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Quantitative and Stereospecific Dihydroxylations of Δ^5-Steroids: A Green Synthesis of Plant Growth Hormone Intermediates

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Supporting Information

ABSTRACT: Dihydroxylated Δ^5-steroids are key intermediates in preparing steroids bearing a 5α-hydroxy-6-oxo moiety, which are plant growth hormones. Quantitative and stereospecific dihydroxylations of Δ^5-steroids have been realized, using H_2O_2 catalyzed by KI and H_2SO_4 at 80 °C in aqueous dioxane. The workup consisted only of concentrating the solvents and filtering the products; no chromatography was needed. The reaction conditions tolerate various functional groups on the Δ^5-steroids. A mechanism for this reaction is proposed and the reason that the reaction is quantitative and stereospecific is explained.

KEYWORDS: *dihydroxylation, quantitative, stereospecific, Δ^5-steroids, H_2O_2*

INTRODUCTION

Brassinolide[1] is a plant growth hormone used worldwide on various crops that can increase crop yields by more than 10%.[2] Since the amount of the hormone found in nature is extremely low,[2] it is often synthesized at great cost from naturally occurring steroids, which requires several steps and gives very low yields.[3] Steroids bearing a 5α-hydroxy-6-oxo moiety have been shown to exhibit similar plant growth promoting effects,[4] and in field tests, the yields for crops were even better than those with brassinolide.[5] These compounds can be synthesized from the corresponding 5,6-diols,[6] which are accessible from abundant and naturally occurring Δ^5-steroids. A convenient one-pot high-yield procedure for converting Δ^5-steroids to the corresponding diols is desired so that 5α-hydroxy-6-oxo steroids can be produced on a large scale. In addition, steroidal 5,6-diols are bioactive compounds that have been found to be effective for the following diseases: tumors,[7] cognitive dysfunction,[8] neuroblastoma,[9] chest pain,[10] muscular diseases,[11] Niemann-Pick type C (NPC) disease,[12] and cardiovascular disease.[13]

Two procedures are often employed for this transformation. The first is treating Δ^5-steroids with HCOOH and H_2O_2 followed by the hydrolysis of the formates. With this method, the total yields of 5α,6β-dihydroxylated steroids are in the range 40−90%.[14−17] The second method involves treating Δ^5-steroids with peroxyacids such as m-CPBA or peracetic acid followed by ring-opening catalyzed by acids such as H_2SO_4 or $HClO_4$. Here, the total yields of 5α,6β-dihydroxylated steroids are in the range 25−98%.[18−21] A recent procedure using magnesium bis(monoperoxyphthalate) hexahydrate in the epoxidation step followed by ring-opening with $Bi(OTf)_3$ produced 5α,6β-dihydroxylated steroids in excellent yields.[22] In addition, our group recently reported an "on water" ring-opening reaction of steroidal epoxides.[23] The problem with these procedures is that two steps are needed to transform the Δ^5-steroids to 5α,6β-dihydroxylated steroids.

Several one-step procedures have also been reported to transform Δ^5-steroids directly to 5,6-dihydroxylated steroids. These include treating Δ^5-steroids with HIO_4 to produce 5α,6β-dihydroxylated steroids in 62% yield;[24] treating Δ^5-steroids with NBS to give 5α,6β-dihydroxylated steroids in 55% yield;[25] treating cholesterol with p-toluenesulfonic acid and H_2O_2 to produce 5α,6β-dihydroxylated cholesterol in 56% yield.[26] The biotransformation of Δ^5-steroids using fungi gave 5α,6β-dihydroxylated steroids in very poor yields.[27] Metal oxides such as RuO_4 and OsO_4 have been used to convert Δ^5-steroids to 5α,6α-dihydroxylated steroids in 40%[28] and 5−86% yields, respectively.[29−32] $MeReO_3$ can convert Δ^5-steroids to 5α,6β-dihydroxylated steroids in 94% yield.[33] However, the problem with these one-step procedures is that most of the yields are only moderate or expensive metal catalysts are involved. Other well-known *trans*-dihydroxylation methods for nonsteroidal olefins are the SeO_2/H_2O_2 method,[34] the NAFION/H_2O_2 method,[35] the OXONE method,[36] and the I_2/AgOBz method.[37]

Herein, a methodology for the direct quantitative *trans*-dihydroxylation of Δ^5-steroids using catalytic potassium iodide, sulfuric acid, and 30% hydrogen peroxide is described.

MATERIALS AND METHODS

General Experimental Information. All of the chemicals were obtained from commercial sources or prepared according to standard methods. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 and 100 MHz, respectively) or a Bruker Avance III spectrometer (600 and 150 MHz, respectively), using tetramethylsilane (TMS) as the internal standard (δ = 0). Infrared (IR) spectra were obtained using a BIO-RAD FTS 3000 spectrometer, using potassium bromide disks and the spectra were scanned from 400 to 4000 cm^{-1}. Melting points were recorded on an X-4 Micromelting Point Apparatus. High resolution mass spectra (ESI) were obtained on a Bruker microTOF-QII.

General Procedure for the Preparation of 5α,6β-Dihydroxylated Steroids. Steroid **1a−1o** (1 g, 1 equiv), KI (0.16 equiv), and

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dioxane/water (12 mL/6 mL) (for **1h**, **1i**, and **1m**, dioxane/water = (13 mL/5 mL), (13 mL/5 mL), and (14 mL/4 mL), respectively) were added to a 100-mL flask. To this vigorously stirred mixture, H_2SO_4 (98%, 0.4 equiv) and H_2O_2 (30%, 1.8 equiv) were sequentially added at room temperature. An exothermic reaction and a red color then occurred. Then, the system was heated to 80 °C, and the reaction was monitored by TLC (thin layer chromatography) until completion. The reaction was neutralized by anhydrous Na_2CO_3 (0.4 equiv) and treated with $NaHSO_3$ (saturated solution, 0.1 mL), followed by concentration under atmospheric pressure to about one-third of the original volume (Caution: Distillation under reduced pressure causes foaming).

