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Catalytic Enantioselective Synthesis of (14*R*)-14-Hydroxy-4,14-*retro*-retinol from Retinyl Acetate

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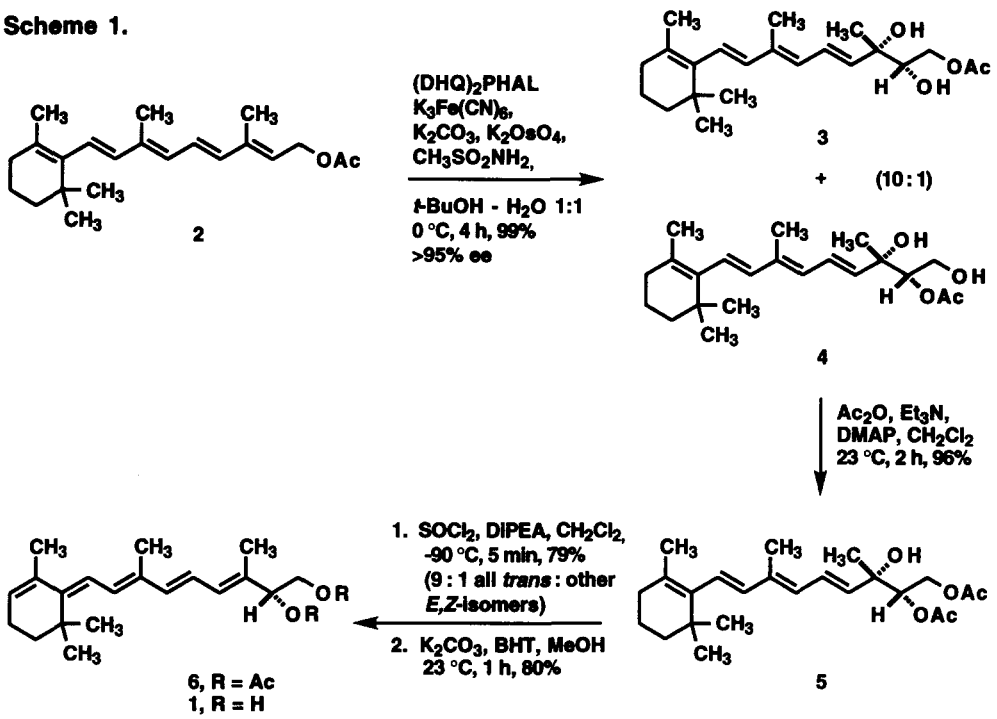
Summary: A simple and efficient synthesis of the biologically important vitamin A-derived retinoid (14R)-14-hydroxy-4,14-retro-retinol (1) from retinyl acetate in four steps is described.

The known role of retinol (vitamin A) in mammalian life has recently broadened to include a progenitor (prohormone) function for other biologically important retinoids, specifically anhydroretinol (AR) and (14*R*)-14-hydroxy-4,14-*retro*-retinol (**1**, 14-HRR). These retinoids appear to play a role in human T- and B-immune cell proliferation and activation, and bind to a common signal-transducing protein with opposing effects.[1-5] In retinol-depleted, serum-free cultures of HL-60 cells 14-HRR serves as a growth factor whereas retinoic acid is an inducer of differentiation followed by growth arrest.[6] Naturally formed **1** is available in trace amounts, and only after tedious isolation procedures. Two multistep syntheses of **1** have recently been reported which produce **1** admixed with various isomers.[7,8] We report herein a simple, enantioselective and efficient synthesis of **1** from commercially available retinyl acetate (**2**). This four-step conversion, which is outlined in Scheme 1, was based on our recent finding that the Sharpless asymmetric dihydroxylation, which is unsatisfactory for allylic alcohols or their bulky silyl ethers, proceeds very well with *p*-methoxybenzoate or certain other esters.[9]

