DOI: 10.1002/ejoc.201300528

Synthesis of a *trans*-Hydrindanone, Precursor for the Preparation of Vitamin D Analogues

Zoila Gándara,*[a] Marcos L. Rivadulla,[a] Manuel Pérez,[a] Generosa Gómez,[a] and Yagamare Fall*[a]

Dedicated to Dr. Simeon Arseniyadis

Keywords: Vitamins / Criegee rearrangement / Oxidation / Dioxenium ion / Rearrangement / Hormones / Ozonolysis

We developed a very efficient and practical method for the large-scale synthesis of a *trans*-hydrindan derivative related to vitamin D, based on the Criegee rearrangement. This ketone is a valuable synthon for the preparation of Gemini-type vitamin D analogues or other calcitriol analogues modified at C-20, C-21 or the D-ring. Our methodology is superior to those previously reported when considering efficiency and expediency.

Introduction

1α,25-Dihydroxyvitamin D_3 [**2**, 1α,25-$(OH)_2$-D_3, calcitriol] (Figure 1), the hormonally active form of vitamin D_3[1] (**1**, cholecalciferol), is one of the most potent inducers of calcitropic effects, notably intestinal calcium absorption and bone calcium mobilization. Besides regulating the metabolism of calcium and phosphorus, calcitriol promotes cell differentiation, inhibits the proliferation of tumor cells, and has numerous indirect effects on the immune system.[2] However, the clinical utility of this hormone for treatment of cancers and skin disorders is limited by its hypercalcemic effects. Accordingly, there is a great deal of interest in the design and synthesis of analogues of **2** with high cell-differentiating properties and low or negligible calcemic effects.

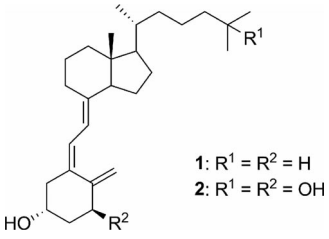


Figure 1. Structures of cholecalciferol (**1**) and 1α,25-$(OH)_2$-D_3 (**2**).

[a] Departamento de Química Orgánica, Facultade de Química, Universidade de Vigo,
36310 Vigo, Spain
E-mail: yagamare@uvigo.es
zoiliac@hotmail.com

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201300528.

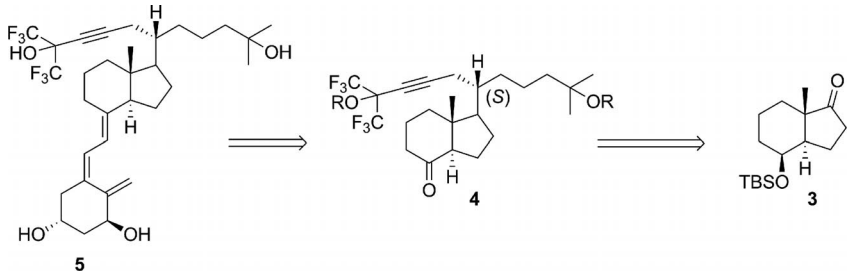
Results and Discussion

As part of our ongoing program focusing on the synthesis of vitamin D metabolites and analogues, we recently designed a new and versatile synthetic methodology for the preparation of Gemini analogue **5**[3] (Scheme 1).

