A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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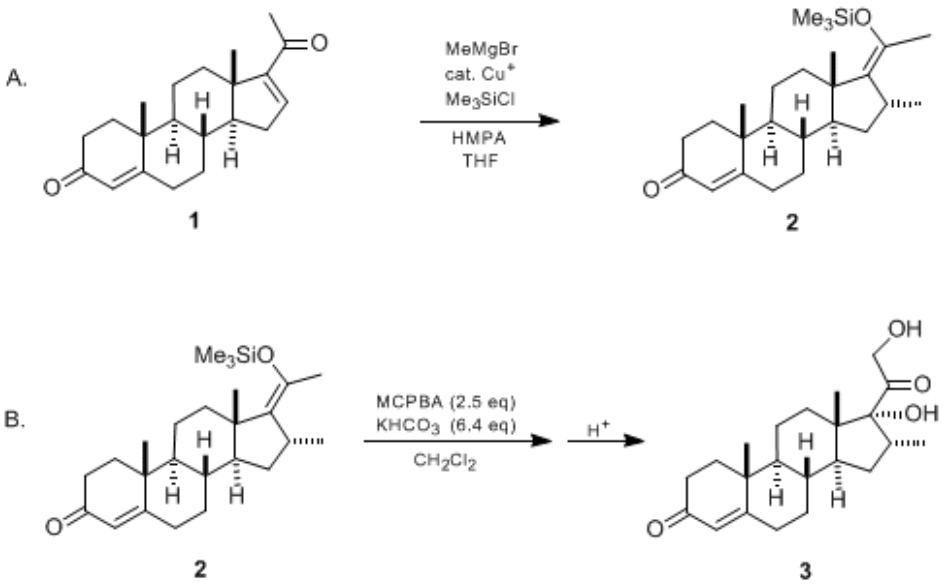
Organic Syntheses, Coll. Vol. 9, p.564 (1998); Vol. 73, p.123 (1996).

DOUBLE HYDROXYLATION REACTION FOR CONSTRUCTION OF THE CORTICOID SIDE CHAIN: 16α-METHYLCORTEXOLONE

[Pregn-4-ene-3,20-dione, 17,21-dihydroxy-16-methyl-, (16α)-(±)-]



Submitted by Yoshiaki Horiguchi, Eiichi Nakamura, and Isao Kuwajima[1].
Checked by Ronald W. Regenye, Miguel Pagan, and David L. Coffen.

1. Procedure

Caution! Reactions and subsequent operations involving peracids and peroxy compounds should be run behind a safety shield. Peroxy compounds should be added to the organic material, never the reverse. For relatively fast reactions, the rate of addition of the peroxy compound should be slow enough so that it reacts rapidly and no significant unreacted excess is allowed to build up. The reaction mixture should be stirred efficiently while the peroxy compound is being added, and cooling should generally be provided since many reactions of peroxy compounds are exothermic. New or unfamiliar reactions, particularly those run at elevated temperatures, should be run first on a small scale. Reaction products should never be recovered from the final reaction mixture by distillation until all residual active oxygen compounds (including unreacted peroxy compounds) have been destroyed. Decomposition of active oxygen compounds may be accomplished by the procedure described in Korach, M.; Nielsen, D. R.; Rideout, W. H. Org. Synth. 1962, 42, 50 (Org. Synth. 1973, Coll. Vol. 5, 414). [Note added January 2011].

CAUTION: Hexamethylphosphoramide (HMPA) has been identified as a carcinogen. Glove protection is required during the handling in Part A. In addition, the column chromatography in Part B using chloroform as the eluent should be conducted in a well-ventilated hood.

A. *(Z)-16α-Methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one* **(2)**. (All transfers are conducted under dry nitrogen; reagents are introduced into reaction vessels through rubber septa using a syringe.) An oven-dried, 300-mL, two-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen-vacuum inlet, and rubber septum is charged with 6.25 g (20 mmol) of 16-dehydroprogesterone **(1)** and 0.20 g (1.0 mmol) of cuprous bromide-dimethyl sulfide complex (Note 1). After the apparatus is flushed with nitrogen, 100 mL of tetrahydrofuran (THF) and 7.7 mL (44 mmol) of hexamethylphosphoramide are added (Note 1). The resulting clear solution, upon cooling to –78°C, becomes a white slurry to which 5.1 mL (40 mmol) of chlorotrimethylsilane is added dropwise (Note 1). To the resulting yellow solution is added 23.7 mL (22 mmol) of a 0.93 M solution of methylmagnesium

