Vitamin D Heterocyclic Analogues; Part 2: Synthesis of the First Vitamin D Analogues with a Tetrazole Ring at the Side Chain

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Abstract: Access to the calcitriol analogues with a tetrazole ring at the side chain was very efficiently achieved using the Calverley–Choudhry approach instead of the Wittig–Horner method, which gave very low yields.

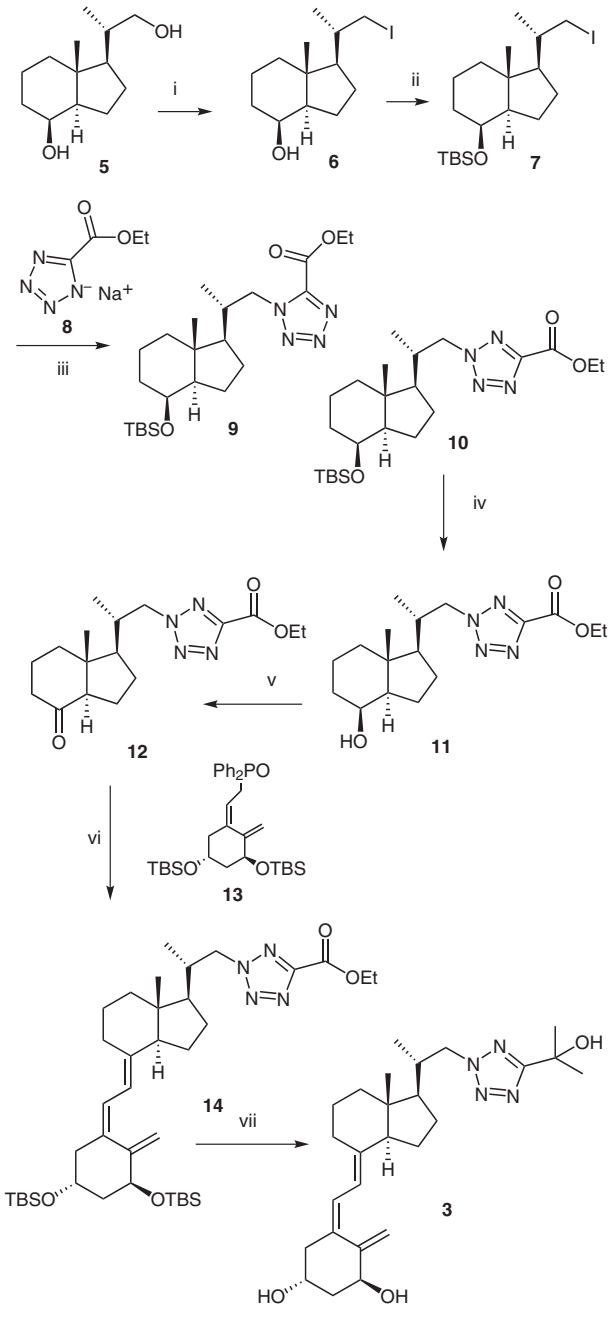
Key words: 1α,25-dihydroxyvitamin D_3, tetrazole, heterocycles, azasteroids, Windhaus–Grundmann ketone

1α,25-Dihydroxyvitamin D_3 [**1**, 1α,25-$(OH)_2$-D_3, calcitriol], the hormonally active form of vitamin D_3[1] (**2**, cholecalciferol) (Figure 1), 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 certain indirect effects on the immunological system.[2] However, the clinical utility of this hormone for treatment of cancers and skin disorders is limited by its hypercalcemic effects. There is accordingly much interest in the design and synthesis of analogues of **1** having high cell-differentiating properties and low or negligible calcemic effects.[2]

Despite the fact that azasteroids show noteworthy pharmacological activity,[3] very few aza-analogues of vitamin D have been known.[3,4] We report here a straightforward access to the side chain of vitamin D analogues **3** and **4** bearing a tetrazole moiety (Figure 1). The synthesis of analogue **3** is detailed in Scheme 1.

Selective iodation of the primary alcohol of diol **5** gave iodide **6**[5] in 96% yield. Protection of the secondary hydroxy group of **6** (85%), followed by tetrazole displacement of the C-22 primary iodide afforded tetrazoles **9** and **10** in 41% and 52% yield, respectively.

Removal of the silyl protecting group of **10** by reaction with HF in acetonitrile at room temperature, gave alcohol **11** in 93% yield. Oxidation of alcohol **11** with TPAP gave ketone **12** in 88% yield, so setting the stage for the Wittig–Horner reaction with phosphine oxide **13**.[6] The effect of the scale of the coupling reaction on its effectiveness reported by Posner et al.[7] could explain the low yield obtained. With key intermediate **14** in hand, its reaction with MeLi was carried out followed by desilylation to afford



Scheme 1 *Reagents and conditions*: (i) Ph_3P, I_2, imidazole, THF, 0 °C (90%); (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, –10 °C (85%); (iii) **8**, DMF, r.t. (**9**, 41%; **10**, 52%); (iv) HF, MeCN, r.t. (93%); (v) TPAP, NMO, CH_2Cl_2, r.t. (88%); (vi) **13**, *n*-BuLi, THF, –78 °C (13%); (vii) (a) MeLi, Et_2O, –20 °C (b) TBAF, THF, r.t. (95%, two steps).

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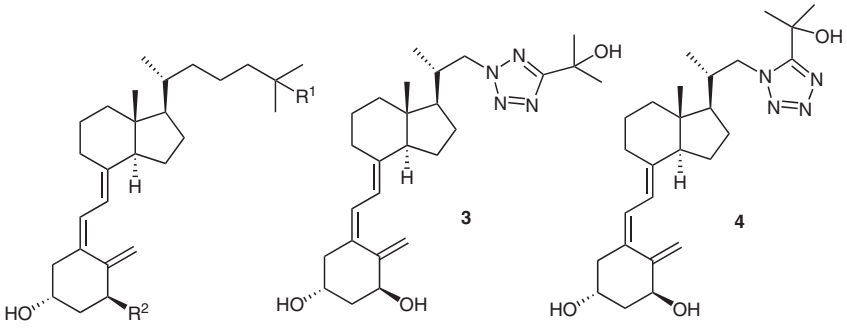


Figure 1 tructures of 1α,25-dihydroxyvitamin D_3 (**1**), cholecalciferol (**2**), and the tetrazole analogues **3** and **4**

new vitamin D analogue **3** bearing a tetrazole ring at the side chain (95% yield for the two steps).

