AN ALTERNATIVE ROUTE TO 2α,3α-DIOLS FROM 2,3-UNSATURATED 5α-STEROIDS AVOIDING THE USE OF OSMIUM TETROXIDE*

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A method for preparation of 2α,3α-dihydroxy-5α-steroids from 2,3-unsaturated 5α-steroids without the use of OsO_4 is described. It involves the sequence of epoxidation, cleavage of the oxirane ring by HI, acetylation, oxidative replacement of iodine by hydroxyl and alkaline hydrolysis (*I* → *VI*) without purification of the intermediates. The presence of a 6-keto group does not decrease the yields. The yields are comparable with those obtained by osmylation and the method can find general use, particularly in the synthesis of brassinolide analogs.

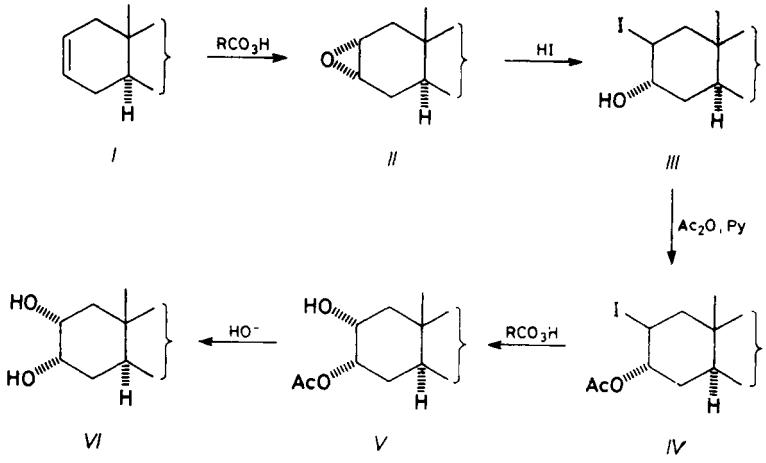
The 2α,3α-diol moiety is a characteristic feature of barassinosteroids and is essential for their activity promoting plant growth. Thus far, synthetic introduction of this grouping has been limited to the addition of OsO_4 to 2,3-unsaturated 5α-steroids. The starting olefins are readily accessible, the osmylation method is methodically simple and provides good yields due to high stereoselectivity. However, even though the amount of OsO_4 can be diminished by the use of catalytic methods[1], a disadvantage of this procedure remains the high price and toxicity of the reagent. In particular, application on a large scale is a difficult problem. For these reasons, a search for an alternative method appeared very desirable.

In the present paper we report a procedure consisting of a proper combination of several per se known reactions, which enable preparation of 2α,3α-diols from the corresponding olefins without the use of osmium tetroxide. The reaction sequence is shown in Scheme 1.

To distinguish this approach from the osmylation procedure in the following discussion, we call it the peroxy acid method. The individual steps in this sequence are simple reactions with high stereoselectivity and nearly quantitative yields. Therefore, the intermediates need not be purified and the corresponding losses are thus eliminated. The completion of the individual reactions can be easily monitored by TLC.

* Part CCCXLIV in the series On Steroids; Part CCCXLIII: Collect. Czech. Chem. Commun. *54*, 1888 (1989).

The first step in this sequence is the preparation of a 2α,3α-epoxide *II* from the corresponding 2,3-olefin *I*. With common steroids, where no disturbing influences (e.g., neighboring group participation) are present, the reaction is known to provide



I *II* *III* *IV* *V* *VI*

SCHEME 1

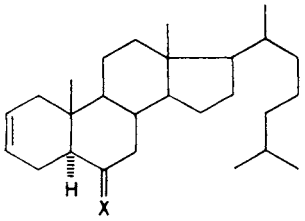
virtually exclusively the 2α,3α-epoxide[2]. The cleavage of the oxirane ring with hydrogen iodide in the next step is a rapid and stereoselective reaction[3] giving the diaxial iodohydrin *III*.

