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REGIO AND STEREOCHEMICALLY CONTROLLED RING OPENING OF EPOXIDES WITH GRIGNARD REAGENTS. STEREOCONTROLLED SYNTHESIS OF THE STEROID SIDE CHAINS. FIRST STEREOSELECTIVE HEMISYNTHESIS OF 20S ISOLANOSTEROL.

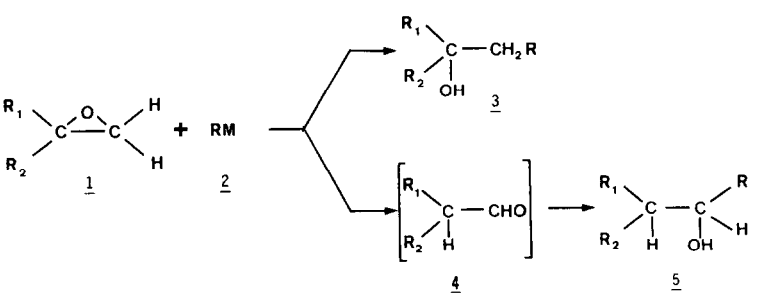
*J.R. Schauder and A. Krief**

Department of Chemistry
Facultés Universitaires N.D. de la Paix
Rue de Bruxelles, 61, B-5000-Namur, Belgium

Title compound was efficiently prepared taking advantage of a stereoselective hydride shift during the reaction between the Grignard reagent derived from ethoxyacetylene and an epoxide. The solvent was found to have a crucial role in this and related reactions.

Epoxides [1-3] react in a versatile manner with organometallics, producing depending upon the nature of the reagents and the conditions used, alcohols 3 resulting from nucleophilic ring opening or rearranged alcohols 5 arising from the attack of the organometallics on an intermediary carbonyl compound 4 (Scheme 1).

SCHEME 1



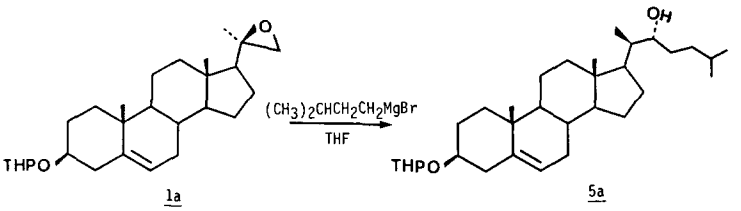
1 2 3 4 5

The first type of reaction is not clearly reported in the case of Grignard reagents. Blaise [4a] in 1902 had mainly obtained the corresponding halohydrins if the reactions were conducted in ether at room temperature ; and later, Grignard [4b,4c] found that an exothermic reaction takes place on distillation of ether, producing the rearranged alcohols 5. In several instances depending upon the nature of the reagent and the conditions used, different ratio of the halohydrins and the two alcohols 3 and 5 are obtained.

Recently, Koreeda [5] has described that the reaction of isoamylmagnesium bromide in THF with the epoxide 1a derived from pregnenolone produced a rearranged alcohol 5a and interestingly found that a 100% stereoselective hydride shift occurred during that transformation (Scheme 2).

We were interested to use such reaction for the synthesis of 20S isolanosterol, an unnatural compound needed for comparison purposes in our work related to sterol biosynthesis.

SCHEME 2



1a 5a

The strategy planned for its preparation required the degradation of the lanosterol side chain till the carbon C-20 in order to destroy the chiral center and then the stereoselective building of the same side chain but possessing now the unnatural 20S stereochemistry.

In relation with Koreeda's work [5] on cholesterol and our own results reported herein, we decided to use as the key step the reaction of Grignard reagent on the epoxide 8 derived from lanosterol.

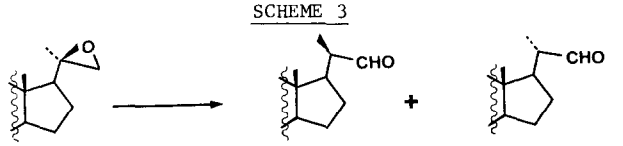
The one step introduction of the C_5 carbon chain from isopentenyl magnesium bromide was not attempted since this ambident nucleophile is known [6] to react with carbonyl compounds through its more substituted carbon atom.

