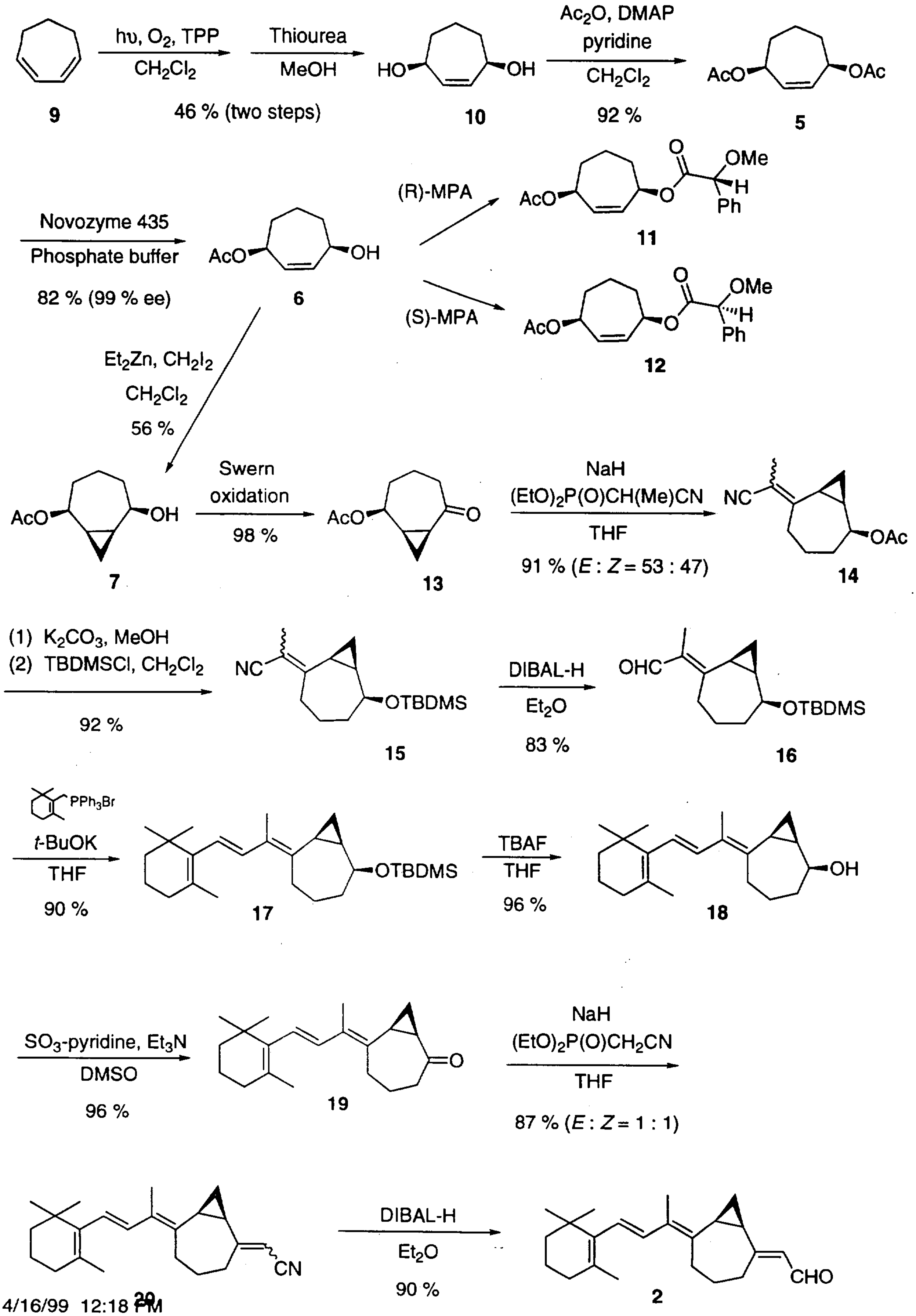
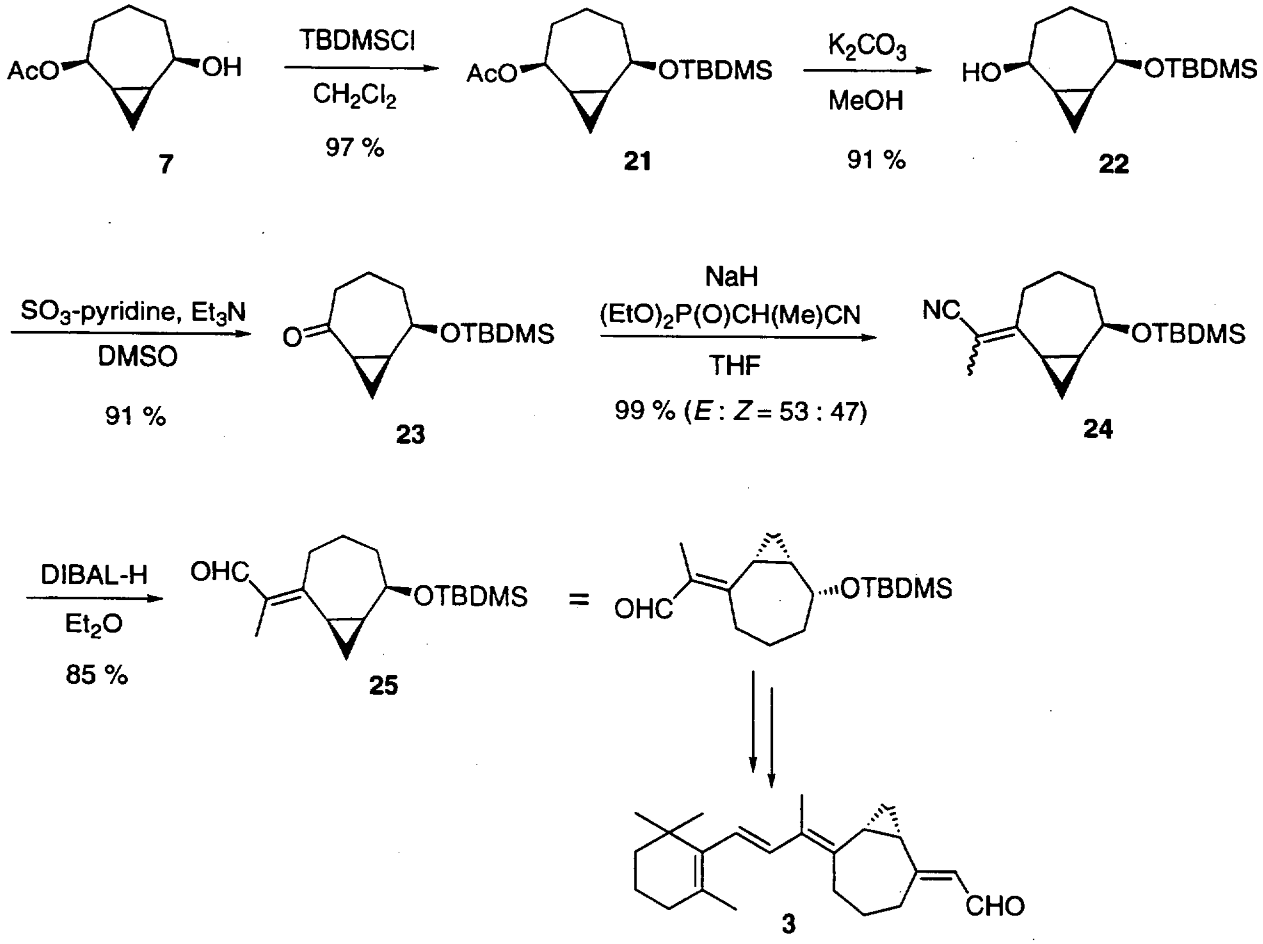
Synthesis of Retinal Analog 2

