HETEROCYCLES, Vol. 81, No. 2, 2009, pp. 381 - 394. © The Japan Institute of Heterocyclic Chemistry
Received, 5th November, 2009, Accepted, 3rd December, 2009, Published online, 4th December, 2009
DOI: 10.3987/COM-09-11871

# SYNTHESIS OF 20-EPI-ELDECALCITOL [20-EPI-1α,25-DIHYDROXY-2β-(3-HYDROXYPROPOXY)VITAMIN $D_3$: 20-EPI-ED-71][*1,2]

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**Abstract** – A convergent synthesis of biologically interesting 20-epi-eldecalcitol which possesses an inverted C-21 methyl substituent at the 20-position of the side chain of 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin $D_3$ (eldecalcitol) is described.

## INTRODUCTION

There is intense interest in obtaining analogs more potent than calcitriol [1α,25-dihydroxyvitamin $D_3$, (**1**)] in terms of regulatory effects on calcium and phosphorus metabolism with the objective of treating bone diseases such as osteoporosis.[3] Eldecalcitol [1α,25-dihydroxy-2β-(3-hydroxylpropoxy)vitamin $D_3$, developing code; ED-71, (**2**)], an analog of calcitriol (**1**) from which a hydroxypropoxy substituent at the 2β-position of the A-ring is appended, is such an analog that shows potent effects on bone therapy.[4-6] Recent completion of phase III clinical trials of **2** for bone fracture prevention produced excellent results. Eldecalcitol (**2**) is now in preparation for approval as a promising medicine for the treatment of osteoporosis in Japan.

To explore structure-biological activity relationships between eldecalcitol (**2**) and related analogs, we have already synthesized 1-epi-eldecalcitol,[7] 3-epi-eldecalcitol,[8] and 1,3-diepi-eldecalcitol[9] with inherent biological interest of each targeted analogs and evaluated their biological responses. It has been reported that 20-epi-calcitriol (**3**), a diastereomer of calcitriol (**1**), which possesses an inverted C-21

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[*]*This paper is dedicated to Professor Hector F. DeLuca of the University of Wisconsin-Madison on the occasion of his 80th birthday.*

methyl substituent at the 20-position of the side chain, shows remarkably enhanced biological activities compared to parent compound, **1**.[10] For example, 20-epi-calcitriol (**3**) exhibits 18 times the potency of induction of human myeloid leukemia cell (HL-60) differentiation.[11] Furthermore **3** shows 50 times the inhibition of the human histiocytic lymphoma cell (U937) proliferation,[12] and 4.5 times the increase in osteocalcin concentration in the human osteosarcoma cell (MG-63)[13] compared to **1**. These findings prompted our interest in analogs of eldecalcitol (**2**) epimerized at the 20-position and its biological resoponses. In this paper, we describe the synthesis of 20-epi-eldecalcitol (**4**) as a continuation of our modification studies on eldecalcitol (**2**) and preliminary biological evaluation using HL-60, U937, and MG-63 compared to **2** (Figure 1).

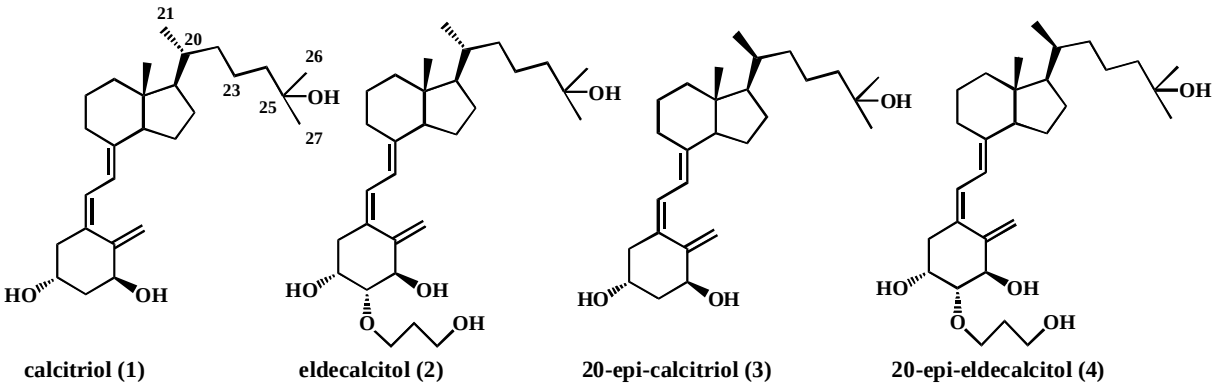
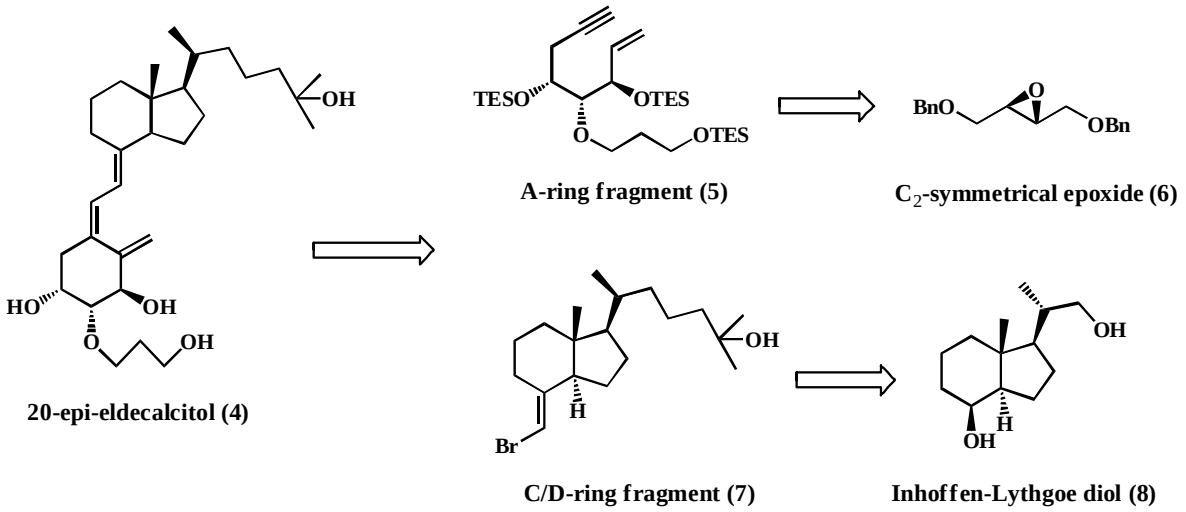



