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Development of a Commercial Process to Produce Oxandrolone

John E. Cabaj,* David Kairys, and Thomas R. Benson

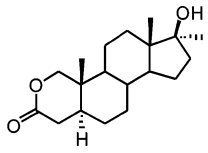
Process Research and Development, Cedarburg Pharmaceuticals, Inc., 870 Badger Circle, Grafton, Wisconsin 53024, U.S.A.

Abstract:

A manufacturing scale process for the preparation of the anabolic steroid Oxandrolone was developed. Key elements included the following: the bromination of methylandrostanolone with perbromide to give the 2-bromoketone in ca. 80% yield with minimal dehydration, subsequent elimination of the bromide with Li_2CO_3/LiBr to give the 2-enone in ca. 70% yield with minimal formation of methyltestosterone, and an ozonolysis procedure to give the penultimate intermediate in ca. 90% yield. The overall yield from methylandrostanolone to Oxandrolone using the described process was 45% as compared to the original Searle yield of 8%.

Introduction

Oxandrolone **1** is an anabolic steroidal lactone currently being used to promote weight gain and for the relief of bone pain associated with osteoporosis. Oxandrolone was originally developed by the G.D. Searle Company during their investigation of the anabolic and androgenic activity of 2-oxasteroids. The original synthesis was developed by



Oxandrolone

1

Counsell, Pappo, and co-workers.[1] In our synthetic planning we felt that the Searle approach was the most direct. Other approaches involving the late introduction of the 17-tertiary alcohol, which would eliminate the issue of dehydration during the early stages of the process (*vide infra*), were not pursued due to the inherent selectivity issues that would need to be addressed between A and D ring functionality. Also, the raw material for the Searle approach, methylandrostanolone (**2**), is readily available from a variety of vendors at a reasonable price.[2] However, we found that the synthesis described by the Searle workers was not suitable for large-scale production. We therefore developed a new process, based on the Searle approach, which was ultimately used to produce multikilogram quantities of USP Oxandrolone.[3] The development work that culminated in the final process is summarized herein.

Discussion

The original Counsell/Pappo synthesis is summarized in Scheme 1. The need to purify the α-bromoketone **3** as well as the enone **4** by column chromatography, the use of the highly toxic OsO_4 and $Pb(OAc)_4$, and the low to moderate yields in each of the four steps of the synthesis made use of the Searle procedure unsuitable for scale-up. With these issues in mind we proceeded to develop a scaleable method based on the general approach of the Searle workers.

Bromination of Methylandrostanolone. Bromination of methylandrostanolone (**2**) according to the Searle procedure (Br_2, NaOAc, acetic acid) resulted in multiple product formation as determined by NMR analysis of the crude reaction product.[4] The major product isolated after column chromatography was **6**, the product of Wagner−Meerwein rearrangement of the 18-methyl group (Scheme 2).[5] A control experiment in which **2** was treated with HBr/acetic acid showed that dehydration was indeed caused by the acidic media generated during the bromination. Also, there is ample precedent for such dehydrations in similar substrates.[6] Bromination with bromine in DMF, according to the Searle patent, gave several products by TLC and ^{1}HNMR analysis and therefore was not pursued further.

Due to the sensitivity of the 17-alcohol to dehydration, a protecting group strategy was briefly examined (Scheme 3). Subjecting the corresponding 17-acetate to the Searle reaction conditions resulted in dehydration as well, while treatment of the 17-trimethylsilyl ether of **2** with HBr (the byproduct of the bromination reaction) led to desilyation.

Esterification of **2** with benzoyl chloride (PhCOCl, pyridine, DMAP, CH_2Cl_2, reflux) gave the benzoate ester **9** in 33% yield after column chromatography. When the benzoate ester was treated with bromine, ^{1}HNMR analysis of the crude reaction product showed that bromine incorporation had occurred at C-2; however, a significant amount

* To whom correspondence should be addressed. Telephone: (262)-376-1467. Fax: (262)-376-1068. E-mail: john.cabaj@cedarburgpharma.com.

(1) (a) Counsell, R. E.; Klimnstra, P. D.; Colton, F. B. *J. Org. Chem.* **1962**, *27*, 248. (b) Pappo, R.; Jung, C. J. *Tetrahedron Lett.* **1962**, *9*, 365. (c) Pappo, R. U.S. Patent 3,128,283, 1964.

(2) Approximate cost of **2** is ca. $1,300/kg.

(3) For more recent syntheses of Oxandrolone, see: Ferraboschi, P.; Colombo, D.; Prestileo, P. *Tetrahedron: Asymmetry* **2003**, *14*, 2781. Desai, S. R.; Ray, D. W., Jr.; Sayed, Y. A. U.S. Patent Appl. US2003/0109721, 2003. Sánta, C.; Tuba, Z.; Mahó, S.; Széles, J.; Ferenczi, K.; Horváth, P.; Láncos, K.; Mester, T.; Trompler, Á. World Patent, WO 00/77025 2000.

(4) For a discussion on the origin of the regioselectivity of the bromination, see: Djerasi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1947**, *69*, 2404. Fieser, L. F.; Dominguez, X. A. *J. Am. Chem. Soc.* **1953**, *75*, 1704. Berkoz, B.; Chavez, E. V.; Djerassi, C. *Steroids* **1962**, 1323.

(5) Monneret, C.; Choay, P.; Khuong-Huu, Q.; Goutarel, R. *Tetrahedron Lett.* **1971**, *19*, 3223.

(6) Smith, D. M.; Steele, J. W. *Can. J. Pharm. Sci.* **1981**, *16*, 68.

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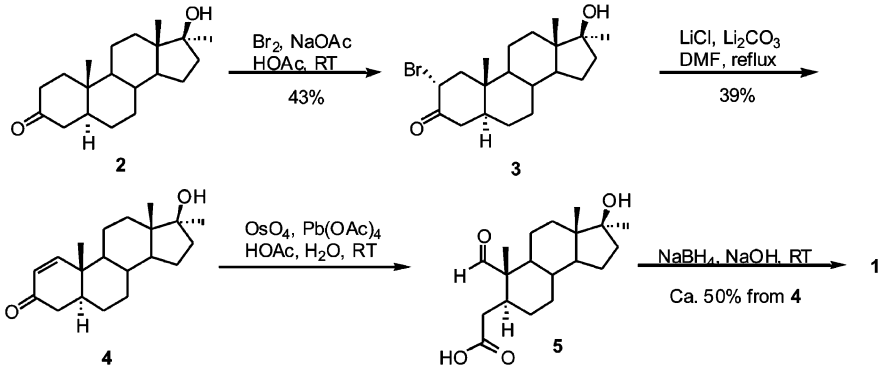
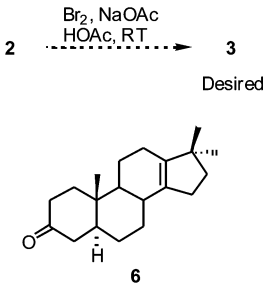
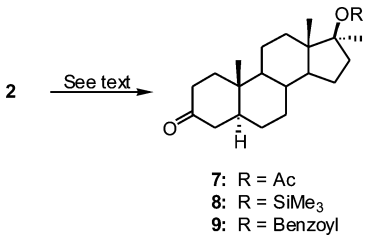
Scheme 1. **Counsell/Pappo synthesis of Oxandrolone**



Scheme 2. **Counsell bromination of methylandrostanolone**



Scheme 3. **Protecting group study of bromination reaction**

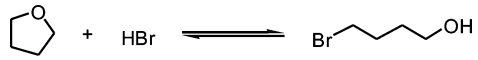


of starting material remained as well. Due to the low yield in the benzoylation this approach was not pursued further. Other protecting groups were not examined.