Reaction of iodide **7** with tetrazole **8** led to compounds **9** and **10** corresponding to N1 and N2 alkylation respectively. NMR analyses were performed in order to determine the regiochemistry of the alkylation.[8] For tetrazole **9**, a ^{15}N-^{1}H HMBC spectrum showed a correlation between the C_{22}-H_2 group and N1 and N2. In the case of tetrazole **10** a ^{15}N-^{1}H HMBC spectrum showed a correlation between the C_{22}-H_2 group and N1, N2, and N3 (Figure 2).

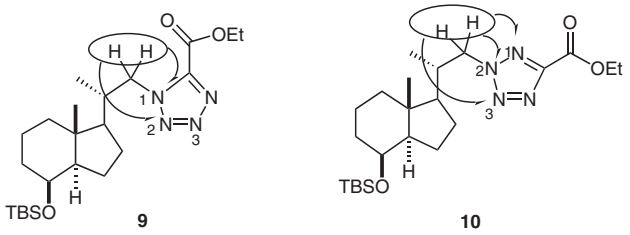


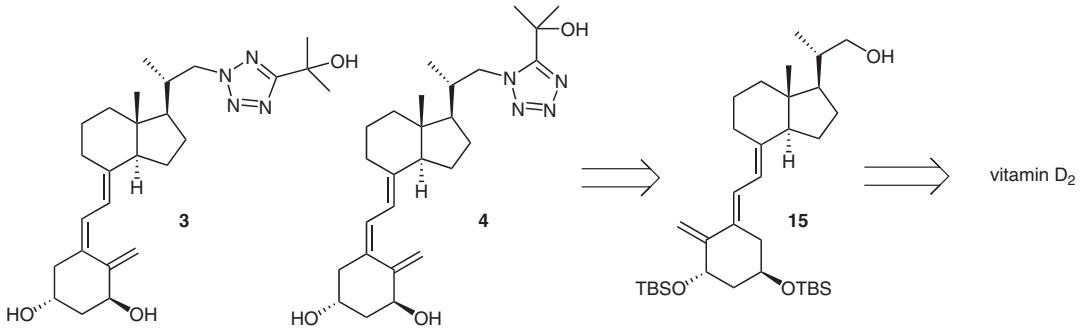
Figure 2 ^{15}N-^{1}H HMBC correlations for **9** and **10**

Due to the low yield obtained in the Wittig–Horner coupling reaction towards the synthesis of analogue **3**, we decided to overcome this shortcoming by switching to a totally different approach described some years ago by Calverley[9b] and later modified by Choudhry.[9c] 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.[9] Among the approaches, the one using the preparation and subsequent thermolysis of the sulfur dioxide adducts of vitamin D_2[9b,c] seemed to us more appropriate for a large scale synthesis of a late-stage intermediate such as **15** (Scheme 2).

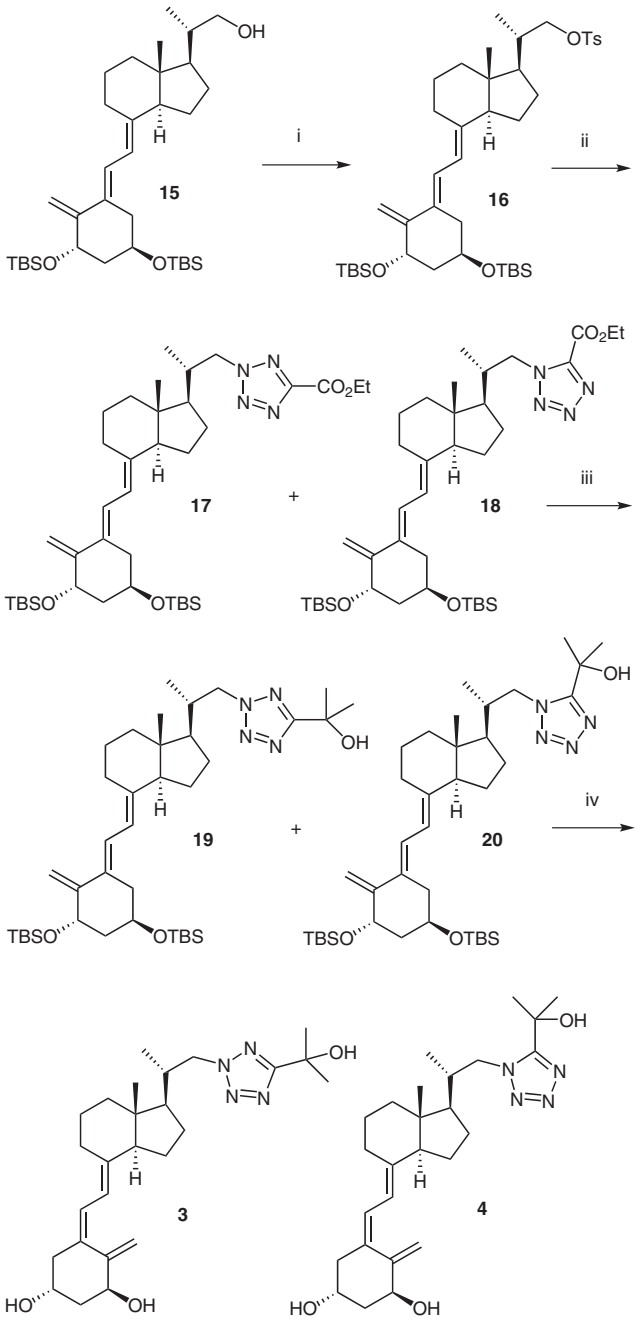
Accordingly alcohol **15** was easily obtained using this method and then led to target analogues **3** and **4** as depicted in Scheme 3.

Tosylation of alcohol **15** gave tosylate **16** in 91% yield. Displacement of the C-22 tosylate with tetrazole salt **8** afforded compounds **17** and **18** in 93% yield. Compounds **17** and **18** were rather difficult to separate by column chromatography, reason why the mixture was submitted to the next reaction with methyllithium affording alcohols **19** and **20**, which were easily separable by chromatography. Nonetheless, for characterization purposes pure samples of **17** and **18** were isolated. Removal of the silyl protecting groups of **19** and **20**, followed by photosensitized isomerization using anthracene as triplet sensitizer afforded target compounds **3** and **4** in 88% and 71% overall yield, respectively, from **19** and **20**.

