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SYNTHESIS OF 1-DEOXYMAXACALCITOL

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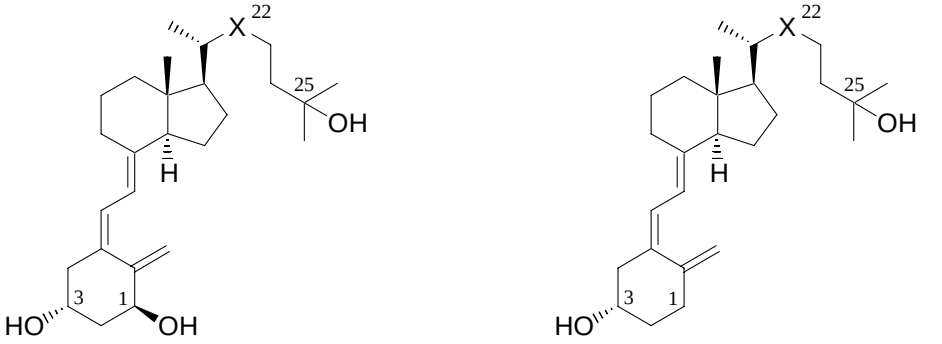
Abstract – 1-Deoxymaxacalcitol, the 1-deoxygenated derivative of maxacalcitol practically used for the treatment of secondary hyperparathyroidism and psoriasis, has been synthesized for the biological evaluation. Although purification of the key intermediate containing 1,3-cyclohexadiene moiety was extremely difficult owing to inseparable contaminants, treatment of the mixture with the heterocyclic dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) formed the readily separable Diels-Alder adduct from which the target 1-deoxymaxacalcitol could be obtained in a pure state.

INTRODUCTION

Maxacalcitol (**1**) is a vitamin D analogue having the 22-oxa-structure of the naturally occurring 1α,25-dihydroxyvitamin D3 (calcitriol) (**2**) which is notable for its calcemic activity and a variety of other interesting biological activities.[1] As we have found that this unnatural analogue does not exhibit high calcemic activity but, by preserving the high differentiation-inducing and antiproliferation activities comparable to its natural counterpart,[2] we succeeded in developing it as a practical drug for the treatment of secondary hyperparathyroidism and psoriasis. Calcitriol (**2**) has been proven to be generated biologically from 25-hydroxyvitamin D3 (**3**) and to exhibit its activity,[3] thus, we were interested in both the synthesis and the biological activity of its unnatural 22-oxa analogue 1-deoxymaxacalcitriol (**4**) (Figure 1). We report here the synthesis of 1-deoxymaxacalcitol (**4**) from dehydroepiandrosterone (**5**) employing the same procedure established in the synthesis of maxacalcitol (**1**).[4] The synthesis could be carried out without difficulty except the step introducing 7-olefinic functionality in which the diene (**13**) generated was accompanied by

inseparable contaminants including the unreacted cyclohexene precursor (**11**). This particular step was overcome by employing a purification procedure involving a forward and backward hetero-Diels-Alder reaction sequence first devised by Barton and coworkers.[5,6]



Maxacalcitol **(1) :** X= O
Calcitriol **(2) :** X = CH_2

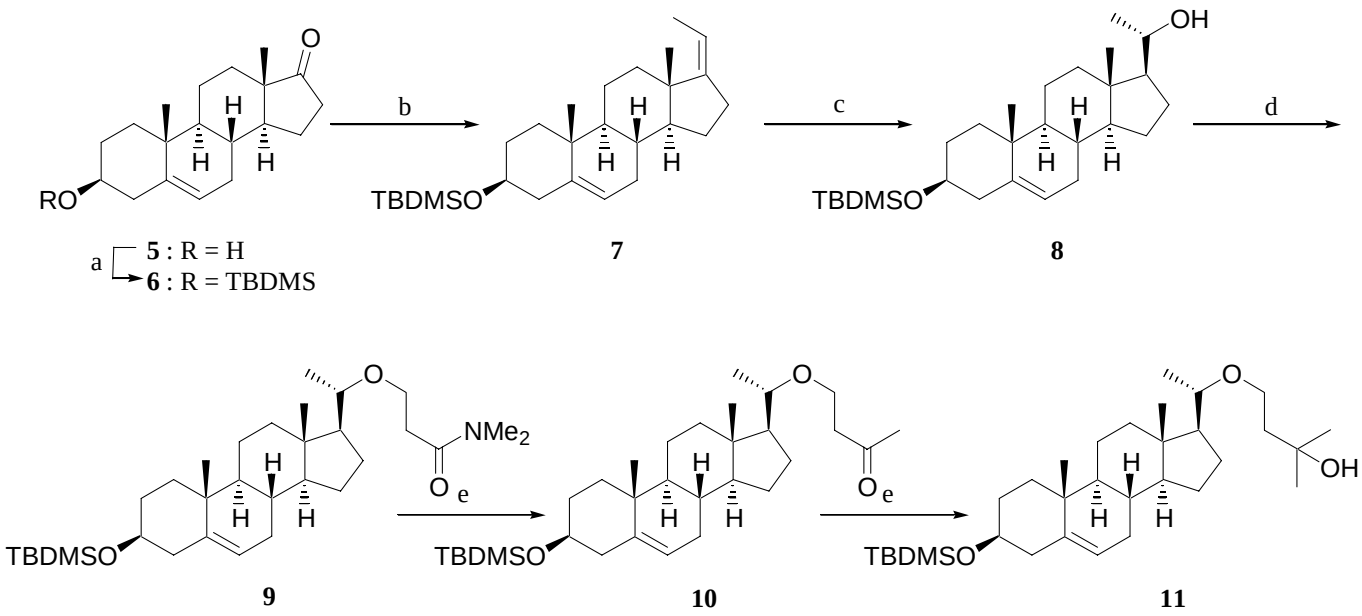
25-Hydroxyvitamin D_3 **(3) :** X= CH_2
1-Deoxymaxacalcitol **(4) :** X= O

