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EFFICIENT INVERSIONS OF SECONDARY ALCOHOLS USING CESIUM ACETATE AND 18-CROWN-6

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Reaction of alcohol mesylate with cesium acetate and 18-crown-6 in benzene is an effective method for the inversion of cyclopentyl and cyclohexyl alcohols.

The inversion of a hydroxy functionality is one of the most important synthetic tasks in the prostaglandin and related fields.[1] Three original methods are now available for such transformation, among which a method using cesium salts[2] may provide useful versatility.

During our research on prostaglandin, the quite effective inversion of cyclopentanol was required for its analog synthesis. The inversion of the model alcohol (1) according to Mitsunobu procedure[3] and the original procedure using CsOAc[2] was attempted at first, but resulted in the predominant formation of cyclic ether or eliminated products. This unwanted olefin formation seems to be a general phenomenon in the case of cyclic alcohols.[3,4] After several attempts, we have finally reached a goal that 1 was successfully converted to 2 in 70% yield from 1 by the reaction of the corresponding crude mesylate with cesium acetate (3 equiv.) and 18-crown-6 (0.5 equiv.) in benzene at reflux for 1 h (Entry 1).[5] In this reaction, it should be noted that olefin formation was suppressed within 5% yield.

Similarly, the acetate (4) was obtained in 92.5% yield from 3 along with a small amount of olefinic products (4% yield, Entry 2). Without crown ether, substantial olefinic products were formed, and other combination such as potassium acetate and 18-crown-6 gave expectedly unsatisfactory results.

As shown in Table 1, this method was applied to the crude mesylates derived from other prostanoid alcohols, yielding the corresponding inverted acetates in 70-75.5% yields from the starting alcohols (Entries 3,4,5). The efficient inversion of the 3S-hydroxy group of cholestanol (Entry 6) and the regiocontrolled inversion of the 15R-hydroxy group to its 15S-isomer in the ω-chain (Entry 7) could be effectively achieved. The structure of all inverted acetates was confirmed either by the direct comparison with authentic materials or by the spectral data (NMR, IR).

In terms of the wide applicability to complex molecules involving the common protective groups and the minimization of olefin formation, this new method could be a first choice for the inversion of cyclopentyl and cyclohexyl alcohols.

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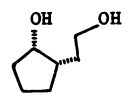
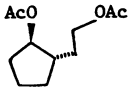
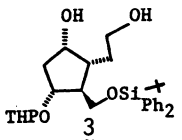
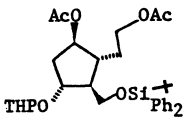
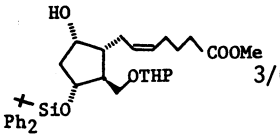
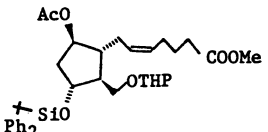
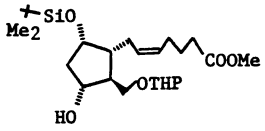
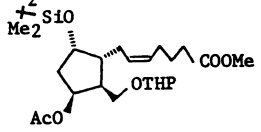
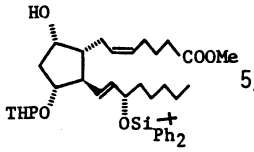
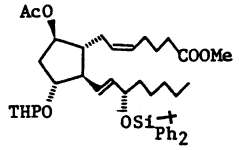
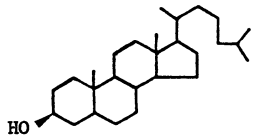
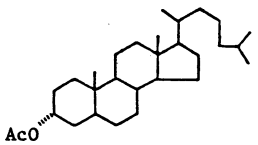
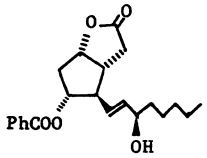
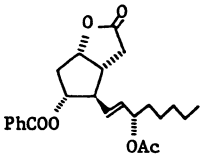
Table 1. Inversion of Secondary Alcohols by Reactions of the Corresponding Mesylates with CsOAc/ 18-Crown-6

Entry	Alcohols	CsOAc/18-Crown-6 (equiv.)	Reaction conditions	Inverted acetate	Yield(%) from alcohols Inverted acetate	Olefin
1	 1	3/0.5	benzene 1 h	 2	70	4.8
2	 3	3.2/0.75	benzene 2 h	 4	92.5	3.5
3		3/0.5	benzene 5 h		72.5	5.5
4		5/1	toluene 10 h		70	5
5		5/1	toluene 1 h		75.5	4.5
6		5/1	benzene 20 h		74	-
7		3/0.5	benzene r.t., 2 h		65	10

References

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5) For the inclusion ability of 18-crown-6 to a cesium ion, see H.K.Frensdorff, J. Am. Chem. Soc., 93, 600 (1971).

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