**Figure 1. Structures of calcitriol, eldecalcitol, 20-epi-calcitriol, and 20-epi-eldecalcitol**

## RESULTS AND DISCUSSION

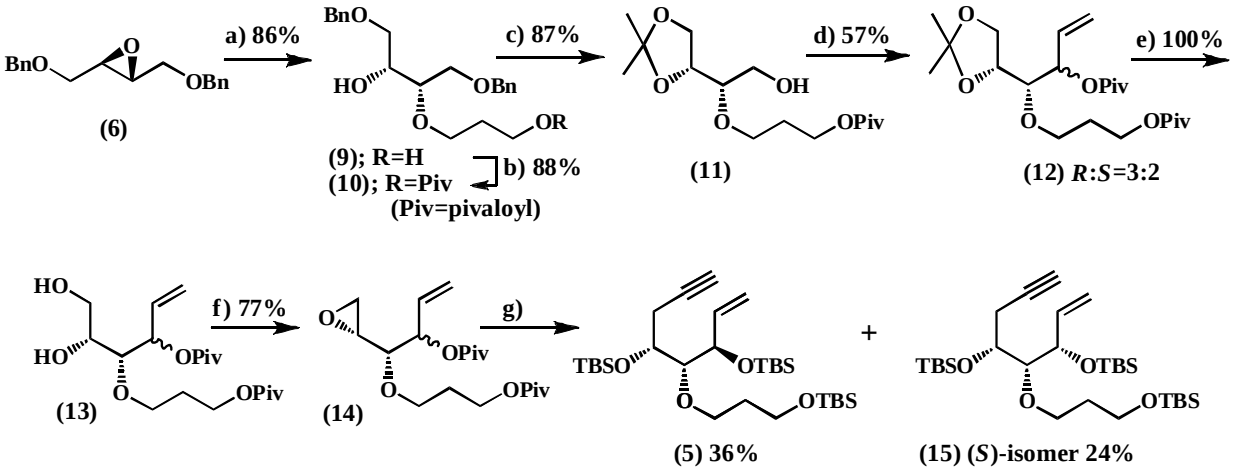
Our synthesis of 20-epi-eldecalcitol (**4**) was envisioned using the Trost coupling reaction of A-ring fragment **5** derived from $C_2$-symmetrical epoxide **6** with C/D-ring fragment **7**. Fragment **7** can be obtained from the Inhoffen-Lythgoe diol (**8**) *via* a known protocol (Scheme 1).[14,15]

The required A-ring fragment **5** for the synthesis of 20-epi-eldecalcitol (**4**) was synthesized based upon the methodology that has been previously established by our group.[16] Thus, cleavage of the known $C_2$-symmetrical epoxide **6**[17] with 1,3-propanediol [$HO(CH_2)_3OH$] in the presence of potassium *tert*-butoxide (*t*-BuOK) gave diol **9** in 86% yield. After protection of the primary hydroxyl group in **9** to give pivalate **10** in 88% yield, cleavage of the benzyl ether moiety in **10** and subsequent protection of the resulting 1,2-diol as the acetonide gave alcohol **11** in 87% overall yield. Swern oxidation of **11** and subsequent Grignard reaction of the resulting aldehyde with vinylmagnesium bromide ($CH_2$=CHMgBr) followed by pivaloylation of the resulting alcohol afforded the dipivalate **12** as an epimeric mixture (*R/S* = 3/2) in 57% yield. Without separation of the epimeric mixture, the acetonide moiety in **12** was



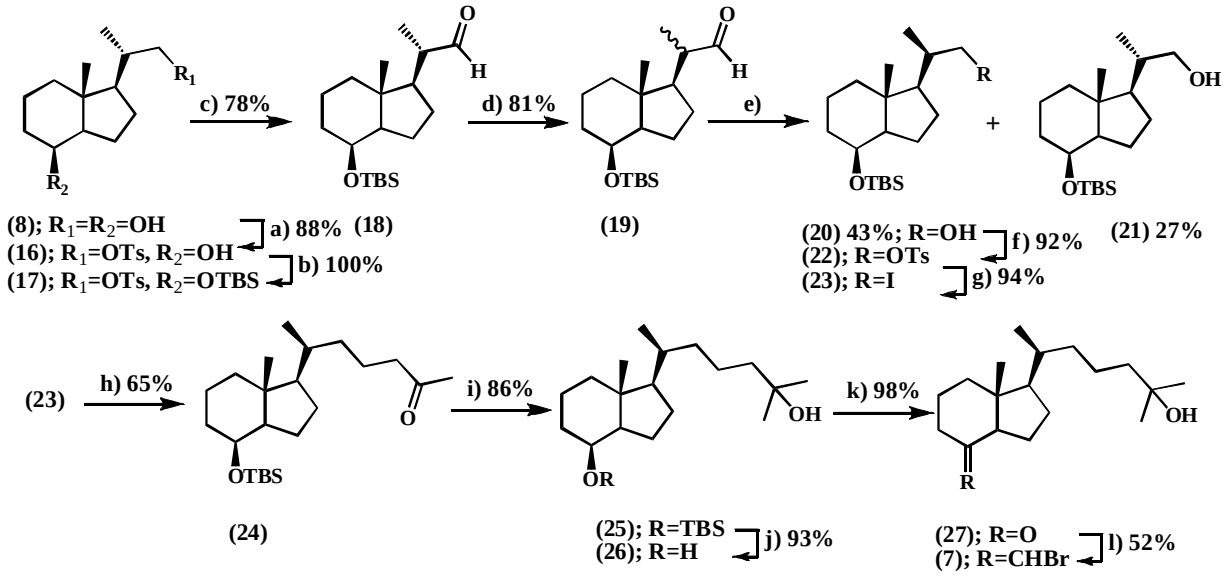

**Scheme 1. Retrosynthesis of 20-epi-eldecalcitol (4).**

cleaved quantitatively to give diol **13**. Exposure of **13** to Mitsunobu conditions[18] afforded epoxide **14** in 77% yield. The acetylene unit was successfully installed by the regioselective epoxide-opening of **14** with lithium trimethylsilylacetylide (LiC≡CTMS) in the presence of boron trifluoride diethyl etherate ($BF_3$-$OEt_2$) at -78 °C to provide ene-yne **5** as the A-ring fragment of 20-epi-eldecalcitol (**4**) in 36% yield after protecting group exchange from pivalate to *tert*-butyldimethylsilyl (TBS) ether. The accompanied (*S*)-ismoer **15**, which consists of the requisite stereochemistry to obtain 1-epi-eldecalcitol, was separated in 24% yield by simple column chromatography (Scheme 2).