Figure 1

RESULTS AND DISCUSSION

The introduction of an extra two-carbon unit to dehydroepiandrosterone (**5**) generating two extra stereogenic centers was carried out in a diastereoselective manner in three steps. Thus, **5** was first protected as the silyl ether (**6**) which was then treated with the ylide generated by treating ethyltriphenylphosphonium bromide with potassium *tert*-butoxide to afford stereoselectively 17-*Z*-olefin (**7**) in excellent yield. From reaction of 9-BBN (1.5 equiv.) in THF followed by alkaline aqueous hydrogen peroxide, the diene (**7**) furnished regio- and diastereoselectively the 20-*S*-alcohol (**8**) as the single product. Because we encountered difficulty with the etherification of 20-*S*-hydroxy functionality under Williamson reaction conditions in our previous synthesis of maxacalcitol (**1**),[4] we chose the Michael addition route developed during the improved synthesis of **1**.[4c] The reaction of the secondary alcohol (**8**) with a threefold excess of *N,N*-dimethylacrylamide in THF in the presence of 2 equiv. of sodium hydride at 0 ºC afforded satisfactory yield of the 1,4-adduct ether (**9**) after careful workup for preventing undesired secondary reactions such as retrograde Michael reaction and polymerization of the generated acrylamide. The conversion of the resulting tertiary amide (**9**) into methyl ketone (**10**) as well as the conversion of the latter product into tertiary alcohol (**11**) under the same conditions with a standard methyl nucleophile such as methyllithium and methylmagnesium halide induced competitive retrograde Micheal reaction to form a considerable amount of the secondary alcohol

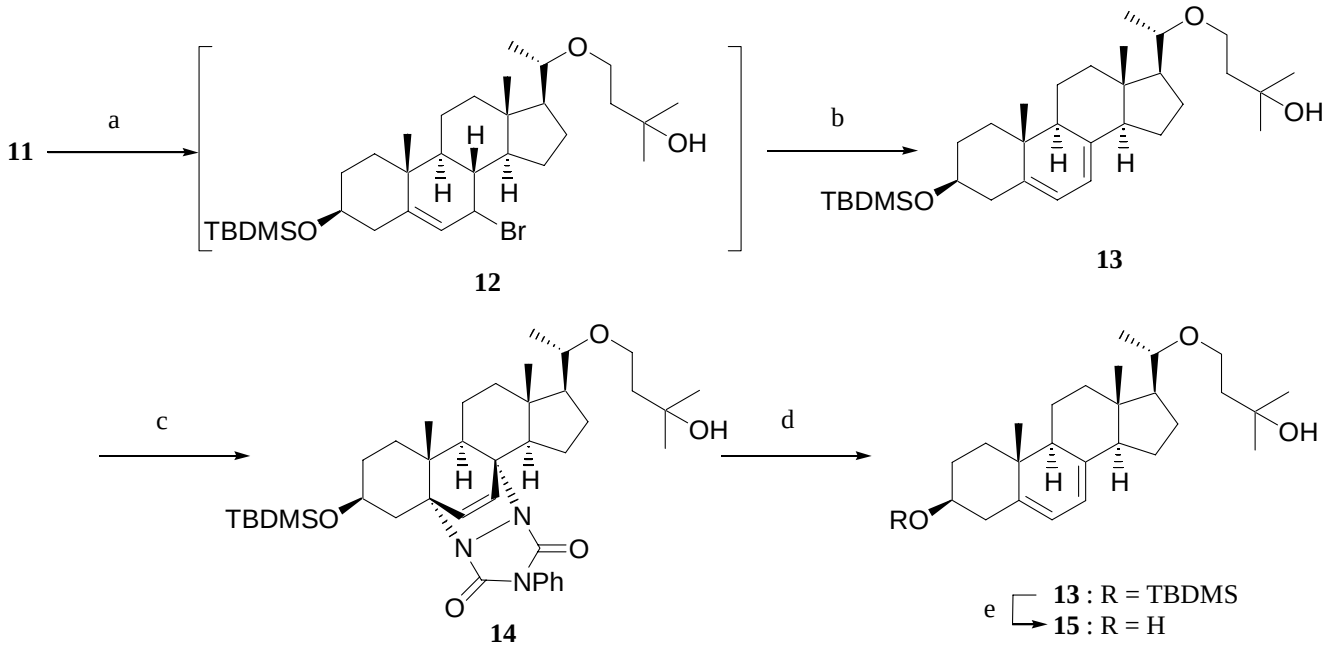
(**8**) as a byproduct. We therefore had to use the methylcerium reagent[4,7] generated *in situ* from methylmagnesium bromide and cerium(III) chloride to carry out these two steps without formation of the undesired byproduct. Thus, the reaction of the amide (**9**) with a fourfold excess of the cerium reagent prepared *in situ* in THF in the same reaction flask afforded methyl ketone (**10**) which, on the same treatment, gave tertiary alcohol (**11**) in 87 % overall yield as crystals (Scheme 1).



