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Industrial Synthesis of Maxacalcitol, the Antihyperparathyroidism and Antipsoriatic Vitamin D_3 Analogue Exhibiting Low Calcemic Activity

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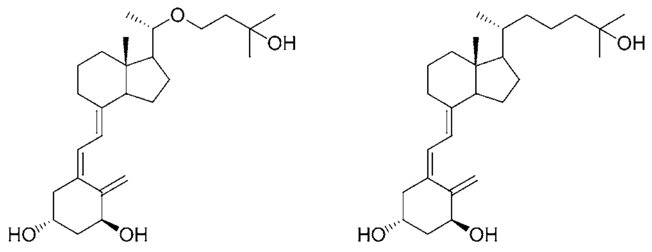
Abstract:

Maxacalcitol, the 22-oxa-derivative of 1α,25-dihydroxyvitamin D_3 and used currently as an antihyperparathyroidism and antipsoriatic drug, has been synthesized in seven chemical steps from 1α-hydroxydehydroepiandrosterone on the basis of our previously developed route. The present synthesis allows the production of the protected form of the penultimate intermediate in 26% overall yield in a kilogram scale reaction employing neither difficult reaction conditions nor chromatographic purification, having overcome all the difficulties involved in the previous route.



1α,25-dihydroxy-22-oxavitamin D_3 (Maxacalcitol) **1**

1α,25-dihydroxyvitamin D_3 (Calcitriol) **2**

Figure 1

Introduction

Maxacalcitol[1,2] (**1**) is the 22-oxa-analogue of 1α,25-dihydroxyvitamin D_3[2] (**2**) (calcitriol) and used currently as the antihyperparathyroidism and antipsoriatic drug with low calcemic activity (Figure 1). The first synthesis of maxacalcitol (**1**) was carried out in a sequence of nine chemical steps of reactions[1a] starting from 1α-hydroxydehydroepiandrosterone **(3)** which is accessible from dehydroepiandrosterone by microbial oxidation.[3] The nine-step synthesis involved the following critical seven steps besides the protection–deprotection steps, namely (i) introduction of 7,8-double bond by sequential treatment with NBS and γ-collidine to give the diene **6** via the bromide **5**, (ii) two-carbon elongation by the Wittig reaction to give the *Z*-olefin **7**, (iii) formation of the secondary alcohol **8** by diastereoselective hydroboration–oxidation reaction, (iv) the Williamson etherification forming the 22-ether **9**, (v) the Wacker oxidation forming the methyl ketone **11**, (vi) the Grignard reaction forming the tertiary alcohol **12**, and (vii) the sequential photolysis and thermolysis forming the triene **14** via the isomeric triene **13**. In carrying out the synthesis, we have encountered four difficulties to reach the target molecule, namely (a) instability of the conjugated diene system in the intermediates during the synthesis, (b) sluggish etherification of the secondary alcohol **8**, giving rise to a 1:1 mixture of the target ether **9** and the useless *endo*-olefin byproduct **10**, (c) facile enolization of **11** preventing the nucleophilic addition, and (d) indispensability of chromatographical purification throughout the synthesis (Scheme 1).

Of these difficulties, we have so far circumvented the etherification step by replacing the Williamson etherification by the Michael addition using *N*,*N*-dimethylacrylamide as the electrophile in our second synthesis.[4] Thus, on treatment of the secondary alcohol **8** with a large excess of the acrylamide in the presence of sodium hydride in THF afforded a good yield of the ether **15**. However, the Michael reaction was found to be very capricious, owing to secondary reactions such as the retro-Michael reaction and polymerization under these basic conditions necessitating chromatographical purification to separate the target molecule **15** from undesired byproducts. Moreover, the obtained new ether **15**

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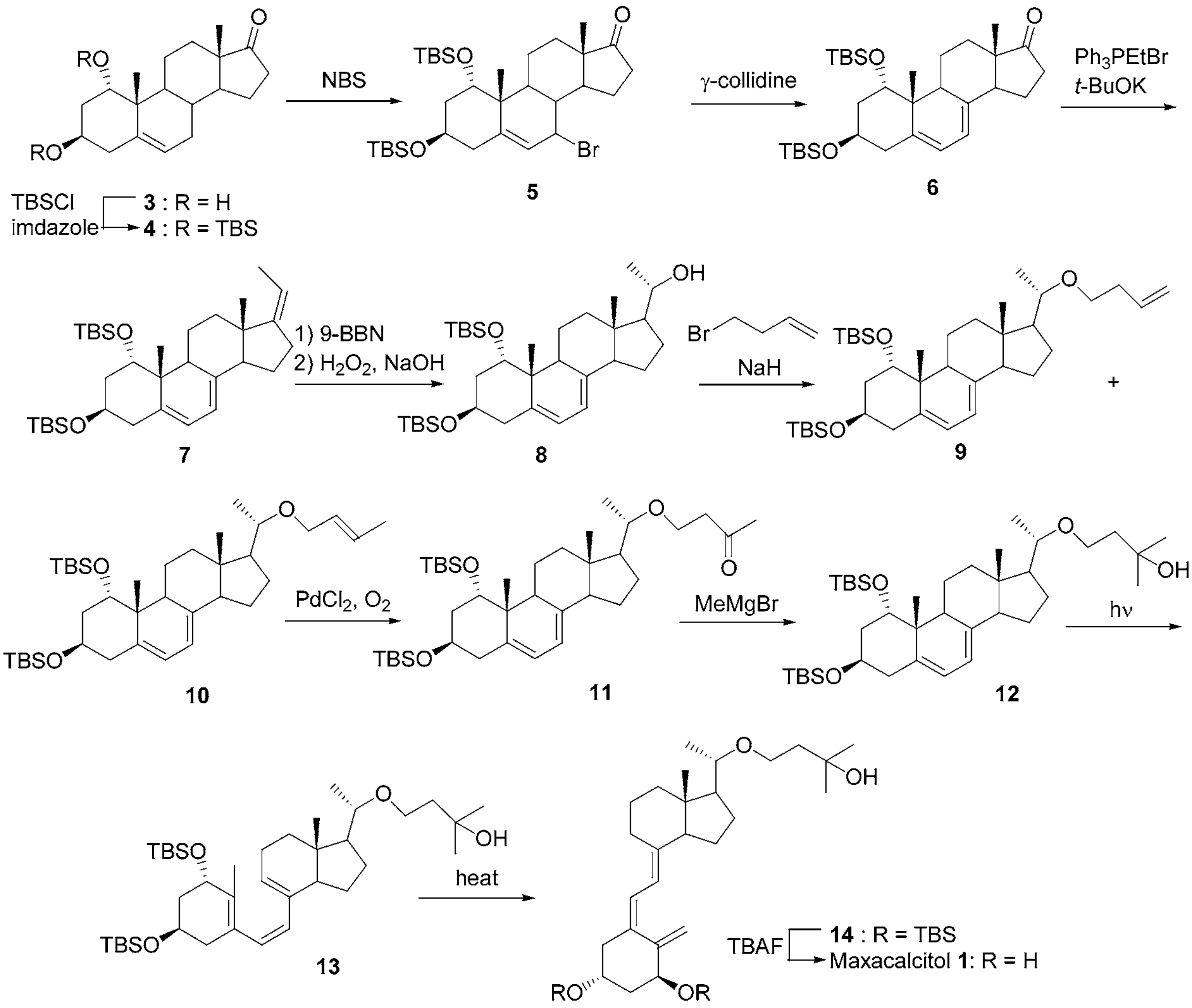
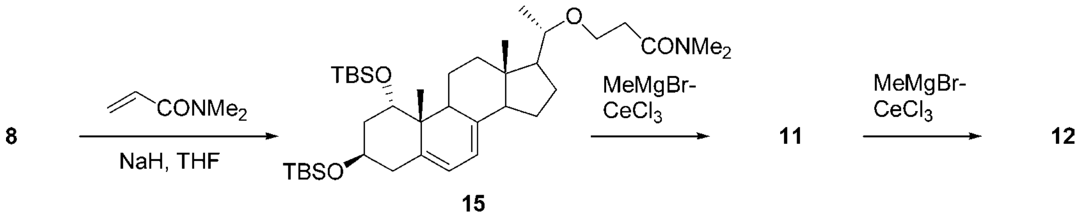
10.1021/op049822x CCC: $30.25