The mechanistic model which we have presented for the bis-cinchona alkaloid–OsO_4-catalyzed dihydroxylation of olefins[10,11] led to the expectation that **2** or the corresponding *p*-methoxybenzoate ester might undergo position-selective dihydroxylation at the 13,14-olefinic linkage with high enantioselectivity.[12] This was confirmed experimentally as detailed in Scheme 1. The dihydroxylation of **2** occurred *exclusively* at the 13,14-olefinic linkage and with >40 : 1 enantioselectivity to give the desired diol **3** along with a little of **4**, the product of acetyl O,O-migration. Acetylation of the mixture afforded cleanly the 14,15-diacetate **5** which by dehydration with $SOCl_2$–diisopropylethylamine at -90 °C generated diacetate **6** of approximately 90% isomeric purity. At higher temperatures the elimination product contained >15% of various *E,Z*-isomers. Finally, deacetylation produced **1** of approximately 90% purity as determined by HPLC and ^1H NMR analysis. The experimental details for the transformations outlined in Scheme 1 appear below.

Three views of the proposed transition state for the enantioselective dihydroxylation of retinyl acetate **2** by the $(DHQ)_2PHAL$–OsO_4 complex are shown in Figure 1 and Figure 2. Dihydroxylation of the 13,14-olefinic linkage from the indicated enantioface is favored by extensive π-contacts between the polyene chain of **2** with the

Scheme 1.



catalytic U-shaped binding pocket composed of the two parallel methoxyquinoline units, OsO_4, and the phthalazine connector, as shown. Additional favorable contacts exist between the acetate group of **2** and the face of the phthalazine linker, and between the cyclohexyl ring of **2** and the edge of the methoxyquinoline walls of the catalyst. Reaction at other olefin positions is disfavored both by steric interactions between the cyclohexyl moiety of the substrate and the methoxyquinoline units of the catalyst and by the energetically unfavorable disruption of conjugation in the polyene chain of **2**.

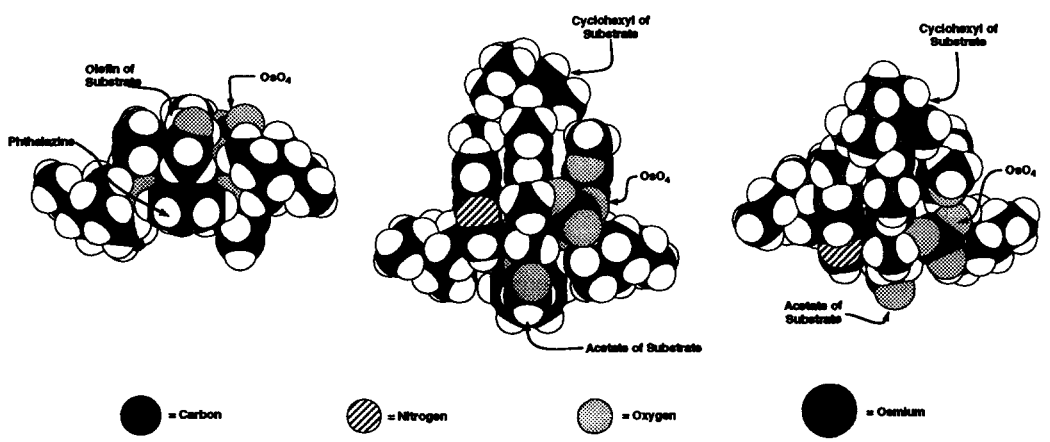


Figure 1. Three views of the proposed transition state of the asymmetric dihydroxylation of **2**.

