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A NOVEL α-ALKYLATION OF α,β-EPOXY KETONES

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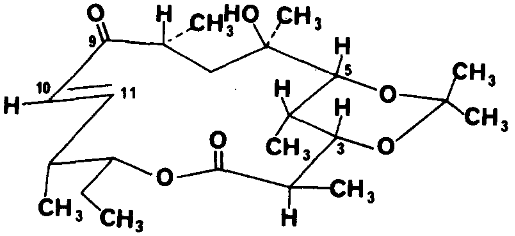
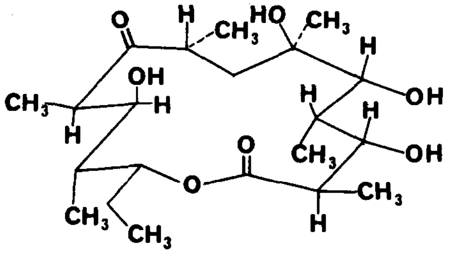
In connection with studies on the total synthesis of the aglycone of erythromycin B, erythronolide B (II), it was of interest to devise a method for the conversion of the α,β-unsaturated ketone I to II. The ketone I is an especially attractive synthetic intermediate for several reasons including accessibility from an acyclic precursor.[1] Alkaline peroxidation of I can be expected to form stereospecifically the 10,11β-oriented epoxide[1] placing the substituents at C-11 in the required stereo-arrangement. It would only remain to replace the C-10 oxygen substituent by methyl with retention of configuration and to cleave the acetonide grouping by the known procedure[1] to complete the synthesis of II. Because the introduction of the required methyl group is not feasible using conventional methods, a new approach was sought.

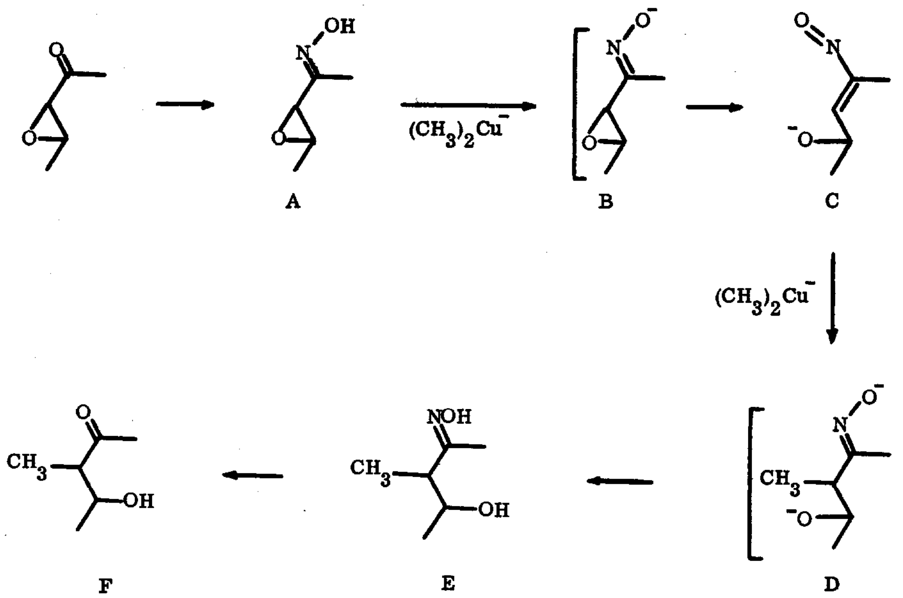


I



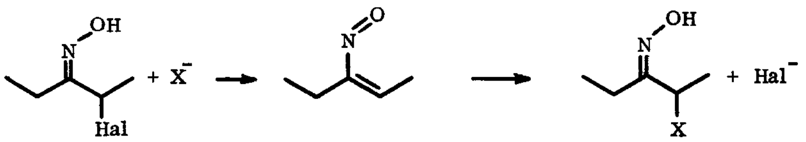
II

An attractive possibility for accomplishing the needed conversion is outlined in Scheme 1 which utilizes the oxime (A) corresponding to an α,β-epoxy ketone. Reaction of this ketoxime with dimethylcuprate (Gilman) reagent was expected a priori to proceed via the deprotonated oxime (B) to the α,β-unsaturated nitroso system (C) and thence by conjugate addition of methyl Gilman reagent to the dianion



Scheme 1

(D) of the β-hydroxy-α-methyl ketoxime (E), hydrolysis of which would provide the desired product F. Reasonable analogy exists for the critical stage of this process in the form of the well-known nucleophile (X^-) induced elimination-addition reaction of α-halo oximes[2,3] (Scheme 2). Further, conjugate addition of methyl to the vinyl nitroso intermediate C as opposed to addition to nitrogen would seem to be especially favorable with a cuprate reagent.[4] The stereochemistry expected from such a process as applied to the erythronolide case coincides with that which is required.[1,5] Finally, the very unreactive[1] lactone carbonyl group in the macrolide ring should not be affected by the Gilman reagent.[6]

