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A Ruthenium Catalyzed Oxidation of Steroidal Alkenes to Enones

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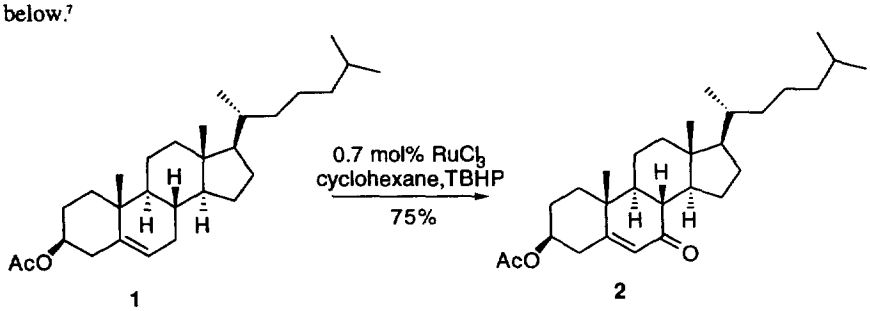
Abstract : A new protocol for oxidizing steroidal alkenes to enones has been developed. Copyright © 1996 Elsevier Science Ltd

In the course of studying the preparation of Merck's type I 5-α reductase inhibitor,[1] MK-386[2] a practical allylic oxidation of cholesteryl acetate (**1**) to 7-keto cholesteryl acetate (**2**) was required. Examination of the literature showed numerous chromium-mediated reagents for this difficult transformation, however these methodologies were rejected due to the environmentally unacceptable nature of chromium.[3] Additionally, several non-chromium containing reagents have been reported,[4] but these processes suffer from low yield or from difficulties with scale up, thus a new oxidation protocol was sought. The ruthenium-catalyzed tert-butyl hydroperoxide (TBHP) oxidation of a variety of organic substrates has been demonstrated by Murahashi and others.[5,6] The oxidation of alkene substrates had not been reported for this system, and we speculated that allylic oxidation rather than epoxidation or carbon-carbon bond cleavage would be the preferred reaction pathway. We wish to report the reaction of Ru-TBHP with Δ-5 steroids afforded good yields of enones. In the case of cholesteryl acetate a 75 % yield was obtained after some optimization as discussed below.[7]



1 **2**

Solvent is an important variable for this oxidation as shown in Table 1. There is a correlation in yield improvement with decreasing solvent polarity. With cholesteryl acetate, cyclohexane was the optimal solvent since it provided sufficient solubility for both starting material and product and is non-polar.

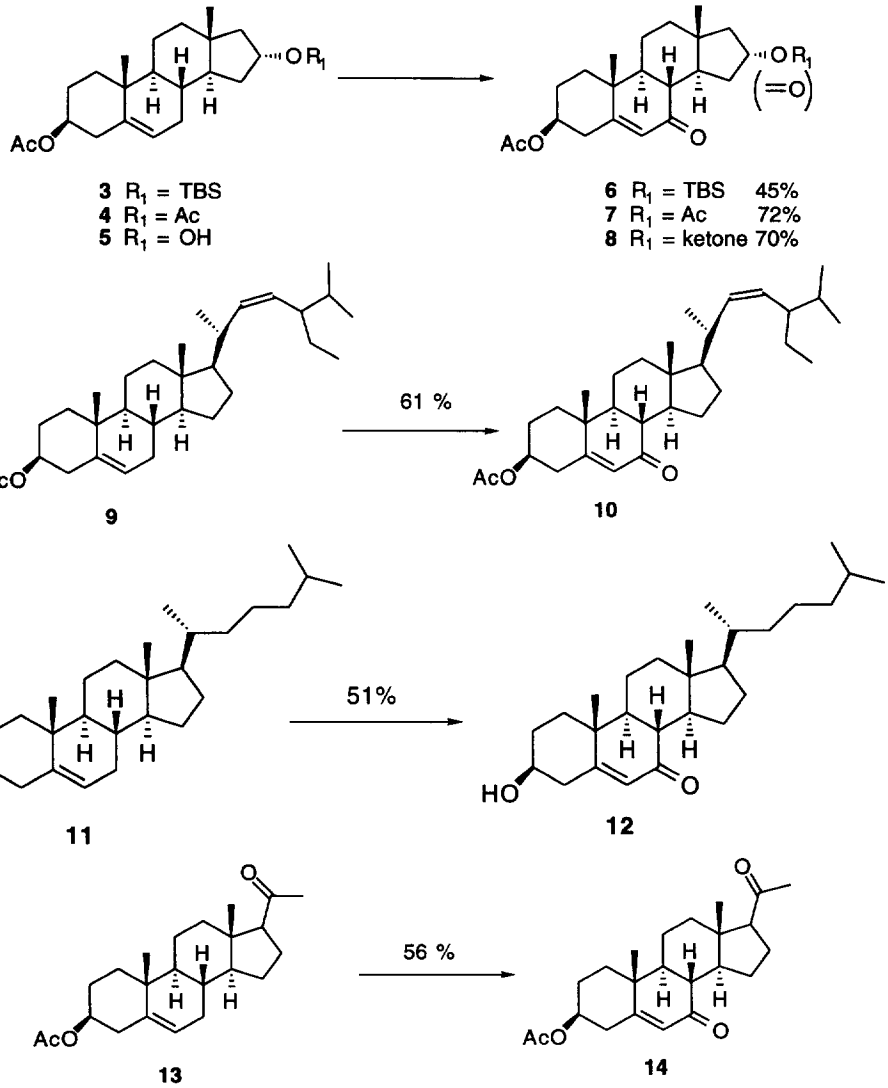
Table 1: Effect of Solvent on the Allylic Oxidation of 1