**Scheme 2. Synthesis of A-ring fragment 5.** Reagents and conditions: a) $HO(CH_2)_3OH$, *t*-BuOK, 120 °C. b) *t*-BuCOCl, pyridine, $CH_2Cl_2$, rt. c) 1) $H_2$, $Pd(OH)_2$, MeOH, rt. 2) $Me_2(OMe)_2$, TsOH, rt. d) 1) DMSO, $(COCl)_2$, $CH_2Cl_2$ -60 °C. 2) $CH_2$=CHMgBr, THF -60 °C. 3) *t*-BuCOCl, $Et_3N$, DMAP, $CH_2Cl_2$, rt. e) 1M HCL MeOH, rt. f) $Ph_3P$, DEAD, benzene, reflux. g) 1) LiC≡CTMS, $BF_3$-$OEt_2$, THF, -78 °C. 2) 10N NaOH, MeOH, rt. 3) TBSOTf, $Et_3N$, $CH_2Cl_2$ 0 °C.

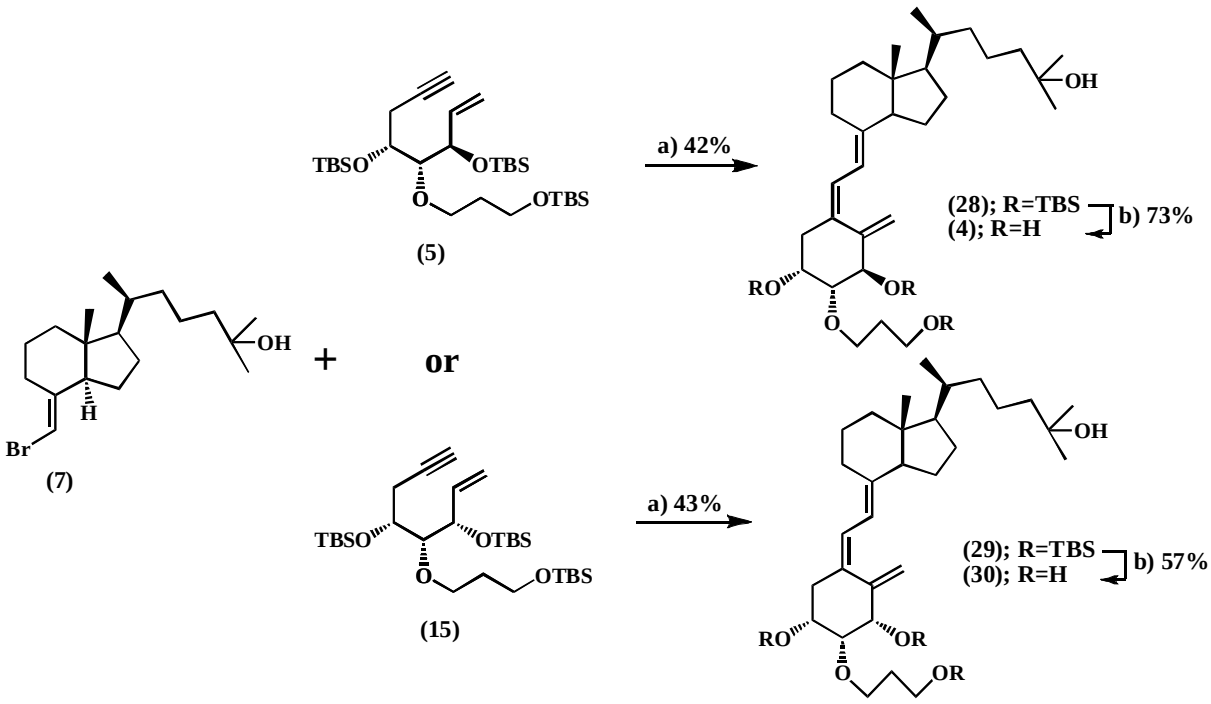
Next, we performed the synthesis of C/D-ring fragment **7**. Based on the reported route[19] to **7** from the Inhoffen-Lythgoe diol (**8**), which is obtained *via* ozonolysis of vitamin $D_2$,[20] we developed a convenient approach for the facile introduction of the C-23 – C-27 side chain fragment. Thus, after tosylation of the primary hydroxyl group in **8**, the secondary hydroxyl moiety in **16** was protected as its TBS ether to give **17** in 88% overall yield from **8**. Oxidation of **17** using dimethyl sulfoxide (DMSO) and *s*-collidine afforded aldehyde **18** in 78% yield. Aldehyde **18** was then subjected to the epimerization conditions to give an approximately 3:2 mixture of the aldehyde **19** in favor of the C-20-epimer. Reduction of the mixture with sodium borohydride ($NaBH_4$) provided the corresponding C-20 epimeric alcohols. The alcohols were separated by column chromatography to obtain the desired 20-epi alcohol **20** and the naturally configured alcohol **21** in 43% and 27%, respectively.[19,21] Tosylation of the primary hydroxyl group in **20** afforded tosylate **22** in 92% yield, which was treated with sodium iodide (NaI) to give iodide **23** in 94% yield. Reaction of **23** with methyl vinyl ketone (MVK) in the presence of zink (Zn) and cuprous iodide (CuI) furnished ketone **24** in 65% yield. Grignard reaction of **24** with methylmagnesium bromide (MeMgBr) gave rise to alcohol **25** with the desired side chain in 86% yield. Desilylation of **25** with 47% hydrofluoric acid (HF) followed by oxidation of **26** with tetrapropylammonium perruthenate (TPAP) and *N*-methylmolpholine *N*-oxide (NMO) gave ketone **27** in 98% yield gave ketone **27** in 98% yield. Ketone **27** was then reacted with (bromomethylene)triphenyl-




**Scheme 3. Synthesis of C/D-ring fragment 7.** Reagents and conditions: a) TsCl, DMAP, pyridine, rt. b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, -40 °C. c) DMSO, *s*-collidine, 150 °C. d) *n*-$Bu_4NOH$, $CH_2Cl_2$, rt. e) $NaBH_4$, EtOH, THF, 0 °C. f) TsCl, DMAP, pyridine, rt. g) NaI, DMF, 85 °C. h) MVK, Zn, CuI, EtOH, $H_2O$, 20-30 °C. i) MeMgBr, THF, 0 °C. j) 47% HF, MeCN, THF, 0 °C. k) TPAP, NMO, $CH_2Cl_2$, rt. l) $Ph_3P^+CH_2Br/Br^-$, NaHMDS, rt.