This compound is acetylated without difficulties by the standard acetic anhydride–pyridine procedure at room temperature. Protection of the hydroxyl group by acetylation is a prerequisite for the successful replacement of the iodine atom by hydroxyl in the next step. If acetylation is omitted, the ensuing treatment with peroxy acid results in the re-formation of *II*.

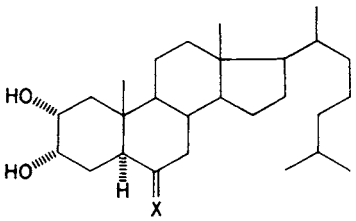
The treatment of *IV* with 3-chloroperbenzoic acid is again a highly stereoselective reaction[4] and yields the *cis*-diol monoacetate *V*. Alkaline hydrolysis of the latter provides the desired diol *VI* which is isolated by chromatography. Alternatively, the compound *IV* can be treated with cupric acetate in acetic acid[5] to yield the corresponding *cis*-diol diacetate convertible to diol *VI* by alkaline hydrolysis.

The purity of the starting 2,3-unsaturated steroids deserves some comment. The usual methods of their preparation involve elimination of 3β-tosyloxy or halogeno derivatives achieved by treatment with tertiary amines, a suitable adsorbent or lithium salts in dimethylformamide. Generally, the products are accompanied by a certain amount of the 3,4-isomer; sometimes its separation cannot be achieved by chromatography and crystallization. Therefore, the purity of 2,3-olefins *I* was checked by ^{1}H NMR spectroscopy: the degree of contamination by the 3,4-isomer

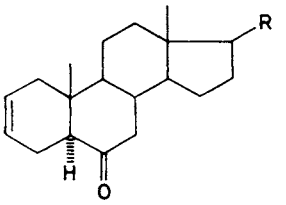
was determined from the integral intensities ratio of the lines related to the angular methyls of the major substance and admixture. For comparison of the peroxy acid and osmylation method the same preparations of the corresponding 2,3-olefins were always used. The results are summarized in Table I.



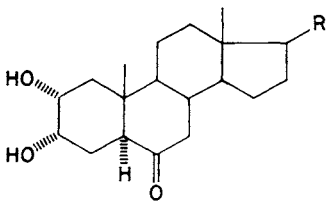
VIII, X = H_2
X, X = O



VII, X = H_2
IX, X = O



XII, R = $COCH_3$
XIV, R = $OOCCH_3$
XVI, R = H



XI, R = $COCH_3$
XIII, R = OH
XV, R = H

TABLE I

Yields of 2α,3α-diol by peroxyacid method and osmylation method

Starting compound	Yield, %	
	peroxy acid method	osmylation method
5α-Cholest-2-ene (*VIII*)	57[a,b]	59[a,b]
5α-Cholest-2-en-6-one (*X*)	62[a], 56[a,b]	50[a,b]
5α-Pregn-2-en-6,20-dione (*XII*)	16[a,b]	56[a,b]
17β-Acetoxy-5α-androst-2-en-6-one (*XIV*)	69[b]	51[b]
5α-Androst-2-en-6-one (*XVI*)	54[a,b]	54[a,b]

Products purified until satisfactory m.p. and $[\alpha]_D$ were obtained (cf. Experimental) by: [a] chromatography: [b] crystallization.

The method can be applied to simple 2,3-olefins equally well as to 2,3-unsaturated 6-ketones. This is of interest since for the 6-ketones a concomitant Baeyer–Villiger reaction could be expected to occur to some extent. Evidently, the rate of the Baeyer–Villiger reaction in this case is too slow to compete with the peroxy acid attack at the 2,3-double bond. On the other hand, an experiment on the 20-ketone *XII* gave a much lower yield of the desired diol than osmylation. Thus, the peroxy acid method appears unsuitable for 20-ketones. In all other cases investigated the yields by the peroxy acid method are comparable with those obtained by the osmylation procedure. In spite of the multistep character of the method, the whole reaction sequence can be performed in three days and we believe that it can be a useful alternative to the OsO_4 procedure in many cases.

