Supporting Information for:

Efficient and Practical Synthesis of the A-Ring Precursor of 19-nor-1α,25-Dihydroxyvitamin D_3 and its ^{13}C- or ^{2}H-Labeled Derivative

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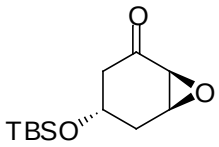
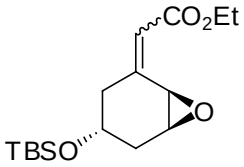
General. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, on a Varian Gemini-2000 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00). IR spectra were recorded on an FT-IR spectrometer (JASCO FT/IR-230. Elemental analyses were performed on an Elemental automatic analyzer. GC-MS (low-resolution mass spectrum, EI) analyses were performed on a Shimadzu QP-5000 GC-mass spectrometer. All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF, ethyl ether, and toluene) were purchased from Kanto Chemicals. Other chemicals are commercially available, unless otherwise indicated, and were used as received. 5-(*tert*-Butyldimethylsilyloxy)-2-cyclohexenone (**2**) was prepared from commercially available ethyl (*R*)-3-hydoxy-4-chlorobutyrate by the reported procedure.[1]

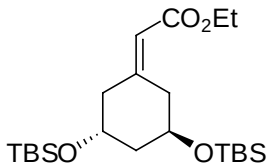


(1*S*,4*S*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-7-oxa-bicyclo[4.1.0]heptan-2-one (**3**)**:** To a mixture of (*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-cyclohexenone (**2**) (2.26 g, 10.0 mmol) and 35% aqueous H_2O_2 (8.67 mL, 100 mmol) in MeOH (400 mL) was added aqueous 3N NaOH (0.5 mL, 1.5 mmol) at –20 °C. The resulting mixture was stirred vigorously for 6 h at –20 °C. After addition of aqueous saturated NH_4Cl (400 mL), the volume was reduced to half by removing the solvents *in vacuo.* The residue was extracted with Et_2O (3 x 100 mL), dried ($MgSO_4$), and concentrated to give a pale yellow oil which was purified by column chromatography (SiO_2, hexane-Et_2O) to yield **3** (2.1 g) in 87% yield. Diasteromeric ratio was found to be >96 : <4 by GC analysis [HR-1 capillary column, Shinwa

Chemical Industries, LTD, 0.25 ϕ x 30 m, He 0.5 mL/min, starting at 60 °C (2 min) to 280 °C at the rate of 10 °C/min: retention time = 12.57 min for the major isomer and 12.72 min for the minor isomer]. **3**: ^{1}H NMR δ 4.21-4.30 (m, 1H), 3.55 (br s, 1H), 3.26 (d, *J* = 3.9 Hz, 1H), 2.76 (dd, *J* = 15.3 and 3.0 Hz, 1H), 2.39 (dd, *J* = 15.3 and 3.9 Hz, 1H), 2.19 (dd, *J* = 15.3 and 6.6 Hz, 1H), 2.00 (br d, *J* = 15.3 Hz, 1H), 0.85 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR δ 204.8, 67.3, 55.4, 54.7, 44.9, 32.9, 25.5, 17.8, -5.0, -5.1; IR (neat) 2929, 2888, 2857, 1726, 1472, 1406, 1361, 1331, 1255, 1075, 1031, 985, 935, 871, 837, 778, 715 cm^{-1}; Anal. Calcd. for $C_{16}H_{27}O_4Si$: C, 59.46; H, 9.15. Found: C, 59.15; H, 8.98.