phosphonium bromide ($Ph_3P^+CH_2Br/Br^-$) in the presence of sodium hexamethyldisilazide (NaHMDS) to furnish C/D-ring fragment **7** in excellent overall yield (Scheme 3). Spectroscopic data of **26, 27, and 7** were identical to those reported in the literature.[19]

With A-ring fragment **5** and C/D-ring fragment **7** in hand, we next investigated the Trost coupling reaction. Upon treatment of excess **5** and **7** in the presence of tetrakis(triphenylphosphine)palladium (0) [$Pd(PPh_3)_4$] and triethylamine ($Et_3N$) in toluene, the coupled product **28** was obtained in 42% yield. The silyl protecting groups were removed using 47% HF in acetonitrile (MeCN) to afford 20-epieldecalcitol (**4**) in 73% yield (Scheme 4). The $^1H$ NMR chemical shift of the C-21 methyl resonance in 20-epi-eldecalcitol (**4**) (0.87 ppm) is shifted upfield by 0.04 ppm relative to natural configuration of eldecalcitol (**2**) (0.91 ppm)[4] and is consistent with this general pattern.[22-24]




**Scheme 4. Synthesis of 20-epi-eldecalcitol (4) and 1,20-diepi-eldecalcitol (30).** Reagents and conditions: a) $Pd(PPh_3)_4$, $Et_3N$, toluene, reflux. b) 47% HF, MeCN, rt.

The results of preliminary *in vitro* biological evaluation of synthetic 20-epi-eldecalcitol (**4**) in comparison with eldecalcitol (**2**) and calcitriol (**1**) are summarized in Table 1. As anticipated, 20-epi-eldecalcitol (**4**) showed greatly enhanced activity toward the induction of HL-60 differentiation (6085.99/49.6 = 122.7 times),[11] inhibition of U937 proliferation (738.74/4.15 = 178.0 times),[12] and increase in osteocalcine concentration in MG-63 (2980/15 = 198.7 times),[13] compared to eldecalcitol (**2**) (Table 1).[25]

Finally, A-ring fragment **15** was coupled with C/D-ring fragment **7** to give 1,20-diepi-eldecalcitol (**30**) under comparable conditions and yields to furnish 20-epi-eldecalcitol (**4**) *via* **29** (Scheme 4).

**Table 1. Preliminary biological evaluation of 20-epi-eldecalcitol (4)**

| | HL-60 | U937 | MG-63 |
|---|---|---|---|
| calcitriol (**1**) | 100 | 100 | 100 |
| eldecalcitol (**2**) | 49.6 | 4.15 | 15 |
| 20-epi-eldecalcitol (**4**) | 6085.9 | 738.74 | 2980 |

HL-60: Relative potency of induction of human myeloid leukemia cell differentiation.[11]
U937: Relative potency of inhibition of human histiocytic lymphoma proliferation.[12]
MG-63: Relative potency of transcriptional activity of osteocalcin of human osteosarcoma cell.[13]

## CONCLUSION

Based on the Trost coupling methodology involving A-ring fragments **5** and **15** and C/D-ring fragment **7**, the synthesis of 20-epi-eldecalcitol (**4**) and 1,20-diepi-eldecalcitol (**30**) has been successfully achieved. In *in vitro* preliminary biological evaluations, 20-epi-eldecalcitol (**4**) showed greatly enhanced potencies toward HL-60, U937, and MG-63 cell lines. We are very interested in the *in vivo* biological activity of **4** on bone. Further biological studies with 20-epi-eldecalcitol analogs including 1,20-diepi-eldecalcitol (**30**) will be reported elsewhere.

## EXPERIMENTAL

Anhydrous THF was purchased from Kanto Chemical Co., Inc., MeOH and EtOH were distilled from sodium, toluene was distilled from phosphorus pentoxide, and $CH_2Cl_2$, $Et_3N$, DMF and pyridine were distilled from calcium hydride. All other purchased solvents and reagents were used without further purification. All reactions were carried out under an atmosphere of argon unless otherwise noted. Celite 545 was purchased from Nacarai Tesque Inc. All extracts were dried over magnesium sulfate and evaporated under reduced pressure with a rotary evaporator. Chromatographic purification was carried out with Silica Gel 60N Cat. No. 37560-84 purchased from Kanto Chemical Co., Inc., flash column chromatography with Silica Gel 60N Cat. No. 37563-84 from Kanto Chemical Co., Inc., and preparative thin layer chromatography (TLC) with Merck Kieselgel 60 $PFR_{254}$ Art. 1.05744.0009 or Art. 1.05715.0009.

Optical rotations were measured with JASCO DIP-370 polarimeter. $^{1}H$ and $^{13}C$ NMR spectra were

recorded on VARIAN Gemini-300 and Gemini-400 spectrometers using $CDCl_3$ as a solvent. Chemical shifts are reported in parts per million (ppm) calibrated from $CHCl_3$ (7.26 ppm) or tetramethylsilane (0.00 ppm) for $^1$H NMR and $CDCl_3$ (77.1 ppm) for $^{13}$C NMR. Infrared (FTIR) spectra were obtained using JASCO FT/IR-5300, JEOL JIR-6000, and Hitachi 270-30 spectrophotometers. Mass spectra (MS) were measured with JEOL JMS-DX303 instrument. High resolution mass spectra (HRMS) were recorded on JEOL JMS-AX-500 and VG Auto Spec Q instruments.

**(*S*)-2((3*R*,3a*R*,7*S*,7a*R*)-Octahydro-7-hydroxy-3a-methyl-1*H*-inden-3-yl)propyl 4-Methylbenzene-sulfonate (16):** To a stirred solution of **8** (1.14 g, 5.30 mmol) in pyridine (21 mL), were added TsCl (1.54 g, 8.10 mmol) and DMAP (640 mg, 0.53 mmol) at 0 °C. The resulting mixture was stirred at rt for 20 h. To the stirred mixture, was added 3M HCl (25 mL). The resulting mixture was extracted with $Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (8:1) gave **16** (1.70 g, 88%) as a colorless oil. $^1$H-NMR ($CDCl_3$): δ 0.89 (3H, s), 0.96 (3H, d, *J*=6.4 Hz), 1.10-1.94 (14H, m), 2.45 (3H, s), 3.82 (1H, dd, *J*=6.4, 9.4 Hz), 3.95 (1H, dd, *J*=3.0, 9.4 Hz), 4.07 (1H, s), 7.34 (2H, d, *J*=8.1 Hz), 7.78 (2H, d, *J*=8.1 Hz). FTIR (neat): ν 3562, 1464, 1358, 1178 cm$^{-1}$.