Scheme 1



Scheme 2



brought about a new problem as it was found to be so enolizable in the reaction with methylmagnesium halides or methyllithium that the desired nucleophilic reaction was prevented. Although the desired reaction proceeded by using cerium(III) chloride as an additive,[4a,5] it required more than a stoichiometric amount of the cerium reagent to transform the amide **15** into the methyl ketone **11** which must be isolated as the reaction terminated at this stage. The ketone **11** obtained was more enolizable, and it again required the cerium additive to transform it into the tertiary alcohol **12** (Scheme 2). We therefore explored a more practical procedure and have developed an alternative procedure without employing the Michael addition procedure in the etherification step, allowing truly industrial production of the key intermediate **12** of maxacalcitol (**1**) in seven chemical steps in a kilogram scale with no chromatographical purification.

Results and Discussion

In the present synthesis, we first examined the etherification of the secondary alcohol **17** prior to the introduction of the 7,8-double bond to alleviate instability caused by the presence of the conjugated diene system in the molecule under the basic conditions involved in the synthesis. The 1α-hydroxydehydroepiandrosterone (**3**) was thus transformed directly into the secondary alcohol **17** in 61% overall yield via the *endo*-olefin **16** in a 20-kg-scale reaction without chromatographical purification by sequential stereoselective Wittig olefination and stereo- and regio-selective hydroboration−oxidation reaction under the same conditions as for the diene counterparts **6** and **7**. In this large-scale transforma-

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Scheme 3

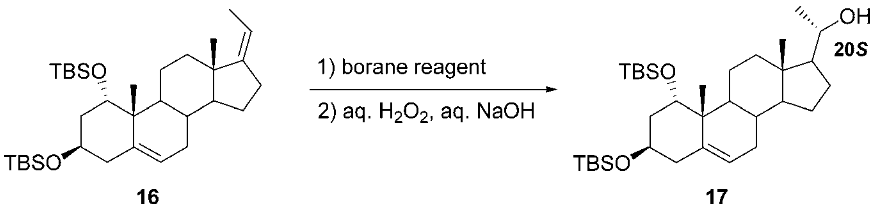


Table 1. **Hydroboration−oxidation of *Z*-olefin 16**

entry	reagent[a]	temp. (°C)	time (h)	production ratio[b] of **17** (**20*S***:**20*R***)
1	BH_3-THF	rt	4	81.3:18.7
2	9-BBN	rt	4	reaction was incomplete (conversion 78%[b])
3	9-BBN	45	4	95.8:4.2

[a] 2 equiv of borane reagent was used. [b] Determined by HPLC.

tion, we had to find an appropriate solvent to enable complete bis-silylation of **3**, owing to its low solubility in cyanoalkanes, such as acetonitrile, propionitrile, and butyronitrile, which are used as good solvents for *O*-silylation with *tert*-butyldimethylsily chloride (TBS-Cl). The silylation did not complete in each of these solvents, each containing 0.1 equiv of 4-*N*,*N*-(dimethylamino)pyridine (DMAP) as an additive, with more than 3 equiv of TBS-Cl in the presence of more than 6 equiv of imidazole even at 90−130 °C. However, the desired reaction was found to proceed completely without any additive when **3** was treated with 3 equiv of TBS-Cl in DMF in high concentration (ca. 20%w/v) in the presence of 6 equiv of imidazole at 125 °C for 6 h to give the crystalline bis-silyl ether **4** in 74% yield without chromatographical purification. In the Wittig reaction, it was found that temperature control is critical for the stereoselective formation of the *Z*-olefin **16** as a substantial amount of the undesirable *E*-olefin isomer (~8.6%) was generated when the reaction temperature exceeded 65 °C. Transformation of the *Z*-olefin **16** into the secondary alcohol **17** could be carried out in a regio- and stereoselective manner as reported, but it was dependent on the conditions (Scheme 3). As shown in Table 1, 9-BBN gave the desired secondary alcohol **17** in satisfactory yield without affecting the internal olefin functionality in THF at 45 °C. Although the stereoselectivity was 91% de, the secondary alcohol **17** was obtained in 90% yield as crystals with spontaneous removal of the undesired diastereomer in the crystallization stage in a large-scale production.

Etherification the secondary alcohol **17** was first carried out by application of the method employed for the diene counterpart **8** in our previous industrial production of maxacalcitol (**1**). In the same way as the diene **8**, **17** afforded the Michael adduct **18** only with *N*,*N*-dimethylacrylamide under basic conditions (Scheme 4). Again a complex mixture was generated with either methyl vinyl ketone or methyl acrylate under basic conditions. During the preliminary experiment, we have confirmed the monoene **17** to be much more stable than the diene counterpart **8** under the same basic conditions employed in the previous synthesis. As shown in Table 2, the reaction using the acrylamide was highly dependent on the conditions. Among the bases examined,

Scheme 4

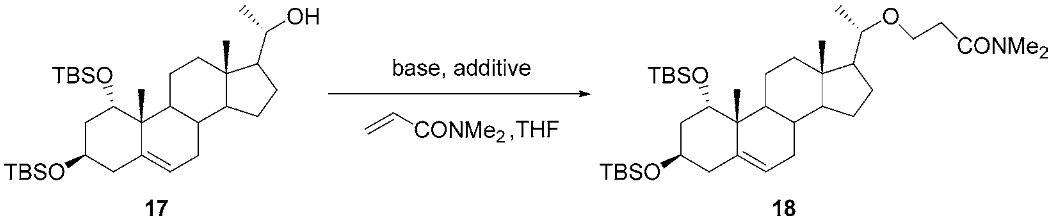
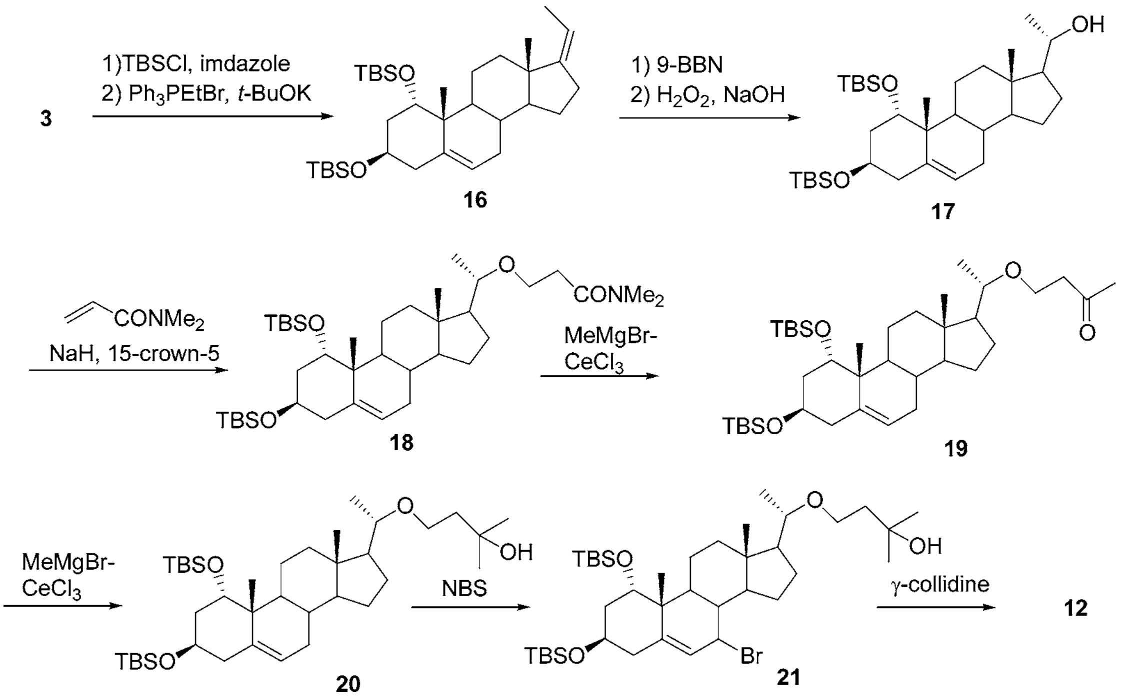


