Tetrahedron Letters,Vol.26,No.40,pp 4925-4928,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

# CHEMISTRY OF DIHYDRO-1,4-DIOXIN III [1]

## A NEW METHOD FOR THE PREPARATION OF α,α'-DIHYDROXY KETONES FROM KETONES AND ALDEHYDES

Marcel FETIZON*, Pierre GOULAOUIC and Issam HANNA

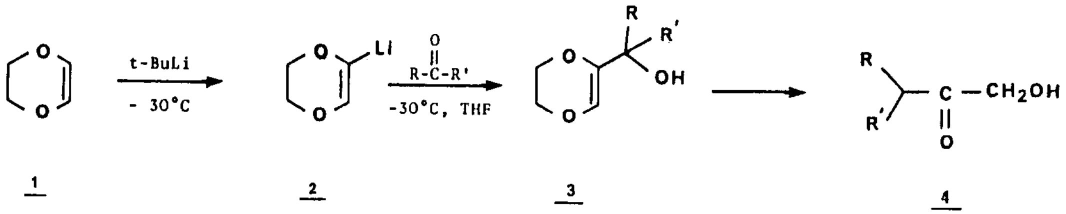
*Laboratoire de Synthèse Organique - Ecole Polytechnique*

*91128 PALAISEAU Cedex, France.*

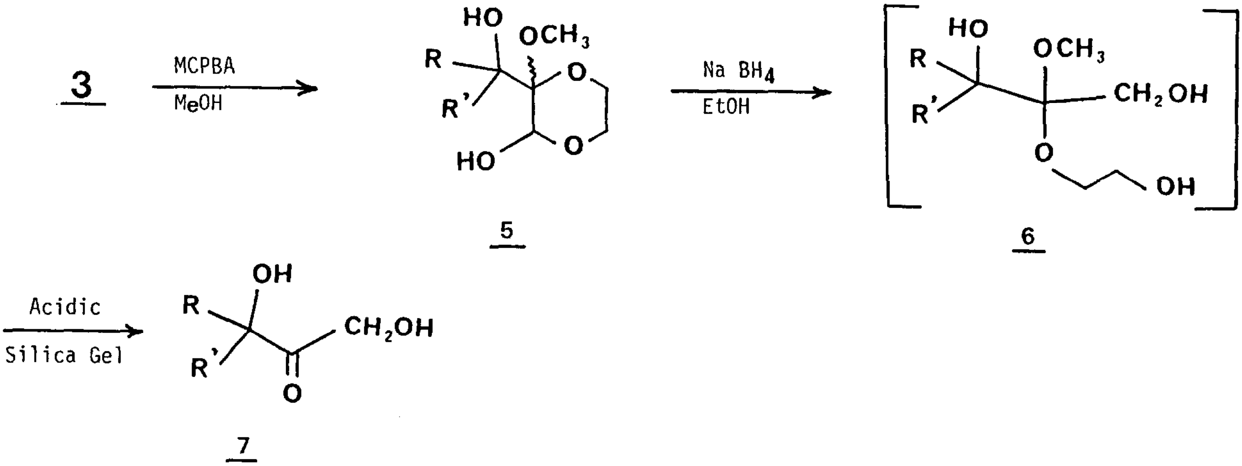
Summary : *Title compounds, 7, were prepared from ketones and aldehydes via the intermediate 3 by methanolic peracid epoxidation followed by NaBH$_4$ reduction and acidic hydrolysis . Application of this method to the preparation of the unnatural corticoid side chain was reported.*

Dihydro-1,4-dioxin-2-yl lithium 2, prepared by lithiation of dihydro-1,4-dioxin 1 with t-butyl lithium, reacts with ketones and aldehydes to give alcohols 3 . These adducts, which are moderately stable, undergo various transformations and are interesting synthetic intermediates. In a previous communication, we have described a method for the preparation of α-hydroxy ketones 4 from ketones and aldehydes via these intermediates (scheme I)[1] . We now report a new procedure, starting from the same alcohols 3, for the preparation of α,α'- dihydroxy ketones 7 .