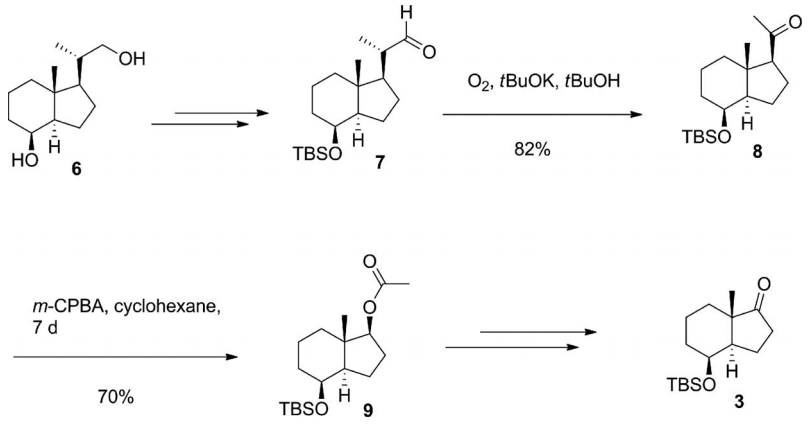
Analogue **5** was previously synthesized by Uskokovic and co-workers,[4] but their procedure relied on an ene reaction for non-selective generation of the double side-chain precursor and the subsequent separation of isomers. In contrast, our synthetic procedure uses a key sigmatropic rearrangement, providing a versatile method for the introduction of novel side-chains to the vitamin D scaffold giving access to a variety of analogues with potentially interesting biological properties. We used *trans*-hydrindanone **3** as a starting material for the synthesis of key intermediate ketone **4**. Compound **3** has been used by Mouriño and co-workers[5] as a precursor for a large number of calcitriol analogues. To the best of our knowledge, the first and only synthesis of ketone **3** was described by Mouriño and co-workers[6] (Scheme 2).

DeLuca and co-workers[7] used the same synthetic sequence to generate 17-ketone **3a** with some modification; they prepared analogous methyl ketone **8a** from aldehyde **7a**, as described by Posner[8] (Scheme 3).

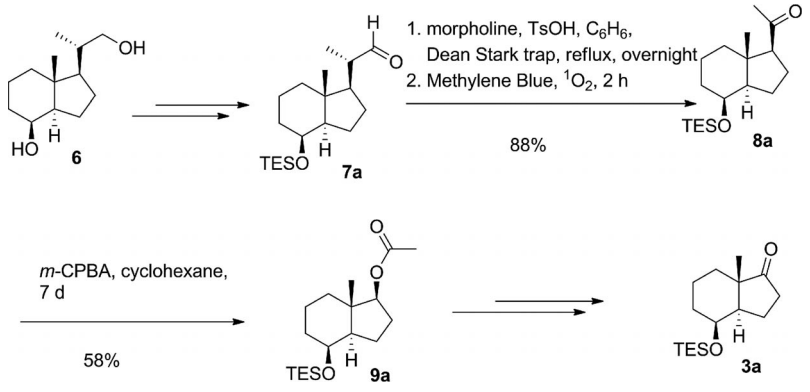
One major drawback of Mouriño's methodology is the Bayer–Villiger oxidation step requiring an unreasonable 7 d reaction time. Moreover, aldehyde **7** was rather unstable, and its transformation into ketone **8** through the intermediacy of α-hydroperoxy aldehyde by reaction with O_2 and potassium *tert*-butoxide, in our hands, consistently provided yields well below 50%. The alternative approach proposed by DeLuca and co-workers may give better yields of ketone **8** but does not avoid the time-consuming Bayer–Villiger oxi-



Scheme 1.



Scheme 2. Mouriño's method of calcitriol analog generation.