**(*S*)-2((3*R*,3a*R*,7*S*,7a*R*)-Octahydro-7-*tert*-butyldimethylsilyloxy-3a-methyl-1*H*-inden-3-yl)propyl 4-Methylbenzenesulfonate (17):** To a stirred solution of **16** (1.70 g, 4.64 mmol) in $CH_2Cl_2$ (40 mL), were added 2,6-lutidine (1.60 mL, 13.9 mmol) and TBSOTf (1.60 mL, 6.96 mmol) at -40 °C. The resulting mixture was stirred at -40 °C for 2 h, diluted with $H_2O$ (20 mL), extracted with $Et_2O$, washed with 0.5 M HCl and saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (40:1) gave **17** (2.26 g, 100%) as a colorless oil. $[\alpha]_D$ +28.9 ° (*c* 1.02, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.00 (6H, s), 0.86 (9H, s), 0.91 (3H, s), 0.94 (3H. d, *J*=6.6 Hz), 1.12-1.81 (12H, m), 2.45 (3H, s), 3.47 (1H, q, *J*=6.6 Hz), 3.79 (1H, dd, *J*=6.3, 9.2 Hz), 3.94 (1H, d, *J*=9.2 Hz), 3.97 (1H, m), 7.34 (2H, d, *J*=8.2 Hz), 7.77 (2H, d, *J*=8.2 Hz). $^{13}$C NMR ($CDCl_3$): δ 13.3, 16.4, 17.2, 21.3, 22.6, 25.5, 26.2, 34.0, 35.4, 41.8, 52.3, 68.7, 127.6, 129.4, 144.2. FTIR (neat): ν 1362, 1252, 1177, 1085, 1023 cm$^{-1}$. MS (EI) *m/z* 480 ($M^+$), 177 (100%). HRMS (EI) calcd for $C_{26}H_{44}O_4SSi$ ($M^+$) 486.2849, found 486.2823.

**(*S*)-2((3*R*,3a*R*,7*S*,7a*R*)-Octahydro-7-*tert*-butyldimethylsilyloxy-3a-methyl-1*H*-inden-3-yl)propanal (18):** To a stirred solution of **17** (1.45 g, 3.02 mmol) in DMSO (16 mL), was added *s*-collidine (0.6 mL, 4.6 mmol) at rt. The resulting mixture was stirred at 150 °C for 40 min, cooled to rt, extracted with

$Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (50:1 then 6:1) gave **18** (761 mg, 78%) as a yellow oil. $[\alpha]_D$ +38.5 ° (*c* 0.95, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.01 (6H, d, *J*=5.7 Hz), 0.88 (9H, s), 0.96 (3H, s), 1.09 (3H, d, *J*=6.9 Hz), 1.10-1.93 (12H, m), 2.35 (1H, m), 4.03 (1H, d, *J*=2.4 Hz), 9.58 (1H, d, *J*=3.3 Hz). $^{13}$C NMR ($CDCl_3$): δ 13.6, 14.4, 17.8, 18.3, 23.6, 26.1, 26.5, 34.7, 42.9, 52.0, 52.7, 69.4, 205.6. FTIR (neat): ν 1727, 1461, 1254, 1165, 1083, 1023 cm$^{-1}$. MS (EI) *m/z* 324 ($M^+$), 75 (100%). HRMS (EI) calcd for $C_{19}H_{36}O_2Si$ ($M^+$) 324.2485, found 324.2479.

**2-((1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1yl)propanal (20):** To a stirred solution of **18** (1.0 g, 3.1 mmol) in $CH_2Cl_2$ (15 mL), was added 40% aqueous *n*-$Bu_4NOH$ (1.0 mL, 1.5 mmol) at rt. The resulting mixture was stirred at rt for 16 h, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (100:1) gave a mixture of **18** and **19** (805 mg, 81%) as a colorless oil. To the stirred mixture of **18** and **19** in EtOH (15 mL) and THF (12 mL), was added $NaBH_4$ (100 mg, 2.6 mmol) at 0 °C. The resulting mixture was stirred at rt for 1 h, quenched with saturated aqueous $NH_4Cl$ at 0 °C, extracted with $Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (40:1) gave **20** (425 mg, 43%) as a colorless oil and **21** (268 mg, 27%) as a colorless oil. **20**: $[\alpha]_D$ +54.7 ° (*c* 1.00, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.00 (3H, s), 0.01 (3H, s), 0.88 (9H, s), 0.93 (3H, s), 0.95 (3H, d, *J*=6.6 Hz), 1.11 (12H, m), 3.45 (1H, dd, *J*=6.6, 10.8 Hz), 3.70 (1H, dd, *J*=3.6, 10.5 Hz), 4.00 (1H, m). $^{13}$C NMR ($CDCl_3$): δ -5.2, -4.8, 14.1, 16.5, 17.6, 18.0, 22.8, 25.8, 26.7, 34.4, 37.5, 40.1, 41.9, 53.0, 60.4, 66.9, 69.3. FTIR (neat): ν 3345, 1465, 1370, 1254, 1166, 1088, 1026 cm$^{-1}$. MS (EI) *m/z* 326 ($M^+$), 251 (100%). HRMS (EI) calcd for $C_{19}H_{38}O_2Si$ ($M^+$) 326.2641, found 326.2641. Spectroscopic data of **20** were identical to those reported in the literature.[19]

**(*R*)-2-((1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1yl)propyl 4-Methylbenzenesulfonate (22):** To a stirred solution of **20** (690 mg, 2.10 mmol) in pyridine (8.5 mL), were added TsCl (600 mg, 3.10 mmol) and DMAP (26 mg, 0.21 mmol) at 0 °C. The resulting mixture was stirred at rt for 13 h, poured into 1M HCl (20 mL), extracted with $Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (20:1) gave **22** (922 mg, 92%) as a colorless oil. $[\alpha]_D$ +15.4 ° (*c* 1.05, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ -0.02 (3H, s), 0.01 (3H, s), 0.81 (3H, s), 0.87 (9H, s), 0.88 (3H, s), 1.02-1.73 (12H, m), 2.45 (3H, s), 3.78 (1H, dd, *J*=6.9, 9.2 Hz), 3.96 (1H, m), 4.11 (1H, dd, *J*=3.6, 9.2 Hz), 7.33 (2H, d, *J*=8.1 Hz), 7.77 (2H, d, *J*=8.1 Hz). $^{13}$C NMR ($CDCl_3$): δ -4.8, -4.4, 14.4, 17.1, 17.9, 18.4, 22.0, 23.1, 26.2, 27.0, 34.6, 35.1,