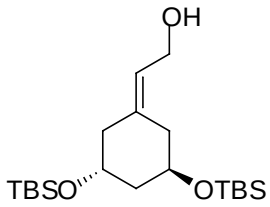


[(1*R*,4*R*,6*S*)-4-(*tert*-Butyldimethylsilyloxy)-7-oxa-bicyclo[4.1.0]hept-2-ylidene]acetic acid ethyl ester (**4**): To a suspension of NaH (0.54 g, 55% in oil, 13 mmol) in THF (20 mL) was slowly added diethylphonoacetic acid ethyl ester (2.6 ml, 13 mmol) at 0 °C with efficient stirring. The mixture was allowed to warm to room temperature and stirred for 30 min. To this was added a solution of **3** (2.42 g, 10 mmol) in THF (10 ml) at 0 °C. The stirring was continued for 1 h at 0 °C. After addition of aqueous saturated NH_4Cl (30 ml) at 0 °C, the mixture was extracted with Et_2O (3 x 20 ml), dried ($MgSO_4$) and concentrated to give a yellow residue, which was purified by flash-chromatography (SiO_2, hexane-Et_2O gradient) to afford **4** (2.99 g) as a colorless oil in 94% yield. A 1 : 1 mixture of *E*- and *Z*-**4**: ^{1}H NMR δ 6.09 (s, 1H), 5.93 (s, 1H), 4.78 (d, *J* = 3.9 Hz, 1H), 4.07-4.27 (m, 4H), 3.92-4.03 (m, 2H), 3.40-3.48 (m, 2H), 3.37 (d, *J* = 3.6 Hz, 1H), 2.97 (dd, *J* = 7.2, 16.5 Hz, 1H), 2.76 (dt, *J* = 2.7, 16.5 Hz, 1H), 2.50 (d, *J* = 14.7 Hz, 1H), 2.20-2.36 (m, 2H), 2.06 (dd, *J* = 6.6, 14.7 Hz, 1H), 1.76-1.91 (m, 2H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.26 (t. *J* = 7.2 Hz, 3H), 0.83 (s, 18H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR δ 165.4, 165.2, 152.4, 151.9, 123.0, 121.9, 65.4, 64.9, 60.1, 59.9, 56.0, 54.9, 54.6, 49.9, 39.7, 33.8, 33.4, 25.8, 18.0, 14.3, -4.6, -4.7, -4.8, -4.9; IR (neat) 2955, 2856, 1717, 1650, 1471, 1386, 1256, 1153, 1093, 1040, 870, 835, 778 cm^{-1}.

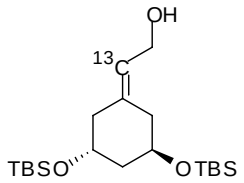


[(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)cyclohexylidene]acetic acid ethyl ester (**6**)**:** To a solution of $Pd_2(dba)_3CHCl_3$ (13.4 mg, 0.13 mmol) in dioxane (5 mL) was added *n*-Bu_3P (0.065 mL, 0.26 mmol) at ambient temparature. To the mixture was added a solution of formic acid (0.98 mL, 25.5 mmol) and Et_3N (1.2 mL, 10.2 mmol) in 1,4-dioxane (10 mL) at room temperature. After stirring for 5 min, to this was added a solution of the epoxide **4** (1.59 g, 5.1 mmol) in dioxane (15 mL). The reaction was intiated by heating to 40 °C for a few minutes and then the mixture was stirred at room temperature for 30 min. After addition of H_2O (20 mL), the mixture was extracted with Et_2O (3 x 15 mL). The

combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a yellow residue. To a solution of the resulting crude residue and imidazole (1.02 g, 15.0 mmol) in DMF (15 mL) was added TBSCl (1.57 g, 10 mmol) in several portions. The mixture was stirred for 12 h at room temperature. After addition of H_2O (20 mL), the mixture was extracted with hexanes (3 x 25 ml), dried ($MgSO_4$), and concentrated *in vacuo* to give a residue which was purified by flash chromatography (SiO_2; only hexane) to yield **6** (1.92 g) in 90% yield. $[\alpha]^{29}_D$ +18.0 (*c* 0.26, $CHCl_3$); ^{13}C NMR δ 166.2, 156.5, 117.3, 68.0, 67.9, 59.6, 46.1, 43.2, 37.5, 25.9, 25.8, 18.1, 14.4, -4.67, -4.71, -4.9, -5.0. Spectroscopic data of ^{1}H NMR and IR were in good agreement with those reported.[2]