In summary, this is the first report on the synthesis of a vitamin D analogue bearing a tetrazole moiety at the side chain. The synthesis of the side chain is straightforward using the Inhoffen–Lythgoe diol **5** easily obtained by degradation of vitamin D_2 and commercially available tetrazole **8**. The synthesis of analogues **3** and **4** using the Caverley approach proved to be in this case more efficient than the Wittig–Horner approach. The synthesis of a series of analogues of **3** and **4** modified at C-25 using inter-



Scheme 2



Scheme 3 *Reagents and conditions*: (i) *p*-TsCl, DMAP, pyridine, 0 °C (91%); (ii) **8**, DMF, 70 °C (93%); (iii) MeLi, Et_2O, –10 °C (**19**, 65%; **20**, 27%); (iv) (a) TBAF, THF, r.t.; (b) anthracene, Et_3N, *hν*, CH_2Cl_2, toluene (2 steps, 88% for **3**; 71% for **4**).

mediates **17** and **18** is currently under way in our laboratory with a view to their biological evaluation.

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected.

^{1}H and ^{13}C NMR spectra were recorded in a Bruker ARX-400 spectrometer (400 MHz for ^{1}H, 100.61 for MHz ^{13}C) using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. 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 F254, 0.25 mm).

Preparation of 3 by Wittig–Horner Method

(1*R*,3a*R*,4*S*,7a*R*)-Octahydro-1-[(*S*)-1-iodopropan-2-yl]-7a-methyl-1*H*-inden-4-ol (6)

To a solution of diol **5** (4.50 g, 21.23 mmol) in THF (90 mL) at –20 °C were added I_2 (5.92 g, 23.34 mmol), Ph_3P (6.68 g, 25.47 mmol), and imidazole (4.33 g, 63.67 mmol). The reaction mixture was stirred at –20 °C for 15 min, then allowed to reach r.t. After stirring at r.t. for 1 h 30 min, the mixture was cooled to 0 °C before adding sat. aq $NaHCO_3$ (50 mL). The product was extracted with Et_2O (2 × 60 mL) and the combined organic phases washed with sat. aq $Na_2S_2O_3$ (20 mL) and H_2O (15 mL), and dried (Na_2SO_4). Filtration and solvent evaporation afforded a residue, which was chromatographed on silica gel using 8% EtOAc–hexane as eluent giving 6.34 g (96%) of **6**; white solid; mp 108 ° C; R_f = 0.66 (30% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 4.09 (1 H, m, H-8), 3.32 (1 H, dd, *J* = 2.1, 9.5 Hz, H-22), 3.18 (1 H, dd, *J* = 4.8, 9.5 Hz, H-22), 185 (4 H, m), 1.45 (5 H, m), 1.15 (4 H, m), 1.00 (3 H, d, *J* = 5.5 Hz, CH_3-21), 0.97 (3 H, s, CH_3-18).

^{13}C NMR ($CDCl_3$): δ = 69.1 (CH-8), 55.9 (CH_2), 52.3 (CH_2), 42.23 (C-13), 40.49 (CH_2-22), 36.74 (CH_3-18), 33.94 (CH_2), 26.93 (CH_2), 22.79 (CH_2), 21.73 (CH_2), 21.07 (CH), 17.3 (CH_2), 14.3 (CH-21).

HRMS: *m*/*z* calcd for $C_{13}H_{23}IO$: 322.0816; found: 322.0814.

{(1*R*,3a*R*,4*S*,7a*R*)-Octahydro-1-[(*S*)-1-iodopropan-2-yl]-7a-methyl-1*H*-inden-4-yloxy}(*tert*-butyl)dimethylsilane (7)

To a solution of iodide **6** (408 mg, 1.26 mmol) in anhyd CH_2Cl_2 (2 mL) at –10 °C was added 2,6-lutidine (0.3 mL, 2.54 mmol) and TBSOTf (0.5 mL, 1.91 mmol). The mixture was stirred at this temperature for 12 h, quenched with aq $NaHCO_3$ (6 mL), and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with aq 10% HCl (2 × 50 mL). After drying (Na_2SO_4) and solvent evaporation, the residue was chromatographed on silica gel using 10% EtOAc–hexane as eluent to afford 437 mg (85%) of iodide **7**; colorless oil; R_f = 0.74 (50% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 4.00 (1 H, m, H-8), 3.34 (1 H, dd, *J* = 2.4, 7.12 Hz, H-22), 3.18 (1 H, dd, *J* = 4.4, 5.0 Hz, H-22), 2.85 (2 H, m), 2.65 (2 H, m), 1.35 (6 H, m), 1.00 (3 H, d, *J* = 5.8 Hz, H-21), 0.95 (3 H, s, H-18), 0.88 (9 H, s, *t*-C_4H_9), –0.01 (3 H, s, $SiCH_3$), –0.02 (3 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 69.30 (CH-8), 55.99 (CH), 52.77 (CH), 42.08 (C-13), 40.38 (CH_2-22), 36.442 (CH_3-18), 34.31 (CH_2), 26.66 (CH_2), 25.65 [$C(CH_3)_3$], 22.89 (CH_2), 21.40 (CH_2), 20.72 (CH), 18.01 [$C(CH_3)_3$], 17.59 (CH_2), 14.56 (CH_3-21), –4.77 ($SiCH_3$), –5.05 ($SiCH_3$).

Ethyl 1-((*S*)-2-{(1*R*,3a*R*,4*S*,7a*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7a-methyloctahydro-1*H*-inden-1-yl}propyl)-1*H*-tetrazole-5-carboxylate (9) and Ethyl 2-((*S*)-2-{(1*R*,3a*R*,4*S*,7a*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-7a-methyloctahydro-1*H*-inden-1-yl}propyl)-2*H*-tetrazole-5-carboxylate (10)

To a solution of iodide **7** (150 mg, 0.34 mmol) in anhyd THF (3 mL) was added tetrazole salt **8** (113 mg, 0.69 mmol). The mixture was stirred at r.t. for 12 h, and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (40 mL) and dried (Na_2SO_4). Filtration and solvent evaporation gave a residue, which was chromatographed on silica gel using 10% EtOAc–hexane as eluent, to afford 64 mg (41%) of tetrazole **9**; yellow oil; R_f = 0.37(20% EtOAc–hexane) and 80 mg (51%) of tetrazole **10**; yellow oil; R_f = 0.49 (20% EtOAc–hexane).

