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Click chemistry approach to a series of calcitriol analogues with heterocyclic side chains

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Abstract: We report a straightforward synthesis of a series of novel calcitriol analogues from vitamin $D_2$with some modification of the procedures described by Calverley and Choudhry. This approach allows the large scale synthesis of a late-stage intermediate common to all the analogues of the series.This intermediate was successfully employed to synthesize a huge number of calcitriol analogues using a "click" chemistry approach.

Keywords: Calcitriol; Vitamin D_2; triazole; azaanalogue; "Click" chemistry.

Introduction

1,25-Dihydroxyvitamin D_3 (**1**, calcitriol) (Fig.1), the hormonally active metabolite of vitamin D_3 (2), acts as a regulator in calcium and phosphate homeostasis[1]. Next to these classical activities, calcitriol has been shown to inhibit cellular proliferation and to induce cellular differentiation[2]. However the therapeutic utility of **1** is hampered by the effective doses leading to calcemic side effects and this has stimulated the search for analogues having a relatively weak systemic effect on calcium metabolism while maintainig potent regulatory effects on cell differentiation and proliferation.

As part of our ongoing program on the synthesis of vitamin D analogues modified at the side chain,[3] we envisaged the synthesis of various calcitriol analogues having heteroatoms on their side chain. The rational that could explain this choice was: we have already synthesized Aza-vitamin D analogues[3r] and the biological activity of some of these derivatives was later studied showing that they had less calcemic effect than calcitriol. The strategy we used so far involved construction of the triene unit on the CD fragment following the introduction of the side chain. This strategy is inconvenient if a lengthy series of analogues with modified side chains are to be prepared for systematic biological evaluation.

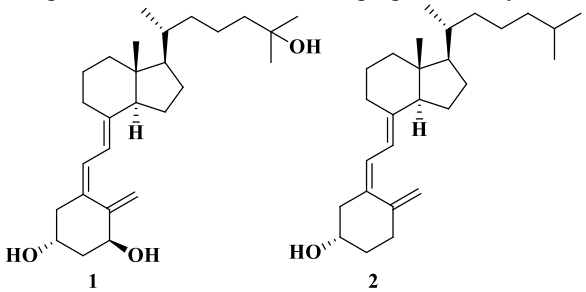

Figure 1. Structures of 1,25-Dihydroxyvitamin D_3 (**1**) and vitamin D_3 (**2**).

Results and Discussion

We examined the possibility of preparing a series of analogues modified at the side chain from a common intermediate, in which the labile triene system was already present. The use of this strategy involved the concept of the triene system protection to allow chemical modification of the vitamin D side chain. This concept received relatively little attention.[4] Among these approaches, the one using the preparation and subsequent thermolysis of the sulfur dioxide adducts of vitamin D_2[4b,c] seemed to us more appropriate for a large scale synthesis of a late-stage intermediate such as **10** (Scheme 1).

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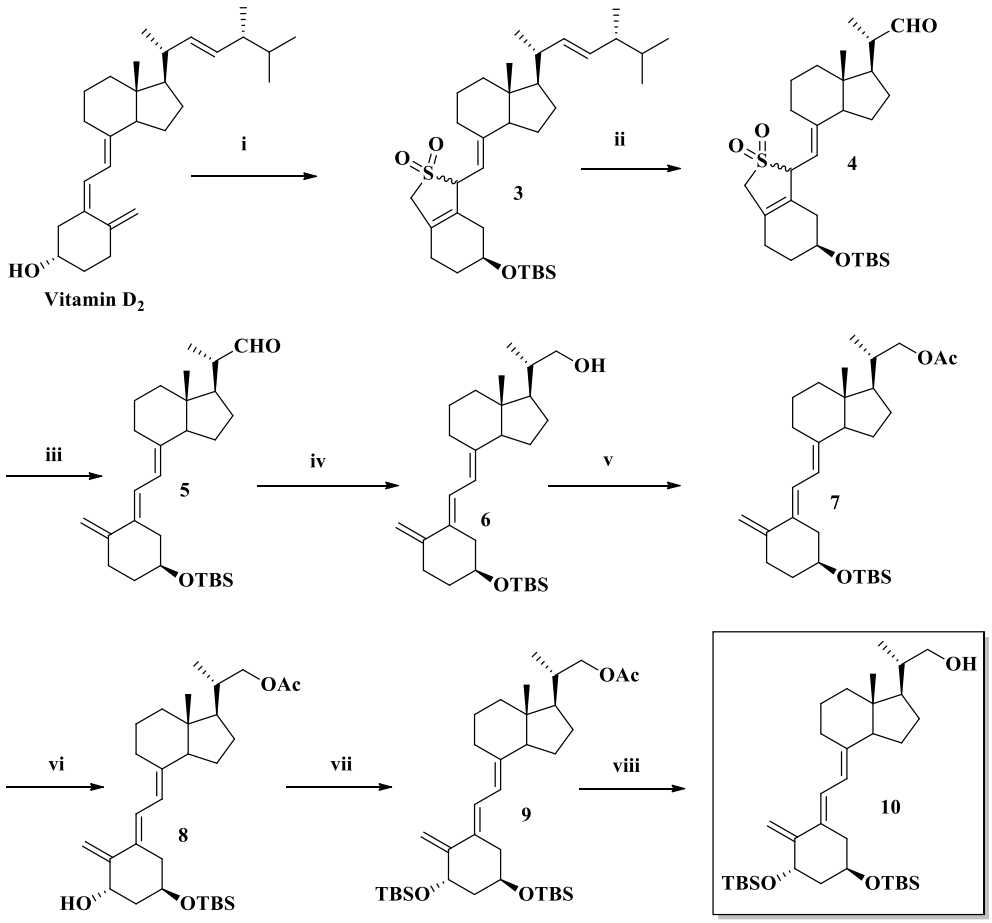
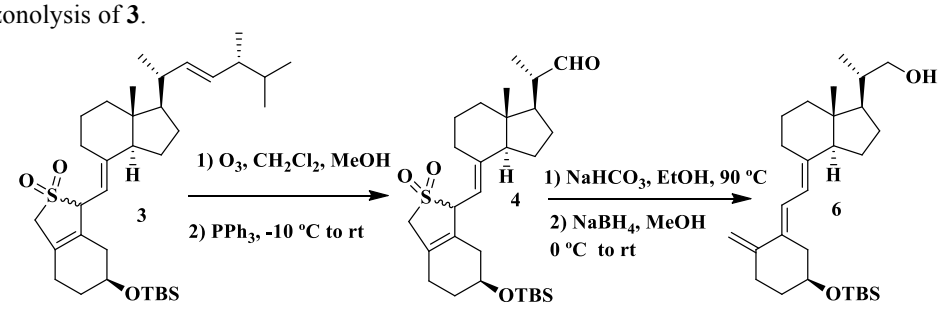


Scheme 1. Synthesis of intermediate **10** from vitamin D_2. *Reagents and conditions*: (i) a) SO_2, CH_2Cl_2, -25 ºC to -10º C; b) TBSCl, cat. DMAP, CH_2Cl_2, -5º C to rt (97%, 2 steps); (ii) a) O_3, CH_2Cl_2, MeOH, -78º C; b) PPh_3, 0º C to 25º C; (iii) $NaHCO_3$, EtOH, reflux; (iv) $NaBH_4$, MeOH, 0º C (85% from **3**); (v) Ac_2O, Et_3N, DMAP (96%); (vi) a) SeO_2, MeOH, reflux; b) **7**, NMO, 50º C (60 %); (vii) TBSCl, imidazole, DMAP, CH_2Cl_2 (88%); (viii) K_2CO_3, MeOH (94%).