Scheme 1 *Reagents and conditions*: a) TBDMSCl, imidazole, DMF, rt. b) $EtPPh_3Br$, *tert*-BuOK, THF, 40 ºC. c) 9-BBN, THF, rt., 40 ºC, then 30% H_2O_2-3N NaOH, 0 ºC. d) *N,N*-dimethylacrylamide, THF, 0 ºC. e) MeMgBr-$CeCl_3$, THF, –10 ºC.

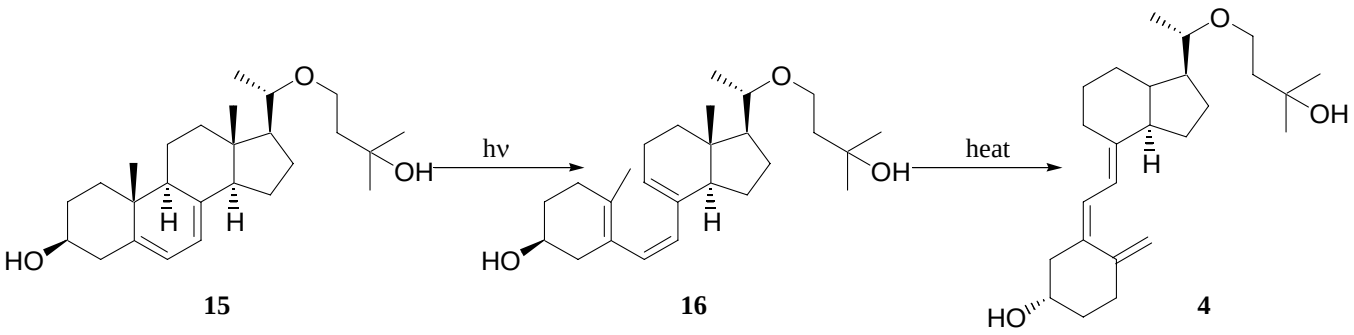
Having installed the requisite 17-side chain, the tertiary alcohol (**11**) was refluxed with 1.1 equiv. of *N*-bromosuccinimide (NBS) in hexane in the presence of 0.25 equiv. of azo-*bis*-isobutyronitrile (AIBN) to give a mixture of the product containing the allyl bromide (**12**) which after evaporation of the solvent was immediately refluxed with about four-fold excess of γ-collidine in toluene to carry out dehydrobromination to generate the 5,7-diene (**13**). The reaction produced a complex mixture from which the crude diene (**13**) was separated out as crystals. Since neither recrystallization nor chromatographic separation allowed complete removal of the impurities in particular the unreacted cyclohexene precursor (**11**), we sought an alternative method and found that a pure diene (**13**) could be obtained by application of the purification method involving the forward and backward Diels-Alder reaction sequence originally developed by Barton and coworkers.[5] Thus, the reaction of the crude diene (**13**) with the heterocyclic

dienophile 4-phenyl-1,2,4-triazorine-3,5-dione (PTAD) in dichloromethane at room temperature gave the adduct (**14**) which could be purified by silica gel column chromatography with complete removal of the accompanied impurities. From thermolysis at 160 ºC for 2 h under the modified conditions[7] using 1,3-dimethylimdazoline-2,4-dione (DMI) as the solvent, the adduct (**14**) produced a pure diene (**13**) by retro-Diels-Alder extrusion of the heterocyclic dienophile moiety. Overall yield of the diene (**13**) from the monoene (**11)** was 31% (Scheme 2).



Scheme 2 *Reagents and conditions*: a) NBS, AIBN (cat.), hexane, reflux. b) γ-collidine, toluene, reflux. c) PTAD, CH_2Cl_2, rt. d) DMI, 160 ºC. e) TBAF, THF, rt.