bromide in THF (Note 2) over a 30-min period. The resulting yellow slurry is then stirred at ~ −55 to −60°C (Note 3) for 12 hr followed by addition of 5.6 mL (40 mmol) of triethylamine dropwise (Note 1). The reaction mixture is then poured into a vigorously stirred mixture of 50 mL of saturated aqueous sodium bicarbonate, 50 g of ice, and 200 mL of hexane. After stirring for 15 min, the mixture is transferred to a 1-L separatory funnel, and the organic phase is separated. The remaining aqueous phase is extracted three times with 50-mL portions of hexane. The combined organic phases are washed successively with 50 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 6.84–8.67 g of crude (Z)-16α-methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one **(2)** as an amorphous white solid. Analysis of crude **2** by ^{1}H NMR indicates a chemical purity of 90–95% and a geometrical ratio of >95% (Z) (Note 4).

B. *16α-Methylcortexolone* **(3)**. An oven-dried, 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen-vacuum inlet, 200-mL addition funnel topped with a nitrogen inlet, and a rubber septum, is charged with 7.20 g of the crude (Z)-16α-methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one **(2)**. The apparatus is flushed with nitrogen and 200 mL of methylene chloride (CH_2Cl_2) is added (Note 1). Quickly under nitrogen flow, the rubber septum is removed from the flask and 12.8 g (128 mmol) of finely powdered, dry potassium bicarbonate (Note 5) is added to the solution, and the flask is resealed with the rubber septum. The flask is then immersed in an ice bath. With vigorous stirring of the mixture, 100 mL of a 0.5 M solution (50 mmol) of m-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 is added dropwise via the addition funnel over a 2.5-hr period followed by a few mL of $CH_2Cl_2$to rinse the addition funnel (Note 6). TLC is used to monitor the progress of the reaction (Note 7). After stirring the reaction mixture for an additional 10 min after the addition is complete, the addition funnel, nitrogen-vacuum inlet, and rubber septum are removed and 100 mL of aqueous 0.5 M sodium thiosulfate solution is added, vigorous stirring is maintained at room temperature for 30 min. The mixture is then transferred to a 1-L separatory funnel, and the organic phase is separated. The aqueous phase is extracted three times with 50 mL of CH_2Cl_2. The combined organic extracts are concentrated on a rotary evaporator. The residue is dissolved in 100 mL of THF, and the solution is acidified to ~ pH 1 by addition of 10 mL of 1 N hydrochloric acid (HCl) to effect desilylation of the 21-trimethylsilyl ether of 16α-methylcortexolone **(6)** (Note 8). The homogeneous solution is allowed to stand at room temperature for 30 min and then most of the solvent is removed by rotary evaporation under reduced pressure. The residue is dissolved in 300 mL of CH_2Cl_2, transferred into a 1-L separatory funnel, and the solution washed with 50 mL of saturated aqueous sodium bicarbonate solution. After separation of the organic phase, the aqueous phase is extracted three times with 50-mL portions of CH_2Cl_2. The combined organic extracts are washed with 50 mL of brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give 6.0 g of a white solid. Chromatographic purification on silica gel (300 g) with 30~40% ethyl acetate/chloroform eluent gives 2.92 g (40.5%, 2 steps) of 16α-methylcortexolone **(3)** (Note 9).

2. Notes

1. 16-Dehydroprogesterone **(1)** was purchased from Sigma Chemical Company and used without further purification. Cuprous bromide-dimethyl sulfide complex was prepared according to House's procedure.[2] Hexamethylphosphoramide, chlorotrimethylsilane, and triethylamine were purchased from Tokyo Kasei Kogyo Co., Ltd., Japan and distilled from calcium hydride (CaH_2). Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl immediately prior to use. Methylene chloride was distilled from phosphorus pentoxide (P_2O_5).

2. A THF solution of methylmagnesium bromide was purchased from Tokyo Kasei Kogyo Co., Ltd., Japan and titrated with sec-butyl alcohol using 1,10-phenanthroline as indicator. Rapid addition might raise the internal temperature and use of excess methylmagnesium bromide would cause undesired methylation of the A-ring enone.

3. The reaction temperature was controlled by an electric cooling system. A higher reaction temperature would cause undesired methylation of the A-ring enone.

