.68 (m, 2H), 1.69-1.86 (m, 3H), 1.87-1.96 (m, 1H), 2.23 (ddd, *J* = 16.6, 9.4, 6.9 Hz, 1H), 2.34 (ddd, *J* = 16.6, 9.6, 3.9 Hz, 1H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.9, 17.5, 18.0, 19.3 (d, *J* = 1.5 Hz), 22.9, 24.7 (d, *J* = 55.5 Hz), 25.8, 27.2, 33.1 (d, *J* = 2.4 Hz), 34.2, 40.3, 42.2, 52.9, 55.4 (d, *J* = 3.1 Hz), 69.2, 119.1; IR (neat) 772, 834, 1020, 1083, 1164, 1251, 2190, 2856, 2929 cm^{-1}; HRMS (ESI-TOF) m / z calcd for $C_{19}{}^{13}CH_{37}NOSiNa$ 359.2570 [M + Na]+, found 359,2572; $[\alpha]_D^{20}$ + 52.6 (*c* 2.0, $CHCl_3$).

O-Silylated C,D-Ring Methyl Ester 6. To a stirred solution of **4** (1.51 g, 4.50 mmol) in dry DCM (50 mL), a solution of DIBAL (1.0 M in toluene, 15.8 mL, 15.8 mmol) was added dropwise at 0 °C and stirred 4 h at this temperature. The reaction was quenched with a solution of saturated aqueous NH_4Cl (15 mL) and stirred for 30 min at 0 °C. TBME

(75 mL) was added to the viscous suspension and stirred for 30 min at 0 °C. The mixture was dried over $MgSO_4$, filtered through celite, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield the O-silylated C,D-ring aldehyde (1.10 g, 72%) as a slightly yellow oil: R_f 0.45 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.96 (s, 3H), 0.99 (d, J = 6.4 Hz, 3H), 1.07-1.21 (m, 2H), 1.22-1.32 (m, 2H), 1.33-1.44 (m, 3H), 1.51-1.62 (m, 1H), 1.63-1.90 (m, 3H), 1.91-1.99 (m, 1H), 2.00-2.08 (m, 1H), 2.09-2.19 (m, 1H) 2.40-2.49 (m, 1H), 3.97-4.03 (m, 1H), 9.74 (dd, J = 3.4, 1.4 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.7, 17.6, 18.0, 20.0, 23.0, 25.8, 27.6, 31.3, 34.3, 40.6, 42.3, 50.8, 53.0, 56.6, 69.3, 203.6.To a stirred solution of the O-silylated C,D-ring aldehyde (1.08 g, 3.19 mmol) in tert-butanol (60 mL) and 2-methyl-2-butene (15 mL), a mixture of sodium chlorite (2.66 g, 29.4 mmol) and monosodium phosphate monohydrate (2.66, 19.3 mmol) in H_2O (25 mL) was added at room temperature. The reaction mixture was stirred for 1.5 h and concentrated under reduced pressure. The residue was treated with H_2O (100 mL) and extracted with cyclohexane (100 / 50 / 50 mL). The organic layers were washed with H_2O (50 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 2 : 8) to yield the O-silylated C,D-ring acid (1.11 g, 98%) as a white solid: R_f 0.35 (EtOAc : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.95 (s, 3H), 1.01 (d, J = 6.3 Hz, 3H), 1.06-1.19 (m, 2H), 1.21-1.32 (m, 2H), 1.33-1.44 (m, 3H), 1.50-1.62 (m, 1H), 1.63-1.71 (m, 1H), 1.72-1.86 (m, 2H), 1.87-2.06 (m, 3H), 2.47 (dd, J = 14.2, 2.7 Hz, 1H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.7, 17.6, 18.0, 19.5, 23.0, 25.8, 27.3, 33.2, 34.4, 40.6, 41.3, 42.3, 53.1, 56.5, 69.4, 180.3. Trimethylsilyldiazomethane (2 M in diethyl ether, 2.3

