Tetrahedron Letters,Vol.24,No.15,pp 1577-1580,1983 0040-4039/83/151577-04$03.00/0
Printed in Great Britain

REARRANGEMENT OF STEROIDAL EPOXIDES AND OPENING OF STEROIDAL KETALS BY ALKYLLITHIUMS

Herbert L. Holland* and Jahangir
Department of Chemistry, Brock University
St. Catharines, Ontario, Canada. L2S 3A1

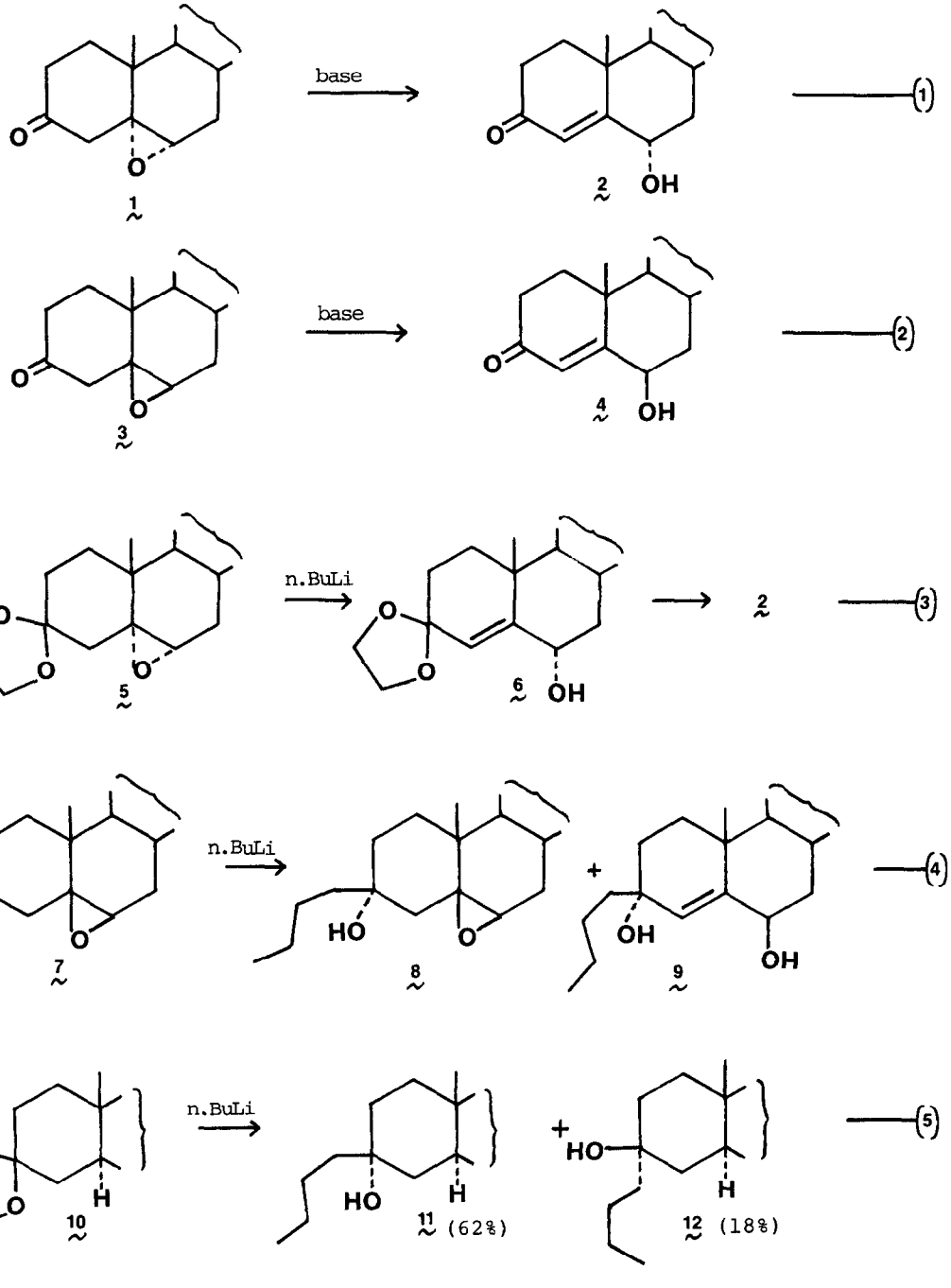
Abstract:
The ethylene ketal of 5,6α-epoxycholestan-3-one is converted to a ketalised Δ^4-6α-ol on treatment with n-BuLi. However, the corresponding β epoxide undergoes opening of the ketal ring in the same reaction. Methyl- and n-butyllithium also react with the ethylene ketal of 3-ketocholestanes to give 3-alkyl cholestan-3-ols. The stereoselectivity of this reaction is discussed and a mechanism involving a 1,2 hydride shift is proposed.

