tography on silica gel (30:1 CH_2Cl_2–ether) afforded 37 mg (15%) of **30** as a light yellow oil, which decomposed on standing: ^1H NMR 5.12 (dddd, 1, J = 2.2, 2.2, 2.2, 0.6), 4.99 (dddd, 1, J = 2.2, 2.2, 2.2, 0.6), 3.36 (m, 1), 3.21 (dddd, 2, J = 2.6, 2.6, 2.6, 2.6), 2.43–2.39 (m, 2), 2.34–2.25 (m, 2), 2.09–2.01 (m, 2), 1.80–1.60 (m, 2), 0.80 (t, 3, J = 7.4); ^{13}C NMR 197.4, 166.1, 149.4, 136.6, 108.4, 54.4, 37.8, 35.8, 25.0, 24.9, 23.4, 9.2; IR (neat) 1670, 890 cm^{-1}; $[\alpha]^{29}_D$ −52° (c = 0.37, CH_2Cl_2); CD $\Delta\epsilon_{336}$ = +0.023 (c = 0.115 g/dm^3, CH_2Cl_2), $\Delta\epsilon_{247}$ = −0.56 (c = 4.60 × 10^{-4} g/dm^3, CH_2Cl_2).

1-Ethyl-3,5,6,7-tetrahydro-2-methyl-4*H*-inden-4-one (31). A solution of **30** (17 mg, 0.10 mmol), (2*R*,3*R*)-(−)-2,3-butanediol (11 mg, 0.012 mmol) and a trace of pyridinium *p*-toluenesulfonate in 20 mL of benzene was heated at reflux for 21 h on a Dean–Stark apparatus. The reaction mixture was washed (water), dried ($MgSO_4$), and evaporated in vacuo to give 12 mg of a dark orange oil, which contained mainly **31**: ^1H NMR 3.12 (t, 2, J = 1.2), 2.57–2.50 (m, 2), 2.45–2.39 (m, 2), 2.35–2.26 (m, 2), 2.07 (br q, 2, J = 7.0), 2.04 (s, 3), 1.03 (t, 3, J = 7.0).

1-(Phenylsulfonyl)-5-hexen-2-one (32). To a suspension of NaH (100 mg, 60% oil dispersion, 2.5 mmol) in 5 mL of THF at 0 °C was added (phenylsulfonyl)acetone (500 mg, 2.5 mmol) in 8 mL of THF. The mixture was stirred at 0 °C for 30 min and *n*-BuLi (1.1 mL, 2.4 M in hexane, 2.6 mmol) was added. The orange-yellow solution was stirred for 30 min and allyl bromide (0.02 mL, 2.5 mmol) was added via syringe. The mixture was stirred at 25 °C for 2 h, quenched (saturated NH_4Cl solution), acidified (10% HCl), and extracted with CH_2Cl_2. The organic layer was washed (brine), dried (Na_2SO_4), and evaporated in vacuo to give 687 mg of a yellow oil. Flash chroamtography on silica gel (1:1 hexane–EtOAc) yielded 372 mg (61%) of **32** and 10% of the dialkylated product **33**. The ^1H NMR and IR data of **32** are identical with those previously reported.[21]

4-(Phenylsulfonyl)-1,8-nonadien-5-one (33). To a suspension of NaH (50 mg, 60% oil dispersion, 1.25 mmol) in 1 mL of DMF was added a solution of **32** (300 mg, 1.26 mmol) in 2 mL of DMF. The mixture was stirred at 25 °C for 15 min and allyl bromide (0.14 mL, 1.60 mmol) was added via syringe. The reaction was stirred for 2 h, quenched (saturated NH_4Cl and 5% HCl), and extracted with CH_2Cl_2. The organic layer was washed (brine), dried (Na_2SO_4), and evaporated in vacuo. Flash chromatography on silica gel (4:1 hexane–EtOAc) gave 158 mg (50%) of **33**: ^1H NMR 7.75–7.80 (m, 2), 7.65–7.75 (m, 1), 7.52–7.65 (m, 2), 5.77 (ddt, 1, J = 17.1, 10.3, 6.5), 5.56 (ddt, 1, J = 17.5, 9.6, 6.4), 4.97–5.09 (m, 4), 4.16 (dd, 1 J = 10.5, 4.5), 2.83–3.02 (m, 2), 2.52–2.70 (m, 2), 2.26–2.37 (m, 2); ^{13}C NMR 200.8, 136.3, 134.4, 131.6, 129.5, 129.1, 119.2, 115.7, 74.2, 44.3, 31.3, 27.0 (one aromatic peak coincided with one of the peaks for the aromatic/alkenyl carbons); IR (neat) 3085, 1727, 1648, 1325, 1312, 1152, 1088, 1000, 920 cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_3S$: C, 64.72, H, 6.52; S, 11.52. Found: C, 64.89; H, 6.48; S, 11.63.

6-Methylene-1-(phenylsulfonyl)bicyclo[3.2.1]oct-2-one (34) and 7-Methylene-1-(phenylsulfonyl)bicyclo[3.3.0]octan-2-one (36). Oxidative cyclization of **32** (37 mg, 0.13 mmol) at 55 °C for 22 h produced 25 mg of crude product. Flash chromatography on silica gel (1:1 hexane–EtOAc) afforded 6.4 mg of **34** (20%) followed by 1.2 mg of **36** (4%).