An alternative concentration method is to use an air pump to evaporate the reaction solvents to about one-third of the original volume and to recover the solvents in a cooling trap. The remaining mixture is then neutralized by anhydrous Na_2CO_3 (0.4 equiv) and treated with $NaHSO_3$ (saturated solution, 0.1 mL).

One of the following three methods was used in the rest of the workup.

Method A. Cooling the concentrated solution and filtering the crystals afforded products **2e**, **2f**, **2g**, **2h**, **2i**, and **2m** in quantitative yields.

Method B. Cooling the concentrated solution and filtering the crystals afforded some of the product. The mother liquor was then extracted with ethyl acetate (3 × 5 mL) followed by concentration under vacuum to give the rest of the product. Combination of the two parts gave **2a**, **2b**, **2c**, **2d**, **2k**, **2l**, and **2o** in quantitative yields.

This procedure was applied to the quantitative synthesis of choletane-3β,5α,6β-triol (**2a**) from 11 g cholesterol (**1a**).

Method C. Extraction of the concentrated solution with ethyl acetate (3 × 10 mL) followed by concentration under vacuum gave products **2j** and **2n** in quantitative yields.

Products **2a**,[22] **2b**,[38] **2d**,[6] and **2l**[39] are known compounds.

*Cholestane-3β,5α,6β-triol (**2a**).* White solid; mp 222−224 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 4.38 (1H, d, J = 4.1 Hz, 6-OH), 4.16 (1H, d, J = 5.7 Hz, 3-OH), 3.80 (1H, m, 3α-H), 3.62 (1H, s, 5-OH), 3.30 (1H, s, 6α-H), 1.03 (3H, s, 19-CH$_3$), 0.88 (3H, d, J = 6.3 Hz, 21-CH$_3$), 0.85 (6H, dd, J = 6.5 Hz and 1.5 Hz, 26-CH$_3$ and 27-CH$_3$), 0.63 (3H, s, 18-CH$_3$); IR (KBr, cm^{-1}) ν: 3424, 2939, 2868, 1468, 1376, 1293, 1042, 1016, 960.

*Androstane-3β,5α,6β-triol (**2b**).* White solid; mp 216−218 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.24−4.03 (1H, m, 3α-H), 3.56 (1H, s, 6α-H), 1.20 (3H, s, 19-CH$_3$), 0.74 (3H, s, 18-CH$_3$); IR (KBr, cm^{-1}) ν: 3424, 2939, 2869, 1453, 1378, 1289, 1249, 1162, 1055, 1040, 961, 871.

*Pregnane-3β,5α,6β-triol (**2c**).* White solid; mp 216−219 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.09−4.16 (1H, m, 3α-H), 3.56 (1H, s, 6α-H), 1.21 (3H, s, 19-CH$_3$), 0.89 (3H, t, J = 7.3 Hz, 21-CH$_3$), 0.60 (1H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 74.87, 74.63, 66.22, 55.77, 53.04, 45.52, 42.36, 41.38, 38.39, 38.35, 35.08, 32.54, 31.57, 30.48, 28.27, 24.71, 23.16, 20.99, 16.73, 13.68, 12.90; IR (KBr, cm^{-1}) ν: 3418, 2938, 2867, 1642, 1455, 1378, 1063, 1035, 1011, 961, 871. HRMS calcd. for $C_{21}H_{36}O_3Na$ [M + Na]$^+$: 359.2557. Found: 359.2557.

*Androstane-3β,5α,6β,17β-tetrol (**2d**).* White solid; mp 262−265 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 4.39 (1H, s, 17-OH), 3.79 (1H, dd, J = 10.6 Hz and 5.2 Hz, 3α-H), 3.63 (1H, s, 5-OH), 3.42 (1H, t, J = 8.4 Hz, 17α-H), 3.29 (1H, s, 6α-H), 1.03 (3H, s, 19-CH$_3$), 0.62 (3H, s, 18-CH$_3$); IR (KBr, cm^{-1}) ν: 3419, 2937, 2867, 1451, 1400, 1239, 1214, 1159, 1124, 1054, 1042, 1020, 1002, 873, 752, 700.

*(21E)-Benzylidene-3β,5α,6β-trihydroxypregnanone (**2e**).* White solid; mp 237−240 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.70 (2H, m, Ar−H), 7.49−7.53 (1H, d, J = 16.1 Hz, ArC<u>H</u>CH), 7.43 (3H, m, Ar−H), 6.91 (1H, d, J = 16.1 Hz, ArCHC<u>H</u>), 3.81 (1H, m, 3α-H), 3.39 (1H, s, 6α-H), 1.01 (3H, s, 19-CH$_3$), 0.51 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 200.29, 141.24, 135.02, 130.77, 129.41, 128.80, 127.64, 74.82, 74.56, 66.20, 61.16, 56.47, 45.25, 45.09, 41.36, 39.10, 38.32, 35.00, 32.47, 31.53, 30.70, 24.74, 22.76, 21.19, 16.71, 14.02; IR (KBr, cm^{-1}) ν: 3542, 3423, 2934, 2869, 1678, 1640, 1606, 1450, 1398, 1199, 1135, 1106, 1042, 771, 700. HRMS calcd. for $C_{28}H_{38}O_4Na$ [M + Na]$^+$: 461.2662. Found: 461.2662.

*(16E)-Benzylidene-3β,5α,6β-trihydroxyandrostanone (**2f**).* White solid; mp 220−223 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.37−7.56 (6H, m, Ar−H and ArCH), 4.10−4.14 (1H, m, 3α-H), 3.63 (1H, s, 6α-H), 1.26 (3H, s, 19-CH$_3$), 1.00 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 209.08, 137.05, 135.66, 132.11, 130.69, 129.72, 129.24, 74.90, 74.42, 66.17, 49.14, 47.57, 45.35, 41.29, 38.61, 33.97, 32.43, 32.04, 31.55, 29.88, 29.40, 20.50, 16.69, 14.65; IR (KBr, cm^{-1}) ν: 3452, 2940, 2860, 1706, 1628, 1492, 1449, 1375, 1118, 1096, 1036, 871, 770, 693. HRMS calcd. for $C_{26}H_{34}O_4Na$ [M + Na]$^+$: 433.2349. Found: 433.2349.