We decided therefore to complete the side chain stepwise, using ethoxyethynyl magnesium bromide first and later isopropylidene triphenyl phosphorane. Thus the ketone 6 (Scheme 3) available from lanosterol in three steps [7] (21% overall yield) was stereoselectively transformed to the epoxide 8 using a set of reactions already described in our laboratory [8] and known to preclude an equilibrium between the ketone and its enolate (especially its C_{17}-C_{20} one). Reaction of methylselenomethyllithium [8] (1.8eq/THF/-78°/4h) with the ketone 6 followed by formation of the β-hydroxyselenonium salt (CH_3OSO_2F,1.5eq/ether,0° to 20°,2hr) and its reaction with base (aq.KOH/ether, 20°,14hr) affords the desired epoxide 8 in 60% overall yield. However, we were unable to obtain the desired alcohol 10 when reacting ethoxyethynyl magnesium bromide [9] with the epoxide 8 under the conditions described by Koreeda (THF,80°,4h). We therefore decided to look in a more detailed manner to that reaction, to use as a model the readily available epoxide 1a derived from pregnenolone and to repeat the work of Koreeda [5].

The yield of the expected alcohol 5a was rather low (20%) when we reacted[5] isoamyl magnesium bromide in THF (0°,0.25hr;20°,0.25hr;80°,4h) several unidentified compounds being formed.

We planned to perform the reaction in two discrete steps and to synthesize first the 20R aldehyde 4a, the hypothetical intermediate in the previous reaction. We were disappointed since a mixture of the two isomeric compounds 20R/20S (Scheme 3) was formed whatever the conditions used [5].

SCHEME 3



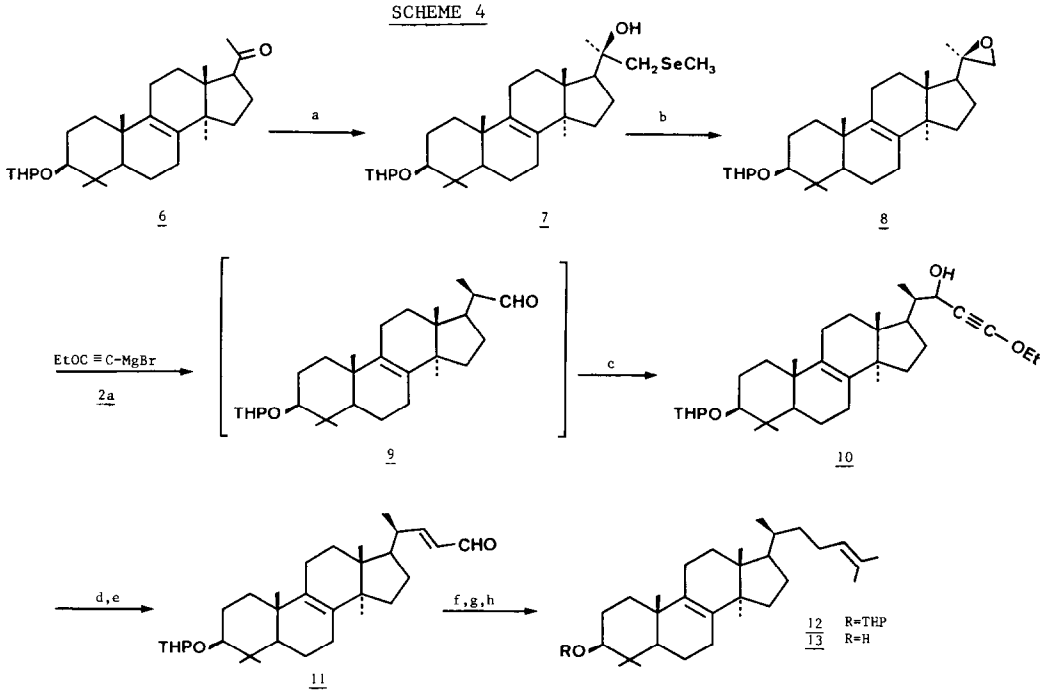
1a 20R 4a 20S

[$BF_3.Et_2O/CH_2Cl_2$, -78°, -40°, 20°, respectively 69%, 70%, 75% overall yield of 4a (20R/20S, 70/30, 64/36, 62/38); $BF_3.Et_2O$/Benzene,5°,72% (47/53); $BF_3.Et_2O$/ether, 20°,59% (65/35); $BF_3.Et_2O$/THF,20°, 70% 51/49), $MgBr_2$/ether,-40° to 0°, 60% (70/30); 0° to 20°,77% (80/20)].

However, no reaction was observed if the reaction is conducted in THF at 20°, but a 65% yield of the corresponding bromohydrin is formed under forced conditions (80°,18h).

These last results were particularly instructive since they show the crucial role of the solvent in controling the reaction of magnesium salt with epoxides. This observation led us to perform the reaction between the epoxide 1a and Grignard reagents in ether at 20° instead of in THF at reflux. The results were encouraging especially if an ether/benzene mixture (3/1) was used (20°, 1h) (Scheme 2). The later conditions, which were in fact the ones originally used in Koreeda's laboratory [10a] were found to be general [10b] and suitable for the synthesis of the acetylenic alcohol 10 (Scheme 2). The synthesis of 20S isolanosterol from that stage was achieved as follows (Scheme 4).