Accordingly vitamin D_2 was converted to its SO_2-adducts **3** in 97% yield by dissolving in liquid sulfur dioxide and subsequent silylation. The ozonolysis of **3** resulted to be extremely troublesome and after much experimentation the best reaction conditions could be established. The results are summarized in Table 1.

Table 1. Ozonolysis of **3**.



Entry	3 quantity (g)	F(x100L /h) F = gas flow	I(A) I = current	Reaction time	Yield % of 6 (from 3)
1	1	1.5	0.6	10 mn	0
2	1	1.5	0.3	10 mn	0
3	1	1.0	0.1	15 mn	30
4	1	1.0	0.03	1 h	85
5	5	1.0	0.03	5 h	85

The optimized reaction conditions for running the ozonolysis of **3** were as described in entries 4 and 5.

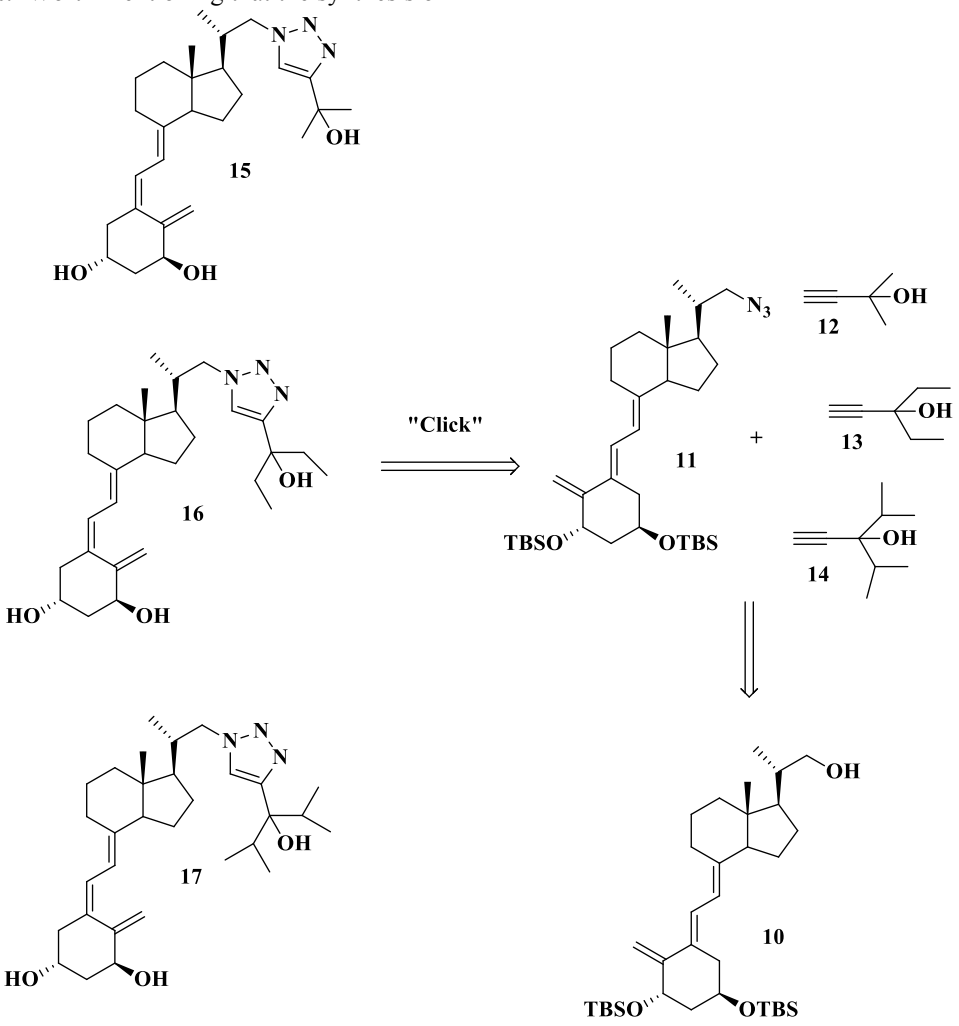
The time necessary for the ozonolysis to be completed was substrate dependant (1 h to ozonolyze 1 g of substrate **3**). Aldehyde **4** was unstable and was immediately converted to alcohol **6** by thermal chelotropic extrusion of sulfur dioxide (SO_2) in the presence of sodium bicarbonate ($NaHCO_3$) followed by sodium borohydride reduction of the intermediate aldehyde **5**. Alcohol **6** was obtained in 85% overall yield (3 steps).

Reaction of alcohol **6** with acetic anhydride gave 96% yield of acetate **7** which was hydroxylated at C-1 with selenium dioxide in the presence of 4-methylmorpholine *N*-oxide (NMO) to afford allylic alcohol **8** in 60% yield. The latter was silylated, giving 88% yield of acetate **9**. Reaction of the latter with potassium carbonate (K_2CO_3) in methanol afforded key intermediate **10** with the 5-(*E*) triene system.

The overall yield of intermediate **10** from vitamin D_2 was 39%. Worth mentioning that the synthesis of **10** could be carried out in multigrams quantities and the compound could be stored in the fridge during months without alteration. Compound **10** is more stable than its 5-(*Z*) isomer and can be further elaborated in order to introduce the desired side chain.