EXPERIMENTAL

The melting points were determined on a Kofler block and are not corrected. Optical measurements were carried out in chloroform, with a $\pm 3°$ error, at concentrations ranging from 1·2—2·0. The infrared spectra were measured in chloroform on a Zeiss UR 20 spectrometer. The identity of the samples was checked by mixture melting point determination, thin-layer chromatography (TLC) and infrared spectra. The ^1H NMR measurements were conducted on a Varian XL-200 apparatus.

General Procedures

A) Peroxy acid method. 2,3-Unsaturated steroid (2·7 mmol) was dissolved in benzene (40 ml), 900 mg (4·2 mmol) of 82% 3-chloroperbenzoic acid was added, kept at room temperature, and the course of the reaction was monitored by TLC. When the starting compound was no longer present (about 3 h), the solution was washed with aqueous NaOH solution (1%), Na_2SO_3 and H_2O, dried and evaporated, dissolved in chloroform (30 ml) and shaken with aqueous HI (3 ml, 57%, stabilized with H_3PO_2) for 4 min. The solution was then washed with H_2O, Na_2SO_3, $NaHCO_3$ and H_2O, dried and evaporated under reduced pressure at $t < 30°C$. The residue was immediately acetylated with a pyridine (10 ml)–acetic anhydride (5 ml) mixture at room temperature overnight. The mixture was poured onto ice, extracted with ether and the solution washed with H_2O, HCl (5%), $NaHCO_3$, dried and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml) and 3-chloroperbenzoic acid (0·8 g) was added. The reaction started immediately (liberation of iodine) and its completion (TLC) required 3—5 h. After washing with H_2O, Na_2SO_3, NaOH (3%), H_2O and drying, the solvent was removed under reduced pressure. The residue was dissolved in methanol (100 ml) and a solution of KOH (2 g) in H_2O (3·5 ml) was added. After standing overnight the mixture was concentrated to a small volume, water was added and the product extracted into chloroform (or another suitable solvent). Usually, the crude product was then separated by chromatography on silica gel. The purity of the chromatographically homogeneous product was checked by m.p. and optical rotation determination. In most cases further purification by crystallization was necessary.

B) The osmylation method[6]. 2,3-Unsaturated steroid (2·7 mmol) was dissolved in tetrahydrofuran (50 ml), water (10 ml), OsO_4 (50 mg) in tert.butanol (1 ml) and N-methylmorpholine-N-oxide (1 g, 8·5 mmol) were added. The mixture was stirred and treated with three portions of

Na_2SO_3 (0·5 g each at 1 h intervals) and the stirring continued for an additional 2 h. After concentration to a small volume, the product was precipitated by the addition of water, extracted into chloroform, the solution washed with H_2O and $NaHCO_3$, dried and the solvent removed under reduced pressure. The purity of the product was checked by TLC, m.p. and optical rotation determination. None of the crude products showed satisfactory purity, all but one had to be chromatographed, all had to be crystallized. Comparison of the yields is presented in Table I.

5α-Cholestan-2α,3α-diol (*VII*)

a) 5α-Cholest-2-ene (*VIII*, ref.[8]), m.p. 74–75°C, $[\alpha]_D$ +66°, containing 7% of the 3,4-isomer, was treated as given above using the peroxy acid method and the crude product was purified by chromatography on silica gel in benzene, then benzene–ether (1 : 1) to give a homogeneous fraction (910 mg), m.p. 205–215°C, $[\alpha]_D$ +33°. Crystallization from methanol gave the product *VII* (626 mg, 57%), m.p. 210–215°C, $[\alpha]_D$ +31°; reported[7] m.p. 212–214°C, $[\alpha]_D$ +32°. IR spectrum: 3 615, 3 580, 1 042 cm^{-1} (OH).