*(16E)-(4-Nitrobenzylidene)-3β,5α,6β-trihydroxyandrostanone (**2g**).* Yellow solid; mp 230−233 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 8.28 (2H, d, J = 8.4 Hz, Ar−H), 7.90 (2H, d, J = 8.5 Hz, Ar−H), 7.39 (1H, s, ArCH), 3.82 (1H, m, 3α-H), 3.39 (1H, s, 6α-H), 1.10 (3H, s, 19-CH$_3$), 0.89 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 208.71, 147.49, 142.28, 141.05, 131.59, 129.67, 124.17, 74.88, 74.38, 66.16, 48.82, 47.74, 45.32, 41.30, 38.59, 33.94, 32.43, 31.95, 31.55, 29.90, 29.44, 20.46, 16.66, 14.55; IR (KBr, cm^{-1}) ν: 3439, 2934, 2861, 1711, 1628, 1595, 1522, 1343, 1097, 1041. HRMS calcd. for $C_{26}H_{33}NO_6Na$ [M + Na]$^+$: 478.2200. Found: 478.2201.

*(21E)-Benzylidene-16α,17α-epoxy-3β,5α,6β-trihydroxypregnanone (**2h**).* White soild; mp 240−243 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71 (1H, d, J = 15.9 Hz, ArCH), 7.57 (2H, m, Ar−H), 7.40 (3H, m, Ar−H), 6.83 (1H, d, J = 15.9 Hz, ArCHC<u>H</u>), 4.12 (1H, s, 3α-H), 3.76 (1H, s, 16β-H), 3.58 (1H, s, 6α-H), 1.23 (3H, s, 19-CH$_3$), 1.14 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 195.10, 143.08, 134.79, 131.04, 129.37, 129.09, 121.97, 74.91, 74.49, 71.10, 66.18, 60.33, 45.55, 45.23, 42.17, 41.31, 38.54, 34.60, 32.39, 32.22, 31.52, 28.22, 27.48, 20.69, 16.61, 15.56; IR (KBr, cm^{-1}) ν: 3508, 3422, 2988, 2939, 2862, 1676, 1604, 1455, 1376, 1340, 1031, 1007, 987, 761. HRMS calcd. for $C_{28}H_{36}O_5Na$ [M + Na]$^+$: 475.2455. Found: 475.2454.

*(16E)-Piperonylidene-3β,5α,6β-trihydroxyandrostanone (**2i**).* Yellow solid; mp 202−205 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 7.31−7.09 (3H, m, Ar−H), 7.01 (1H, d, J = 7.9 Hz, ArCH), 6.09 (2H, d, J = 3.6 Hz, ArO$_2$CH$_2$), 3.81 (1H, s, 3α-H), 3.74 (1H, s, 6α-H), 1.09 (3H, s, 19-CH$_3$), 0.85 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 209.07, 148.73, 148.16, 134.98, 132.18, 129.92, 126.23, 109.93, 109.12, 101.98, 74.90, 74.44, 66.16, 49.24, 47.48, 45.36, 41.29, 38.60, 33.96, 32.42, 32.06, 31.55, 29.86, 29.35, 20.51, 16.68, 14.69; IR (KBr, cm^{-1}) ν: 3423, 2936, 2862, 1699, 1614, 1593, 1501, 1450, 1399, 1261, 1101, 1035, 920, 802. HRMS calcd. for $C_{27}H_{34}O_6Na$ [M + Na]$^+$: 477.2248. Found: 477.2247.

*(17E)-Ethyl-3β,5α,6β-trihydroxypregn-17-en-21-oate (**2j**).* White solid; mp 236−239 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.55 (1H, s, 20-H), 4.16 (2H, q, J = 7.0 Hz, 23-H), 4.04−4.13 (1H, m, 3α-H), 3.58 (1H, s, 6α-H), 1.22 (3H, s, 19-CH$_3$), 0.86 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO) δ 176.79, 166.73, 108.33, 74.83, 74.49, 66.17, 59.43, 53.42, 46.45, 45.26, 41.34, 38.43, 35.48, 34.83, 32.49, 31.55, 30.61, 30.28, 24.42, 21.07, 18.71, 16.73, 14.69; IR (KBr, cm^{-1}) ν: 3533, 3406, 2943, 2914, 2870, 1714, 1645, 1392, 1371, 1188, 1154, 1037, 962, 860. HRMS calcd. for $C_{23}H_{36}O_5Na$ [M + Na]$^+$: 415.2455. Found: 415.2454.

*(17E)-3β,5α,6β-Trihydroxypregn-17-en-21-oic Acid (**2k**).* White solid; mp 268−271 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.75 (1H, s, COOH), 5.42 (1H, s, 20-H), 3.81 (1H, s, 3α-H), 3.67 (1H, s, 6α-H), 1.06 (3H, s, 19-CH$_3$), 0.77 (3H, s, 18-CH$_3$); ^{13}C NMR (101 MHz, DMSO-d$_6$) δ 176.01, 168.38, 109.30, 74.88, 74.53, 66.21, 53.45, 46.28, 45.30, 41.30, 38.43, 35.63, 34.80, 32.49, 31.50, 30.49, 30.30, 24.44, 21.09, 18.77, 16.73; IR (KBr, cm^{-1}) ν: 3485, 3346, 3144, 2988, 2958, 2873, 1690, 1656, 1447, 1393, 1188, 1157, 1035, 1014, 957, 863. HRMS calcd. for $C_{21}H_{32}O_5Na$ [M + Na]$^+$: 387.2142. Found: 387.2144.