Data for **34**: ^1H NMR 8.06–8.09 (m, 2), 7.61–7.66 (m, 1), 7.51–7.56 (m, 2), 5.17 (m, 1), 5.09 (m, 1), 3.40 (ddd, 1, J = 17, 2.6, 2.6), 3.10 (m, 1), 2.78 (ddd, 1, J = 11.7, 5.2, 2.5), 2.65 (ddd, 1, J = 17, 2, 1), 2.28–2.50 (m, 2), 1.99 (dd, 1, J = 11.7, 2.0), 1.76–1.90 (m, 2); ^{13}C NMR 148.1, 138.1, 133.8, 130.5, 128.5, 109.1, 78.1, 41.9, 38.6, 37.6, 36.4, 32.7 (carbonyl carbon not observed); IR (neat) 3073, 1723, 1305, 1145, 723, 686 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_3S$: 276.0821. Found: 276.0834.

Data for **36**: ^1H NMR 7.78–7.83 (m, 2), 7.68–7.78 (m, 1), 7.56–7.68 (m, 2), 4.90 (s, 1), 4.80 (s, 1), 3.60 (m, 1), 2.91 (br d, 1, J = 16.5), 2.85 (dd, 1, J = 15.3, 8.5), 2.55–2.80 (m, 1), 2.43 (br d, 1, J = 16.5), 2.35–2.40 (m, 3), 2.20 (br d, 1, J = 15); ^{13}C NMR 134.6, 130.6, 129.1, 109.4, 40.5, 39.2, 39.1, 30.0, 25.3 (four quaternary carbons not observed); IR (neat) 3065, 1745, 1305, 1150, 718, 686 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_3S$: 276.0821. Found: 276.0842.

Acknowledgment. We thank the National Science Foundation and National Institutes of Health for financial support. We thank Mark A. Dombroski for experimental assistance and helpful discussions.

Supplementary Material Available: Experimental details for the X-ray diffraction study of **13b**, and tables of (i) atomic coordinates, (ii) anisotropic thermal parameters, (iii) bond lengths and angles, and (iv) hydrogen atom positions, and (v) ORTEP diagram showing atom numbers (9 pages). Ordering information is given on any current masthead page.

(21) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

Efficient C-21 Deoxygenation of 21-Alkoxy-20-keto Corticoid Steroids with Trimethylsilyl Iodide in the Presence of Methanol

Masao Nagaoka, Yurie Kunitama, and Mitsuteru Numazawa*

Tohoku College of Pharmacy, 4-1 Komatsushima-4-chome, Sendai 981, Japan

Received April 27, 1990

Reaction of 21-alkyl ethers **1**, **4–6**, **8**, and **9** with a large excess of trimethylsilyl iodide (TMSI) produced the deoxygenated products **3** and **11** in low to moderate yields along with a small amount of 21-alcohols **2** and **10**. The deoxygenation reaction in the presence of 1.5 molar equiv of MeOH gave the products in much higher yields than those without MeOH, except the reaction of the ethyl and *n*-propyl ethers **4** and **5**. Treatment of **1** and **8** with trimethylsilyl chloride/NaI in the presence of MeOH gave similar results to those with TMSI. Compound **3** was also produced in high yields by reaction of **1** and **4** with HI under mild conditions. On the other hand, treatment of 17α-ketol **7** with TMSI in the presence of MeOH yielded 17aβ-methyl D-homo steroid **15**. The results along with deuterium-labeling experiments with MeOD and IR and ^1H NMR spectral analysis during the reaction with TMSI suggest that dealkylation of the 21-alkyl ethers precedes the deoxygenation, in which HI produced in situ by reaction of MeOH with TMSI would be involved.

Introduction

The use of organosilicon reagents in organic synthesis has become widespread during recent years. Trimethylsilyl iodide (TMSI), which was developed independently in Olah's[1] and Jung's[2] laboratories, has gained importance for the cleavage of esters,[1,2a] lactones,[3] ethers,[2b,3] ketals,[4] and cabamates[5] as well as for the conversion of alcohols[6]

(1) Ho, T. L.; Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 774. Ho, T. L.; Olah, G. A. *Synthesis* **1977**, 417. Ho, T. L.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *75*, 4.

0022-3263/91/1956-0334$02.50/0

Table I. Deoxygenation of 21-Alkyl Ethers with TMSI[a]

		conditions			product (isolated yield, %)		
entry	compd	solvent	Me_3SiI (molar equiv)	time (h)	21-ether	21-alcohol	20-ketone
a	1	$CHCl_3$	20	4	1 (83)	2 (8)	3 (8)
b		$CHCl_3$	20	18	1 (71)	2 (8)	3 (18)
c		MeCN	20	4	1 (nd)	2 (18)	3 (63)
d		MeCN	20	18	1 (nd)	2 (nd)	3 (67)
e	4	MeCN	20	24	4 (nd)	2 (nd)	3 (58)
f	5	MeCN	20	24	5 (nd)	2 (nd)	3 (20)
g	6	MeCN	4	0.25	6 (nd)	2 (76)	3 (24)
h		MeCN	20	2	6 (nd)	2 (nd)	3 (85)
i	8	MeCN	20	24	8 (nd)	10 (nd)	11 (48)
j	9	MeCN	20	2	9 (nd)	10 (5)	11 (45)
k	12	MeCN	20	5	12 (94)	13 (nd)	14 (nd)
l		MeCN	20	24	12 (nd)	13 (nd)	14 (nd)

[a] Reaction was carried out at room temperature. nd: not detected by thin-layer chromatographic analysis.