b) 5α-Cholest-2-ene (*VIII*) of the same purity was converted to 3α-acetoxy-2β-iodo derivative as given above and refluxed in aqueous acetic acid (94%, 63 ml) with cupric acetate monohydrate (396 mg) for 1b. After cooling, the inorganic material was filtered off and washed with acetic acid. The filtrate was poured onto ice, the solid substance separated by suction, dissolved in ether, the solution washed with $KHCO_3$ and water, dried with Na_2SO_4 and the solvent evaporated. The oily residue (1·6 g) was dissolved in benzene (60 ml), aqueous (5 ml) methanolic (55 ml) KOH (6 g) was added and the mixture refluxed for 3 h. The solution was concentrated to a small volume, the product precipitated by the addition of ice and separated by suction. The crude product showed m.p. 205–225°C, $[\alpha]_D$ +37°. Since the TLC indicated good purity, the product was directly crystallized from methanol and then from ethanol to yield the product *VII* (560 mg, 52%), m.p. 212–216°C, $[\alpha]_D$ +31°.

c) 5α-Cholest-2-ene (*VIII*) of the same purity was treated with OsO_4 as given above. The crude product (1·07 g) of insufficient purity (m.p. 203–213°C, $[\alpha]_D$ +42°) was chromatographed in benzene–ether (1 : 1) without reaching good purity (1 g, m.p. 200–213°C, $[\alpha]_D$ +29°). Recrystallization from CH_3OH yielded the pure diol (640 mg, 59%), m.p. 215–217°C, $[\alpha]_D$ +31°. IR spectrum: identical with that of the above sample.

2α,3α-Dihydroxy-5α-cholestan-6-one (*IX*)

a) 5α-Cholest-2-en-6-one (*X*, ref.[10]), m.p. 106–107°C, $[\alpha]_D$ +34°, with no detectable admixture of the 3,4-isomer, was treated as described above for the peroxy acid procedure. The crude fraction (700 mg, 62%) was obtained by chromatography on silica gel (benzene–ether, 9 : 1) and showed satisfactory physical constants: m.p. 205–207°C, $[\alpha]_D$ +7°; crystallizazion from methanol gave the product (628 mg, 56%), m.p. 206–209°C, $[\alpha]_D$ +7°. Literature[9] reports m.p. 206–207°C, $[\alpha]_D$ +7°. IR spectrum: 3 615, 3 675, 1 044 cm^{-1} (OH); 1 710 cm^{-1} (CO).

b) 5α-Cholest-2-en-6-one (*X*) of the same purity was treated with OsO_4 as described above, the crude product chromatographed on silica gel using successively benzene–ether (15%) and benzene–ether (50%). The major fraction (1·08 g, m.p. 180–210°C, $[\alpha]_D$ +5° was crystallized from ethanol (570 mg, 50%), m.p. 207·5–208·5°C, $[\alpha]_D$ +7°. IR spectrum: identical with that of the above sample.

2α,3α-Dihydroxy-5α-pregnan-6,20-dione (*XI*)

a) 5α-Pregn-2-en-6,20-dione (*XII*, ref.[12]), m.p. 157–159°C, $[\alpha]_D$ +95°, containing 22% of the 3,4-isomer, was treated according to the peroxy acid procedure as given above and the crude product was chromatographed on silica gel using a benzene–ether (2 : 1) mixture for elution of the less polar impurities and benzene–ether (1 : 2) for elution of the crude product (651 mg) which after crystallization from aqueous ethanol and from benzene gave pure diol *XI* (150 mg, 16%) m.p. 204·5–205·5°C, $[\alpha]_D$ +62°. Literature[11] reports m.p. 206–211°C, $[\alpha]_D$ +62°. IR spectrum: 3 615, 3 570 cm^{-1} (OH); 1 710, 1 360 cm^{-1} ($COCH_3$).

b) 5α-Pregn-2-en-6,20-dione (*5II*) of the same purity was treated with OsO_4 as given above. The crude product was dissolved and adsrobed on silica gel in chloroform, elution was performed with benzene containing in succession 5, 20 and 75% of ether. The major fraction (900 mg) was crystallized from aqueous ethanol and from benzene to give the diol *XI* (524 mg, 56%), m.p. 204–205·5°C, $[\alpha]_D$ +62°. IR spectrum: identical with that of the above product.