Entry	Solvent	Yield(%)
1	Cyclohexane	75
2	Heptane	75
3	Toluene	63
4	tBuOH	24
5	MEK	48
6	Ethyl Acetate	68
7	Dichloroethane	75

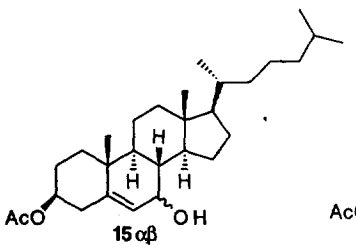
#The reaction was run at 15-20°C, with 0.7mol% $RuCl_3$ and 10 eq of TBHP. After 24h the reaction was stopped and assayed for yield by HPLC.

For other steroidal substrates, the use of non-polar solvents was impractical due to solubility constraints. In these cases, the use of chlorobenzene or dichloroethane provided good solubility for starting materials and products without yield loss.

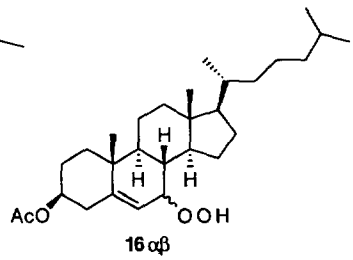
Several other Δ-5 steroids were examined under the reaction conditions with moderate to good yields, though none was optimized. In the case of the androst-5-ene derivative **5**, the hydroxyl function at the 16-position was oxidized quickly to the ketone along with allylic oxidition, but when protected as the acetate **4**, no 16-ketone was observed. Attempted protection of the hydroxyl with TBS (**3**) gave moderate yields of the desired 7-enone. In this case the product was contaminated with the 16-ketone as well as TBS-OH(10%). In the case of stigmasterol **9**, only 7-allylic oxidation was observed. Cholesterol **11** oxidized preferentially at the 7-position without oxidizing the 3-OH.



Four compounds which convert to enone were observed by HPLC during the oxidation of **1** and they were identified as the two 7-OH diastereomers (**15** α,β) and the two 7-OOH diastereomers (**16**α,β) by independent synthesis.[8,9] Since both 7-OH's and 7-OOH's were observed during the reaction and both convert to product, more than one reaction pathway is likely. In the reaction of androstene derivative **3** which contained 10mol% BHT, no 7-OH's or enones were observed until the BHT had been consumed, suggesting a radical pathway.

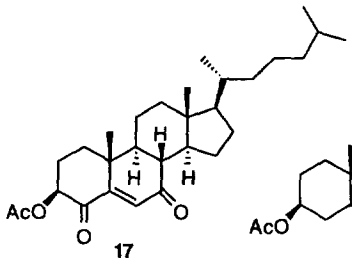


15αβ

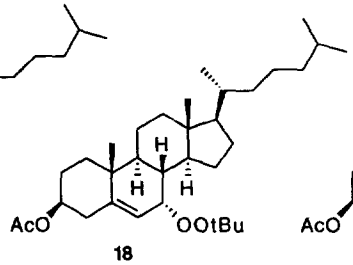


16αβ

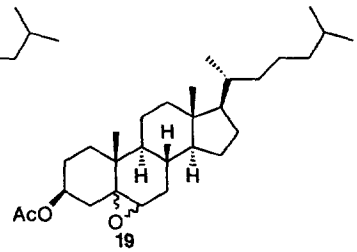
A number of undersired by-products were identified and help explain the mass balance in this reaction. Unreacted 7-alcohols accounted for about 3 % of the yield. Over-oxidation to the 3,7 dione **17** accounted for 5-10% of the yield.[10] Another compound which formed mostly at the beginning of the reaction is the 7-OOtBu **18** which accounts for 5%.[11] The 5,6 epoxides were observed in about 5% yield.