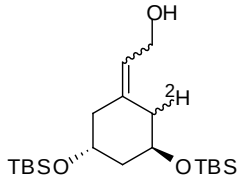


2-[(3*R*,5*R*)-3,5-Bis-(*tert*-butyldimethylsilyloxy)cyclohexylidene]ethanol (**1**)**:** To a stirred solution of **6** (2.14 g, 5 mmol) in toluene (25 mL) was added dropwise diisobutylaluminum hydride (13 mL, 1.14 M in toluene, 15 mmol) over 30 min at –78 °C. After 2 h, methanol (5 mL) and H_2O (5 mL) were cautiously added at –78 °C, and the solution was stirred for 0.5 h at room temperature. To this were added NaF (5 g) and Celite (5 g), and stirred for 1 h. The mixture was filtered through Celite and concentrated *in vacuo* to give a residue which was purified by flash chromatography (SiO_2; hexanes-Et_2O gradient) to yield **1** (1.81 g) as a white solid in 94% yield. mp 63-65 °C (lit.,[2] mp 63-65 °C) $[\alpha]^{29}_D$ +17.9 (*c* 1.02, $CHCl_3$) [lit.,[2] $[\alpha]_D$ +18.4 (*c* 1%, $CHCl_3$)]; ^{13}C NMR δ 138.2, 125.2, 68.1, 67.9, 58.4, 45.6, 43.4, 36.6, 25.9, 18.2, -4.6, -4.66, -4.70, -4.74. Spectroscopic data of ^{1}H NMR, EI-MS and IR were in good agreement with those reported.[2,3]



Compound 6-^{13}C-1: Prepared from **3** according to the same procedure for preparation of **1**, except for the use of $(EtO)_2(O)P$-$^{13}CH_2CO_2Et$ instead of $(EtO)_2(O)PCH_2CO_eEt$ for conversion of **3** to **4**, in a similar yield. ^{13}C Atom incorporation was calculated to be more than >98% by GC/EI-MS analysis [*m/z* 238 (34), 212 (29.6), 198 (48.8), 172 (100): HR-1 capillary column, Shinwa Chemical Industries, LTD, 0.25 ϕ x 30 m, He 40 kPa, starting at 120 °C (2 min) to 280 °C at the rate of 10 °C/min: retention time = 16.3-20.3 min] ^{1}H NMR δ 5.58 (dt, $J_{C\text{-}H}$ = 154.2 Hz and *J* = 7.2 Hz, 1H), 3.95-4.18 (m, 2H), 2.26-2.38 (m, 2H), 2.18 (dt, *J* = 10.5, 3.6 Hz, 1H), 1.99-2.09 (m, 1H), 1.76-1.85 (m, 1H), 1.63 (ddd, *J* = 3.0, 8.7, 13.0 Hz, 1H), 1.45 (br s, 1H, OH), 0.87 (s, 18H), 0.05 (s, 6H), 0.04 and 0.03 (2s, each 3H); ^{13}C NMR δ 138.2 (d, $J_{C\text{-}C}$ = 72.8 Hz), 125.2 (^{13}C atom present at the C-6 position, the steroid-numbering),