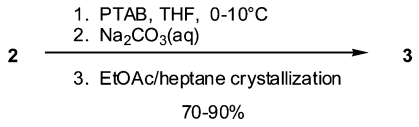
Hershberg and co-workers at Schering discovered that attempted NBS mediated oxidation of a 3-hydroxy steroid in the pregnane series gave a mixture of brominated ketones.[7] We therefore tried to brominate the silyl ether **8** using these conditions (NBS, HBr/HOAc, *t*-BuOH, CH_2Cl_2, RT) and obtained **3** contaminated with succinimide in 46% yield. No reaction occurred without the addition of HBr. Presumably the HBr is needed to promote enol formation. Not surprisingly, the silyl ether was cleaved in the process. While the NBS method appeared to have some promise, we did not pursue it further since bromination with perbromides gave far superior results.[8]

The use of a perbromide for this transformation was first reported by Doorenbos in which he obtained a 41% yield of **3** from **2** by using pyridinium tribromide in THF.[9] In our initial experiment, **2** was dissolved in THF and 1.1 equiv of the perbromide phenyltrimethyl ammonium bromide (PTAB)

Scheme 4. **THF trapping of HBr**



Scheme 5. **Process summary for the production of 3 (50-L scale)**



was added as a solution at 0−10 °C.[10] We were delighted to find that after workup and crystallization **3** was obtained in 85% yield. Very little dehydration was evident by TLC analysis.

A brief solvent screen showed that the reaction could also be run in CH_2Cl_2, $CHCl_3$, and diethyl ether; however, the reaction is not as clean in these solvents as it is in THF (TLC result) or (in the case of diethyl ether) prohibitively slow. Presumably, the THF is acting as an HBr trap as shown below in Scheme 4 thus resulting in reduced dehydration of the 17-alcohol in this solvent.[11] The reversible nature of this reaction would necessitate a process change prior to scaling this step to reactor scale (*vide infra*).

The bromination reaction was worked up by adjusting the pH with Na_2CO_3 followed by ethyl acetate extraction and water washing. The ethyl acetate solution of **3** was then concentrated to a set volume, and the resulting white solid was further precipitated by adding heptane at ambient temperature. The crystallization proved effective at removing what little dehydration product was present. Drying of the product at ca. 40 °C gave **3** in 70−90% yield. The initially white product cake tended to discolor upon drying (light pink). This was not a major issue on the 50-L scale as drying times were fairly short and the downstream chemistry worked reliably well with this material; however, the discoloration was a concern since we did not know its origin. We were fairly pleased that we were able to produce enough material using this procedure to meet the customer's initial bulk drug requirements. Although the brominating agent used in the process is considerably more expensive than molecular

(7) Hershberg, E. B.; Gerold, C.; Oliveto, E. P. *J. Am. Chem. Soc.* **1952**, *74*, 3849.
(8) LaCour, T. G.; Guo, C.; Bhanbaru, S.; Boyd, M. R.; Fuchs, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 692.
(9) Doorenbos, N. J.; Dorn, C. P., Jr. *J. Pharm. Sci.* **1962**, *51*, 414.
(10) Chodounská, H.; Slavíková, B.; Kasal, A. *Collect. Czech. Chem. Commun.* **1994**, *59*, 435.
(11) For an example of THF opening with aqueous HBr, see: Segi, M.; Takahashi, M.; Nakajima, T.; Suga, S. *Synth. Commun.* **1989**, *19*, 2431. For a related opening with BBr_3, see: Kulkarni, S. U.; Patil, V. D.; Wetherill, R. B. *Heterocycles* **1982**, *18*, 163.

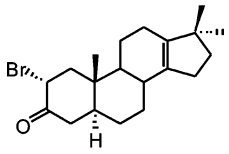
Table 1. **Bromination of 2 using PTAB in various solvents**

entry	conditions	percent yield[a] (%)	percent purity[b]	comments
1	THF/0 °C EtOAc extraction (50-L procedure)	75	92−94	discoloration upon drying
2	DME/0 °C	64	not determined	solubility problem in workup
3	DME/0 °C THF added in extraction	70	not determined	solubility problem in workup
4	EtOAc/0 °C	73	97	solubility problem in workup
5	CH_2Cl_2/0 °C	not determined	not determined	dehydration occurs
6	EtOH/RT	88	90	ethyl ketal formed
7	EtOH/RT CH_2Cl_2 extraction	68	not determined	emulsion problem in workup
8	EtOH/8% H_2O/RT	84	89	reaction complete in 5.5 h
9	EtOH/14% H_2O/RT	82	91	reaction slow (24 h)
10	2-propanol/RT H_2O knockout	70	86	-----
11	MeOH/RT	not determined	-----	ketal major product
12	*n*-PrOH/RT	84	not determined	not as clean as EtOH reaction (TLC result)

[a] Purity not included in yield calculation. [b]Weight percent by HPLC analysis.

bromine, the ease of handling this solid compared to volatile bromine outweighed the cost differential.[12] A summary of the 50-L process to produce **3** (ca. 1 kg per run) is shown in Scheme 5.

As the need to produce larger quantities of Oxandrolone grew, it became obvious that production would have to be performed at reactor scale. Since our 50-L procedure to produce **3** worked adequately, we initially transferred this procedure directly to the plant without any changes. The reaction itself worked well at this scale; however, upon drying at 35−45 °C, the intermediate **3** uniformly turned from white to dark green. TLC and NMR analysis of this material indicated that **3** had dehydrated upon drying giving **10** as the major product.[13]



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After a brief investigation it was determined that HBr had caused the dehydration; however, the source of the HBr was initially unknown since a base quench was used. Also, quenching of residual bromine with metabisulfite or thiosulfate did not eliminate the discoloration during drying. We then reasoned that the source of the HBr was most likely 4-bromo-1-butanol, which is produced from ring opening of THF by HBr (Scheme 4). To prove this theory a sample of the bromoalcohol was made by simply bubbling HBr gas through THF at the same reaction temperature as the bromination reaction (ca. 0−5 °C). Upon heating of the product from this reaction in a vacuum oven the entire oven was coated with an orange residue, as was the case when **3** was dried. A significant amount of the bromoalcohol generated in the bromination reaction presumably carries through to the wet cake. Drying of the cake (40−45 °C) can then cause closure of the bromoalcohol back to THF and liberation of HBr. Variability in cake colors and extent of decomposition may be attributed to differences in cake washing efficiency. Detection of the bromoalcohol in process streams has been complicated due to its instability to GC analysis.

Since the decomposition was occurring during the drying of **3**, we first attempted to bypass the drying by performing a solvent displacement with DMF, the solvent used in the next step. The elimination reaction was then run using the standard conditions (see discussion below). However, the overall yields of **4** from methylandrostanolone were only 39% on two trials. The reason for the low yield is currently unknown; however, it appears that the bromoalcohol level was sufficiently reduced as there was no evidence of discoloration upon drying of the product enone **4**.

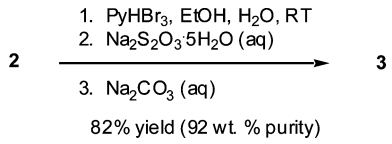
The second option we examined to eliminate the dehydration was performing the reaction in a solvent other than THF. This option was more appealing since the formation of the bromoalcohol would no longer be an issue. The results of the solvent screen using PTAB as the brominating agent are shown in Table 1.

While brominations in DME and EtOAc went to completion and appeared to be fairly clean by TLC, the workup was complicated by the insolubility of **3** in the reaction solvent (entries 2 and 4). Reaction in DME with the addition of THF after reaction quenching did not improve the solubility to an appreciable extent (entry 3). Interestingly, dehydration occurs to a much greater extent in CH_2Cl_2 than in any of the other solvents examined (entry 5). The bromination reaction also works in alcoholic solvents, which made isolation via water precipitation possible. We initially ran this reaction in ethanol alone (entry 6). By TLC analysis a new product in addition to **3** is also formed. Addition of water (pH 1−2) and stirring for several hours lead to collapse

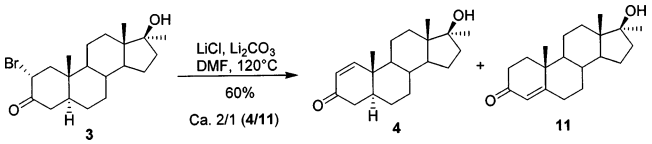
(12) The cost of molecular bromine (Aldrich, 2.5 kg) is ca. $24.80/mol of Br_2. The cost of technical grade pyridinium tribromide (Aldrich, 500 g) is $138/mol of Br_2.

(13) Hewett, C. L.; Gibson, S. G.; Redpath, J.; Savage, D. S. *J. Chem. Soc., Perkin Trans. 1* **1974**, *12*, 1432.