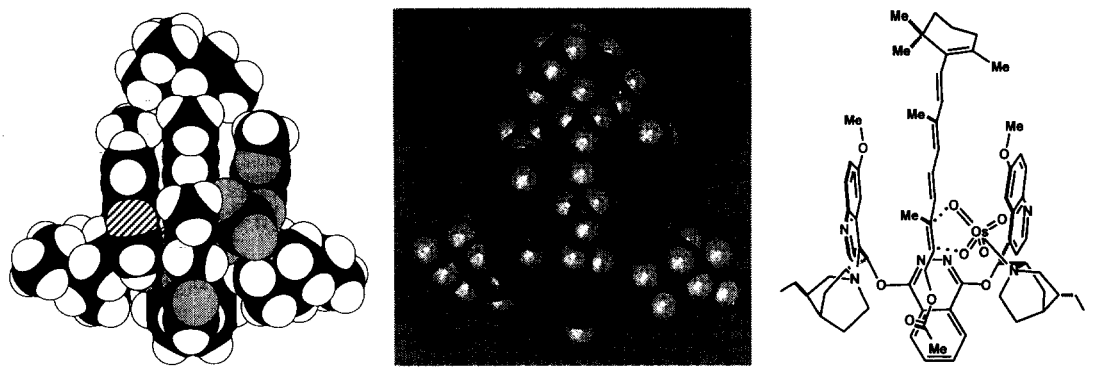


Figure 2. Three different representations of a front view of the proposed transition state for the asymmetric dihydroxylation of **2.**

Asymmetric Dihydroxylation of Retinyl Acetate (2). To a solution of retinyl acetate (**2**) (2.18 g, 6.02 mmol) in 84 mL of 1:1 *t*-BuOH–H_2O was added $K_3Fe(CN)_6$ (6.01 g, 18.3 mmol), K_2CO_3 (2.49 g, 18.3 mmol), methanesulfonamide (0.573 g, 6.02 mmol) and $(DHQ)_2PHAL$ (0.047 g, 0.060 mmol), and the mixture was cooled to 0 °C. $K_2OsO_4 \cdot 2H_2O$ (0.022g, 0.06 mmol) was added to the suspension, and the mixture was stirred vigorously for 4 h. Saturated aqueous Na_2SO_3 (50 mL) was added to the suspension, and the resulting mixture was extracted into ethyl acetate (3 x 75 mL). The combined organic layers were washed with 20 mL of 1M NaOH, 2 x 20 mL of brine, dried over Na_2SO_4 and concentrated. Filtration of the residue through a small plug of silica gel with 2:1 ethyl acetate–hexane containing 5% triethylamine afforded 2.4 g (99%) of a 10:1 mixture of **3** and **4**. Trituration with pentane afforded pure **3** (1.5 g, 63%) as a colorless solid: m.p. 87 °C; R_f = 0.18 (hexanes–EtOAc 50:50, Et_3N coated silica plate); UV (EtOH): λ 289, 224; $[\alpha]_D^{20}$ -7.8° (*c* 0.40, EtOH); FTIR (film) 3458, 2960, 2928, 2864, 1742, 1727, 1451, 1370, 1242, 1086, 1062, 1034, 973 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.85 (dd, 1H, *J* = 11.1, 15.2 Hz), 6.26 (s, 2H), 6.09 (d, 1H, *J* = 11.2 Hz), 5.69 (d, 1H, *J* = 15.2 Hz), 4.27 (dd, 1H, *J* = 2.7, 11.7 Hz), 4.11 (dd, 1H, *J* = 8.1, 11.7 Hz), 3.60 (dd, 1H, *J* = 2.4, 7.9 Hz), 2.48 (bs, 1H), 1.98 (bs, 1H), 1.96 (t, 2H, *J* = 6.2 Hz), 1.85 (s, 3H), 1.78 (s, 3H), 1.60 (s, 3H), 1.58 (m, 2H), 1.47 (m, 2H), 1.20 (s, 3H), 1.10 (s, 6H) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 170.9, 138.4, 138.2, 136.9, 136.0, 130.0, 129.1, 127.1, 126.2, 76.4, 74.1, 66.0, 39.9, 34.5, 33.2, 29.1 (2C), 24.0, 21.9, 20.4, 19.7, 12.7 ppm; EIMS (*m/z*) 362 $[M]^+$, 259, 175; HRMS calc'd for $[C_{22}H_{34}O_4]^+$: 362.2458, found 362.2444; ^1H NMR integration of mono-MTPA esters (400 MHz, C_6D_6): δ 4.70 (major), 4.50 (minor) determined enantiomeric purity of **3**.