40.3, 42.2, 53.0, 53.1, 69.6, 74.7, 128.4, 130.1, 133.7. FTIR (neat): ν 1473, 1458, 1361, 1251, 1176 $cm^{-1}$. MS (EI) *m/z* 480 ($M^+$), 177 (100%). HRMS (EI) calcd for $C_{26}H_{44}O_4SSi$ ($M^+$) 480.2750, found 480.2711. Spectroscopic data of **22** were identical to those reported in the literature.[19]

**(1*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)octahydro-1-((*R*)-1-iodopropan-2-yl)-7a-methyl-1*H*-indene (23):** To a stirred solution of **22** (900 mg, 1.87 mmol) in DMF (20 mL), was added NaI (890 mg, 5.98 mmol) at rt. The resulting mixture was stirred at 85 °C for 2 h, poured into saturated aqueous NaCl at rt, extracted with $Et_2O$, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (50:1) gave **23** (770 mg, 94%) as a yellow oil. $[\alpha]_D$ +1.49 ° (*c* 1.55, $CHCl_3$). $^1H$ NMR ($CDCl_3$): δ -0.01 (3H, s), 0.01 (3H, s), 0.88 (9H, s), 0.92 (3H, s), 0.95 (3H, d, *J*=6.3 Hz), 1.18-1.84 (12H, m), 3.17 (1H, dd, *J*=6.3, 9.3 Hz), 3.46 (1H, dd, *J*=2.7, 9.3 Hz), 4.00 (1H, m). $^{13}C$ NMR ($CDCl_3$): δ -5.2, -4.8, 14.1, 17.6, 18.0, 19.5, 21.4, 22.8, 25.8, 26.9, 34.2, 36.1, 40.5, 42.0, 52.5, 55.2, 69.3. FTIR (neat): ν 2932, 2860, 1463, 1372, 1255, 1165, 1078, 1024, 833 $cm^{-1}$. MS (EI) *m/z* 436 ($M^+$), 379 (100%). HRMS (EI) calcd for $C_{19}H_{37}OSiI$ (M+) 436.1654, found 436.1661. Spectroscopic data of **23** were identical to those reported in the literature.[19,21]

**(*S*)-6-((1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1-yl)heptan-2-one (24):** To a stirred solution of **23** (150 mg, 0.34 mmol) in EtOH (7 mL) and $H_2O$ (2.5 mL), were added CuI (160 mg, 0.85 mmol), Zn (220 mg, 3.4 mmol) and MVK (0.31 mL, 3.7 mmol). The resulting mixture was sonicated at 20-30 °C for 2 h, diluted with $Et_2O$, filtrated through Celite pad, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (30:1) gave **24** (83 mg, 65%) as a colorless oil. $[\alpha]_D$ +23.7 ° (*c* 1.06, $CHCl_3$). $^1H$ NMR ($CDCl_3$): δ -0.01 (3H, s), 0.00 (3H, s), 0.81 (3H, d, *J*=6.3 Hz), 0.88 (9H, s), 1.06-1.86 (20H, m), 2.13 (3H, s), 2.35-2.38 (2H, m), 3.99 (1H, m). $^{13}C$ NMR ($CDCl_3$): δ -5.2, -4.8, 14.0, 17.7, 18.0, 18.5, 20.7, 22.9, 27.1, 29.8, 34.4, 34.7, 40.7, 42.2, 53.1, 56.2, 69.4, 209.4. FTIR (neat): ν 1717, 1367, 1254, 1077, 1027 $cm^{-1}$. MS (EI) *m/z* 380 ($M^+$), 323 (100%). HRMS (EI) calcd for $C_{23}H_{44}O_2Si$ ($M^+$) 380.3144, found 380.3090.

**(*S*)-6-((1*R*,3a*R*,4*S*,7a*R*)-4-(*tert*-Butyldimethylsilyloxy)-7a-methyloctahydro-1*H*-inden-1-yl)-2-methylheptan-2-ol (25):** To a stirred solution of **24** (380 mg, 1.0 mmol) in THF (9 mL), was added MeMgBr (35% $Et_2O$ solution, 2.0 mL, 5.0 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h, quenched with saturated aqueous $NH_4Cl$, extracted with $Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (15:1) gave **25** (340 mg,

86%) as a colorless oil. $[\alpha]_D$ +20.3 (*c* 1.00, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ -0.01 (3H, s), 0.00 (3H, s), 0.82 (3H, d, *J*=6.4 Hz), 0.88 (9H, s), 0.91 (3H, s), 1.06-1.86 (27H, m), 3.99 (1H, m). $^{13}$C NMR ($CDCl_3$): δ -5.2, -4.8, 14.0, 17.7, 20.8, 23.0, 25.8, 29.3, 34.5, 35.7, 39.8, 40.7, 42.0, 44.0, 44.3, 53.1, 56.4, 60.7, 69.4, 71.1, 72.9, 139.2. FTIR (neat): ν 3366, 1465, 1371, 1254, 1163, 1085, 1026 cm$^{-1}$. MS (EI) *m/z* 396 ($M^+$), 381 ($M^+$-Me), 247 (100%). HRMS (EI) calcd for $C_{25}H_{48}O_2Si$ ($M^+$) 396.3411, found 396.3431.

**(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-1*H*-inden-4-ol (26):** To a stirred solution of **25** (270 mg, 0.68 mmol) in MeCN (5.4 mL) and THF (4.6 mL), was added 47% HF (3.35 mL, 0.09 mmol) at rt. The resulting mixture was stirred at rt for 1 h, poured into saturated aqueous $NaHCO_3$ (20 mL), extracted with $Et_2O$, washed with saturated aqueous NaCl, evapolated and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (3:1) gave **26** (179 mg, 93%) as a colorless oil. $[\alpha]_D$ +10.4 ° (*c* 1.25, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.82 (3H, d, *J*=6.4 Hz), 0.93 (3H, s), 1.11-1.57 (23H, m), 1.75-1.85 (3H, m), 1.94-1.98 (1H, m), 4.07 (1H, m). $^{13}$C NMR ($CDCl_3$): δ 13.8, 17.5, 18.5, 20.8, 22.4, 23.0, 27.1, 29.25, 33.4, 33.6, 34.7, 35.7, 36.6, 40.3, 41.9, 44.3, 47.1, 52.6, 70.4, 71.1. FTIR (neat): ν 3391, 1465, 1375, 1265, 1162, 1081 cm$^{-1}$. MS (EI) *m/z* 282 ($M^+$), 43 (100%). HRMS (EI) calcd for $C_{18}H_{34}O_2$ (M+) 282.2591, found 282.2546. Spectroscopic data of **26** were identical to those reported in the literature.[19]