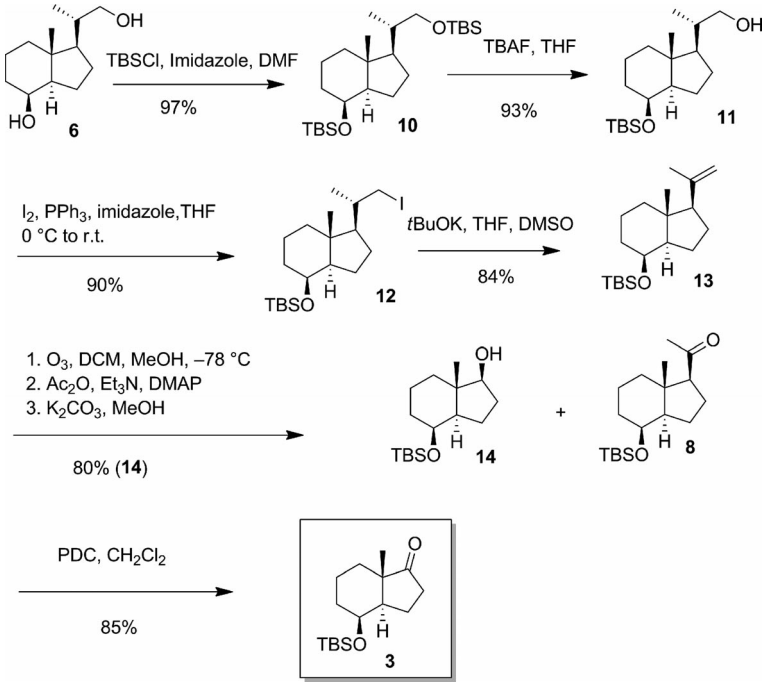


Scheme 3. DeLuca approach to **3a** production.

dation step. A more efficient and reliable method for the large-scale synthesis of ketone **3** is therefore needed. We anticipated that known alkene **13**[9] might suffer degradation of its isopropenyl side chain through a Criegee rearrangement[10] leading to alcohol **14**, a precursor of ketone **3** (Scheme 4).

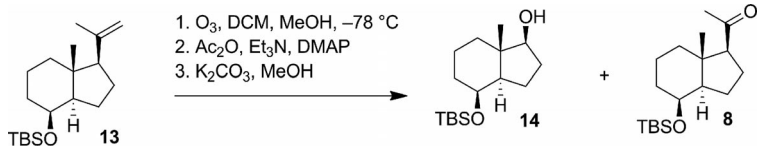
Accordingly, we uneventfully prepared alkene **13**[9] from Inhoffen–Lythgoe diol **6** and carried out the Criegee rearrangement. After much experimentation, optimal reaction conditions were established; results are summarized below in Table 1.

The outcome of the Criegee rearrangement of alkene **13** depended on its molar concentration, on the current intensity during ozonolysis, and the temperatures of acetylation and hydrolysis. Alcohol **14** can be obtained in 80% (Table 1, Entry 8) or 75% yield (Table 1, Entry 10) together with 16% or 2% yield, respectively, of ketone **8**. Ketone **8**, which is also a useful starting material for the synthesis of valuable calcitriol analogues,[11] can be obtained in 80% yield (Table 1, Entry 5). The quantity of Et_3N and Ac_2O seems to be important for the selectivity of the reaction. In general, a large excess of both reagents is necessary. Formation of ketone **8** is favored when a larger excess of Et_3N is used; 36 equiv. of Et_3N and 15.4 equiv. of Ac_2O (Table 1, Entry 5). On the other hand when there is a slightly larger excess of Ac_2O, formation of alcohol **14** was found to be



Scheme 4. Putative Criegee rearrangement-based method evaluated herein.

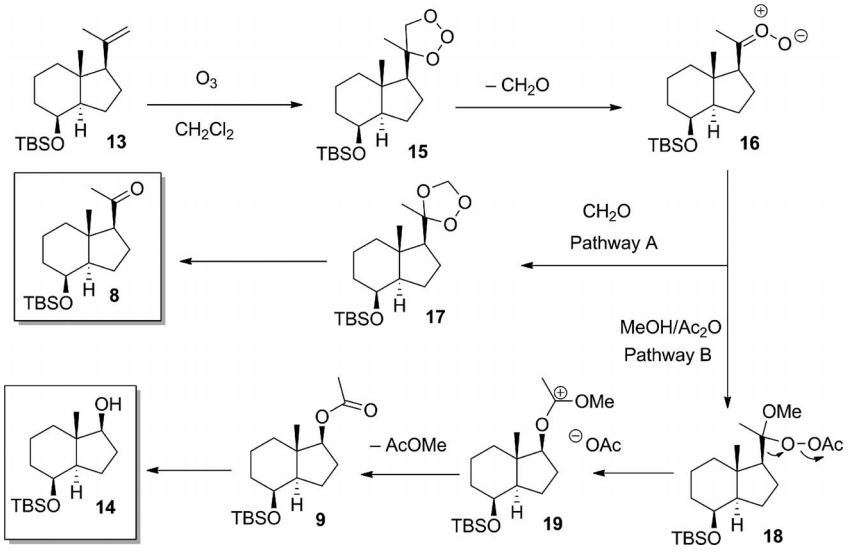
Table 1. Optimization of the Criegee rearrangement of alkene **13**.