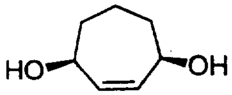


Synthesis of Retinal Analog 3



meso-2-Cycloheptene-1,4-diol (10)

To a solution of 1,3-cycloheptadiene (**9**) (97 %, 5.1 g, 52.6 mmol) in 400 mL of dry CH_2Cl_2 was added 15 mg of tetraphenylporphyrin. The resultant purple solution was irradiated with a 600 W tungsten halogen lamp at room temperature while oxygen was continuously bubbled through it. After 12 hours, the reaction was completed as indicated by TLC (visualized by $KMnO_4$ solution). The reaction mixture was concentrated on rotary evaporator to give c.a. 6.7 g endoperoxide contaminated with tetraphenylporphyrin. The endoperoxide was dissolved in anhydrous methanol (100 mL), and to this solution was added thiourea (4.1 g, 53 mmol). The mixture was stirred at room temperature for 24 hours and TLC showed that the reaction was complete (visualized by CAM solution). The resulting suspension was filtered through a layer of celite, and the filtrate was concentrated by rotary evaporator. The residue was purified by flash column chromatography (5-10 % methanol-CH_2Cl_2) to give 3.1 g *meso*-2-cyclohepten-1,4-diol (**10**) in 46 % yield.



^{1}H NMR ($CDCl_3$):

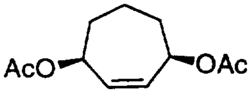
δ 5.73 (s, 2 H), 4.28 (d, *J* = 10.0 Hz, 2 H), 2.01 (m, 1 H), 1.78 (m, 2 H), 1.53-1.70 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ 135.67, 71.37, 35.98, 23.05.

MS (CI, NH_3): M/Z 129 $[M+1]^+$, 146 $[M+18]^+$

meso-2-Cycloheptene-1,4-diyl Diacetate (5)

To a solution of *meso*-2-cyclohepten-1,4-diol (**10**) (2.5 g, 19.5 mmol), pyridine (7.9 mL, 98 mmol) and 4-dimethylaminopyridine (10 mg) in anhydrous CH_2Cl_2 (50 mL) was added acetic anhydride (3.9 mL, 41 mmol) dropwise. The solution was stirred at room temperature overnight. The next morning, water (50 mL) was added and the mixture was extracted with Et_2O (4 x 50 mL). The combined ether extract was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The remaining residue was purified by flash column chromatography (10 % EtOAc-hexanes) to give 3.8 g *meso*-2-cyclohepten-1,4-diacetate (**5**) in 92 % yield.



^{1}H NMR ($CDCl_3$):

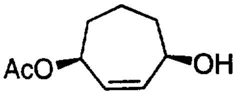
δ 5.66 (s, 2 H), 5.36 (dd, *J* = 10.3, 2.5 Hz, 2 H), 2.06 (m, 6 H), 1.98 (m, 1 H), 1.88 (m, 2 H), 1.80 (m, 1 H), 1.59 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ 169.98, 132.46, 73.55, 32.26, 22.89, 21.10.

MS (CI, NH_3): M/Z 230 $[M+18]^+$

Monoacetate (6)

In 225 mL of sodium phosphate buffer (pH 8.0, 100 mM), was added finely powdered *meso*-2-cyclohepten-1,4-diacetate (**5**) (3.75 g, 17.7 mmol), Novozym 435 (from Novo Nordisk, 0.75 g), and sodium azide (10 mg). The suspension was heated to 50°C by oil bath and was stirred at this temperature for 24 hours before cooling down to room temperature. The mixture was filtered through a layer of Celite and the solid was washed with EtOAc. The filtrate was extracted with EtOAc (4 x 50 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (40-100 % EtOAc-hexanes) to give 2.47 g monoacetate (**6**) in 82 % yield (99 % ee). 250 mg *meso*-2-cyclohepten-1,4-diol (11% yield from diacetate) was also isolated.



^{1}H NMR ($CDCl_3$):

δ 5.77 (d, *J* = 12.2 Hz, 1 H), 5.60 (d, *J* = 12.2 Hz, 1 H), 5.31 (d, *J* = 10.8 Hz, 1 H), 4.37 (d, *J* = 10.5 Hz, 1 H), 2.06 (s, 3 H), 1.99 (m, 1 H), 1.85 (m, 2 H), 1.74 (m, 1 H), 1.58 (m, 2 H).