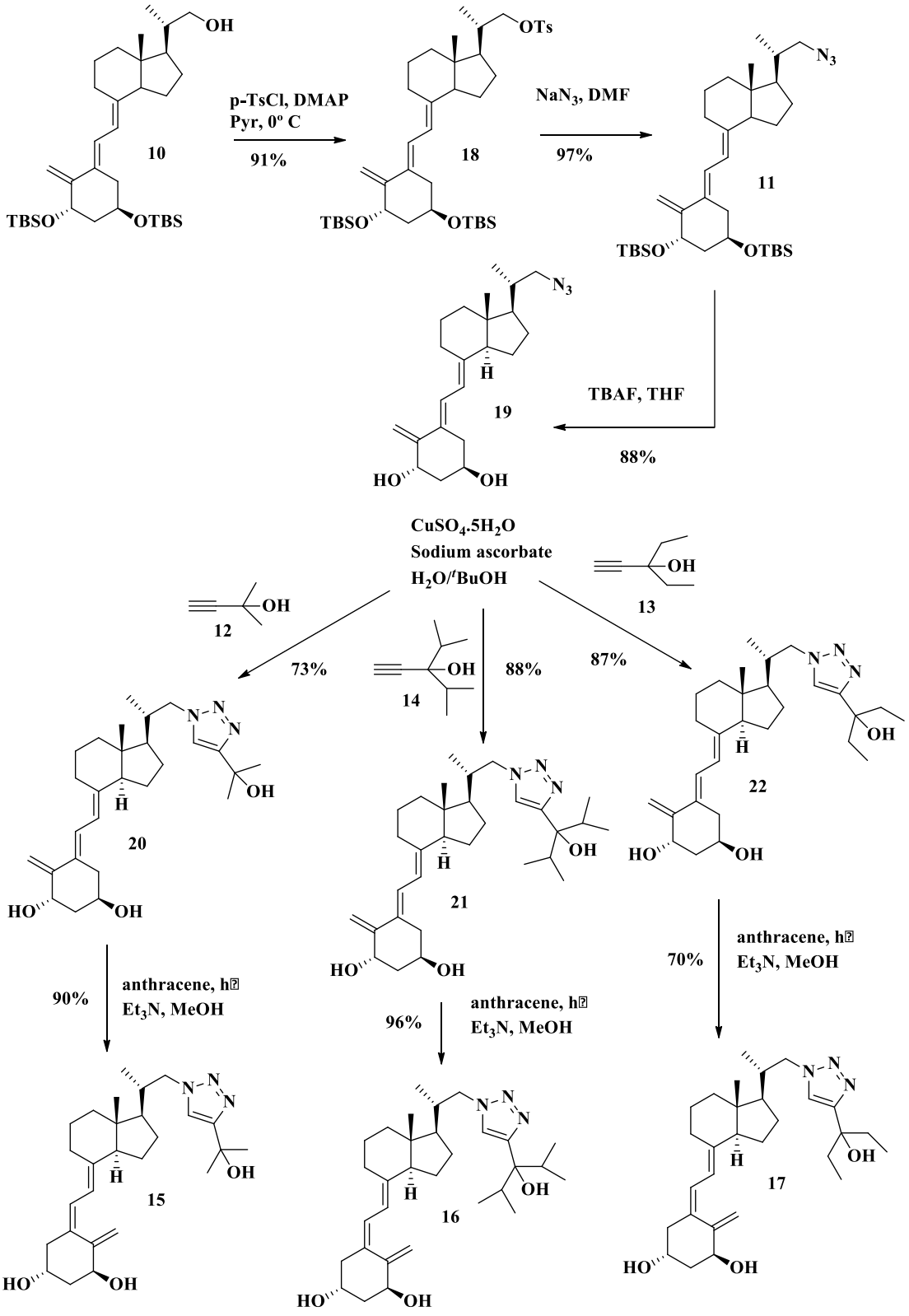
The advantages of this present approach compared to Calverley and Choudhry's approaches are: 1) Only one SO_2 triene protection is needed, hence one SO_2 extrusion. 2) The ozonolysis of the side chain is carried out before the C-1 hydroxylation. 3) For the synthesis of **10** from vitamin D_2, we found an overall yield of 39% which is a bit better then 37% calculated using Calverley's procedure.

We anticipated that intermediate **10** could lead to calcitriol analogues **15**, **16**, and **17** using a "Click" chemistry approach[5] between azide **11** and commercially available alkynes **12**, **13**, and **14**. Our retrosynthetic basis is outlined in Scheme 2.



Scheme 2. Retrosynthetic analysis of analogues **15, 16** and **17**

Accordingly compounds **15-17** were prepared as outlined in Scheme 3.



Scheme 3. Synthesis of analogues **15, 16** and **17**

Tosylation of alcohol **10** followed by displacement of the C-22 tosylate of **18** with sodium azide, led to key azide **11** in 88% overall yield. Removal of the silyl protecting groups of **11** afforded azide **19** which underwent a [3+2]-cycloaddition[5] with alkynes **12**, **13** and **14** to afford triazoles **20**, **21** and **22** in 73, 88 and 87% yields respectively.

Computational studies carried out by Sharpless and co-workers,[6] proved that the exclusive regioselectivity of the triazole formation could be explained by a stepwise mechamism involving unprecedented matallacycle intermediates (Figure 2).

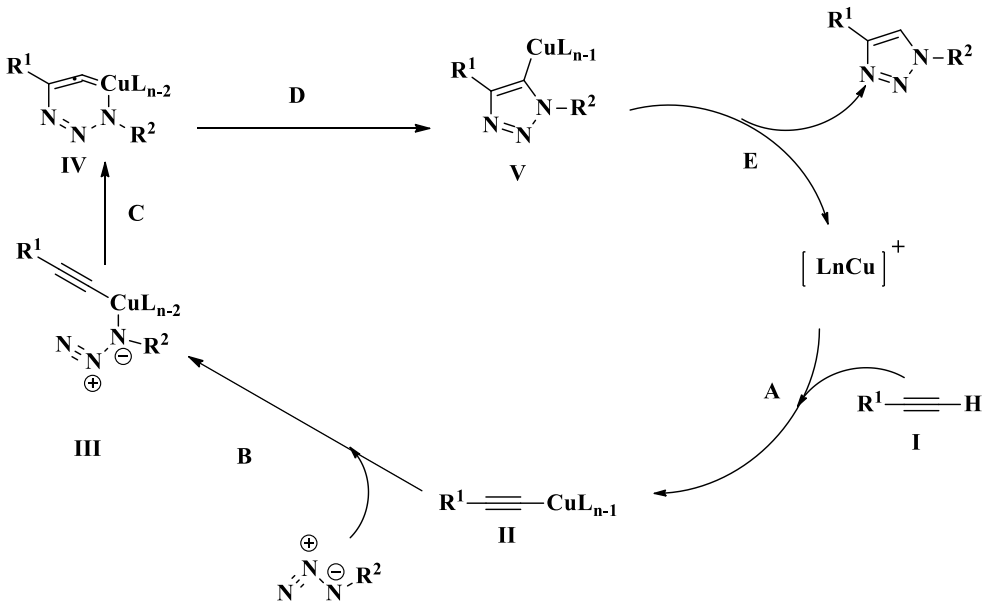


Figure 2. Sharpless proposed mechanism for the formation of 1,4-disubstituted 1,2,3-triazoles

Photosensitized isomerization of **20**, **21** and **22** using anthracene as triplet sensitizer afforded target Vitamin D analogues **15, 16** and **17** in 90%, 96% and 70% yields respectively.

Conclusion

In conclusion, we have improved the method described by Calverley and Choudhry for the large scale synthesis of a late-stage intermediate which leads to a straightforward access to some calcitriol analogues with a triazole ring in their side chain. The use of intermediates mentioned above to access new calcitriol analogues is underway in our laboratory.
The preliminary results of the biological activity of some of our azavitamin D analogues showed that they had less calcemic effect than calcitriol. These results as well as the activities of the whole series of the synthesized analogues will be published in due time after patent protection.

Acknowledgements

This work was supported financially by the Xunta de Galicia (project CN 2012/184).The work of the NMR, SC-XRD and MS divisions of the research support services of the University of Vigo (CACTI) is also gratefully acknowledged. A.F; M.S.; M.G. and O.D. thank the University Cheikh Anta Diop (Dakar, Sénégal) for financial support for a research stay at the University of Vigo.

Experimental Section

General Procedures

Solvents were purified and dried by standard procedures. Flash chromatography was performed on silicagel (Merck 60, 230–400 mesh). Analytical TLC was performed on plates precoated with silica gel (Merck 60 F254, 0.25 mm). Melting points were obtained using a Gallenkamp apparatus and are uncorrected. Optical rotations were obtained using a Jasco P-2000 polarimeter. IR spectra were obtained using a Jasco FT/IR-6100 Type A spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker ARX-400 spectrometer using TMS as the internal standard; chemical shifts (δ) are quoted in ppm and coupling constants (J) in Hz. Mass spectrometry (MS and HRMS) was carried out using a Hewlett-Packard 5988A spectrometer. The reactions were carried out protecting the glassware from light using aluminum foil.