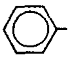
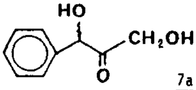
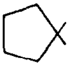
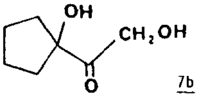
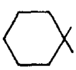
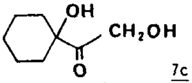
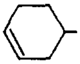
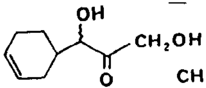
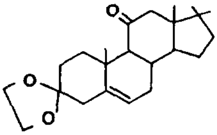
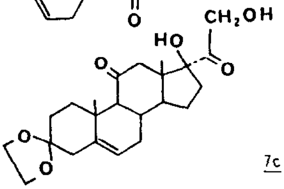
Scheme I



## Scheme II



## Table

| Entry | R | R' | 3 | Yield % | 5 | Yield % | α,α'-dihydroxy ketone 7 [6] | Yield %⁑ |
|---|---|---|---|---|---|---|---|---|
| a |  | H | 3a | 52 | 5a | 55 |  7a | 65 |
| b |  | | 3b | 56 | 5b | 55 |  7b | 45 |
| c |  | | 3c | 54 | 5c | 63 |  7c | 60 |
| d |  | H | 3d | 60 | 5d | 75 |  7d | 70 |
| e |  | | 3e | 64 | 5e | 82 |  7c | 90 |

⁑ The yields (not optimized) are given for the pure isolated products .

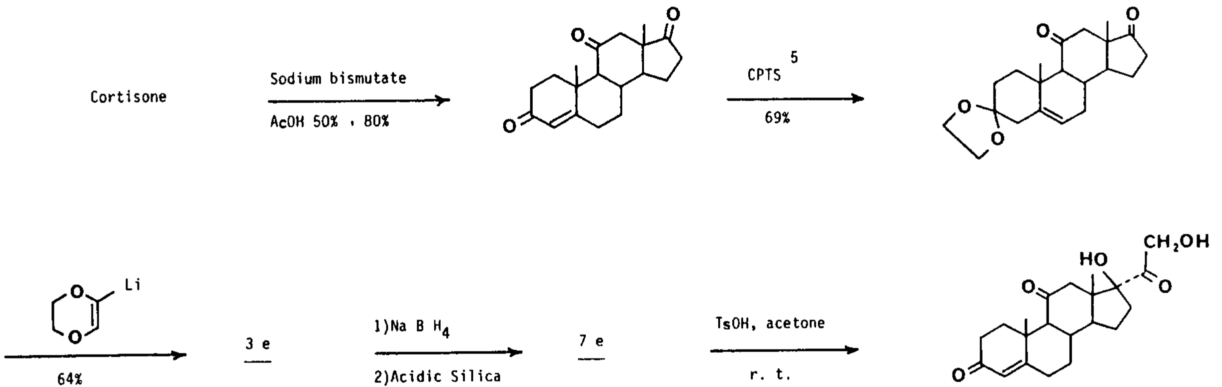
As in 2,3-dihydropyran [2] and enol ethers [3], allylic alcohols 3 smoothly undergo epoxidation with m-chloroperbenzoic acid in methanol at 0°C leading to the α-ketoaldehyde equivalent 5 (Scheme II) . $^1H$ and $^{13}C$ NMR spectra showed that 5, although homogenous in TLC, consisted of a mixture of two diastereoisomers . It is noteworthy that the epoxidation proceeded in a highly regio-selective manner : reaction always occured on the dioxene group double bond when another double bond is present in the molecule (Table, entries d and e) .

Sodium borohydride reduction of 5 and subsequent hydrolysis with wet silica gel [4] afforded α,α'-dihydroxy ketones 7 [6] in fair yields (see table) .

A typical experiment is as follows : adduct 3d (0,6g, ≃ 3mmol) in methanol (15ml) was epoxidized by known procedure [2] except that methanol was evaporated under reduced pressure before extraction with $CH_2Cl_2$. The crude product purified by flash chromatography (1:1 ethyl acetate-petroleum ether) affording 5d as a diastereomeric mixture (0,51g, 75% yield) . Understirring 5d (456 mg, 2mmol) in ethanol (15 ml) was reduced by solid $NaBH_4$ (75mg) for 1h. Evaporation of ethanol under reduced pressure and extraction with ethyl acetate, gave crude 6d which was hydrolyzed with wet silica gel (2g) in $CH_2Cl_2$ (6ml) and 10% aquous oxalic acid (7 drops)[4]. Flash chromatography of the crude product afforded pure α, α'-dihydroxy ketone 7d (240 mg, 70% yield) .

The utilization of the present reaction sequence, a conversion of carbonyl compounds to α, α'-dihydroxy ketones, is illustrated by the stereoselective synthesis of 17-epicortisone 8 with unnatural stereochemistry (Scheme III) .