Entry	[M][a]	*I*[b]	Ac_2O [eqiv.]	Et_3N [equiv.]	*T* [°C][c]	Base (equiv.)	*T* [°C][d]	**14** [%]	**8** [%]
1	0.3	0.7	15.4 × 2	15.4 × 2	60	K_2CO_3 (0.5)	60	33	22
2	0.03	0.4	15.4 × 2	15.4 × 2	r.t	K_2CO_3 (0.5)	room temp.	50	37
3	0.01	0.4	15.4 × 2	18 × 2	60	K_2CO_3 (1.0)		30	67
4	0.02	0.4	15.4 × 2	18 × 2	r.t	K_2CO_3 (1.0)	room temp.	43	–
5	0.03	0.4	15.4	18 × 2	room temp.	K_2CO_3 (1.0)	room temp.	–	80
6	0.04	0.4	7.5 × 2	7.0 × 2	room temp.	K_2CO_3 (1.0)	room temp.	44	39
7	0.04	0.4	15.0 × 2	15.0 × 2	–30 (→ 2 h) –10 (→ 1 d) room temp. (→ 2 d)	K_2CO_3 (1.0)	room temp.	60	23
8	0.04	0.4	20 × 2	18 × 2	–30 (→ 5 min) –10 (→ 12 h) room temp. (→ 1 d)	K_2CO_3 (5.0)	room temp.	80	16
9	0.04	0.4	30 × 2	28 × 2	–30 (→ 5 min) –10 (→ 12 h) room temp. (→ 1 d)	NaOAc (0.2) K_2CO_3 (5.0)	room temp. 40	– 61	– 5
10	0.04	0.4	40 × 2	38 × 2	–30 (→ 5 min) –10 (→ 12 h) room temp. (→ 4 h)	K_2CO_3 (10)	40	75	2

[a] Molar concentration of alkene **13**. [b] Intensity of current during ozonolysis (in A). [c] Temperature of acetylation step. [d] Temperature of acetate hydrolysis.

favored; examples include reactions containing (i) 40 equiv. of Ac_2O and 36 equiv. of Et_3N (Table 1, Entry 8) or (ii) 80 equiv. of Ac_2O and 76 equiv. of Et_3N (Table 1, Entry 10). The mechanism of formation of methyl ketone **8** (pathway A) and alcohol **14** (pathway B) is rationalized in Scheme 5. With alcohol **14** in hand we uneventfully prepared target ketone **3** in 85% yield by PDC oxidation (Scheme 4).



Scheme 5. Mechanism of the formation of methyl ketone **8** and alcohol **14**.

Conclusions

We have developed a very efficient and practical method for the safe and scalable synthesis of large quantities of *trans*-hydrindan derivatives related to vitamin D. This methodology includes high-yielding steps and avoids the time-consuming Bayer–Villiger reaction (7 d) that typifies the majority of previously reported methods.