Table 2. **Reaction between 17 and *N, N*-Dimethyacrylamide**[a]

entry	base[b]	additive (mol %)	concentration [**17**(g):THF(mL)]	temp. (°C)	production ratio[c] (**17**:**18**)	yield of **18** (%)[d]
1	KH	−	1:6	0	>99.9:0.1	−
2	MeONa	−	1:6	0	29.0:71.0	−
3	*t*-BuOK	−	1:6	0	>99.9:0.1	−
4	NaH	−	1:6	0	7.3:92.7	70.2
5	NaH	−	1:6	45	19.8:80.2	31.0
6	NaH	−	1:6	reflux	>99.9:0.1	−
7	NaH	18-crown-6 (10)	1:6	0	6.2:93.8	81.0
8	NaH	15-crown-5 (10)	1:6	0	3.0:97.0	86.7
9	NaH	15-crown-5 (30)	1:6	0	1.2:98.8	81.9
10	NaH	15-crown-5 (30)	1:4	0	1.1:98.9	85.6
11	NaH	15-crown-5 (30)	1:3	0	1.2:98.8	83.1

[a] 3 equiv of *N, N*-dimethylacrylamide was used. [b] 1.5 equiv of base was used. [c] Determined by HPLC. [d] Isolated yield.

Scheme 5



sodium hydride only afforded the desired ether **18** in high yield with some recovery of the starting material, indicating the reaction to be in an equilibrium state. We found that the reaction reached up to 98.9:1.1 on the product side by addition of a catalytic amount of crown ether, particularly, 15-crown-5, although the reaction was never completed. After an extensive examination, the construction of the 22-ether linkage was finally optimized to a practical level to carry out the Michael addition using more than a 10 kg of **17** in a minimum amount of THF (ca. 20% w/v) as solvent in the presence of sodium hydride and a catalytic amount of 15-crown-5. Thus, 11.1 kg of **17** was introduced in THF containing 1.5 equiv of sodium hydride and 10 mol % of 15-crown-5 at 0 °C to generate the alkoxide which then was treated with 3 equiv of *N,N*-dimethylacrylamide at the same temperature to produce the desired ether **18** in 87% yield as crystals without chromatographical purification. It should be noted that sodium hydride may be used as dispersion form in mineral oil, which is more safe than sodium hydride itself and easier to handle in this large-scale production as the oil included could be readily removed during the separation stage of the ether **18** as crystals.

In contrast, both potassium hydride and potassium *tert*-butoxide, even with a crown ether, did not promote the addition reaction but induced the retrograde reaction which was confirmed by the separate experiment. Thus, on exposure to 1.5 equiv of either potassium hydride or potassium *tert*-butoxide at room temperature, the ether **18** collapsed completely into the secondary alcohol **17** very facilely.

Although the transformation of the ether **18** into the tertiary alcohol **20** through the methyl ketone **19** had to use the cerium reagent,[6a] owing to facile enolization of the ether **18** as well as the methyl ketone **19** thereof the target molecule **20** was obtained in 71% yield in a two-step sequence using the same conditions employed for the diene counterparts **15** and **11**. The transformation, however, could be carried out more easily than that for the diene counterparts due to higher stability of the monoene intermediates **18** and **19** as well as the monoene product **20**. All the monoenes were accompanied by a much smaller amount of byproducts than that for their diene counterparts and gave rise to the crystalline tertiary alcohol **20** without requiring chromatographical purification.

Transformation of the monoene alcohol **20** into the diene alcohol **12** was carried out by employing the same conditions those employed in the transformation of the monoene **4** into the diene **6**[6a] using hepatane in place of hexane in the bromination step and toluene in place of xylene in the dehydrobromination step. When hexane was used as the solvent in the bromination of **20** as for the monoene **4**, the reaction took place violently in foams, while the use of heptane allowed the reaction to proceed in a controllable manner. The use of toluene, in place of xylene used for **5**, in the dehydrobromination step allowed facile crystallization to make purification of the product **12** easier. The yield of the diene **12** in a large-scale production was a little less than satisfactory, but the product could be obtained as crystals without chromatographical purification. Thus, treatment of 19.6 kg of **20** with 1.2 equiv of NBS in heptane at 78 °C in the presence of 12 mol % of AIBN afforded the allyl bromide **21** which, on immediate heating with 2 equiv of γ-collidine at 110 °C in toluene, furnished the diene **12** in 43% overall yield after crystallization (Scheme 5).

Seemingly, all the difficulties mentioned above, namely (a) instability owing to the diene functionality, (b) sluggishness in etherification, (c) facile enolization, and (d) indispensability of chromatography, have been solved at this point.

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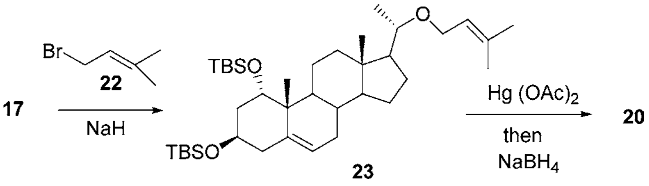
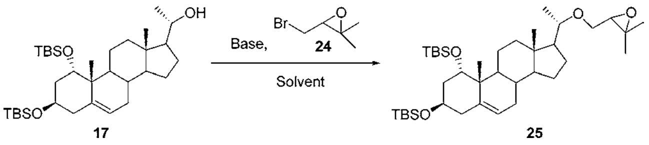
Scheme 6



Scheme 7



However, it is still less than satisfactory from the industrial viewpoint, in particular the two steps to transform the amide **18** into the tertiary alcohol **20** via the ketone **19** in which more than a stoichiometric amount of cerium (III) chloride was required to alleviate enolization and left a large amount of useless waste. Since this cannot be overcome as long as the present etherification method is employed, we sought an alternative route to eliminate the cerium reagent and have established an efficient alternative route without requiring the cerium reagent.

As mentioned above, we have thus far found in the previous syntheses that the secondary alcohol **8** reacted very sluggishly with alkyl halides under Williamson etherification conditions which brought about rearrangement of the olefin functionality of the desired product **9** to give rise to a substantial amount of the undesired isomer **10**. On the other hand, we have found that the secondary alcohol **17** reacted smoothly with prenyl bromide **22** to give the prenyl ether **23** which gave regioselectively the desired tertiary alcohol **20** in good yield by application of the oxymercuration–reduction method[6a,7] in which use of the mercury salt was unavoidable (Scheme 6). During the investigation, we knew the report described that the epoxide[8] **24** exhibited high reactivity toward primary and secondary alcohols as its allylic precursor **22** under Williamson conditions to give the corresponding ethers.[8,9,10] We, thus, examined the preparation of the tertiary alcohol **20** via the epoxy ether **25** by application of this etherification followed by reductive cleavage of the epoxy functionality. The Williamson etherification of **17** with the racemic epoxy bromide **24** afforded the expected epoxy ether **25** in excellent yield in THF in the presence of sodium hydride. However, either when potassium *tert*-butoxide in place of sodium hydride or when DMF in place of THF was used, the yield of the ether **25** was diminished considerably (Scheme 7 and Table 3).