Scheme 6. **Plant process summary for the production of 3**



Scheme 7. **Counsell elimination to generate 4**



of this less polar component to the desired bromide. Running the reaction in the presence of water reduces the level of this compound and gives fairly high quality material (entry 8). We have tentatively assigned this less polar compound as the diethyl ketal of **3** but have not yet characterized it as such. Presumably the presence of water leads to hydrolysis of the ketal to give the ketone. Doubling the amount of water slows the reaction substantially (entry 9). The sterically more encumbered isopropanol gives slightly poorer quality material after precipitation with water (entry 10). Use of methanol gave mainly the dimethyl ketal of methylandrostanolone (entry 11) while *n*-propanol led to a more complicated reaction mixture (entry 12). Thus, an ethanol/water mixture appeared to be the most promising solvent system for this reaction and was therefore used for scaleup.

While PTAB works as a brominating agent in ethanol, the cost of production quantities of pyridinium tribromide ($PyHBr_3$) is approximately half the cost of PTAB.[14] Also, unlike PTAB, $PyHBr_3$ is soluble in ethanol thus making convenient solution charging possible. We initially ran this reaction in the absence of water and obtained a 69% yield of **3** (98 wt % purity); however, this result was not reproducible as lower purity **3** was obtained when this reaction was repeated (88 wt % purity). Removal of ethanol (ca. 1/3 of original 14 mL/g) after water precipitation gave a 91% yield of **3** but with substantially lower purity (75% by weight). As was the case when PTAB was used for the bromination, a higher spot on TLC was formed during the reaction. This spot collapsed to **3** upon addition of aqueous sodium thiosulfate (pH 1−2), which serves to quench residual perbromide. When the reaction is run in ethanol/water mixtures (8% H_2O), the yield and purity are comparable to those of the **3** made using the 50-L procedure (82% yield, 92 wt % purity). The plant process that was used for the production of **3** in 20−30 kg batches is summarized in Scheme 6.

Initially we had ruled out alcoholic solvents, since we were concerned about reaction between the alcohol and the perbromide as is observed with bromine.[15] However, addition of pyridinium tribromide ($PyHBr_3$) to ethanol lead to only a mild 4 °C exotherm over 2.5 h. Also, differential scanning calorimetry analysis on pyridinium tribromide showed no significant events (exothermic or endothermic) until a temperature of 106 °C was reached (ca. 80 °C over operation temperature). Given this stability data, we felt comfortable running this reaction at reactor scale.

(14) The cost of $PyHBr_3$ is $184/kg versus $370/kg for PTAB.

(15) Urben, P. *Bretherick's Handbook of Reactive Chemical Hazards, Fourth Edition*; Kluwer Academic Publishers: 1999.

Table 2. **Examination of the elimination conditions to form 4**

entry	conditions	**4/11**[a]
1	$CaCO_3$, DMA[b], reflux	2/1 (100% crude yield)
2	KOH, MeOH, H_2O, 80 °C	multiple product formation[c]
3	DBU, CH_2Cl_2, rt	multiple product formation[c]
4	collidine, 150 °C	multiple product formation[c]
5	Li_2CO_3, DMF, H_2O, 100−120 °C	1/5 (68% crude yield)
6	Li_2CO_3, DMF, 110−115 °C	multiple product formation[c]
7	LiCl, DMF, reflux	ca. 2/1[c]

[a] Determined by HPLC. [b]DMA = *N*,*N*-Dimethylacetamide. [c]TLC result.

Table 3. **Optimization of LiBr promoted elimination**

entry	conditions	**4/11**[a]
1	LiBr, Li_2CO_3, DMF, 110−120 °C	15/1 (91% crude yield)
2	LiBr, K_2CO_3, DMF, 110−120 °C	1/1[b]
3	LiBr, Na_2CO_3, DMF, 110−120 °C	1/1[b]
4	LiBr, $CaCO_3$, DMF, 110−120 °C	1/1[b]
5	LiBr, Li_2CO_3, DMA, 110−120 °C	46/1 (97% crude yield)
6	LiBr, Li_2CO_3, DMSO, 110−120 °C	multiple product formation[b]
7	LiBr, pyridine, DMF, 110−115 °C	1/1[b]
8	LiBr, Li_2CO_3, DMF, H_2O, 110−120 °C	multiple product formation[b]
9	LiBr, DMF, 110−120 °C	mainly dehydration product

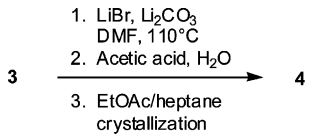
[a] Determined by HPLC. [b]TLC result.

Formation of Enone 4. Counsell and co-workers at Searle reported that treatment of **3** with $LiCl/Li_2CO_3$ in refluxing DMF gave a 93% yield of crude **4** contaminated with approximately 5 to 10% methyltestosterone (**11**).[1] After column chromatography and recrystallization they obtained **4** in only 39% yield. In our hands, we obtained a 60% yield of crude **4** with a **4/11** ratio of only 2/1 (area percent) as shown in Scheme 7. Since we needed kilogram quantities of this intermediate, column chromatography, as a means of purification, was not an option. Also, initial recrystallization attempts did not improve the ratio to a useful level.

Since the Searle procedure was not suitable for scaleup we examined different conditions to perform this transformation (Table 2). Treatment of **3** with both inorganic and organic bases led to multiple product formation or poor ratios (entries 1−4). Addition of water to help solubilize the Li_2CO_3 gave **11** as the major product (entry 5). Use of Li_2CO_3 in the absence of LiCl also led to multiple product formation while use of LiCl in the absence of Li_2CO_3 gave a poor **4/11** ratio (entry 7).

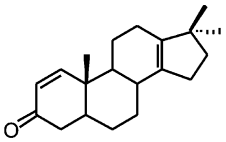
It was not until the effect of the Lewis acid was examined that the real breakthrough in this transformation occurred. We first examined the use of $MgBr_2$ in place of LiCl and discovered that the ratio of **4/11** was improved to 10/1 (area

Scheme 8. **Process to produce enone 4**



percent HPLC). We were able to improve this ratio to 15/1 by using LiBr as the Lewis acid and Li_2CO_3 as the base.[8] A screen of other bases in combination with LiBr was undertaken. The results are summarized in Table 3. Yields were only determined when synthetically useful **4/11** ratios were obtained.

Use of other carbonate bases as well as pyridine resulted in a 1/1 mixture of the two regioisomers (entries 2−4 and 7). The elimination can also be successfully performed in DMA (dimethylacetamide) but not in DMSO. The addition of water to help solubilize the Li_2CO_3 (as in entry 5 of Table 2) resulted in multiple product formation (entry 8). Finally, when the reaction was run in the absence of base, the main product was the17-gem-dimethyl olefin **12** (entry 9).[12]



12

Presumably, the acidic nature of the reaction medium leads to dehydration and methyl migration in this case, as in the formation of **6**. It should be noted that **12** is also one of the impurities generated under normal processing conditions and is removed after crystallization.

Based on the results in Table 3 the reagent combination of $LiBr/Li_2CO_3$ was used for scale-up with DMF as the solvent. The current operating conditions for this transformation are summarized in Scheme 8. Thus the bromide **3** is heated in the presence of LiBr and Li_2CO_3 until the reaction is complete. Acetic acid is added to adjust the pH and dissolve the lithium salts. After ethyl acetate extraction and azeotropic drying, heptane is added to precipitate the enone **4** in 60−80% yield (93−97 wt % purity).[16] The process summarized above was used to produce 10−15 kg batches of the key enone **4**.

Interestingly, the particle size of the Li_2CO_3 was crucial to the success of the reaction. We first became aware of this during a 100-gal reactor scale campaign in which an approximately 1/1 ratio of **4/11** was obtained. Comparison of the particle size of the Li_2CO_3 and the ratio of **4/11** produced shows an interesting trend. In earlier laboratory runs ACS grade Li_2CO_3 (Aldrich catalog number 25,582-3, 99+%) that typically has a smaller particle size than bulk Li_2CO_3 (Aldrich catalog number 20,926-0, −40 mesh, 99%) was used and an acceptable ratio of **4/11** was obtained (Table 4, entries 1 and 2). In the failed production run the particle size was much larger (entry 3).

