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ON THE STERIC COURSE OF ADDITION OF GRIGNARD REAGENTS ONTO α,β-DIALKOXY ERYTHRO AND THREO CHIRAL ALDEHYDES. SYNTHESIS OF (+) AND (-)-EXO AND ENDO-BREVICOMIN

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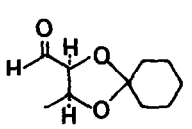
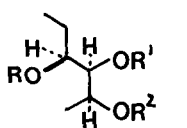
Addition of $BrMgCH_2CH_3$ onto the erythro and threo aldehydes (1) and (2) to form (3)+(6) and (9)+(10) proceeds with 6:4 and 8:2 threo-erythro selectivity, respectively. From (3) and (6), (2S) and (2R)-2-benzyloxy butyraldehyde (13) and (14) have been prepared. Addition of $ClMgCH_2CH_2CH(C\overset{O}{\underset{O}{\rangle}})CH_3$ onto (13) and (14) proceeds with 6:4, threo-erythro selectivity, to give after preparative gas chromatographic separation, the enantiomeric forms of exo- and endo-brevicomin (19), (21) and (20), (22).

In the preceding paper[1] we have shown that addition of allylmagnesium bromide onto the erythro and threo aldehydes (1) and (2), bearing α and β-oxygen substituents embedded into a pentacyclic ketal framework, takes place with different degrees of stereocontrol in the diastereoisomeric composition of the reaction products. Due to the relevance to the chiral synthesis of natural products of the addition of carbon nucleophiles onto the carbonyl carbon of α- and β-alkoxy carbonyl compounds as a means of stereocontrolled chain elongation,[2] we have been studying the steric course of the addition of ethylmagnesium bromide onto (1) and (2). We present now these results, together with the synthetic applications of the reaction products, which allowed the enantiomeric forms of the western pine beetle pheromone exo and endo-brevicomin (19), (21) and (20) and (22) to be obtained.



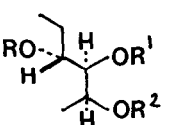
(1)



(3) R= H; R^1-R^2=

(4) R= $CH_2C_6H_5$; R^1-R^2= 

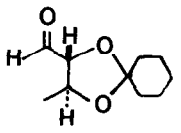
(5) R= $CH_2C_6H_5$; R^1= R^2= H



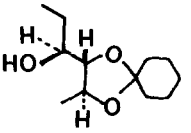
(6) R= H; R^1-R^2= 

(7) R= $CH_2C_6H_5$; R^1-R^2= 

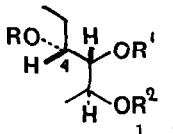
(8) R= $CH_2C_6H_5$; R^1= R^2= H



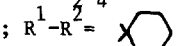
(2)



(9)



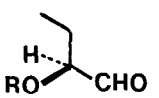
(10) R= H; R^1-R^2= $(CH_2)_4$

(11) R= $CH_2C_6H_5$; R^1-R^2= 

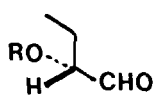
(12) R= $CH_2C_6H_5$; R^1= R^2= H

Addition of $BrMgCH_2CH_3$ in tetrhydrofuran at -78°C onto (1) gave a 6:4 mixture (75%) of two easily separable oily products (3) and (6), shown to be the threo and erythro isomers, respectively Indeed, compound (3), $[\alpha]^{\dagger}$ 5.8°, once benzylated (NaH, dimethylformamide, $C_6H_5CH_2Cl$) (90%) to oily (4), $[\alpha]$ -55° and quantitatively hydrolysed (50% aqueous acetic acid) to (5), $[\alpha]$ 44.6°, gave, upon HIO_4 cleavage in dry tetrahydrofuran, in 85% yield the (2S)-aldehyde (13), $[\alpha]$ -95°. The absolute stereochemistry of the aldehyde (13) is based on its conversion into (2S) 1,2-butandiol.[3] Similarly, the erythro alcohol (6), via the O-benzylderivative (7), $[\alpha]$ -19.5 and the diol (8), $[\alpha]$ -18.6, gave, eventually, the (2R)-aldehyde (14), $[\alpha]$ 93.8°.

The threo aldehyde (2) reacted with $BrMgCH_2CH_3$ in THF at -78°C and -120°C giving rise, in the same 8:2 ratio, to the threo and erythro adducts (10) and (9), respectively. Again, the major isomer (10) was degraded via (11) and (12), to the (2R)-aldehyde (14), thus assigning the stereochemistry at C-4.