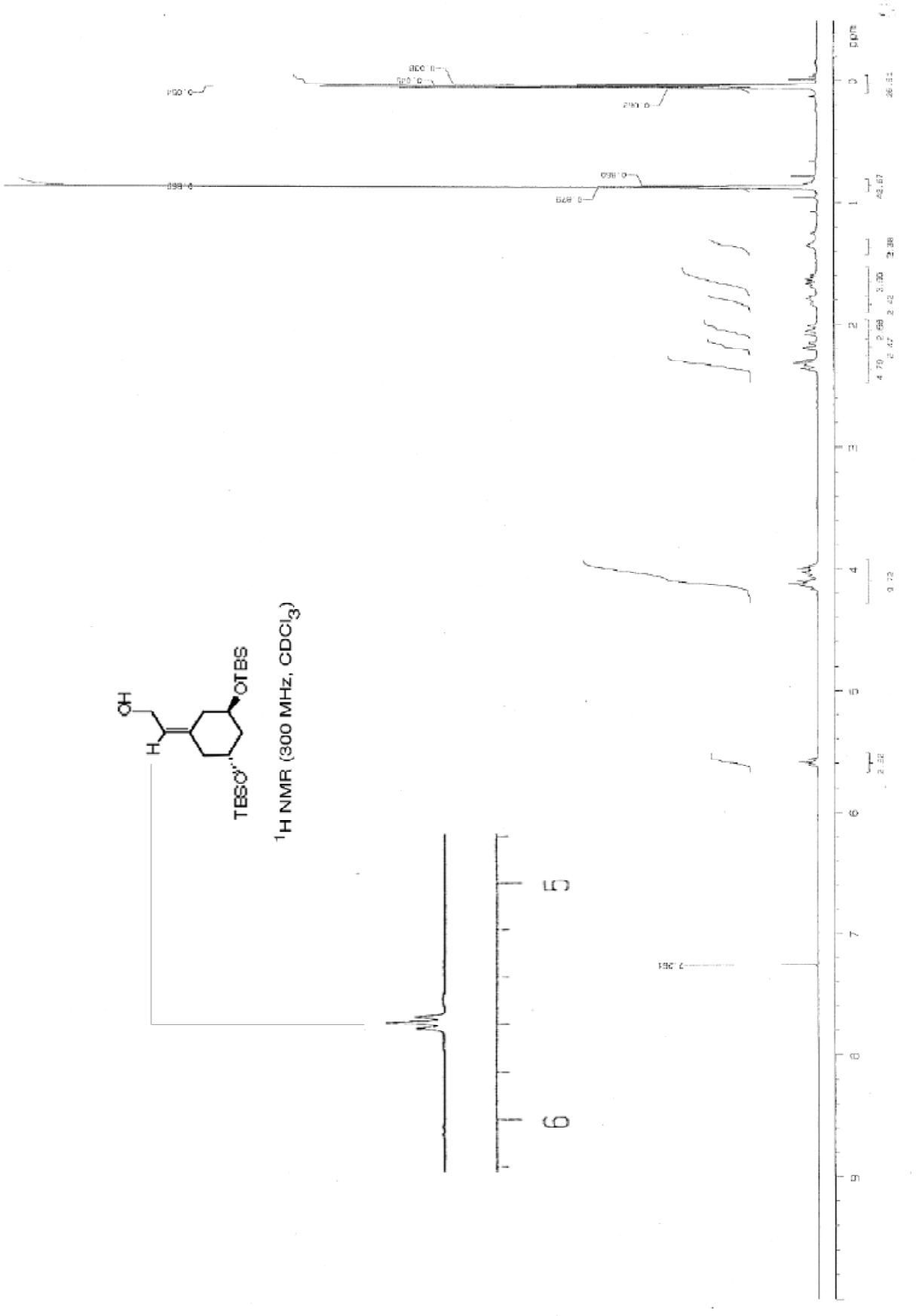
68.1 (d, $J_{C\text{-}C}$ = 2.8 Hz), 67.8 (d, $J_{C\text{-}C}$ = 2.6 Hz), 58.4 (d, $J_{C\text{-}C}$= 46.7 Hz), 45.7, 43.4, 36.7, 25.9, 18.2, -4.56, -4.66, -4.6, -4.74.

