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REGIOSELECTIVE CLEAVAGE OF TRISUBSTITUTED EPOXY-LINKAGE USING LITHIUM TRIALKYLBOROHYDRIDE REAGENTS: A NEW ROUTE TO THE KEY INTERMEDIATE OF MAXACALCITOL

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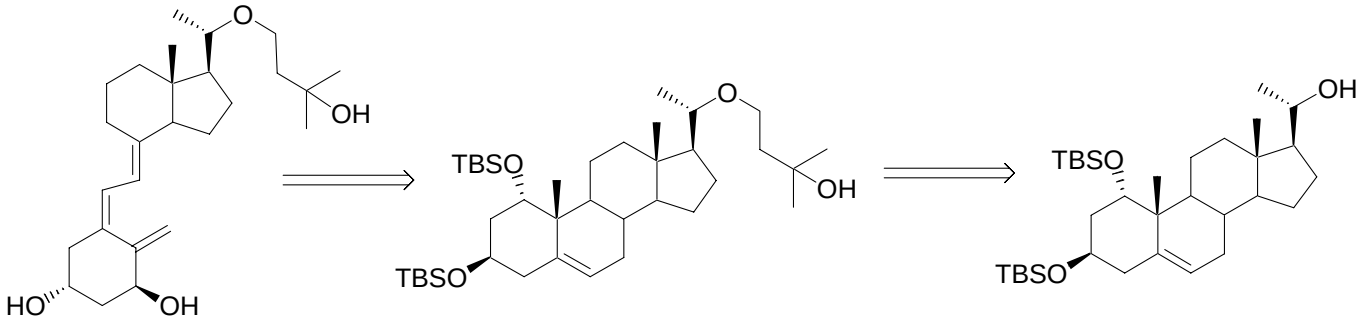
Abstract – Optimal conditions for the reductive cleavage of a trisubstituted epoxide leading regioselectively to the key intermediate tertiary alcohol of Maxacalcitol, used for the treatment of secondary hyperparathyroidism and psoriasis, have been established using lithium tri(*sec*-butyl)borohydride (L-Selectride) in THF.

INTRODUCTION

Maxacalcitol (**1**) is the C-22 oxygen analogue of 1α,25-dihydroxyvitamin D_3 and marketed for the treatment of secondary hyperparathyroidism and psoriasis.[1,2] It has so far been prepared[1,3] from the steroidal secondary alcohol (**3**) via the tertiary alcohol (**2**) (Scheme 1). Although the conversion of the intermediate (**2**) to Maxacalcitol (**1**) may be carried out in exactly the same way that established in the synthesis[4] of 1α,25-dihydroxyvitamin D_3, the acquisition of the key intermediate (**2**), which requires a three-step sequence involving a capricious Michael addition step and two cerium-mediated Grignard addition steps, produces a substantial amount of environmentally undesirable cerium by-product.[3,5] We have been, therefore, seeking the development of an alternative procedure executing the acquisition of the tertiary alcohol (**2**) in a much more facile way without formation of undesirable by-product. Here, we wish to report a convenient method for the preparation of the key tertiary alcohol (**2**) starting from the same secondary alcohol (**3**) in a one-pot sequence involving the Williamson ether synthesis and

L-Selectride-mediated regioselective cleavage of the epoxy-linkage of the transient epoxide intermediate (**6**).[5]