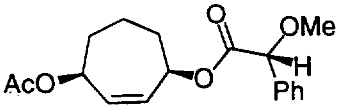
^{13}C NMR ($CDCl_3$): δ 170.37, 136.74, 130.98, 73.97, 71.40, 35.84, 32.28, 23.41, 21.13.

MS (CI, NH_3): M/Z 171 $[M+1]^+$, 188 $[M+18]^+$

Optical rotation: $[\alpha]_D = +6.95°$ (*c* 1.20, $CHCl_3$)

(*R*)-MPA ester (11)

To a solution of monoacetate (**6**) (26 mg, 0.15 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (125 mg, 0.65 mmol) and 4-dimethylaminopyridine (10 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (5 mL) was added (*R*)-(-)-α-methoxyphenylacetic acid (99% ee, 100 mg, 0.60 mmol). The reaction was stirred at room temperature for 30 min before water (15 mL) was added. The mixture was extracted with Et_2O (3 x 15 mL), dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (5-15 % EtOAc-hexanes) to give 39 mg (*R*)-MPA ester (**11**) in 80 % yield.



^{1}H NMR ($CDCl_3$):

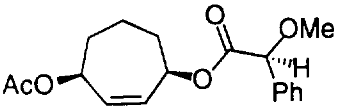
δ 7.41 (m, 2 H), 7.33 (m, 3 H), 5.56 (dm, *J* = 12.2 Hz, 1 H), 5.39 (m, 2 H), 5.28 (d, *J* = 10.8 Hz, 1 H), 4.73 (s, 1 H), 3.38 (s, 3 H), 2.00 (s, 3 H), 1.94 (m, 1 H), 1.84 (m, 2 H), 1.74 (m, 1 H), 1.49-1.62 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ 170.04, 169.70, 136.00, 132.75, 131.72, 128.70, 128.58, 127.07, 82.54, 74.34, 73.52, 57.27, 32.24, 32.21, 22.79, 21.14.

MS (CI, NH_3): M/Z 319 $[M+1]^+$

(*S*)-MPA ester (12)

Following similar procedure as in the synthesis of (*R*)-MPA ester, 20 mg monoacetate (**6**) was coupled with (*S*)-(+)-α-methoxyphenylacetic acid (99% ee, 100 mg, 0.60 mmol) to give 31 mg (*S*)-MPA ester (**12**) in 83 % yield.



^{1}H NMR ($CDCl_3$):

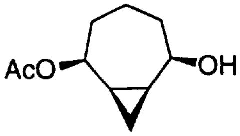
δ 7.41 (m, 2 H), 7.33 (m, 3 H), 5.63 (s, 2 H), 5.40 (d, *J* = 10.7 Hz, 1 H), 5.30 (d, *J* = 10.7 Hz, 1 H), 4.74 (s, 1 H), 3.39 (s, 3 H), 2.02 (s, 3 H), 1.82 (m, 2 H), 1.66 (m, 2 H), 1.51 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ 170.09, 169.73, 136.08, 133.03, 131.75, 128.70, 128.58, 127.08, 82.53, 74.25, 73.50, 57.32, 32.26, 31.85, 22.50, 21.18.

MS (CI, NH_3): M/Z 319 $[M+1]^+$

Cyclopropyl monoacetate (7)

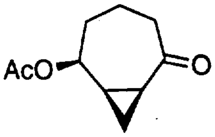
Diethylzinc (1.0 M solution in hexanes, 10 mL, 10 mmol) was added slowly to a solution of diiodomethane (5.49 g, 20.5 mmol) in anhydrous CH_2Cl_2 (80 mL) at 0°C. The mixture was stirred at this temperature for 10 min before it was cooled down to -78°C by dry ice / acetone bath. A solution of monoacetate (**6**) (710 mg, 4.2 mmol) in CH_2Cl_2 (10 mL) was introduced slowly. The mixture was warmed up slowly to room temperature and stirred for an additional 2 hours. The reaction was quenched by addition of saturated ammonium chloride aqueous solution (50 mL) at 0°C and stirred for 10 min. The mixture was extracted with Et_2O (4 x 50 mL), and the combined ether extract was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by flash column chromatography (40-50 % EtOAc-hexanes) to give 436 mg cyclopropyl monoacetate (**7**) in 56 % yield.



^{1}H NMR ($CDCl_3$):
δ 5.15 (dt, *J* = 11.5, 3.2 Hz, 1 H), 4.05 (dt, *J* = 11.2, 3.2 Hz, 1 H), 2.03 (s, 3 H), 1.78 (m, 2 H), 1.60 (m, 1 H), 1.16-1.33 (m, 4 H), 1.01 (m, 1 H), 0.80 (m, 1 H), 0.51 (m, 1 H).
^{1}H NMR (C_6D_6):
δ 5.19 (dt, *J* = 11.5, 3.4 Hz, 1 H), 3.68 (m, 1 H), 1.71 (s, 3 H), 1.57 (m, 1 H), 1.46 (m, 1 H), 1.02-1.18 (m, 3 H), 0.95 (m, 1 H), 0.85 (m, 1 H), 0.54-0.66 (m, 2 H), 0.20 (m, 1 H).
^{13}C NMR ($CDCl_3$): δ 170.51, 74.33, 71.50, 34.98, 31.27, 21.47, 21.21, 20.76, 18.25, 0.53.
MS (CI, NH_3): M/Z 185 $[M+1]^+$, 202 $[M+18]^+$
Optical rotation: $[\alpha]_D$ = - 49.8° (*c* 0.85, $CHCl_3$)

Cyclopropyl ketone (13)

To a solution of oxalyl chloride (2 mL, 2.0 M solution in CH_2Cl_2, 4 mmol) in anhydrous CH_2Cl_2 (8 mL) was added a solution of methyl sulfoxide (0.62 mL, 9 mmol) in CH_2Cl_2 (2 mL) at -60°C. The mixture was stirred for 10 min at -60°C before a solution of cyclopropyl monoacetate (7) (350 mg, 1.9 mmol) in CH_2Cl_2 (4 mL) was introduced to it, also at -60°C. The resulting mixture was stirred at this temperature for an additional 20 minutes. Triethylamine (2 mL) was added to the reaction mixture, and the suspension was warmed up slowly to room temperature. Water (50 mL) was added to the mixture which was then extracted with Et_2O (4 x 40 mL). The combined ether extract was washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated by rotary evaporator, and purified by flash column chromatography (30 % EtOAc-hexanes) to give 340 mg cyclopropyl ketone (**13**) in 98 % yield.