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^{1}H NMR ($CDCl_3$): δ = 4.77 (1 H, dd, *J* = 3.8, 9.3 Hz, H-22), 4.51 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.39 (1 H, dd, *J* = 2.5, 10.3 Hz, H-22), 4.00 (1 H, d, *J* = 2.3 Hz, H-8), 2.07 (1 H, m, H-14), 1.90 (2 H, m),

1.76 (1 H, td, *J* = 3.5, 6.3 Hz, H-17), 1.59 (2 H, m), 1.51 (1 H, m, H-20), 1.46 (3 H, t, OCH_2CH_3), 1.37 (2 H, m), 1.32 (2 H, m), 1.27 (2 H, m), 0.93 (3 H, s, H-18), 0.87 (9 H, s, *t*-C_4H_9), 0.72 (3 H, d, *J* = 10.4 Hz, H-21), 0.03 (3 H, s, CH_3Si), 0.02 (3 H, s, CH_3Si).

^{13}C NMR ($CDCl_3$): δ = 156.82 (C=O), 145.95 (NC=N), 69.19 (CH-8), 63.46 (OCH_2CH_3), 54.81 (CH-14), 54.71 (CH_2-22), 52.79 (CH), 42.62 (C-13), 40.50 (CH_2), 37.18 (CH_3-18), 34.28 (CH_2), 26.71 (CH_2), 25.80 [$C(CH_3)_3$], 23.09 (CH_2), 18.92 [$C(CH_3)_3$], 17.50 (CH_2), 16.25 (CH), 14.05 (OCH_2CH_3), 13.79 (CH_3-21), –4.79 ($SiCH_3$), –5.14 ($SiCH_3$).

LRMS: *m*/*z* (%) = 451.26 [M^+ + 1, (100)], 449.24 (9), 393.19 (8), 319.15 (6), 177.18 (33), 171.14 (11).

HRMS: *m*/*z* calcd for $C_{23}H_{43}N_4O_3Si_{28}$: 451.3101; found: 451.3104.

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^{1}H NMR ($CDCl_3$): δ = 4.63 (1 H, dd, *J* = 3.8, 9.4 Hz, H-22), 4.54 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.40 (1 H, dd, *J* = 3.9, 9.3 Hz, H-22), 3.96 (1 H, m, *J* = 2.3 Hz, H-8), 2.17 (1 H, H-14), 1.90 (2 H, m, H-9), 1.74 (1 H, m, H-17 or 20), 1.59 (2 H, m), 1.43 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.34 (1 H, m, H-20 or 17), 1.11 (2 H, m), 0.91 (3 H, s, H-18), 0.83 (9 H, *t*-C_4H_9), 0.79 (3 H, d, *J* = 6.5 Hz, H-21), –0.03 (3 H, s, $SiCH_3$), –0.04 (3 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 157.98 (C=O), 157.63 (NC=N), 69.14 (CH-8), 62.60 (OCH_2CH_3), 59.48(CH_2-22), 54.22 (CH-14), 52.75 (CH), 42.51 (C-13), 40.41 (CH_2), 37.07 (CH_3-18), 34.24 (CH_2), 26.99 (CH_2), 25.79 [$C(CH_3)_3$], 23.05 (CH_2), 18.01 [$C(CH_3)_3$], 17.51 (CH_2), 16.89 (CH), 14.19 (OCH_2CH_3), 13.80 (CH_3-21), –4.79 ($SiCH_3$), –5.15 ($SiCH_3$).

LRMS: *m*/*z* (%) = 451.23 [M^+ + 1, (100)], 393.15 (14), 319.13 (8), 177.76 (27), 175.15 (9), 171.11 (11), 154.08 (14).

HRMS: *m*/*z* calcd for $C_{23}H_{43}N_4O_3Si$: 451.3106; found: 451.3104.

Ethyl 2-{(*S*)-2-[(3*R*,3a*R*,7*S*,7a*R*)-Octahydro-7-hydroxy-3a-methyl-1*H*-inden-3-yl]propyl}-2*H*-tetrazole-5-carboxylate (11)

To a solution of tetrazole **10** (0.13 g, 0.29 mmol) in anhyd MeCN (15 mL) was added 48% aq HF (34 drops) and the mixture stirred at r.t. for 3 h. Sat. aq $NaHCO_3$ (14 mL) was added and the mixture stirred for 40 min and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with brine (2 × 30 mL) and dried (Na_2SO_4). After solvent evaporation, the residue was chromatographed on silica gel using 30% EtOAc–hexane as eluent to afford 93 mg (93%) of alcohol **11**; yellowish oil; R_f = 0.30 (35% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 4.63 (1 H, dd, *J* = 3.8, 9.4 Hz, H-22), 4.50 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.41 (1 H, dd, *J* = 4.0, 9.17 Hz, H-22), 4.05 (1 H, d, *J* = 2.47 Hz, H-8), 2.18 (1 H, m, H-14), 1.96 (2 H, m), 1.88 (2 H, m), 1.78 (1 H, m), 1.64 (4 H, m), 1.60 (3 H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.35 (1 H, m), 1.22 (2 H, m), 0.94 (3 H, s, H-18), 0.80 (3 H, d, *J* = 6.6 Hz, H-21).

^{13}C NMR ($CDCl_3$): δ = 157.86 (C=O), 157.55 (NC=N), 68.83 (CH-8), 62.54 (OCH_2CH_3), 59.29 (CH_2-22), 53.98 (CH), 52.23 (CH), 42.17 (C-13), 40.06 (CH_2), 40.06 (CH_2), 36.92 (CH_3-18), 33.47 (CH_2), 26.78 (CH_2), 22,48 (CH_2), 17.23 (CH_2), 16.73 (CH), 14.09 (OCH_2CH_3), 13.54 (CH_3-21).

LRMS: *m*/*z* (%) = 336.22 [M^+ + 1, (66)], 318.45 (23), 291.36 (15), 176.25 (24), 150.82 (13).

HRMS: *m*/*z* calcd for $C_{17}H_{28}N_4O_3$: 336.2204; found: 336.2217.

Ethyl 2-{(*S*)-2-[(3*R*,3a*R*,7a*R*)-Octahydro-3a-methyl-7-oxo-1*H*-inden-3-yl]propyl}-2*H*-tetrazole-5-carboxylate (12)

To a solution of alcohol **11** (101 mg, 0.30 mmol) in anhyd CH_2Cl_2 (5 mL) were added 4 Å molecular sieves (188 mg), NMO (73 mg, 0.64 mmol), and TPAP (catalytic amount). The reaction mixture was stirred at r.t. for 12 h. The organic solvent was removed by rotary evaporation and the residue was chromatographed on silica gel using 43% EtOAc–hexane as eluent to afford 89 mg (88%) of ketone **12**; yellow oil; R_f = 0.42 (50% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 4.67 (1 H, dd, *J* = 3.8, 9.4 Hz, H-22), 4.50 (3 H, m, H-22 and OCH_2CH_3), 2.46 (1 H, dd, *J* = 4.1, 7.5 Hz, H-14), 2.20 (6 H, m), 1.80 (2 H, m), 1.50 (4 H, m), 1.44 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3), 0.90 (3 H, d, *J* = 6.6 Hz, H-21), 0.67 (3 H, s, H-18).