Table 3. **Reaction between 17 and the epoxy bromide 24**

entry	base (equiv)	epoxy bromide **24** (equiv)	solvent	temp. (°C)	time (h)	product (%)[a] of **25**
1	*t*-BuOK (6.0)	6.8	THF	50	2	42
2	NaH (3.0)	12.0	DMF	80	5	45
3	NaH (3.0)	2.0	THF	50	4	88

[a] Determined by HPLC.

In this transformation, a byproduct was formed consistently (though in 0.5% yield and readily removable during the crystallization of the major product **25** in the optimized conditions). It was isolated and determined as the pivalate **30** spectroscopically and unambiguously by the separate synthesis. The generation of the pivalate **30** may be due to the generation of the allene oxide **26** generated from the epoxy bromide **24** by competing dehydrobromination under the basic conditions employed. As has been well established,[11] the allene oxide **26** could rearrange to the cyclopropanone **27** which would then react with the steroid alkoxide **28** to undergo the Favorskii rearrangement to give rise to the pivalate **30** by regioselective cleavage[12] (Scheme 8).

Although our expected sodium bis(methoxyethoxy)aluminohydride (Red-Al), which was known to reduce 2,3-epoxy alcohols into the corresponding 1,3-diols in a regioselective manner,[13] failed to give rise to the tertiary alcohol **20**, we have found good conditions applicable to a large-scale production after extensive examination using boron and aluminum hydride reagents. Among the reagents examined,[6,14] the cleavage of the epoxide **25** proceeded regioselectively in the desired way with the boron reagents to give rise to tertiary alcohol **20** as the major product, in particular, with lithium triethylborohydride (Super Hydride) or lithium *sec*-butylborohydride (L-Selectride) in THF. Very interestingly, the reaction did not proceed with potassium *sec*-butylborohydride (K-Selectride) or other lithium borohydrides even under more forcing conditions (Scheme 9 and Table 4).

In these alkylation and reduction reactions to transform **17** into **20** involving the diastereomeric intermediates **24** and **25**, no diastereomeric discrimination could be observed. Since these two reactions were carried out in the anhydrous THF solution, we attempted to perform these two steps in the same reaction vessel without isolation of the epoxide intermediate **25** to facilitate industrial preparation. The reaction did really proceed in an expected way to give rise to the crystalline tertiary alcohol **20** when the secondary alcohol **17** in THF was treated with the epoxy bromide **24** in the presence of sodium hydride, followed by L-Selectride.

This one-pot reaction could be carried out in 17.2 kg in THF in high concentration (50% w/w) in the presence of 2 equiv of sodium hydride with 1.3 equiv of the epoxy bromide **24** at refluxing temperature for 1 h, followed by 1.8 equiv of 1 M THF solution of L-Selectride at the same temperature for 1 h to furnish the crystalline alcohol **20** in 99% yield. Two points should be noted in this one-pot reaction. The first is the use of sodium hydride in a dispersion form without

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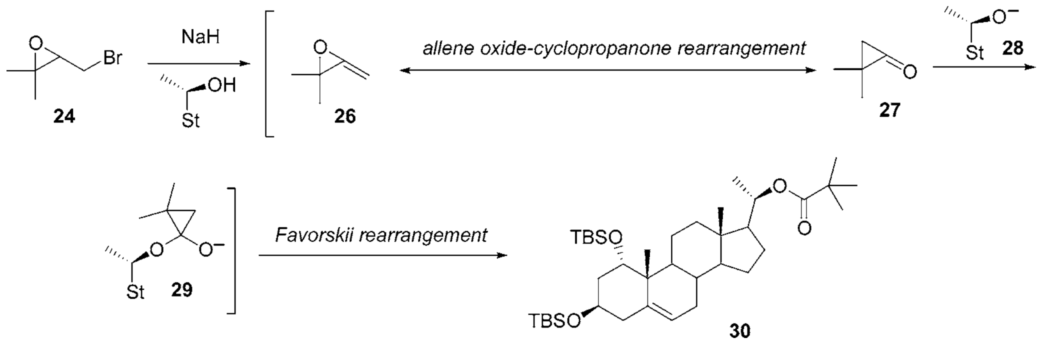
Scheme 8



Scheme 9

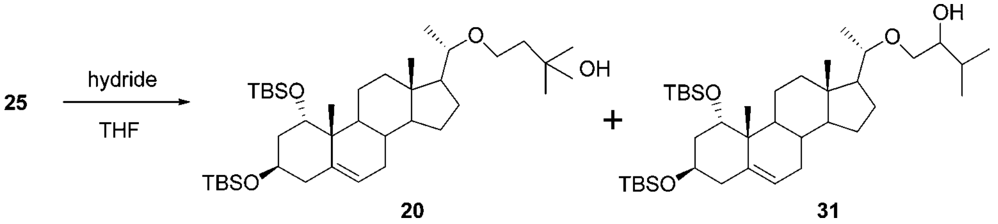
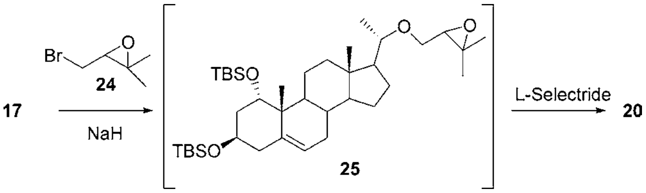


Table 4. **Reaction of the epoxide ether 25 with hydrides**

entry	hydride (equiv)	temp. (°C)	time (h)	conv. (%)[a]	production ratio[a] (**20**:**31**)
1	Red-Al[b](5.0)	reflux	6.5	0	–
2	$LiAlH_4$ (3.0)	rt	4	94	92.6:7.4
3	*i*-Bu_2AlH (5.0)	rt	2	72	15.4:84.6
4	$NaBH_4$ (10.0)	reflux	5	5	n.d.[c]
5	$LiEt_3BH$[d](5.0)	rt	3	100	98.2:1.8
6	Li-*s*-Bu_3BH[e] (5.0)	rt	2.5	100	99.7:0.3
7	K-*s*-Bu_3BH[f] (10.0)	reflux	8	4	n.d.
8	Li-*s*-Am_3BH[g] (10.0)	rt	24	50	n.d.
9	K-*s*-Am_3BH[h] (10.0)	rt	18	0	–
10	$LiPh_3BH$ (10.0)	reflux	7	7	n.d.

[a] Determined by HPLC. [b] Sodium bis(2-methoxyethoxy)aluminum hydride. [c] Not determined. [d] Super Hydride. [e] L-Selectride. [f] K-Selectride. [g] LS-Selectride. [h] KS-Selectride.

Scheme 10



removal of the mineral oil. As described in the preparation of the ether **18**, utilization of sodium hydride in a dispersion form undoubtedly facilitates a large-scale production. The oil contained could be readily removed in the following stage. The second point is the use of alkaline hydrogen peroxide in the termination of the reaction. The one-pot reaction may proceed accompanied by an intractable byproduct mixture derived from the reducing agent disturbing the crystallization of **20** unless treated with the alkaline peroxide in the workup (Scheme 10).

The epoxy bromide **24** was prepared from prenyl bromide **22** on oxidation with *m*-chloroperbenzoic acid in dicloromethane. To avoid the use of undesirable solvent, an alternative route capable of carrying out in aqueous media was examined on the basis of the report by Strauss and Kühnel[15] in 1933 who found one-sep generation of the bromoepoxide from 1,1-dimethylallyl alcohol **32** with aqueous hypobromite solution. Although later in 1954, Winstein and Goodman[8] proposed the involvement of the conjugate base **33** of the alcohol **32** and hypobromous acid in this reaction, no study intending the practical utilization of this reaction has been reported to date. We therefore examined the synthesis of the epoxy bromide **24** by employing the aqueous conditions and have established a large-scale production. Thus, the reaction of 1 kg of the tertiary alcohol **32** upon exposure to 1.5 equiv of potassium hypobromite, prepared in situ in 10 L of water, furnished the desired epoxy bromide **24** directly in 82% yield after distillation (Scheme 11).