In order to transform the diene (**13**) into the target 1-deoxymaxacalcitol (**3**), the protective group was first removed with tetrabutylammonium fluoride (TBAF) to leave the diol (**15**). Upon photolysis under a high pressure mercury lamp through Vycol filter at 0 ºC, the diene (**15**) isomerized into the seco-triene (**16**) by the expected electrocyclic ring-opening at a much faster rate than the 1α-hydroxy analogue presumably due to the steric reason. Although the reaction was not complete, photolysis was terminated after 30 min to prevent a secondary reaction and afforded the triene (**16**) in 14% yield with recovery of 39% of the starting diene (**15**) after separation by silica gel column chromatography. The triene (**16**) was next refluxed in THF for 2 h to initiate thermal [1,7]-hydrogen migration to give 1-dehydroxymaxacalcitol (**4**) in 18% yield as an oil containing a trace of the triene isomer (**16**) (<0.3% by HPLC). The overall yield of 1-deoxymaxacalcitol (**4**) from the diene (**13**) was 2.5% without taking into account the recovery of the unreacted diene intermediate (**15**) (Scheme 3).



Scheme 3

CONCLUSION

We have synthesized 1-deoxymaxacalcitol (**4**), the 1-deoxy analogue of maxacalcitol (**1**) presently used for the treatment of secondary hyperparathyroidism and psoriasis, based on the procedure developed for the latter product. The difficulty encountered in the synthesis was overcome by employing a purification sequence involving a forward and inverse hetero-Diels-Alder sequence.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and used without further purification. NMR spectra were measured on a JEOL EX-270 spectrometer at 270 MHz for ^{1}H and 67.8 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million (ppm) referenced to $CHCl_3$ at 7.26 for ^{1}H, and $CDCl_3$ at 77.0 for ^{13}C. Coupling constants (*J*) are reported in Hertz. IR spectra were recorded on a JEOL JIR-6000 spectrophotometer as KBr pellets with a scan range of 4000-400 cm^{-1}. The melting points were determined on a hot-stage and are uncorrected. Ultraviolet spectra were measured on a HITACH U3210 spectrometer. Mass spectra were measured on a SHIMADZU GCMS-QP1000. Elemental analysis was carried out by Toray Research Center.

(*3S*)-3-*tert*-Butyldimethylsilyloxyandrost-5-en-17-one (6). To a stirred solution of dehydroepiandrosterone (**5**) (56.7 g, 197 mmol), imidazole (41.7 g, 613 mmol) in DMF (100 mL), was added *tert*-butyldimethylsilyl chloride (46.1 g, 306 mmol) at rt. The mixture, after stirring for 2 h at the same temperature, was diluted with MeOH (150 mL) to separate out crystals which were then collected, washed with MeOH (100 mL), and dried (60 ºC) to give silyl ether (**6**) as colorless crystals (73.7 g, 93.1 %): mp 149 °C (from MeOH). IR (KBr): ν 2932, 2864, 1748, 1464, 1382, 1256, 1218, 1094, 1060, 1032, 1008, 1032, 960, 938, 888, 872, 838, 804, 774; ^{1}H NMR ($CDCl_3$): δ 5.34 (1H, d, $J_{6\text{-}7}$ = 5.0, *H6*), 3.42-3.54 (1H, m, *H3*), 1.04 (3H, s , *H19*), 0.88 (9H, s, *tBu*), 0.87 (3H, s , *H18*), 0.05 (6H, s, Si-(CH_3)$_2$);

^{13}C NMR ($CDCl_3$): δ 221.2, 141.8, 120.4, 72.4, 51.8, 50.3, 47.5, 42.8, 37.3, 36.7, 35.8, 32.0, 31.5, 31.5, 30.8, 25.9, 21.9, 20.3, 19.5, 18.2, 13.5, –4.6. *Anal*. Calcd for $C_{25}H_{42}O_2Si$: C, 74.57; H, 10.51; Si, 6.97. Found: C, 74.52; H, 10.35; Si, 6.88.