^{13}C NMR ($CDCl_3$): δ = 210.91 (C-8), 157.72 (C=O, NC=N), 62.63 (OCH_2CH_3), 61.44 (CH), 59.10 (CH_2-22), 53.90 (CH), 49.82 (C-13), 40.76 (CH_2), 38.76 (CH_2), 37.03 (CH_3-18), 27.17 (CH_2), 23.77 (CH_2), 19.17 (CH_2), 17.00 (CH), 14.14 (OCH_2CH_3), 12.56 (CH_3-21).

LRMS: *m*/*z* (%) = 335.25 [M^+ + 1, (100)], 334.25 [M^+, (5)], 307.14 (13), 175.26 (8), 165.23 (5), 155.23 (18), 154.22 (54).

HRMS: *m*/*z* calcd for $C_{17}H_{24}N_4O_3$: 335.2081; found: 335.2083.

Ethyl 2-{(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*Z*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl}-2*H*-tetrazole-5-carboxylate (14)

To a solution of phosphine oxide **13** (5 mL, 0.19 M in THF) at –78 °C was added *n*-BuLi (0.23 mL of a 2.5 M solution in hexane, 0.59 mmol). The deep red mixture was stirred for 2 h at –78 °C in the dark. A solution of ketone **12** (82 mg, 0.24 mmol) in anhyd THF (2 mL) was then added via a canula. The mixture stirred at –78 °C for 5 h in the dark, quenched with aq NH_4Cl (a few drops) and extracted with EtOAc (2 × 20 mL). The combined organic phases were washed with sat. aq $NaHCO_3$ (2 × 10 mL). After solvent evaporation, the residue was chromatographed on silica gel using 5–10% EtOAc–hexane as eluent to afford 22 mg (13%) of **14**; colorless oil; R_f = 0.45 (50% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 6.22 and 6.02 (2 H, AB, *J* = 11.2 Hz, H-6 and 7), 5.17 (1 H, d, *J* = 1.67 Hz, H-19), 4.85 (1 H, d, *J* = 2.3 Hz, H-19), 4.67 (1 H, dd, *J* = 3.7, 9.5 Hz, H-22), 4.52 (2 H, q, *J* = 7.1 Hz, CH_2OAc), 4.44 (1 H, dd, *J* = 3.9, 9.17 Hz, H-22), 4.35 (1 H, m, H-1), 4.17 (1 H, m, H-3), 2.80 (1 H, m), 2.44 (1 H, m), 2.19 (2 H, m), 2.03 (3 H, m), 1.95 (2 H, m), 1.66 (3 H, m), 1.45 (3 H, t, *J* = 7.1 Hz, OCH_2CH_3), 1.30 (5 H, m), 0.86 (18 H, s, CH_3-*t*-BuSi), 0.57 (3 H, s, H-18), 0.05 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 157,94 (C=O), 157.64 (NC=N), 148.16 (C-10), 139.97 (C-8), 135.53 (C-5), 122.90 (CH-6), 118.36 (CH_2-19), 72.06 (CH-1 or 3), 67.45 (CH-1 or 3), 62.69 (OCH_2CH_3), 59.44 (CH_2-22), 55.92 (CH_2), 53.87 (CH), 46.00 (CH_2), 44.72 (CH_2), 40.26 (CH_2), 37.86 (CH), 28.69 (CH), 27.39 (CH_2), 25.83 [$C(CH_3)_3$], 25.78 [$C(CH_3)_3$], 23.26 (CH_2), 22.20 (CH_2), 18.21 [$C(CH_3)_3$], 18.51 [$C(CH_3)_3$], 17.03 (CH_3-21), 14.18 (OCH_2CH_3), 12.06 (CH_3-18), –4.70 ($SiCH_3$), –4.72 ($SiCH_3$), –4.82 ($SiCH_3$), –5.08 ($SiCH_3$).

LRMS: *m*/*z* (%) = 699.49 [M^+ + 1, (15)], 698.48 [M^+, (14)], 567.41 (48), 379.25 (17), 248.16 (100), 221.13 (28), 207.09 (23).

HRMS: *m*/*z* calcd for $C_{38}H_{67}N_4O_4Si_2$: 699.4724; found: 699.4701.

(1*R*,3*S*,5*Z*)-5-[(*E*)-2-((1*R*,3a*S*,7a*R*)-Hexahydro-1-{(*S*)-1-[5-(2-hydroxypropan-2-yl)-2*H*-tetrazol-2-yl]propan-2-yl}-7a-methyl-1*H*-inden-4(7a*H*)-ylidene)ethylidene]-4-methylenecyclohexane-1,3-diol (3) (Wittig–Horner Method)

To a solution of alcohol **14** (13 mg, 0.02 mmol) in anhyd Et_2O (1 mL) at 10 °C was added MeLi (0.06 mL, 1.5 M). The mixture was stirred at this temperature in the dark for 5 h 30 min, then quenched with H_2O (few drops), and extracted with EtOAc (2 × 10 mL).The combined organic phases were washed with H_2O (10 mL) and dried (Na_2SO_4). Filtration and solvent evaporation afforded a residue, which was dissolved in anhyd THF (5 mL). TBAF (0.2 mL, 1.0 M)

was added and the mixture stirred for 12 h at r.t., then quenched with aq NH_4Cl (1 mL), and extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with sat. aq NH_4Cl (2 × 20 mL). After drying (Na_2SO_4) and solvent evaporation, the residue was chromatographed on silica gel using 20% EtOAc–hexane as eluent to afford 12 mg (95%) of **3**; colorless oil; R_f = 0.15 (30% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 6.36 and 6.03 (2 H, AB, *J* = 11.1 Hz, H-6 and 7), 5.33 (1 H, br s, H-19), 4.99 (1 H, br s, H-19), 4.56 (1 H, dd, *J* = 3.7, 9.5 Hz, H-22), 4.36 (1 H, br s, H-3 or 1), 4.33 (1 H, dd, *J* = 4.1, 9.1 Hz, H-22), 4.22 (1 H, br s, H-1 or 3), 2.84 (1 H, m, H-14), 2.81 (2 H, m), 2.31 (1 H, m), 2.06 (1 H, m), 2.01 (8 H, m), 1.62 [6 H, br s, (CH_3)$_2$COH], 1.26 (4 H, m), 0.91 (3 H, d, *J* = 6.3 Hz, H-21), 0.60 (3 H, s, H-18).