mL, 4.6 mmol) was added dropwise to a solution of the O-silylated C,D-ring acid (1.10 g, 3.10 mmol) in toluene (18 mL) and methanol (12 mL) at room temperature. The reaction mixture was stirred for 1 h. Excess of diazomethane was destroyed with acetic acid. The mixture was concentrated and the residue purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **6** (1.06 g, 93%) as a slightly yellow liquid: R_f 0.50 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.95 (s, 3H), 0.96 (d, *J* = 5.8 Hz, 3H), 1.01-1.18 (m, 2H), 1.20-1.31 (m, 2H), 1.32-1.43 (m, 3H), 1.50-1.62 (m, 1H), 1.63-1.71 (m, 1H), 1.72-1.86 (m, 2H), 1.87-2.04 (m, 3H), 2.42 (dd, *J* = 13.8, 2.6 Hz, 1H), 3.65 (s, 3H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.8, 17.6, 18.0, 19.5, 23.0, 25.8, 27.3, 33.4, 34.4, 40.6, 41.4, 42.3, 51.3, 53.1, 56.6, 69.4, 174.1; IR (neat) 772, 834, 1021, 1089, 1162, 1251, 1739, 2856, 2930 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{21}H_{40}O_3SiNa$ 391.2639 $[M + Na]^+$, found 391.2635; $[\alpha]_D^{20}$ + 41.9 (*c* 2.0, $CHCl_3$).

[23-^{13}C] O-Silylated C,D-Ring Methyl Ester 7. To a stirred solution of **5** (1.99 g, 5.91 mmol) in dry DCM (50 mL), a solution of DIBAL (1.0 M in toluene, 21.4 mL, 21.4 mmol) was added dropwise at 0 °C and stirred 4 h at this temperature. The reaction was quenched with a solution of saturated aqueous NH_4Cl (15 mL) and stirred for 30 min at 0 °C. TBME (75 mL) was added to the viscous suspension and stirred for 30 min at 0 °C. The mixture was dried over $MgSO_4$, filtered through celite, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield the [23-^{13}C] O-silylated C,D-ring aldehyde (1.50 g, 75%) as a slightly yellow oil: R_f 0.45 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, CDCl3) δ 0.00 (s, 3H), 0.01 (s, 3 H), 0.89 (s, 9H), 0.96 (s, 3 H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.07-1.21 (m, 2H), 1.22-1.32 (m, 2H), 1.33-1.43 (m, 3H), 1.51-1.62 (m, 1H), 1.63-1.90 (m, 3H), 1.91-1.99 (m, 1H), 2.00-

2.08 (m, 1H), 2.09-2.19 (m, 1H) 2.39-2.50 (m, 1H), 3.97-4.03 (m, 1H), 9.74 (ddd, *J* = 169.1, 3.4, 1.4 Hz, 1H); ^{13}C-NMR (75 MHz, CDCl3) δ -5.2, -4.8, 13.7, 17.6, 18.0, 20.0 (d, *J* = 1.4 Hz), 23.0, 25.8, 27.6, 31.3, 34.3, 40.6, 42.3, 50.8 (d, *J* = 39.2 Hz), 53.0, 56.6 (d, *J* = 3.7 Hz), 69.3, 203.6. To a stirred solution of the [23-^{13}C] O-silylated C,D-ring aldehyde (178 mg, 0.524 mmol) in tert-butanol (10 mL) and 2-methyl-2-butene (2.5 mL), a mixture of sodium chlorite (0.43 g, 4.76 mmol) and monosodium phosphate monohydrate (0.43, 3.12 mmol) in H_2O (4 mL) was added at room temperature. The reaction mixture was stirred for 1.5 h and concentrated under reduced pressure. The residue was treated with H_2O (30 mL) and extracted with cyclohexane (30 / 15 /15 mL). The organic layers were washed with H_2O (15 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 2 : 8) to yield the [23-^{13}C] O-silylated C,D-ring acid (182 mg, 98%) as a white solid: R_f 0.35 (EtOAc : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.95 (s, 3H), 1.00 (d, *J* = 6.3 Hz, 3H), 1.06-1.19 (m, 2H), 1.21-1.32 (m, 2H), 1.33-1.44 (m, 3H), 1.50-1.62 (m, 1H), 1.63-1.71 (m, 1H), 1.72-1.85 (m, 2H), 1.86-2.06 (m, 3H), 2.47 (ddd, *J* = 14.0, 7.1, 2.6 Hz, 1H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.7, 17.6, 18.0, 19.5, 23.0, 25.8, 27.3, 33.2, 34.4, 40.6, 41.3 (d, *J* = 55.0 Hz), 42.3, 53.1, 56.5 (d, *J* = 4.1 Hz), 69.4, 180.1. Trimethylsilyldiazomethane (2 M in diethyl ether, 0.38 mL, 0.76 mmol) was added dropwise to a solution of the [23-^{13}C] O-silylated C,D-ring acid (182 mg, 0.512 mmol) in toluene (3 mL) and methanol (2 mL) at room temperature. The reaction mixture was stirred for 1 h. Excess of diazomethane was destroyed with acetic acid. The mixture was concentrated and the residue was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **7** (168 mg, 89%) as a slightly yellow liquid: R_f 0.50 (EtOAc :

cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 3H), 0.01 (s, 3H), 0.89 (s, 9H), 0.94 (s, 3H), 0.95 (d, *J* = 5.9 Hz, 3H), 1.01-1.17 (m, 2H), 1.20-1.31 (m, 2H), 1.32-1.44 (m, 3H), 1.49-1.62 (m, 1H), 1.63-1.71 (m, 1H), 1.72-1.86 (m, 2H), 1.87-2.04 (m, 3H), 2.42 (ddd, *J* = 13.9, 7.3, 2.7 Hz, 1H), 3.65 (d, *J* = 3.8 Hz, 3H), 3.97-4.03 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.2, -4.8, 13.8, 17.6, 18.0, 19.5 (d, *J* = 1.0 Hz), 23.0, 25.8, 27.3, 33.4 (d, *J* =1.5 Hz), 34.4, 40.6, 41.4 (d, *J* = 57.3), 42.3, 51.3 (d, *J* = 2.8 Hz), 53.1, 56.6 (d, *J* = 4.2 Hz), 69.4, 174.1; IR (neat) 772, 834, 1021, 1089, 1164, 1251, 1698, 2855, 2929 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{20}{}^{13}CH_{40}O_3SiNa$ 392.2672 [M + Na]$^{+}$, found 392.2677; $[\alpha]_D^{20}$ + 41.6 (*c* 2.0, $CHCl_3$).

C,D-Ring Ketone 8. A solution of **6** (1.02 g, 2.77 mmol) in dry DCM (30 mL) was treated with TFA (3 mL) at 0 °C. The reaction mixture was stirred for 90 min and then allowed to warm up to room temperature. The mixture was concentrated and the residue was purified by column chromatography (EOAc : cyclohexane 2 : 8) to yield the C,D-ring alcohol (0.52 g, 74%) as a slightly yellow oil: R_f 0.30 (EtOAc : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.2 Hz, 3H), 0.97 (s, 3H), 1.05-1.22 (m, 2H), 1.24-1.39 (m, 2H), 1.40-1.51 (m, 3H), 1.52-1.66 (m, 2H), 1.73-1.88 (m, 3H), 1.89-2.05 (m, 3H), 2.43 (dd, *J* = 14.0, 2.9 Hz, 1H), 3.66 (s, 3H), 4.04-4.11 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.6, 17.4, 19.4, 22.5, 27.2, 33.4, 33.6, 40.3, 41.3, 42.0, 51.4, 52.6, 56.4, 69.2, 174.0. PDC (1.48 g, 3.93 mmol) was added to a stirred solution of C,D-ring alcohol (0.50 g, 1.97 mmol) in dry DCM (100 mL) and stirred overnight at room temperature. TBME (100 mL) was added and the suspension filtered through celite. The filtrate was concentrated and the residue was purified by column chromatography (EtOAc : cyclohexane 2 : 8) to yield **8** (0.49 g, 98%) as a slightly yellow oil: R_f 0.35 (EtOAc : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H),

1.21-1.43 (m, 1H), 1.44-1.67 (m, 3H), 1.68-1.80 (m, 1H), 1.81-2.15 (m, 6H), 2.16 -2.34 (m, 2H), 2.38-2.53 (m, 2H), 3.67 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.5, 19.1, 19.6, 24.0, 27.5, 33.4, 38.8, 40.9, 41.1, 49.8, 51.4, 56.3, 61.9, 173.6, 211.6; IR (neat) 1150, 1190, 1710, 1733, 2874, 2953 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{15}H_{24}O_3Na$ 275.1618 $[M + Na]^+$, found 275.1623; $[\alpha]_D^{20}$ – 6.9 (*c* 2.0, $CHCl_3$).