*Androstane-5α,6β,17β-triol (**2l**).* White solid; mp 186−188 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 3.72 (1H, s, OH), 3.66 (1H, t, J = 8.4 Hz, 17α-H), 3.51 (1H, s, 6α-H), 1.18 (3H, s, 19-CH$_3$), 0.77 (3H, s, 18-CH$_3$); IR (KBr, cm^{-1}) ν: 3425, 2936, 2866, 1445, 1377, 1254, 1117, 1076, 1050, 1017, 960, 919, 872.

*(16E)-(4-Nitrobenzylidene)-5α,6β-dihydroxyandrostanone (**2m**).* Yellow solid; mp 232−234 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.27 (2H, d, J = 8.1 Hz, Ar), 7.67 (2H, d, J = 8.1 Hz, Ar), 7.45 (1H, s, ArCH), 3.60 (1H, s, 6α-H), 1.23 (3H, s, 19-CH$_3$), 1.00 (3H, s, 18-CH$_3$); ^{13}C

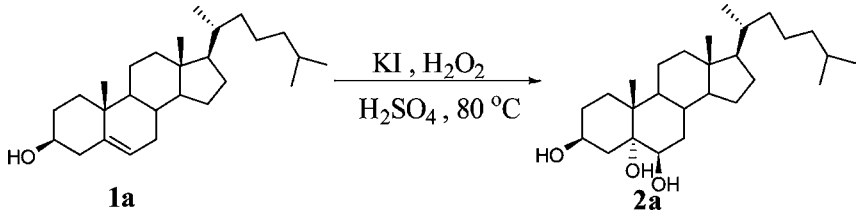
NMR (101 MHz, DMSO-d_6) δ 208.78, 147.49, 142.30, 141.09, 131.61, 129.66, 124.18, 74.58, 72.99, 48.87, 47.74, 45.60, 39.06, 34.23, 33.08, 31.93, 31.40, 29.85, 29.42, 21.30, 20.55, 20.04, 16.44, 14.55; IR (KBr, cm^{-1}) ν: 3507, 2933, 2860, 1722, 1631, 1595, 1520, 1457, 1411, 1343, 1182, 1081, 851, 685. HRMS calcd. for $C_{26}H_{33}NO_5Na$ $[M + Na]^+$: 462.2251. Found: 462.2250.

*3β-(2-Hydroxyethoxy)-5α,6β-cholestanediol (**2n**).* White solid; mp 106–108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (1H, m, 3α-H), 3.76–3.57 (4H, m, $HOCH_2CH_2O$), 3.56 (1H, s, 6α-H), 1.19 (3H, s, 19-CH_3), 0.92 (3H, d, J = 6.3 Hz, 21-CH_3), 0.88 (6H, dd, J = 6.5 Hz and 1.2 Hz, 26-CH_3 and 27-CH_3), 0.69 (3H, s, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 75.95, 75.77, 75.58, 69.24, 61.90, 56.32, 55.99, 45.75, 42.75, 39.98, 39.50, 38.49, 37.84, 36.18, 35.81, 34.42, 32.13, 30.24, 28.22, 27.99, 27.30, 24.16, 23.91, 22.80, 22.55, 21.18, 18.67, 16.77, 12.18; IR (KBr, cm^{-1}) ν: 3416, 2936, 2867, 1639, 1467, 1383, 1248, 1105, 1066, 1046, 1016, 965, 867. HRMS calcd. for $C_{29}H_{52}O_4Na$ $[M + Na]^+$: 487.3758. Found: 487.3757.

*3β-(2-Hydroxyethyloxy)ethyloxy-5α,6β-cholestanediol (**2o**).* White solid; mp 84–86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (1H, m, 3α-H), 3.78–3.58 (8H, m, $HOCH_2CH_2OCH_2CH_2O$), 3.55 (1H, s, 6α-H), 1.19 (3H, s, 19-CH_3), 0.92 (3H, d, J = 6.3 Hz, 21-CH_3), 0.88 (6H, dd, J = 6.5 Hz and 1.2 Hz, 26-CH_3 and 27-CH_3), 0.69 (3H, s, 18-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 76.01, 75.76, 75.70, 72.58, 71.04, 67.55, 61.76, 56.31, 56.02, 45.84, 42.75, 39.99, 39.50, 38.45, 37.70, 36.17, 35.79, 34.35, 32.19, 30.23, 28.22, 27.98, 27.33, 24.12, 23.88, 22.80, 22.55, 21.18, 18.67, 16.77, 12.16; IR (KBr, cm^{-1}) ν: 3418, 2935, 2867, 1645, 1468, 1384, 1249, 1116, 1094, 1052, 1010, 968, 870. HRMS calcd. for $C_{31}H_{56}O_5Na$ $[M + Na]^+$: 531.4020. Found: 531.4019.

General Procedure for the Trisubstituted Alkene Oxidations. Trisubstituted alkene **1p–1v** (0.2 g, 1 equiv), KI (0.16 equiv), and dioxane (5 mL) were added to a 50 mL-flask. To this vigorously stirred mixture, H_2SO_4 (98%, 0.4 equiv) and H_2O_2 (30%, 1.8 equiv) were sequentially added at room temperature. An exothermic reaction and a red color then occurred. Then, the system was heated to 80 °C and the reaction was monitored by TLC (thin layer chromatography)

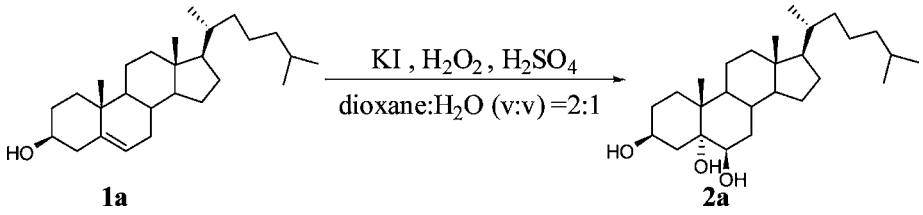
Table 1. Optimization of the Solvent Systems for Cholesterol (1a) Dihydroxylation[a]



entry	solvent	time (h)	yield[b] (%)
1	AcOH	15	trace
2	AcOH/H_2O (v/v) = 20:1	15	trace
3	ethylene glycol	15	trace
4	ethylene glycol/H_2O (v/v) = 20:1	15	trace
5	DMF	15	trace
6	DMSO	5	10
7	DMSO/H_2O (v/v) = 2:1	5	trace
8	CH_3CN	5	49
9	CH_3CN/H_2O (v/v) = 2:1	5	60
10	THF	5	35
11	2-methoxyethanol	5	40
12	dioxane/H_2O (v/v) = 2:1	2	>99

[a]Reaction conditions: cholesterol (1 g), KI (1 equiv), H_2SO_4 (1 equiv), H_2O_2 (3 equiv) and solvent (18 mL) at 80 °C. [b]Determined by ^1H NMR.