^{13}C NMR ($CDCl_3$): δ = 172.09 (NC=N), 147.65 (C-10), 142.21 (C-8), 133.43 (C-5), 124.77 (CH-6), 117.48 (CH-7), 111.85 (CH_2-19), 70.83 (CH-1 or 3), 68.69 (C–OH), 66.85 (CH-1 or 3), 58.64 (CH_2), 56.01 (CH), 54.08 (CH), 46.10 (C-13), 45.26 (CH_2), 42.88 (CH_2), 40.23 (CH_2), 37.66 (CH), 29.71 (CH_3C–OH), 29.67 (CH_3C–OH), 28.94 (CH_2), 27.32 (CH_2), 23.40 (CH_2), 22.38 (CH_2), 17.19 (CH_3-21), 12.10 (CH_3-18).

LRMS: *m*/*z* (%) = 601.47 [M$^+$ + 1, (5)], 505.42 (10), 410.27 (17), 394.29 (41), 282.15 (18), 264.12 (19), 250.11 (48).

HRMS: *m*/*z* calcd for $C_{26}H_{40}N_4O_3$: 457.3179; found: 457.3178.

Preparation of 3 by Calverley Method

(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*E*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl 4-methylbenzenesulfonate (16)

To a solution of **15** (990 mg, 1.72 mmol) in pyridine (9 mL) at 0 °C was added *p*-TsCl (660 mg, 3.44 mmol) and DMAP (cat.). The mixture was stirred at this temperature for 9 h, quenched with aq NH_4Cl (10 mL), then allowed to reach r.t. The product was extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with $CuSO_4$ (3 × 20 mL). After drying (Na_2SO_4) and solvent evaporation, the residue was chromatographed on silica gel using 3% EtOAc–hexane as eluent to afford 1.1 g (91%) of tosylate **16**; white solid; mp 50–53 °C; R_f = 0.87 (30% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 7.72 (2 H, d, *J* = 8.2 Hz, H_{arom}), 7.27 (2 H, d, *J* = 8.0 Hz, H_{arom}), 6.37 (1 H, d, *J* = 11.3 Hz, H-6), 5.74 (1 H, d, *J* = 11.3 Hz, H-7), 4.91 (1 H, s, H-19), 4.88 (1 H, s, H-19), 4.48 (1 H, m, H-1), 4.45 (1 H, m, H-3), 3.92 (1 H, m, H-22), 3.90 (1 H, m, H-22), 2.75 (1 H, m), 2.43 (1 H, m), 2.37 (3 H, s, ArCH_3), 2.17 (1 H, m), 1.85 (3 H, m), 1.55 (5 H, m), 1.37 (3 H, m), 1.15 (3 H, m), 0.93 (3 H, d, *J* = 6.5 Hz, H-21), 0.84 (9 H, s, *t*-C_4H_9), 0.80 (9 H, s, *t*-C_4H_9), 0.44 (3 H, s, H-18), 0.00 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 154.00 (C-10), 144.97 (C-8), 142.92 (C_{arom}), 136.09 (C-5), 133.60 (C_{arom}), 130.17 (CH_{arom}), 128.30 (CH-6), 121.98 (CH-7), 107.07 (CH_2-19), 75.90 (CH_2-22), 70.60 (CH-1), 67.20 (CH-3), 56.40 (CH-14), 52.62 (CH-17), 46.25 (C-13), 44.34 (CH_2), 40.58 (CH_2), 36.99 (CH-20), 36.93 (CH_2), 29.23 (CH_2), 27.31 (CH_2), 26.33 [C(CH_3)$_3$], 26.28 [C(CH_3)$_3$], 26.20 [C(CH_3)$_3$], 23.78 (CH_2), 22.60 (CH_2), 22.03 (ArCH_3), 18.63 [C(CH_3)$_3$], 18.45 [C(CH_3)$_3$], 17.39 (CH_3-18), 12.37 (CH_3-21), –4.36 ($SiCH_3$), –4.47 ($SiCH_3$), –4.50 ($SiCH_3$).

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 for $C_{41}H_{68}O_5Si_2S$: 729.4404; found: 729.4418.

Ethyl 2-{(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*E*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl}-2*H*-tetrazole-5-carboxylate (17) and Ethyl 1-{(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*E*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl}-1*H*-tetrazole-5-carboxylate (18)

To a solution of tosylate **16** (480 mg, 0.65 mmol) in anhyd DMF (6 mL) was added tetrazole salt **8** (430 mg, 2.62 mmol). The mixture was heated at 70 °C for 8 h, then allowed to reach r.t., then quenched with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel using 3% EtOAc–hexane to afford 418 mg of the mixture of tetrazoles **17** and **18** (93%).

17

White solid; mp 49–51 °C; R_f = 0.69 (30% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 6.38 (1 H, d, *J* = 11.3 Hz, H-6), 5.78 (1 H, d, *J* = 11.3 Hz, H-7), 4.91 (1 H, s, H-19), 4.88 (1 H, s, H-19), 4.63 (1 H, dd, *J* = 3.6, 9.6 Hz, H-22), 4.47 (2 H, q, *J* = 7.1 Hz, OCH_2CH$_3$), 4.40 (2 H, m, H-1 and H-22), 4.16 (1 H, s, H-3), 2.77 (1 H, m), 2.45 (1 H, m), 2.22 (2 H, m), 2.05 (2 H, m), 1.55 (6 H, m), 1.39 (3 H, t, *J* = 7.1 Hz, OCH$_2$CH_3), 1.15 (6 H, m), 0.85 (3 H, d, *J* = 7.4 Hz, H-21), 0.83 (9 H, s, *t*-C_4H_9), 0.80 (9 H, s, *t*-C_4H_9), 0.54 (3 H, s, H-18), 0.00 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 157.83, 157.59 (C=O, NC=N), 153.53 (C-10), 142.06 (C-8), 135.92 (C-5), 121.39 (CH-6), 116.81 (CH-7), 106.56 (CH_2-19), 70.06 (CH-1), 67.88 (CH-3), 67.12 (OCH_2CH$_3$), 59.30 (CH_2-22), 55.97 (CH-14), 53.84 (CH-17), 46.09 (C-13), 43.83 (CH_2), 40.10 (CH_2), 37.32 (CH-20), 36.49 (CH_2), 28.69 (CH_2), 27.20 (CH_2), 25.69 [C(CH_3)$_3$], 23.23 (CH_2), 22.24 (CH_2), 18.13 [C(CH_3)$_3$], 16.97 (CH_3-18), 14.07 (OCH$_2$$CH_3$), 12.10 ($CH_3$-21), –4.98 ($SiCH_3$).