Experimental Section

General Procedures: Solvents were purified and dried by standard procedures before use. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX-400 spectrometer (400 MHz for ^{1}H NMR, 100.61 MHz for ^{13}C NMR) by using TMS as the internal standard (chemical shifts δ in ppm, coupling constants J in Hz). Flash chromatography (FC) was performed on silica gel (Merck 60, 230–400 mesh); analytical TLC was performed on plates precoated with silica gel (Merck 60 F_{254}, 0.25 mm). Ozonolyses were carried out with an Erwin Sander Labor ozonizer. Mass spectra (FAB, EI) were recorded with a Fisons VG mass spectrometer and electron spray ionization mass spectra (ESI-MS) were recorded with a Bruker FTMS APEXIII. IR spectra were recorded with a JASCO FT/I(*R*)-6100 spectrophotometer. Elemental analyses were recorded with a Carlo Erba 1108/combustion chromatography fundamental analyser.

[1*R*-(1α,3aβ,4α,7aα)]-(1,1-Dimethylethyl)dimethyl{[octahydro-7a-methyl-1-(1-methylethenyl)-1*H*-inden-4-yl]oxy}silane (13): To a stirred solution of iodide **12** (3.0 g, 6.88 mmol) in THF (30 mL) was added *t*BuOK (1.5 g, 13.7 mmol) in DMSO (15 mL). The mixture was stirred under Ar for 40 min and then poured into a mixture of hexanes (40 mL) and water (40 mL). The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (100% hexane) to afford alkene **13** (1.78 g, 84%) as a colorless oil. R_f = 0.9 (30% EtOAc/hexane). $[\alpha]_D^{21}$ = +35.5 (c = 3.2, $CHCl_3$). IR (NaCl, neat): $\tilde{\nu}$ = 2938, 2861, 1639, 1462, 1370, 1253, 1163, 1078, 976, 882, 839, 776, 684 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 4.82 (s, 1 H, 22-H), 4.70 (s, 1 H, 22-H), 4.03 (s, 1 H, 8-H), 1.99 (t, J = 9.3 Hz, 1 H, 17-H), 1.87–1.77 (m, 3 H), 1.75 (s, 3 H, 21-H), 1.73–1.59 (m, 3 H), 1.49–1.34 (m, 4 H), 1.18 (m, 1 H), 0.90 (s, 9 H, CH_3 *t*BuSi), 0.81 (s, 3 H, 18-H), 0.03 (s, 3 H, CH_3 SiMe), 0.02 (s, 3 H, CH_3 SiMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 145.46 (C-20), 110.86 (CH_2-22), 69.26 (CH-8), 57.99 (CH-17), 53.03 (CH-14), 42.74 (C-13), 39.67 (CH_2), 34.45 (CH_2), 25.81 (CH_3 *t*BuSi), 24.74 (CH_3-21), 24.48 (CH_2), 22.92 (CH_2), 18.02 (C *t*BuSi), 17.78 (CH_2), 14.75 (CH_3-18), –4.78 (CH_3 SiMe), –5.15 (CH_3 SiMe) ppm.

[1*S*-(1α,3aβ,4α,7aβ)]-Octahydro-4-(*tert*-butyldimethylsilyl)oxy-7a-methyl-1*H*-inden-1-ol (14) and [1S-(1α,3aβ,4α,7aβ)]-Octahydro-1-acetyl-4-[(*tert*-butyldimethylsilyl)oxy]-7a-methyl-1*H*-indene (8): An ozonolysis reactor was charged with a solution of alkene **13** (1.2 g, 3.83 mmol) in DCM/MeOH (6:1) (93 mL). Ozone (flow 1.0 mL/min, current intensity 0.4 A) was continuously passed through the reaction mixture at –78 °C. The reaction turned pale blue after 15 min, indicating complete reaction. Excess ozone was then removed by purging with Ar for 15 min. Et_3N (21 mL, 153 mmol), DMAP (catalytic amount), and Ac_2O (14 mL, 145 mmol) were successively added to the mixture at –78 °C, and stirring was continued for 5 min. The solution was then warmed to –30 °C and stirred for another 5 min, then slowly warmed to –10 °C and stirred for 12 h. Et_3N (21 mL, 153 mmol), DMAP (catalytic amount), and Ac_2O (14 mL, 145 mmol) were then added to the mixture, and stirring was continued at room temp. for 4 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (15 mL) at 0 °C, and the solvent was removed. The reaction mixture was then extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with brine (3 × 70 mL), dried with $MgSO_4$, filtered, and concentrated. The resulting residue was dissolved in MeOH (20 mL), and K_2CO_3 (5.2 g, 383 mmol) was added. The mixture was heated at 40 °C for 2 h. The reaction was quenched with water at room temp. and the solvent then removed. The reaction mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (100% hexane → 10% EtOAc/hexane) to afford alcohol **14** (805 mg, 75%) and methyl ketone **8** (22 mg, 2%).