Scheme III



8 Unnatural cortisone [6]
(17β,21-Dihydroxypregn-4-en-3,11,20-trione)

## References and Notes

1. For part II, see M. FETIZON, I. HANNA and J. RENS, Tetrahedron Lett. 1985, in the press .
2. A.A. FRIMER, Synthesis 1977, 578 .
3. F. HUET, A. LECHEVALLIER, J.M. CONIA, Synthet. Commun. 1980, 10, 83.
   G.M. RUBOTTOM, R. MARRERO, ibid. 1981, 11, 505.
4. F. HUET, A. LECHEVALLIER, M. PELLET, J.M. CONIA, Synthesis, 1978, 63.
5. T.J. NITZ, L.A. PAQUETTE, Tetrahedron Lett. 1984, 25, 3047.
6. All new compounds gave satisfactory analytical and spectral data .

   7a : oil, IR ($CCl_4$) 700, 710, 1110, 1715, 3040, 3070, 3540 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 4.25 (s,2H), 5.16 (s,1H), 7.30 (s,5H); $^{13}$C NMR ($CDCl_3$) $\delta$ 64.8 (t), 77.3 (d), 126.7 (d), 129.0 (d), 137.0 (s), 209 (s) .

   7b : m.p. 39-41°C (petroleum ether-ether); IR ($CCl_4$) 1710, 3500, 3620 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.87 (m, 8H), 3.0 (m, 2H), 4.59 (s, 2H); $^{13}$C NMR ($CDCl_3$) 24.4 (t), 39.4 (t), 64.9 (t), 86.4 (s), 214.2 (s) .

   7c : m.p. 88-89°C (ether-pentane); IR ($CCl_4$) 1710, 3520, 3620 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.61 (m, 10H), 2.73 (m, 2H), 4.51 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5 (t), 24.7 (t), 33.9 (t), 64.2 (t), 77.5 (s), 214.4 (s) .

   7d : m.p. 92-94° (ether); IR ($CCl_4$) 1715, 3025, 3380, 3440, 3530, 3640 cm$^{-1}$; $^1$H NMR (60MHz, $CDCl_3$) $\delta$ 1.08-2.41 (m, 7H), 3.06 (m, 2H), 4.21 (m, 1H), 4.40 (br. s, 2H), 5.61 (br. s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.8, 23.7, 24.9, 25.1, 25.5, 27.8, 37.7, 37.9, 66.0, 78.4, 125.2, 125.7, 126.6, 126.7 .

   7e : m.p. 239-241 (methanol); $[\alpha]_D$ = -40.5 (c = 0.3, pyridine); IR (Nujol) 3480, 3390, 1705, 1090 cm$^{-1}$; $^1$H NMR (Py-d5) $\delta$ 1.06 (s, 3H), 1.33 (s, 3H), 3.88 (s, 4H), 5.0 (br. s, 2H), 5.36 (m, 1H); $^{13}$C NMR (Py-d5) $\delta$ 15.2, 18.1, 24.7, 31.4, 32.3, 34.2, 35.2, 36.2, 37.1, 41.9, 48.1, 50.4, 51.9, 59.7 ($C_9$), 64.3 (2C, $C_{22}$, $C_{23}$), 67.8 ($C_{21}$), 88.7 ($C_{17}$), 109.5 ($C_3$), 120.9 ($C_6$), 140.9 ($C_5$), 209.2 ($C_{20}$), 217.5 ($C_{11}$) .

   8 : (unnatural cortisone) : m.p. 179-180 (benzene) ; $[\alpha]_D$ = + 108 (c = 0.27, abs. ethanol); IR ($CHCl_3$) 3420, 1710, 1665, 1615 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 0.90 (s, 3H), 1.40 (s, 3H), 4.50 (br. s, 2H), 5.70 (br. s, 1H) ; $^{13}$C NMR ($CDCl_3$) $\delta$ 14.7, 16.9, 23.6, 29.5, 31.6, 32.0, 33.5, 34.2, 36.6, 37.2, 38.0, 47.7, 50.8, 62.0 ($C_9$), 67.0 ($C_{21}$), 88.2 ($C_{17}$), 124.3 ($C_4$), 169.0 ($C_5$), 200.1 ($C_3$), 207.8 ($C_{20}$), 215.5 ($C_{11}$) .

(Received in France 18 July 1985)