We have now truly overcome all the difficulties encountered in our previous synthesis leading to the protected form **12** of the penultimate intermediate **34** of maxacalcitol (**1**). We have now been able to carry out the final photochemical reaction utilizing the tetracyclic diene **34** in a 100-g scale after deprotection of the disilyl ether **12** thus obtained. Thus, the photolysis of the triol **34** in THF by irradiation with a high-pressure mercury lamp at 10 °C generated the pre-22-oxa-D_3 product **35** as crystals, after purification by HPLC, which on stirring in THF at 25 °C, furnished maxacalcitol (**1**)**.** Overall yield of Maxacalcitol (**1**) from the diene **34** was 16% after HPLC purification (Scheme 12).

We can now summarize our present synthesis leading to maxacalcitol (**1**) in a sequence of seven chemical steps starting from 1α-hydroxydehydroepiandrosterone (**3**) in Scheme 13. The present method allowed the production of the key intermediate **12** in 26% overall yield in a kilogram-scale conversion without formation of any undesired byproducts employing neither difficult reaction conditions nor chromatographic purification during the conversions involved.

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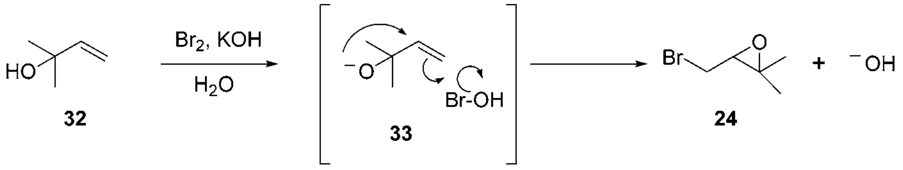
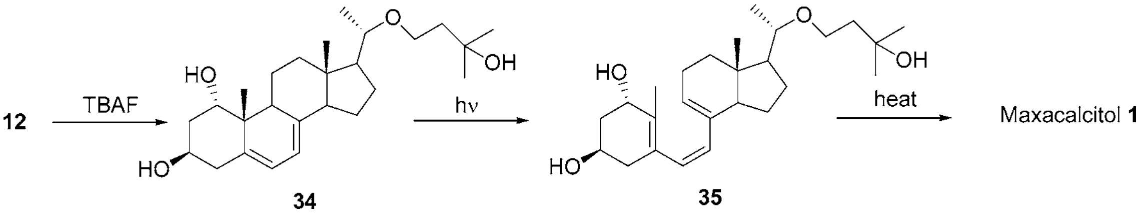
[15] Strauss, F.; Kühnel, R. *Ber.* **1933**, *66B*, 1834.

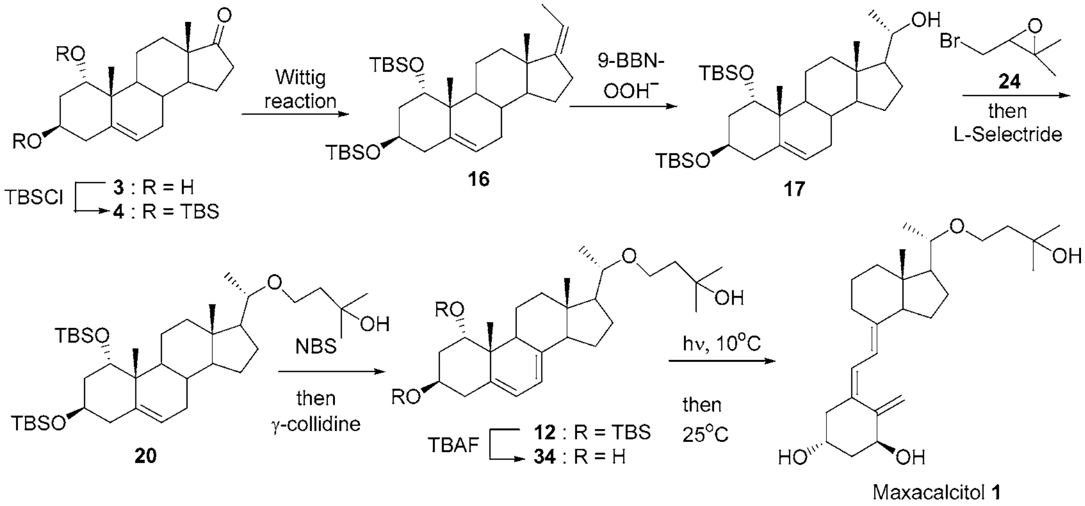
Scheme 11



Scheme 12



Scheme 13



Conclusions

A practical seven-step synthesis of maxacalcitol (**1**) from 1α-hydroxydehydroepiandrosterone (**3**) has been developed on the basis of our original synthesis by exclusion of all the difficulties encountered in the original method. The present synthesis allowed a multikilogram-scale production, except the final photoreaction stage, employing neither difficult conditions nor chromatographic separation.

Experimental Section

General Methods. 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 77.00 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. Optical rotations were determined on a JASCO model DIP-1000 polarimeter. Both **35** and **1** were isolated by HPLC (SiO_2 column: Merck art. no. 9385, Φ 20 cm × 100 cm, UV: 254 nm) at room temperature using a mixture of hexane/AcOEt as the mobile phase (flow rate: 1.0 L/min). The retention times of **35** and **1** were 280 and 160 min, respectively.

(1*S*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)androst-5-en-17-one (4). To a stirred solution of 1α-hydroxydehydroepiandrosterone **3** (7.13 kg, 23.42 mol) and imidazole (9.57 kg, 140.57 mol) in DMF (35.7 L) was added *tert*-butyldimethylsilyl chloride (10.50 kg, 69.66 mol) at 20 °C. The mixture was heated at 125 °C, and the stirring was continued for 6 h at the same temperature. After cooling to 30 °C, the mixture was diluted with MeOH (21.4 L) with stirring to separate crystalline precipitate, and the stirring was continued at same temperature for 4 h. The product separated was collected centrifugally and dried at 50 °C to give **4** as light-yellow crystals (9.2 kg, 74.0%): mp 153 °C; $[\alpha]^{20}_D$ +53.0° (c 1.02, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 2954, 2927, 2856, 1740, 1471, 1462, 1255, 1103, 1084, 837, 775, 669; ^{1}H NMR ($CDCl_3$): δ 5.48 (1H, d, $J = 5.6$), 3.99−4.05 (1H, m), 3.78 (1H, br s), 2.38−2.52 (1H, m), 2.00−2.17 (1H, m), 1.95−2.12 (1H, m), 1.90−2.05 (1H, m), 1.80−1.95 (1H, m), 1.75−1.87 (1H, m), 1.70−1.90 (1H, m), 1.60−1.75 (1H, m), 1.50−1.70 (2H, m), 1.45−1.65 (1H, m), 1.25−1.35 (1H, m), 1.15−1.32 (1H, m), 0.95 (3H, s), 0.88 (18H, s), 0.64 (3H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s). Anal. Calcd for $C_{31}H_{56}O_3Si_2$: C, 69.86; H, 10.59. Found: C, 68.87; H, 10.64.

(17*Z*)-(1*S*,3*R*)-1,3-Bis(*tert*-butyldimethylsilyloxy)pregna-5, 17-dien (16). To a stirred solution of the ylide, prepared in situ by treating EtPPh$_3$Br (28.0 kg, 75.42 mol) with potassium *tert*-butoxide (8.50 kg, 75.74 mol) in THF (101 L) at 20 °C, was added **4** (20.1 kg, 37.71 mol) at 25 °C, and the temperature was raised to 30 °C. After stirring for 4 h at the same temperature, the mixture was cooled to 25 °C, and to this mixture was added THF (60 L), heptane (161 L), and water (85 L) sequentially. After stirring for 0.5 h at the same temperature, the organic layer was separated and was washed with brine (114 L × 2) and concentrated under reduced pressure to leave a solid residue. The residue was dissolved in heptane (175 L) with stirring at 15 °C for 1 h, and the insoluble material was removed by filtration. The filtrate was evaporated under reduced pressure to leave a colorless solid. This was dissolved in acetone (500 L) at 35 °C, and to this solution was added H$_2$O (60 L) at the same temperature; the mixture was then cooled to −5 °C to separate out a crystalline material.