Alcohol 14: White solid. M.p. 69–71 °C. R_f = 0.2 (10% EtOAc/hexane). $[\alpha]_D^{21}$ = +37.6 (c = 2.0, $CHCl_3$). IR (NaCl, neat): $\tilde{\nu}$ = 3338, 2938, 2860, 1463, 1360, 1253, 1078, 1020, 920, 839, 772, 679 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.97 (d, J = 2.7 Hz, 1 H, 8-H), 3.55 (t, J = 8.5 Hz, 1 H, 17-H), 2.15–1.96 (m, 1 H, 14-H), 1.83–1.62 (m, 5 H), 1.49–1.30 (m, 4 H), 1.20 (m, 1 H), 0.95 (s, 3 H, 18-H), 0.88 (s, 9 H, CH_3 *t*BuSi), 0.01 (s, 3 H, CH_3 SiMe), –0.01 (s, 3 H, CH_3 SiMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 82.07 (CH-17), 69.09 (CH-8), 47.95 (CH-14), 42.06 (C-13), 37.34 (CH_2), 34.35 (CH_2), 29.37 (CH_2), 25.75 (CH_3 *t*BuSi), 22.11 (CH_2), 17.96 (C *t*BuSi), 17.22 (CH_2), 12.53 (CH_3-18), –4.65 (CH_3-SiMe), –5.19 (CH_3 SiMe) ppm. MS (ESI): m/z (%) = 285.22 $[M + 1]^+$ (30), 265.19 $[M^+ – H_2O]$ (100), 177.11 (20). HRMS (ESI): calcd. for $C_{16}H_{33}O_2Si$ 285.22469; found 285.22443. $C_{16}H_{32}O_2Si$ (284.51): calcd. C 67.55, H 11.34; found C 67.47, H 11.48.

Methyl Ketone 8: Colorless oil. R_f = 0.4 (10% EtOAc/hexane). $[\alpha]_D^{21}$ = +71.1 (c = 0.6, $CHCl_3$). IR (NaCl, neat): $\tilde{\nu}$ = 2933, 2858, 1705, 1463, 1356, 1253, 1160, 1078, 1024, 922, 838, 774, 682 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.04 (s, 1 H, 8-H), 2.48 (t, J = 9.0 Hz, 1 H, 17-H), 2.21 (m, 1 H), 2.10 (s, 3 H, CH_3 Ac), 2.01 (dt, J = 12.3, 3.6 Hz, 1 H), 1.90–1.77 (m, 1 H), 1.74–1.56 (m, 3 H), 1.53–1.36 (m, 5 H), 0.88 (s, 9 H, CH_3 *t*BuSi), 0.86 (s, 3 H, 18-H), 0.02 (s, 3 H, CH_3 SiMe), 0.00 (s, 3 H, CH_3 SiMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 209.51 (C=O), 68.86 (CH-8), 64.45 (CH-17), 53.18 (CH-14), 43.67 (C-13), 43.67 (CH_2), 39.74 (CH_2), 31.51 (CH_3-21), 25.70 (CH_3 *t*BuSi), 17.57 (CH_2), 15.48 (CH_2), –4.89 (CH_3 SiMe), –5.25 (CH_3 SiMe) ppm. MS (ESI): m/z (%) = 311.46 $[M + 1]^+$ (43), 253.32 $[M^+ – t\text{Bu}]$ (89), 225 (21), 179 (9). HRMS (ESI): calcd. for $C_{18}H_{35}O_2Si$ 311.35677; found 311.37368. $C_{18}H_{34}O_2Si$ (310.55): C 69.62, H 11.03; found C 69.76, H 11.26.