[23-^{13}C] C,D-Ring Ketone 9. A solution of **7** (554 mg, 1.50 mmol) in dry DCM (15 mL) was treated with TFA (2 mL) at 0 °C. The reaction mixture was stirred for 90 min and then allowed to warm up to room temperature. The mixture was concentrated and the residue purified by column chromatography (EOAc : cyclohexane 2 : 8) to yield the [23-^{13}C]-C,D-ring alcohol (281 mg, 73%) as a slightly yellow oil: R_f 0.30 (EtOAc : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J* = 6.3 Hz, 3H), 0.96 (s, 3H), 1.05-1.22 (m, 2H), 1.24-1.40 (m, 2H), 1.41-1.53 (m, 3H), 1.54-1.67 (m, 1H), 1.73-1.88 (m, 3H), 1.89-2.06 (m, 3H), 2.43 (ddd, *J* = 13.5, 7.0, 2.7 Hz, 1H), 3.26 (s, 1H), 3.66 (d, *J* = 3.8 Hz, 3H), 4.05-4.14 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 13.5, 17.4, 19.4 (d, *J* = 1.0 Hz), 22.5, 27.2, 33.36 (d, *J* = 1.5 Hz), 33.39, 40.2, 41.3 (d, *J* = 57.3 Hz), 42.0, 51.4 (d, *J* = 2.8 Hz), 52.5, 56.4 (d, *J* = 4.2 Hz), 69.5, 174.1. PDC (0.81 g, 2.15 mmol) was added to a stirred solution of [23-^{13}C]-C,D-ring alcohol (274 mg, 1.07 mmol) in dry DCM (50 mL) and stirred overnight at room temperature. TBME (50 mL) was added and the suspension filtered through celite. The filtrate was concentrated and the residue was purified by column chromatography (EtOAc : cyclohexane 2 : 8) to yield **9** (252 mg, 93%) as a slightly yellow oil: R_f 0.35 (EtOAC : cyclohexane 2 : 8); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.68 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 1.21-1.43 (m, 1H), 1.45-1.67 (m, 3H), 1.68-1.80 (m, 1H), 1.81-2.15 (m, 6H), 2.16 -2.35 (m, 2H), 2.38-2.54 (m, 2H), 3.67 (d, *J* = 3.8 Hz, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.5, 19.1, 19.6 (d, *J* = 1.0 Hz), 24.0, 27.5, 33.4 (d, *J* =

1.4 Hz), 38.8, 40.9, 41.1 (d, *J* = 57.5 Hz), 49.8, 51.4 (d, *J* = 2.8 Hz), 56.3 (d, *J* = 4.2 Hz), 61.9, 173.6, 211.6; IR (neat) 1138, 1189, 1691, 1710, 2874, 2953 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{14}{}^{13}CH_{24}O_3Na$ 276.1651 $[M + Na]^+$, found 276.1650; $[\alpha]_D{}^{20}$ – 6.9 (*c* 2.0, $CHCl_3$).

O-bis-Silylated Calcitroic Acid Methyl Ester 11. A solution of n-BuLi (1.6 M in hexane, 0.30 mL, 0.480 mmol) was added dropwise to a solution of A-ring phosphine oxide **10** (306 mg, 0.525 mmol) in dry THF (6 mL) at -78 °C. The deep red solution was stirred at -78 °C for 1 h, followed by the dropwise addition of a solution of **8** (69.7 mg, 0.276 mmol) in dry THF (3 mL). The solution was stirred for 5 h at -78 °C and then allowed to warm up to room temperature. The reaction mixture was quenched with H_2O (10 mL) and extracted with TBME (2 x 30 mL). The organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **11** (153 mg, 89%) as a slightly yellow oil: R_f 0.45 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.04-0.09 (m, 12H), 0.57 (s, 3H), 0.88 (s, 18H), 0.99 (d, *J* = 6.2 Hz, 3H), 1.23-1.38 (m, 3H), 1.40-1.59 (m, 3H), 1.60-1.69 (m, 2H), 1.70-1.80 (m, 1H), 1.81-1.94 (m, 3H), 1.95-2.07 (m, 3H), 2.21 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.38-2.51 (m, 2H), 2.75-2.87 (m, 1H), 3.66 (s, 3H), 4.13-4.25 (m, 1H), 4.37 (dd, *J* = 6.5, 3.6 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 5.17 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.24 (d, *J* = 11.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.1, -4.8, -4.68, -4.67, 12.0, 18.1, 18.2, 19.7, 22.1, 23.4, 25.8, 25.9, 27.7, 28.8, 34.1, 40.5, 41.4, 44.8, 45.8, 46.1, 51.3, 56.30 (2C), 67.5, 72.1, 111.3, 118.1, 123.1, 135.2, 140.6, 148.3, 174.0; IR (neat) 773, 831, 1071, 1251, 1740, 2855, 2928, 2949 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{36}H_{64}O_4Si_2Na$ 639.4235 $[M + Na]^+$, found 639.4235; $[\alpha]_D{}^{20}$ + 25.3 (*c* 2.0, $CHCl_3$).