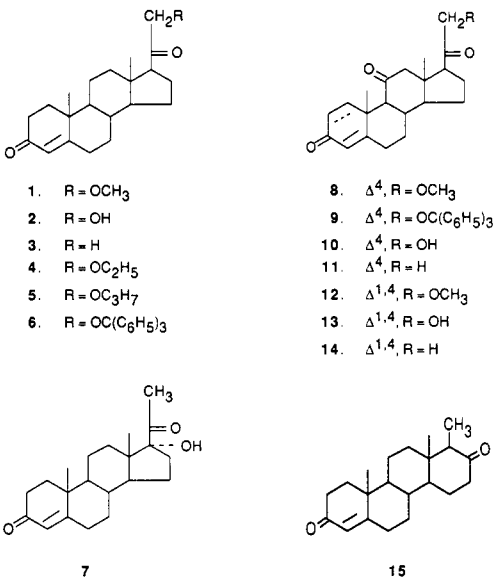
and sulfoxides[7] to the corresponding iodides and sulfides. Ho[8] has reported the usefulness of TMSI in the transformation of α-ketols to ketones. TMSI has also been used in the reductive removal of the *tert*-hydroxy group of α,β-unsaturated γ-*tert*-hydroxy ketones[9] and in the deoxygenation of *vic*-diols,[10] epoxides,[11] and carbonyl conjugated allylic ethers.[12] We[13] have previously reported the regiospecific deoxygenation of C-17 of the dihydroxyacetone and the corresponding 17-methyl ether of corticoid steroids and the efficient transformation of 21-hydroxy-20-keto steroids to the 20-ketones with TMSI, while the 17α-hydroxy-20-keto isomer and its 17-methyl ether are recovered unchanged.

During the course of these studies, we became interested in the reaction of the 21-alkoxy-20-keto side chain of corticoid steroids. We now report an efficient deoxygenation of the 21-alkoxy group and the conversion of the 17α-hydroxy 20-ketone to a D-homosteroid upon treatment with TMSI in the presence of MeOH.

Results and Discussion

The reaction of 21-methoxypregn-4-ene-3,20-dione (1) (Chart I) with a large excess (20 molar equiv) of TMSI was initially carried out in $CHCl_3$ or MeCN at room temperature (Table I, entries a–d). When MeCN was employed as a reaction solvent, the deoxygenation product, 20-ketone 3, was obtained in good yield. When $CHCl_3$ rather than MeCN was used, most of the starting material was recovered, accompanied by small amounts of 21-alcohol 2 and 3. The marked solvent effect on the reaction prompted us to employ MeCN for studies of the deoxygenation of other 21-alkyl ethers 4–6 with TMSI. All of these ethers were also converted into 3 (Table I, entries e–h). Yields of 3 from the ethyl (4) and *n*-propyl (5) ethers were relatively low while the reaction with the trityl ether 6 proceeded somewhat faster than that with the other ethers, giving 3 in high yield. Introduction of an 11-oxo function to 1 and 6 lowered yields of the deoxygenation product 11 (Table I, entries i and j), and when a double bond was introduced at C-1 of 21-methoxide 8, 20-ketone 14 was not produced at all, rather a complex mixture of byproducts was formed (Table I, entries k and l).

Chart I



The relative yields of the ketone 3 and the ethers 1, 4, 5, and 6 (Table I) are in accordance with those observed previously by Jung et al.[2b] in the dealkylation of the corresponding ethers of cyclohexanol with TMSI. The production of the alcohol 2, which is efficiently converted to 3 through 21-iodide 16 by reaction with TMSI,[13b] was observed during the course of the deoxygenation reaction with the silyl reagent. These results suggest that dealkylation of the 21-alkyl ethers should precede the deoxygenation.

Rakhit et al.[14] have reported that treatment of alcohol 2 with a large excess of HI in AcOH under drastic conditions (heating on a steam bath) afforded ketone 3 in high yield. Considering this, along with the previous finding that iodide ion is involved in the deoxygenation reaction with TMSI,[10-13] it was expected that the addition of MeOH to the reaction mixture containing the 21-ethers and TMSI, producing HI in situ by reaction with the silyl

(2) (a) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968. (b) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761. (c) Jung, M. E.; Mazurek, M. A.; Lim, R. M. *Synthesis* **1978**, *588*.
(3) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.
(4) Jung, M. E.; Andrew, W. A.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, 4175.
(5) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315.
(6) Jung, M. E.; Ornstein, P. L. *Tetrahedron Lett.* **1977**, 2659.
(7) Olah, G. A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1977**, 583.
(8) Ho, T. L. *Synth. Commun.* **1979**, *9*, 665.
(9) Sarma, D. N.; Sarma, J. C.; Barua, N. C.; Sharma, R. P. *J. Chem. Soc., Chem. Commun.* **1984**, 813.
(10) Sarma, J. C.; Barua, N. C.; Sharma, R. P.; Barua, J. N. *Tetrahedron* **1983**, *39*, 2846.
(11) Denis, J. N.; Magnane, R.; Eenoo, M. V.; Krief, A. *Neuv. J. Chim.* **1979**, *3*, 705. Jung, K.-Y.; Koreeda, M. *J. Org. Chem.* **1989**, *54*, 5667.
(12) Hartman, D. A.; Curley, R. W., Jr. *Tetrahedron Lett.* **1989**, *30*, 645.
(13) (a) Numazawa, M.; Nagaoka, M.; Kunitama, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 31. (b) Numazawa, M.; Nagaoka, M.; Kunitama, Y. *Chem. Pharm. Bull.* **1986**, *24*, 3722.
(14) Rakhit, S.; Gut, M. *J. Org. Chem.* **1968**, *33*, 1196.