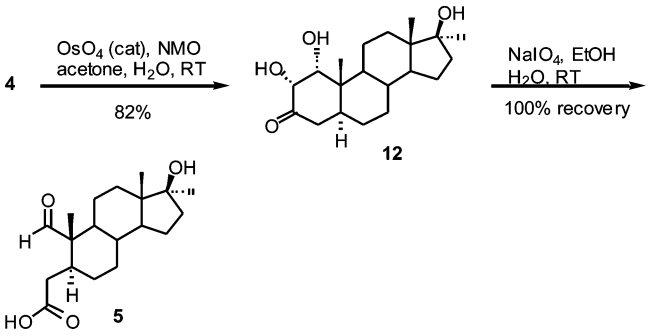
(16) We initially isolated **4** by water knockout from DMF; however, drying of the DMF wet cake was difficult, and recrystallization from ethyl acetate/heptane was typically needed to provide adequate product purity.

Table 4. **4/11 ratio as a function of Li_2CO_3 particle size**

entry	*D*[v, 0.10], μm	*D*[v, 0.50], μm	*D*[v, 0.90], μm	**4/11**[a]
1	3.74	14.96	51.01	13/1
2	2.92	17.52	26.69	99/1
3	200.93	627.39	827.73	1/1

[a] Determined by HPLC.

Scheme 9. **Upjohn dihydroxylation to produce 5**



Other factors that presumably reduce the amount of available carbonate such as the presence of heptane (lower solubility of Li_2CO_3) from insufficient drying of **3**, use of less solvent, and decreased agitation tend to gave higher levels of **11**. Tight control over particle size of Li_2CO_3 has therefore been established.[17]

Oxidation of 4 to 5. Oxidation of the enone **4** according to the Searle patent ($OsO_4/Pb(OAc)_4$) gave the acid **5** which was converted into Oxandrolone using $NaBH_4$. The overall yield from **4** using these conditions was only 7% after chromatographic purification. The extremely low yield in this reaction made it necessary for us to develop an alternative oxidation protocol.

We initially investigated a two-step oxidation procedure in which the intermediate diol would be isolated and then converted to the acid via diol cleavage. When **4** was dihydroxylated using the Upjohn method the diol **12**[18] was obtained in 82% yield.[19] Oxidative cleavage with $NaIO_4$ gave **5** fairly cleanly in 100% recovery contaminated with inorganic salts (Scheme 9). Although we were able to produce **5** efficiently via this route, we decided that the extreme toxicity of OsO_4 warranted the development of an alternative oxidation method.

We initially examined accessing the diol **12** via an epoxide opening strategy (Scheme 10). Treatment of **4** with H_2O_2 cleanly gave the epoxide **13**[20] in 87% yield. However,

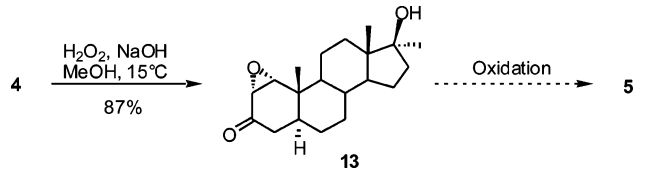
(17) The formation of **11** during this reaction is not well understood; however, Djerassi has shown that the rearrangement of 2,2-dibromoandrostan-17α-ol-3-one to the 2,4-dibromo regioisomer is mediated by HBr (Djerassi, C.; Scholz, C. R. *J. Am. Chem. Soc.* **1947**, *69*, 2404). In our system, it is conceivable that reaction of the liberated HBr with the Li_2CO_3 is dependent on the degree of suspension of the base and ultimately to the particle size of the Li_2CO_3. The larger particle size Li_2CO_3 is most likely not as efficient at sequestering the HBr as material with a smaller particle size. Therefore, rearrangement to the 4-bromo regioisomer is more prevalent when larger particle size Li_2CO_3 is used. Elimination of HBr in the 4-bromo regioisomer would give **11**. Also, the fact that this is a kinetic effect was proven when the **4/11** ratio of a sample of **4** did not change (98/2) upon re-exposure of the enone to the reaction conditions.

(18) Pappo, R.; Jung, C. J. *Tetrahedron Lett.* **1962**, *12*, 365.

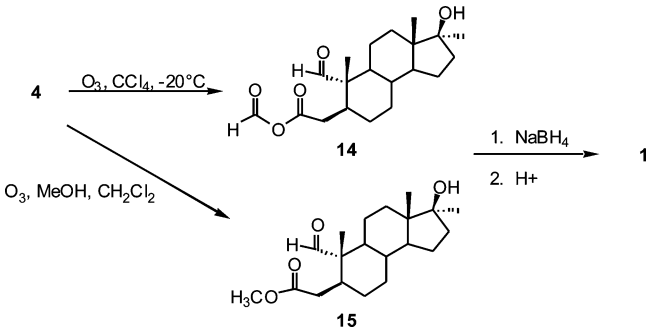
(19) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *24*, 1973.

(20) Pelc, B.; Hodkova, J. *Collect. Czech. Chem. Commun.* **1967**, *32*, 410.

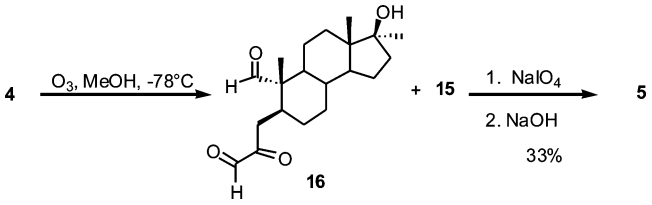
Scheme 10. **Attempted epoxide opening of 13**



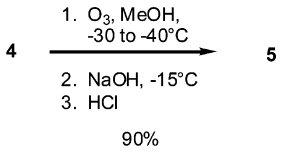
Scheme 11. **Original Searle ozonolysis to produce oxandrolone**



Scheme 12. **Ozonolysis with dimethylsulfide workup**



Scheme 13. **Ozonolysis with caustic workup**



attempted oxidative epoxide opening using $Pb(OAc)_4$ or periodic acid led to multiple product formation.[21] Attempted epoxide opening to generate the diol under acidic (H_2SO_4, $HClO_4$, or $MeSO_3H$) or basic (NaOH/DMSO) conditions also led to multiple products by TLC analysis.

With our lack of success in using the epoxide as an entry to Oxandrolone we turned our attention toward an ozonolytic approach.[22] A thorough search of the patent literature revealed that in fact this approach was used by a group at Searle to synthesize Oxandrolone.[23] The Searle patent describes the ozonolysis of **4** in CCl_4 to give the mixed anhydride **14**, which is converted directly to Oxandrolone after reduction of the aldehyde and cyclization (Scheme 11).

Alternatively, the Searle group obtained the methyl ester **15** when the ozonolysis was performed in a mixture of methanol and methylene chloride. The use of the carcinogenic CCl_4 and the presumably thermal decomposition of the potentially dangerous ozonide or peroxide intermediate made the Searle procedure unsuitable for scaleup.

(21) Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, *21*, 4599.
(22) For a review of production scale ozonolysis, see: Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.*, submitted for publication.
(23) Nysted, N.; Pappo R. U.S. Patent 3,109,016, 1963.

Table 5. **Effect of temperature on ozonolysis of 4**

entry	temperature (°C)	percent yield[a]	purity[b]
1	−40 to −50	83	95
2	−30 to −40	90	99
3	−10 to −20	92	90
4	0 to −10	88	89
5	ambient	not determined	multiple product formation[c]

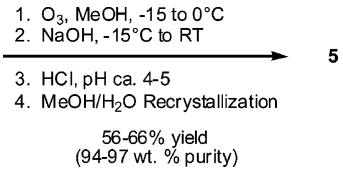
[a] Isolated yield after filtration and drying. [b] Area percent as determined by HPLC. [c] TLC result.

Table 6. **Ranging of temperature at plant accessible temperatures**

entry	temperature (°C)	percent yield	percent purity[a]
1	−15 to −10	93	90
2	−10 to 0	92	92

[a] Determined by weight percent HPLC.