(*17Z*)-(*3S*)-3-*tert*-Butyldimethylsilyloxypregna-5,17-diene (7). To a stirred solution of the ylide, prepared *in situ* by treating $EtPPh_3Br$ (250 g, 673 mmol) with potassium *tert*-butoxide (70.0 g, 624 mmol) in THF (400 mL) at 40 °C for 1.5 h, was added **6** (70.0 g, 174 mmol) at the same temperature, after which the temperature was raised to 60 °C. After stirring for 1.5 h at the same temperature, the mixture was cooled to rt and to this mixture was added hexane (200 mL) and water (400 mL) sequentially, and the organic layer was separated. The aqueous layer was extracted with hexane (300 mL) and the organic layer was separated. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was stirred in hexane (300 mL) at rt to separate out insoluble triphenylphosphine oxide which was removed by filtration and the filtrate was evaporated under reduced pressure to leave a crystalline residue. Trituration of the residue in a mixture of acetone (200 mL) and MeOH (300 mL) at rt, followed by separation of the crystals by filtration gave the diene (**7**) as colorless crystals (68.8 g, 95.4%): mp 98-101 °C (from MeOH-CH_2Cl_2). IR (KBr): ν 2940, 2860, 1254, 1094, 888, 838, 776; ^{1}H NMR ($CDCl_3$): δ 5.33 (1H, d, $J_{6\text{-}7}$=5.3, *H6*), 5.09-5.17 (1H, m, *H20*), 3.42-3.54 (1H, m, *H3*), 1.66 (3H, m, *H21*), 0.98 (3H, s, *H19*), 0.88 (12H, s, *H18* and *tBu*), 0.06 (6H, s, Si-(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 151.3, 141.6, 121.3, 113.4, 72.6, 72.6, 56.6, 50.2, 44.1, 44.0, 42.8, 37.3, 37.0, 36.6, 32.1, 31.7, 31.4, 26.1, 26.0, 25.9, 25.9, 25.8, 24.5, 21.2, 19.6, 19.5, 19.3, 18.3, 16.8, 16.7, 16.6, 13.3, 13.2, 13.0, –4.5, –4.5, –4.6, –4.7. *Anal*. Calcd for $C_{27}H_{46}OSi$: C, 78.19; H, 11.18; Si, 6.77. Found: C, 78.29; H, 11.24; Si, 6.42.

(*3S,20S*)-3-*tert*-Butyldimethylsilyloxy-20-hydroxypregn-5-ene (8). To a stirred solution of 9-BBN (0.5 mol/L in THF, 500 mL, 250 mmol), was added **7** (65.7 g, 158 mmol) at rt and the mixture was stirred at 40 °C for 2 h. After cooling to 0 °C, the mixture was treated sequentially with 3*N* NaOH (420 mL) and 30% H_2O_2 (340 g) with vigorous stirring continued at rt for 3 h. The mixture was extracted with AcOEt (500 mL) and the aqueous layer was extracted with AcOEt (2 x 150 mL). The combined organic layer was washed successively with saturated aqueous $NaHCO_3$ (300 mL) and brine (300 mL x 2), dried over $MgSO_4$, and evaporated under reduced pressure to leave a crystalline residue. The residue was triturated with MeOH (250 mL) and filtered to give the secondary alcohol (**8**) as colorless crystals (56.3 g, 82%): mp 162-163 ºC (from MeOH). IR (KBr): ν 3392, 2940, 1462, 1386, 1258, 1088, 888, 870, 840, 772; ^{1}H NMR ($CDCl_3$): δ 5.31 (1H, d, $J_{6\text{-}7}$ = 4.9, *H6*), 3.68-3.72 (1H, m, *H20*), 3.46-3.50 (1H, m, *H3*), 1.22 (3H, d, $J_{20\text{-}21}$=6.3, *H21*), 0.96 (3H, s, *H19*), 0.88 (9H, s, *tBu*), 0.68 (3H, s, *H18*), 0.06, 0.05 (each 3H, each s, Si-CH_3); ^{13}C NMR ($CDCl_3$): δ 141.6, 121.0, 72.6, 70.4, 58.4, 56.6, 50.1, 42.8, 41.6, 38.8, 37.4, 36.6, 32.1,

31.9, 31.5, 25.9, 25.7, 24.2, 23.5, 20.8, 19.4, 18.3, 12.4, –4.6. *Anal*. Calcd for $C_{27}H_{48}O_2Si$: C, 74.94; H, 11.18; Si, 6.49. Found: C, 74.31; H, 11.33; Si, 6.37.