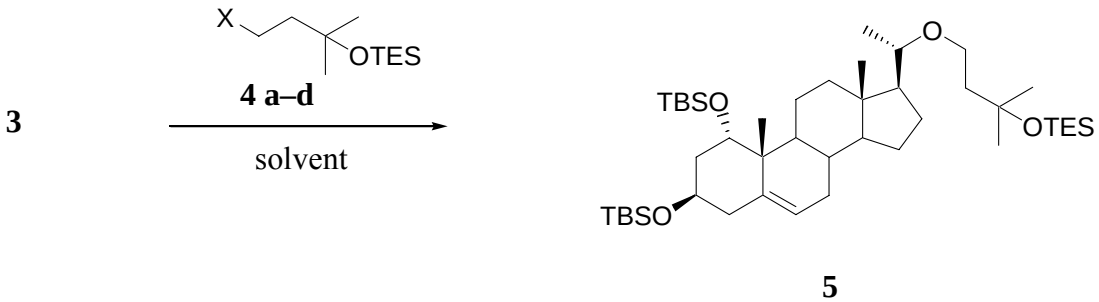


Maxacalcitol **1** **2** **3**

Scheme 1

RESULTS AND DISCUSSION

In order to obtain the key intermediate (**2**) in a straightforward way, we first attempted direct alkylation of the secondary alcohol (**3**) with primary halides **(4a,b**) and sulfates (**4c,d**) under basic conditions employed in the typical Williamson synthesis[6] to yield the silyl ether (**5**), a protected form of the key intermediate (**2**) (Scheme 2). However, the reaction did not proceed at all under the conditions and the starting alcohol (**3**) remained unchanged (Table 1).



5

Scheme 2

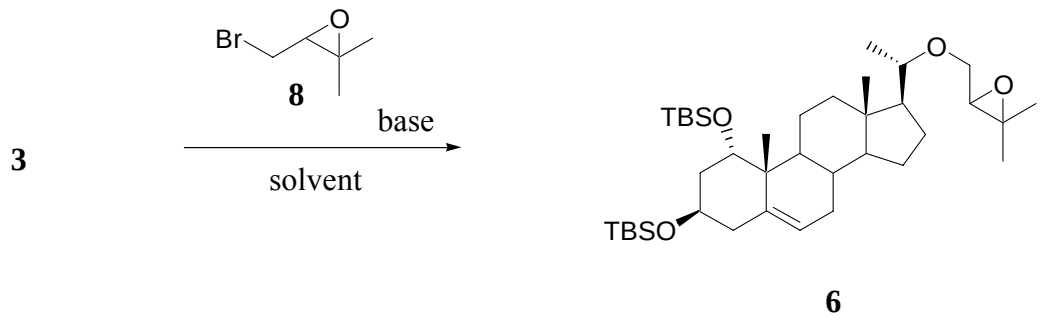
Since the desired Williamson reaction between the alcohol (**3**) and each of the alkylating agents (**4a~d**) was presumed to be suppressed by steric hindrance both of the electrophile and the nucleophile, we next chose β,γ-epoxy bromide[7] (**8**) as the alkylating agent as it seemed to be not only sterically less hindered, but also more reactive than the above-mentioned alkylating agents (**4a~d**) owing to its similarity to prenyl

bromide which was found to give the ether without difficulty on reaction with **3** under basic conditions[5] (Scheme 3).

Table 1: Reaction of the Alcohol (3) with Alkylating Agents (4)

Entry	**4 :** (equiv.)	Base (equiv.)	Solvent	Temp. (ºC): Time (h)	Product (**5**)
1	a: X=Br: (2.0)	NaH (1.5)	Xylene	reflux : 6	n.d.[a)]
2	a: X=Br: (10.0)	NaH (6.0)	DMF	65~110 : 6	n.d.
3	b: X=I: (10.0)	NaH (1.5)	THF	50 : 4	n.d.
4	c: X=Ms: (10.0)	NaH (1.5)	THF	50 : 4	n.d.
5	d: X=Ts: (10.0)	NaH (1.5)	THF	50 : 4	n.d.

a) not detected.



Scheme 3

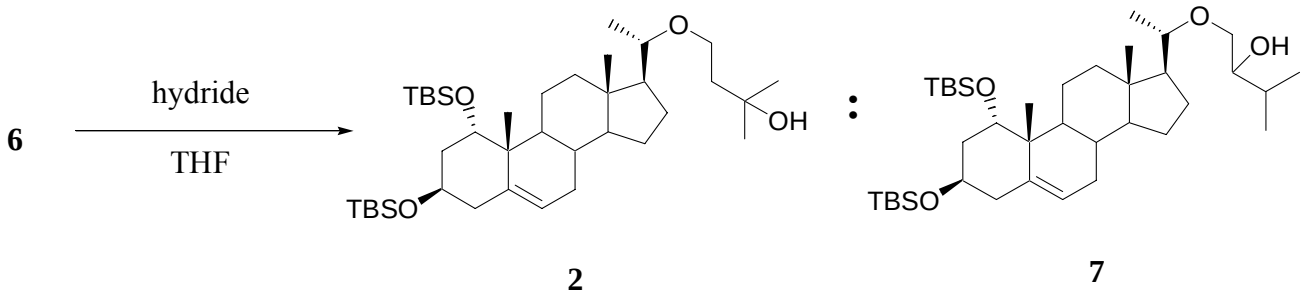
Table 2: Reaction of the Alcohol (3) with the Bromide (8)