8β-[(*tert*-Butyldimethylsilyl)oxy]des-A,B-androstan-17-one (3): To a stirred solution of alcohol **14** (935 mg, 3.29 mmol) in DCM (30 mL) was added PDC (3.71 g, 9.87 mmol) and a catalytic amount of PPTS at room temp. After 16 h, the reaction mixture was filtered through a bed of Celite, and the solvent was removed. The reaction mixture was extracted with EtOAc (3 × 40 mL). The organics layers were washed with aqueous NaCl (3 × 40 mL), dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash column chromatography (100% hexane → 10% EtOAc/hexane) to afford ketone **3** (790 mg, 85%) as a colorless oil. R_f = 0.4 (10% EtOAc/hexane). $[\alpha]_D^{21}$ = +36.2 (c = 0.6, $CHCl_3$). IR (NaCl, neat): $\tilde{\nu}$ = 2935, 2889, 2858, 1741, 1465, 1375, 1165, 1078, 1029, 974, 901, 839, 777, 688 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.08 (s, 1 H, 8-H), 2.36 (m, 1 H), 1.93 (m, 2 H), 1.68 (m, 4 H), 1.45 (m, 2 H), 1.33 (m, 1 H), 1.15 (m, 1 H), 1.03 (s, 3 H, 18-H), 0.83 (s, 9 H, CH_3 *t*BuSi), –0.02 (s, 6 H, CH_3 SiMe) ppm. ^{13}C NMR ($CDCl_3$): δ = 220.51 (C=O), 69.69 (CH-8), 48.49 (CH-14), 47.24 (C-13), 35.04 (CH_2), 34.06 (CH_2), 32.02 (CH_2), 25.71 (CH_3 *t*BuSi), 21.31 (CH_2), 17.76 (C *t*BuSi), 16.94 (CH_2), 16.38 (CH_3-18), –4.86 (CH_3 SiMe), –5.17 (CH_3 SiMe) ppm. MS (ESI-TOF): m/z (%) = 283.20 $[M + 1]^+$ (19), 267.19 $[M^+ – Me]$ (63), 226.19 $[M^+ – t\text{BuSi}]$ (63). HRMS (ESI): calcd. for $C_{16}H_{31}O_2Si$ 283.20839; found 283.2078. $C_{16}H_{30}O_2Si$ (282.50): C 68.03, H 10.70; found C 67.64, H 10.75.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra for **13**, **14**, **8** and **3**.

Acknowledgments

This work was supported financially by the Xunta de Galicia (No. EXPTE CN 2012/184). The work of the NMR, and MS divisions of the research support services of the University of Vigo (CACTI) is also gratefully acknowledged. Z. G. thanks the Xunta de Galicia for an Angeles Alvariño contract.