The base catalysed rearrangement of steroidal 5,6α-epoxy-3-ketones (1) to 6α-hydroxy-Δ^4-3-ketones (2) (Eqn. 1) and of the corresponding β epoxides 3 to give 6β alcohols 4 (Eqn. 2) are key steps in the preparation of these alcohols.[1,2] The mechanism of these reactions has been investigated in detail.[2]

We now report that a similar rearrangement occurs with the corresponding ketal (5),[3] a precursor of 1, when treated directly with n-BuLi (15 eq) in THF solution (30 min at 0°C, 2h at rt) (Eqn. 3). Neutral work-up afforded only 6 whereas work-up under hydrolytic conditions gave 2 (76% from 5). Treatment of 5 with LDA gave a comparable result. The regioselectivity observed in the epoxide opening of 5 may be attributable to a directing influence of the ketal oxygen atoms, as the analogous C-3 unsubstituted 5,6α epoxide is rearranged by base to both Δ^4 and Δ^6 products.[4,5]

Whereas reaction of the corresponding 5,6β epoxide 7[3] with LDA resulted in the anticipated formation of the alcohol 4 (following hydrolytic work-up), an analogous reaction did not occur with n-butyllithium. In this case, opening of the ketal occurred to give the 3β-n-butyl derivatives 8 (10% isolated yield) and 9 (76% isolated yield) (Eqn. 4).

The reason for the cleavage of the supposedly base stable ketal by butyllithium may be rationalised if reaction of 7 occurs from conformation A, Fig. 1. Then not only is the stereospecificity explicable, but also the reason for the predominance of ketal cleavage over epoxide opening becomes apparent. Such a


base
1
2
OH
(1)
base
3
4
OH
(2)
n.BuLi
5
6
OH
2
(3)
n.BuLi
7
HO
8
+
OH
OH
9
(4)
n.BuLi
10
H
HO
H
11 (62%)
+
HO
H
12 (18%)
(5)

conformation for ring A of 3β substituted 5,6β epoxy steroids is supported by ^{13}C nmr data,[4,6] notably the absence of the γ gauche effect at C-1 anticipated for the alternative half-chair conformation (B, Fig. 1). The stereospecific introduction of the 3β alkyl substituent is now consistent with attack occurring only from the less hindered β face of the molecule;[7] concerted epoxide opening is disfavoured because the dihedral angles between the C-4 hydrogens and the epoxide oxygen (60° for C-4Hβ, 40° for C-4Hα) are incompatible with those required for a concerted base catalysed reaction by either a syn (preferable)[8] or anti[2] mechanism. The α isomer 5, however, can rearrange readily by a mechanism involving removal of the C-4α hydrogen, located syn to the epoxide oxygen.

Opening of the ketal ring also occurred in the absence of an epoxide grouping. Thus the ketal 10 is opened by butyllithium (Eqn. 5) and methyllithium (Eqn. 5) (reaction time, 4 d) to give the tertiary alcohols 11-14. In the latter case, unreacted starting material (40%) was also obtained. The product distribution in Equations 5 and 6 is consistent with steric control of the reaction; the smaller methyl reagent shows less steric preference for attack from the more open β face of 10. The ratio of α to β alcohols in Equation 6 (1.15:1) is close to that obtained by Barton and coworkers[9] for methyl Grignard addition to the corresponding 3-ketone (1.32:1).

The opening of a ketal ring by an alkyllithium reagent has little precedent; a mechanistic precedent is, however, provided by the route established by Murai *et al.*[10] for the intramolecular opening of an ethylene ketal (Eqn. 7), and the ketal openings reported herein may proceed by an analogous mechanism.