Table II. Deoxygenation of 21-Alkyl Ethers with TMSI in the Presence of MeOH[a]

entry	compd	conditions: solvent	conditions: Me_3SiI (molar equiv)	conditions: time (h)	product (isolated yield, %): 21-ether	21-alcohol	20-ketone
m	1	$CHCl_3$	20	6	1 (72)	2 (12)	3 (2)
n		$CHCl_3$	20	12	1 (nd)	2 (6)	3 (89)
o		MeCN	3	6	1 (73)	2 (15)	3 (3)
p		MeCN	10	6	1 (nd)	2 (nd)	3 (87)
q	4	MeCN	10	22	4 (nd)	2 (nd)	3 (22)
r	5	MeCN	10	24	5 (nd)	2 (nd)	3 (15)
s	6	MeCN	10	1.3	6 (nd)	2 (nd)	3 (94)
t	8	MeCN	10	10	8 (nd)	10 (4)	11 (72)
u	9	MeCN	10	2.5	9 (nd)	10 (7)	11 (55)
v	12	MeCN	10	24	12 (nd)	13 (nd)	14 (51)
w	2	$CHCl_3$	8	2		2 (nd)	3 (96)

[a] Reaction was carried out in the presence of 1.5 molar equiv of MeOH at room temperature. nd: not detected by thin-layer chromatographic analysis.

Table III. Deoxygenation of 21-Alkyl Ethers 1 and 4 and 21-Alcohol 2 with HI[a]

compd	conditions: HI (molar equiv)	conditions: time (h)	product (isolated yield, %): 21-ether	21-alcohol	20-ketone
1	1.5	3	1 (14)	2 (12)	3 (65)
4	1.5	3.75	4 (30)	2 (7)	3 (50)
2	1.5	2		2 (7)	3 (50)

[a] Reaction was carried out in $CHCl_3$ at room temperature.

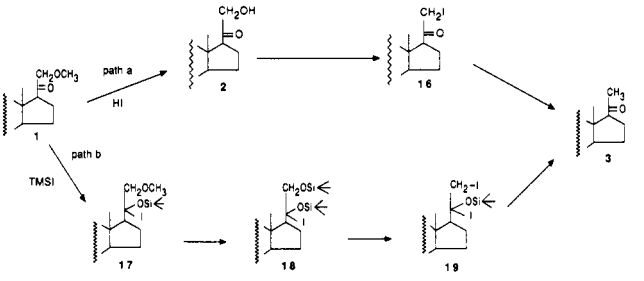
reagent, would accelerate the deoxygenation reaction. When the ether 1 was treated with an excess of TMSI in the presence of 1.5 molar equiv of MeOH, the deoxygenation took place faster, irrespective of the reaction solvent, than in the absence of MeOH, giving ketone 3 in excellent yields (Table II, entries n and p). The reactions with MeOH require less TMSI than those without MeOH. The trityl ether 6 was also converted to 3 in almost quantitative yield (Table II, entry s). Ketones 11 and 14, which have an 11-carbonyl group, were also obtained in much improved yields from the corresponding 21-alkyl ethers 8, 9, and 12 (Table II, entries t–v), in the presence of MeOH. It should be noted that 14 was not produced under the reaction conditions without MeOH but was isolated in 51% yield with MeOH. However, the MeOH addition did not improve the conversions of the ethyl and *n*-propyl ethers 4 and 5 to 3 (Table II, entries r and s). Reaction of the 21-alcohol 2 with TMSI in the presence of MeOH gave the ketone 3 in almost quantitative yield (Table II, entry w), which is higher than that (59%) without MeOH.[13b]

When α-methoxy ketones 1 and 8 were treated with a convenient in situ TMSI reagent[3,15] [trimethylsilyl chloride (30 molar equiv)/NaI] in the presence of MeOH (1.5 molar equiv) in MeCN, the deoxygenation also occurred to give the 20-ketones 3 (81%) and 11 (76%), respectively.

We next explored the reactions of ethers 1 and 4 with 1.5 molar equiv of HI in $CHCl_3$ under mild conditions (room temperature) (Table III). The 20-ketone 3 was produced in moderate yields, accompanied by a small amount of the 21-alcohol 2, in each experiment. Treatment of 2 with HI also gave 3 in high yield. The deoxygenation of the ethers with HI also proceeds through 2 in a reaction sequence that was reported previously[14,16] (Scheme I, path a).

The course of the reaction of the methyl ether 1 with TMSI (20 molar equiv)–MeOH (1.5 molar equiv) was monitored by IR and ^1H NMR spectroscopy. Upon adding

Scheme I[a]



[a] TMSI, trimethylsilyl iodide.