Entry	**8** (equiv.)	Base (equiv.)	Solvent	Temp. (ºC): Time (h)	Product (**6**) (%)
1	6.8	*t*-BuOK (6.0)	THF	rt : 17	63
2	6.8	*t*-BuOK (6.0)	THF	50 : 2	42
3	1.3	NaH (1.5)	DMF	80 : 5	15
4	12.0	NaH (3.0)	DMF	80 : 5	45
5	2.0	NaH (3.0)	THF	50 : 4	88

Although few, there are actually some precedents[8,9] that suggested pronounced reactivity and regioselectivity of the β, γ-epoxy bromide (**8**) in the Williamson ether synthesis. Encouraged by these precedents, we examined the reaction between the secondary alcohol (**3**) and the bromide (**8**) and have found that the reaction proceeded in an expected way to give the desired epoxy ether (**6**). As appeared from Table 2, the reaction was strongly affected by the conditions. Thus, the ether (**6**) was formed in a satisfactory yield when the reaction was carried out in warm THF in the presence of a three-fold excess of

sodium hydride (Table 2: Entry 5). The reaction, however, furnished the ether (**6**) in a much lower yield when potassium *tert*-butoxide in place of sodium hydride (Table 2: Entries 1 and 2) or DMF in place of THF was used (Table 2: Entries 3 and 4).

Having established the optimal conditions to yield the ether (**6**), we then sought the optimal conditions for the reductive cleavage of its epoxy-linkage to generate the tertiary alcohol (**2**) in a regioselective manner (Scheme 4). We first chose sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al)[10] as its regiocontrol ability in the reductive cleavage of 2, 3-epoxy alcohols giving rise to the corresponding 1,3-diols has been well established.[11] However, the reaction of the epoxide (**6**) with this reducing agent in THF did not proceed either at rt or at the refluxing temperature leaving the starting material unchanged (Table 3: Entries 1 and 2).



2 **7**

Scheme 4

Table 3: Reaction of the Epoxide (6) with Aluminum Hydrides in THF

Entry	Hydride (equiv.)	Temp. (ºC): Time (h)	Conversion[a] (%)	Ratio[a] (%) **2**	Ratio[a] (%) **7**
1	Red-Al[b] : (5.0)	rt : 19	0	—	—
2	Red-Al: (5.0)	reflux : 6.5	0	—	—
3	$LiAlH_4$: (3.0)	rt : 4	94	92.6	7.4
4	$LiAlH_4$: (3.0)	60 : 4	100	75.3	24.7
5	$LiAlH_4$: (10.0)	rt : 4	100	62.9	37.1
6	*i*-Bu_2AlH : (5.0)	rt : 2	72	15.4	84.6
7	*i*-Bu_2AlH : (10.0)	rt : 8	89	42.3	57.7

a) determined by HPLC. b) sodium bis(2-methoxyethoxy)aluminum hydride.

Regioselective cleavage of the epoxy-linkage of 2,3-epoxybutyl ether derivatives using lithium aluminum hydride has been reported.[8,9] However, the outcome was embarrassing since one gave the 2-hydroxy ether[8] and the other gave the 3-hydroxy ether.[9] When our epoxide (**6**) was treated with 3 molar excess of

lithium aluminum hydride in THF at rt, the cleavage reaction occurred in 94% conversion to give the desired tertiary alcohol (**2**) and its regio-isomer (**7**) in a ratio of 92.6:7.4 (Table 3: Entry 3). When the same reaction was carried out at 60 ºC, a mixture of the alcohols (**2)** and (**7)** was generated in a ratio of 75.3:24.7 though the reaction proceeded to completion (Table 3: Entry 4). Use of 10 molar excess of the reducing agent brought about completion of the reaction at rt, but the ratio of the alcohols (**2)** and (**7)** was 62.9:37.1 (Table 3: Entry 5). The reductive cleavage also occurred with a stronger Lewis acidic diisobutylaluminum hydride,[9] but the ratio of the alcohols（**2**） and (**7)** were 15.4:84.6 in 72% conversion with a five-fold excess of the hydride and 42.3:57.7 in 89% conversion with a ten-fold excess of the hydride, respectively (Table 3: Entries 6 and 7). Based on the observation, we concluded that the aluminum hydride reagents are inappropriate for the present purpose with respect to the regioselectivity.