[23-^{13}C] O-bis-Silylated Calcitroic Acid Methyl Ester 12. A solution of n-BuLi (1.6 M in hexane, 0.29 mL, 0.46 mmol) was added dropwise to a solution of A-ring phosphine oxide **10** (296 mg, 0.507 mmol) in dry THF (5 mL) at -78 °C. The deep red solution was stirred at -78 °C for 1 h followed by the dropwise addition of a solution of **9** (67.6 mg, 0.267 mmol) in dry THF (2.5 mL). The solution was stirred for 5 h at -78 °C and then allowed to warm up to room temperature. The reaction mixture was quenched with H_2O (10 mL) and extracted with TBME (2 x 30 mL). The organic layers were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 3 : 97) to yield **12** (143 mg, 87%) as a slightly yellow oil: R_f 0.45 (EtOAc : cyclohexane 3 : 97); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.03-0.08 (m, 12H), 0.57 (s, 3H), 0.88 (s, 18H), 0.99 (d, *J* = 6.2 Hz, 3H), 1.21-1.37 (m, 3H), 1.41-1.59 (m, 3H), 1.60-1.69 (m, 2H), 1.70-1.81 (m, 1H), 1.82-1.94 (m, 3H), 1.95-2.07 (m, 3H), 2.21 (dd, *J* = 13.1, 7.5 Hz, 1H), 2.37-2.50 (m, 2H), 2.75-2.87 (m, 1H), 3.66 (d, *J* = 3.8 Hz, 3H), 4.13-4.25 (m, 1H), 4.37 (dd, *J* = 6.5, 3.6 Hz, 1H), 4.86 (d, *J* = 2.4 Hz, 1H), 5.17 (dd, *J* = 2.4, 0.8 Hz, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.24 (d, *J* = 11.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ -5.1, -4.8, -4.68, -4.67, 12.0, 18.15, 18.22, 19.7, 22.1, 23.4, 25.8, 25.9, 27.7, 28.8, 34.1, 40.5, 41.4 (d, *J* = 57.3 Hz), 44.8, 45.8, 46.1, 51.3 (d, *J* = 2.7 Hz), 56.29, 56.31 (d, *J* = 4.2), 67.5, 72.1, 111.3, 118.1, 123.1, 135.2, 140.6, 148.3, 174.0; IR (neat) 773, 831, 1071, 1251, 1698, 2855, 2928, 2949 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{35}{}^{13}CH_{64}O_4Si_2Na$ 640.4269 $[M + Na]^+$, found 640.4275; $[\alpha]_D^{20}$ + 24.2 (*c* 2.0, $CHCl_3$).

Calcitroic Acid 1. A solution of tetrabutylammonium fluoride (1 M in THF, 2.6 mL, 2.60 mmol) was added to a solution of **11** (159 mg, 0.258 mmol) in dry THF (25 mL) at room temperature and stirred overnight. The reaction mixture was treated with a saturated

aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (50 /25 mL). The organic layer were washed with brine (25 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 7 : 3) to yield the calcitroic acid methyl ester (97 mg, 97%) as a yellow oil: R_f 0.35 (EtOAc : cyclohexane 7 : 3); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 1.22-1.38 (m, 3H), 1.42-1.61 (m, 3H), 1.62-1.77 (m, 2H), 1.80-2.07 (m, 7H), 2.15 (s, 2H), 2.31 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.44 (dd, *J* = 14.2, 2.9 Hz, 1H), 2.58 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.82 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.66 (s, 3H), 4.15-4.26 (m, 1H), 4.42 (dd, *J* = 7.7, 4.4 Hz, 1H), 4.95-5.01 (m, 1H), 5.28-5.35 (m, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H), ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.0, 19.7, 22.2, 23.5, 27.6, 29.0, 34.1, 40.3, 41.3, 42.8, 45.2, 45.9, 51.4, 56.27 (2C), 66.7, 70.7, 111.8, 117.3, 124.7, 133.4, 142.5, 147.6, 174.0. The calcitroic acid methyl ester (84 mg, 0.216 mmol) was dissolved in a solution of KOH (10% in MeOH : H_2O 9 : 1, 20 mL) and stirred for 1.5 h at 60 °C. The reaction mixture was cooled to room temperature and acidified with concentrated HCl solution to pH 2. The mixture was concentrated, diluted with H_2O (20 mL) and extracted with EtOAc (4 x 20 mL). The organic layers were washed with brine (2 x 20 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc) to yield **1** (60 mg, 74%) as a white amorphous solid: R_f 0.40 (EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 3H), 1.04 (d, *J* = 6.3 Hz, 3H), 1.22-1.40 (m, 3H), 1.42-1.61 (m, 3H), 1.62-1.77 (m, 2H), 1.80-2.11 (m, 7H), 2.15 (s, 2H), 2.31 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.48 (dd, *J* = 14.6, 3.0 Hz, 1H), 2.59 (dd, *J* = 13.4, 3.3 Hz, 1H), 2.82 (d, *J* = 11.8, 3.1 Hz, 1H), 4.18-4.28 (m, 1H), 4.43 (dd, *J* = 7.7, 4.4 Hz, 1H), 4.97-5.03 (m, 1H), 5.29-5.36 (m, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.37 (d, *J* = 11.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.0, 19.7, 22.2, 23.5, 27.6, 29.0, 33.9, 40.3, 41.2, 42.8, 45.2, 45.9, 56.2, 56.3, 66.9,

70.8, 111.9, 117.3, 124.9, 133.2, 142.7, 147.5, 178.9; IR (neat) 1051, 1704, 2871, 2927, 3344 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{23}H_{34}O_4Na$ 397.2349 $[M + Na]^+$, found 397.2349; $[\alpha]_D^{20}$ -5.5 (*c* 2.0, $CHCl_3$).

[23-^{13}C] Calcitroic Acid 13. A solution of tetrabutylammonium fluoride (1 M in THF, 1.1 mL, 1.1 mmol) was added to a solution of **12** (64.4 mg, 0.107 mmol) in dry THF (11 mL) at room temperature and stirred overnight. The reaction mixture was treated with a saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (2 x 25 mL). The organic layer were washed with brine (25 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 7 : 3) to yield the [23-^{13}C] calcitroic acid methyl ester (41.1 mg, 98%) as a yellow oil: R_f 0.35 (EtOAc : cyclohexane 7 : 3); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 3H), 0.99 (d, *J* = 6.3 Hz, 3H), 1.23-1.38 (m, 3H), 1.42-1.61 (m, 3H), 1.62-1.77 (m, 2H), 1.80-2.07 (m, 9H), 2.31 (dd, *J* = 13.4, 6.5 Hz, 1H), 2.44 (ddd, *J* = 14.0, 7.5, 2.9 Hz, 1H), 2.59 (dd, *J* = 13.4, 2.3 Hz, 1H), 2.82 (dd, *J* = 11.8, 3.3 Hz, 1H), 3.66 (d, *J* = 3.8 Hz, 3H), 4.15-4.26 (m, 1H), 4.42 (dd, *J* = 7.5, 4.4 Hz, 1H), 4.95-5.02 (m, 1H), 5.28-5.35 (m, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.36 (d, *J* = 11.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.0, 19.7, 22.2, 23.5, 27.6, 29.0, 34.1 (d, *J* = 1.3 Hz), 40.3, 41.3 (d, *J* = 57.3 Hz), 42.8, 45.2, 45.9, 51.4 (d, *J* = 2.8 Hz), 56.28, 56.28 (d, *J* = 4.0 Hz), 66.8, 70.8, 111.8, 117.3, 124.8, 133.3, 142.6, 147.6, 174.0. The [23-^{13}C] calcitroic acid methyl ester (41.1 mg, 0.106 mmol) was dissolved in a solution of KOH (10% in MeOH : H_2O 9 : 1, 10 mL) and stirred for 1.5 h at 60 °C. The reaction mixture was cooled to room temperature and acidified with concentrated HCl to pH 2. The mixture was concentrated, diluted with H_2O (15 mL) and extracted with EtOAc (4 x 15 mL). The organic layers were washed with brine (2 x 15 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column