The product was collected centrifugally and dried at 60 °C to give the diene **16** as colorless crystals (18.5 kg, 90.0%): mp 123 °C; $[\alpha]_D^{20}$ +21.1° (*c* 1.00, CHCl$_3$); FT-IR (KBr, cm^{-1}): ν 2954, 2856, 1471, 1373, 1255, 1082, 837, 771, 671; ^{1}H NMR (CDCl$_3$): δ 5.46 (1H, d, J = 5.6), 5.13 (1H, m), 3.99 (1H, m), 3.78 (1H, m), 2.20−2.40 (1H, m), 2.15−2.40 (2H, m), 2.10−2.50 (2H, m), 1.90−2.05 (1H, m), 1.66 (3H, m), 1.60−1.95 (2H, m), 1.60−1.85 (1H, m), 1.55−1.75 (1H, m), 1.50−1.70 (1H, m), 1.40−1.50 (1H, m), 1.40−1.60 (1H, m), 1.35−1.60 (2H, m), 1.10−1.35 (1H, m), 1.05−1.30 (1H, m), 0.98 (3H, s), 0.89 (3H, s), 0.88 (18H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (CDCl$_3$): δ 150.5, 138.3, 123,1, 113.4, 73.5, 67.6, 56.7, 44.1, 42.3, 42.3, 41.0, 38.9, 36.8, 31.6, 31.5, 31.5, 26.0, 25.9, 24.6, 20.7, 19.3, 18.1, 18.1, 16.8, 13.2, −3.8, −4.4, −4.5, −5.2. Anal. Calcd for $C_{33}H_{60}O_2Si_2$: C, 72.73; H, 11.10. Found: C, 72.09; H: 11.09.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-hydroxypregn-5-ene (17). To a stirred solution of 9-BBN (0.5 mol/L in THF, 133 kg, 74.38 mol) was added **16** (18.5 kg, 33.94 mol) at room temperature, and the mixture was stirred at 45 °C for 4 h. After cooling to −5 °C, the mixture was treated sequentially with 10% NaOH (99.0 kg, 247.50 mmol) and 35% H$_2$O$_2$ (42.0 kg, 407.99 mmol) with stirring; the stirring was continued at 25 °C for 1 h. Then the mixture was extracted with AcOEt (222 L), and the extract was washed sequentially with aqueous Na$_2$S$_2$O$_3$ (53.0 kg, 213.55 mmol in H$_2$O, 161 L) and brine (294 L × 2) and evaporated under reduced pressure to leave a colorless solid. The solid was dissolved in MeOH (149 L) at 35 °C and then cooled to 8 °C for 1.5 h to separate a crystalline material. The product separated was collected centrifugally and dried at 60 °C to give the secondary alcohol **17** as colorless crystals (17.2 kg, 90.0%): mp 183 °C; $[\alpha]^{20}_D$ +12.0° (*c* 1.05, CHCl$_3$); FT-IR (KBr, cm^{-1}): ν 3408, 2954, 2856, 1471, 1380, 1257, 1101, 1084, 835, 773, 675; ^{1}H NMR: δ 5.45 (1H, d, J = 5.6), 3.75−3.77 (1H, m), 3.99 (1H, m), 3.78 (1H, m), 2.15−2.37 (2H, m), 1.80−2.05 (1H, m), 1.80−2.00 (2H, m), 1.60−2.00 (2H, m), 1.55−1.85 (1H, m), 1.50−1.80 (1H, m), 1.50−1.70 (1H, m), 1.40−1.65 (1H, m), 1.25−1.53 (3H, m), 1.20−1.40 (1H, m), 1.05−1.20 (1H, m), 1.00−1.25 (2H, m), 0.90−1.20 (1H, m), 1.22 (3H, s), 0.96 (3H, s), 0.88 (18H, s), 0.68 (3H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR: δ 138.4, 123.2, 73.5, 70.3, 67.5, 58.5, 56.8, 42.3, 42.2, 41.6, 41.0, 38.9, 38.7, 31.7, 31.6, 26.0, 25.9, 25.6, 24.3, 23.5, 20.2, 19.3, 18.1, 18.1, 12.6, −3.7, −4.4, −4.5, −5.2. Anal. Calcd for $C_{33}H_{62}O_3Si_2$: C, 70.40; H, 11.10. Found: C, 70.01; H, 11.16.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-{(2-dimethylaminocarbonyl)ethyloxy}preg-na-5-ene (18). To a stirred suspension of the alkoxide generated in situ from the secondary alcohol **17** (11.1 kg, 19.72 mol) and NaH (60% dispersion in mineral oil, 1.18 kg, 29.50 mol) in the presence of 15-crown-5 (0.44 kg, 2.00 mol) in THF (44.4 L) was added *N*,*N*-dimethylacrylamide (5.86 kg, 59.11 mol) at 0 °C, and the stirring was continued for 6 h at the same temperature. The reaction was quenched by addition of aqueous NH$_4$Cl (22.2 L), and the mixture was extracted with AcOEt (36.6 L). The extract was washed with aqueous brine (55.7 L × 2) and concentrated under reduced pressure to leave a solid residue. The residue was suspended in hexane (33.3 L) at room temperature and cooled to −20 °C with stirring. After stirring for 1 h at the same temperature, the crystalline precipitate was collected centrifugally and dried at 50 °C to give **18** as colorless crystals (11.4 kg, 87.3%): mp 153 °C; $[\alpha]_D^{20}$ +25.4° (*c* 1.02, CHCl$_3$); FT-IR (KBr, cm^{-1}): ν 2954, 2854, 1653, 1473, 1252, 1090, 1066, 837, 771, 677; ^{1}H NMR (CDCl$_3$): δ 5.46 (1H, d, J = 5.6), 3.90 (1H, m), 3.86 (1H, m), 3.76 (1H, br s), 3.57 (1H, m), 3.27 (1H, m), 3.02 (3H, s), 2.93 (3H, s), 2.56 (1H, m), 2.15−2.35 (2H, m), 1.15 (3H, d, J = 5.9), 0.95 (3H, s), 0.88 (18H, s), 0.64 (3H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (CDCl$_3$): δ 171.5, 138.3, 123.2, 78.3, 73.5, 67.5, 64.7, 56.9, 56.8, 42.3, 42.2, 41.3, 41.0, 38.9, 38.7, 37.5, 35.3, 34.1 31.7, 31.6, 25.9, 25.9, 25.9, 24.2, 20.2, 19.3, 19.2, 18.1, 18.1, 12.5, −3.8, −4.4, −4.5, −5.3. Anal. Calcd for $C_{38}H_{71}NO_4Si_2$: C, 68.93; H, 10.81; N, 2.12; Si, 8.48. Found: C, 68.83; H, 10.84; N, 2.16; Si, 8.5.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(3-hydroxy-3-methylbuthyloxy)pregn-5-ene (20). To a stirred suspension of CeCl$_3$ (5.77 kg, 23.40 mol) in THF (19.0 L) was added MeMgCl (19.7 L, 1M in THF, 19.70 mol) at −15 °C, and after 0.5 h, to this mixture was added the amide **18** (3.52 kg, 5.32 mol) at the same temperature, and the stirring was continued for 0.5 h at the same temperature. The mixture was diluted with hexane (18.7 L) and the reaction was quenched by addition of aqueous KHSO$_4$ (16.2 kg in H$_2$O 54 L) at −15 °C, and the mixture stirred at the same temperature for 0.5 h. After removal of the insoluble material by filtration, the organic layer was separated and washed sequentially with brine (35.1 L), saturated aqueous NaHCO$_3$ (35.1 L), and brine (35.1 L). Evaporation of the organic layer under reduced pressure left methyl ketone **19** as a pale-yellow oil which was used for the next reaction: FT-IR (KBr, cm^{-1}): ν 2936, 1728, 1464, 1378, 1258, 1096, 886, 872, 838, 774; ^{1}H NMR (CDCl$_3$): δ 5.44 (1H, d, J = 5.6), 3.98 (1H, m), 3.80 (1H, m), 3.77 (1H, br s), 3.52 (1H, m), 3.23 (1H, m), 2.61 (2H, m), 2.15−2.28 (5H, m), 1.14 (3H, d, $J = 5.6$), 0.99 (3H, s), 0.87 (18H, s), 0.80 (3H, s), 0.08 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.03 (3H, s). Anal. Calcd for $C_{37}H_{68}O_4Si_2$: C, 70.19; H, 10.83; Si, 8.87. Found: C, 70.05; H, 10.81; Si, 8.9.