TMSI to a solution of 1 and MeOH in $CHCl_3$, the C-20 carbonyl absorption (1718 cm^{-1}) completely disappeared within 10 min. The ^1H NMR spectrum of the reaction mixture in $CDCl_3$ before the addition of the silyl reagent showed three characteristic signals [δ 4.00 (21-CH_2), 3.50 (*Me*OH), and 3.41 (21-OMe)]. The two methyl signals shifted to 2.20 ppm within 1 h, indicating the formation of MeI from MeOH and the 21-methoxyl group. The results show that the addition of TMSI to the carbonyl function[17] (1 → 17) occurs first in the reaction sequence, followed by cleavage of the methyl ether, giving the 21-silyl ether 18, which is then converted into 3 through the 21-iodide 19[18] (Scheme I, path b).

Considering the results, we propose that the MeOH addition probably produces HI in situ, which accelerates the conversion of silyl ether 18 to the iodide 19 and that of 19 to the ketone 3.

We next employed MeOD instead of MeOH in the deoxygenation reaction. Treatment of the methoxy ketone 1 with TMSI in the presence of MeOD gave deuterium-labeled ketone 3, for which the ^1H NMR spectrum showed that about 39% of the C-21 methyl protons (equivalent to almost one of the three protons) were replaced by deuterium. The mass spectrum also supported that the deuterium labeling occurred at C-21: $[CH_3CO]^+$ fragment derived from a 17β-side chain consisted of d_0 62%, d_1 30%, and d_2 8%. On the other hand, when 1 was treated with TMSI (1.5 molar equiv) and MeOD (2 molar equiv) in $CHCl_3$, any detectable amounts of deuterium were not found at the C-21 position of the recovered 1. These data show that the deuterium labeling at C-21 was achieved principally during the deoxygenation process and not by simple enolization of the C-20 carbonyl function of 1 in

(15) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.
(16) Reusch, W.; LeMahieu, R. *J. Am. Chem. Soc.* **1964**, *86*, 3068.
(17) Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3698. For a review, see: Olah, G. A.; Narang, S. C. *Tetrahedron* **1982**, *38*, 2225.
(18) It is known that reaction of ethers (R–O–R') with a large excess of TMSI produces the corresponding iodides, RI and R'I, in almost quantitative yields.[2b]

the acidic reaction mixture. This supports the notion that the MeOH addition affects the conversion of the iodide **19** to **3**.

We[13] previously reported that 17α-ketol **7** does not react with TMSI in $CHCl_3$. However, the reaction of **7** in the presence of MeOH gave the D-homo steroid **15** (40%), which would be produced by a reaction sequence similar to that reported previously for the reaction of **7** with HI.[14] The reaction proceeds by the initial formation of a carbocation followed by ring D expansion (migration of the C_{13}–C_{17} bond). The intermediate 17aβ-hydroxy-17aα-methyl-D-homo steroid can then be reduced by formation of an allylic alcohol.

Deoxygenation of α-alkoxy ketones with TMSI in the presence of MeOH gave the corresponding ketones in much improved yields compared to the same reactions conducted without MeOH. The results suggest that employment of MeOH for other types of reactions with TMSI might improve the efficiency of the transformations. Related studies are in progress.

Experimental Section

21-Methoxypregn-4-ene-3,20-dione (1). A mixture of 21-hydroxypregn-4-ene-3,20-dione (**2**) (600 mg, 1.8 mmol), Ag_2O (1.8 g, 7.8 mmol), and MeI (20 mL) was heated under reflux with stirring for 15 h. The reaction mixture was filtered and the filtrate was washed with 5% $NaHCO_3$ solution and saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent gave a solid, which was recrystallized from acetone to give **1** (562 mg, 91%) as colorless prisms: mp 156–159 °C; IR (KBr) 1715 and 1660 (C=O) cm^{-1}; UV λ_{max} (EtOH) 241 nm ($\epsilon = 1.68 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.72 (3 H, s, 18-Me), 1.20 (3 H, s, 19-Me), 3.40 (3 H, s, 21-OMe), 4.00 (2 H, S, 21-H_2), 5.75 (1 H, s, 4-H). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.50; H, 9.55.

21-Ethoxypregn-4-ene-3,20-dione (4). A mixture of compound **2** (500 mg, 1.5 mmol), Ag_2O (1.5 g, 6.5 mmol), and EtI (15 mL) was heated under reflux with stirring for 11 h. After the same workup as above, an oily product (610 mg) was purified by silica gel column chromatography (hexane–AcOEt, 4/1) and recrystallized from hexane–acetone to afford **4** (386 mg, 71%) as colorless needles: mp 108–111 °C; IR (KBr) 1722 and 1680 (C=O) cm^{-1}; UV λ_{max} (EtOH) 241 nm ($\epsilon = 1.60 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 1.20 (3 H, s, 19-Me), 1.25 (3 H, t, J = 7 Hz, 21-OCH_2*Me*), 3.55 (2 H, q, J = 7 Hz, 21-OCH_2Me), 4.03 (2 H, s, 21-CH_2), 5.73 (1 H, s, 4-H). Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.06; H, 9.56. Found: C, 76.82; H, 9.84.

21-Propoxypregn-4-ene-3,20-dione (5). A mixture of compound **2** (500 mg, 1.5 mmol), Ag_2O (1.5 g, 6.5 mmol), and C_3H_7I (10 mL) was heated under reflux with stirring for 16 h. The same workup as above afforded an oily product. This was purified by silica gel column chromatography (hexane–AcOEt, 4/1) and recrystallized from AcOEt to yield **5** (100 mg, 17%) as colorless needles: mp 68–70 °C; IR (KBr) 1722 and 1670 (C=O) cm^{-1}; UV λ_{max} (EtOH) 241 nm ($\epsilon = 1.70 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 0.93 (3 H, t, J = 7 Hz, 21-OCH_2CH_2*Me*), 1.20 (3 H, s, 19-Me), 3.40 (2 H, t, J = 6 Hz, 21-OCH_2CH_2Me), 4.00 (2 H, s, 21-CH_2), 5.73 (1 H, s, 4-H). Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.16; H, 9.76.