(6S)-6-((tert-butyldimethylsilyl)oxy)-1-((*E*)-((3aS,7aR)-1-((2R,5R,E)-5,6-dimethylhept-3-en-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)methyl)-1,3,4,5,6,7-hexahydrobenzo[c]thiophene 2,2-dioxide (3)

In a three neckround-bottom flask at -25 ºC was condensed SO_2 (100 mL, 2.00 mol) and a solution of vitamin D_2 (100 g, 0.25 mol) in CH_2Cl_2 (250 mL) was added via cannula. At the end of the addition the orange mixture was stirred at -10 ºC for 90 min and allowed to reach room temperature, thus removing excess SO_2. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and cooled to 5 ºC. Imidazole (22.5 g, 0.33 mol), TBSCl (50 g, 0.33 mol) and a catalytic amount of DMAP were added to the mixture which was stirred overnight, reaching room temperature. H_2O (100 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were washed with brine (25 mL) and dried. Solvent evaporation afforded 140 g (96%) of known compound **3**[4b].

(2S)-2-((3aS,7aR, *E*)-4-((*E*)-2-((S)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propan-1-ol (6)

A solution of **3** (5 g, 8.7 mmol) in MeOH (66 mL) and CH_2Cl_2 (170 mL) was subjected to ozonolysis using the best conditions described in Table 1 and after 5 h at -78º C the mixture was allowed to reach -10º C. PPh_3 (3 g, 11.5 mmol) was added and stirring was continued for 30 min. The mixture was allowed to reach 0 ºC and an aqueous saturated solution of $NaHCO_3$ (40 mL) was added. After extraction with CH_2Cl_2 (3 x 100 mL), the combined organic phases were washed with brine (3 x 50 mL), dried (Na_2SO_4), filtered and concentrated to give 4.43 g of a residue (aldehyde **4**) which was used for the next reaction without further purification. The residue was dissolved in ethanol (45 mL) and $NaHCO_3$ (4.43 g) was added and the mixture was refluxed for 5 h. The solvent was rotatory evaporated affording a residue which was dissolved in CH_2Cl_2 (25 mL) and filtered in order to remove excess $NaHCO_3$. To the filtrate was added brine (50 mL). After extraction with CH_2Cl_2 (3 x 25 mL), the combined organic phases were dried (Na_2SO_4), filtered and concentrated to afford a residue (compound **5**) which was used for the next reaction without further purification. The residue was dissolved in MeOH (45 mL) and cooled to 0 ºC. $NaBH_4$ (400 mg, 10.44 mmol) was added portionwise to the mixture and stirring was continued for 15 min. H_2O (50 mL) was added and the product extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 10% EtOAc/Hexane as eluent, affording 3.3 g (85% , 3 steps) of alcohol **6**, as a white solid, M.p.: 53-55 ºC, Rf = 0.59 (30% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ): 4.74 (1H; d; J=10,08 Hz; H-7); 4.58 (1H; d; J=9,6 Hz; H-6); 3.92 (1H; s; H-3); 3.50 (2H; m; H-22);3.32 (2H; s; CH_2-19); 2.85 (1H, m); 2.43 (2H, m), 2.36 (2H, m); 2.29 (1H, m); 2.06 (1H, m); 1.98 (1H, m); 1.86 (2H, m), 1.65 (7H, m); 1.36 (3H, m),0.99 (3H; d; J=6,48 Hz; CH_3-21); 0.82 (9H; s; *tert*-BuSi); 0.53(3H; s; CH_3-18); 0.01(3H; s; CH_3-TBS); 0.00 (3H; s; CH_3-TBS);

^{13}C-NMR ($CDCl_3$, δ): 150.3 (C-8); 131.1 (C-5); 127.1 (C-10); 116.1 (C-7); 110.2 (CH_2-19); 68.0 (CH_2-22); 67.2 (CH-3 y CH-6); 58.5 (CH_2); 56.2 (C-14); 53.1 (C-17); 46.0 (C-13); 40.3 (CH_2); 39.4 (C-20); 34.5 (CH_2); 31.4 (CH_2); 29.8 (CH_2); 27.4 (CH_2); 26.2 (CH_3-*terc*-BuSi); 25.0 (CH_2); 23.9 (CH_2); 22.6 (CH_2); 18.5 (C-*tert*-Bu); 17.3 (C-21); 12.1 (C-18); -4.6 (CH_3-TBS); -4.7 (CH_3-TBS);

MS (m/z (%)): 445.22 (M^++1, 20); 311.13 (32); 281.09 (20); 267.08 (21); 209.10 (41); 193.15 (100);

HRMS: Calcdfor $C_{28}H_{48}O_2Si$: 445.3502, found: 445.3508.

(2S)-2-((3aS,7aR, *E*)-4-((E)-2-((S)-5-((*tert*-butyldimethylsilyl)oxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propyl acetate (7)

To a solution of alcohol **6** (3.0 g, 6.75 mmol) in CH_2Cl_2 (30 mL) were added pyr (1.2 mL, 14.8 mmol), Ac_2O (0.7 mL, 7.43 mmol) and a catalytic amount of DMAP. The mixture was stirred for 2 h at room temperature and cooled to 0 ºC before adding an aqueous saturated solution of NH_4Cl (30 mL). After extraction with CH_2Cl_2 (3 x 40 mL), the combined organic phases were washed with an aqueous saturated solution of $CuSO_4$ (3 x 40 mL), dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 5% EtOAc/Hexane affording 2.9 g (94%) of acetate **7**, as a yellowish oil; Rf = 0.66(10% EtOAc/Hexane);

^{1}H-NMR($CDCl_3$, δ):6.50 (1H; d; J=11,45 Hz; H-6); 5.88 (1H; d; J=11,50; H-7); 4.94 (1H; s; H-19); 4.65 (1H; s; H-19); 4.10 (1H, dd, J=3.8 y 7.4 Hz, H-22); 3.86 (1H, t, J=3.8 Hz, H-3); 3.81 (1H, dd, J=3.8 y 7.4 Hz, H-22); 2.85 (1H, m); 2.68 (1H, m); 2.52 (1H, m); 2.22 (2H, m); 2.15 (1H, m); 2.07 (3H, s, CH_3-Ac); 2.00 (1H, m); 1.86 (2H, m); 1.65 (7H, m); 1.35 (3H, m); 1.05 (3H; d; J=6.54 Hz; CH_3-21); 0.89 (9H; s; *tert*-BuSi); 0.59 (3H; s; CH_3-18); 0.08(3H, s, CH_3-TBS); 0.07(3H, s, CH_3-TBS);

^{13}C-NMR ($CDCl_3$, δ): 171.4 (C=O); 150.0 (C-10); 143.2 (C-8); 136.5 (C-5); 119.9 (CH-6); 116.2 (CH-7); 107.6 (CH_2-19); 69.6 (CH-3); 69.5 (CH_2-22); 56.1 (CH-14); 53.1 (CH-17); 45.9 (C-13); 40.3 (CH_2); 37.5 (CH_2); 36.2 (CH-20); 35.2 (CH_2); 31.2 (CH_2); 28.9 (CH_2); 27.2 (CH_2); 26.0 (CH_3-*tert*-BuSi); 23.5 (CH_2); 22.3 (CH_2); 23.0 (CH_3-Ac); 18.2 (C-*tert*-BuSi); 17.3 (CH_3-21); 12.1 (CH_3-18); -4,6 (CH_3-TBS);

MS (m/z (%)): 487.33 (M^++1, 12); 486.33 (M^+, 23); 295.20 (21); 193.15 (100); 171.21 (32);

HRMS: Calcd for $C_{30}H_{50}O_3Si$: 486.3529, found: 486.3518.