Table 2. Optimization of the Dihydroxylation Conditions of Cholesterol (1a)[a]



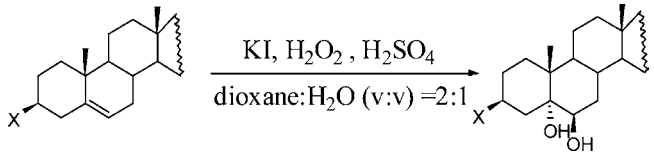
entry	H_2SO_4 (equiv)	H_2O_2 (equiv)	KI (equiv)	temp. (°C)	time (h)	yield[b] (%)
1	1	3	1	rt	-	nr[c]
2	0.8	2.0	0.08	50	80	98
3	0.8	2.0	0.4	80	3.5	>99
4	0.8	2.0	0.08	80	40	>99
5	0.8	1.8	0.08	80	40	>99
6	0.8	1.8	0.16	80	12	>99
7	0.4	1.8	-	80	26.5	48[d]
8	0.4	1.8	0.16	80	18	>99

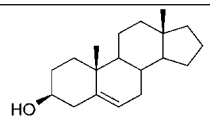
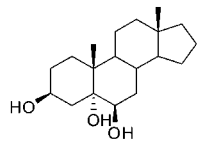
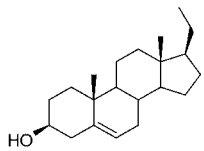
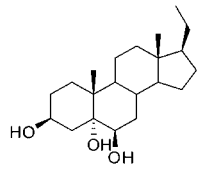
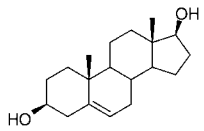
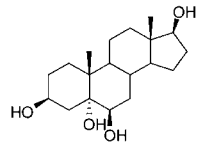
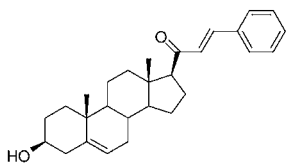
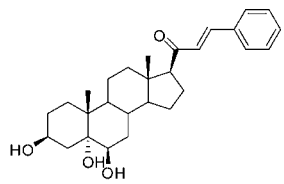
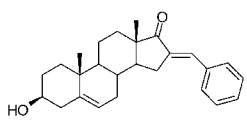
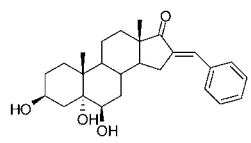
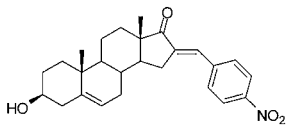
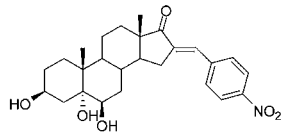
[a]Reaction conditions: cholesterol (1 g), KI, H_2SO_4, H_2O_2 and dioxane/H_2O (v/v) = 2:1 (18 mL) at rt, 50 or 80 °C. [b]Except for entries 1 and 7, all conversions are 100% and all yields are isolated yields. [c]nr: no reaction. [d]Determined by ^1H NMR.

until completion. The reaction mixture were poured into water (15 mL) and extracted with ethyl acetate (3 × 5 mL) followed by concentration. The crude reaction products were purified by column chromatography to give **2s** and **2v** in 64% and 30% yields respectively. As the reaction of **1p**, **1q**, **1r**, **1t**, and **1u** led to complicated mixtures, the products were not separated. Products **2s**[40] and **2v**[41] are known compounds.

*trans-1-Butyl-1,2-cyclohexanediol (**2s**).* Colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.54 (1H, dd, J = 9.7 Hz and 3.7 Hz, 2-H), 1.20−1.85 (14H, m, CH_2), 0.93 (3H, t, J = 6.9 Hz, CH_3);

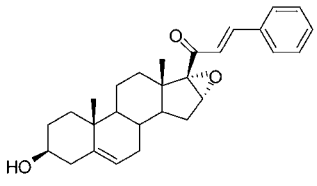
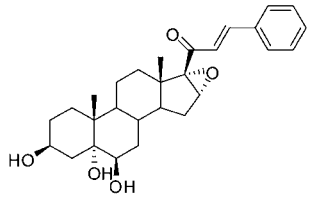
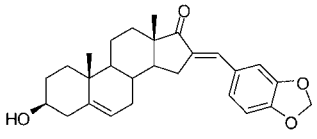
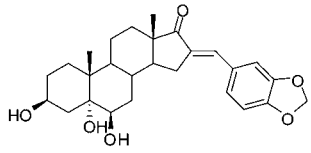
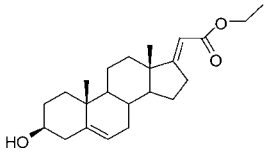
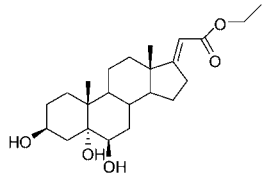
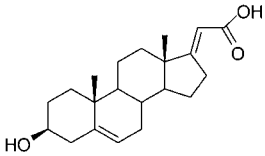
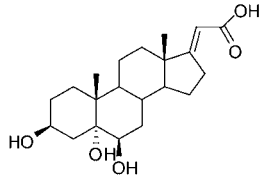
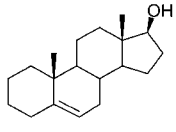
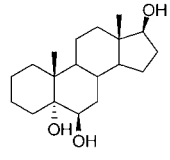
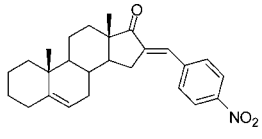
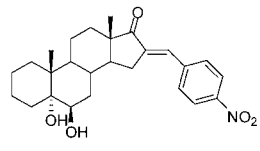
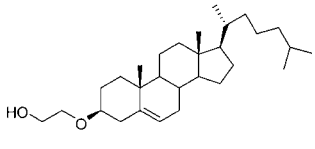
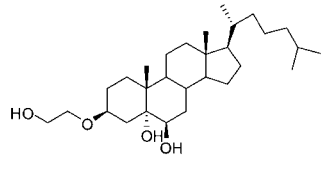
Table 3. Direct Quantitative *trans*-Dihydroxylation of Δ^5-Steroids[a]