SCHEME 4



a) $LiCH_2SeCH_3$, 1.8eq/THF,-78°, 4h, 75% yield ; b) 1° CH_3OSO_2F, 1.5eq/ether, 0° then 20°, 2h, 2° KOH/ether, 20°, 14h, 79% yield ; c) EtO-C≡C-MgBr, 2.7eq/ether-benzene 3-1, 20°, 1h, 67% yield ; d) $LiAlH_4$, 4eq/ether, 20°, 1h ; e) H_2SO_4 2M/ether, 20°, 2h, 62% yield from 20 ; f) H_2/Pd $BaSO_4$/ethylacetate, 20°, 20 min., 81% yield ; g) $P\phi_3{=}C{<}^{CH_3}_{CH_3}$, 13eq/THF, -78°, 0.5h then 20°, 1.5h, 74% yield ; h) P.T.S.A., catalytic amounts/CH_2Cl_2-MeOH 1-1, 20°, 2h, 93% yield.

Reduction of the ynolether 10 by lithium aluminum hydride [11] followed by acidic hydrolysis of the resulting γ-hydroxy enolether [11] produced the α,β-unsaturated aldehyde 11 in 62% overall yield. The stereochemical outcome of the whole set of reactions has been studied at that stage. the aldehyde 11 was found to be a 92/8 mixture of the 20R/20S isomers. The 20R isomer (precursor of the 20S isolanosterol 13)has been obtained free from any other compound (including its 20S epimer) by HPLC purification (column RP SIL 18 HL, 40cm x 1cm, eluant : acetonitrile-water 96-4, rt = 35 min. , flow rate, 7ml/min.). The desired 20S isolanosterol 13 was finally obtained in 3

steps which include : 1) selective reduction of the Δ22 bond - 2) Wittig reaction of the resulting aldehyde with isopropylidene triphenyl phosphorane and 3) removal of the tetrahydropyrannyl protecting group (56% overall yield).

No isomerization at C-20 was observed during these reactions especially at the reduction stage since 20S isolanosterol 13 appeared in gas chromatography (25m x 0.25mm, glass capillary column statically coated with SE 30, column temp. 225°, carrier gas : He, flow rate, 12 ml/min) as a single peak (rt:8.2min.) different from the one of the natural lanosterol possessing the 20R stereochemistry (rt:9.1min.). The spectroscopic data [14] completely agree with the proposed structure for 13.

Moreover in order to ascertain the validity of all the steps presented we have repeated the just reported reactions on the 20S epoxide [15] and we obtained that time the lanosterol with the natural 20R stereochemistry. We have checked the stereochemical purity at the enal stage and found that the hydride shift occurs less stereoselectively during that epoxide ring opening by ethoxyethynyl magnesium bromide (80/20 mixture of the 20S/20R stereoisomer).

Our biochemical results will be soon reported.

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9. Prepared on reacting ethyl magnesium bromide in ether with a commercially available solution of ethoxyacetylene (Merck) freshly distilled, in benzene.
10. a) Personal communication of Professor Koreeda after completion of our work.
    b) Results to be published.
11. W. Sucrow and B. Radüchel, Chem. Ber., 102, 2629 (1969).
12. 20S isolanosterol has in fact already been prepared in a non stereoselective manner. This synthesis appeared to yield 20S isolanosterol along with some unidentified material [13]. We thank Prof. D. Arigoni for communication of these informations.
13. Q. Branca (Ph.D. Thesis, E.T.H., Zürich 1970) and F. Marazza (Ph.D. Thesis, E.T.H. Zürich, 1977).
14. 20S isolanosterol mp (from MeOH) : 152° ; $[\alpha]_D^{20}$ ($CHCl_3$) = +31.7°
    20R lanosterol mp (from MeOH) : 139° ; $[\alpha]_D^{20}$ ($CHCl_3$) = +60°
    The ^1H NMR spectra ($CDCl_3$) of the 2 isomers are similar. The ^{13}C NMR spectra ($CDCl_3$) are identical except the following differences (number refers to ppm, TMS was used as internal standard).
    20S isolanosterol C_{17} : 50.0 C_{19} : 18.9 C_{20} : 35.8 C_{22} : 35.6
    20R lanosterol C_{17} : 50.4 C_{19} : 18.6 C_{20} : 36.3 C_{22} : 36.3
15. This epoxide was obtained stereoselectively (> 95%) on reaction of corresponding C-20,C-22 olefin with osmium tetroxide (1.2 eq., 10°, 1hr, 85% yield) followed by basic cyclisation of the resulting C-20,C-22 diol via its C-22 monomesylate (74% overall yield).

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