**(1*R*,3a*R*,4*S*,7a*R*)-1-((*S*)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-1*H*-inden-4(2*H*)-one (27):** To a stirred mixture of dried (200 °C, 2 h) 4A molecular sieves (180 mg), were added **26** (180 mg, 0.63 mmol) in $CH_2Cl_2$ (12 mL), NMO (130 mg, 1.13 mmol), and TPAP (15 mg, 0.044 mmol) at rt. The resulting mixture was stirred at rt for 2 h, diluted with $Et_2O$, filtrated through Celite pad, evapolated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (3:1) gave **27** (173 mg, 98%) as a colorless oil. $[\alpha]_D$ -8.2 ° (*c* 1.40, CHCl3). $^1$H NMR ($CDCl_3$): δ 0.63 (3H, s), 0.86 (3H, d, *J*=6.3 Hz), 1.22 (6H, s), 1.25-2.27 (19H, m), 2.44 (1H, dd, *J*=6.0, 11.6 Hz). $^{13}$C NMR ($CDCl_3$): δ 12.7, 18.4, 18.9, 20.8, 24.0, 27.1, 29.2, 29.6, 34.8, 35.9, 38.8, 40.9, 44.2, 49.9, 56.2, 62.0, 71.0, 212.0. FTIR (neat): ν 3444, 1711, 1466, 1380, 1257 cm$^{-1}$. MS (EI) *m/z* 280 ($M^+$), 262 (100%). HRMS (EI) calcd for $C_{18}H_{32}O_2$ ($M^+$) 280.2386, found 280.2408. Spectroscopic data of **27** were identical to those reported in the literature.[19]

**(S)-6-((1*R*,3a*R*,7a*R*,*E*)-4-(Bromomethylene)-7a-methyloctahydro-1*H*-inden-1-yl)-2-methylheptane-2-ol (7):** To a stirred mixture of dried (100 °C, 1 h) $Ph_3P^+CH_2Br/Br^-$ (610 mg, 1.40 mmol) in THF (2

mL), was added NaHMDS (1M solution in THF, 1.40 mL, 1.40 mmol) at -60 °C. After being stirred at -60 °C for 1 h, **27** (40 mg, 0.14 mmol) in THF (1.5 mL) was added. The mixture was stirred at rt for 2 h, diluted with saturated aqueous $NH_4Cl$ (5 mL) at 0 °C, extracted with AcOEt, evapolated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (15:1) gave **7** (26 mg, 52%) as a colorless oil. $[\alpha]_D$ +31.9 ° (*c* 0.95, CHCl3). $^1$H NMR ($CDCl_3$): δ 0.56 (3H, s), 0.85 (3H, d, *J*=6.3 Hz), 1.21 (6H, m), 1.25-1.96 (15H, m), 2.85-2.89 (1H, m), 5.64 (1H, s). $^{13}$C NMR ($CDCl_3$): δ 12.5, 18.9, 22.3, 23.0, 27.7, 29.7, 31.5, 35.7, 36.4, 40.1, 44.7, 45.9, 55.8, 56.3, 71.5, 97.8. FTIR (neat): ν 3374, 1727, 1460, 1373, 1151 cm$^{-1}$. MS (EI) *m/z* 356 ($M^+$), 147 (100%). HRMS (EI) calcd for $C_{19}H_{33}BrO$ ($M^+$) 356.1713, found 356.1716. Spectroscopic data of **7** were identical to those reported in the literature.[19]

**(*S*)-6-((1*R*,3a*S*,7a*R*,*E*)-4-((*Z*)-2-((3*R*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-(*tert*-butyldimethylsilyloxy)propoxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1*H*-indene-1-yl)-2-methylheptan-2-ol (28):** To a stirred mixture of **5** (29 mg, 0.052 mmol) and **7** (27 mg, 0.075 mmol) in toluene (1.2 mL), were added $Et_3N$ (0.68 mL) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) at rt. The resulting mixture was stirred at 120 °C for 4 h, diluted with $Et_2O$ (5 mL) at rt, filtrated through Celite pad, evapolated, and chromatographed on silica gel. Elution with *n*-hexane-AcOEt (10:1) gave **28** (18 mg, 42%) as a yellow oil. $[\alpha]_D$ -8.9 ° (*c* 0.85, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.03-0.08 (18H, m), 0.52 (3H, s), 0.84-0.91 (27H, m), 1.21 (6H, s), 1.25-1.80 (14H, m), 1.94-1.97 (2H, m), 2.21 (1H, dd, *J*=3.3, 12.9 Hz), 2.42-2.49 (1H, m), 2.79-2.83 (1H, m), 3.21-3.23 (1H, m), 3.64-3.70 (3H, m), 4.18-4.24 (2H, m), 4.97 (1H, d, *J*=2.4 Hz), 5.25 (1H, m), 6.00 (1H, d, *J*=12.0 Hz), 6.21 (1H, d, *J*=12.0 Hz). $^{13}$C NMR ($CDCl_3$): δ -5.3, -4.9, -4.7, -4.6, -3.6, 1.0, 12.2, 18.1, 18.2, 18.3, 18.6, 20.9, 22.0, 23.5, 25.6, 25.8, 25.9, 26.0, 27.4, 28.8, 29.3, 29.7, 33.6, 35.5, 36.0, 40.5, 41.4, 44.3, 45.8, 56.1, 56.3, 60.5, 68.2, 69.5, 71.1, 84.2, 117.9, 123.2, 134.5, 141.0, 145.8. FTIR (neat): ν 3368, 1467, 1381, 1254, 1099 cm$^{-1}$. MS (FAB) *m/z* 833 (M+), 73 (100%). HRMS (EI) calcd for $C_{48}H_{92}O_5Si_3$ ($M^+$) 832.6253, found 832.6251.