Scheme 14. **Plant process for the production of 5**

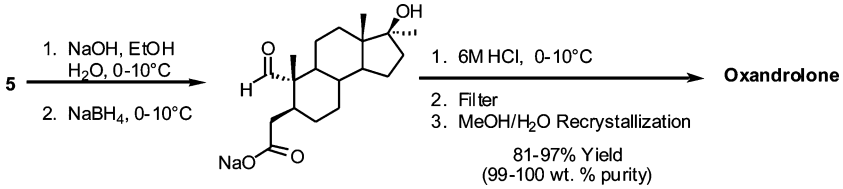


We initially ran the ozonolysis in methanol and used a more traditional methylsulfide workup of the ozonide and discovered that the reaction went to completion but gave multiple products by TLC analysis (Scheme 12). Presumably the keto dialdehyde **16** and the desired ester **15** were the major components of the reaction mixture. Further oxidation of this mixture with $NaIO_4$ gave mainly acid **5** by TLC analysis. Other ozonide cleaving agents ($P(OCH_3)_3$, PPh_3, Zn, etc.) were not tried.

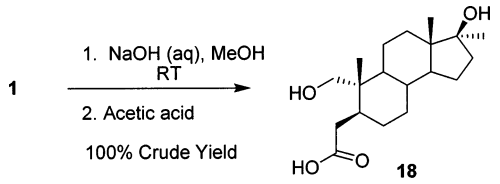
While the two-step oxidation method was somewhat successful, it was cumbersome and gave product that contained multiple unidentified impurities. While considering different methods to workup the initial oxidation product of the ozonolysis we were attracted to a procedure described by Bailey for the workup of ozonolysis products using aqueous sodium hydroxide.[24] This procedure would eliminate the need for odiferous cleavage agents and would allow us to purify the acid during the workup via standard acid base chemistry. Also, further oxidation with $NaIO_4$ would be unnecessary, as the sodium salt of the acid is the initial product formed after base quenching. The fact that a group at Searle had used this workup for a similar ozonolysis also bolstered its attractiveness from a process standpoint.[25] We were extremely happy to find that ozonolysis of **4** in methanol at −30 to − 40 °C, followed by quenching with an aqueous solution of sodium hydroxide at ca. −15 °C, gave the acid **5** in 90% yield after pH adjustment with HCl (Scheme 13). This was a major breakthrough since we were then able to perform the desired oxidation without using

(24) Bailey, P. S.; Bath, S. S. *J. Am. Chem. Soc.* **1957**, *79*, 3120.
(25) Sollman P. B. U.S. Patent 3,281,431, 1966.

Scheme 15. **Reduction and cyclization to produce Oxandrolone**



Scheme 16. **Preparation of seco-acid standard**



OsO_4 and $Pb(OAc)_4$, which not only are highly toxic but also present disposal problems. A temperature study was then done to determine the optimum temperature for running the ozonolysis (Table 5). As can be seen from the table, running the reaction at temperatures of −50 to −30 °C gave high quality **5** (entries 1 and 2), while running the reaction at temperatures of 0 to −20 °C produced somewhat lower quality product (entries 3 and 4). Thus the optimum operating temperature for 50-L glassware production was determined to be −30 to −40 °C since this temperature could be easily maintained and the product purity was high.

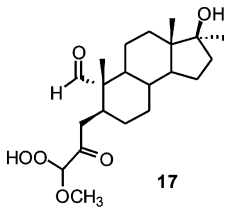
We also examined alternate reaction solvents for the oxidation. Ozonolysis in ethanol led to multiple product formation, while running the ozonolysis in ethyl acetate, CH_2Cl_2, or isopropanol led to slow conversions presumably due to the insolubility of **4** in these solvents. Reaction in a mixed solvent system of CH_2Cl_2/acetic acid led to multiple product formation. The conditions outlined in entry 2 were used to produce **5** in 1−2 kg batches in 50-L glassware (73−78% yield, 85−93 wt % purity). The lower yield and purity on glassware scaleup are unknown at present; however, the incorporation of a recrystallization of crude **5** routinely produced material with a weight percent purity of greater than 96%.

As was the case for production of intermediate **4**, the need to produce larger quantities of the acid **5** necessitated the development of a reactor scale ozonolyis procedure. The main issues that needed to be addressed before reactor scale production could begin were the cooling limitations of the reactors, the destruction of excess ozone, and the potential thermal instability of the peroxide intermediate.

The lowest achievable temperature at Cedarburg's plant is approximately −15 °C. From our initial development work we determined that, while the product purity was 5−10% lower when the reaction was run at higher temperatures, we felt confident that the purity would be suitable for our needs (Table 5). Furthermore, when acid **5** with a purity as low as 76 wt % was taken through the final two process steps acceptable quality Oxandrolone was produced. A brief ranging study was run to confirm the results in Table 5 and better define the temperature range to be used in production (Table 6). Since the yield and quality of the final product produced at a temperature range of −15 to 0 °C were comparable to that obtained using the 50-L procedure, we were confidant that the reaction could be run at the higher temperature. Also, as mentioned above, recrystallization of **5** was part of the normal processing so as to ensure high product purity prior to the final chemical step of the process.

The issue of ozone scrubbing was not an issue on a glassware scale where relatively small amounts of ozone were used; however, reactor scale ozonolysis required treatment of the effluent stream to destroy the excess ozone. We found that an aqueous solution of sodium metabisulfite to which the effluent stream was directed served this purpose (<1 ppm ozone detected after the quench solution).

With respect to the potential instability of the presumed hydroperoxide intermediate **17**, an ARSST (Advanced Reactive System Screening Tool) on a sample of the ozonolysis reaction mixture showed that the hydroperoxide intermediate was stable at 25 to 100 °C, a temperature approximately 100 °C higher than our operating temperature.[26] A summary of the plant procedure that was used to



produce up to 10 kg batches of recrystallized **5** is shown in Scheme 14. Thus, to the enone **4** in MeOH was added ozone at −15 to 0 °C until the reaction was complete. NaOH was then added to generate the sodium salt of **5**. After pH adjustment the product was filtered, dried, and recrystallized to give pure **5**.

Production of Oxandrolone 1. The final processing step to produce Oxandrolone is shown in Scheme 15. While the procedure itself is the most straightforward of the steps, several points are worth mentioning.

Initially we performed the reduction in water alone, but filtration of the product (after acidification) was extremely slow. This was not the case in the water/ethanol mixed solvent system. In 50-L glassware the reduction was performed by adding solid $NaBH_4$ portionwise to the solution of the sodium salt of the carboxylic acid. Since solid addition in a reactor setting was not possible, the commercially available caustic solution of $NaBH_4$ was used instead with no deleterious effects. Acidification of the sodium carboxy-

(26) In particular, when a sample of the reaction mixture was heated from 25 to 100°C at 2°C/min the internal temperature did not increase over the input temperature. Also, the internal pressure did not increase higher than the background pressure caused by the boiling of the methanol solvent.

Scheme 17. **Preparation of regioisomeric lactone impurity**

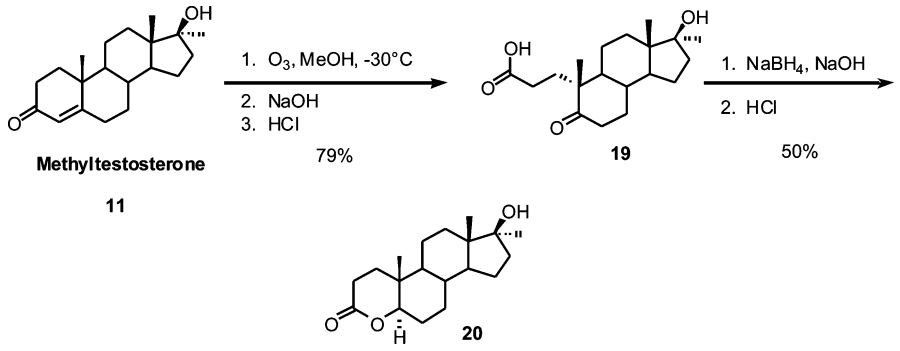


Table 7. **Levels of 17 and 19 present in crude and recrystallized Oxandrolone**

purification state	wt % Oxandrolone[a]	wt % **18**	wt % **20**
crude	97.98	0.17	0.16
first recrystallization	99.36	0.10	0.02
second recryallization	100.1	none detected	none detected

[a] As determined by HPLC.

late salt (pH ca. 1−2) gives the seco-acid **18**, which cyclizes to give crude Oxandrolone. The ethanol/water wet cake is then recrystallized from a 1/1 mixture of methanol/water (by volume, ca. 15 L/kg of each). Recrystallization from ethyl acetate, isopropanol, and acetone/water gave poor recoveries and required the use of larger volumes of solvent. The process outlined in Scheme 15 was used to produce multi-kilogram batches of USP Oxandrolone in 81−97% overall yield from **5** in a purity of 99−100 wt %.