^{1}H NMR ($CDCl_3$):

δ 5.24 (dt, *J* = 11.4, 3.3 Hz, 1 H), 2.29-2.40 (m, 2 H), 2.06 (s, 3 H), 1.95 (m, 2 H), 1.74 (m, 2 H), 1.58 (m, 1 H), 1.41 (m, 1 H), 1.29 (m, 1 H), 1.16 (m, 1 H).

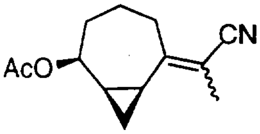
^{13}C NMR ($CDCl_3$): δ 210.03, 170.24, 72.91, 41.12, 30.69, 28.18, 22.68, 21.33, 20.94, 11.07.

MS (CI, NH_3): M/Z 183 $[M+1]^+$, 200 $[M+18]^+$

Optical rotation: $[\alpha]_D$ = - 38.0° (*c* 1.13, $CHCl_3$)

(*E*/*Z*)-Acetoxy nitriles (14)

To a suspension of sodium hydride (60 % in mineral oil, 160 mg, 4 mmol) in anhydrous THF (20 mL) was added a solution of diethyl (1-cyanoethyl)phosphonate (780 mg, 4 mmol) in THF (10 mL) over a period of 5 min. The mixture was stirred at room temperature for 20 min before a solution of cyclopropyl ketone (**13**) (330 mg, 1.8 mmol) in THF (10 mL) was introduced to it. The reaction was allowed to proceed at room temperature for 1 hour before it was quenched by addition of water (40 mL). The mixture was extracted with Et_2O (4 x 40 mL), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, concentrated by rotary evaporator, and purified by flash column chromatography (20 % EtOAc-hexanes) to give 360 mg of (*E*/*Z*)-acetoxy nitriles (**14**) in 91 % yield. The *E*/*Z* (*cis* : *trans* = 47 : 53 as indicated by ^{1}H NMR) isomers of nitriles can not be separated by flash column chromatography, therefore they were used as a mixture for the next reaction and were separated from each other at a later stage.



^{1}H NMR ($CDCl_3$):

δ 5.13 (m, 2 H), 2.80 (m, 1 H), 2.50 (m, 1 H), 2.29 (m, 1 H), 2.04 (m, 1 H) 2.032 (s, 3 H), 2.029 (s, 3 H), 1.97 (s, 3 H), 1.90 (m, 1 H), 1.89 (s, 3 H), 1.73-1.83 (m, 4 H), 1.45-1.71 (m, 5 H), 1.06-1.24 (m, 4 H), 0.97 (m, 2 H).

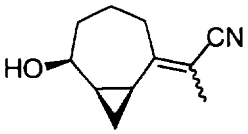
^{13}C NMR ($CDCl_3$): δ 170.26, 170.15, 158.09, 157.88, 120.22, 119.90, 104.64, 104.30, 72.77, 72.63, 33.83, 30.51, 30.31, 29.14, 24.16, 22.90, 22.51, 22.16, 21.95, 21.27, 18.27, 16.33, 16.12, 8.65, 8.45.

MS (CI, NH_3): M/Z 237 $[M+18]^+$

Optical rotation: $[\alpha]_D = -80.5°$ (*c* 1.11, $CHCl_3$)

(*E*/*Z*)-Hydroxy nitriles

To a solution of acetoxy nitriles (**14**) (210 mg, 0.96 mmol) in methanol (20 mL) was added potassium carbonate (100 mg, 0.72 mmol). The mixture was stirred at room temperature for 2 hours and TLC indicated that the reaction was complete. The solution was partitioned between EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (80 % EtOAc-hexanes) to give 164 mg (*E*/*Z*)-hydroxy nitriles in 96 % yield.



^{1}H NMR ($CDCl_3$):

δ 4.04 (m, 2 H), 2.80 (m, 1 H), 2.50 (m, 1 H), 2.31 (m, 1 H), 2.01 (m, 1 H), 1.97 (s, 3 H), 1.90 (m, 1 H), 1.88 (s, 3 H), 1.60-1.86 (m, 7 H), 1.43 (m, 2 H), 1.00-1.21 (m, 4 H), 0.96 (m, 2 H).

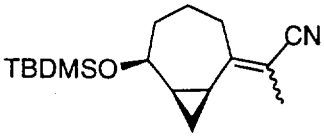
^{13}C NMR ($CDCl_3$): δ 159.2, 159.0, 120.4, 120.0, 103.7, 103.3, 70.28, 70.20, 34.07, 34.05, 34.01, 29.19, 25.62, 25.33, 24.45, 23.21, 22.13, 18.41, 16.24, 16.00, 8.20, 7.86.

MS (CI, NH_3): M/Z 195 $[M+18]^+$

Optical rotation: $[\alpha]_D = -90.4°$ (*c* 1.25, $CHCl_3$)

(*E*/*Z*)-*tert*-Butyldimethylsilyloxy nitriles (15)

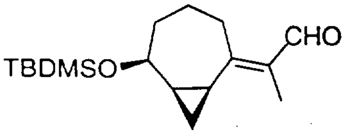
To a solution of (*E*/*Z*)-hydroxy nitriles (110 mg, 0.62 mmol), imidazole (204 mg, 3 mmol) and 4-dimethylaminopyridine (10 mg) in anhydrous CH_2Cl_2 (20 mL) was added *tert*-butyldimethylsilyl chloride (155 mg, 1 mmol). The reaction was stirred at room temperature for 2 hours before it was quenched by addition of water (40 mL). The mixture was extracted with Et_2O (4 x 30 mL), and the combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (10 % Et_2O-hexanes) to give 173 mg (*E*/*Z*)-*tert*-butyldimethylsilyloxy nitriles (**15**) in 96 % yield.