(*3S,20S*)-3-*tert*-Butyldimethylsilyloxy-20-(3-*N,N*-dimethylamidoxapropyloxy)pregn-5-ene (9). To a stirred suspension of the alkoxide generated *in situ* from the secondary alcohol (**8**) (53 g, 123 mmol) and NaH (60% dispersion in mineral oil, 9.8 g, 245 mmol) in THF (420 mL) was added *N,N*-dimethylacrylamide (48.6 g, 490 mmol) at 0 °C and the stirring was continued for 8 h at the same temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and the mixture was extracted with AcOEt (400 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure to leave a crystalline residue which was triturated in hexane (200 mL) to give ether (**9**) (26.4 g) as colorless crystals after filtration. More of the ether (**9**) (2.8 g) was obtained from the filtrate after purification by silica gel column chromatography (elution with AcOEt-hexane 1:10 to 1:0). Total yield of **9** was 29.2 g (73%): mp 142 ºC (from MeOH). IR (KBr): ν 2940, 1632, 1258, 1088, 890, 872, 840, 772; ^{1}H NMR ($CDCl_3$): δ 5.30 (1H, d, $J_{6\text{-}7}$=5.0, *H6*), 3.02, 2.93 (each 3H, each s, N-CH_3), 1.22 (3H, d, $J_{20\text{-}21}$=6.3, *H21*), 0.95 (3H, s , *H19*), 0.87 (9H, s, *tBu*) , 0.63 (3H, s, *H18*), 0.05, 0.04 (each 3H, each s, Si-CH_3); ^{13}C NMR ($CDCl_3$): δ 171.4, 141.5, 121.1, 78.4, 72.6, 64.8, 56.9, 56.6, 50.2, 42.8, 41.3, 38.9, 37.5, 37.4, 36.6, 35.3, 34.1, 32.1, 31.9, 31.6, 26.0, 25.9, 24.2, 20.8, 19.4, 19.2, 18.3, 12.4,-4.6. *Anal*. Calcd for $C_{32}H_{57}NO_3Si$: C, 72.26; H, 10.80; N, 2.63; Si, 5.28. Found: C, 72.12; H, 10.67; N, 2.66; Si, 5.15.

(*3S,20S*)-3-*tert*-Butyldimethylsilyloxy-20-(3-oxobutoxy)pregn–5-ene (10). To a stirred suspension of dried $CeCl_3$ (109 g, 440 mmol) in THF (320 mL) was added MeMgBr (400 mL 1M in THF, 400 mmol) at –10 °C and the mixture was stirred at the same temperature for 0.5 h, then to this mixture was added amide (**9)** (35.2 g, 100 mmol) in THF (105 mL) at the same temperature. After stirring for 0.5 h at the same temperature, the mixture was quenched by the addition of 1*N* NH_4Cl (800 mL), the organic layer was separated and the aqueous layer was further extracted with AcOEt (200 mL). The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to leave the ketone (**10**) as colorless crystals which was used for the next conversion without further purification. Part of the product was recrystallized from MeOH for analysis: mp 109-110 ºC. IR (KBr): ν 2940, 2900, 1718, 1372, 1258, 1088, 888, 872, 840, 772; ^{1}H NMR ($CDCl_3$): δ 5.30 (1H, d, $J_{6\text{-}7}$ = 5.0, *H6*), 3.21-3.26 (1H, m, *H3*), 2.18 (3H, s,

H26), 1.18 (3H, d, $J_{20\text{-}21}$=6.3, *H21*), 0.95 (3H, s, *H19*), 0.87 (9H, s, *tBu*), 0.66 (3H, s, *H18*), 0.05 (6H, s, Si-(CH_3)$_2$) ; ^{13}C NMR ($CDCl_3$): δ 208.0, 141.5, 121.1, 78.5, 77.2, 72.6,63.4, 56.9, 56.6, 50.2, 44.1, 42.8, 41.3, 38.9, 37.4, 36.6, 32.1, 31.9, 31.6, 30.7, 26.2, 25.9, 24.2, 20.8,19.4, 19.0, 18.3, 12.4, –4.6. *Anal*.Calcd for $C_{31}H_{54}O_3Si$: C, 74.05; H, 10.82; Si, 5.59. Found: C, 74.09; H, 10.96; Si, 5.57.

(*3S,20S*)-3-*tert*-Butyldimethylsilyloxy-20-(3-hydroxy-3-methylbutoxy)pregn–5-ene (11). To a stirred suspension of dried $CeCl_3$ (109 g, 440 mmol) in THF (320 mL) was added MeMgBr (400 mL 1M in THF, 400 mmol) at –10 °C and the mixture was stirred at the same temperature for 0.5 h, then to this mixture was added ketone (**10)** (100 mmol) in THF (105 mL) at the same temperature. After stirring for 0.5 h at the same temperature, the mixture was quenched by the addition of 1*N* NH_4Cl (800 mL), the organic layer was separated and the aqueous layer was further extracted with AcOEt (200 mL). The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure to leave a crystalline residue. The residue was triturated with MeOH (200 mL) and filtered to give the tertiary alcohol (**11**) as colorless crystals (45.0 g, 87% from **9**): mp 168 ºC (from MeCN). IR (KBr): ν 3520, 2936, 1382, 1256, 1096, 886, 838, 778; ^{1}H NMR ($CDCl_3$): δ 5.31 (1H, d, $J_{6\text{-}7}$ = 5.0, *H6*), 3.21-3.26 (1H, m, *H3*), 1.22 (6H, s, *H26* and *H27*), 1.17 (3H,d, $J_{20\text{-}21}$ = 5.9, *H21*), 0.95 (3H, s, *H19*), 0.87 (9H, s, *tBu*), 0.66 (3H, s, *H18*), 0.05, 0.04 (each 3H, each s, Si-CH_3); ^{13}C NMR ($CDCl_3$): d 141.4, 121.1, 78.9, 72.6, 70.5, 65.5, 56.7, 56.5, 50.1, 42.8, 41.4, 38.9, 37.4, 36.6, 32.1, 31.9, 31.6, 29.4, 29.0, 26.6, 25.9, 24.2, 20.8, 19.4, 18.7, 18.3, 26.1, 12.4, –4.6. *Anal*. Calcd for $C_{32}H_{58}O_3Si$: C, 74.07; H, 11.27; Si, 5.41. Found: C, 73.93; H, 11.24; Si, 5.40.