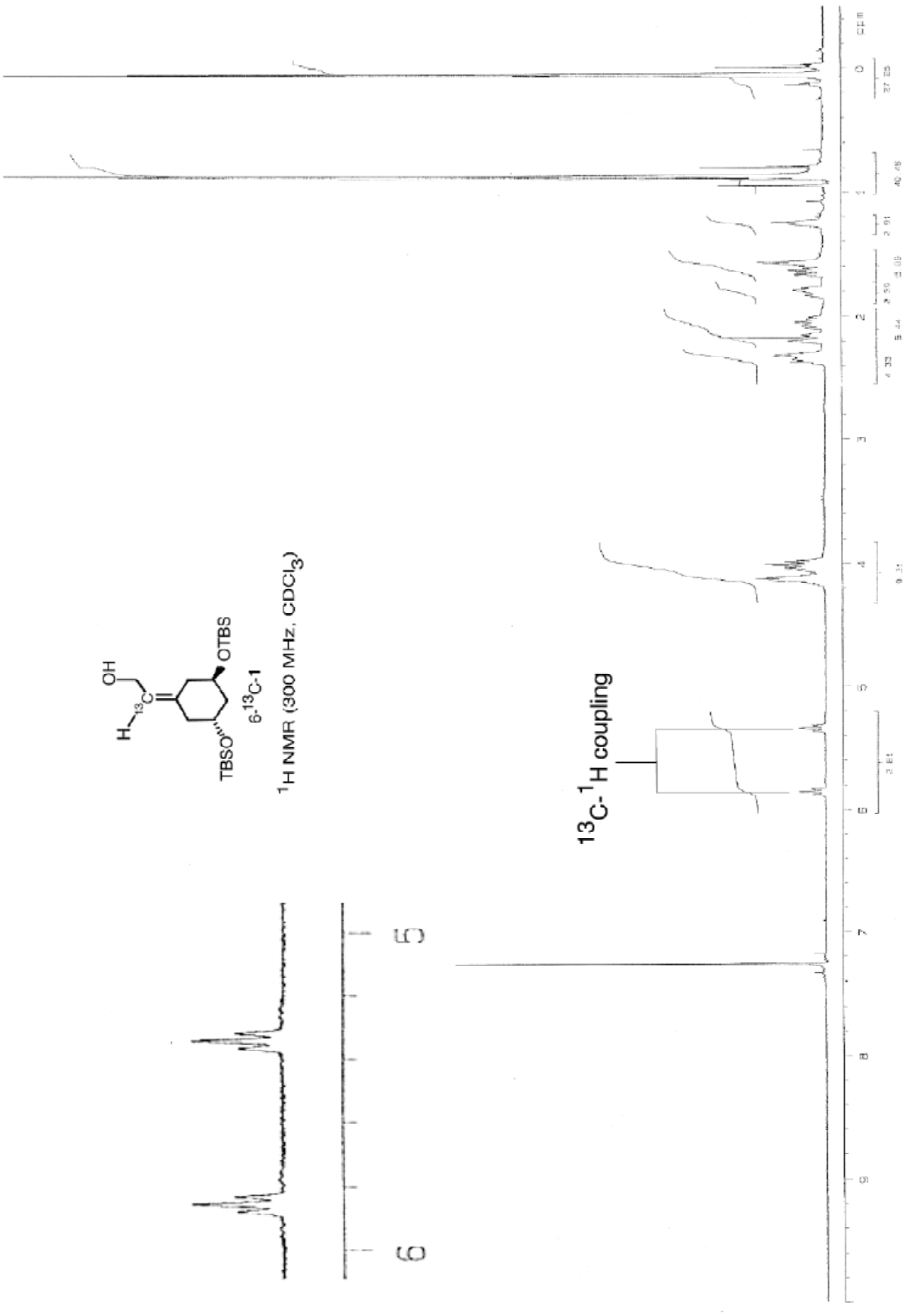


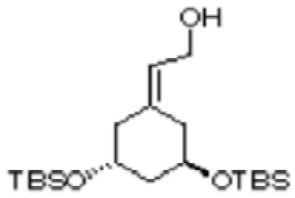
^{2}H-Labeled 1 (a mixture of 4- and 10-^{2}H-1): Prepared from **3** according to the same procedure for preparation of **1**, except for the use of DCO_2D instead of HCO_2H for conversion of **4** to **5**, in a similar yield; The ^{1}H and ^{13}C NMR spectra of the resulting ^{2}H-**1** indicated that the residue consisted of two regioisomers, each of which consisted of two stereoisomers, the ratio of which (total four isomers) was determined to be approximately 36:28:21:15 based on ^{13}C NMR. Deuterium incorporation was calculated to be more than >93% by GC/EI-MS analysis [*m/z* 238 (28.7), 212 (29), 198 (39.5), 172 (100): HR-1 capillary column, Shinwa Chemical Industries, LTD, 0.25 ϕ x 30 m, He 40 kPa, starting at 120 ^{o}C (2 min) to 280 ^{o}C at the rate