(2S)-2-((3aS,7aR, *E*)-4-((*E*)-2-((3S,5R)-5-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propyl acetate (8)

A solution of SeO_2 (0.7 g, 6.32 mmol) in MeOH (50 mL) was refluxed for 45 min. A solution of acetate **7** (2.18 g, 4.47 mmol) in CH_2Cl_2 (52 mL) was also refluxed for 15 min before adding it via cannula to the previous solution of SeO_2. After the addition, the mixture was refluxed for 2 h and allowed to reach room temperature. H_2O (10 mL) was added and the product extracted with CH_2Cl_2 (3 x 25 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 10% EtOAc/Hexane affording 1.37 g (61%) of alcohol **8**,

as a white solid, M.p.: 44º C, Rf = 0.42 (20% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ): 6.45 (1H, d, J=11.4 Hz; H-6); 5.80 (1H, d, J=11.4 Hz; H-7); 4.42(1H, s, H-19); 4,12 (1H, s, H-19); 4,01 (1H, dd, J=7,43 y 3,24 Hz, H-22); 3,74 (1H, dd, J=7,5 y 3,20Hz, H-22); 2.75 (2H, m); 2.43 (1H, m); 2.33 (1H, m); 1,98(3H, s, CH_3-Ac); 1.86 (4H, m); 1.62 (4H, m); 1.46 (3H, m); 1.22 (2H, m); 0,96 (3H, d, J=6,6 Hz;CH_3-21); 0,79 (9H, s, *tert*-BuSi); 0,50(3H, s, CH_3-18); 0,00(6H, s, CH_3-TBS);

^{13}C-NMR ($CDCl_3$, δ): 171.8 (C=O); 153.5 (C-10); 144.0 (C-8); 135.0 (C-5); 122.6 (C-6); 116.8 (C-7); 108.1 (CH_2-19); 70.9 (C-3); 69.8 (CH_2-22); 67.2 (C-1); 56.5 (C-14); 53.5 (C-17); 46.4 (C-13); 43.3(CH_2); 40.7 (CH_2); 37.3 (CH_2); 36.5 (C-20); 29.4 (CH_2); 27.5 (CH_2); 26.2 (CH_3-*terc*-BuSi); 23.9 (CH_2); 22.7 (CH_2); 21.4 (CH_3-Ac); 18.5 (C-*tert*-BuSi); 17.7 (C-21); 12.5 (C-18); -4.3 (CH_3-TBS);

MS (m/z (%)): 503.25 (M^++1, 18); 502.34 (M^+, 23); 307.16 (20); 171.21 (32);

HRMS: Calcdfor $C_{30}H_{50}O_4Si$: 502.3478, found: 502.3495.

(2S)-2-((3aS,7aR,E)-4-((E)-2-((3S,5R)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propyl acetate (9)

To a solution of alcohol **8** (1.90 g, 3.76 mmol) in CH_2Cl_2 (10 mL), at 0 ºC was added imidazole (343 mg, 5.0 mmol), TBSCl (760 mg, 5.0 mmol) and a catalytic amount of DMAP and the mixture was left stirring at room temperature for 5 h. H_2O (10 mL) was added and the product extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 3% EtOAc/Hexane as solvent, affording 2.1 g (90%) of acetate **9**, as a white solid, M.p.: 77-80 ºC, Rf = 0.51 (20% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ):6.40 (1H, d, J=11.32 Hz; CH-6); 5.78 (1H, d, J=11.16 Hz; CH-7); 4.92(1H, s; CH_2-19); 4.88(1H, s; CH_2-19); 4.48 (1H, d; J=4.7Hz; CH-3); 4.16 (1H, s; CH-1); 4.05(1H, dd; J=3.25 Hz; J=7.34 Hz; H-22); 3.74(1H, dd; J_1=3.22 Hz; J_2=7.39 Hz; H-22); 2.86 (1H, m); 2.55 (1H, m); 2.22 (1H, m); 1.98(3H, s; CH_3-Ac); 1.95 (1H, m); 1.85 (3H, m); 1.65 (4H, m); 1.55 (3H, m); 1.33 (3H, m); 1.01 (3H, s, CH_3-21); 0.84(9H, s; CH_3-*tert*-BuSi); 0.80(9H, s; CH_3-*tert*-BuSi); 0.51(3H, s; CH_3-18); 0.00 (12H, s; CH_3-TBS);

^{13}C-NMR ($CDCl_3$, δ): 171.6 (C=O); 154.0 (C-10); 143.1 (C-8); 136.0 (C-5); 122.0 (CH-6); 117.0 (CH-7); 107.0 (CH_2-19); 70.6 (CH-3); 69.8 (CH_2-22); 67.6 (CH-1); 56.5 (CH-14); 53.5 (CH-17); 46.4 (C-13); 44.3 (CH_2); 40.8 (CH_2); 36.9 (CH_2); 36.5 (CH-20); 29.3 (CH_2); 27.5 (CH_2); 26.3 (CH_3-*terc*-BuSi); 23.8 (CH_2); 22.7 (CH_2); 21.3 (CH_3-Ac); 18.6 (C-*tert*-BuSi); 18.4 (C-*tert*-BuSi); 17.7(CH_3-21); 12.4 (CH_3-18); -4.4 (CH_3-TBS); -4.5 (CH_3-TBS);

MS (m/z (%)): 617.44 (M^++1,38); 616.42 (23); 485.33 (52); 284.16 (100); 171.21 (32); 163.22 (20);

HRMS: Calcdfor $C_{36}H_{64}O_4Si_2$: 616.4298, found: 616.4262.

(2S)-2-((3aS,7aR, *E*)-4-((*E*)-2-((3S,5R)-3,5-bis((*tert*-butyldimethylsilyl)oxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propan-1-ol (10)

To a solution of acetate **9** (1.1 g, 1.83 mmol) in MeOH (30 mL) at room temperature was added K_2CO_3 (500 mg, 3.67 mmol) and the mixture was stirred for 10 h. Excess K_2CO_3 was eliminated by firtration and H_2O (100 mL) was added to the filtrate and the product extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (3 x 20 mL), dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 3% EtOAc/Hexane as solvent, affording 990 mg (94%) of alcohol **10**, as a white solid, M.p.: 110-113º C, Rf = 0.63 (30% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ): 6.41 (1H, d, J=11,3 Hz; H-6); 5.78 (1H, d, J=11.3;CH-7); 4.92(1H, s, H-19); 4.87(1H, s, H-19); 4.45 (2H, m, H-22); 4.15 (1H, m, H-1); 3.61 (1H, m, H-3); 2.75 (1H, m); 2.45 (1H, m); 2.27 (1H, m); 1.95 (2H, m); 1.63 (4H, m); 1.51 (3H, m); 1.22 (6H, m);1.00 (3H, d, J=7,6 Hz; CH_3-21); 0.83(9H, s, *tert*-BuSi); 0.80(9H, s,*tert*-BuSi); 0.50(3H, s, CH_3-18); 0.00(12H, s, CH_3-TBS);

^{13}C-NMR ($CDCl_3$, δ): 154.0 (C-10); 143.5 (C-8); 135.9 (C-5); 122.1 (C-6); 116.9 (C-7); 107.1(CH_2-19); 70.7 (C-3); 68.3 (CH_2-22); 67.6 (C-1); 56.6 (C-14); 53.3 (C-17); 46.3 (C-13); 44.3 (CH_2); 40.8 (CH_2) 39.5 (C-20); 37.0(CH_2); 29.3 (CH_2); 27.6(CH_2); 26.3(CH_3-*tert*-BuSi); 26.2 (CH_3-*tert*-BuSi); 23.9 (CH_2); 22.7 (CH_2); 18.6 (C-*tert*-BuSi); 18.5(C-*tert*-BuSi); 17.3 (C-21); 12.5 (C-18); -4,4 (CH_3-TBS);

MS (m/z (%)): 575.36 (M^++1,51); 442.25 (77); 249.11 (45); 247.10 (27);

HRMS: Calcd for $C_{34}H_{62}O_3Si_2$: 575.4316, found: 575.4317.