Preparation of diacetate (5). To a solution of **3** and **4** (0.90 g, 2.5 mmol) in 25 mL of CH_2Cl_2 was added triethylamine (0.44 mL, 0.32 g, 3.1 mmol), DMAP (0.0020 g, 0.016 mmol), and acetic anhydride (0.26 mL, 0.28 g, 2.7 mmol). After stirring for 2 h, the mixture was diluted with 30 mL of saturated aqueous $NaHCO_3$ and was extracted 2x with 50 mL of ethyl acetate. The combined organic layers were washed with 20 mL of brine, dried over Na_2SO_4, filtered and concentrated. Filtration through a small plug of silica gel with 2:1 hexane–ethyl acetate containing 5% triethylamine afforded 0.96 g (96%) of a colorless syrup: R_f = 0.57 (hexanes–EtOAc 50:50, Et_3N coated silica plate); UV (EtOH): λ 289, 222; $[\alpha]_D^{20}$ -41° (*c* 0.42, MeOH); FTIR (film) 3477, 2962, 2929, 2865, 1747, 1446, 1370, 1243, 1225, 1059, 1039, 973 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.85 (dd, 1H, *J* = 11.3, 15.2 Hz), 6.25 (s, 2H), 6.08 (d, 1H, *J* = 12.0 Hz), 5.69 (d, 1H, *J* = 15.2 Hz), 5.32 (dd, 1H, *J* = 2.6, 8.4 Hz), 4.60 (dd, 1H, *J* = 2.6, 12.1 Hz), 4.17 (dd, 1H, *J* = 8.4, 12.1 Hz), 1.95 (t, 2H, *J* = 6.1 Hz), 1.90 (bs, 1H), 1.84 (s, 3H), 1.76 (s, 3H), 1.69 (s, 3H), 1.66 (s, 3H), 1.57 (m, 2H), 1.47 (m, 2H), 1.15 (s, 3H), 1.10 (s, 6H) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 170.3, 169.9, 138.3, 138.2, 136.2, 136.1, 129.7, 129.2, 127.2, 126.0, 76.7, 73.7, 63.3, 39.9, 34.5, 33.2, 29.1 (2C), 25.5, 21.9, 20.5, 20.3, 19.7, 12.6 ppm; EIMS (m/z) 404 $[M]^+$, 259, 175; HRMS calc'd for $C_{24}H_{36}O_5$: 404.2564, found 404.2577.

Preparation of Diacetate (6). To a -90 °C (liquid N_2–heptane bath) solution of **5** (0.91 g, 2.25 mmol) in 22 mL of CH_2Cl_2 was added diisopropylethylamine (1.57 mL, 1.16 g, 9.00 mmol) followed by thionyl chloride (0.17 mL, 0.27 g, 2.3 mmol), and the mixture was stirred for 5 min. Saturated aqueous $NaHCO_3$