To control the regioselectivity in the desired way, reductive cleavage of the epoxide (**6**) with borohydride reagents[10] were next examined. As appeared from Table 4, both sodium borohydride and sodium cyanoborohydride[10] in THF were completely inactive (Table 4: Entries 1 and 2). Lithium borohydride[10] generated a mixture of the cleavage products (**2)** and (**7)**, but in a trace amount (Table 4: Entry 5). A combination of sodium cyanoborohydride and a Lewis acid promoted reductive cleavage, but in overwhelmed generation of the undesired secondary alcohol (**7**) (Table 4: Entries 3 and 4).

During the investigation, we encountered an interesting report by Majetich and co-workers[12] that reported the cleavage of aryl methyl ether functionality by using lithium triethylborohydride (Super Hydride). In this paper, it was noted that a substrate carrying epoxy functionality could not be used owing to a concurrent cleavage of the epoxy linkage at the less substituted site. We, therefore, subjected our epoxide (**6**) to the reaction with Super Hydride as well as with its higher alkyl analogue lithium tri-(*sec*-butyl)borohydride (L-Selectride) [10,13] with the expectation to allow regioselective cleavage at the less substituted center to give the tertiary alcohol (**2**). As desired, both of the reagents allowed regioselective cleavage to give the tertiary alcohol (**2**) in excellent yield, respectively. Thus, on reaction with a five molar excess amount of Super Hydride, the epoxide (**6**) afforded the tertiary alcohol (**2**) in more than 98% yield with less than 2% yield of the secondary alcohol (**7**) in complete conversion at rt (Table 4: Entry 6). The same reaction with L-Selectride carrying bulkier alkyl functionalities proceeded in a better way than Super Hydride, to allow complete conversion of the starting epoxide (**6**) into the tertiary alcohol (**2**) in more than 99% yield with less than 1% of the secondary alcohol (**7**) (Table 4: Entry 10). It was also found that the cleavage reaction occurred excellently in a desired selectivity with lithium 9-borabicyclo[3.3.1]nonylborohydride[9] (Table 4: Entry 9). In contrast to these lithium alkylborohydride reagents, the reaction of the epoxide (**6**) with K-Selectride, the potassium analogue of L-Selectride (Table 4: Entries 11 and 12) and triaryl analogues (Table 4: Entries 7 and 8) proceeded in a less satisfactory way with incomplete conversion. It was suggested that the lithium ion played a critical role in the reactivity as

the addition of an excess lithium salt, in particular, lithium iodide, improved the reaction dramatically (Table 4: Entries 11 - 15).

Table 4: Reaction of the Epoxide (6) with Borohydrides in THF

Entry	Hydride : (equiv.)	Temp. (ºC) : Time (h)	Conversion[a] (%)	Ratio[a] (%) **2**	Ratio[a] (%) **7**
1	$NaBH_4$: (10.0)	reflux : 5	5	n.d.[b]	n.d.
2	$NaBH_3CN$: (5.0)	reflux : 4	0	—	—
3	$NaBH_3CN$: (10.0) BF_3-Et_2O[d] : (2.0)	rt : 18	66	n.d.	28[c]
4	$NaBH_3CN$: (10.0) $AlCl_3$[d] : (1.0)	rt : 3.5	73	n.d.	42[c]
5	$LiBH_4$: (10.0)	rt : 17	3	n.d.	n.d.
6	$LiEt_3BH$[e]: (5.0)	rt : 3	100	98.2	1.8
7	$LiPh_3BH$: (10.0)	reflux : 7	7	n.d.	n.d.
8	KPy_3BH[f]: (10.0)	rt : 18	0	n.d.	n.d.
9	$LiBBNH_2$[g]: (10.0)	rt : 27	100	98.3	1.7
10	L*i*s-Bu_3BH[h]: (5.0)	rt : 2.5	100	99.7	0.3
11	K*s*-Bu_3BH[i]: (10.0)	reflux : 8	4	n.d.	n.d.
12	K*s*-Bu_3BH : (10.0) LiH[d] : (10.0)	rt : 23	33	n.d.	n.d.
13	K*s*-Bu_3BH: (10.0) LiI[d] : (20.0)	rt : 23	100	99.4	0.6
14	L*i*s-Am_3BH[j] : (10.0)	rt : 24	50	n.d.	n.d.
15	K*s*-Am_3BH[k] : (10.0)	rt : 18	0	—	—

a) determined by HPLC. b) not determined. c) isolated yield. d) additive. e) Super Hydride.

