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REPLACEMENT OF A CARBONYL GROUP OF CYCLIC KETONES BY AN OXYGEN ATOM: A FOUR-STEP TRANSFORMATION OF CYCLIC KETONES INTO CYCLIC ETHERS[1]

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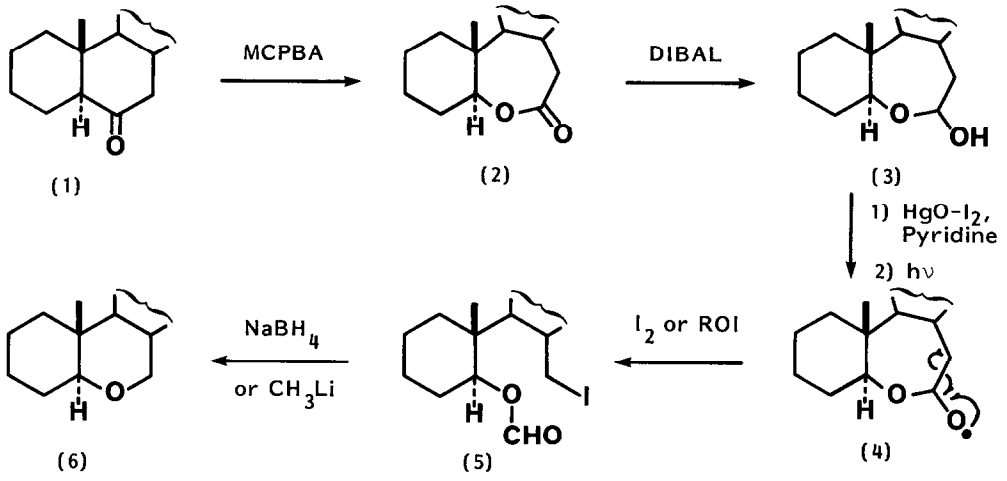
Abstract: We describe a new and versatile method for transforming cyclic ketones into cyclic ethers with the same ring size in which the chirality adjacent to the carbonyl group of the ketones is retained.

In our previous paper[2-4] we reported a new method for a two-step transformation of saturated hydroxysteroids into oxasteroids. The experiments using ^{18}O labeled mercury(II) oxide as a source of $I_2{}^{18}O$ proved that the ring oxygen in the oxasteroids is derived from the hydroxyl group of the starting alcohols and not from the oxygen of mercury(II) oxide.[3,4] This results indicated the pathway of the formation of the novel formates, cyclization of which gave oxasteroids, and indicated that the formates may be obtained by the irradiation of the hypoiodites of lactols derivable from cyclic alcohols and ketones as well as lactones.

In this communication, we wish to report an alternative and a considerably more versatile new method of achieving the synthesis of cyclic ethers from cyclic ketones, whereby cyclic ketones are converted into cyclic ethers with the same ring size as the starting ketones. In this transformation, a chiral centre adjacent to the carbonyl group of the starting ketones is maintained.

The conversion of 5α-cholestan-6-one (1) into 6-oxa-5α-cholestane (6), outlined in Scheme 1, illustrates the new method. Thus, Baeyer-Villiger oxidation of ketone 1 gave B-homo-6-oxa-5α-cholestan-7-one (2)[5] in a 57% yield. The reduction of lactone 2 with DIBAL[6] in hexane at -78°C for 2h readily gave a crystalline lactol 3,[7] m.p. 136.5-137.5°C, in a 96% yield. Lactol 3 (200 mg) in benzene (25 ml) containing mercury(II) oxide (214 mg)-iodine (251 mg) and pyridine (0.7 ml) in a Pyrex vessel was irradiated with a 100-W high pressure mercury arc for 3h under a nitrogen atmosphere to give an oily 6-iodo-5,6-seco-B-nor-5α-cholestan-5β-ol formate (5) in a 90% yield. The heating of 5 in THF containing $NaBH_4$ under reflux for 10h gave 6-oxa-5α-cholestane (6) in a 75% yield.

Following the same reaction sequence, we were able to convert a variety



Scheme 1

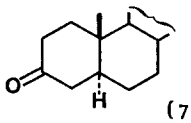
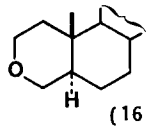
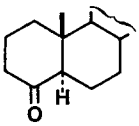
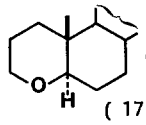
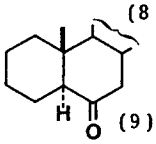
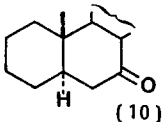
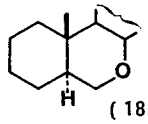
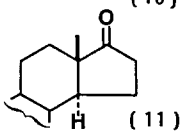
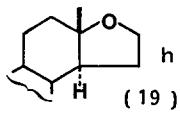
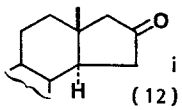
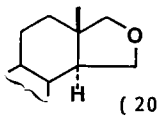
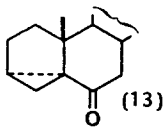
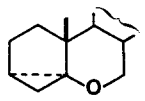
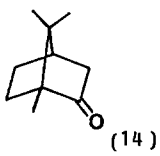
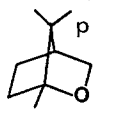
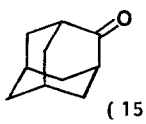
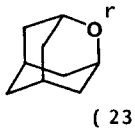
of steroidal ketones, camphor and adamantanone, into the corresponding cyclic ethers via the corresponding lactols. The results are summarized in Table 1.