21-(Trityloxy)pregn-4-ene-3,20-dione (6). A solution of compound **2** (400 mg, 1.2 mmol) and trityl chloride (1.6 g, 5.7 mmol) in 4 mL of pyridine was stirred at room temperature for 12 days. The mixture was diluted with AcOEt (200 mL), washed with water, and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane–AcOEt, 3/1) and recrystallized from acetone to give **6** (440 mg, 63%) as colorless needles: mp 167–169.5 °C; IR (KBr) 1722 and 1672 cm^{-1}; UV λ_{max} (EtOH) 202 nm ($\epsilon = 5.70 \times 10^4$) and 232 nm ($\epsilon = 2.00 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.60 (3 H, s, 18-Me), 1.17 (3 H, s, 19-Me), 3.60 (1 H, d, J = 18 Hz, 21-H_a), 3.93 (1 H, d, J = 18 Hz, 21-H_b), 5.77 (1 H, s, 4-H), 7.10–7.30 (15 H, m, aromatic). Anal. Calcd for $C_{40}H_{44}O_3$: C, 83.87; H, 7.74. Found: C, 83.65; H, 7.68.

21-Methoxypregn-4-ene-3,11,20-trione (8). 21-Hydroxypregn-4-ene-4,11,20-trione (**10**) was methylated as described above [**10** (500 mg, 1.5 mmol), Ag_2O (1.5 g, 6.5 mmol), MeI (17 mL), 12-h reaction time]. Recrystallization of a solid product from acetone gave **8** (400 mg, 77%) as colorless prisms: mp 161–163 °C; IR (KBr) 1720, 1710 and 1660 (C=O) cm^{-1}; UV λ_{max} (EtOH) 239 nm ($\epsilon = 1.65 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.67 (3 H, s, 18-Me), 1.43 (3 H, s, 19-Me), 3.42 (3 H, s, 21-OMe), 3.93 (2 H, s, 21-CH_2), 5.78 (1 H, s, 4-H). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.89; H, 8.72.

21-(Trityloxy)pregn-4-ene-3,11,20-trione (9). A solution of compound **10** (290 mg, 0.84 mmol) and trityl chloride (1 g, 3.6 mmol) in 6 mL of pyridine was stirred at room temperature for 9 days. The same workup as described in the synthesis of **6** afforded an oily product, which was purified by silica gel column chromatography (hexane–AcOEt, 2/1) and recrystallized from EtOH to yield **9** (77 mg, 16%) as colorless needles: mp 154–157 °C; IR (KBr) 1704 and 1675 (C=O) cm^{-1}; UV λ_{max} (EtOH) 202 nm ($\epsilon = 6.00 \times 10^4$) and 230 nm ($\epsilon = 1.37 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.53 (3 H, s, 18-Me), 1.37 (3 H, s, 19-Me), 3.60 (1 H, d, J = 18 Hz, 21-H_a), 3.93 (1 H, d, J = 18 Hz, 21-H_b), 5.73 (1 H, s, 4-H), 7.07–7.70 (15 H, m, aromatic). Anal. Calcd for $C_{40}H_{42}O_4$: C, 81.87; H, 7.22. Found: C, 81.66; H, 7.01.

21-Methoxypregna-1,4-diene-3,11,20-trione (12). 21-Hydroxypregna-1,4-diene-3,11,20-trione (**13**) was methylated as above [**13** (580 mg, 1.7 mmol), Ag_2O (1.8 g, 7.8 mmol), MeI (20 mL), 11-h reaction time]. Silica gel column chromatography (hexane–AcOEt, 2/1) of an oily product and a subsequent recrystallization from acetone afforded **12** (393 mg, 65%) as colorless prisms: mp 183–185 °C; IR (KBr) 1700 and 1662 (C=O) cm^{-1}; UV λ_{max} (EtOH) 239 nm ($\epsilon = 1.50 \times 10^4$); ^1H NMR (60 MHz, $CDCl_3$) δ 0.67 (3 H, s, 18-Me), 1.43 (3 H, s, 18-Me), 3.38 (3 H, s, 21-OMe), 3.90 (2 H, s, 21-CH_2), 6.10 (1 H, d, J = 2 Hz, 4-H), 6.20 (1 H, dd, J = 10 and 2 Hz, 2-H), 7.67 (1 H, d, J = 10 Hz, 1-H). Anal. Calcd for $C_{22}H_{28}O_4$: C, 73.71; H, 7.87. Found: C, 73.49; H, 7.55.

Reaction of Corticoid Steroids with Trimethylsilyl Iodide (TMSI). Typical reaction conditions are as follows: a solution of steroid (0.3 mmol) and TMSI (distilled before use) in MeCN (distilled over CaH_2) or $CHCl_3$ (alcohol free, distilled over P_2O_5) (4–20 mL) in the presence or absence of dry MeOH (1.5 molar equiv) was stirred at room temperature for an appropriate period under N_2. After this time, the mixture was poured into 10% $Na_2S_2O_3$ solution (10 mL) and extracted with AcOEt (50 mL). The organic layer was washed with 5% $NaHCO_3$ solution and saturated NaCl solution and dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt), thin-layer chromatography (hexane/AcOEt), or recrystallization to give the deoxygenated product, the dealkylated derivative, and/or the recovered starting material, which were identical with the corresponding authentic sample in every respect in every experiment.