(20 mL) was added with vigorous stirring, and the cooling bath was removed. The mixture was warmed to 23 °C and was extracted 2x with 75 mL ethyl acetate. The combined organic layers were washed with 20 mL of saturated aqueous $NaHCO_3$, 20 mL of brine, dried over Na_2SO_4 and concentrated at 15 °C. The residue was filtered through a small plug of silica gel eluting with 10:1 hexane–ethyl acetate containing 5% triethylamine, affording 0.69 g (79%) of a light yellow syrup (approx. 9:1 mixture of all *trans* to other geometric isomers, determined by ^1H NMR): R_f = 0.43 (hexanes–EtOAc 90:10, Et_3N coated silica plate); UV (EtOH): λ 332, 349, 369; FTIR (film) 2960, 2920, 1745, 1444, 1369, 1240, 1222, 1045, 1022, 960 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.95 (d, 1H, *J* = 12.3 Hz), 6.54 (d, 1H, *J* = 12.2 Hz), 6.45 (dd, 1H, *J* = 10.5, 14.8 Hz), 6.36 (d, 1H, *J* = 14.9 Hz), 6.32 (d, 1H, *J* = 10.7 Hz), 5.68 (m, 2H), 4.27 (dd, 1H, *J* = 4.0, 11.7 Hz), 4.16 (dd, 1H, *J* = 7.8, 11.7 Hz), 2.00 (m, 2H), 1.92 (s, 3H), 1.85 (s, 3H), 1.70 (s, 3H), 1.66 (s, 3H), 1.64 (s, 3H), 1.47 (t, 2H, *J* = 6.1 Hz), 1.37 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C NMR (100 MHz, C_6D_6) δ 169.9, 169.3, 146.3, 140.3, 135.5, 134.7, 131.8, 130.9, 129.7, 128.8, 122.8, 120.8, 76.3, 64.3, 41.0, 35.3, 29.1 (2C), 23.3, 21.9, 20.6, 20.3, 18.5, 12.1 ppm; EIMS (*m/z*) 386 $[M]^+$; HRMS calc'd for $C_{24}H_{34}O_4$: 386.2458, found 386.2453.

Preparation of (14*R*)-14-hydroxy-4,14-*retro*-retinol (1). A solution of diacetate **6** (0.297 g, 0.768 mmol) and 2,4-di-*tert*-butyl-4-methylphenol (BHT) (0.0017 g, 0.0077 mmol) in 15 mL of methanol at 23 °C was treated with K_2CO_3 (0.027 g, 0.192 mmol). The resulting mixture was stirred for 1 h, diluted with 10 mL of water and extracted with 75 mL of EtOAc. The organic phase was washed with 2x 10 mL of brine and dried with Na_2SO_4. A crystal of BHT was added and the resulting solution was concentrated at 5 °C to afford 0.187 g (80% yield) of desired product **1** as a yellow oil (aprox. 9:1 ratio of all *trans* to other geometric isomers, determined by ^1H NMR). Further purification of this material by preparative HPLC (Zorbax ODS column; methanol–water 75:25; 20 mL/min flow rate; λ=360 nm; 23°C; 30 min) afforded pure all *trans* **1**: R_f = 0.27 (EtOAc, Et_3N coated silica plate); UV (MeOH): λ (ε) 332 (33000), 347 (43000), 366 (36000) nm; $[\alpha]_D^{20}$ +9.1° (*c* 0.55, MeOH); FTIR (film) 3370, 2959, 2921, 2869, 1447, 1363, 1201, 1075, 1044, 1004, 958, 876 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ 6.76 (d, 1H, 12.3 Hz), 6.55 (dd, 1H, *J* = 11.0, 15.2 Hz), 6.42 (d, 1H, *J* = 17.7 Hz), 6.39 (d, 1H, *J* = 12.5 Hz), 6.17 (d, 1H, *J* = 10.9 Hz), 5.79 (m, 1H), 4.02 (m, 1H), 3.49 (m, 1H), 3.37 (m, 1H), 3.11 (bs, 1H), 2.74 (bs, 1H), 2.09 (m, 2H), 1.93 (s, 3H), 1.88 (s, 3H), 1.76 (s, 3H), 1.49 (t, 2H, *J* = 6.2 Hz), 1.27 (s, 6H) ppm; ^{13}C NMR (100 MHz, CD_3CN) δ 146.5, 138.9, 138.7, 136.8, 135.2, 130.2, 129.4, 127.1, 124.7, 121.0, 77.9, 65.8, 41.4, 35.7, 29.1 (2C), 23.5, 21.9, 13.6, 12.3 ppm; CD (MeOH) λ (Δε): 336 (+1.45), 352 (+2.04), 367 (+2.00) nm; EIMS (*m/z*) 302 $[M]^+$, 205; HRMS calc'd for $C_{20}H_{30}O_2$: 302.2247, found 302.2247.[13]

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12. The acetate was used in these studies because of its ready availability and greater solubility as compared with the *p*-methoxybenzoate.

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