Entry	Substrate	Product	Time (h)
1	 **1b**	 **2b**	10
2	 **1c**	 **2c**	11
3	 **1d**	 **2d**	9
4	 **1e**	 **2e**	32
5	 **1f**	 **2f**	20
6	 **1g**	 **2g**	21

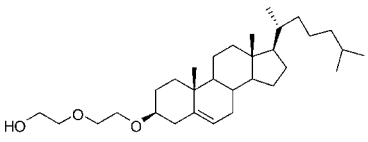
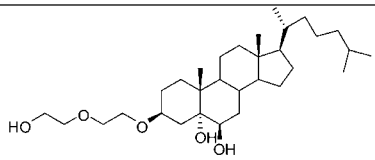
dx.doi.org/10.1021/jf404633y | J. Agric. Food Chem. 2013, 61, 12522−12530

Table 3. continued

Entry	Substrate	Product	Time (h)
7[b]	 **1h**	 **2h**	34
8[b]	 **1i**	 **2i**	30
9	 **1j**	 **2j**	22
10	 **1k**	 **2k**	12
11	 **1l**	 **2l**	10.5
12[c]	 **1m**	 **2m**	45
13	 **1n**	 **2n**	31

dx.doi.org/10.1021/jf404633y | J. Agric. Food Chem. 2013, 61, 12522−12530

Table 3. continued

Entry	Substrate	Product	Time (h)
14			24
	1o	**2o**	

[a]Reaction conditions: a Δ^5-steroid (1 g), H_2SO_4 (0.4 equiv), H_2O_2 (1.8 equiv), KI (0.16 equiv), and dioxane/H_2O (v/v) = 2:1 (18 mL) at 80 °C. All conversions are 100%. All isolated yields are >99%. [b]Dioxane/H_2O (v/v) = 2.6:1. [c]Dioxane/H_2O (v/v) = 3.5:1.

IR (KBr, cm^{-1}) ν: 3415, 2936, 2865, 1459, 1346, 1287, 1215, 1149, 1071, 1011, 907, 856, 605.

*Cholestane-4β,5α-diol (**2v**).* White solid; mp 174−176 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 3.54 (1H, m, 4α-H), 1.17 (3H, s, 19-CH_3), 0.90 (3H, d, J = 6.5 Hz, 21-CH_3), 0.86 (6H, dd, J = 6.6 Hz and 2.6 Hz, 26-CH_3 and 27-CH_3), 0.66 (3H, s, 18-CH_3); IR (KBr, cm^{-1}) ν: 3478, 2937, 2865, 1464, 1379, 1247, 1169, 1122, 1056, 1005, 957, 934.

General Procedure for the Terminal Alkene Oxidations. Terminal alkene **1w** or **1x** (0.2 g, 1 equiv), KI (1.2 equiv), and CH_3CN (5 mL) were added to a 50-mL flask. To this vigorously stirred mixture, H_2SO_4 (98%, 1 equiv) and H_2O_2 (30%, 2.2 equiv) were sequentially added at room temperature. An exothermic reaction and a red color then occurred. Then, the system was heated to 70 °C and the reaction was monitored by TLC (thin layer chromatography) to completion. The reaction mixture was treated with $NaHSO_3$ (saturated solution, 1 mL) and then poured into water followed by extraction with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The crude reaction products were purified by column chromatography to give **2w** and **2x** in 74% and 79% yields, respectively. Product **2w**[42] is a known compound.

*10-Hydroxy-11-iodo-undecanoic Acid (**2w**).* White solid; mp 56−58 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 3.53 (1H, m, CH_2I), 3.41 (1H, dd, J = 10.2 Hz and 3.5 Hz, CH_2I), 3.25 (1H, dd, J = 10.1 Hz and 6.8 Hz, C<u>H</u>OH), 2.37 (2H, t, J = 7.5 Hz, CH_2CO), 1.33−1.67 (14H, m, CH_2); IR (KBr, cm^{-1}) ν: 3399, 2923, 2851, 1712, 1463, 1432, 1287, 1225, 1173, 1076, 1041, 1002, 904, 725.

*N-Butyl-10-hydroxy-11-iodo-undecanamide (**2x**).* White solid; mp 64−66 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, s, NH), 3.51 (1H, m, 10-CH), 3.37−3.40 (1H, dd, J = 10.1 Hz and 3.6 Hz, CHI), 3.21−3.27 (3H, m, CHI and CH_2N), 2.13−2.17 (3H, m, CH_2CO and OH), 1.44−1.63 (7H, m, CH_2), 1.31−1.35 (11H, m, CH_2), 0.94 (3H, t, J = 7.3 Hz, CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.24, 70.78, 39.22, 36.80, 36.47, 31.70, 29.30, 29.23, 29.17, 29.14, 25.74, 25.54, 20.04, 16.26, 13.72; IR (KBr, cm^{-1}) ν: 3300, 2927, 2852, 1642, 1548, 1463, 1421, 1225, 1151, 1114, 942, 893, 718. HRMS calcd. for $C_{15}H_{30}INO_2Na$ $[M + Na]^+$: 406.1213. Found: 406.1213.