LRMS: *m*/*z* (%) = 699.36 [(M + 1)$^+$, (52)], 698.36 [M$^+$, (53)], 697.36 [(M – 1)$^+$, (60)], 567.31 (70), 301.12 (48), 251.1 (25), 248.12 (100).

HRMS: *m*/*z* calcd for $C_{38}H_{66}N_4O_4Si_2$: 699.4701; found: 699.4724.

18

White solid; mp 148–151 °C; R_f = 0.63 (30% EtOAc–hexane).

^{1}H NMR ($CDCl_3$): δ = 6.38 (1 H, d, *J* = 11.1 Hz, H-6), 5.78 (1 H, d, *J* = 11.5 Hz, H-7), 4.92 (1 H, s, H-19), 4.88 (1 H, s, H-19), 4.73 (1 H, dd, *J* = 3.1, 9.7 Hz, H-22), 4.47 (2 H, q, *J* = 7.0 Hz, OCH_2CH$_3$), 4.38 (2 H, m, H-1 and 22), 4.16 (1 H, m, H-3), 2.81 (1 H, m), 2.47 (1 H, m), 2.03 (1 H, m), 1.85 (6 H, m), 1.55 (5 H, m), 1.41 (3 H, t, *J* = 7.0 Hz, OCH$_2$CH_3), 1.25 (3 H, m), 0.83 (9 H, s, *t*-C_4H_9), 0.80 (9 H, s, *t*-C_4H_9), 0.74 (3 H, d, *J* = 6.5 Hz, H-21), 0.52 (3 H, s, H-18), 0.00 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 156.70 (C=O), 153.56 (C-10), 145.98 (NC=N), 142.29 (C-8), 135.89 (C-5), 121.52 (CH-6), 116.86 (CH-7), 106.76 (CH_2-19), 70.25 (CH-1), 67.19 (CH-3), 63.48 (OCH_2CH$_3$), 56.10 (CH-14), 54.74 (CH_2-22), 54.43 (CH-17), 46.22 (C-13), 43.92 (CH_2), 40.34 (CH_2), 37.98 (CH-20), 36.63 (CH_2), 28.83 (CH_2), 27.08 (CH_2), 25.85 [C(CH_3)$_3$], 23.35 (CH_2), 22.37 (CH_2), 18.24 [C(CH_3)$_3$], 16.48 (CH_3-18), 14.04 (OCH$_2$$CH_3$), 12.11 ($CH_3$-21), –4.75 ($SiCH_3$).

LRMS: *m*/*z* (%) = 699.41 [(M + 1)$^+$, (26)], 698. 4 [M$^+$, (22)], 697.40 [(M – 1)$^+$, (25)], 566.33 (74), 435.23 (31), 301.11 (24), 275.0 (18), 249.12 (70), 248.12 (100), 229.08 (21), 217.09 (25), 209.12 (24).

HRMS: *m*/*z* calcd for $C_{38}H_{66}N_4O_4Si_2$: 699.4701; found: 699.4702.

2-(2-{(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*E*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl}-2*H*-tetrazol-5-yl)propan-2-ol (19) and 2-(1-{(*S*)-2-[(1*R*,3a*S*,7a*R*,*E*)-4-((*E*)-2-{(3*S*,5*R*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-2-methylenecyclohexylidene}ethylidene)-7a-methyloctahydro-1*H*-inden-1-yl]propyl}-1*H*-tetrazol-5-yl)propan-2-ol (20)

To a solution of the mixture of tetrazoles **17** and **18** (404 mg, 0.58 mmol) in Et_2O (3 mL) at –10 °C was added MeLi (1.5 M, 2.0 mL, 2.89 mmol). The mixture was stirred at this temperature for 10 min, then quenched with H_2O (10 mL), and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (3 × 10 mL) and dried (Na_2SO_4). Filtration and solvent evaporation gave a residue, which was chromatographed on silica gel using 5% EtOAc–hexane as eluent, to afford 257 mg (65%) of tetrazole **19**; white solid; mp 41–43 °C; R_f = 0.38 (30% EtOAc–hexane)] and 107 mg (27%) of tetrazole **20**; white solid; mp 63–65 °C; R_f = 0.22 (30% EtOAc–hexane)].

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^{1}H NMR ($CDCl_3$): δ = 6.43 (1 H, d, *J* = 11.5 Hz, H-6), 5.83 (1 H, d, *J* = 11.4 Hz, H-7), 4.98 (1 H, s, H-19), 4.94 (1 H, s, H-19), 4.59 (1 H, m, H-1), 4.54 (1 H, dd, *J* = 3.9, 8.7 Hz, H-22), 4.33 (1 H, dd, *J* = 3.9, 9.3 Hz, H-22), 4.22 (1 H, m, H-3), 2.77 (1 H, m), 2.55 (1 H, m), 2.22 (1 H, m), 2.15 (1 H, m), 2.05 (2 H, m), 1.97 (2 H, m), 1.69 (6 H, s, CH_3-29 and 30), 1.55 (6 H, m), 1.35 (3 H, m), 0.9 (3 H, d, *J* = 7.7 Hz, H-21), 0.89 (9 H, s, *t*-C_4H_9), 0.60 (3 H, s, H-18), 0.06 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 172.06 (NC=N), 153.65 (C-10), 142.39 (C-8), 135.90 (C-5), 122.91 (CH-6), 116.85 (CH-7), 106.70 (CH_2-19), 70.20 (CH-1), 68.70 (C-28), 67.23 (CH-3), 58.66 (CH_2-22), 56.12 (CH-14), 54.11 (CH-17), 46.14 (C-13), 45.91 (CH_2), 38.20 (CH-20), 37.71 (CH_2), 29.73 (CH_3-29 or 30), 29.68 (CH_3-29 or 30), 28.83 (CH_2), 25.87 [C(*C*H_3)$_3$], 23.37 (CH_2), 22.36 (CH_2), 18.26 [*C*(CH_3)$_3$], 17.17 (CH_3-18), 12.14 (CH_3-21), –4.87 ($SiCH_3$).

LRMS: *m*/*z* (%) = 685.79 [(M + 1)$^+$, (64)], 684.81 [M$^+$, (38)], 683.79 [(M – 1)$^+$, (23)], 552 (66), 421.43 (50), 249.23 (68), 248.22 (100), 247.22 (37).