17



18



19

In conclusion, a new method for the production of 7-keto steroids has been developed that is general for a variety of substrates. The oxidation is operationally simple and has been successfully scaled up to produce kilogram quantities of enone.

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6 For a discussion of TBHP oxidations of alkenes under metal catalysis, see Sharpless, K.B., Verhoeven, T.R. *Aldrichimica Acta* **1979**, *12*, 63.

7 Experimental Procedure: In a 2L 3-necked flask with an overhead stirrer was added ruthenium trichloride hydrate (240 mg,1.1 mmol), 55 mL water, cholesteryl acetate (75.8 gm, 177 mmol) and cyclohexane (400 mL). 70% t-BuOOH (229 gm, 1.77 mol) was added slowly over 6 hrs. An internal temperature of 15-20 °C was maintained by cooling with a water bath. The reaction was stirred until less than 1.5 wt% of starting material and less than 2 % of the 7-hydroxy cholesteryl acetate intermediates remained, typically 20-24 hrs. The reaction was monitored with a YMC basic column; 90:10 acetonitrile:0.1M aqueous H_3PO_4; flow rate = 1.5 mL/min @ 200nm. R_T cholesteryl acetate = 17.0 min; R_T 7-keto cholesteryl acetate = 7.8 min; R_T enedione 4.5 min R_T 7-hydroperoxides; 7-alcohol epimers = 6.8, 6.9,7.0,8.2 min.; 7-tBuOO-cholesteryl acetates R_T = 18 ,19 min . To the reaction mixture was added 550 mL methyl ethyl ketone 390 mL water, and 39 gms sodium sulfite. The mixture was heated to 70 °C until the enedione **17** is gone (3 hrs). The reaction mixture was cooled to RT, then filtered through a pad of Solka-Flok to remove the ruthenium salts. The clear solution was separated and the organic layer washed with 100 mL 1% brine. The organic solution was turned over to 350 mL of heptane, cooled to -5°C and filtered, washing twice with 150 mL of cold heptane. After drying, the product was obtained in 69 % yield (53.7 gms) as an off-white solid whose spectra was consistent with the literature(reference 3). Mother liquor losses were 4.5 gm/6%.

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9 The peroxides were made according to the procedure in reference 4c.

10 Enedione **17**: ^{1}H NMR (CDCl3) 6.1 (s, 1H), 5.25 (dd, 1H, J = 12.5, 7 Hz), 2.5-1.0 (m, 24H), 2.19 (s, 3H), 1.20(s, 3H), 0.93 (d, 3H, J = 6 Hz), 0.86 (d, 6H, J = 6.5Hz), 0.70 (s,3H). ^{13}C NMR(CDCl3) 201.7, 197.1, 169.8, 158.7, 127.4, 76.1, 54.8, 50.5, 49.8, 45.8, 43.1, 41.1, 39.5, 38.6, 36.0, 35.7, 34.2, 28.5, 28.0, 26.01, 25.98, 23.8, 22.8, 22.6, 21.5, 20.7, 18.9, 18.2, 12.0. IR (neat): 1750, 1720, 1680. HRMS $C_{29}H_{44}O_4$ calcd 456.3239 found 456.3266 ± 2.7amu.

11 tBuOOR **18**: ^{1}H NMR (CDCl3) 5.7 (d, 1H, J = 4.7 Hz), 4.68 (m, 1H), 4.1 (br s, 1H), 2.4 (m, 2H), 2.05 (s, 3H), 2.0-1.0 (m, 24H), 1.2 (s, 9H), 1.05 (s, 3H), 0.95 (d, 3H, J = 6 Hz), 0.90 (d, 6H, J = 6 Hz), 0.65 (s, 3H). ^{13}C NMR(CDCl3) 170.5, 145.1, 122.2, 79.6, 75.9, 73.5, 55.8, 48.8, 42.65, 42.25, 39.49, 38.89, 38.03, 37.50, 36.45, 36.23, 35.94, 28.2, 28.0, 27.5, 26.7, 24.7, 24.0, 22.8, 22.5, 21.38, 20.7, 18.8, 17.9, 11.3. LRMS C_{33} $_{56}O_4$ calcd 516 found [MNH_4^+] 534.

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