of 10 ^{o}C/min: retention time = 16.3-20.3 min (four isomers could not be separated)] and by comparison of the ^{1}H NMR with that of **1** [for **1**: δ 2.25-2.45 (m, 2H), 2.18 (dd, *J* = 3.0, 10.5 Hz, 1H), 2.05 (dd, *J* = 8.1, 13.2 Hz, 1H)]. ^{13}C NMR δ 138.3, 125.4, 68.1, 68.0, 67.84, 67.80, 58.3, 45.54 and 45.47 [observed as main peaks among multiplet (45.8-45.9)], 43.3, 36.57 and 36.50 [observed as main peaks among multiplet (36.0-36.6)], 25.7, 18.0, -4.86, -4.95, -4.99, -5.03.

References

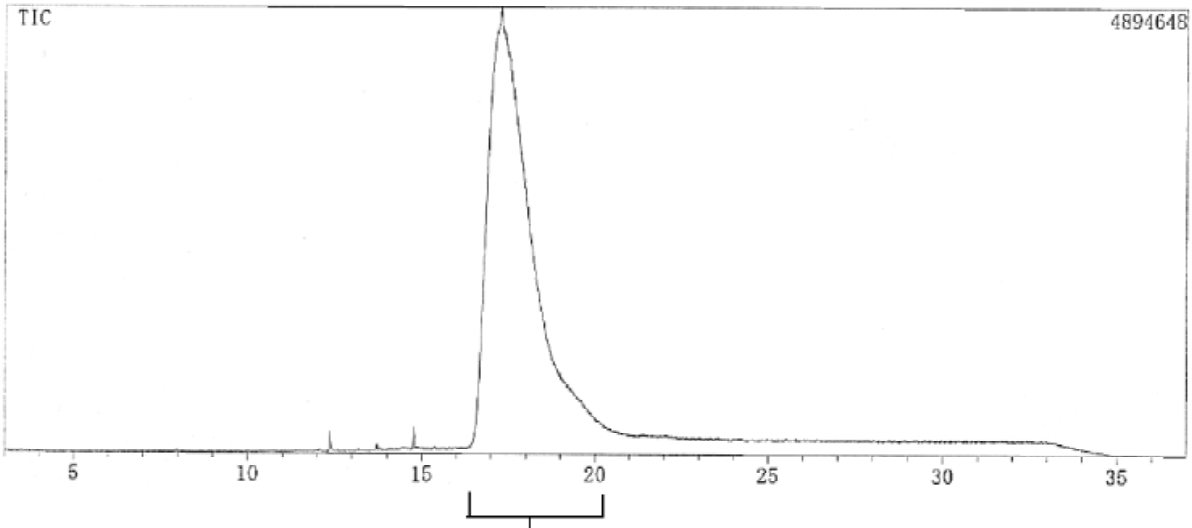
1. Hikichi, S.; Hareau, G. P.-J.; Sato, F. *Tetrahedron Lett*. **1997**, *38*, 8299.
2. Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681.
3. Mikami, K.; Osawa, A.; Isaka, A.; Sawa, E.; Shimizu, M.; Terada, M.; Kubodera, N.; Nakagawa, K.; Tsugawa, N.; Okano, T. *Tetrahedron Lett*. **1998**, *39*, 3359.