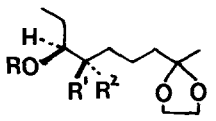
(13) R= $CH_2C_6H_5$



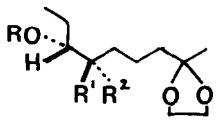
(14) R= $CH_2C_6H_5$

The enantiomeric forms of α-benzyloxy butyraldehyde (13) and (14) were reacted in THF at -78°C with the Grignard reagent $ClMgCH_2CH_2CH_2(C\overset{O}{\underset{O}{\langle}})CH_3$ in order to determinate the degree of stereocontrol. From the reaction of (13) and (14) the adducts (15) and (16), respectively, were obtained. These materials were shown by g.l.c. analysis to be a 6:4 mixture of isomeric products. The mixture (16), upon acid hydrolysis gave the ketone (18), $[\alpha]$ -6.7°. Subsequent debenzylation (H_2-Pd/C 10%) gave a 6:4 mixture of cyclic ketals. Preparative gas chromatographic separation allowed to identify the most abundant component as (1R,7R) exo-brevicomin (21), $[\alpha]$ 70° (c 2, Et_2O) (lit.[4] 84.1°). The minor component was identified on the basis of the n.m.r. data as (1R,7S) endo-brevicomin (22), $[\alpha]$ -76.7° (c 2, Et_2O). From the adduct (15) (prepared from a

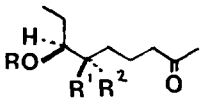
sample of (13) showing $[\alpha]$ -83°), via (17), (1S,7S)exo-brevicomin (19), $[\alpha]$ -66° (c 2, Et_2O) (lit.[4] -80.6), and (1S,7R)endo-brevicomin (20), $[\alpha]$ 74° (C 2.2, Et_2O) were obtained.



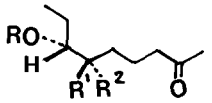
(15) R= $CH_2C_6H_5$; R^1,R^2= H,OH



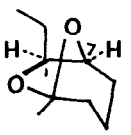
(16) R= $CH_2C_6H_5$; R^1,R^2= H,OH



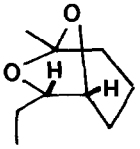
(17) R= $CH_2C_6H_5$; R^1,R^2= H,OH



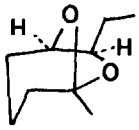
(18) R= $CH_2C_6H_5$; R^1,R^2= H,OH



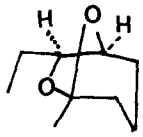
(19)



(20)



(21)



(22)

The present results and those previously obtained with allylmagnesium bromide[1] indicate that the addition onto the carbonyl carbon of the threo α,β-dialkoxy aldehyde (2) of the two Grignar reagents proceeds with nearly identical 8:2, threo-erythro stereoselectivity, as expected for a metal-chelation controlled addition.[2] The α,β-dialkoxy erythro aldehyde (1) and the α-alkoxy aldehyde (13) show with the saturated Grignard reagents, the same 6:4 threo-erythro selectivity The selectivity is inverted in favour of erythro-threo 6:4 ratio adding allylmagnesium bromide onto the aldehyde (1), thus invoking different reaction mechanisms.[2] However, apart from the mechanistic interest, the present results might hold some synthetic significance, as a method for obtaining α-alkoxy aldehydes in a chiral form. Indeed, the alcohols (3) and (6) can be interconverted (triphenylphosphine, benzoic acid, diethylazodicarboxylate, followed by alkalin hydrolysis),thus allowing the obtainment of a single enantiomer of the final aldehyde.

We will explore further the mechanistic and synthetic aspects of these transformations using the easily available C_4 aldehydes (1) and (2)

† We refer to $[\alpha]_D^{20}$. If not otherwise stated, optical rotations were taken in $CHCl_3$ soln. with c= 1.

• Varian Aerograph 90-P3. Column 2m x 1/4"; Pyrex; 20% DEGS on Chrom. W-aw 60/80 column temp. 90°C; He flow: 53 ml/min--

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[3] P.A.Levene and H.L.Haller, J.Biol.Chem.,1927,74,343

[4] K.Mori,Tetrahedron,1974,30,4223

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