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REGIO AND STEREOSPECIFIC SYNTHESIS OF 11β SUBSTITUTED 19 NORSTEROIDS

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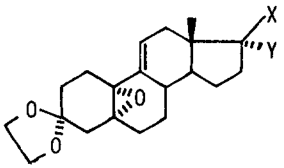
Summary : Treatment of 5α 10α epoxy Δ9 (11) steroids with lithium organocuprates or copper catalyzed Grignard reagents effects exclusive 11β substitution in excellent yield.

Opening vinyl oxiranes with dimethylcopperlithium has been shown to lead mainly to allylic substitution (SN_2') in the case of 3,4 epoxy-1-butene[2] and to a mixture of SN_2 and SN_2' type products (in a ratio close to 1:1) in the case of 1,2 epoxy-3 cyclohexene[3].

The reaction was used recently by J. F. Normant et al. in a synthetically useful scheme[4]. This is one of the reasons which has prompted us to disclose some of our results in the steroid field.

The reaction of an organocuprate reagent with steroidal epoxides of type (1) proceeds with complete regio and stereospecificity, leading exclusively to the 11β substitute compound (2). As an illustration of this, epoxide (1a), when treated with diphenylcopperlithium for 30 min at 0°C in Et_2O-THF yielded 82.5 % of the 11β phenylsteroid (2a)[5]. Evidence of the β configuration of the substituent is given by the large shielding effect in the proton resonance of the 18 methyl group (δ = 0.57 ppm in $CDCl_3$). Similarly the methyl and ethyl substituents were introduced in yields of 100 and 85 % respectively, in chromatographically isolated compounds.

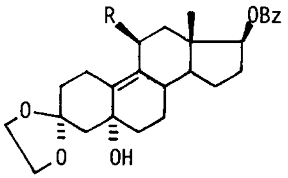
Compounds of type (2) were deketalized and concomitantly dehydrated by short refluxing in 90 % EtOH in the presence of a sulfonic resin, affording the corresponding dienones of type (3). The chemical shift of the 18 methyl group is 0.625 ppm for (3a), 1.15 ppm for (3b) and for (3c), as compared to 1.08 ppm for the unsubstituted analog (3d).



1

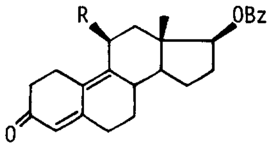
a) X = OBz
Y = H

b) X = CN
Y = $OSiMe_3$



2

a) R = Ph
b) R = Me
c) R = Et
d) R = H



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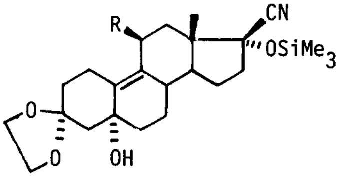
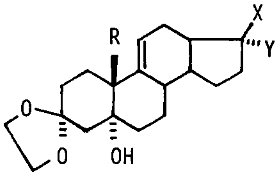


4

a) R = Et
b) R = Ph
c) R = vinyl
d) R = thienyl
e) R = benzyl
f) R = t Bu



5

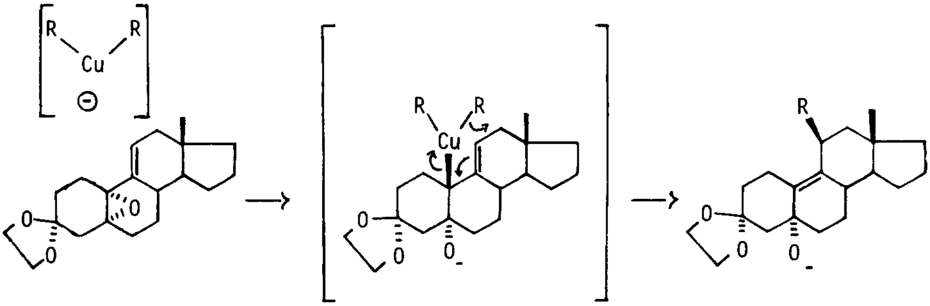
a) R = Me
b) R = CH_2Ph

As some copper reagents are inconvenient to prepare, we investigated the copper catalyzed reaction of Grignard reagents with the same type of epoxides. We found that the reaction does indeed proceed smoothly at temperatures between -40°C and -10°C in THF solution with 5 to 10 % copper (I) chloride per mole RMgX, as a catalyst. To mention one example, epoxide (1b)[6b] afforded compounds (4a) to (4e) (δ 18 Me : 1.06 ppm, 0.54 ppm, 0.95 ppm; 0.66 ppm, 1.17 ppm respectively) in essentially quantitative yield. It is worth noting that epoxides of type (1) react with the uncatalyzed Grignard reagents (i.e. CH_3MgBr or EtMgBr) to give the 10β substituted steroids (5)[6].

In no instance could any 10β substituted isomer be detected in the copper catalyzed reaction. This is especially surprising in the case of the very reactive benzylmagnesium bromide, where the addition of a catalytic amount of copper I chloride is able to shift the substitution completely from the 10β (product (5b); 18 Me at 0.79 ppm) to the 11β position (product (4e)).

The high yields and remarkable regio and stereospecificity, coupled with a rather low sensitivity to steric hindrance [the 11β ter-butyl group could be introduced quantitatively using $(tBu)_2CuLi$ at -25°C for one night, yielding (**4f**)], suggest an initial nucleophilic displacement[7] of the epoxide at C_{10} followed by an allylic rearrangement as shown in the scheme.

The fact that the reaction is not inhibited by addition of radical traps such as triphenylmethane or triethylsilane, shows that there are probably no typically free radical intermediates.



Finally the fact that the corresponding 11α alkyl steroids are available from the epimeric 5β 10β epoxides[8], leaves no doubt about the configuration of the substituents in position 11.

A detailed account of this reaction and its use in the synthesis of novel biologically active steroids is in the process of being prepared and will be published elsewhere.

Acknowledgements

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Notes and References

1. Postdoctoral Fellow 1975 - 1976.

2a. R. J. Anderson, J. Amer. Chem. Soc. 92, 4978 (1970).

b. R. W. Herr and C. R. Johnson, ibid 92, 4979 (1970).

3a. B. Rickborn and J. Staroscik, ibid 93, 3046 (1971).

b. C. R. Johnson and D. M. Wieland, ibid 93, 3047 (1971).

c. The regioselectivity is however increased by using mixed cuprates as shown by J. P. Marino and D. M. Floyd in Tetrahedron Lett., 675 (1979).

4a. A. Alexakis, G. Cahiez and J. F. Normant, Tetrahedron Lett., 2027 (1978).

b. G. Cahiez, A. Alexakis and J. F. Normant, Synthesis, 528 (1978).

5. Satisfactory analytical and spectral data have been obtained for all new compounds; yields are not optimized.

6a. L. Nédélec and J. C. Gasc, Bull. Soc. Chim. France, 2556 (1970).

b. J. C. Gasc and L. Nédélec, Tetrahedron Lett., 2005 (1971).

7a. C. R. Johnson, R. W. Herr and D. M. Wieland, J. Org. Chem. 38, 4263 (1973).

b. R. G. Pearson and C. D. Gregory, J. Amer. Chem. Soc. 98, 4098 (1976).

8. G. Costerousse, A. Farcilli and G. Teutsch, unpublished results.

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