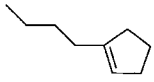
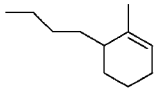
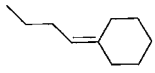
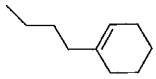
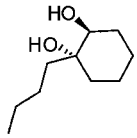
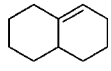
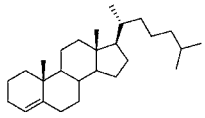
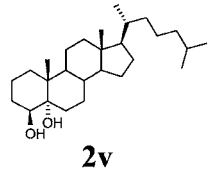
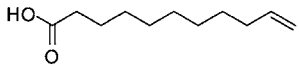
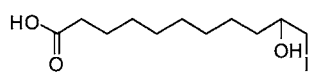
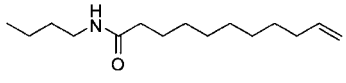
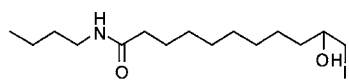
RESULTS AND DISCUSSION

Initially cholesterol (1 g, **1a**) was used as a model substrate to screen the reaction conditions. It was treated with KI (1 equiv), H_2SO_4 (1 equiv) and H_2O_2 (3 equiv) in various solvents (18 mL) at 80 °C, and the results are presented in Table 1. The reaction only produced the dihydroxylated cholesterol (**2a**) in quantitative yield in dioxane/H_2O (v/v) = 2:1 (Table 1, entry 12). A trace of products was generated in AcOH, AcOH/H_2O (v/v) = 20:1, ethylene glycol, ethylene glycol/H_2O (v/v) = 20:1, DMF and DMSO/H_2O (v/v) = 2:1 (Table 1, entries 1−5 and 7). In DMSO, CH_3CN, CH_3CN/H_2O (v/v) = 2:1, THF and 2-methoxyethanol, the yields were 10%, 49%, 60%, 35%, and 40%, respectively (Table 1, entries 6 and 8−11).

The amounts of the reagents and reaction temperatures were then further optimized and the results are summarized in Table 2. Treating cholesterol (1 g, **1a**) with H_2SO_4 (1 equiv), H_2O_2 (3 equiv), and KI (1 equiv) in dioxane/water (12 mL/6 mL) at rt (room temperature) produced no reaction (Table 2, entry 1). In the absence of KI, the reaction yield was lower (48%, Table 2, entry 7). When the reaction temperature was raised to 80 °C and the amounts of H_2SO_4 (1 equiv), H_2O_2 (3 equiv), and KI (1 equiv) were reduced to 0.8, 2, and 0.4 equiv respectively, the reaction time changed from 2 to 3.5 h and the yield was still quantitative (Table 2, entry 3). Further reducing the amount of KI to 0.08 equiv and the reaction temperature to 50 °C led to a sluggish reaction (80 h, Table 2, entry 2). The reaction time was shortened to 40 h after raising the temperature to 80 °C (Table 2, entry 4). After doubling the amount of KI to 0.16 equiv and reducing the amount of H_2SO_4 to 0.4 equiv, the reaction duration became acceptable (18 h, Table 2, entry 8). It is believed that reducing the amount of H_2SO_4 makes the reaction more tolerant to more functional groups. The optimized reaction conditions are H_2SO_4 (0.4 equiv), H_2O_2 (1.8 equiv), KI (0.16 equiv), and dioxane/H_2O (v:v) = 2:1 (18 mL) at 80 °C.

Next the substrate scope was expanded to other 14 Δ^5-steroids and quantitative dihydroxylation yields were still obtained (Table 3). The reaction times ranged from 9 to 45 h. The substrates with more polar groups (**1k**, **1d**) and smaller molecular weights (**1b**−**1d**, **1l**) tended to react faster (**1b**, **1c**, **1d**, **1k**, **1l** vs **1e**, **1h**, **1i**, **1m**, **1n**). The reaction of Δ^5-steroids **1h**, **1i**, and **1m** were sluggish under the optimized conditions (Table 2, entry 8) probably because of their lower solubility in the aqueous media. The reaction rates became acceptable after adjusting the ratios of dioxane to water to 2.6:1, 2.6:1 and 3.5:1, respectively (Table 3, entries 7, 8, and 12). Since the amount of H_2SO_4 used is catalytic, the reaction tolerates primary alcohols (**1n**, **1o**), secondary alcohols (**1a**−**1l**), and nitro (**1g**, **1m**), acetal (**1i**), epoxide (**1h**), ether (**1n**, **1o**), and ester (**1j**) groups. The chemoselectivity of the dihydroxylation was demonstrated in steroids **1a**−**1o**. Only the C^5−C^6 double bonds were dihydroxylated, whereas the double bonds of the α,β-unsaturated ketones (**1e**−**1i**, **1m**), ester (**1j**), and acid (**1k**) remained intact. This is probably because their electron-poor nature makes it more difficult for I^+ to add to them (Figure 1). The workup consisted only of using air pump to evaporate some of the reaction solvent followed by filtration and it is simpler than most of the current methods, which often require chromatography. The dihydroxylation of cholesterol (**1a**) was successfully scaled-up to 11 g. This reaction method gives quantitative yields and forms no side products, and chromatography is not needed. This is the first procedure to achieve all these results.

Table 4. Oxidations of Non-steroidal Alkenes for the Understanding of the Reaction Mechanism

Entry	Alkene	Product	Time (h)	Yield[a] (%)
1[b]	 **1p**	complicated mixture	-	-
2[b]	 **1q**	complicated mixture	-	-
3[b]	 **1r**	complicated mixture	-	-
4[b]	 **1s**	 **2s**	12	64
5[b]	 **1t**	complicated mixture	-	-
6[b]	 **1u**	complicated mixture	-	-
7[b]	 **1v**	 **2v**	18.5	30
8[c]	 **1w**	 **2w**	1	74
9[c]	 **1x**	 **2x**	2	79

[a]Isolated yield. [b]Reaction conditions: trisubstituted alkene (0.2 g), KI (0.16 equiv), H_2O_2 (1.8 equiv), H_2SO_4 (0.4 equiv), and dioxane (5 mL) at 80 °C. [c]Reaction conditions: terminal alkene (0.2 g), KI (1.2 equiv), H_2O_2 (2.2 equiv), H_2SO_4 (1 equiv), and CH_3CN (5 mL) at 70 °C.