f) K (*N*-3, 5-dimethylpyrazolyl)$_3$borohydride. g) Li 9-borabicyclo[3.3.1]nonyl hydride. h) L-Selectride.

i) K-Selectride. j) LS-Selectride. k) KS-Selectride.

In practice, the reductive cleavage of the epoxide (**6**) was carried out using L-Selectride in a sequential way after the above-mentioned alkylation step in the same vessel starting from the secondary alcohol (**3**). Thus, the secondary alcohol (**3**) was first treated with 2, 3-epoxy-3-methylbutyl bromide (**8**) in THF in the presence of sodium hydride to form the ether (**6**). Without isolation of the product, the reaction mixture

was next treated with L-Selectride in the same vessel to give the tertiary alcohol (**2**), regioselectively. This procedure allowed the production of the tertiary alcohol (**2**) in pure state at a 97.3% yield for a 2 Kg scale. The unwanted contamination of the secondary alcohol (**7**) was removed during the isolation stage.

CONCLUSION

An alternative route to the key intermediate (**2**) of Maxcalcitol (**1**) from the steroidal alcohol (**3**) has been established. The synthesis may be carried out in the same vessel in a preparative scale without formation of undesirable by-product through a sequential etherification and regioselective cleavage of the epoxy linkage.

EXPERIMENTAL

The melting points were determined on a hot-stage and are uncorrected. IR spectra were recorded on a JEOL JIR-6000 spectrophotometer. ^{1}H NMR (270 MHz) and ^{13}C NMR (67.8 MHz) spectra were recorded in $CDCl_3$ on a JEOL EX-270 spectrometer. Product ratio was determined on a Shimadzu LC-6A instrument.

(1*S*,3*R*,20*S*)-1,3-Bis(*tert*-butyldimethylsilyloxy)-20-(2,3-epoxy-3-methylbutyloxy)pregn–5-ene (6): To a stirred solution of the secondary alcohol (**3)** (0.5 g, 0.89 mmol) in THF (5 mL) was added NaH (assay 60%, 0.11 g, 2.67 mmol) portionwise at rt. After the evolution of hydrogen, to the resulting suspension was added the bromide (**8)** (0.29 g, 1.78 mmol) dropwise at the same temperature with stirring and the mixture was kept stirring at 50 °C for 4 h. The mixture was then cooled to 0 °C and treated with brine (10 mL). The mixture was extracted with AcOEt (20 mL) and the extract was dried over $MgSO_4$, evaporated, and chromatographed (silica gel, hexane:AcOEt = 20:1) to give a diastereomeric mixture of the epoxy ether (**6**) (0.51 g, 88.0%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.45 (1H, d, *J* = 5.6 Hz), 4.02 - 3.94 (1H, m), 3.77 (1H, br s), 3.68-3.63 (1H, m), 3.45-3.37 (1H, m), 3.33 -3.23 (1H, m), 2.93 - 2.89 (1H, m), 2.29 - 2.19 (2H, m), 1.33 (3H, m), 1.29 - 1.28 (3H, m), 1.20 - 1.15 (3H, m), 0.95 (3H, s), 0.88 (18H, s), 0.67-0.66 (3H, m), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.02 (3H, s). ^{13}C NMR ($CDCl_3$): δ 138.3, 123.2, 78.7, 73.5, 67.5, 67.1, 66.7, 62.6, 62.3, 58.0, 57.6, 56.9, 56.8, 56.7, 42.3, 42.2, 41.4, 41.0, 38.9, 38.8, 31.8, 31.5, 26.2, 25.9, 24.7, 24.2, 20.3, 19.3, 19.1, 18.8, 18.7, 18.1, 18.0, 12.5, -3.8, -4.4, -4.5, -5.3.