To the cerium reagent, prepared in situ from $CeCl_3$ (5.77 kg, 23.40 mol) in THF (19.0 L) and MeMgCl (19.7 L 1M in THF, 19.70 mol) at −15 °C as above, was added the ketone **19** in THF (3.6 L) at −15 °C, and the stirring was continued for 0.5 h at the same temperature. The mixture was diluted with hexane (18.7 L), and the reaction was quenched by addition of aqueous $KHSO_4$ (10.4 kg in H_2O, 35 L) at −15 °C. After stirring at the same temperature for 0.5 h, the organic layer was separated and washed sequentially with brine (35.1 L), saturated aqueous $NaHCO_3$ (35.1 L), and brine (35.1 L) and evaporated under reduced pressure to leave a pale-yellow solid. The solid was dissolved in refluxing MeOH (17.6 L) and cooled to 0 °C with stirring to separate out a crystalline product. After stirring for 1 h at the same temperature, the product was collected centrifugally and dried at 50 °C to give the tertiary alcohol **20** (2.45 kg, 71.0%) as colorless crystals: mp 134 °C; $[\alpha]_D^{20}$ +25.2° (*c* 1.00, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3518, 2956, 2856, 1473, 1381, 1255, 1088, 837, 773, 675; ^{1}H NMR ($CDCl_3$): δ 5.45 (1H, d, $J = 5.6$), 4.85 (1H, m), 3.81 (1H, m), 3.76 (1H, br s), 3.47 (1H, m), 3.25 (1H, m), 2.20−2.28 (2H, m), 1.18 (3H, s), 0.95 (3H, s), 0.88 (18H, s), 0.66 (3H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$): δ 138.3, 123.2, 78.8, 73.5, 70.4, 67.5, 65.4, 56.8, 56.6, 42.3, 42.2, 41.5, 41.4, 40.9, 38.9, 38.7, 31.8, 31.5, 29.3, 29.1, 26.5, 25.9, 25.9, 24.3, 20.2, 19.3, 18.7, 18.1, 18.1, 12.6, −3.8, −4.4, −4.5, −5.2.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(3-hydroxy-3-methylbuthyloxy)pregn-5-ene (20). To a solution of the secondary alcohol **17** (17.2 kg, 30.55 mol) in THF (61.0 kg) was added NaH (60% dispersion in mineral oil, 2.4 kg, 60.0 mol) portionwise with stirring at room temperature so as to control evolution of hydrogen at an appropriate rate. Afte the evolution of hydrogen ceased, to the resulting suspension was added the bromide **24** (7.1 kg, 43.02 mol) dropwise at the same temperature with stirring, and the mixture was refluxed for 1 h. After cooling to room temperature, to this mixture containing the epoxy-ether **25** was added L-Selectride (1 M in THF, 49.0 kg, 55.06 mmol) dropwise, and the mixture was refluxed for 1 h. The mixture was then cooled to −10 °C and treated sequentially with 10% NaOH (91.0 kg, 227.5 mol) and 35% H_2O_2 (43.0 kg, 417.7 mol); the stirring was continued for 1 h at room temperature. To this mixture was then added aqueous $Na_2S_2O_3$ (35.0 kg in H_2O 101 L, 141.0 mol) at the same temperature, and after stirring for 1 h, the mixture was extracted with AcOEt (106 L) and separated. The organic layer was washed sequentially with brine (2 × 110 L) and evaporated under reduced pressure to leave a colorless solid. The solid was dissolved in refluxing methanol (124 L), and to this solution, after cooling to 25 °C, was added water (52 L) with stirring to form a suspension which was cooled to 5 °C; the stirring was continued for 1 h at the same temperature. Then the suspension was centrifuged, and a colorless crystalline solid collected was dried at 50 °C to leave the tertiary alcohol **20** (19.6 kg, 99.0%) as colorless granules: mp 131 °C; $[\alpha]_D^{20}$ +23.3° (*c* 1.00, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3518, 2956, 2856, 1473, 1381, 1255, 1088, 837, 773, 675; ^{1}H NMR ($CDCl_3$): δ 5.45 (1H, d, $J = 5.6$), 4.85 (1H, m), 3.81 (1H, m), 3.76 (1H, br s), 3.47 (1H, m), 3.25 (1H, m), 2.20−2.28 (2H, m), 1.18 (3H, s), 0.95 (3H, s), 0.88 (18H, s), 0.66 (3H, s), 0.08 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR ($CDCl_3$): δ 138.3, 123.2, 78.8, 73.5, 70.4, 67.5, 65.4, 56.8, 56.6, 42.3, 42.2, 41.5, 41.4, 40.9, 38.9, 38.7, 31.8, 31.5, 29.3, 29.1, 26.5, 25.9, 25.9, 24.3, 20.2, 19.3, 18.7, 18.1, 18.1, 12.6, −3.8, −4.4, −4.5, −5.2. Anal. Calcd for $C_{38}H_{72}O_4Si_2$: C, 70.31; H, 11.18; Si, 8.65. Found: C, 70.41; H, 11.10; Si, 8.7.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(3-hydroxy-3-methylbuthyloxy)pregna-5,7-dien (12). A solution of the tertiary alcohol **20** (19.6 kg, 30.2 mol) in heptane (119 L) was stirred with NBS (6.6 kg, 37.1 mol) and AIBN (0.70 kg, 4.26 mol) at 78 °C for 15 min. The mixture after cooling was filtrated, and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in toluene (204 L) and was stirred with γ-collidine (9.60 kg, 79.2 mol) at 110 °C for 2.5 h. The mixture after cooling to 20 °C was filtrated, and the filtrate was evaporated under reduced pressure to leave a light-yellow solid. The solid was dissolved in AcOEt (73 L) at 35 °C, and to this solution was added acetonitrile (235 L) at 40 °C, and the mixture was cooled to −5 °C to separate the crystals. After stirring for 1 h at the same temperature, the crude **12** separated as a light-yellow crystalline solid and was collected centrifugally. The solid was again dissolved in AcOEt (73 L) at 35 °C, and to the solution was added acetonitrile (234 L) at 40 °C; the solution was then cooled at 5 °C for 1 h. The separating crystalline material was collected centrifugally and dried at 45 °C to give the diene **12** as colorless crystals (8.4 kg, 43.0%): mp 146 °C; $[\alpha]_D^{20}$ +14.7° (*c* 1.01, $CHCl_3$); FT-IR (KBr, cm^{-1}): ν 3516, 2960, 2856, 1473, 1380, 1255, 1099, 837, 683; ^{1}H NMR ($CDCl_3$): δ 5.58 (1H, m), 5.32 (1H, d, $J = 5.6$), 4.04 (1H, m), 3.84 (1H, m), 3.69 (1H, br s), 3.49 (1H, m), 3.26 (1H, m), 2.78 (1H, m), 2.30−2.36 (2H, m), 1.23 (3H, s), 1.22 (3H, s), 1.20 (3H, d, $J = 3.2$), 0.89 (3H, s), 0.87 (18H, s), 0.60 (3H, s), 0.10 (3H, s), 0.06 (6H, s), 0.05 (3H, s); ^{13}C NMR ($CDCl_3$): δ 139.7, 137.6, 120.1, 115.3, 79.0, 73.9, 70.4, 66.3, 65.6, 56.4, 54.6, 42.7, 42.0, 41.5, 40.8, 39.0, 38.4, 37.5, 29.3, 29.1, 26.4, 26.0, 25.9, 22.9, 20.5, 18.9, 18.2, 18.0, 16.7, 12.6, −3.8, −4.4, −4.5, −4.9. Anal. Calcd for $C_{38}H_{70}O_4Si_2$: C: 70.53; H: 10.90. Found: C: 70.16; H: 10.83.