(3*S*,20*S*)-3-*tert*-Butyldimethylsilyloxy-20-(3-hydroxy-3-methylbutoxy)pregna–5,7-diene (13). A solution of tertiary alcohol (**11)** (25.9 g, 50 mmol) and NBS (11.1 g, 62.5 mmol) in hexane (300 mL) was refluxed for 30 min in the presence of AIBN (2.46 g, 15.0 mmol). The mixture after cooling was filtered to remove insoluble material and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in toluene (200 mL) containing γ-collidine (25 mL, 189 mmol) and the mixture was refluxed for 1 h. The mixture after cooling was filtered and the filtrate, after dilution with hexane (200

mL), was washed successively with 1*N* HCl (180 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), and dried over $MgSO_4$. The solution was evaporated to *ca*.100 mL and to this solution was added MeCN (400 mL) and cooled to 0 ºC to separate out crystals. The collected crystals were again dissolved in CH_2Cl_2 (30 mL) and crystallized out by addition of MeCN (400 mL) at 0 ºC to give diene (**13**) as powder (5.52 g, 21%) accompanied by inseparable impurities including **11** which was only discernible by ^{1}H NMR spectrum. This product may be used for the follwing reaction without further purification.

The mother liquor was concentrated and chromatographed using a silica gel column (elution with AcOEt - hexane 1:10) to give the diene (**13**) containing inseparable contaminants. This was treated with PTAD (6.0 g, 34 mmol) in CH_2Cl_2 (200 mL) at rt with stirring. After stirring for 45 min, the mixture was evaporated under reduced pressure and the residue was chromatographed using a silica gel column (elution with hexane-AcOEt 10:1 to 2:1) and recrystallized from MeCN to give the adduct (**14**) as colorless crystals (4.71 g): mp 196-197 °C. IR (KBr): ν 3460, 2936, 1760, 1706, 1408, 1252, 1166, 1088, 862, 838, 780; ^{1}H NMR ($CDCl_3$): δ 7.28-7.46 (5H, m, *Ph*), 6.35 (1H, d, $J_{6\text{-}7}$ = 8.3, *H6*), 6.19 (1H, d, $J_{6\text{-}7}$ = 8.3, *H7*), 1.22 (6H, s, *H26* and *H27*), 1.19 (3 H, d, $J_{20\text{-}21}$ = 5.9, *H21*), 0.96 (3H, s, *H19*), 0.88 (9H, s, *tBu*), 0.79 (3H, s, *H18*), 0.10, 0.08 (each 3H, each s, Si-CH_3) ; ^{13}C NMR ($CDCl_3$): δ 148.8, 146.5, 135.9, 131.9, 128.8, 128.5, 127.6, 126.3, 70.4, 67.5, 65.6, 65.4, 64.5, 55.7, 53.0, 49.0, 43.1, 41.6, 41.0, 37.3, 34.9, 34.0, 30.3, 29.4, 29.0, 25.9, 23.5, 23.3, 22.1, 19.2, 17.9, 17.6, 14.0, –4.3, –4.7. *Anal*. Calcd for $C_{40}H_{61}N_3O_5Si$: C, 69.43; H, 8.88; N, 6.07; Si, 4.06. Found: C, 69.70; H, 8.55; N, 6.07; Si, 3.98.

The adduct (**14**) (4.71 g, 6.81 mmol) was dissolved in DMI (50 mL) and heated at 160 ºC for 2 h to induce cycloreversion. After cooling, the mixture was diluted with toluene (40 mL) and washed with brine (40 mL) and the organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure left a crystalline solid which was recrystallized from MeCN (50 mL) to give the diene (**13**) in a pure state[2.47 g , 70% from **14** , total yield of **13** from **11**:8.0g(31%)]: mp 147-149 ºC. IR (KBr): ν 3520, 2964, 2936, 2864, 1464, 1380, 1252, 1166, 1152, 1098, 880, 838, 800, 778; ^{1}H NMR ($CDCl_3$): δ 5.54 (1H, d, $J_{6\text{-}7}$ = 5.6, *H7*), 5.38-5.41 (1H, m, *H6*), 1.23, 1.24 (each 3H, each s, *H26* and *H27*), 1.20 (3H, d, $J_{20\text{-}21}$ = 6.3, *H21*), 0.89 (3H, s, *H19*), 0.88 (9H, s, *tBu*), 0.60 (3H, s, *H18*), 0.06 (6H, s,

Si-(C*H*$_3$)$_2$) ; ^{13}C NMR ($CDCl_3$) : δ 140.8, 140.3, 119.2, 116.7, 79.0, 71.2, 70.5, 65.6, 56.4, 54.2, 46.2, 42.0, 41.5, 41.3, 38.5, 38.3, 37.1,32.4, 29.3, 29.1, 26.4, 25.9, 22.9, 20.9, 18.8, 18.2, 16.3, 12.4, –4.6. *Anal*. Calcd for $C_{32}H_{56}O_3Si$: C, 74.36; H, 10.92; Si, 5.43. Found: C,74.12; H, 11.13; Si, 5.41.