^{1}H NMR ($CDCl_3$):
δ 4.15 (m, 1 H), 4.09 (m, 1 H), 2.57 (m, 1 H), 2.27 (m, 2 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.95 (s, 3 H), 1.85 (s, 3 H), 1.73 (m, 1 H), 1.59-1.68 (m, 6 H), 1.42 (m, 2 H), 1.24 (m, 3 H), 1.13 (m, 1 H), 0.94 (m, 2 H), 0.86 (s, 18 H), 0.047 (s, 3 H), 0.038 (s, 3 H), 0.029 (s, 3 H), 0.018 (s, 3 H).
^{13}C NMR ($CDCl_3$): δ 159.3, 159.1, 120.4, 120.1, 103.6, 103.2, 69.61, 69.21, 35.27, 34.68, 34.59, 30.96, 25.76, 24.76, 24.15, 23.49, 21.94, 18.42, 18.39, 18.12, 18.09, 16.21, 16.15, 9.63, 9.57, -4.80, -4.82, -4.88, -4.93.
MS (CI, NH_3): M/Z 309 $[M+18]^+$
Optical rotation: $[\alpha]_D$ = - 43.7° (*c* 0.88, $CHCl_3$)

(*E*/*Z*)-*tert*-Butyldimethylsilyloxy aldehydes (16 and 16')

To a solution of (*E*/*Z*)-*tert*-butyldimethylsilyloxy nitriles (**15**) (170 mg, 0.58 mmol) in anhydrous Et_2O (10 mL) was added diisobutylaluminum hydride (1.0 M solution in hexanes, 1.0 mL, 1.0 mmol) over a period of 5 min at -78°C. The reaction was stirred at -78°C for 5 hours before it was quenched by addition of EtOAc (5 mL). The mixture was warmed up to room temperature slowly and poured into silica gel / water (3 mL) suspension in Et_2O which was then stirred at room temperature for 30 min. The silica gel was removed by filtration and was washed with additional EtOAc (50 mL). The filtrate was concentrated by rotary evaporator and purified by flash column chromatography (10 % EtOAc-hexanes) to give 142 mg (*E*/*Z*)-*tert*-butyldimethylsilyloxy aldehydes (**16** and **16'**) in 83 % yield. The *E*/*Z* isomers of the aldehydes were separated by flash column chromatography (3-8 % EtOAc-hexanes).



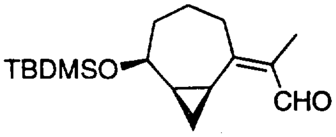
16

^{1}H NMR ($CDCl_3$):

δ 10.07 (s, 1 H), 4.18 (m, 1 H), 2.65 (m, 1 H), 2.59 (m, 1 H), 1.83 (s, 3 H), 1.80 (m, 1 H), 1.58-1.76 (m, 3 H), 1.47 (m, 1 H), 1.39 (m, 1 H), 1.17 (m, 1 H), 0.98 (m, 1 H), 0.83 (s, 9 H), 0.025 (s, 3 H), 0.010 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ 191.0, 162.0, 133.2, 69.20, 34.24, 30.29, 29.30, 25.75, 24.63, 21.83, 18.15, 11.24, 10.25, -4.85.

MS (CI, NH_3): M/Z 312 $[M+18]^+$



16'

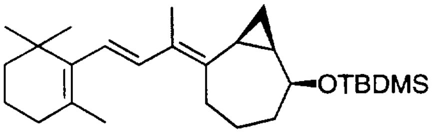
^{1}H NMR ($CDCl_3$):

δ 10.45 (s, 1 H), 4.30 (m, 1 H), 2.64 (m, 1 H), 2.14 (m, 1 H), 1.82 (m, 1 H), 1.69 (s, 3 H), 1.58-1.74 (m, 4 H), 1.08-1.20 (m, 3 H), 0.77 (s, 9 H), -0.030 (s, 3 H), -0.033 (s, 3 H).

MS (CI, NH_3): M/Z 312 $[M+18]^+$

tert-Butyldimethylsilyl ether (17)

Butyllithium (2.5 M solution of hexanes, 0.6 mL, 1.5 mmol) was added to a suspension of β-cyclocitryl triphenylphosphonium bromide (820 mg, 1.71 mmol) in anhydrous THF (5 mL). The mixture turned into a deep red solution which was stirred at room temperature for 10 min before a solution of *tert*-butyldimethylsilyloxy aldehyde (**16**) in THF (1 mL) was introduced to it. The reaction was allowed to proceed at room temperature overnight. The mixture was poured into water and extracted with hexanes (2 x 15 mL). The combined organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (eluted with hexanes) to give 61 mg of *tert*-butyldimethylsilyl ether (**17**) in 90 % yield.



^{1}H NMR ($CDCl_3$):

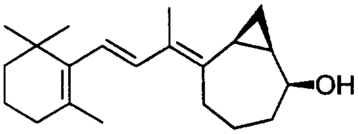
δ 6.39 (d, *J* = 16.0 Hz, 1 H), 6.00 (d, *J* = 16.0 Hz, 1 H), 4.24 (m, 1 H), 2.51 (m, 1 H), 2.08 (m, 1 H), 2.00 (m, 2 H), 1.94 (s, 3 H), 1.70 (s, 3 H), 1.42-1.66

(m, 6 H), 1.19-1.33 (m, 2 H), 1.01 (s, 6 H), 0.82-0.97 (m, 4 H), 0.85 (s, 9 H), 0.04 (s, 3 H), 0.02 (s, 3 H).