Reductive cleavage of the epoxide (6) with lithium aluminum hydride: To a solution of the epoxy ether (**6)** (100 mg, 0.16 mmol) in THF (2 mL) was added lithium aluminum hydride (61 mg, 1.6 mol) at rt and the stirring was continued for 8 h at the same temperature. The mixture, after cooling to 0 °C, was treated with brine (2 mL) and extracted with AcOEt (25 mL). The extract was dried over $MgSO_4$ and evaporated to give a mixture the tertiary alcohol (**2**) and the secondary alcohol (**7**), (**2**:**7** = 62.9:37.1 by

HPLC). The product was separated by column chromatography (SiO_2, elution with hexane and AcOEt 9:1) to give the tertiary alcohol (**2**) as crystals and a diastereomeric mixture of the secondary alcohol (**7**) as an oil: (1*S*,3*R*,20*S*)-1, 3-bis(*tert*-butyldimethylsilyloxy)-20-(3-hydroxy-3-methylbutyloxy)pregn-5-ene (**2**): mp 134 ºC, $[\alpha]_D^{20}$ +25.1° (c 1.00, $CHCl_3$). IR (KBr): ν 3540, 2960, 1464, 1382, 1258, 1150, 1090, 972, 886, 872, 838, 812, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.45 (1H, d, *J*=5.6 Hz), 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-(2-hydroxy-3-methylbutyloxy)pregn–5-ene (**7**): ^1H NMR ($CDCl_3$): δ 5.45 (1H, d, *J*=5.6 Hz), 4.02-3.94 (1H, m), 3.76 (1H, br s), 3.69-3.65 (0.5H, m), 3.44-3.29 (3H, m), 3.11-3.05 (0.5H, m), 2.29-2.21 (2H, m), 1.19-1.16 (3H, m), 0.98 (3H, s), 0.96 (3H, s), 0.91 (3H, s), 0.88 (18H, s), 0.66 (3H, s), 0.07 (3H, s), 0.05 (3H, s), 0.04 (3H, s), 0.02 (3H, s). ^{13}C NMR ($CDCl_3$): δ 138.3, 123.2, 78.9, 78.1, 75.6, 75.1, 73.6, 70.7, 70.0, 67.5, 57.1, 56.9, 56.8, 42.3, 42.2, 41.4, 41.0, 38.9, 38.8, 31.8, 31.6, 30.9, 26.2, 26.1, 25.9, 24.2, 20.3, 19.3, 19.2, 19.1, 18.7, 18.4, 18.3, 18.1, 18.0, 12.6, -3.7, -4.4, -4.5, -5.2.

One-pot preparation of (1*S*,3*R*,20*S*)-1, 3-bis(*tert*-butyldimethylsilyloxy)-20-(3-hydroxy-3-methylbutyloxy)pregn-5-ene (2) from the secondary alcohol (3): To a stirred solution of the secondary alcohol (**3**) (2.0 Kg, 3.35 mol) in THF (8 L) was added NaH (95% purity, 179.5 g, 7.11 mol) portionwise at rt in an appropriate rate to control an evolution of hydrogen. To this stirred solution, after the evolution of the hydrogen, was added the bromide (**8**) (762 g, 4.62 mol) dropwise at the same temperature and the mixture was refluxed for 3 h. After cooling to room temperature, to this mixture containing the epoxy ether (**6**) was added L-Selectride (1 M in THF, 9.9 L, 9.9 mol) dropwise and the mixture was refluxed for 3 h. The mixture was then cooled to –10 ºC and 3M NaOH (8 L) and 35% H_2O_2 (10 L) were added sequentially, the mixture was stirred for 2 h at rt. The remaining hydrogen peroxide was decomposed by addition of aqueous $Na_2S_2O_3$ (7 Kg in 20 L) and the mixture was extracted with AcOEt (8 L) after stirring for 1 h at rt. The extract was washed sequentially with saturated aqueous $NaHCO_3$ (6 L) and brine (2 x 6 L) and evaporated under reduced pressure to leave a colorless solid. The residue was dissolved in refluxing methanol (14 L) and the solution, after cooling to 25 ºC was diluted with water (6 L) with stirring to separate out crystals. After cooling at –5 ºC for 1 h, the crystalline material was collected using a centrifuge and dried at 50 ºC to give the tertiary alcohol (**2**) (2.1 Kg, 97.3%) as colorless granules. Physical and spectroscopic data were identical with those of an authentic material.[3]

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