The mechanism shown in Figure 1 is proposed for the reaction. Under acidic conditions, I^- is oxidized by H_2O_2 to I^+. An addition of the I^+ to the Δ^5-steroid leads to the iodonium ion **I**. The iodonium is in the α-configuration because of the steric effect of the C^{10}-Me moiety. Water then attacks the C^6 of **I** which leads to 5α,6β-iodohydrin **II**. Since **II** is a tertiary iodide

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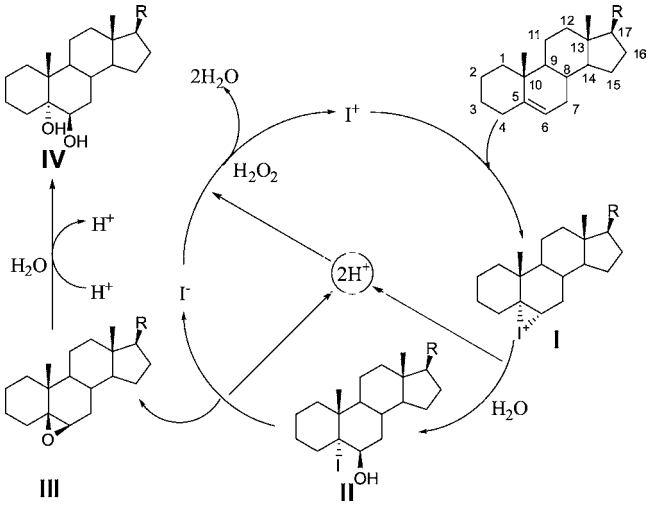

Figure 1. Plausible mechanism for the *trans*-dihydroxylation of Δ^5-steroids.

and both C^6–OH and C^5–I are axial, the epoxidation is favorable at elevated temperatures and epoxide **III** is formed. The ring-opening of the epoxide by water leads to dihydroxylated product **IV**. The stereochemistry of the ring-openings of **I** and **III** is supported by the one of 5*α*,6*α*-epoxide and 5*β*,6*β*-epoxide which leads to the same product: 5*α*, 6*β*-diol.[23,43]

Catalytic PTSA (p-toluenesulfonic acid) and H_2O_2 have been used in the high yield conversion of olefins to diols.[26] In most cases, the yields were excellent. However, in the case of cholesterol, the dihydroxylation yield was only 55.8%. A mechanism involving an intermediate epoxide similar to our intermediate **III** (Figure 1) has been proven by an ^{18}O-enriched PTSA experiment.

Our dihydroxylation conditions are quite similar to those used by the Barluenga group to convert olefins to iodohydrins.[44] The differences are the reaction temperature (80 °C vs rt), the amounts of iodide and acid (catalytic vs stoichiometric), the products (diols vs iodohydrins), and the yields (quantitative vs 65–94%). Our reaction does not stop at the iodohydrin stage, probably because the C^5–I and C^6–OH of the iodohydrin **II** (Figure 1) are both axial and the dihedral angles are close to 180°. Consequently, the subsequent epoxidation is preferred, especially at 80 °C. In contrast, the corresponding groups of iodohydrins synthesized via Barluenga's procedure[44] are either equatorial or open chains in an array with dihedral angles are far less than 180°. Therefore, epoxidation does not occur and the reaction ends at the iodohydrin stage.

To further understand the reaction mechanism, terminal alkenes **1w** and **1x** were subjected to the reaction conditions using stoichiometric amounts of iodide, acid, and H_2O_2 at 70 °C (Table 4, entries 8 and 9), generating iodohydrins **2w** (74%) and **2x** (79%), respectively, which is similar to the results reported by Barluenga's group.[44] Trisubstituted alkenes **1p**, **1q**, **1r**, **1s**, **1t**, **1u**, and **1v** were subjected to our optimized dihydroxylation conditions (Table 4, entries 1–7). Trisubstituted alkenes **1p**, **1q**, **1r**, **1t**, and **1u** gave complicated products whereas trisubstituted alkenes **1s** and **1v** produced diols **2s** (64%) and **2v** (30%), respectively. Increasing the amount of acid and iodide to stoichiometric amounts did not change the trisubstituted alkenes oxidation results.

The results of all these reactions suggest that one possible reason for our quantitative and stereospecific dihydroxylation of the Δ^5-steroids is the strong resistance of the Δ^5-steroids to protonation, which is due to the high instability of the carbocations at the steroidal C^5 or C^6 positions. If the carbocation were at C^5 or C^6, both the conformationally-"locked" Δ^5-steroidal[45] A and B rings would have to deform to meet the planarity requirement of the carbocation. On the other hand, a protonation at C^5 in a Δ^4-steroid leads to a carbocation at C^4, which only requires the deformation of ring A; this is allowed and the monohydration can then take place to give 4-hydroxylated steroid. ^1H NMR analysis of the crude dihydroxylation products of cholest-4-ene (**1v**, Table 4, entry 7) showed that the molar ratio of monool (5*α*-cholestane-4*β*-ol)[46] to diol (5*α*-cholestane-4*β*,5-diol)[41] was 1:5 (see Supporting Information).

In conclusion, a methodology for the quantitative and stereospecific conversion of Δ^5-steroids to the corresponding 5*α*,6*β*-dihydroxylated steroids has been described. This method should have wide applications in the agriculture, food, and pharmaceutical industries, because of its simplicity, its inexpensiveness, its high effectiveness, and its compatibility with numerous functional groups.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedure for the preparation of choletane-3*β*,5*α*,6*β*-triol (**2a**) on a 11 g scale and ^1H NMR analysis of the crude oxidation product of cholest-4-ene (**1v**) and ^1H NMR and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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