(S)-2-((1R,3aS,7aR, *E*)-4-((*E*)-2-((3S,5R)-3,5-bis((tert-butyldimethylsilyl)oxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1H-inden-1-yl)propyl 4-methylbenzenesulfonate (18).

To a solution of **10** (990 mg, 1.72 mmol) in Py (9 mL) at 0 ºC was added p-TsCl (660 mg, 3.44 mmol) and DMAP (c.c.). The mixture was stirred at this temperature for 9 h, quenched with NH_4Cl (10 mL), then allowed to reach room temperature. The product was extracted with EtOAc (3×15 mL). The organic phase was washed with $CuSO_4$ (3×20 ml).

After drying (Na_2SO_4) and solvent evaporation, the residue was chromatographed on silicagel using 3% EtOAc-hexane as eluent, to afford 1.1 g of tosylate **18** [91%, white solid; Mp= 50-53 ºC; Rf: 0.87 (30% EtOAc-hexane)].

^{1}H-NMR ($CDCl_3$, δ): 7.72 (2H, d, *J*=8.2 Hz, H-Ts), 7.27 (2H, d, *J*=8.0 Hz, H-Ts), 6.37 (1H, d, *J*=11.3 Hz, H-6), 5.74 (1H, d, *J*=11.3 Hz, H-7), 4.91 (1H, s, H-19), 4.88 (1H, s, H-19), 4.48 (1H, m, H-1), 4.45 (1H, m, H-3), 3.92 (1H, m, H-22), 3.90 (1H, m, H-22), 2.75 (1H, m), 2.43 (1H, m), 2.37 (3H, s, CH_3-Ts), 2.17 (1H, m), 1.85 (3H, m), 1.55 (5H, m), 1.37 (3H, m), 1.15 (3H, m), 0.93 (3H, d, *J*=6.5 Hz, H-21), 0.84 (9H, s, CH_3-*terc*-BuSi), 0.80 (9H, s, CH_3-*terc*-BuSi), 0.44 (3H, s, H-18), 0.00 (12H, s, CH_3-SiMe);
^{13}C-NMR ($CDCl_3$, δ): 154.0 (C-10), 145.0 (C-8), 142.9 (C-Ts), 136.1 (C-5), 133.6 (C-Ts), 130.2 (CH-Ts), 128.3 (CH-6), 122.0 (CH-7), 107.1 (CH_2-19), 75.9 (CH_2-22), 70.6 (CH-1), 67.2 (CH-3), 56.4 (CH-14), 52.6 (CH-17), 46.2 (C-13), 44.3 (CH_2), 40.6 (CH_2), 37.0 (CH-20), 36.9 (CH_2), 29.2 (CH_2), 27.3 (CH_2), 26.3 (CH_3-*terc*-BuSi), 26.3 (CH_3-*terc*-BuSi), 26.2 (CH_3-*terc*-BuSi), 23.8 (CH_2), 22.6 (CH_2), 22.0 (CH_3-Ts), 18.6 (C-*terc*-BuSi), 18.4 (C-*terc*-BuSi), 17.4 (CH_3-18), 12.4 (CH_3-21), -4.4 (CH_3-SiMe), -4.5 (CH_3-SiMe), -4.5 (CH_3-SiMe);
LRMS: : [m/z %]:729.35 [$(M+1)^+$, (23)], 728.35 [M^+, (22)], 727.34 [M^+-1, (14)], 597.28 (32), 596.28 (46), 425.27(35), 379.19 (16), 249.13 (47), 248.13(100), 247.11 (33).
HRMS: m/z calcd $C_{41}O_5Si_2SH_{68}$ for: 729.4404; found: 729.4418.

(((1R,3S,*E*)-5-((E)-2-((3aS,7aR)-1-((S)-1-azidopropan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (11)

To a solution of tosylate **18** (933 mg, 1.28 mmol) in DMF (15 mL) was added NaN_3 (832 mg, 12.8 mol) and the mixture was stirred at room temperature for 42 h. CH_2Cl_2 (25 mL) was added and the organic phase was washed with H_2O (3 x 15 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to afford a residue which was chromatographed on silica gel using 5% EtOAc/Hexane as solvent, affording 750 mg (97%) of azide **11**, as a white solid, M.p.: 104 ºC, Rf = 0.75 (10% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ): 6.43 (1H, d, J=11.4 Hz, H-6), 5.82 (1H, d, J=11.3 Hz, H-7), 4.95 (2H, d, J=16.2 Hz, H-19), 4.63 (1H, m, H-22), 4.43 (1H, m, H-22), 3.46 (1H, dd, J=,11.9 y 3.1 Hz, H-1), 3.05 (1H, m, H-3), 2.81 (1H, m); 2.77 (1H, m); 2.56 (1H, m); 2.12 (1H, m); 1.92 (4H, m), 1.85 (4H, m); 1.63 (2H, m); 1.53 (3 H, s, CH_3-18), 1.21 (3H, m); 1.05 (3 H, d, J= 6.5 Hz, CH_3-21), 0.89 (9H, s, *tert*-BuSi), 0.85 (9H, s, *tert*-BuSi), 0.05 (12 H, s, CH_3-TBS);
^{13}C-RMN ($CDCl_3$, δ):153.6 (C-10), 142.7 (C-8), 135,7 (C-5), 121.6 (C-6), 116.2 (C-7), 106.7 (CH_2-19), 70.2 (C-3), 67.2 (C-22), 58.0 (CH_2), 56.2 (C-14), 53.6 (C-17), 43.9 (CH_2), 40.3 (CH_2), 37.2 (C-20), 36.6 (CH_2), 28.9 (CH_2), 27.4 (CH_2), 25.9 (CH_3-*tert*-BuSi), 23.4 (CH_2), 22.3 (CH_2), 18.2 (C-*tert*-BuSi), 17.9 (C-21), 12.1 (C-18), -4.8 y -4.9 (CH_3-TBS);
MS (m/z (%)): 600,43 (M+1, 40); 599.44 (M+, 46); 570.43 (21); 542.37 (27); 467.34 (73); 440.32 (20); 248.15 (100);
HRMS: Calcd for $C_{34}H_{61}N_3O_2Si_2$: 599.4302, found: 599.4302.