chromatography (EtOAc) to yield **13** (29.5 mg, 74%) as a white amorphous solid: R_f 0.40 (EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.58 (s, 3H), 1.04 (d, *J* = 6.3 Hz, 3H), 1.22-1.40 (m, 3H), 1.42-1.61 (m, 3H), 1.62-1.77 (m, 2H), 1.80-2.11 (m, 7H), 2.15 (s, 2H), 2.31 (dd, *J* = 13.4, 6.6 Hz, 1H), 2.47 (ddd, *J* = 14.3, 7.2, 2.8 Hz, 1H), 2.59 (dd, *J* = 13.4, 3.1 Hz, 1H), 2.82 (dd, *J* = 11.8, 3.1 Hz, 1H), 4.18-4.28 (m, 1H), 4.43 (dd, *J* = 7.6, 4.4 Hz, 1H), 4.97-5.03 (m, 1H), 5.29-5.36 (m, 1H), 6.02 (d, *J* = 11.2 Hz, 1H), 6.37 (d, *J* = 11.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 12.0, 19.7, 22.2, 23.5, 27.6, 29.0, 33.9, 40.3, 41.2 (d, *J* = 55.1 Hz), 42.7, 45.1, 45.9, 56.2 (d, *J* = 4.2 Hz), 56.3, 66.9, 70.8, 111.9, 117.3, 124.8, 133.2, 142.6, 147.5, 178.9; IR (neat) 1050, 1663, 2870, 2925, 3343 cm^{-1}; HRMS (ESI-TOF) *m / z* calcd for $C_{22}{}^{13}CH_{34}O_4Na$ 398.2383 $[M + Na]^+$, found 398.2380; $[\alpha]_D{}^{20}$ – 4.7 (*c* 2.0, $CHCl_3$).

Alcohol Metabolite 14. A solution of tetrabutylammonium fluoride (1 M in THF, 1.2 mL, 1.20 mmol) was added to a solution of **11** (72.0 mg, 0.117 mmol) in dry THF (10 mL) at room temperature and stirred overnight. The reaction mixture was treated with a saturated aqueous NH_4Cl solution (25 mL) and extracted with EtOAc (50 /25 mL). The organic layer were washed with brine (25 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography (EtOAc : cyclohexane 7 : 3) to yield calcitroic acid methyl ester (44.4 mg, 97%) as a yellow oil: R_f 0.35 (EtOAc : cyclohexane 7 : 3). $LiAlH_4$ (8.8 mg, 0.232 mmol) was added to calcitroic acid methyl ester (44.4 mg, 0.114 mmol) in dry THF (5 mL) at 0 °C. The mixture was stirred for 15 min at 0 °C and then allowed to warm up to room temperature. After 2 h stirring at room temperature the reaction mixture was quenched with a saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. The crude product was purified

by column chromatography (EtOAc) to yield **14** (31.8 mg, 78%) as a white amorphous solid: R_f 0.35 (EtOAc); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.96 (d, *J* = 6.5 Hz, 3H), 1.20-1.38 (m, 4H), 1.42-1.59 (m, 4H), 1.62-1.80 (m, 3H), 1.80-2.07 (m, 8H), 2.31 (dd, *J* = 13.4, 6.6 Hz, 1H), 2.59 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.82 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.57-3.78 (m, 2H), 4.18-4.28 (m, 1H), 4.42 (dd, *J* = 7.8, 4.4 Hz, 1H), 4.97-5.02 (m, 1H), 5.28-5.35 (m, 1H), 6.02 (d, *J* = 11.3 Hz, 1H), 6.37 (d, *J* = 11.3 Hz, 1H); HRMS (ESI-TOF) *m / z* calcd for $C_{23}CH_{36}O_3Na$ 383.2557 $[M + Na]^+$, found 383.2554;

ASSOCIATED CONTENT

Supporting Information

Electronic supplementary information (ESI) available: Images of 1H and 13C NMR of all products

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Notes

The authors declare no competing financial interest.

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