Reaction of the 21-Ethers 1 and 8 with Trimethylsilyl Chloride/Sodium Iodide. Trimethylsilyl chloride (distilled before use, 548 mg, 5.23 mmol), NaI (784 mg, 5.2 mmol), and MeOH (8.2 mg, 0.25 mmol) were added to separate solutions of **1** and **8** (0.17 mmol) in 4 mL of MeCN. The mixture was stirred at room temperature for an appropriate period under N_2. The same workup as described above yielded oily products, which were purified by silica gel column chromatography (hexane/AcOEt) to give **3** (39 mg, 81%) and **11** (46 mg, 77%), respectively. The products **3** and **11** were identical with the authentic samples in every respect.

Reaction of the 21-Ethers 1 and 4 and the 21-Alcohol 2 with Hydriodic Acid. A 12% HI solution in $CHCl_3$ was prepared from 55% HI aqueous solution and P_2O_5 according to the method reported previously,[19] and its concentration was determined by titration with 0.05 M KIO_3 solution. The HI solution (0.46 mL, equivalent to 0.043 mmol of HI) was added to individual solutions of **1**, **2**, and **4** (0.29 mmol) in 2 mL of $CHCl_3$. The mixture was stirred at room temperature for an appropriate period under N_2. The same workup as described above afforded oily products, which were purified by silica gel column chromatography (hexane/AcOEt), silica gel thin-layer chromatography (hexane/AcOEt), and/or recrystallization to yield **2** and **3**, which were identical with

(19) Rollefson, G. K.; Booher, J. E. *J. Am. Chem. Soc.* **1931**, *53*, 1728.

the authentic samples in every respect.

21-Hydroxypregn-4-ene-3,20-dione (2): mp 136–137.5 °C (lit.[13b] mp 135–137 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 1.20 (3 H, s, 19-Me), 4.18 (2 H, s, 21-CH_2), 5.77 (1 H, s, 4-H).

Pregn-4-ene-3,20-dione (3): mp 116–119 °C (lit.[13b] mp 117–118 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 1.20 (3 H, s, 19-Me), 2.12 (3 H, s, 21-Me), 5.77 (1 H, s, 4-H).

21-Hydroxypregn-4-ene-3,11,20-trione (10): mp 153–157 °C (lit.[13b] mp 153–157 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.67 (3 H, s, 18-Me), 1.40 (3 H, s, 19-Me), 4.18 (2 H, s, 21-CH_2), 5.73 (1 H, s, 4-H).

Pregn-4-ene-3,11,20-trione (11): mp 167–169 °C (lit.[13b] mp 172–173 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.65 (3 H, s, 18-Me), 1.42 (3 H, s, 19-Me), 2.12 (3 H, S, 21-Me), 5.73 (1 H, s, 4-H).

Pregna-1,4-diene-3,11,20-trione (14): mp 163–165 °C (lit.[20] mp 167–169 °C); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 1.47 (3 H, s, 19-Me), 2.13 (3 H, s, 21-Me), 6.18 (1 H, d, J = 2 Hz, 4-H), 6.20 (1 H, dd, J = 10 and 2 Hz, 2-H), 7.70 (1 H, d, J = 10 Hz, 1-H).

17aβ-Methyl-D-homoandrost-4-ene-3,17-dione (15). To a solution of 17α-hydroxypregn-4-ene-3,20-dione (97 mg, 0.29 mmol) in $CHCl_3$ were added TMSI (118 mg, 5.87 mmol) and MeOH (14 mg, 0.45 mmol), and the mixture was stirred at room temperature for 9 h. The same workup of the mixture as above gave an oily product, which was purified by silica gel column chromatography (hexane/AcOEt) and then recrystallized from AcOEt to give **15** (37 mg, 40%) as colorless prisms: mp 208–209 °C (lit.[14] mp 210–212 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 0.94 (3 H, d, J = 6.6 Hz, 17aβ-Me), 1.18 (3 H, s, 19-Me), 5.75 (1 H, d, J = 0.7 Hz, 4-H).

Compound **15** was identical with the authentic sample obtained according to the method previously reported by Rakhit et al.[14] in every respect.

Deuterium-Labeling Reaction. (1) TMSI (290 mg, 1.45 mmol) and MeOD (99 atom %, 3.6 mg, 0.109 mmol) were added to a solution of **1** (25 mg, 0.073 mmol) in 1 mL of $CHCl_3$. The mixture was stirred at room temperature for 9 h under N_2 and the crude product obtained as above was purified by silica gel thin-layer chromatography (hexane/AcOEt) and recrystallization from acetone–hexane to give deuterium-labeled **3** (15 mg, 66%): mp 113–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (3 H, s, 18-Me), 1.18 (3 H, s, 19-Me), 2.13 (1.85 H, s, 21-Me), 2.30–2.47 (3.28 H, m, 2α, 2β, 6α, and 6β protons), 2.54 (0.29 H, m, 17α-H), 5.74 (0.86 H, s, 4-H); EI-MS m/z 314 (M^+) d_0 20%, d_1 34%, d_2 27%, d_3 15%, and d_4 4%, m/z 43 (CH_3CO^+) d_0 62%, d_1 30%, and d_2 8%. The spectral data show that deuterium was incorporated into the C-2, C-4, C-6, C-17α, and C-21 positions.