Synthesis of Potential Impurities. Several potential impurities were synthesized for HPLC identification in the final product. The most obvious potential impurity is the seco-acid **18**. A sample of this compound was made by saponifying Oxandrolone with NaOH in methanol followed by acidification with acetic acid (Scheme 16).

As was discussed above, a major impurity in the synthesis of enone **4** was methyltestosterone (**11**, Scheme 8). Since crystallization of **4** does not entirely remove **11**, a certain percentage (ca. 2−6% by area) was carried into the ozonolysis reaction. We therefore thought it would be prudent to process authentic **11** through the ozonolysis and reduction sequence to determine the level of the regioisomeric lactone **20** present in the final product. Thus, ozonolysis of methyltestosterone followed by reduction of the resulting keto-acid **19** and cyclization gave lactone **20** (Scheme 17). The trans A/B ring juncture was assigned based on the J_{ax-ax} and J_{ax-eq} couplings of 12 and 4 Hz, respectively. The amounts of the seco-acid **18** and lactone **20** impurities present in a representative production lot of final product are shown in Table 7. As can be seen from the table, one recrystallization from methanol/water reduces the level of these two impurities to ≤0.1%. A second recrystallization reduces them to below the detection limit and gives Oxandrolone with a purity of 100 wt % (USP specification 98−102 wt %).

Summary and Conclusion

A scaleable process for the kilogram scale synthesis of Oxandrolone was developed. Key elements in the process include the following: a method to brominate methylandrostanolone without significant dehydration of the tertiary alcohol, conversion of bromide **3** to the enone **4** with good Δ-1/Δ-4 selectivity, and an efficient reactor scale ozonolysis procedure to produce the penultimate intermediate acid **5**. Work to improve the overall yield and to streamline the process is underway.

Experimental Section

General. All raw materials were used as supplied by vendors. All reactions were performed under nitrogen in glassware or glass-lined reactors as described below. All of the reactions described were monitored by quantitative TLC analysis using ethyl acetate/heptane or methanol/CH_2Cl_2 mixtures. Product purity was determined by reversed phase HPLC using a Phenomenex Licrosphere RP 18 column (UV detection at 198 nm) with a water/CH_3CN gradient as the mobile phase (2 mL/min). NMR data were obtained using a Varian 400 MHz instrument. Chemical shifts are reported in ppm. IR data were obtained using a Bruker Vector 22 FTIR. MS data were obtained using a Finnigan model TSQ 7000 instrument. Melting points were determined using a Thomas Hoover Unimelt capillary melting point apparatus and are uncorrected. Ozonolyses were performed using an ozone generator from Pacific Ozone Technology (model SGA-44, 122 g ozone/h output).

Preparation of 17-α-Methyl-5-α-androstan-17-β-benzoyl-3-one (9). To a nitrogen purged three-neck 100 mL round-bottom flask was added 2.01 g (6.61 mmol) of **2**, 10 mL of CH_2Cl_2, 0.64 mL (7.9 mmol) of pyridine, 0.84 mL (7.2 mmol) of benzoyl chloride, and 81 mg (0.66 mmol) of DMAP. After 2 h at ambient temperature no TLC analysis inidicated the presence of only starting material. The reaction mixture was heated at reflux for 9 h and then allowed to stir at ambient temperature overnight. An additional 0.32 mL (4.0 mmol) of pyridine, 0.42 mL (3.6 mmol) of benzoyl chloride, and 41 mg (0.33 mmol) of DMAP were added, and the reaction was stirred for an additional 4.5 h at reflux. An additional 0.12 g (0.98 mmol) of DMAP was added, and the reaction was stirred at reflux for an additional 19 h. Starting material remained as determined by TLC analysis. An additional 5.0 mL (62 mmol) of pyridine and 0.84 mL

(7.2 mmol) of benzoyl chloride were added, and the reaction was heated at reflux for an additional 3 h. TLC analysis indicated only a trace of starting material remaining. The solution was cooled to ambient temperature, and 10 mL of water were added to the slurry. The mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were then washed successively with 1 M HCl (2 × 10 mL), saturated $NaHCO_3$ (1 × 10 mL), and water (1 × 10 mL). After drying over Na_2SO_4 the solution was concentrated to an oil. TLC analysis indicated the presence of pyridine salts. The oil was then dissolved in ca. 50 mL of MTBE and ca. 5 mL of ethyl acetate. The solution was then washed successively with ca. 20 mL of 1 M HCl, 40 mL of saturated $NaHCO_3$, and finally ca. 20 mL of water. The organic layer was then dried over Na_2SO_4 and concentrated to give 3.52 g of a solid. A 1 g amount of the crude product was chromatographed using 10% ethyl acetate/heptane as the eluent to give 0.33 g of purified **9** as a white solid. Mp 198−202 °C. ^{1}H NMR ($CDCl_3$): δ 8.0 (dd, J = 8.0, 1.5 Hz, 2H), 7.5 (t, J = 8.0 Hz, 1H), 7.4 (t, J = 8 Hz, 2H), 2.3 (m, 5H), 2.1 (m, 2H), 1.2−1.8 (m, 13H), 1.6 (s, 3H), 1.1 (s, 3H), 1.0 (s, 3 H), 0.9 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 211.9, 165.7, 132.4, 131.9, 129.3, 128.2, 91.4, 53.7, 48.9, 47.0, 46.7, 44.6, 38.5, 38.1, 36.5, 35.9, 35.7, 32.2, 31.5, 28.8, 23.8, 21.5, 21.0, 14.9, 11.5 ppm. IR (KBr pellet): 1710, 1450, 1290, 1115, 721 cm^{-1}. MS (CI−CH_4): m/z 409 (M + H$^+$), 287 (M − BzOH + H$^+$).

Preparation of 2-α-Bromo-17-α-methyl-5-α-androstan-17-β-ol-3-one (3) Using Phenyltrimethylammonium Tribromide. To a nitrogen purged 50-L four-neck round-bottom flask equipped with an addition funnel, temperature probe, nitrogen inlet adapter, and stirrer apparatus were added 650 g (2.14 mol) of methylandrostanolone (**2**) and 5.8 L of THF. The solution was cooled to an internal temperature of 0−10 °C. To the solution was added a THF solution of phenyltrimethylammonium tribromide (884 g, 2.36 mol, 2 L of THF) over ca. 1 h while maintaining an internal temperature of 0−10 °C. When the addition was complete the resulting thick slurry was stirred for an additional 1 h at 0−10 °C at which point TLC analysis indicated that the reaction was complete. To the slurry was added an aqueous solution of Na_2CO_3 (377 g in 3.9 L of water) over ca. 1 h at 0−10 °C. Additional water (4 L) was added, and the mixture was allowed to warm to room temperature. The layers were then allowed to settle for ca. 1 h and then separated. The aqueous layer was extracted twice with 4 L of ethyl acetate, and the combined organic extracts were washed with 4.5 L of water. The organic layer was then concentrated using a vacuum to a volume of ca. 2 L. To the resulting white slurry at ca. room temperature were added 4.6 L of heptane over 2 h. The slurry was cooled to ca. 0−10 °C and held at this temperature for ca. 2 h. The slurry was then filtered, washed three times with 600 mL of 0−10 °C heptane, and dried to a constant weight under a high vacuum at ca. 40 °C to give 621 g (76% yield, mp 195−197 °C, uncorrected, literature 196−198 °C[1a]) of 2-α-bromo-17-α-methyl-5-α-androstan-17-β-ol-3-one (**3**) as a pink solid. This material was used without purification in the elimination reaction.