(1*S*,3*R*,20*S*)-20-(3-Hydroxy-3-methylbuthyloxy)pregna-5,7-dien-1,3-diol (34). To a stirred solution of TBAF in THF (1.0 M solution, 66.0 kg, 73.08 mmol) was added **12** (8.4 kg, 12.98 mol) at 20 °C, and the mixture was heated at 66 °C for 9 h. After cooling to 25 °C, the mixture was diluted with H_2O (378 L) at 20 °C with stirring. After stirring for 1.5 h at the same temperature, crude **34** was separated as a light-yellow crystalline solid and was again dissolved in acetone (45 L) at 30 °C and cooled at −18 °C for 1 h to leave a crystalline material. Centrifugal collection gave the triol **34** as colorless crystals (4.1 kg, 75.5%) after drying at 35 °C: mp 185 °C; $[\alpha]_D^{20}$ −38.0° (*c* 1.00, EtOH); IR (KBr, cm^{-1}): ν 3458, 3371, 2972, 2875, 1464, 1369, 1146, 1049, 941, 825, 771; ^{1}H NMR ($CDCl_3$): δ 5.71 (1H, dd, $J = 1.6$, 5.3), 5.38 (1H, dd, $J = 2.6$, 5.5), 4.05 (1H, m), 3.85 (1H, m), 3.76 (1H, br s), 3.49 (1H, m), 3.27 (1H, m), 2.73 (1H, m), 2.54 (1H, m), 2.34 (1H, m), 2.13 (1H, m), 1.26 (3H, s), 1.23 (3H, s), 1.20 (3H, d, $J = 6.3$), 0.91 (3H, s), 0.61 (3H, s); ^{13}C NMR ($CDCl_3$+ 5% DMSO-d_6): δ 140.2, 136.9, 120.9, 115.2, 78.6, 71.9, 70.1, 65.2, 64.4, 56.2, 54.1, 41.9, 41.7, 41.3, 39.8, 38.3, 38.0, 37.3, 29.0, 28.8, 26.0, 22.6, 20.0, 18.6, 15.9, 12.2; Anal. Calcd for $C_{26}H_{42}O_4$: C, 74.60; H, 10.11. Found: C, 74.36; H, 9.93.

(+)-(5*Z*,7*E*)-(1*S*,3*R*,20*S*)-20-(3-Hydroxy-3-methylbutyloxy)-9,10-secopregna-5,7,10(19)triene-1,3-diol (1). A stirred solution of the triol **34** (100 g, 0.239 mmol) in THF (2.5 L) was irradiated at 10 °C for 420 min in a quartz apparatus equipped with a high-pressure mercury lamp (1 kW). After evaporation of the solvent under reduced pressure, the residue was triturated in acetone (0.25 L) to separate out the unreacted triol **34** (43.0 g, 0.103 mmol) as crystals, which were recovered by filtration. The filtrate containing the photoproduct was evaporated under reduced pressure, and the residue was purified by preparative HPLC (AcOEt: hexane = 85:15) to give the pre-triene **35**. The pre-triene **35** was dissolved in THF (0.4 L), and the solution was stirred at 25 °C for 85 h. After evaporation of the solvent under reduced pressure, the residue was purified by HPLC (AcOEt: hexane = 85:15) to leave a colorless oil **1** which was crystallized from hexane and AcOEt to give maxacalcitol (**1**) as colorless crystals (16.0 g, 16.0%): mp 122 °C; $[\alpha]_D^{20}$ +49.4° (*c* 1.00, EtOH); FT-IR (KBr, cm^{-1}): ν 3350, 3344, 3332, 2966, 2926, 2872, 2846, 1635, 1471, 1433, 1431, 1377, 1367, 1329, 1221, 1146, 1092, 1057, 1012, 957, 908, 899, 879, 800, 752; ^{1}H NMR ($CDCl_3$): δ 6.35 (1H, d, $J = 11.2$), 6.02 (1H, d, $J = 11.2$), 5.32 (1H, s), 4.98 (1H, s), 4.42 (1H, m), 4.22 (1H, m), 3.85 (1H, m), 3.47 (1H, m), 3.26 (1H, m), 2.82 (1H, dd, $J = 0.3$, 12.9), 2.58 (1H, dd, $J = 3.6$, 7.0), 2.30 (1H, dd, $J =7.3$, 13.2), 1.82−2.20 (8H, m), 1.63−1.75 (4H, m), 1.46−1.52 (4H, m), 1.18−1.32 (10H, m), 0.53 (3H, s); ^{13}C NMR ($CDCl_3$): δ 147.6, 142.1, 133.4, 124.6, 117.5, 111.8, 78.7, 70.7, 70.6, 66.7, 65.5, 57.0, 56.0, 45.2, 44.7, 42.8, 41.4, 39.5, 29.2, 29.1, 28.9, 25.5, 23.2, 22.2, 18.8, 12.6; UV (EtOH): λ_{max} 263 nm.

Original Synthesis of 1-Bromomethyl-2,2-dimethyloxirane (24). To a stirred solution of commercial (purity >95%) 1-bromo-3-methyl-2-butene **22** (100 g, 0.671 mol) in CH_2Cl_2 (2 L) was slowly added mCPBA (80−85%, 200 g, 0.93−0.99 mol) at room temperature. The reaction mixture was stirred for 2 h, and the resulting solid was removed by filtration. An aqueous 5% $Na_2S_2O_4$ solution (1 L) was added to the filtrate and stirred for 1 h. The CH_2Cl_2 layer was then separated, washed with saturated aqueous $NaHCO_3$ (2 L × 2) and brine (2 L), and dried over $MgSO_4$. After evaporation of the solvent, the remaining liquid was distilled to afford epoxy bromide **24** (88.6 g, 80.0%) as a colorless oil.

Industrial Synthesis of 1-Bromomethyl-2,2-dimethyloxirane (24). To a stirred solution of aqueous KOH (2.9 kg in H_2O 10 L) was slowly added bromine (2.8 kg, 17.42 mol) at 5 °C. The mixture was stirred for 15 min at the same temperature, and then to this solution was added 2-methyl 3-buten-2-ol **32** (1.0 kg, 11.61 mol) at 10 °C and stirred for 20 h. The mixture was diluted with hexane (5 L) at the same temperature; the organic layer was separated and evaporated under reduced pressure and distilled to afford epoxy bromide **24** (1.6 kg, 82.0%) as a colorless oil: bp 52 °C/25 mmHg; FT-IR (KBr, cm^{-1}): ν 2966, 2929, 1456, 1435, 1412, 1381, 1319, 1252, 1221, 1130, 1022, 922, 885, 843, 742, 685, 652, 496, 436, 432, 409; ^{1}H NMR ($CDCl_3$): δ 3.48 (1H, dd, $J =$ 10.4, 6.0), 3.23 (1H, dd, $J = 10.4$, 7.0), 3.05 (1H, dd, $J =$ 7.5, 6.0), 1.33 (3H, s), 1.29 (3H, s); ^{13}C NMR ($CDCl_3$): δ 62.1, 60.5, 29.8, 24.3, 18.1.

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