Steroidal cyclic ethers, 3-oxa[2]-, 4-oxa-[8,9], and 6-oxa-5α-cholestanes, 16, 17, and 6, as well as 16-oxa-5α-androstane (20) can be readily synthesized following this method while these oxasteroids can not be obtained from the cyclic alcohols by the previous two-step procedure.[2] A low yield (51%) of the formate in a β-scission of the lactol derived from ketone 8 is due to the fact that the lactol in the solution is in an equilibrium with the ring-opened aldehyde (33%).

Oxasteroids can readily be obtained by the present procedure even when Baeyer-Villiger oxidation of ketones (e.g., 7, and 12) leads to a mixture of the two lactones. In these cases, the mixtures of the lactones were directly subjected to DIBAL reduction, β-scission and cyclization to the oxasteroids without isolating pure lactones. The β-scission of nearly all the lactols gave the corresponding lactones as the accompanying minor products. Irradiation of the hypoiodite of the lactol derived from adamantanone (15) gave a mixture of the lactone[10,11] (53%) and the formate (44%) but the latter was spontaneously cyclized to give 2-oxaadamantane (23)[12] at room temperature. We were able to achieve cyclization of the formates derived from ketones 8, 12, 13, and 14 with methyllithium at -78°C in good yields.

A survey of the literature indicates that only a limited number of the procedures for the synthesis of cyclic ethers[12] and oxasteroids[8,9] and 13 have been available previously. The present procedure should thus be applicable to a facile transformation of cyclic ketones into cyclic ethers and especially oxasteroids under very mild conditions. Studies of a further extension of the scope of this method are in progress and will be reported in due course.

Table 1. Conversion of Cyclic Ketones into Cyclic Ethers

Cyclic Ketone	Yield of lactone, %[a]	Yield of lactol, %[a]	Yield of formate, %[a]	Product cyclic ether	Yield, %[a]	M.P.
 (7)	67[b]	91[c]	66[d]	 (16)	74	86~87°C
 (8)	63[e]	85[f]	51	 g (17)	84	89.5~90.5°C
 (9)	57	96	90	(6)	75	62~62.5°C
 (10)	89	94	94	 (18)	74	89.5~91°C
 (11)	85	87	74	 h (19)	71	90.5~91.5°C
 i (12)	80[j]	98[k]	60	 (20)	74	78~80°C
 (13)	83	90	14[l]	 (21)	85	96~98°C
 (14)	54[m]	88[n]	60[o]	 p (22)	79	34~37°C
 (15)	91[q]	93	–	 r (23)	44	226~229°C (sealed tube)

Footnote for Tabel 1

a) The all products were isolated by preparative t.l.c. The yields refer to those after recrystallization whenever they were obtained as crystals.
b) A mixture of 3-oxa-4-one and 4-oxa-3-one.
c) A mixture of 3-oxa-4-ols and 4-oxa-3-ols.
d) A mixture of two formates.
e) W. Klyne, D. N. Kirk, J. Tilley. and H. Suginome, Tetrahedron, 1980, 36 1543.
f) M.p. 111~114°C. A 2:1 equilibrium mixture of 4a-oxa-A-homo-5α-cholestan-4-ol and the corresponding ring-opened aldehyde in $CDCl_3$ (^1H NMR).
g) Lit.[8] m.p. 89~90°C; Lit.[9] m.p. 93~94°C, Lit.[14] m.p. 94~95°C.
h) Ref. 2.
i) Ref. 15.
j) A 9:1 mixture of 17-oxa-D-homo-5α-androstan-16-one and 16-oxa-D-homo-5α-androstan-17-one after one recrystallization from methanol-acetone. Several recrystallization gave the crystals which melted at 193~195°C.
k) A mixture of 17-oxa-16-ols and 16-oxa-17-ols.
l) A by-product having iodine and no cyclopropane ring was obtained.
m) A mixture of 1,8,8-trimethyl-3-oxabicyclo[3.2.1]oct-2-one and 1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-3-one, c.f. R. R. Sauers, J. Amer. Chem. Soc., 1959, 81, 925.
n) An endo lactol contaminated by a small amount of an exo isomer.
o) 1,8,8-trimethyl-2-oxabicyclo[3.2.1]oct-3-one (26%) was a by-product.
p) Isolated by preparative GLC.
q) Ref. 10.
r) Lit.[10] m.p. 232°C (sealed tube); Lit.[11] m.p. 225~230°C (sealed tube).

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