Preparation of 3 using Pyridinium Tribromide. To a nitrogen purged 1 L four-neck round-bottom flask equipped with a mechanical stirrer, thermocouple, addition funnel, and nitrogen inlet were added 25.0 g (82.2 mmol) of **2**, 100 mL of absolute ethanol, and 25 mL of distilled water. To the slurry were added 36.0 g (107 mmol) of pyridinium tribromide in 200 mL absolute ethanol over 2 h at 24 to 27 °C. The orange color of the $PyHBr_3$ persisted through the addition. The orange slurry thinned to a fine orange suspension, and eventually an off-white slurry formed. After stirring for an additional 3.25 h, the reaction was complete as determined by TLC analysis. To the off-white slurry were added 6.0 g (24 mmol) of sodium thiosulfate pentahydrate in 100 mL of water over 10 min (pH ca. 1). The snow white slurry was then stirred for 30 min at room temperature. To the slurry were then added 22.0 g (208 mmol) of sodium carbonate in 200 mL of water over 5 min (pH 7−8). The resulting slurry was stirred for 15 min and filtered. The white cake was then washed successively with 100 mL of a cold mixture of water/ethanol (0−5 °C, 2/1 (v/v)), 3 times with 125 mL of water, and once with ca. 100 mL of heptane. The white solid was then dried at 50−60 °C in a high vacuum oven for 19 h to give 24.0 g of **3** as an off-white solid (77% yield, 92 wt % purity).

Preparation of 17-β-Hydroxy-17-α-methyl-5-α-androst-1-ene-3-one (4). To a 5-L four-neck round-bottom flask equipped with a thermoprobe, nitrogen inlet adapter, and mechanical stirrer were added 200 g (0.52 mol) of **3** and 1.2 L of DMF. To the slurry at room temperature were added 42.6 g (0.58 mol) of ACS grade Li_2CO_3 followed by 76.2 g (0.89 mol) of LiBr. The slurry was then heated to 110−115 °C and held at this temperature for 3 h after which point TLC analysis indicated that the reaction was complete. The slurry was cooled to an internal temperature of 35 °C, and 1.4 L of ethyl acetate were added. An aqueous solution of acetic acid (62 mL of acetic acid in 600 mL of water) was then added over ca. 0.5 h. The reaction mixture was then stirred at room temperature for ca. 8 h and then held at 0−10 °C in the refrigerator over the weekend. The reaction mixture was then warmed to room temperature, the layers were separated, and the aqueous layer was extracted three times with 1.2 L of ethyl acetate. The combined organic extracts were washed three times with 1.0 L of water and then concentrated to a total volume of ca. 500 mL. To the resulting slurry were added 1.8 L of heptane over 0.5 h at room temperature. The slurry was held at an internal temperature of 0−10 °C for ca. 2 h. The slurry was then filtered, washed twice with 200 mL of 0−10 °C heptane, and dried to constant weight in a high vacuum oven at ca. 45 °C to give 128 g (81% yield) of 17-β-hydroxy-17-α-methyl-5-α-androst-1-ene-3-one (**4**) as an off-white solid (90.3% weight percent purity, mp (uncorrected) 153−154 °C, literature 155−156 °C[1a]).

Preparation of Epoxide 13 (1,2-α-Epoxy-17-α-methyl-5-α-androstan-17-β-ol-3-one). To a nitrogen purged 100 mL three-neck round-bottom flask were added 2.01 g (6.66 mmol) of **4**, 15 mL of methanol, and 0.86 mL (7.6 mmol) of 30% aqueous H_2O_2. The solution was cooled to an internal

temperature of 16 °C at which point 0.20 mL (1.2 mmol) of 6 M HCl was added via syringe over ca. 15 s. The solution darkened, and the internal temperature rose to 27 °C after the addition. The solution was cooled further with an ice bath and held at an internal temperature of ca. 0−15 °C for 1 h. Thin layer chromatography indicated that the reaction was complete at this point. At an internal temperature of 12 °C, 5 mL of saturated Na_2SO_3 were added followed by an additional 10 mL of H_2O. The slurry was cooled to 0−10 °C and stirred for ca. 30 min. The slurry was then filtered, washed with ca. 20 mL of water, and dried at 40−50 °C in a high vacuum oven to give 1.82 g (87% yield) of the known epoxide **13** as a white solid.[19]

Preparation of 17-β-Hydroxy-17-α-methyl-1-oxo-1,2-seco-A-nor-5-α-androstan-2-oic Acid (5). Compound **4** (250 g, 0.828 mol) was dissolved in 2.5 L of MeOH, and the resulting solution was cooled to −30 to −40 °C. Ozone was then bubbled into the solution through a sparge tube. After 6 h the reaction was judged to be complete by TLC analysis. The solution was allowed to warm to −10 °C, and an aqueous solution of NaOH (109 mL of concentrated NaOH in 3.13 L of H_2O) was added dropwise over 2 h. An 8 °C exotherm was observed during the addition. The reaction mixture was allowed to warm to ambient temperature at which point methanol was removed under reduced pressure (2.8 L removed). The aqueous solution of the sodium salt was washed with MTBE (2 × 1.0 L) and then acidified to a pH of 4 using 6.0 M HCl. After stirring for ca. 1 h, the slurry was filtered and washed with water (2 × 300 mL) and 200 mL of *n*-heptane. The product was then dried to constant weight via high vacuum at 40−60 °C to give 211 g of **5** as an off-white solid (79% yield).

Recrystallization of 5. To a 50-L four-neck round-bottom flask equipped with a condenser, thermocouple, nitrogen inlet adapter, 2-L addition funnel, and heating mantle were charged 2.96 kg of crude **5** and 20.7 L of methanol. After heating the solution of **5** to an internal temperature of 59 °C, 25.7 L of water were added over a ca. 2 h period at 59−65 °C. The slurry was cooled slowly to room temperature and then to 0−10 °C and held at this temperature for ca. 2 h. The slurry was filtered and washed with 1 L of a 0−5 °C 2/1 mixture of water/methanol (by volume), followed by portionwise washing of the cake with an additional 6 L of the cold 2/1 mixture. The highly crystalline white solid was then dried to constant weight at 45 °C via high vacuum to give 2.11 kg of **5** (86% yield, 100% pure by weight, mp (uncorrected) = 176−179 °C, literature 166−173 °C[1b]).

Preparation of Oxandrolone (17-β-Hydroxy-17-α-methyl-2-oxa-5-α-androstane-3-one). To a 50-L four-neck round-bottom flask equipped with a stir assembly, thermocouple, nitrogen inlet adapter, and 2-L addition funnel were charged 1.10 kg (3.42 mol) of recrystallized **5**, 8.4 L of absolute ethanol, and 8.4 L of distilled water. The slurry was cooled to an internal temperature of 8 °C at which point a 25% solution of NaOH (198 mL 50% NaOH, 198 mL water) was added over 16 min at an internal temperature of 8−9 °C. To the resulting yellow solution of the carboxylate were added 188 g (5.0 mol) of $NaBH_4$ in four equal portions over 1.5 h at an internal temperature of 5−7 °C (Note: there may be vigorous evolution of hydrogen during the first and second additions). When the addition was complete, the solution was stirred for an additional 1 h at which point the reaction was judged to be complete by TLC analysis. To the solution containing the sodium salt of the seco-acid **22** was carefully added a 6.0 M solution of HCl (0.9 L of 37% HCl, 0.9 L of water) over 4 h at an internal temperature of 1−9 °C (Note: the addition will generate hydrogen and be highly exothermic). The resulting thick slurry was stirred at 1−3 °C for 4.75 h at which point the reaction was judged to be complete by TLC analysis. As the seco-acid cyclizes, the slurry thins and becomes easier to stir. The slurry was then filtered and washed with a 0−10 °C solution of 1/1 EtOH/water (664 mL of each), followed by 4.2 L of water and finally 3.2 L of heptane. The solids were dried via high vacuum at 40−50 °C to a constant weight to give 973 g of crude Oxandrolone as a white solid (94% yield, weight percent purity = 100%).