The reaction reported herein has synthetic utility in that it is not necessary to deprotect a ketalised carbonyl in order to achieve the addition of an alkyllithium reagent. The application of this procedure to the generation of tertiary alcohols directly from ketals is currently being investigated.

All the steroids referred to herein belonged to the normal cholestane series, and gave satisfactory spectral (^{1}H nmr, ^{13}C nmr, ms, ir) and analytical data.

Acknowledgements

Financial support was provided by the Natural Sciences and Engineering Research Council of Canada. We are grateful to Mr. T. Jones for technical support.

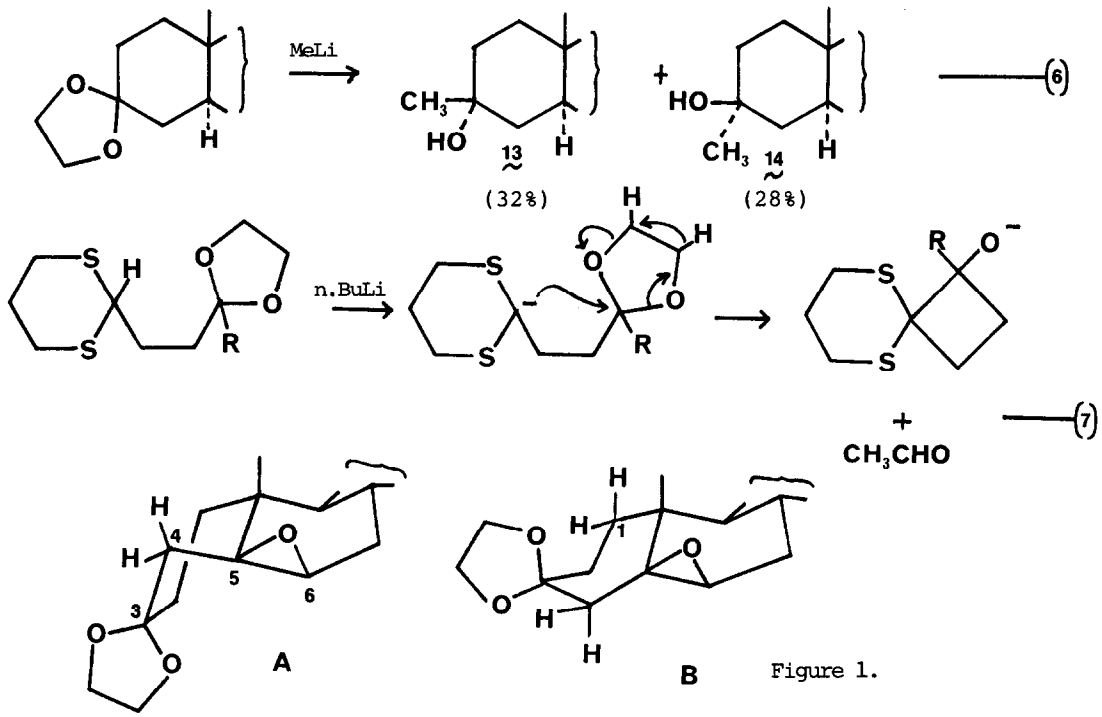


Figure 1.

References

1. D. H. R. Barton and Y. Housiner. J. Chem. Soc. Perkin Trans. 1, 919 (1972).
2. P. B. D. de la Mare and R. D. Wilson. J. Chem. Soc. Perkin Trans. 2, 975 (1977).
3. K. J. Sax, R. Antonucci, S. Bernstein, R. Little and W. H. William. J. Org. Chem. 17, 1314 (1952).
4. H. L. Holland and Jahangir. Unpublished data.
5. M. R. Detty. J. Org. Chem. 45, 924 (1980).
6. H. L. Holland, P. R. P. Diakow and G. J. Taylor. Can. J. Chem. 56, 3121 (1978).
7. D. N. Kirk and M. P. Hartshorn. Steroid Reaction Mechanisms, Elsevier Publishing Co., Amsterdam, 1968.
8. R. T. Thummel and B. Rickborn. J. Org. Chem. 37, 3919 (1972).
9. D. H. R. Barton, A. Campos-Neves and R. C. Cookson. J. Chem. Soc. 3500 (1956).
10. A. Murai, M. Ono and T. Musamura. J. Chem. Soc. Chem. Commun. 573 (1977).

(Received in USA 24 January 1983)