(1R,3S, *E*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-azidopropan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (19)

To a solution of azide **11** (116 mg, 0.19 mmol) in THF (2 mL) was added TBAF (1.16 mL, 1.16 mmol, 1M sln in THF) and the mixture was stirred for 16 h. Aqueous saturated solution of NH_4Cl (10 mL) was added and the product was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 50% EtOAc/Hexane as solvent, affording 72 mg (99%) of azide **19**, as a colourless oil, Rf = 0.11 (20% EtOAc/Hexane);

^{1}H-NMR ($CDCl_3$, δ): 6.55 (1H, d, J= 11.5 Hz, H-6); 5.86 (1H, d, J= 11.5 Hz, H-7); 5.10 (1H, s; H-19); 4.95 (1H, s, H-19); 4.47 (1H, m, CH_2-22); 4.22 (1H, m, CH_2-22); 3.37 (1H, dd, J=11.9 y 3.1 Hz, H-1); 3.06 (1H, m, H-3); 2.86 (1H, m); 2.75 (1H, m), 2.66 (1H, m); 2.43 (1H, m); 1.85 (5H, m); 1.66 (5H, m); 1.55 (2H, m); 1.32 (3H, m), 1.05, (3H, d, J= 6.6 Hz, CH_3-21); 0.56 (3 H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$, δ):151.7 (C-10); 144.5 (C-8); 133,0 (C-5); 123.2 (C-6); 116.1 (C-7); 106.7 (CH_2-19); 71.1 (C-3); 67.5 (C-22); 57.9 (CH_2); 56.2 (C-14); 53.6 (C-17); 42.0 (CH_2); 40.2 (CH_2); 37.2 (C-20); 36.4 (CH_2); 29.0 (CH_2); 27.3 (CH_2); 23.4 (CH_2); 22.3 (CH_2); 17.9 (C-21); 12.1 (C-18);
MS (m/z (%)): 371.25 (M^+,56), 354.24 (35); 322.22 (23); 307.07 (100), 289.07 (44), 273.08 (20);
HRMS: Calcd for $C_{22}H_{33}N_3O_2$:371.2573, found: 371.2565.

General procedure for the click chemistry reaction of azide **19** with alkynes **12**, **13** and **14** to afford compounds **20**, **21** and **22**.

To a solution of azide **19** (70 mg, 0.19 mmol) in *tert*-BuOH (2 mL) and H_2O (1 mL) was added a catalytic amount of $CuSO_4.5H_2O$, sodium ascorbate (13υL of 1M aqueous sln), and the chosen alkyne (0.20 mmol). The mixture was stirred at room temperature for 7 h. H_2O (10 mL) was added and the product was extracted with EtOAc (3 x 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated to afford a residue which was chromatographed on silica gel using 50% EtOAc/Hexane as solvent to afford the corresponding triazoles **20**, **21** or **22**.

(1R,3S,*E*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(2-hydroxypropan-2-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (20)

Yield 73%, Brownish solid, M.p.: 106 ºC, Rf = 0.31 (EtOAc);

^{1}H-NMR ($CDCl_3$, δ) : 7.38 (1H, s, H-23); 6.55 (1H, d, J=11.4 Hz, H-6); 5.89 (1H, d, J=11.4 Hz, H-7); 5.19 (1H, s, H-19); 4.96 (1H, s, H-19); 4.57-4.50 (2H, m, H-22); 4.21 (1H, m, H-1); 4.04 (1H, m, H-3); 2.99 (2H, m); 2.76 (1H, m); 2.66 (1H, m); 2.43 (1H, m); 1.89 (5H, m); 1.75 (4H, m); 1.63 (6H, s, CH_3-25); 1.43 (2H, m); 1.21 (2H, m); 0.87 (3 H, d, J= 6.5 Hz, CH_3-21); 0.60 (3H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$,δ): 155.4 (C-10); 151.6 (C-24); 144.2 (C-8); 133.2 (C-5);123.6 (C-23); 123.0 (C-6); 116.3 (C-7);109.7 (CH_2-19); 76.7 (C-25); 71.1 (C-3); 67.5 (C-1);56.1 (C-13); 55.9 (CH_2-22); 54.1 (C-17);42.0 (CH_2); 40.2 (CH_2); 38.2 (C-26 o C-27); 36.7 (CH_2), 30.5 (C-26 o C-27); 28.9 (CH_2); 27.6 (CH_2); 25.8 (C-25); 23.3 (CH_2); 22.4 (CH_2); 17.2 (C-21); 12.2 (C-18);
MS (m/z (%)): 456.34 (M+1,40); 307.11 (20); 289.10 (23); 155.27 (38);
HRMS: Calcd for $C_{27}H_{42}N_3O_3$: 456.3226, found: 456.3224.

(1R,3S,E)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(3-hydroxy-2,4-dimethylpentan-3-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (21)

Yield 86%, White solid, M.p.: 123 ºC, Rf = 0.41 (EtOAc);

^{1}H-NMR ($CDCl_3$, δ): 7.30 (1H, s, H-23); 6.53(1H, d, J= 11.3 Hz, H-6); 5.87 (1H, d, J= 11.3 Hz, H-7); 5.07 (1H, s, H-19); 4.93 (1H, s, H-19); 4.47 (1H. m. H-1); 4.36 (1H, m, H-3); 4.33 (2H, m, H-22); 2.82 (2H, m); 2, 76 (2H, m); 2.66 (2H, m); 2.44 (2H, m);1.66 (5H, m); 1.43 (4H, m); 1.22 (2H, m); 1.11 (3H, m), 1.08(3H, d, J=12.8 Hz, CH_3-21); 0.80 (12H, m, CH_3-*iso*propyl); 0.60 (3H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$,δ): 171.7 (C-10); 151.7 (C-8); 141.0 (C-24); 133.3 (C-5); 123.4 (C-23); 122.8 (C-6); 117.2 (C-7); 109.6 (CH_2-19); 72.0 (C-25); 70.0 (C-3);65.7 (C-1); 56.1 (C-13); 55.8 (CH_2-22); 54.2 (C-17); 41.9 (CH_2); 40.1 (CH_2); 38.1; 36.6 (CH_2); 34.1 (CH-*iso*propyl); 30.5; 28.9 (CH_2); 27.5 (CH_2); 23.3 (CH_2); 22.4 (CH_2); 17.1 (C-21); 14.1 (CH_3-*iso*propyl); 12.2 (C-18);
MS (m/z (%)): 512.53 (M^++1,100); 511.46 (M^+, 30) 394.43 (20); 322.31 (34); 307.16 (20); 154.24 (96);
HRMS: Calcd for $C_{31}H_{49}N_3O_3$: 511.3852, found: 511.3868.

(1R,3S,*E*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(3-hydroxypentan-3-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (22)

Yield 87%, White solid, M.p.: 110 ºC, Rf = 0.41 (EtOAc);

^{1}H-NMR ($CDCl_3$, δ): 7.37 (1H, s, H-23); 6.55 (1H, d, J= 11.4 Hz, H-6); 5.89 (1H, d, J= 11.4 Hz, H-7); 5.09 (1H, s, H-19); 4.96 (1H, s, H-19); 4.47 (1H, m, H-1), 4.36 (1H, m, H-3); 4.33 (2H, m, H-22); 2.82 (2H, m); 2.76 (2H, m), 2.66 (1H, m); 2.43 (1H, m); 2.05 (4H,m, CH_2-Et); 1.88 (4H, m); 1.66 (5H, m); 1.43 (3H, m); 1.22 (3H, m); 0.85(9 H, m,CH_3-Et y CH_3-21); 0.60 (3H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$,δ): 151.7 (C-10); 144.6 (C-24); 144.6 (C-8); 133.3 (C-5); 123.0 (C-23); 119.6 (C-6); 116.3 (C-7);109.7 (CH_2-19); 76.7(C-25); 71.1 (C-3);65.8 (C-1); 56.2 (C-13); 55.9 (CH_2-22); 54.2 (C-17); 42.0 (CH_2); 40.2 (CH_2); 38.2 ; 36.7 (CH_2); 33.9 (CH_2-Et); 30.5; 28.9 (CH_2); 27.5 (CH_2); 23.3 (CH_2); 22.4 (CH_2); 17.1 (C-21); 12.2 (C-18); 7.8 (CH_3-Et);
MS (m/z (%)): 484.51 (M^++1, 37); 307.17 (28); 235.25 (20); 155.26 (33);
HRMS: Calcd for $C_{29}H_{46}N_3O_3$: 484.3539, found: 484.3546.