Recrystallization of Oxandrolone. To a 50-L four-neck round-bottom flask equipped with a stir assembly, thermocouple, condenser, nitrogen inlet adapter, and heating mantle were charged 962 g of crude Oxandrolone and 13 L of methanol. The slurry was heated to an internal temperature of 65 °C. To the solution 48.8 g of activated carbon were added. The slurry was heated at 65−70 °C for 1.25 h and hot filtered into a clean 50-L four-neck flask through a methanol-moistened pad of celite. The original flask was rinsed with 1.5 L of warm methanol. The filtrate contained in the 50-L flask was heated to an internal temperature of 61 °C. Water (13 L) was then added to the solution at 61−62 °C over 3.5 h. The slurry was then cooled to 35 °C over 6 h. The slurry was then pressure transferred to a clean 50-L four-neck round-bottom flask in a cooling tub using 1.5 L of water as a rinse (Note: this operation was incorporated due to the potential for flask breakage upon attempted lifting of the flask from the heating mantle into a cooling bath. The slurry was then cooled to an internal temperature of 10 °C over 1 h and held at 2−10 °C for 2 h. The slurry was then filtered through a fritted funnel and washed consecutively with a 5 °C 2/1 mixture of water/methanol (392 mL water, 200 mL methanol), 800 mL of water, and 2 L of heptane. The highly crystalline solid was then dried to a constant weight via high vacuum at 43−50 °C to give 817 g of USP grade Oxandrolone (85% yield, 100.2% pure by weight, mp (uncorrected) 221−225 °C, USP standard (uncorrected) 212−216 °C, literature 235−238 °C[1b]).

Preparation of Seco-acid Impurity 18 (17β-Hydroxy-17∝-methyl-1-ol-1,2-seco-A-nor-5∝-androstan-2-oic Acid). To a 1-L four-neck round-bottom flask equipped with a stir assembly, thermocouple, addition funnel, and nitrogen inlet adapter were added 40.00 g (130.7 mmol) of Oxandrolone, 240 mL of methanol, and 240 mL of water. To the slurry at ambient temperature was added 15 mL (290 mmol) of 50% aqueous NaOH via addition funnel. After approximately 15 min the solids were completely in solution, and TLC analysis of a pH 4 buffer/EtOAc quenched reaction aliquot (10% $MeOH/CH_2Cl_2$ eluent) indicated that the saponification was

complete. The methanol was then removed via rotary evaporation, and the resulting aqueous solution of the carboxylate salt was washed twice with 100 mL of MTBE. To the aqueous solution of the carboxylate salt were added 12 mL of acetic acid in 100 mL of water over 30 min at 23−26 °C. An additional 100 mL of water were added to improve the stirring of the thick slurry. The pH of the slurry was 7−8 as determined by pH paper. The thick slurry was then filtered, washed twice with 50 mL of water, and dried to constant weight via high vacuum at 25−35 °C to give 20.3 g of **18** as a white powder (52% yield, relative retention time 0.19). TLC analysis indicated that a trace of Oxandrolone was present in this sample. ^{1}H NMR (DMSO): δ 3.21 (AB_q, J = 12 Hz, 2 H), 2.40 (dd, J = 16, 4 Hz, 1 H), 1.95 (m, 1 H), 1.80−1.10 (m, 16 H), 1.08 (s, 3 H), 0.75 (m, 1 H), 0.72 (s, 3 H), 0.51 (s, 3 H). ^{13}C NMR (DMSO): δ 175.2, 79.7, 63.2, 50.4, 45.1, 44.8, 39.8, 38.4, 36.8, 35.8, 35.6, 31.4, 31.2, 27.2, 26.1, 23.2, 20.4, 14.0, 11.4 ppm. IR (KBr pellet): 3250, 1710 cm^{-1}. MS (ESI/MS): *m*/*z* 347 (M + Na), 325 (M + H$^+$), 307 (M− OH), 289 (M − OH − H_2O).

Preparation of Regioisomeric Lactone 20 (17β-Hydroxy-17α-methyl-4-oxa-5α-androstane-3-one). To a 1-L four-neck round-bottom flask with a stir assembly, thermocouple, sparge tube, and nitrogen inlet adapter were added 14.8 g (49.0 mmol) of methyltestosterone and 300 mL of methanol. The solution was cooled to an internal temperature of −31 °C and then purged with argon gas via the sparge tube. After sparging with argon for approximately 2 min, the solution was sparged with ozone for a total of 1.5 h at −29 to −31 °C. The solution was then sparged with argon for 5 min to remove the excess ozone. TLC analysis indicated that the reaction was complete. The argon sparge was continued for an additional 30 min. To the solution was added 7 mL of 50% aqueous NaOH in 170 mL of water over approximately 30 min at −30 to −10 °C. The solution was slowly warmed to ambient temperature over approximately 2 h. Methanol (250 mL) was then removed via rotary evaporation. The aqueous solution of the carboxylate was then washed twice with 50 mL of MTBE, and the aqueous layer was then stored overnight at 0−10 °C. The next day the solution was warmed to 14 °C, and 26 mL of 6 M HCl were added dropwise (final pH 1−2, paper). The product oiled out initially and then solidified. The slurry was stirred for 2 h at ambient temperature. The slurry was then filtered, washed with water (6 × 25 mL, pH of last wash 3−4, paper) followed by heptane (50 mL), and dried at 45−55 °C to give 13.8 g of the keto-acid **19** (87% yield), which was used directly in the reduction. To a 500-mL four-neck round-bottom flask equipped with a stir assembly, thermocouple, addition funnel, and nitrogen inlet adapter were added 12.53 g (38.91 mmol) of the crude keto-acid **19**, 95 mL of ethanol, and 95 mL of water. The slurry was cooled to 4 °C, and 2.3 mL (43 mmol) of 50% aqueous NaOH in 5 mL of water were added. To the resulting thin suspension were added 2.21 g (58.4 mmol) of solid $NaBH_4$ portionwise at 4−5 °C over 20 min. After 1 h the reduction was judged to be complete by TLC analysis (10% MeOH/CH_2Cl_2 eluent). To the reaction was then added 20 mL of 6 M HCl at 5−15 °C (pH 1−2, paper) over approximately 30 min. After approximately 3.5 h the cyclization was judged to be complete by TLC analysis (10% MeOH/CH_2Cl_2 eluent). Ethanol (110 mL) was removed via rotary evaporation, and the resulting white slurry was held at approximately 5 °C for 45 min. The slurry was then filtered and washed successively with 30 mL of 0−10 °C ethanol/water (1/1 by volume), water (5 × 25 mL), and finally heptane (50 mL). The white solid was then dried overnight on a high vacuum pump at 40−50 °C to give 8.8 g of the crude lactone **20** as a white solid (74% yield). To a 500-mL round-bottom flask were added 8.6 g of crude **20** and 26 mL of ethyl acetate. While the resulting slurry was heating, 20 mL of additional ethyl acetate were added portionwise to try and dissolve the crude solid. The undissolved solid material was filtered off with the aid of an ethyl acetate moistened celite bed, and the filtrate was concentrated to a wet solid (23.0 g total weight). To the solid was added ethyl acetate (14 mL), and the slurry was heated. An additional 50 mL of ethyl acetate were added in 5 mL portions to completely dissolve the steroid. While the solution was cooling, 75 mL of heptane were added dropwise over approximately 15 min. After the addition was complete 75 mL of solvent were removed via rotary evaporator, and the resulting slurry was cooled with an ice−water bath. After approximately 1 h of cooling the slurry was filtered and washed twice with 15 mL of a 0−10 °C heptane/ethyl acetate mixture (3/1 by volume). The solids were then dried overnight on a high vacuum pump at approximately 35−40 °C to give 6.1 g of recrystallized **20** as a white powder. ^{1}H NMR (DMSO): δ 4.07 (s, 1 H), 4.03 (dd, J = 12, 4 Hz, 1 H), 2.58 (m, 1 H), 2.42 (m, 1 H), 1.67 (m, 4 H), 1.48 (m, 6 H), 1.33 (m, 2 H), 1.15 (m, 3 H), 1.07 (s, 3 H), 0.90 (m, 1 H), 0.82 (s, 3 H), 0.75 (m, 4 H). ^{13}C NMR (DMSO): δ 171.2, 83.6, 79.6, 50.6, 48.6, 38.9, 38.2, 35.3, 35.1, 32.1, 31.2, 28.4, 27.0, 26.4, 26.1, 22.9, 20.3, 14.1, 11.7 ppm. IR (KBr pellet): 3500, 1712 cm^{-1}. MS (APCI): *m*/*z* 307 (M + H$^+$), 289 (M − H_2O + H$^+$).

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