MS (CI, NH_3): M/Z 432 $[M+18]^+$

Cyclopropyl alcohol (18)

To a solution of *tert*-butyldimethylsilyl ether (**17**) (45 mg, 0.108 mmol) in THF (20 mL) was added tetrabutylammonium fluoride (1.0 M solution in THF, 0.3 mL, 0.3 mmol). The mixture was stirred at 70 °C for 4 hours before it was concentrated by rotary evaporator. The residue was purified by flash column chromatography (7 % EtOAc-hexanes) to render 30 mg cyclopropyl alcohol (**18**) in 96 % yield.



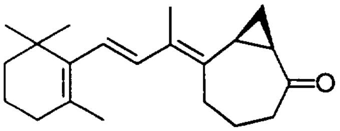
^{1}H NMR (C_6D_6):

δ 6.62 (d, *J* = 16.0 Hz, 1 H), 6.25 (d, *J* = 16.0 Hz, 1 H), 4.01 (m, 1 H), 2.37 (m, 1 H), 2.03 (m, 1 H), 2.01 (s, 3 H), 1.95 (t, *J* = 6.3 Hz, 2 H), 1.80 (s, 3 H), 1.26-1.62 (m, 8 H), 1.13 (s, 6 H), 1.10 (m, 1 H), 0.88 (m, 1 H), 0.77 (m, 1 H), 0.58 (m, 1 H).

MS (CI, NH_3): M/Z 301 $[M+1]^+$

Cyclopropyl ketone (19)

To a solution of cyclopropyl alcohol (**18**) (20 mg, 0.067 mmol) in anhydrous DMSO (4.0 mL) was added triethylamine (0.4 mL, 2.8 mmol) and followed by sulfur trioxide pyridine complex (120 mg, 0.75 mmol). The mixture was stirred at room temperature for 40 min before it was poured into water and extracted with a mixture of hexanes and ether (1 : 2). The combined organic phase was washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (6 % EtOAc-hexanes) to give 16.0 mg cyclopropyl ketone (**19**) in 80% yield.



^{1}H NMR ($CDCl_3$):

δ 6.36 (d, J = 16.0 Hz, 1 H), 6.16 (d, J = 15.9 Hz, 1 H), 2.76 (m, 1 H), 2.24 (m, 2 H), 1.97-2.11 (m, 5 H), 2.02 (s, 3 H), 1.69 (s, 3 H), 1.62 (m, 3 H), 1.55 (m, 2 H), 1.47 (m, 2 H), 1.35 (m, 1 H), 1.02 (s, 3 H), 1.01 (s, 3 H).

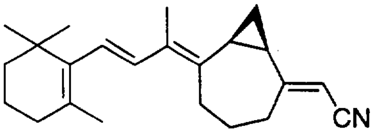
^{1}H NMR (C_6D_6):

δ 6.46 (d, J = 16.0 Hz, 1 H), 6.26 (d, J = 16.1 Hz, 1 H), 2.47 (m, 1 H), 1.95 (t, J = 6.1 Hz, 2 H), 1.90 (m, 1 H), 1.88 (s, 3 H), 1.82 (m, 2 H), 1.75 (s, 3 H), 1.55-1.63 (m, 3 H), 1.48 (m, 3 H), 1.25 (m, 2 H), 1.114 (s, 3 H), 1.107 (s, 3 H), 0.84 (m, 2 H).

MS (CI, NH_3): M/Z 299 $[M+1]^+$

(13*E*/13*Z*)-11,12-Cyclopropylretinyl nitriles (20)

To a suspension of sodium hydride (60 % in mineral oil, 40 mg, 1 mmol) in anhydrous THF (5 mL) was added diethyl cyanomethylphosphonate (180 mg, 1 mmol) in THF (5 mL) at 0°C under argon. The mixture was stirred for 20 min at room temperature. A solution of ketone (**19**) (30 mg, 0.1 mmol) in THF (3 mL) was introduced. The reaction was allowed to proceed at room temperature for 2 hours and was quenched by addition of iced water (20 mL). The mixture was extracted with Et_2O (3 x 20 mL), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (10-15 % EtOAc-hexanes) to give 28 mg nitriles (**20** and **20'**) in 87 % yield. The nitriles were a mixture of 13-*cis* (**20'**) / 13-*trans* (**20**) isomers which could be separated by preparative thin-layer chromatography (10 % EtOAc-hexanes). **20** and **20'** was characterized by ^{1}H NMR NOE experiments.

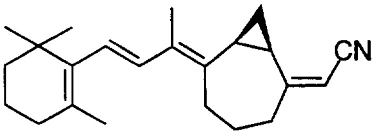


20

^{1}H NMR (C_6D_6):

δ 6.47 (d, J = 16 .1 Hz, 1 H), 6.26 (d, J = 15.9 Hz, 1 H), 4.66 (s, 1 H), 2.45 (m, 1 H), 2.35 (m, 1 H), 1.95 (m, 2 H), 1.88 (s, 3 H), 1.76 (s, 3 H), 1.58 (m, 2 H), 1.48 (m, 2 H), 1.36 (m, 4 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 0.88 (m, 2 H), 0.69 (m, 1 H), 0.54 (m, 1 H).

MS (CI, NH_3): M/Z 322 $[M+1]^+$, 339 $[M+18]^+$



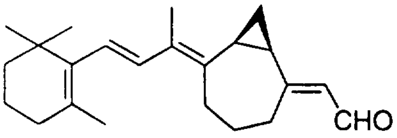
20'

^{1}H NMR (C_6D_6):

δ 6.49 (d, J = 16 .0 Hz, 1 H), 6.24 (d, J = 15.7 Hz, 1 H), 4.46 (s, 1 H), 2.29 (m, 1 H), 2.22 (m, 1 H), 1.95 (m, 2 H), 1.85 (s, 3 H), 1.77 (s, 3 H), 1.58 (m, 2 H), 1.48 (m, 2 H), 1.31 (m, 4 H), 1.11 (s, 6 H), 0.96 (m, 2 H), 0.80 (m, 1 H), 0.62 (m, 1 H).