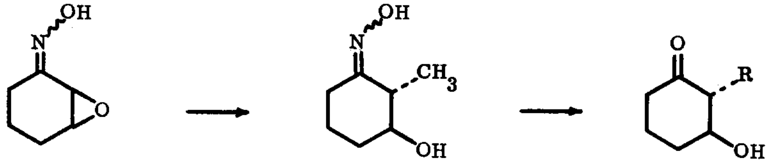


Scheme 2

In fact, the reaction of a variety of simple α,β-epoxy ketoximes with Gilman reagents has been found to follow the predicted course and to constitute a highly useful route to α-alkylated β-hydroxy ketones. The following procedure involving the conversion of 2,3-epoxycyclohexanone to trans-2-methyl-3-hydroxycyclohexanone is illustrative:

2,3-Epoxycyclohexanone was converted to the corresponding oxime (III) by treatment with 1.1

equiv of hydroxylamine hydrochloride and 2.2 equiv of sodium acetate in methanol (10 ml/g of $HONH_3Cl$) at 0° for 30 min. Isolation of crude product by extractive work-up and recrystallization from pet. ether--ether gave pure III, mp 84-85°, in 95% yield. Addition of a solution of III in ether (40 ml/g of III) to 0.5-M dimethylcopperlithium[4] (5 equiv) in ether at -25° and reaction at that temperature for 1.25 hr followed by quenching (below -25°) with a cold solution (10%) of acetic acid (20 equiv) in ether and filtration afforded an ethereal solution of oxime IV. Evaporation of solvent and treatment of crude IV in tetrahydrofuran with an aqueous solution of 2 equiv of titanium trichloride and 12 equiv of ammonium acetate at 0°[7] for 1 hr gave after evaporation of solvent 90% of trans-3-hydroxy-2-methylcyclohexanone (V) as a colorless oil of 90-95% purity. Pure β-hydroxy ketone V[8] can be obtained by chromatography on silica gel (R_f for III and V, 0.47 and 0.36, respectively, using ether for plate development); found, ir max for CO at 1708 cm^{-1} in $CHCl_3$; pmr spectrum $J_{2,3}$ = 9 Hz, $J_{3a,4a}$ = 9 Hz, $J_{3a,4e}$ = 4 Hz.



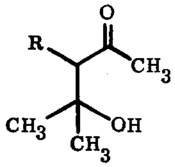
III

IV

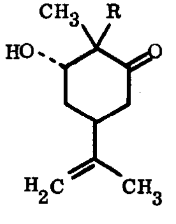
V, R = CH_3
VI, R = n-C_4H_9

By an analogous procedure the epoxy ketoxime III was converted to trans-3-hydroxy-2-n-butylcyclohexanone (VI) in 85% yield using di-n-butylcopperlithium as reagent (5 equiv, 4 hr at -25°).

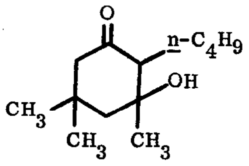
In addition, the α,β-epoxy oxime derived from mesityl oxide was converted to the β-hydroxy ketones VII (Me_2CuLi, 5 equiv in ether, -25°, 7 hr, 85% yield) and VIII (Bu_2CuLi, 5 equiv in ether, -25°, 4.5 hr, 60% yield). Similarly, the oxime of α,β-epoxycarvone[9] was transformed into the β-hydroxy



VII, R = CH_3
VIII, R = n-C_4H_9



IX, R = CH_3
X, R = n-C_4H_9



XI, R = n-C_4H_9

ketone IX (85% yield) and also the β-hydroxy ketone X (50% yield as a mixture of diastereomers in a ratio of *ca.* 2 : 1). Finally, the oxime of epoxy isophorone yielded 80% of XI (with di-*n*-butylcopperlithium) as a mixture of two diastereomers.

The β-hydroxy ketones reported above are in general rather unstable and easily dehydrated to enones. In consequence, the new method described herein also constitutes a process for the α-alkylation (*vs.* α'-alkylation) of α,β-enones. We hope to describe in due course the application of the epoxy ketoxime alkylation to the total synthesis of macrolides such as erythronolide B (II).[10]

References

1. See E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *J. Amer. Chem. Soc.*, **97**, 654 (1975).
2. See M. Ohno, N. Naruse, and I. Terasawa, "Organic Syntheses," John Wiley and Sons, Coll. Vol. V, p 266.
3. (a) O. Wallach, *Ann.*, **306**, 278 (1899); (b) G. Matthaipoulos, *Chem. Ber.*, **31**, 2396 (1898); (c) H. Korten and R. Scholl, *ibid.*, **34**, 1901 (1901); (d) A. Dornow and H. D. Jorden, *ibid.*, **94**, 76 (1961).
4. G. H. Posner, "Organic Reactions," John Wiley and Sons, Vol. 19, p 1.
5. For evidence of strong conformational control of reactions in the erythronolide series, see E. J. Corey and L. S. Melvin, Jr., *Tetrahedron Lett.*, 929 (1975).
6. G. H. Posner, Ph.D. dissertation, Harvard University, 1968.
7. (a) J. E. McMurray and J. Melton, *J. Org. Chem.*, **38**, 4367 (1973); (b) G. H. Timms and E. Wildsmith, *Tetrahedron Lett.*, 195 (1971).
8. Satisfactory infrared (ir), proton magnetic resonance (pmr), and mass spectroscopic data were obtained for V and the other β-hydroxy ketones obtained in this study.
9. E. Klein and G. Ohloff, *Tetrahedron*, **19**, 1091 (1963).
10. This work was assisted financially by the National Institutes of Health.