4. Crude **2** is free from HMPA. The spectral properties of **2** were as follows: IR (neat) cm^{-1}: 1670, 1610, 1265, 1250, 1230; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.19 (s, 9 H), 0.90 (s, 3 H), 0.99 (d, 3 H, J = 7.1), 1.09–2.71 (m including two s at 1.19 and 1.79, 25 H), 5.73 (s (br), 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 1.07, 17.1, 17.3, 20.6, 21.3, 22.1, 32.1, 32.9, 33.5, 34.0, 34.2, 34.3, 35.6, 37.3, 38.7, 44.0, 52.1, 54.1, 123.6, 132.5, 139.9, 171.3, 199.2. The geometry was determined based on observed NOEs from 20-methyl to 16β-H and 16α-methyl.

5. Potassium bicarbonate was purchased from Koso Chemical Co., Ltd., Japan. It was finely powdered and dried under reduced pressure (~ 0.1 mm) at ambient temperature over P_2O_5.

6. m-Chloroperoxybenzoic acid (MCPBA) of 85% purity was purchased from Aldrich Chemical Company, Inc. and purified according to Schwartz's procedure[3] to remove any remaining m-chlorobenzoic acid. Slow addition of MCPBA is required to avoid hydrolysis of the transient, intermediate epoxide **4** by rapid formation of free m-chlorobenzoic acid.

7. Progress of the double hydroxylation reaction can be monitored by TLC analysis. The R_f values of the products with 30% ethyl acetate/hexanes as the eluent are as follows: 0.70 for **2**, 0.59 for **5**, 0.29 for **6**, and 0.18 for **7**. Additional MCPBA may be added until the intermediate hydroxy enol silyl ether **5** has completely reacted.

8. Desilylation of **6** can be monitored by TLC analysis. The R_f values of **3** and **6** are 0.32 and 0.67, respectively, with 50% ethyl acetate/hexanes as the eluent.

9. A portion of this compound is recrystallized from 1:1 ethyl acetate/hexanes to yield white plates with mp 194–197°C (Anal. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.24; H, 8.98). The spectral properties were as follows: IR ($CDCl_3$) cm^{-1}: 3650–3100, 1705, 1660, 1615; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.79 (s, 3 H), 0.93 (d, 3 H, J = 7.3), 0.97–2.49 (m including s at 1.18), 2.62 (s, 1 H), 2.94–3.14 (m, 1 H), 3.20 (s (br), 1 H), 4.30 (dd, 1 H, J = 20, 4.8), 4.62 (dd, 1 H, J = 20, 4.8), 5.73 (s (br), 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.8, 15.2, 17.4, 20.5, 30.4, 32.0, 32.5, 32.8, 33.9, 35.6, 35.7, 36.8, 38.6, 49.7, 49.8, 53.3, 67.8, 90.5, 123.8, 170.8, 199.3, 212.4. The stereochemistry of the 16- and 17-positions were determined based on the observed NOEs from the 18-methyl (δ 0.79, s) to both 16β-H (δ 2.94–3.14, m) and 21-H (δ 4.63, dd). The submitters obtained an overall yield of 68%

Waste Disposal Information

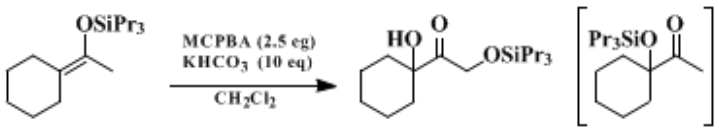
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The present procedure is an efficient two-step preparation of the 17-dihydroxyacetone side chain with a 16α-methyl substituent from the 16-dehydro-17-acetyl substructure.[4] The D-ring substructure of the product is of pharmaceutical importance as seen in synthetic corticoids such as betamethasone.[5] The two-step conversion consists of 1) conjugate addition of a methyl group into the 16-position and 2) a novel, double hydroxylation of the resultant enol silyl ether.

Although the chlorotrimethylsilane-accelerated conjugate addition of the catalytic methylcopper reagent[6] proceeds at the sterically less congested D-ring enone in a highly chemoselective manner under the reaction conditions discussed in the procedure, a higher reaction temperature and/or use of excess methylmagnesium bromide might cause undesired methylation of the A-ring enone.