(13*E*/13*Z*)-11,12-Cyclopropylretinyl aldehydes (2)

To a solution of (13*E*)-nitrile (**20**) (10 mg, 0.031 mmol) in anhydrous Et_2O (5 mL) was added diisobutylaluminum hydride (1.0 M solution in hexanes, 0.2 mL, 0.2 mmol) at -78°C under argon. The reaction mixture was stirred at -78°C for 2 hours and was quenched by addition of EtOAc (2 mL) at -78°C. The mixture was warmed up to room temperature and poured into a slurry of wet silica gel suspension in Et_2O. The suspension was stirred at room temperature for 30 min. The silica gel was removed by filtration and washed with additional Et_2O (100 mL). The filtrate was concentrated and purified by flash column chromatography (10-15 % EtOAc-hexanes) to give 9 mg (13*E*)-aldehyde (**2**) in 90 % yield. (13*Z*)-Aldehyde (**20'**) was obtained from the reduction of (13*Z*)-nitrile (**2'**) following a similar procedure.

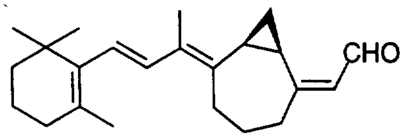


2

^{1}H NMR (C_6D_6):

δ 9.89 (d, J = 8.0 Hz, 1 H), 6.51 (d, J = 16.1 Hz, 1 H), 6.28 (d, J = 15.7 Hz, 1 H), 6.07 (d, J = 7.7 Hz, 1 H), 2.45 (m, 2 H), 1.96 (m, 2 H), 1.78 (s, 3 H), 1.63 (s, 3 H), 1.60 (m, 2 H), 1.48 (m, 2 H), 1.27 (m, 4 H), 1.13 (s, 3 H), 1.12 (s, 3 H), 0.81 (m, 3 H), 0.76 (m, 1 H).

MS (CI, NH_3): M/Z 325 $[M+1]^+$



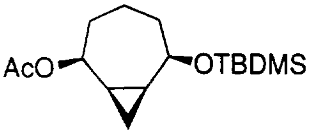
2'

^{1}H NMR (C_6D_6):

δ 10.08 (d, J = 7.5 Hz, 1 H), 6.53 (d, J = 15.7 Hz, 1 H), 6.27 (d, J = 14.8 Hz, 1 H), 5.87 (d, J = 7.5 Hz, 1 H), 2.29 (m, 2 H), 1.96 (m, 2 H), 1.76 (s, 3 H), 1.63 (s, 3 H), 1.60 (m, 2 H), 1.48 (m, 2 H), 1.24 (m, 4 H), 1.12 (s, 6 H), 0.88 (m, 3 H), 0.80 (m, 1 H).

tert-Butyldimethylsilyloxy cyclopropyl acetate (21)

To a solution of cyclopropyl monoacetate (**7**) (300 mg, 1.63 mmol), imidazole (544 mg, 8 mmol) and 4-dimethylaminopyridine (10 mg) in anhydrous CH_2Cl_2 (20 mL) was added *tert*-butyldimethylsilyl chloride (310 mg, 2 mmol). The mixture was stirred at room temperature for 1 hour before it was poured into water (40 mL) and extracted with ether (3 x 40 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (10-15 % EtOAc-hexanes) to render 469 mg *tert*-butyldimethylsilyloxy cyclopropyl acetate (**21**) in 97 % yield.



^{1}H NMR ($CDCl_3$):

δ 5.15 (dm, J = 9.7 Hz, 1 H), 4.05 (dm, J = 9.4 Hz, 1 H), 2.05 (s, 3 H), 1.71 (m, 2 H), 1.60 (m, 1 H), 1.20-1.32 (m, 4 H), 0.98 (m, 1 H), 0.89 (s, 9 H), 0.84 (m, 1 H), 0.51 (m, 1 H), 0.079 (s, 3 H), 0.062 (s, 3 H).

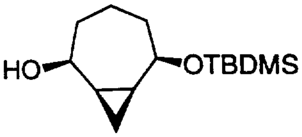
^{13}C NMR ($CDCl_3$): δ 170.54, 74.67, 72.38, 35.00, 31.16, 25.89, 21.66, 21.47, 21.09, 18.24, 17.91, 0.94, -4.63,-4.67.

MS (CI, NH_3): M/Z 299 $[M+1]^+$, 316 $[M+18]^+$

Optical rotation: $[\alpha]_D$ = - 14.3° (c 1.08, $CHCl_3$)

tert-Butyldimethylsilyloxy cyclopropyl alcohol (22)

To a solution of *tert*-butyldimethylsilyloxy cyclopropyl acetate (**21**) (423 mg, 1.42 mmol) in methanol (5 mL) was added potassium carbonate (250 mg, 1.81 mmol). The reaction was stirred at room temperature for 5 hours before a mixture of hexanes (20 mL) and ether (20 mL) was added to it. The mixture was filtered and concentrated by rotary evaporator. The residue was purified by flash column chromatography (10 % EtOAc-hexanes) to give 332 mg *tert*-butyldimethylsilyloxy cyclopropyl alcohol (**22**) in 91 % yield.



^{1}H NMR ($CDCl_3$):

δ 4.37 (t, J = 5.4 Hz, 1 H), 4.20 (t, J = 5.6 Hz, 1 H), 1.86 (m, 2 H), 1.74 (m, 1 H), 1.62 (m, 2 H), 1.38 (m, 1 H), 1.03 (m, 1 H), 0.97 (m, 1 H), 0.92 (s, 9 H), 0.89 (m, 1 H), 0.57 (m, 1 H), 0.121 (s, 3 H), 0.096 (s, 3 H).

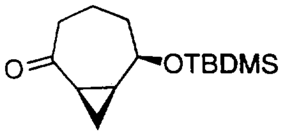
^{13}C NMR ($CDCl_3$): δ 69.53, 67.71, 36.19, 36.14, 25.74, 21.28, 21.24, 18.22, 17.16, 5.10, -5.17.