(2) A solution of **1** (55 mg, 0.16 mmol) in 2 mL of $CHCl_3$ containing TMSI (48 mg, 0.24 mmol) and MeOD (99 atom %, 11 mg, 0.32 mmol) was stirred at room temperature for 5 h under N_2. The same workup as described above yielded **1** (51 mg, 93%): mp 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.70 (3 H, s, 18-Me), 1.18 (3 H, s, 19-Me), 2.29–2.46 (4 H, m, 2α, 2β, 6α, and 6β protons), 2.59 (0.8 H, t, J = 9.1 Hz, 17α-H), 3.41 (3 H, s, 21-OMe), 3.96 (1 H, d, J = 17.2 Hz, 21-Ha), 4.03 (1 H, d, J = 17.2 Hz, 21-Hb), 5.73 (0.8 H, s, 4-H).

^{1}H NMR and IR Spectrometric Studies of the Deoxygenation Reaction of the Ether 1. (1) IR Analysis. TMSI (83 μL, 0.581 mmol) was added to a solution of **1** (10 mg, 0.029 mmol) and MeOH (2 μL, 0.048 mmol) in 0.17 mL of $CHCl_3$, the mixture was immediately transferred to an IR cell (NaCl, 0.1 mm), and the spectrum between 5000 and 330 cm^{-1} was first obtained at 1-min reaction time (scan time: 4 min). The spectra were then measured repeatedly at 10-min intervals up to 1-h reaction time.

(2) ^{1}H NMR Analysis. TMSI (206 μL, 1.82 mmol) was added to a solution of **1** (25 mg, 0.072 mmol) and MeOH (4.5 μL, 0.111 mmol) in $CDCl_3$ in an NMR tube, and the spectra (60 MHz) between 0 and 10 ppm were obtained repeatedly at 10-min intervals for the first 1-h reaction time (scan time: 250 s).

Acknowledgment. We thank Prof. T. Nambara of Tohoku University for providing elemental analysis data and Drs. K. Hisamichi and S. Suzuki for 400-MHz ^{1}H NMR and MS analysis.

Registry No. 1, 20380-14-7; 2, 64-85-7; 3, 57-83-0; 4, 19953-77-6; 5, 129786-18-1; 6, 26623-68-7; 7, 68-96-2; 8, 129786-19-2; 9, 129786-20-5; 10, 72-23-1; 11, 516-15-4; 12, 129786-21-6; 13, 67067-81-6; 14, 4368-11-0; 15, 15296-76-1; TMSI, 16029-98-4; MeOH, 67-56-1.

(20) British Drug Houses Ltd., Brit. Patent 854343, 1960; *Chem. Abstr.* **1960**, *55*, 18813i.

Stereocontrolled Synthesis of Functionalized Diquinanes from Pauson–Khand-Derived *exo*-Tricyclo[5.2.1.0^{2,6}]decenones

Susan E. MacWhorter and Neil E. Schore*

Department of Chemistry, University of California, Davis, California 95616

Received April 16, 1990

A 10-step sequence is described for the conversion of 4-methyl-*exo*-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (the Pauson–Khand cycloaddition product of norbornadiene with propyne) into 3,3-dimethyl-2-[(2-methoxyethoxy)methoxy]-8-(1-methyl-2-oxopropyl)bicyclo[3.3.0]octan-6-ol. The latter diquinane, formed with complete stereocontrol and well-differentiated functionality, is appropriately substituted to serve as an entry to highly functionalized linearly fused triquinanes, although attempts to close a third five-membered ring via an enolate–epoxide ring-opening process were unsuccessful.

The intramolecular Pauson–Khand cycloaddition reaction has seen considerable recent development in the synthesis of natural products containing the bicyclo[3.3.0]octenone ("diquinane") structural unit.[1-3] In a typical example, Magnus utilized this methodology to convert an appropriately functionalized enyne into a bicyclo[3.3.0]octenone (eq 1) which, in turn became the precursor to the linearly fused triquinane natural product coriolin (1).[4,5]

(1) Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436.

(2) General reviews: (a) Pauson, P. L.; Khand, I. U. *Ann. N.Y. Acad. Sci.* **1977**, *295*, 2. (b) Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855. (c) Pauson, P. L. In *Organometallics in Organic Synthesis. Aspects of a Modern Interdisciplinary Field*; de Meijere, A., Dieck, H. T., Eds.; Springer: Berlin, 1988; p 233. See also: (d) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081.

(3) E.g., (a) hirsutic acid: Magnus, P.; Exon, C.; Albaugh-Robertson, P. *Tetrahedron* **1985**, *41*, 5861. (b) Pentalenene: Hua, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 3835. Also (c) Schore, N. E.; Rowley, E. G. *J. Am. Chem. Soc.* **1988**, *110*, 5224. (d) Quadrone: Magnus, P.; Principe, L. M.; Slater, M. J. *J. Org. Chem.* **1987**, *52*, 1483. (e) Pentalenolactone: Hua, D. H.; Coulter, M. J.; Badejo, I. *Tetrahedron Lett.* **1987**, *28*, 5465.

0022-3263/91/1956-0338$02.50/0