(*3S,20S*)-20-(3-Hydroxy-3-methylbutoxy)pregna–5,7-dien-3-ol (15). To a stirred solution of the silyl ether (**13)** (7.60 g, 14.7 mmol) in THF (40 mL) was added TBAF in THF (45 mL, 1.0 mol/L solution, 45 mmol) at rt; the stirring was continued for 9 h at the same temperature. The mixture was diluted with AcOEt (50 mL) and washed sequentially with 1*N* HCl (90 mL), saturated aqueous $NaHCO_3$, and brine, and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was triturated in acetone (50 mL) to give the diol (**15**) as colorless crystals (4.50 g, 79%): mp 162-164 °C (from MeCN). IR (KBr): ν 3504, 3432, 2968, 2936, 2872, 1368, 1156, 1092, 1072, 1044; ^{1}H NMR ($CDCl_3$): δ 5.55 (1H, m, *H7*), 5.35-5.39 (1H, m, *H6*), 1.22, 1.23 (each 3H, each s, *H26* and *H27*), 1.19 (3H, d, $J_{20\text{-}21}$ = 5.9, *H21*), 0.91 (3H, s, *H19*), 0.59 (3H, s, *H18*). *Anal*. Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51; O, 11.92. Found: C, 77.60; H, 10.52; O,11.87. UV nm (λ max : MeOH): 293 (9670), 291 (10600), 271 (6140).

(*3S,20S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,(10),6,8-trien-3-ol (16). An ice-cold solution of the diene (**16)** (2.3 g, 5.7 mmol) in THF (230 mL) was irradiated through a Vycol filter under Argon for 30 min with a high-pressure mercury lamp. After evaporation to some extent (*ca*. two thirds) of the solvent under reduced pressure, the unreacted **15** separated was collected by filtration (0.9 g, 39%) and the filtrate was concentrated and separated by preparative HPLC (silica gel-60, elution with AcOEt-CH_2Cl_2 1:5) to give the secotriene (**16**) as a colorless oil (330 mg, 14%, 24% based on the recovered **16**). ^{1}H NMR ($CDCl_3$): δ 5.94 (1H, d, $J_{6\text{-}7}$ = 12.5, *H7*), 5.67 (1H, d, $J_{6\text{-}7}$ = 12.5, *H6*), 5.49 (1H, d, $J_{9\text{-}11}$ = 2.3, *H9*), 1.62 (3H, s, H19), 1.22, 1.23 (each 3H, each s, *H26* and *H27*), 1.20 (3H, d, $J_{20\text{-}21}$=6.3, *H21*), 0.68 (3H, s, *H18*).

(*3S,20S*)-20-(3-Hydroxy-3-methylbutoxy)-9,10-secopregna-5,7,10(19)-trien-3-ol (1). The secotriene (**16**) (330 mg, 0.82 mmol) was dissolved in THF (15 mL) and the solution was refluxed for 2 h under argon. After evaporation of the solvent under reduced pressure, the residue was separated by preparative HPLC (silica gel-60, elution with AcOEt-CH_2Cl_2 1:5) to give 1-deoxymaxacalcitol (**4**) as a colorless oil (60 mg, 18%) which contained a trace of the staring triene (**16**) (<0.3% by HPLC analysis): IR (KBr): δ 3409, 2968, 2933, 2873, 1440, 1376, 1371, 1265, 1151, 1089, 1052, 738; ^{1}H NMR ($CDCl_3$): δ 6.21 (1H, d, $J_{6\text{-}7}$ = 11.2, *H6*), 6.03 (1H, d, $J_{6\text{-}7}$ = 11.2, *H7*), 5.04 (1H, d, *J* = 1.3, *H19*), 4.80 (1H, d, *J* = 1.3, *H19*), 3.90-3.96 (1H, m, *H3*), 3.79-3.87 (1H, m, *H23*), 3.22-3.27 (1H, m, *H20*), 1.22 (6H, s, *H26* and *H27*), 1.18 (3H, d, $J_{20\text{-}21}$ = 6.3, *H21*), 0.52 (3H, s, *H18*); UV (λ max : MeOH): 270 nm (13600); MS : m/z 402(M^+).

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