Photosensitized isomerization of **20**,**21** and **22** to afford **15**, **16** and **17**, using anthracene as triplet sensitizer was carried out following the general procedure described for compound **20**.

To a solution of **20** (10 mg, 0.02 mmol) in MeOH (10 mL) was added anthracene (3 mg, 0.01 mmol) and a catalytic amount of Et_3N. The mixture was irradiated with a 200 W lamp for 6 h, diluted with CH_2Cl_2 (15 mL) and washed with brine (10 mL). After solvent evaporation the resulting residue was chromatographed on silica gel using CH_2Cl_2 and 10% MeOH/CH_2Cl_2 as solvent, affording 9 mg (90%) of analogue **15.**

(1R,3S,*Z*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(2-hydroxypropan-2-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (15)

Yield 90%, White solid, M.p.: 110 ºC, Rf = 0.31 (10% MeOH/CH_2Cl_2);

^{1}H-NMR ($CDCl_3$, δ): 7.34 (1H, s, H-23); 6.35 (1H, d, J=11.1 Hz, H-6), 6.02 (1H, d, J=11.2 Hz, H-7), 5.32 (1H, s, H-19); 4.99 (1H, s, H-19), 4.57-4.50 (2H, m, H-22), 4.21 (1H, m, H-1), 4.04 (1H, m, H-3); 2.99 (2H, m); 2.76 (1H, m), 2.66 (1H, m);2.43 (1H, m); 1.89 (5H, m); 1.75 (4H, m); 1.63 (6H, s, CH_3-25); 1.43 (2H, m); 1.21 (3H, m); 0.86 (3 H, d, J= 6.5 Hz, CH_3-21); 0.58 (3H, s, CH_3-18);

^{13}C-NMR ($CDCl_3$,δ): 155.4 (C-10), 147.6 (C-24), 142.2 (C-8); 133.4 (C-5); 124.6 (C-23),119.6 (C-6); 117.4 (C-7); 111.8 (CH_2-19); 76.7(C-25); 70.8 (C-3); 67.5 (C-1);56.3 (C-13); 55.7(CH_2-22); 54.1 (C-17);42.3 (CH_2); 40.2 (CH_2); 38.2 (C-26 o C-27); 36.7 (CH_2); 30.5 (C-26 o C-27); 28.9 (CH_2); 27.6 (CH_2); 25.8 (C-25); 23.3 (CH_2); 22.4 (CH_2); 17.2 (C-21); 12.2 (C-18);
MS (m/z (%)): 456.34 (M+1, 40), 307.11 (20), 289.10 (23); 155.27 (38);
HRMS: Calcd for $C_{27}H_{42}N_3O_3$: 456.3226, found: 456.3224.

(1R,3S,*Z*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(3-hydroxy-2,4-dimethylpentan-3-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (16)

Yield 96%, colourless oil, Rf = 0.41 (10% MeOH/CH_2Cl_2);
^{1}H-NMR ($CDCl_3$, δ): 7.28 (1H, s, H-23); 6.36 (1H, d, J=11.4 Hz, H-6); 6.03 (1H, d, J=11.4 Hz, H-7); 5.33 (1H, s, H-19); 4.99 (1H, s, H-19); 4.39 (1H, m, H-1); 4.36 (1H, m, H-3); 4.33 (2H, m, H-22); 2.82 (2H, m), 2, 76 (2H, m); 2.66 (2H, m); 2.44 (2H, m);1.66 (5H, m); 1.43 (4H, m); 1.22 (2H, m); 1.11 (3H, m), 1.08 (3H, d, J=12.8 Hz, CH_3-21); 0.80 (12H, m, CH_3-*iso*propyl); 0.59 (3H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$,δ): 150.7 (C-10); 147.7 (C-24); 142.3 (C-8); 133.5 (C-5); 124.3 (C-23); 121.4 (C-6); 117.4 (C-7); 111.6 (CH_2-19); 72.0 (C-25); 70.7 (C-3); 65.7 (C-1); 56.1 (C-13); 55.8 (CH_2-22); 54.2 (C-17); 41.9 (CH_2); 40.1 (CH_2); 38.2; 36.6 (CH_2); 34.1 (CH-*iso*propyl), 30.48; 28.9 (CH_2); 27.5 (CH_2); 23.4 (CH_2); 22.4 (CH_2); 17.1 (C-21); 14.1(CH_3-*iso*propyl); 12.2 (C-18);
MS (m/z (%)): 512.53 (100); 394.43 (20); 322.31 (34); 307.16 (20); 154.24 (96);
HRMS: Calcd for $C_{31}H_{50}N_3O_2$: 512.3852, found: 512.3868.

(1R,3S,*Z*)-5-((*E*)-2-((3aS,7aR)-1-((S)-1-(4-(3-hydroxypentan-3-yl)-*1H*-1,2,3-triazol-1-yl)propan-2-yl)-7a-methylhexahydro-*1H*-inden-4(*2H*)-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol (17)

Yield 90%, colourless oil, Rf = 0.41 (10% MeOH/CH_2Cl_2);
^{1}H-NMR ($CDCl_3$, δ): 7.33 (1H, s, H-23); 6.36 (1H, d, J= 11.4 Hz, H-6), 6.02 (1H, d, J= 11.4 Hz, H-7); 5.32 (1H, s, H-19); 4.99 (1H, s, H-19); 4.47 (1H. m. H-1), 4.36 (1H, m, H-3); 4.33 (2H, m, H-22);2.82 (2H, m); 2.76 (2H, m), 2.66 (1H, m); 2.43 (1H, m); 2.05 (4H,m, CH_2-Et);1.88 (4H, m); 1.66 (5H, m), 1.43 (3H, m); 1.22 (3H, m); 0.85(9 H, m,CH_3-Et y CH_3-21); 0.59 (3H, s, CH_3-18);
^{13}C-NMR ($CDCl_3$,δ): 151.7 (C-10); 147.6 (C-24); 142.6 (C-8); 133.4 (C-5); 124.0 (C-23); 120.6 (C-6); 117.3 (C-7);111.7 (CH_2-19); 76.7(C-25); 71.1 (C-3);65.8 (C-1); 56.3 (C-13); 56.2 (CH_2-22); 54.2 (C-17); 42.0 (CH_2); 40.2 (CH_2), 38.2; 36.7 (CH_2); 33.9 (CH_2-Et); 31.5; 28.9 (CH_2); 27.6 (CH_2); 23.2 (CH_2); 22.3 (CH_2); 17.2 (C-21); 12.2 (C-18); 7.8 (CH_3-Et);
MS (m/z (%)): 484.51 (M^++1, 37); 307.17 (28); 235.25 (20); 155.26 (33);
HRMS: Calcd for $C_{29}H_{46}N_3O_3$: 484.3539, found: 484.3546.

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