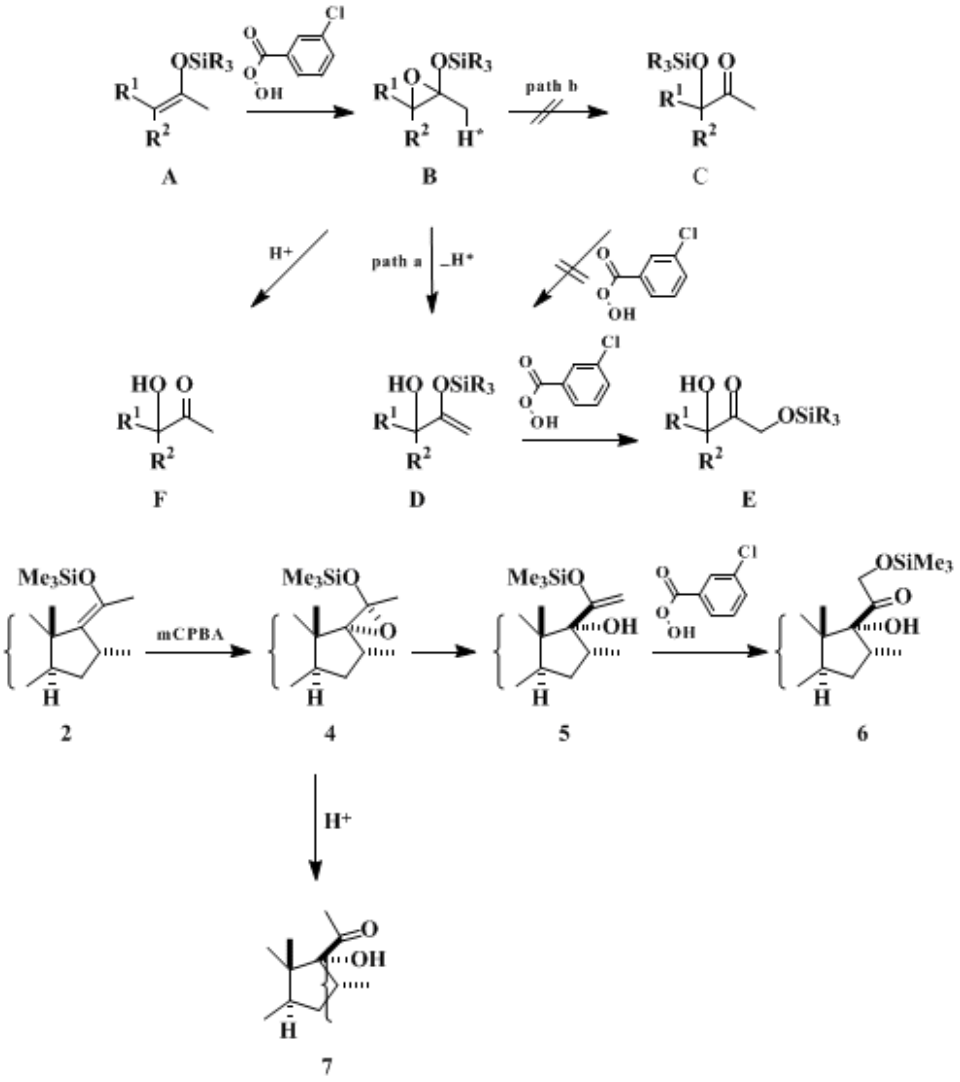
Since Hassner's initial report in 1975,[7] oxidation of an enol silyl ether with peracid has been a reliable method for the preparation of α-siloxy and α-hydroxy ketones. However, the submitters have found that, if the enol silyl ether possesses certain structural features, the reaction, with more than two equivalents of the oxidant, affords α,α'-dihydroxylated ketones (i.e., introduction of two oxygen atoms in a single-step) instead of the expected monohydroxylated compounds.[8]



Mechanistic investigations carried out in some depth suggested an interesting reaction pathway (*path a*, Scheme I), in which rearrangement of the intermediate epoxide **B** to the hydroxy enol silyl ether **D** (with loss of H^*) represents the crucial step. In the normal Hassner reaction (*path b*), rearrangement of epoxide **B** to the siloxy ketone **C** proceeds through migration of the silyl group from the enol oxygen to the epoxide oxygen. The inertness of **C** under the reaction conditions indicated that *path a* and *path b* are independent reactions. The hydroxy enol silyl ether **D** has been shown to be the primary product of the reaction by its isolation upon use of only one equivalent of the oxidant, and its subsequent conversion to

E upon addition of another equivalent of the oxidant.