OH
H
OTBS
TBSO
^{1}H NMR (300 MHz, CDCl$_3$)


OH
OTBS
TBSO
6-13C-1
1H NMR (300 MHz, CDCl3)
13C- 1H coupling

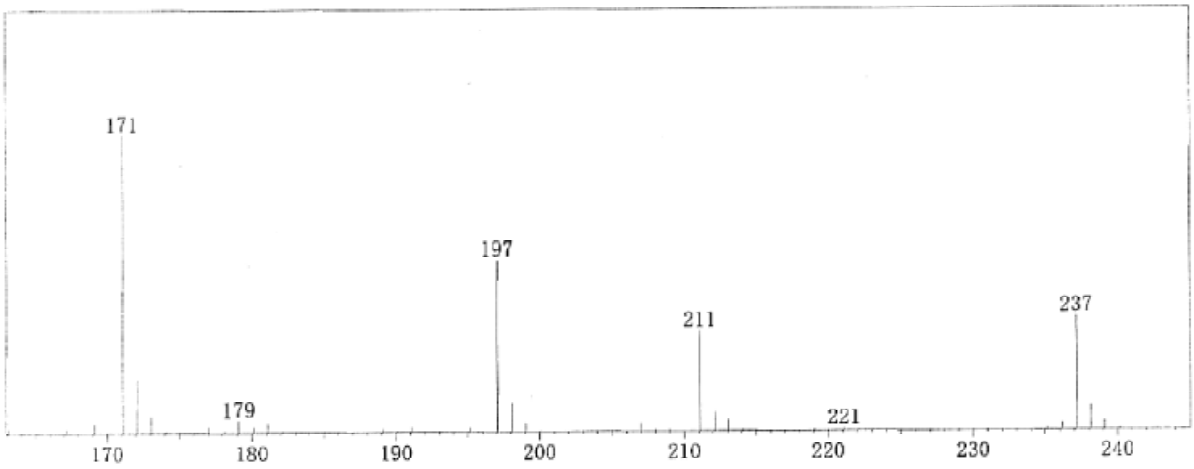


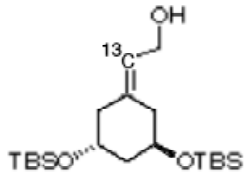
Total Ion Chromatography



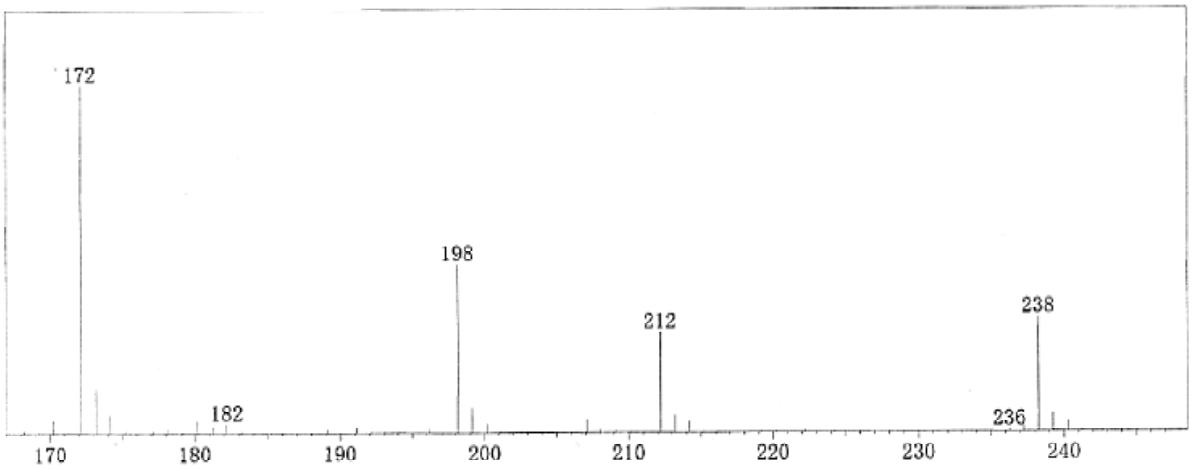
All scaning data of this region were averaged.

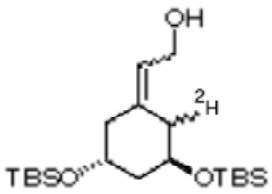
EI-MS spectra





EI-MS spectra





EI-MS spectra