MS (CI, NH_3): M/Z 257 $[M+1]^+$, 274 $[M+18]^+$

Optical rotation: $[\alpha]_D = +12.8°$ (c 1.06, $CHCl_3$)

tert-Butyldimethylsilyloxy cyclopropyl ketone (23)

To a solution of *tert*-butyldimethylsilyloxy cyclopropyl alcohol (**22**) (280 mg, 1.10 mmol) in anhydrous DMSO (7 mL) was added triethylamine (1.0 mL, 7.2 mmol) followed by addition of sulfur trioxide pyridine complex (700 mg, 4.4 mmol). The mixture was stirred at room temperature for 40 min before it was poured into water and extracted with Et_2O (3 x 30 mL). The combined organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (9 % EtOAc-hexanes) to give 256 mg *tert*-butyldimethylsilyloxy cyclopropyl ketone (**23**) in 91 % yield.



^{1}H NMR ($CDCl_3$):

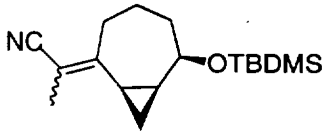
δ 4.17 (dt, J = 10.4, 3.2 Hz, 1 H), 2.33 (m, 2 H), 1.86 (m, 2 H), 1.73 (m, 1 H), 1.62 (m, 2 H), 1.43 (m, 1 H), 1.27 (m, 1 H), 1.13 (m, 1 H), 0.90 (s, 9 H), 0.091 (s, 3 H), 0.084 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ 210.95, 70.84, 41.07, 34.47, 28.48, 26.10, 25.78, 21.18, 18.14, 11.22, -4.75.

MS (CI, NH_3): M/Z 255 $[M+1]^+$, 272 $[M+18]^+$
Optical rotation: $[\alpha]_D = +37.0°$ (*c* 0.90, $CHCl_3$)

(*E*/*Z*)-*tert*-Butyldimethylsilyloxy cyclopropyl nitriles (24)

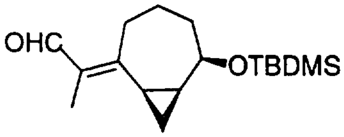
To a suspension of sodium hydride (60 % in mineral oil, 96 mg, 4.0 mmol) in anhydrous THF (14 mL) was added a solution of diethyl (1-cyanoethyl)phosphonate (880 mg, 4.6 mmol) in THF (2 mL). The mixture was stirred at room temperature for 15 min before a solution of *tert*-butyldimethylsilyloxy cyclopropyl ketone (**23**) (230 mg, 0.91 mmol) in THF (5 mL) was introduced to it. The reaction was allowed to proceed at room temperature for 1 hour before it was poured into water and extracted with ether (3 x 20 mL). The combined ether extract was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated by rotary evaporator. The residue was purified by flash column chromatography (3-8 % EtOAc-hexanes) to give 263 mg (*E*/*Z*)-*tert*-butyldimethylsilyloxy cyclopropyl nitriles (**24**) in 99 % yield. The *E*/*Z* isomers (*cis* : *trans* = 47 : 53 as indicated by ^1H NMR) isomers of nitriles can not be separated by flash column chromatography, they were used as a mixture for the next reaction and separated at that stage.



^1H NMR ($CDCl_3$):
δ 4.15 (m, 1 H), 4.09 (m, 1 H), 2.57 (m, 1 H), 2.27 (m, 2 H), 2.08 (m, 1 H), 1.98 (m, 1 H), 1.96 (s, 3 H), 1.86 (s, 3 H), 1.74 (m, 1 H), 1.60-1.68 (m, 6 H), 1.42 (m, 2 H), 1.25 (m, 3 H), 1.14 (m, 1 H), 0.96 (m, 2 H), 0.87 (s, 18 H), 0.046 (s, 3 H), 0.037 (s, 3 H), 0.029 (s, 3 H), 0.018 (s, 3 H).
^{13}C NMR ($CDCl_3$): δ 159.3, 159.1, 120.4, 120.1, 103.6, 103.2, 69.61, 69.21, 35.27, 34.68, 34.59, 30.96, 25.76, 24.76, 24.15, 23.49, 21.94, 18.42, 18.39, 18.12, 18.09, 16.21, 16.15, 9.63, 9.57, -4.80, -4.82, -4.88, -4.93.
MS (CI, NH_3): M/Z 309 $[M+18]^+$
Optical rotation: $[\alpha]_D = +45.0°$ (*c* 1.09, $CHCl_3$)

(*E*/*Z*)-*tert*-Butyldimethylsilyloxy cyclopropyl aldehydes (25 and 25')

Following similar procedure as in the synthesis of **16**, **24** was reduced by DIBAL-H to give **25** in 85 % yield. **25** was converted to retinal analog **3** following similar procedures as in the synthesis of analog **2**.



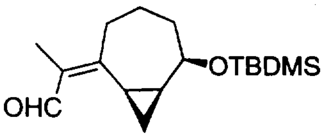
25

^{1}H NMR (CDCl$_3$):

δ 10.07 (s, 1 H), 4.18 (m, 1 H), 2.65 (m, 1 H), 2.59 (m, 1 H), 1.83 (s, 3 H), 1.80 (m, 1 H), 1.58-1.76 (m, 3 H), 1.47 (m, 1 H), 1.39 (m, 1 H), 1.17 (m, 1 H), 0.98 (m, 1 H), 0.83 (s, 9 H), 0.025 (s, 3 H), 0.010 (s, 3 H).

^{13}C NMR (CDCl$_3$): δ 191.0, 162.0, 133.2, 69.20, 34.24, 30.29, 29.30, 25.75, 24.63, 21.83, 18.15, 11.24, 10.25, -4.85.

MS (CI, NH$_3$): M/Z 312 $[M+18]^+$



25'

^{1}H NMR (CDCl$_3$):

δ 10.45 (s, 1 H), 4.30 (m, 1 H), 2.64 (m, 1 H), 2.14 (m, 1 H), 1.82 (m, 1 H), 1.69 (s, 3 H), 1.58-1.74 (m, 4 H), 1.08-1.20 (m, 3 H), 0.77 (s, 9 H), -0.030 (s, 3 H), -0.033 (s, 3 H).