HRMS: *m*/*z* calcd for $C_{38}H_{68}N_4O_3Si_2$: 685.4908; found: 685.4972.

20

^{1}H NMR ($CDCl_3$): δ = 6.43 (1 H, d, *J* = 11.5 Hz, H-6), 5.83 (1 H, d, *J* = 11.4 Hz, H-7), 4.98 (1 H, s, H-19), 4.94 (1 H, s, H-19), 4.59 (1 H, m, H-1), 4.54 (1 H, dd, *J* = 3.9, 8.7 Hz, H-22), 4.33 (1 H, dd, *J* = 3.9, 9.3 Hz, H-22), 4.22 (1 H, m, H-3), 2.77 (1 H, m), 2.55 (1 H, m), 2.22 (1 H, m), 2.15 (1 H, m), 2.05 (2 H, m), 1.97 (2 H, m), 1.69 (6 H, s, CH_3-29 and 30), 1.55 (6 H, m), 1.35 (3 H, m), 0.9 (3 H, d, *J* = 7.7 Hz, H-21), 0.89 (9 H, s, *t*-C_4H_9), 0.60 (3 H, s, H-18), 0.06 (12 H, s, $SiCH_3$).

^{13}C NMR ($CDCl_3$): δ = 172,06 (NC=N), 151.65 (C-10), 144.00 (C-8), 133.38 (C-5), 122.91 (CH-6), 116.85 (CH-7), 106.70 (CH_2-19), 70.20 (CH-1), 68.70 (C-28), 67.23 (CH-3), 58.66 (CH_2-22), 56.12 (CH-14), 54.11 (CH-17), 46.14 (C-13), 45.91 (CH_2), 38.20 (CH-20), 37.71 (CH_2), 29.73 (CH_3-29 or 30), 29.68 (CH_3-29 or 30), 28.83 (CH_2), 25.87 [C(*C*H_3)$_3$], 23.37 (CH_2), 22.36 (CH_2), 18.26 [*C*(CH_3)$_3$], 17.17 (CH_3-18), 12.14 (CH_3-21), –4.87 ($SiCH_3$).

LRMS: *m*/*z* (%) = 685.79 [(M + 1)$^+$, (64)], 684.81 [M$^+$, (38)], 683.79 [(M – 1)$^+$, (23)], 552 (66), 421.43 (50), 249.23 (68), 248.22 (100), 247.22 (37).

HRMS: *m*/*z* calcd for $C_{38}H_{68}N_4O_3Si_2$: 685.4908; found: 685.4972.

Tetrazole 3 (Calverley Method)

To a solution of tetrazole **19** (30 mg, 0.04 mmol) in anhyd THF (1.0 mL) was added TBAF (0.24 mL, 1.0 M, 0.24 mmol), and the mixture stirred at r.t. for 48 h. The reaction was quenched with H_2O (2 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 (1 mL) and MeOH (5 mL), and catalytic amounts of anthracene and Et_3N were added. The mixture was irradiated with a lamp (200 W) for 2 h. The resulting mixture was then diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (3 × 15 mL), and dried (Na_2SO_4). The solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel using 50% EtOAc–hexane as eluent to afford 15.5 mg (88%) of tetrazole **3**; white solid; mp 35–37 °C; R_f = 0.57 (EtOAc).

The spectral data were identical with that of **3** obtained by the Wittig–Horner method (vide supra).

(1*R*,3*S*,5*Z*)-5-[(*E*)-2-((1*R*,3a*S*,7a*R*)-Hexahydro-1-{(*S*)-1-[5-(2-hydroxypropan-2-yl)-1*H*-tetrazol-1-yl]propan-2-yl}-7a-methyl-1*H*-inden-4(7a*H*)-ylidene)ethylidene]-4-methylenecyclohexane-1,3-diol (4)

To a solution of tetrazole **20** (30 mg, 0.04 mmol) in anhyd THF (1.0 mL) was added TBAF (0.24 mL, 1.0 M, 0.24 mmol), and the mixture stirred at r.t. for 48 h. The reaction was quenched with H_2O (2 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4), and the solvent was evaporated. The resulting residue was dissolved in CH_2Cl_2 (1 mL) and MeOH (5 mL), and catalytic amounts of anthracene and Et_3N were added. The mixture was irradiated with a lamp (200 W) for 2 h. The resulting mixture was then diluted with CH_2Cl_2 (10 mL). The organic layer was washed with brine (3 × 15 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the crude mixture was purified by flash column chromatography on silica gel using 50% EtOAc–hexane as eluent, to afford 12.5 mg (71%) of tetrazole **4**; white solid; mp 47–49 °C; R_f = 0.31 (10% MeOH–CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 6.55 (1 H, d, *J* = 11.3 Hz, H-6), 5.89 (1 H, d, *J* = 11.3 Hz, H-7), 5.12 (1 H, s, H-19), 4.97 (1 H, s, H-19), 4.56 (1 H, dd, *J* = 3.9, 9.4 Hz, H-22), 4.47 (1 H, m, H-1), 4.32 (1 H, m, H-22), 4.15 (1 H, m, H-3), 2.77 (2 H, m), 2.15 (3 H, m), 2.00 (4 H, m), 1.77 (3 H, s, H-29 or 30), 1.74 (3 H, s, H-29 or 30), 1.55 (7 H, m), 1.20 (3 H, m), 0.84 (3 H, d, *J* = 6.5 Hz, H-21), 0.62 (3 H, s, H-18).

^{13}C NMR ($CDCl_3$): δ = 159.15 (NC=N), 151.62 (C-10), 144.32 (C-8), 133.17 (C-5), 123.15 (CH-6), 116.33 (CH-7), 109.81 (CH_2-19), 71.12 (CH-1), 69.57 (C-28), 65.94 (CH-3), 56.16 (CH-14), 54.80 (CH-17), 54.18 (CH_2-22), 46.29 (C-13), 41.98 (CH_2), 40.30 (CH_2), 37.46 (CH-20), 36.76 (CH_2), 30.59 (CH_3-29 and 30), 29.68 (CH_2), 28.97 (CH_2), 27.08 (CH_2), 23.38 (CH_2), 23.38 (CH_2), 22.39 (CH_2), 16.79 (CH_3-18), 12.26 (CH_3-21).

LRMS: *m*/*z* (%) = 457.19 [M$^+$ + 1, (100)], 456.8 [M$^+$, (10)], 455.18 [M$^+$ – 1, (5)], 439.19 (17), 277.06 (11), 185.13 (93).

HRMS: *m*/*z* calcd for $C_{26}H_{40}N_4O_3$: 457.3179; found: 457.3175.

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