2α,3α,17β-Trihydroxy-5α-androstan-6-one (*XIII*)

a) 17β-Acetoxy-5α-androst-2-en-6-one (*XIV*, refs[13,14]) m.p. 168–170°C, $[\alpha]_D$ +12°, containing no detectable admixture of the 3,4-isomer, was treated applying the peroxy acid method as described above. After the last step (alkaline hydrolysis), water (about half the volume) was added and the solution concentrated under reduced pressure to half volume and the less polar impurities removed by washing the solution with ether. More water (10 ml) was added to introduce crystallization of the product (397 mg). The filtrate was neutralized with HCl and the solvent removed under reduced pressure. The solid residue was repeatedly extracted with ethanol, the solution concentrated to a small volume and water was added (50 ml). Repeated concentration and dilution with water induced crystallization to yield a second crop (230 mg). Crystallization of the combined products from aqueous ethanol yielded the pure product *XIII* (600 mg, 69%), m.p. 225–226·5°C, $[\alpha]_D$ −9°; literature[11] reports m.p. 220–225°C, $[\alpha]_D$ 0°. IR spectrum: 3 605, 3 590, 1 073, 1 040, 1 014 cm^{-1} (OH); 1 705 cm^{-1} (CO).

b) 17β-Acetoxy-5α-androst-2-en-6-one (*XIV*) of the same purity was treated with OsO_4 and worked up as described above but the crude material was then subjected to alkaline hydrolysis by standing overnight with KOH (800 mg) in CH_3OH (100 ml). The solution was neutralized with HCl and evaporated to dryness. The residue was extracted six times with boiling ethanol, evaporated to dryness, dissolved in $CHCl_3$–CH_3OH (95 : 5) and filtered through a layer of silica gel (to remove colloidal impurity). The filtrate was evaporated to dryness and crystallized from aqueous ethanol to give the diol *XIII* (620 mg, 71%), m.p. 218–220°C, $(\alpha]_D$ −5°, after recrystallization from the same solvent: 440 mg (51%), m.p. 225–227·5°C, $[\alpha]_D$ −5°. IR spectrum: identical with that of the above product.

2α,3α-Dihydroxy-5α-androstan-6-one (*XV*)

a) 5α-Androst-2-en-6-one (*XVI*, ref.[16]) m.p. 71–72°C, $[\alpha]_D$ +21°, containing 9% of the isomeric 3,4-olefin, was treated according to the peroxy acid method, the crude product chromatographed on silica gel and successively eluted with benzene–ether (30, 40, and 50%) to give the major fraction (540 mg, m.p. 150–153°C, $[\alpha]_D$ −15°). Crystallization from aqueous methanol gave pure diol (442 mg, 54%), m.p. 157–158°C, $[\alpha]_D$ −20°. Literature[15] reports m.p. 151–157°C, $[\alpha]_D$ −18°. IR spectrum: 1 711 cm^{-1} (CO); 2 620, 3 575, 1 041 cm^{-1} (OH).

b) 5α-Androst-2-en-6-one (*XVI*) of the same purity was treated with OsO_4 as described above, the crude product (803 mg, m.p. 125–135°C) was chromatographed on silica gel in benzene–

-ether (as above). The major fraction (752 mg, m.p. 125—135°C) was repeatedly crystallized from aqueous methanol (445 mg, 54%), m.p. 157—158°C, $[\alpha]_D$ −22°. IR spectrum: identical with that of the above product.

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