**(1*R*,2*R*,3*R*,*Z*)-5-((*E*)-2-((1*R*,3a*S*,7a*R*)-1-((*S*)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyldihydro-1*H*-inden-4-(2*H*,5*H*,6*H*,7*H*,7a*H*)-ylidene)ethylidene)-2-(3-hydroxypropoxy)-4-methylenecyclohexane-1,3-diol (4):** To a stirred solution of **28** (19 mg, 0.023 mmol) in MeCN (1 mL), was added 47% HF (70 μL) at 0 °C. The resulting mixture was stirred at rt for 10 h, basified with $NaHCO_3$ (20 mg) at 0 °C, extracted with AcOEt, washed with saturated aqueous NaCl, evapolated. The residue was purified by preparative TLC developed with AcOEt to give **4** (8.3 mg, 73%) as a colorless oil. $[\alpha]_D$ -74.6 ° (*c* 0.54, MeOH). $^1$H NMR ($CD_3OD$): δ 0.57 (3H, s), 0.87 (3H, d, *J*=7.0 Hz), 1.17 (6H, s),

1.24-1.56 (12H, m), 1.65-1.72 (2H, m), 1.79-1.88 (4H, m), 1.98-2.04 (2H, m), 2.35 (1H, d, *J*=13.5 Hz), 2.47 (1H, dd, *J*=6.0, 14.0 Hz), 2.86 (1H, dd, *J*=4.0, 10.0 Hz), 3.10 (1H, dd, *J*=4.5, 14.8 Hz), 3.60-3.71 (6H, m), 3.71-3.75 (2H, m), 4.19 (1H, m), 4.23 (1H, d, *J*=8.0 Hz), 4.98 (1H, t, *J*=2.0 Hz), 5.42 (1H, t, *J*=2.0 Hz), 6.06 (1H, d, *J*=11.0 Hz), 6.30 (1H, d, *J*=11.0 Hz). $_{13}$C NMR ($CDCl_3$): δ 1.0, 12.2, 14.2, 18.5, 20.9, 22.2, 23.7, 27.3, 29.2, 29.7, 31.8, 35.4, 36.6, 40.3, 44.3, 45.9, 56.2, 60.4, 61.1, 66.5, 68.2, 71.1, 71.5, 85.4, 111.8, 117.2, 124.4, 132.1, 142.9, 144.2. FTIR (neat): ν 3407, 1463, 1375, 1260, 1215, 1105 $cm^{-1}$. MS (EI) *m/z* 490 ($M^+$), 472 (100%). HRMS (EI) calcd for $C_{30}H_{50}O_5$ ($M^+$) 490.3676, found 490.3641.

**(*S*)-6-((1*R*,3a*S*,7a*R*,*E*)-4-((*Z*)-2-((3*S*,4*R*,5*R*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-4-(3-(*tert*-butyldimethylsilyloxy)propoxy)-2-methylenecyclohexylidene)ethylidene)-7a-methyloctahydro-1*H*-indene-1-yl)-2-methylheptan-2-ol (29):** To a stirred mixture of **15** (25 mg, 0.044 mmol) and **7** (26 mg, 0.073 mmol) in toluene (1.5 mL), were added $Et_3N$ (0.68 mL) and $Pd(PPh_3)_4$ (17 mg, 0.015 mmol) at rt. The resulting mixture was stirred at 120 °C for 4 h, diluted with $Et_2O$ (5 mL) at rt, filtrated through Celite pad, and evapolated. The residue was purified by chromatograpy on silica gel with *n*-hexane-AcOEt (20:1) and then preparative TLC developed with *n*-hexane-AcOEt (10:1) to give **29** (16 mg, 43%) as a yellow oil. $[\alpha]_D$ +14.8 ° (*c* 0.86, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.01-0.10 (18H, m), 0.52-0.56 (12H, m), 0.84-0.95 (29H, m), 1.21 (6H, s), 1.25-1.64 (20H, m), 1.76-1.97 (2H, m), 2.10-2.28 (2H, m), 3.53 (1H, s), 3.67-3.79 (3H, m), 3.96 (1H, s), 4.98 (1H, s), 5.37 (1H, t, *J*=2.4 Hz), 5.96 (1H, d, *J*=11.5 Hz), 6.23 (1H, d, *J*=11.5 Hz). $^{13}$C NMR ($CDCl_3$): δ -5.3, -4.7, -4.6, 1.0, 8.6, 12.3, 18.6, 20.9, 21.9, 23.4, 25.9, 27.4, 28.9, 29.3, 29.7, 33.9, 35.4, 36.0, 40.4, 44.3, 45.8, 56.1, 56.3, 61.0, 70.3, 73.9, 84.4, 112.2, 117.8, 122.6, 134.3, 141.9, 144.1. FTIR (neat): ν 3379, 1719, 1465, 1371, 1253, 1088 $cm^{-1}$. MS (FAB) *m/z* 833 ($M^+$), 73 (100%) HRMS (EI) calcd for $C_{48}H_{92}O_5Si_3$ ($M^+$) 832.6253, found 832.6270.

**(1*R*,2*R*,3*S*,*Z*)-5-((*E*)-2-((1*R*,3a*S*,7a*R*)-1-((*S*)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyldihydro-1*H*-inden-4-(2*H*,5*H*,6*H*,7*H*,7a*H*)-ylidene)ethylidene)-2-(3-hydroxypropoxy)-4-methylenecyclohexane-1,3-diol (30):** To a stirred solution of **29** (8 mg, 0.0096 mmol) in MeCN (1 mL), was added 47% HF (40 μL) at 0 °C. The resulting mixture was stirred at rt for 10 h, basified with $NaHCO_3$ (20 mg) at 0 °C, extracted with AcOEt, washed with saturated aqueous NaCl, evapolated. The residue was purified by preparative TLC developed with AcOEt to give **30** (3 mg, 53%) as a colorless oil. $[\alpha]_D$ -26.8 ° (*c* 0.37, $CHCl_3$). $^1$H NMR ($CDCl_3$): δ 0.53 (3H, s), 0.84 (3H, d, *J*=6.3 Hz), 1.21-2.09 (14H, m), 2.40 (1H, d, *J*=9.3 Hz), 2.56 (1H, dd, *J*=5.4, 12.4 Hz), 2.83 (1H, d, *J*=11.2 Hz), 3.82-3.92 (6H, m), 4.31 (1H, s), 5.09 (1H, s), 5.38 (1H, s), 6.03 (1H, d, *J*=11.2 Hz), 6.43 (1H, d, *J*=11.2 Hz). $^{13}$C NMR

($CDCl_3$): δ 1.0, 12.2, 14.1, 18.5, 20.9, 22.1, 23.7, 27.3, 29.3, 29.7, 31.9, 35.4, 36.0, 40.3, 44.3, 45.9, 56.4, 60.4, 60.8, 66.2, 68.1, 71.1, 74.0, 80.9, 104.6, 117.2, 125.8, 126.0, 138.5, 143. FTIR (neat): ν 3373, 1458, 1373, 1265, 1081 $cm^{-1}$. MS (EI) *m/z* 490 (M+), 472 (100%). HRMS (EI) calcd for $C_{30}H_{50}O_5$ ($M^+$) 490.3676, found 490.3641.

**ACKNOWLEDGEMENTS**

We are grateful to Professor David Horne of Department of Molecular Medicine, City of Hope for helpful suggestions and reading of the manuscript.

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