[1] A. W. Norman, *Vitamin D the Calcium Homeostatic Steroid Hormone*, Academic Press, New York, **1979**.
[2] For general reviews of vitamin D chemistry and biology, see: a) *Vitamin D: Chemistry, Biology and Clinical Application of the Steroid Hormone* (Eds.: A. W. Norman, R. Bouillon, R. Thomasset), Vitamin D Workshop, Riverside, CA, **1997**; b) D. Feldman, F. H. Glorieux, J. W. Pike, *Vitamin D*, Academic Press, San Diego, CA, **1997**; c) R. Pardo, M. Santelli, *Bull. Soc. Chim. Fr.* **1985**, *1*, 98–114; d) H. Dai, G. H. Posner, *Synthesis* **1994**, *12*, 1383–1398; e) G.-D. Zhu, W. H. Okamura, *Chem. Rev.* **1995**, *95*, 1877–1952; f) G. H. Posner, M. Kahraman, *Eur. J. Org. Chem.* **2003**, *20*, 3889–3895.
[3] a) Y. Fall, G. Gomez, M. Perez, Z. Gandara, X. Perez, G. Pazos, G. Kurz, PCT Int. Appl. WO 2011121152 A1 20111006, **2011**; b) G. Pazos, Ph.D. Thesis, University of Vigo, **2011**.
[4] H. Maehr, M. R. Uskokovic, *Eur. J. Org. Chem.* **2004**, *8*, 1703–1713.
[5] a) J. A. Martínez Pérez, Ph.D. Thesis, University of Santiago de Compostela, **1994**; b) M. A. Rey Liste, Ph.D. Thesis, University of Santiago de Compostela, **1997**; c) J. Zorgdrager, M. A. Rey, A. Mouriño, Y. Fall, K. M. Halkes, A. Fernández-Gacio, European Patent EP 0884308 A2, **1998**; d) A. Fernández-Gacio, Ph.D. Thesis, University of Santiago de Compostela, **1999**; e) A. Fernández-Gacio, C. Vitale, A. Mouriño, *J. Org. Chem.* **2000**, *65*, 6978–6983; f) R. Riveiros, Ph.D. Thesis, University of Santiago de Compostela, **2001**; g) M. A. Rey, J. A. Martinez-Pérez, A. Fernández-Gacio, K. Halkes, Y. Fall, J. Granja, A. Mouriño, *J. Org. Chem.* **1999**, *64*, 3196–3206; h) R. Riveiros, A. Rumbo, L. A. Sarandeses, A. Mouriño, *J. Org. Chem.* **2007**, *72*, 5477–5485.
[6] B. Fernandez, J. A. Martinez Perez, J. Granja, L. Castedo, A. Mouriño, *J. Org. Chem.* **1992**, *57*, 3173–3178.
[7] R. Barycki, R. R. Sicinski, L. A. Plum, P. Grzywacz, M. Clagett-Dame, H. F. DeLuca, *Bioorg. Med. Chem.* **2009**, *17*, 7658–7669.
[8] G. H. Posner, K. Crawford, M.-L. Siu-Caldera, G. Satyanarayana Reddy, S. F. Sarabia, D. Feldman, E. Van Etten, C. Mathieu, L. Gennaro, P. Vouros, S. Peleg, P. M. Dolan, T. W. Kensler, *J. Med. Chem.* **2000**, *43*, 3581–3586.
[9] a) A. W. Norman, P. S. Manchand, M. R. Uskokovic, W. H. Okamura, J. A. Takeuchi, J. E. Bishop, J.-I. Hisatake, H. P. Koeffler, S. Peleg, *J. Med. Chem.* **2000**, *43*, 2719–2729; b) M. J. Calverley, *Steroids* **2001**, *66*, 249–255.
[10] a) R. Criegee, R. Kaspar, *J. Liebigs Ann. Chem.* **1948**, *560*, 127; b) R. Criegee, *Angew. Chem.* **1975**, *87*, 765; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 745–752; c) A. R. Daniewski, L. M. Garofalo, S. D. Hutchings, M. M. Kabat, W. Liu, M. Okabe, R. Radinov, G. P. Yiannikour, *J. Org. Chem.* **2002**, *67*, 1580–1587.
[11] a) S. Hourai, L. C. Rodrigues, P. Antony, B. Reina-San-Martin, F. Ciesielski, B. C. Magnier, K. Schoonjans, A. Mouriño, N. Rochel, D. Moras, *Chem. Biol.* **2008**, *15*, 383–392; b) P. Antony, R. Sigueiro, T. Huet, Y. Sato, N. Ramalanjaona, L. C. Rodrigues, A. Mouriño, D. Moras, N. Rochel, *J. Med. Chem.* **2010**, *53*, 1159–1171.

Received: April 11, 2013
Published Online: July 23, 2013