Scheme 1



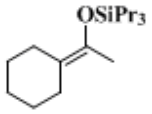
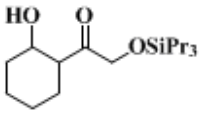
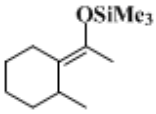
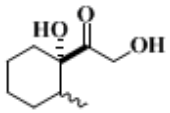
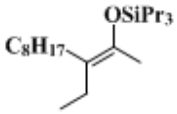
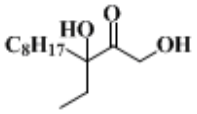
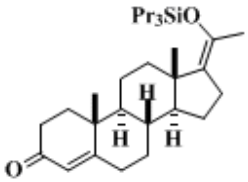
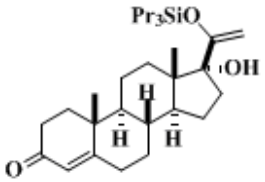
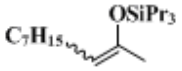
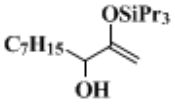
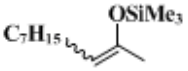
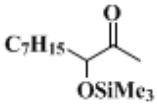
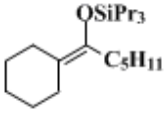
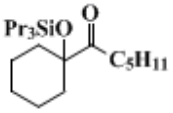
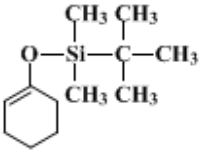
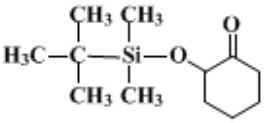
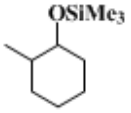
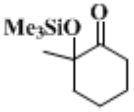
The major by-product in the double hydroxylation reaction is the α-hydroxy ketone **F** which forms presumably by protiodesilylation of the transient, intermediate epoxide **B**. In order to exclude free m-chlorobenzoic acid that might cause this side reaction, MCPBA is purified and added very slowly to the substrate in the presence of excess, finely powdered potassium bicarbonate. In the case of the example presented above, the mechanism presumably is as follows:

Examples of the double hydroxylation reaction observed for several representative substrates illustrate the scope of this reaction (Table). *Path a* is generally preferred by the internal olefinic isomer of the enol silyl ether of methyl alkyl ketones (entries 1–4, and 9) among which methyl sec-alkyl ketones (entries 1–3, and 9) overwhelmingly prefer the *path a*. Choice of the silyl group substantially affects *path a* vs. *path b* ratio: *path a* becomes the favored pathway when the bulky tripropylsilyl group was used in place of the trimethylsilyl group (cf. entries 4 and 5). Thus steric hindrance at the site of the initial oxidation, the nature of the site of the proton removal (i.e., H^* in **B**), and the steric effect of the silyl group all contribute to the relative amounts of the two pathways.

TABLE

DOUBLE HYDROXYLATION OF ENOL SILYL ETHERS

Entry	Substrate	MCPBA, equiv	Path a: Path b	Combined %Yield	Major product

1		2.5	100:0	72	
2		2.5	100:0	79[a]	
3		3.3	100:0	74[a]	
4		1.0	100:0	91	
5		1.0	63:35	75	
6		1.0	32:68	94	
7		2.0	25:75	88	
8		2.0	0:100	nd[b]	
9		2.0	0:100	nd[b]	

[a]Isolated after acidic workup.
[b]Not determined. A major portion of the initial monooxygenation product was lost by further

oxidation with
excess MCPBA.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

hexanes

brine

sodium-benzophenone ketyl

16-dehydroprogesterone

cuprous bromide-dimethyl sulfide

17-dihydroxyacetone

hydrochloric acid (7647-01-0)

ethyl acetate (141-78-6)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

oxygen (7782-44-7)

sodium thiosulfate (7772-98-7)

nitrogen (7727-37-9)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

methylmagnesium bromide (75-16-1)

Tetrahydrofuran (109-99-9)

hexane (110-54-3)

triethylamine (121-44-8)

potassium bicarbonate (298-14-6)

calcium hydride (7789-78-8)

hexamethylphosphoramide (680-31-9)

sec-butyl alcohol (78-92-2)

1,10-phenanthroline (66-71-7)

CHLOROTRIMETHYLSILANE (75-77-4)

silyl ether (13597-73-4)

phosphorus pentoxide (1314-56-3)

m-chloroperoxybenzoic acid (937-14-4)

m-chlorobenzoic acid (535-80-8)

(Z)-16α-Methyl-20-trimethylsiloxy-4,17(20)-pregnadien-3-one (122315-01-9)

16α-Methylcortexolone,
Pregn-4-ene-3,20-dione, 17,21-dihydroxy-16-methyl-, (16α)-(±)- (122405-63-4)

21-trimethylsilyl ether of 16α-methylcortexolone